Polymersomes Containing a Hydrogel Network for High Stability and Controlled Release

Shin-Hyun Kim, Jin Woong Kim, Do-Hoon Kim, Sang-Hoon Han, and David A. Weitz**

Capillary microfluidic devices are used to prepare monodisperse polymersomes consisting of a hydrogel core and a bilayer membrane of amphiphilic diblock-copolymers. To make polymersomes, water-in-oil-in-water double-emulsion drops are prepared as templates through single-step emulsification in a capillary microfluidic device. The amphiphile-laden middle oil phase of the double-emulsion drop dewets from the surface of the innermost water drop, which contains hydrogel prepolymers; this dewetting leads to the formation of a bilayer membrane. Subsequently, the oil phase completely separates from the innermost water drop, leaving a polymersome. Upon UV illumination of the polymersome, the prepolymers encapsulated within the interior are crosslinked, forming a hydrogel core. The hydrogel network within the polymersomes facilitates sustained release of the encapsulated materials and increases the stability of the polymersomes through the formation of a scaffold to support the bilayer. In addition, this approach provides a facile method to make monodisperse hydrogel particles directly dispersed in water.

1. Introduction

Polymersomes, vesicle structures whose membrane is composed of a bilayer of amphiphilic block-copolymers, have great potential for encapsulation and controlled delivery of active materials due to their high stability and low permeability by comparison with liposomes composed of a lipid bilayer.[1] The inner compartment of polymersomes can be used to encapsulate large amounts of water-soluble ingredients, and these encapsulants can be released upon triggered breakup of the bilayer membrane.[2] Recent advances in microfluidics have enabled the production of such polymersomes with uniform size and high encapsulation efficiency, which is difficult to achieve with conventional approaches such as electroformation or bulk hydration of dried amphiphiles.[3] In addition, polymersomes with multicompartments are prepared by a microfluidic emulsification, which enables the encapsulation of multicomponent ingredients while avoiding cross-contamination.[4] However, despite this progress, the use of such polymersomes is limited due to the poor stability of the molecular bilayer under osmotic pressure or mechanical stress, which leads undesired rupture of the membrane. Moreover, the encapsulated materials dissolved in the aqueous core are quickly released upon destruction of the membrane, making it difficult to use the polymersomes for controlled release of ingredients.

In this paper, we report a microfluidic approach to make polymersomes composed of a hydrogel core and a bilayer

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membrane of biocompatible amphiphilic diblock-copolymer; the hydrogel core provides enhanced stability of the bilayer and sustained release of the encapsulants. Using a capillary microfluidic device, we prepare monodisperse water-in-oil-in-water (W/O/W) double-emulsion drops which are transformed into polymersomes through a dewetting of amphiphile-laden middle oil phase onto the surface of innermost drop containing hydrogel prepolymers. Upon UV-irradiation, the prepolymers encapsulated in the polymersomes are crosslinked, resulting in hydrogel cores covered by a bilayer membrane. The hydrogel network facilitates the sustained release of encapsulated materials owing to a considerable increase of the diffusion path and a decrease of diffusivity. In addition, the swollen hydrogel supports the bilayer membrane, preventing its sharp deformation when subjected to external stress; this leads to enhanced stability of the polymersomes. Moreover, we demonstrate that these polymersomes provide facile templates for the production of monodisperse hydrogel particles directly dispersed in water.

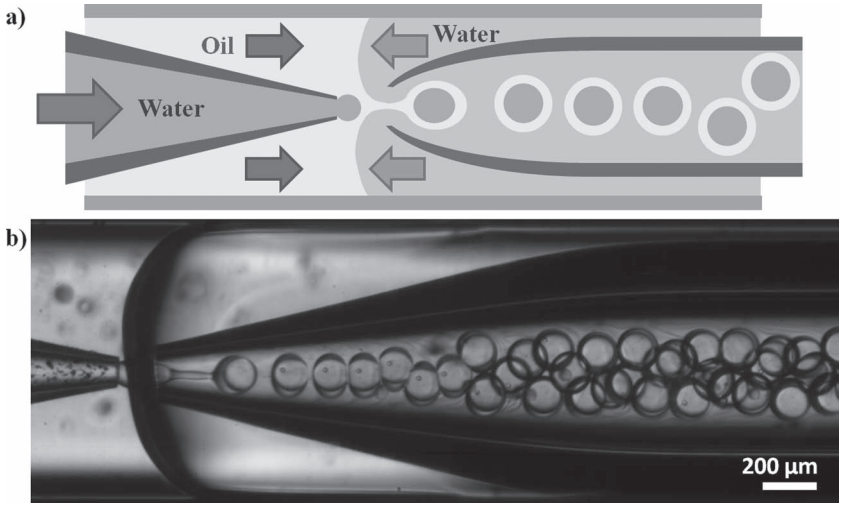

Figure 1. (a) Schematic illustration of the microfluidic capillary device for preparation of water-in-oil-in-water (W/O/W) double-emulsion drops. (b) Optical microscope image showing double-emulsion drop generation in the dripping mode.

2. Results and Discussion

2.1. Preparation of Polymersomes with a Hydrogel Core

The Microfluidic device is comprised of two tapered cylindrical capillaries inserted in a square capillary whose inner dimension is slightly larger than that of outer diameter of the cylindrical capillaries, as shown in **Figure 1**. One circular capillary is tapered to have smaller orifice of 73 μm in inner diameter and is treated with n-octadecyltrimethoxyl silane to make the surface hydrophobic; this is used for injection of the innermost aqueous phase: the hydrophobic surface prevents wetting of the aqueous phase on the outer wall of the capillary. The other circular capillary is tapered to have a larger orifice of 142 μm in inner diameter and is treated with 2-[methoxy(polyethyleneoxy)propyl] trimethoxyl silane to make the surface hydrophilic; this is used for collection of double-emulsion drops: the hydrophilic surface prevents wetting of the middle oil phase on the inner wall of the capillary.

As an innermost phase, we use 10 wt% or 15 wt% aqueous solution of poly(ethylene glycol)diacrylate (PEGDA, M_w 4000 g/mol) as an innermost phase of double-emulsion drops; we employ 10 wt% solution to study equilibrium states of polymersomes with hydrogel core, while 15 wt%

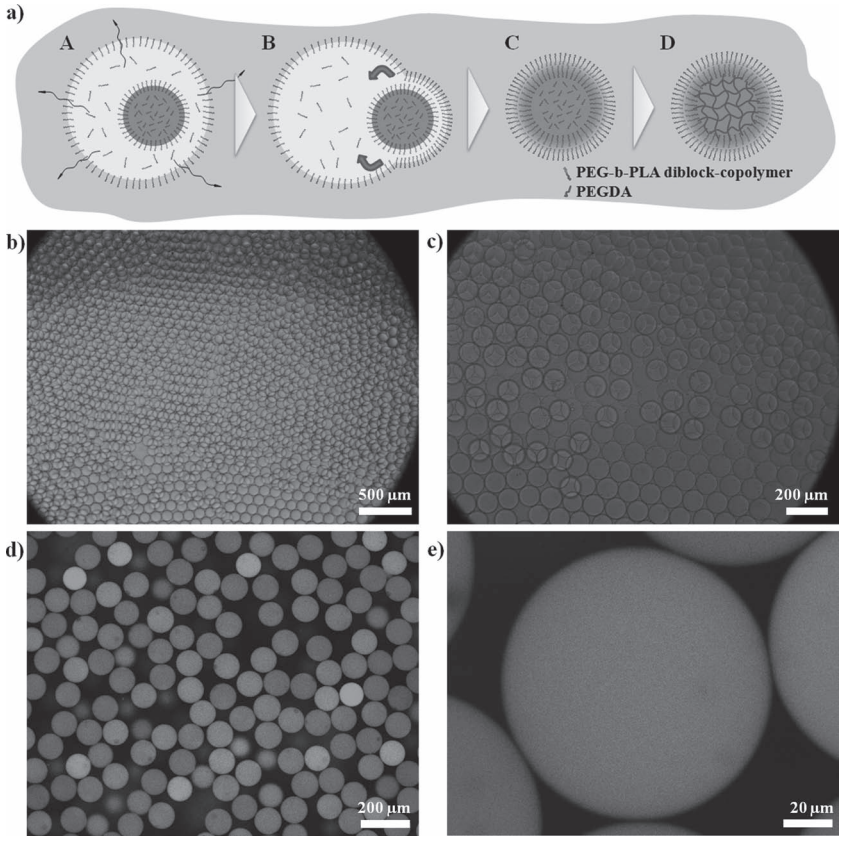

Figure 2. (a) Schematic illustration of preparation of polymersomes consisting of a hydrogel core of PEG and a bilayer membrane of PEG–*b*–PLA diblock-copolymers from templates of double-emulsion drops. Dewetting and subsequent separation of the middle phase creates a polymersome as denoted with steps A–C; UV-induced polymerization of PEGDA makes a hydrogel network in a core of the polymersome as denoted with steps C–D. (b,c) Optical microscope images of monodisperse polymersomes with PEG hydrogel cores. (d,e) Confocal microscope images of the polymersomes encapsulating FITC–dextran molecules.

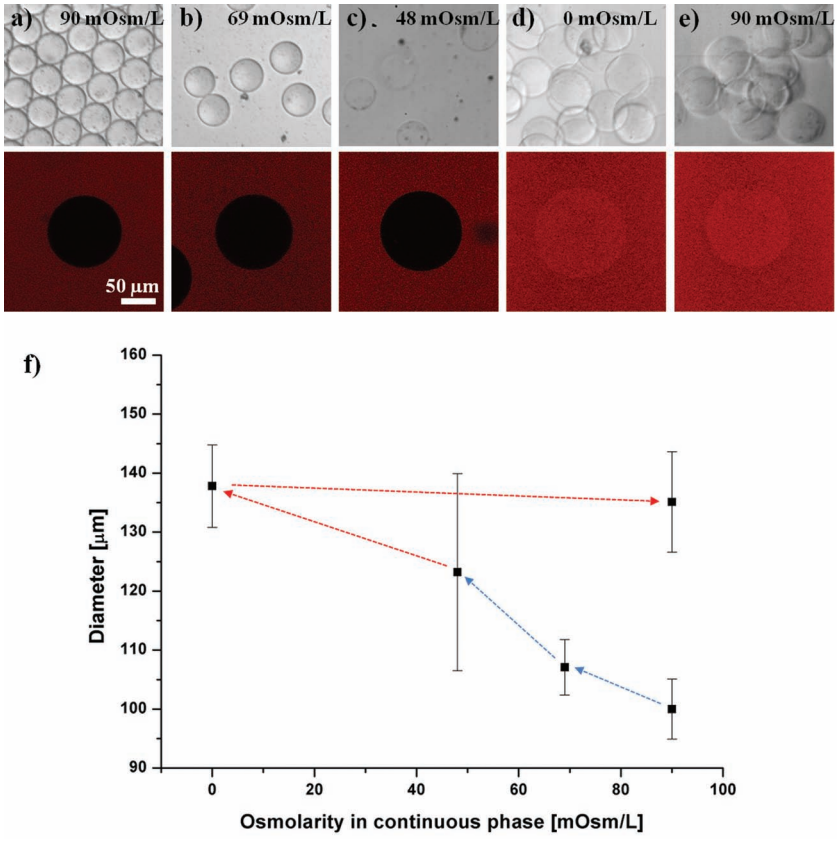

Figure 3. (a–e) Sets of optical and confocal microscope images of polymersomes with a hydrogel core dispersed in aqueous solutions of NaCl and red dye with osmolarities denoted in the images. The hydrogel is prepared by polymerization of 10 wt% PEGDA in aqueous cores. (f) Diameter of polymersomes with a PEG core as a function of osmolarity of continuous phase. Once the bilayer is ruptured in the continuous phase with low osmolarity, the hydrogel cores are fully swollen with water molecules and remain constant in size, regardless of the osmolarity of the continuous phase.

solution to study dynamic behavior of swelling of the polymersomes or release of encapsulants. Photoinitiator is added into the aqueous solution at a concentration of 0.2 wt%. We dissolve poly(ethylene glycol) (PEG, M_w 5000 g/mol)–*b*–poly(lactic acid)(PLA, M_w 10 000 g/mol) diblock-copolymer (Polysciences, Inc.) at a concentration of 5 mg/mL in a mixture of chloroform and hexane in a volume ratio of 38:62 and use it as a middle phase. We use 10 wt% aqueous solution of polyvinyl alcohol (PVA, M_w 13 000–23 000 g/mol) as the continuous phase. We inject the aqueous solution of PEGDA through injection capillary at 1000 μL/h to form the innermost drops. The oil phase of PEG–*b*–PLA diblock-copolymers is injected through the interstices of the injection and square capillaries at 800 μL/h to form the outer drops. We inject the continuous phase, an aqueous solution of PVA, through the interstices of the collection and square capillaries at 3500 μL/h as a counter flow to the innermost and middle phases. The aqueous core drops are generated at the tip of injection capillary in a dripping mode,[5] and they trigger a breakup of the middle phase, resulting in formation of monodisperse double-emulsion drops, as shown in Figure 1b and Movie S1 of the Supporting Information; small satellite drops of oil are produced, but they are easily removed by exploiting their density difference from the double-emulsion drops. The double-emulsion drops are collected in 45 mM aqueous solution of NaCl for 10 wt% innermost solution of PEGDA and 70 mM aqueous solution of NaCl for 15 wt% innermost solution of PEGDA; these collection liquids have slightly smaller osmolarity than that of the innermost aqueous phase, but much lower density. Therefore, resultant polymersomes can be collected at the bottom of the collection bath, and water flux through the bilayer membrane is eliminated. As chloroform quickly evaporates, the amphiphile-laden middle oil layer is expelled from dense arrays of the diblock-copolymers at each of the two interfaces, one separating the inner water drop and the middle oil and the second separating the middle oil and the continuous water; this expulsion is caused by an increase of the concentration of hexane in the oil layer; this is a poor solvent for PEG–*b*–PLA diblock-copolymer.[6] Therefore, the middle oil phase dewets onto the surface of the innermost drop, forming a bilayer membrane as schematically illustrated in steps A–B of **Figure 2**a. Subsequently, the middle phase separates from the drop in about one minute, producing a polymersome, a bilayer compartment of the innermost drop, as schematically illustrated in steps B–C of Figure 2a. After incubation of the polymersomes for 20 min at room temperature, we expose them to UV light with 2 W/cm^2 in the collection bath for 30 s to fully polymerize the PEGDA prepolymers within the core; this leads the formation of hydrogel core in the interior of polymersomes, as schematically illustrated in steps C–D of Figure 2a. The highly monodisperse polymersomes with a hydrogel core are collected on the bottom of the collection bath as shown in Figures 2b,c. These polymersomes can encapsulate any water soluble ingredient in their gel cores; for example, polymersomes containing fluorescein isothiocyanate (FITC)–dextran molecules (M_w 20 000 g/mol) are shown in the confocal microscope images in Figures 2d,e.

2.2. Properties of Polymersomes with a Hydrogel Core

To explore the enhanced stability of the polymersomes which have the hydrogel core, we investigate their behavior when exposed to negative or positive osmotic pressures. We prepare polymersomes with a hydrogel core through polymerization of 10 wt% aqueous solution of PEGDA. Although the osmolarity decreases as the PEGDA molecules are polymerized, the decrease is not significant because the number of molecular subunits, ethylene oxide, remains constant during

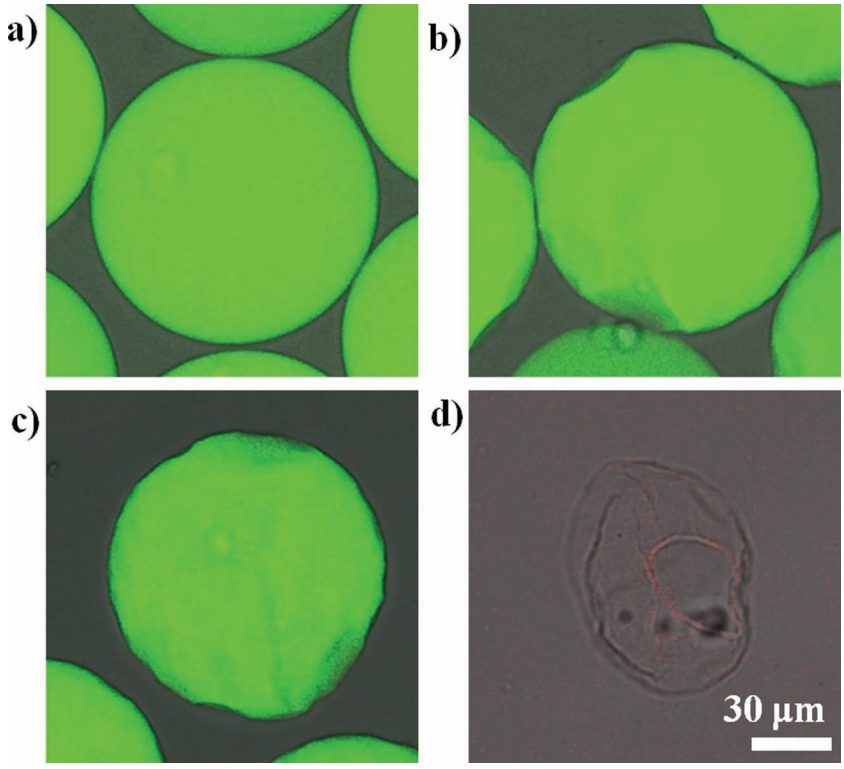

Figure 4. (a–c) Confocal microscope images of polymersome with a hydrogel core which are taken in (a) 5 min, (b) 16 min, and (c) 25 min after they are dispersed in aqueous solution of NaCl with 250 mOsm/L, where the hydrogel core is prepared by polymerization of 15 wt% PEGDA in aqueous cores. (d) Confocal microscope image of shrunken and disintegrated polymersome without a hydrogel core dispersed in the same aqueous solution of NaCl with 250 mOsm/L.

polymerization;[7] thus, the osmolarity of the innermost phase, which originally contains 10 wt% of 4000 g/mol PEGDA, remains at approximately 100 mOsm/L. The polymersomes are dispersed in aqueous solution of NaCl with various concentrations with osmolarities of 90, 69, 48, and 0 mOsm/L, to achieve negative osmotic pressure; in addition, red dye, sulforhodamine B, is dissolved in the continuous phase to help probe the integrity of the polymersomes. The size of the polymersomes is observed to increase as the osmolarity of the continuous phase decreases, as shown in optical and confocal microscope images of polymersomes, taken in 1 h after they are redispersed in the continuous phase, in **Figure 3**. As the osmolarity is lowered from 90 mOsm/L to 48 mOsm/L, the diameter of the polymersomes increases owing to the inward flux of water through the bilayer membrane caused by the higher osmolarity in the core, as shown in Figures 3a–c,f. The water flux stops when the osmotic pressure difference across the membrane becomes negligible. Nevertheless, the dye molecules cannot penetrate through the bilayer wrapping the hydrogel core even though it is swollen, as shown in the confocal microscope images; all polymersomes do not allow penetration of the dye molecules in the aqueous solutions with 90 or 68 mOsm/L, while approximately 10% of the polymersomes permit penetration into their cores for the aqueous solution with 48 mOsm/L. Although surface area of polymersomes increases as 14% in the aqueous solutions with 68 mOsm/L, resulting in small gaps between amphiphiles in bilayer membrane, the size of the gaps is not large enough to allow the diffusion of the dye molecules. In the aqueous solutions with 48 mOsm/L, polymersomes which exhibit increase of surface area less than critical value, approximately 40%, retain the dye molecules, while polymersomes which have large increase of surface area allow the diffusion of the dye through the resultant large gaps between amphiphiles. Further reduction of the osmolarity to 0 mOsm/L induces significant increase of the diameter and, ultimately, rupture of all membranes as shown in Figures 3d,f. Due to the inward water flux, the polymersomes are inflated and, finally, the molecular bilayer cannot cover the large surface area of the swollen hydrogel core; this results in rupture of the membrane, as shown in Figure S1 of the Supporting Information. Once the membrane ruptures, sodium and chloride ions can freely diffuse into the hydrogel network. In this case, the osmolarity of the continuous phase has very little influence on the size of hydrogel core; for example, hydrogel cores which are transferred from distilled water into an aqueous solution of NaCl with 90 mOsm/L exhibit only a very small decrease in size as shown in Figures 3e,f. We attribute this very small decrease to the reduction of the osmolarity contrast between the interior and the exterior of the hydrogel by comparison with that of hydrogel in distilled water; because of the slightly higher concentration of ions in the continuous phase compared to that in the hydrogel network, the osmotic pressure difference decreases, thereby reducing the degree of swelling.

Polymersomes dispersed in water that has higher osmolarity than that of their cores exhibit the outward flux of water, resulting in their shrinkage and ultimately their rupture.[3c] The stability of polymersomes against such a positive osmotic pressure can also be enhanced by a hydrogel core. For example, when polymersomes with a hydrogel core, made by polymerization of 15 wt% PEGDA, are dispersed in an aqueous solution of NaCl with 250 mOsm/L, they remain as spherical in shape for several minutes and then shrink slowly without rupture of the membrane, retaining the encapsulated FITC–dextran molecules inside them, as shown in **Figures 4**a–c. By contrast, under the same conditions, normal polymersomes, containing unpolymerized 15 wt% PEGDA, exhibit rapid shrinkage with rupture of their membranes in just a few minutes, thereby releasing the encapsulants, as shown in Figure 4d. We attribute this increased stability of the polymersomes with a hydrogel core to the formation of a hydrogel scaffold which supports the bilayer membrane; this prevents sharp undulation of the bilayer membrane during

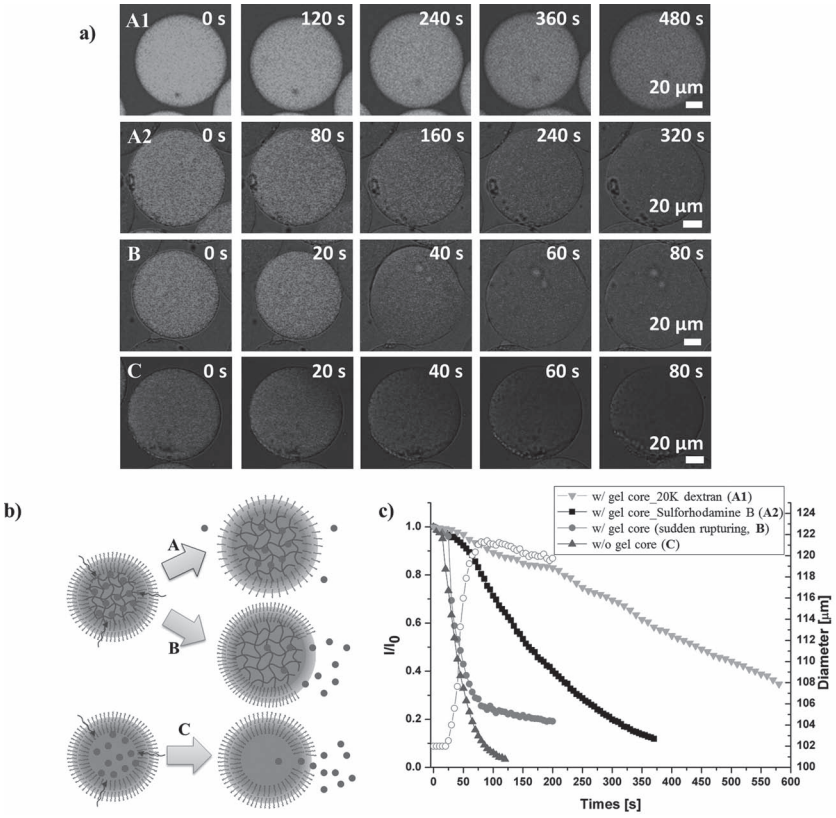

Figure 5. (a) Series of confocal microscope images of polymersomes with and without a hydrogel core, where the hydrogel core is prepared by polymerization of 15 wt% PEGDA in aqueous cores. Polymersomes with a hydrogel core exhibits slow release of FITC–dextran with molecular weight of 20 000 g/mol as denoted with 'A1' and sulforhodamine B with molecular weight of 558.7 g/mol as denoted with 'A2'. Sudden burst of polymersome containing sulforhodamine B is denoted with 'B', whereas polymersome without a hydrogel core is denoted with 'C'. (b) Schematic illustration of responses of polymersomes with and without a hydrogel core dispersed in distilled water. The arrows denote inward flux of water through membrane. (c) Normalized fluorescence intensity of FITC–dextran and sulforhodamine B molecules encapsulated in polymersomes as a function of time after release begins; slow releases of FITC–dextran and sulforhodamine B from polymersomes with a hydrogel core are denoted with inverted triangles (▼) and squares (■), respectively, whereas sudden release of sulforhodamine B by rupture is denoted with circles (●). The release of sulforhodamine B from polymersomes without a hydrogel core is denoted with triangles (▲). Diameter of polymersome which exhibits sudden burst is added in right axis (○).

outward water flux, ensuring its integrity is maintained, as shown in Figures 4a–c.

We investigate dynamic release behavior of encapsulated materials from the polymersomes with a hydrogel core under negative osmotic pressure. Polymersomes are prepared by polymerization of 15 wt% PEGDA and either FITC–dextran or sulforhodamine B are encapsulated in the aqueous core as model encapsulants. When they are transferred from 70 mM NaCl solution to distilled water, their diameter increases due to the inward flux of water through the bilayer membrane; nevertheless, there is no release of the encapsulants for a few minutes. However, the polymersomes ultimately swell enough that small gaps in the bilayer appear and release of the encapsulants begins. This occurs even before the hydrogel is fully swollen, as shown in series of confocal microscope images in **Figure 5**a; the first row (A1) shows release of FITC–dextran (M_w 20 000 g/mol) and the second row (A2) shows release of sulforhodamine B (M_w 558.7 g/mol). Although the bilayers maintain their integrity, intermolecular distance in the bilayers increases, enabling leakage of dye molecules through the bilayer; we estimate the critical value of increase of surface area for release of sulforhodamine B as approximately 40%. Approximately 5% of the polymersomes exhibit a sudden burst of the bilayer membrane, followed by rapid release of the encapsulants as shown in the third row (B) of Figure 5a; we attribute this premature destruction of the bilayer membrane to defects in its structure. By contrast, the polymersomes without a hydrogel core immediately release their encapsulants as soon as they are dispersed into distilled water, as shown in the bottom row (C) of Figure 5a. We summarize these three different release behaviors schematically in Figure 5b and in Movie S2 of the Supporting Information. Polymersomes without a hydrogel core release half their original red sulforhodamine B dye in 35 s. By contrast, it takes approximately 160 s after release begins for the polymersomes with a hydrogel core to release half of their original sulforhodamine B dye. We illustrate this by plotting time-dependence of the normalized fluorescence intensities of FITC–dextran or sulforhodamine B in the core of the polymersomes during the course of release in Figure 5c. This extended release of the dye molecules is a result of the hydrogel network, which limits the diffusion rates of dye molecules. Even for the polymersomes which exhibit a sudden burst of their bilayer, 25% of original red dye still remains in the hydrogel core, and this is released slowly after the burst; this is summarized as solid circles in Figure 5c. For comparison, we determine the time dependence of the diameter of the polymersome using $(4A/\pi)^{1/2}$, where A is the area of the hydrogel core in the images in the third row (B) of Figure 5a. By plotting the time dependence of the diameter, we clearly observe the coincidence with the sudden release upon bursting of the membrane, as shown by the open circles in Figure 5c. Inhibition of diffusion through the hydrogel is more effective when the size of encapsulants is closer to size of the hydrogel mesh. Therefore, the retardation of the release is greater for FITC–dextran (M_w 20 000 g/mol) than for sulforhodamine B (M_w 558.7 g/mol); it takes about 3 times as long, 440 s, to release of half of their original FITC–dextran. The low-magnification confocal-microscope images of the polymersomes encapsulating FITC–dextran, taken

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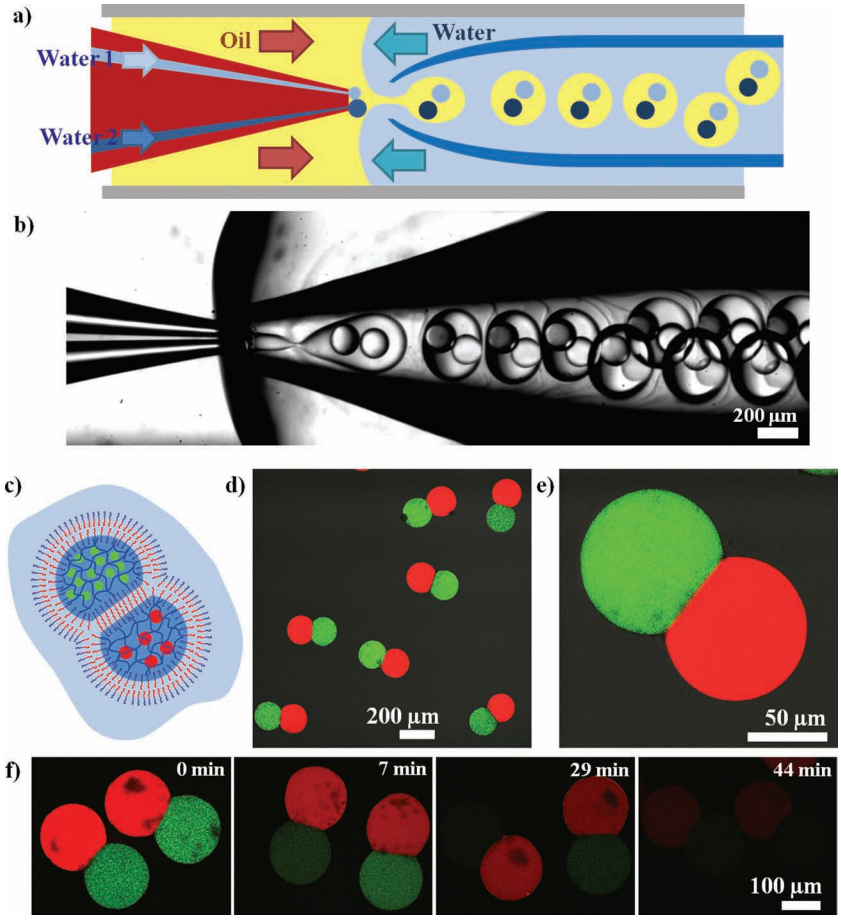

Figure 6. (a,b) Schematic illustration and optical microscope image of the capillary microfluidic device for preparation of W/O/W double-emulsion drops with dual cores. (c) Schematic illustration and (d,e) confocal microscope images of dumbbell-shaped polymersomes with two distinct hydrogel bulbs, where the hydrogel core is prepared by polymerization of 15 wt% PEGDA in aqueous cores; one bulb contains rhodamine-tagged BSA (M_w 66 500 g/mol) and the other bulb contains FITC–dextran (M_w 20,000 g/mol). (f) Series of confocal microscope images of the polymersomes dispersed in distilled water, taken at the times denoted in the images; release of dextran molecules is faster than that of BSA molecules.

1 min and 30 min after they are dispersed in distilled water, are shown in Figure S2 of the Supporting Information.

Dumbbell-shaped polymersomes can encapsulate two different materials by enclosing each material in its own internal shell, thereby preventing mixing. These can be prepared by using templates of double-emulsion drops with two distinct innermost drops.[4b] We use a dual bore capillary for injection of the innermost phases, and encapsulate two distinct components into separate bulbs of dumbbell-shaped polymersomes, as shown in **Figures 6**a,b and Movie S3 of the Supporting Information. Upon polymerization of prepolymers, hydrogel cores are formed in both bulbs of the dumbbell, as shown in Figures 6c–e, where one core contains rhodamine-tagged bovine serum albumin (BSA, M_w 66 500 g/mol) and the other core contains FITC–dextran (M_w 20 000 g/mol). When the dumbbells are transferred into distilled water, they begin to release the encapsulants from both bulbs, but with two different release rates, as shown in Figure 6f; release of dextran molecules is relatively faster than that of BSA molecules due to their smaller size.

2.3. Hydrogel Microparticles

Microfluidic techniques provide a convenient method to make monodisperse hydrogel particles; this is accomplished by employing water-in-oil emulsion drops as templates to make hydrogel microparticles.[8] After polymerization, the hydrogel particles are transferred from oil to water, which requires inconvenient washing steps. By contrast, our approach enables the production of hydrogel microparticles dispersed directly in water; if necessary, the bilayer membrane can be removed by simple washing with distilled water. Therefore, this approach is potentially useful for encapsulation of live cells in hydrogel microparticles while retaining high viability; such cell-laden hydrogel microparticles have potential value for immunoisolation, drug delivery, and tissue engineering.[9] In addition, these hydrogel microparticles can potentially be used to encapsulate delicate biomolecules.

Hydrogel microparticles produced without bilayer exhibits different diameter, depending on the solvent, as shown in **Figure 7**. In water, the low interaction parameter between water and PEG causes the hydrogel microparticles highly swollen, as shown in Figure 7a; here, the osmolarity of the continuous phase has very little influences on the diameter of the microparticles as shown in Figure 7e. The diameter of the hydrogel microparticles decreases in acetone and ethanol as shown in Figures 7b and c, respectively; we attribute this to larger interaction parameters between these solvents and PEG than that between water and PEG. In isopropyl alcohol (IPA), the microparticles are collapsed to a nonspherical shape, as shown in Figure 7d, expelling the IPA molecules outside them due to even larger interaction parameter between IPA and PEG. An image of a dried microparticle, obtained by a scanning electron microscope (SEM), is shown in Figure S3 of the Supporting Information.

3. Conclusion

In this work, we report a method to produce monodisperse polymersomes with a hydrogel core; these provide enhanced stability and sustained release of encapsulated materials. Polymersomes containing hydrogel prepolymers are prepared from templates of W/O/W double-emulsion drops; subsequent photo-polymerization of the prepolymers creates a hydrogel network in the interior of the polymersomes. This hydrogel core facilitates sustained release of encapsulants by creating a diffusion barrier, and enhances the stability of

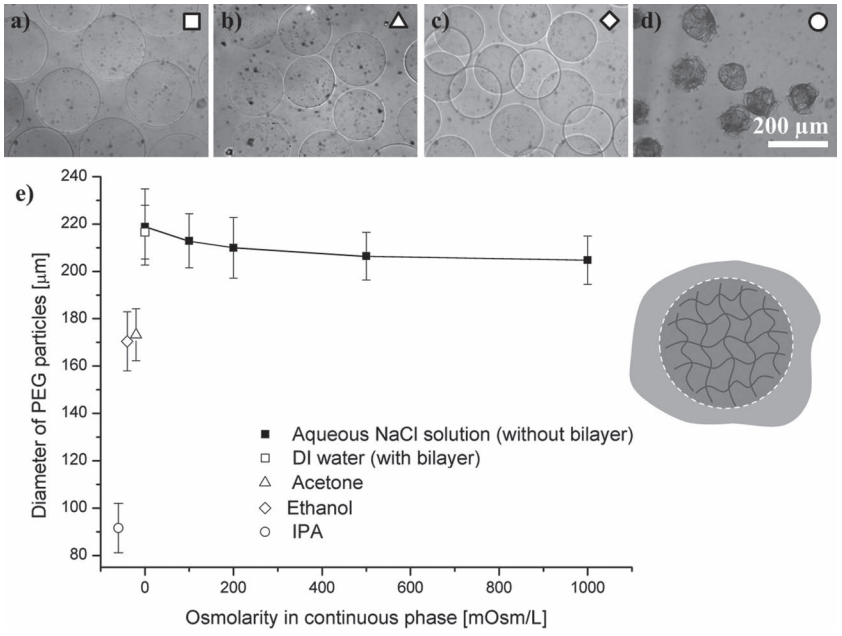

Figure 7. (a–d) Optical microscope images of PEG microparticles without a bilayer dispersed in solvent (a) water, (b) acetone, (c) ethanol, and (d) isopropanol. The PEG microparticles are prepared by polymerization of 15 wt% PEGDA in aqueous cores of polymersomes and subsequent removal of bilayer membrane. (e) Diameter of hydrogel microparticles with bilayer in distilled water and without bilayer depending on the continuous phase of each solvent, and microparticles without bilayer depending on osmolarity in the continuous water phase.

polymersomes through formation of scaffold to support the bilayer. Accordingly, polymersomes with a hydrogel core can encapsulate and deliver active materials in a more safe and precise fashion, preventing undesired rupture of the bilayer and providing controlled rate of release. In addtition, these polymersomes can serve as templates to produce hydrogel particles direcly in water, enabling safe embeding of cells or other water-soluble materials in hydrogel microparticles. Therefore, this novel approach to make a hydrogel network in polymersomes will provide new oppotunities for a wide range of encapsulation and delivery applications of active ingredients such as drugs, cosmetics, nutrients, and cells. Moreover, the hydrogel core can serve as a model cytoskeletal element when the polymersomes are employed as artificial system to study fundamental cell functions.[10,11]

4. Experimental Section

Materials: To make hydrogel core in polymersomes, we use 10 wt% or 15 wt% aqueous solution of PEGDA (M_w 4000 g/mol, Polyscience, Inc.) containing 0.2 wt% 4-(2-hydroxyethoxy)phenyl-(2-hydroxy-2-propyl)ketone as a photoininitator. To make the bilayer membranes, we dissolve PEG (M_w 5000 g/mol)–*b*–PLA (M_w 10 000 g/mol) diblock-copolymer (Polysciences, Inc.) at a concentration of 5 mg/mL in a mixture of chloroform:hexane 38:62 (by volume). We use 10 wt% aqueous solution of PVA (M_w 13 000–23 000 g/mol, Sigma-Aldrich) as the continuous phase. A water-soluble red dye of sulforhodamine B (Aldrich), FITC–dextran (Aldrich, M_w 20 000 g/mol), and rhodamine-tagged BSA (M_w 66 500 g/mol) are dissolved in the innermost phase of the polymersomes to probe the release of encapsulated material from the polymersomes.

Drop Generation and Polymerization: Two cylindrical capillaries (World precision instruments, Inc., 1B100-6) are tapered to have orifice of 73 μm in inner diameter and orifice of 142 μm in inner diameter, respectively and inserted in a square capillary (AIT glass); prior to insertion, the cylindrical capillary with smaller orifice is treated with n-octadecyltrimethoxyl silane (Aldrich) to make the surface hydrophobic, whereas the cylindrical capillary with larger orifice is treated with 2-[methoxy(polyethyleneoxy) propyl] trimethoxyl silane (Gelest, Inc.) to make the surface hydrophilic. To control flow rates of three phases we use syringe pumps (Harvard Apparatus) and the flow is observed using an inverted microscope equipped with a high speed camera (Phantom V9.0). The PEGDA in core of polymersomes are polymerized by UV exposure for 30 s (Omnicure S1000, 100W) and the resultant polymersomes containing hydrogel core are observed with a confocal laser scanning microscope (Leica, TCS SP5).

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

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