VIP Microfluidics

DOI: 10.1002/ange.201102946

One-Step Emulsification of Multiple Concentric Shells with Capillary Microfluidic Devices**

*Shin-Hyun Kim and David A. Weitz**

Emulsions have long been utilized to make materials for foods, drugs, cosmetics, and displays because of their efficient encapsulation properties. While they are most commonly made in bulk, recent advances in microfluidics have enabled the design and manipulation of emulsion drops with unprecedented control and flexibility,[1] albeit only on a drop-by-drop basis. Multiple-phase emulsions of very high uniformity in size can be prepared using precise control of flow that can be achieved in tailored poly(dimethylsiloxane) (PDMS) or capillary devices.[2] The monodisperse single and double emulsion drops produced by such microfluidic devices can be employed to make functional microparticles and microcapsules, respectively. For example, nonspherical and Janus microparticles with optical, electrical, and magnetic functionalities can be prepared from monodisperse single emulsion drops.[3] Moreover, polymeric microcapsules, vesicles, and colloidosomes can be prepared from double emulsion drops.[4] Double emulsion drops provide particularly effective encapsulation of active materials with high encapsulation efficiency; in addition, many routes to controlled release are feasible. Even greater structural and functional enhancement of the microcapsules can be achieved with multiple emulsion drops of yet higher order. For example, multiple emulsion drops of high order are useful in the production of complex microcapsules for encapsulation and sequential release of multi-component active materials while avoiding cross-contamination. However, production of such multiple emulsion drops remains a challenge. Most previous approaches utilize sequential emulsification using a series of single drop makers.[1a,5] Thus, the device fabrication entails complex procedures and delicate control of flow rates required to synchronize the frequencies of drop generations in all drop makers. Moreover, the dispersed phases are used as the continuous carrier fluid of the inner drops before the sequential emulsification, making it difficult to achieve full control of a diameter of each layer in the multiple emulsion drops. By contrast, single-step emulsification obviates the shortcomings of sequential emulsification and enhances the controllability and the stability of the generation of multiple emulsion drops using an even simpler device design. Although double emulsion drops have been prepared through single-step emulsification,[2b] coaxial introduction of four or more immiscible fluids into a single channel is challenging, making it difficult to produce higher-order multiple emulsion drops through single-step emulsification.

Herein, we report a facile one-step emulsification approach to make monodisperse multiple emulsion drops of high order using stable biphasic flows in confining channels. Through controlled surface modification of glass capillary devices, immiscible multiphase streams flow through a single orifice, forming layered coaxial interfaces. Breakup of the interfaces is achieved in dripping or jetting modes, determined by the flow rates. In the dripping mode, breakup is triggered by inserting a drop in the core of the emulsion, facilitating the production of monodisperse triple or quadruple emulsion drops with an onionlike configuration. In addition, by using the jetting breakup mode, the number of drops in the core can be manipulated.

The essential strategy of our approach relies on the stable flow of two fluids through a single channel without the formation of drops, which commonly occurs because of Rayleigh-Plateau instability. The flow of two immiscible fluids through a single capillary channel exhibits two distinct patterns consisting of either drops or a jet, depending on several control parameters.[6] In either case, the fluid with the higher affinity to the wall forms the continuous phase while that with the lower affinity flows through the center, without contacting the wall, either as distinct drops or a jet. In most cases, this jet is unstable to formation of drops because of the Rayleigh-Plateau instability. However, the spatial confinement of the interface because of the geometry of capillary can, in fact, provide additional stability to the jet, suppressing the breakup into drops. This is the particularly effective when the width of the inner fluid is large, so that the interface between the two fluids is formed near the capillary wall; then strong confinement of the continuous fluid helps prevent the Rayleigh-Plateau instability and the subsequent breakup into drops. We exploit this feature to produce high-order multiple emulsions through a one-step emulsification process. The design of the device for producing triple emulsion drops of water-in-oil-in-water-in-oil ($W_1/O_2/W_3/O_4$) phases comprises two tapered cylindrical capillaries, one for injection and the other for collection. Each is inserted into a square capillary, the inner dimension of which is slightly larger than the outer diameter of the cylindrical capillary before they are tapered, as shown schematically in Figure 1 a. The cylindrical capillaries are treated to make them hydrophobic; the outer square capillary is treated to make it hydrophilic. In addition, a small tapered capillary is inserted into the space between the collection and the square capillaries to simultaneously

[*] Dr. S.-H. Kim, Prof. D. A. Weitz
School of Engineering and Applied Sciences, Department of Physics
Harvard University, Cambridge, MA 02138 (USA)
E-mail: weitz@seas.harvard.edu
Homepage: http://weitzlab.seas.harvard.edu/

[**] This work was supported by Amore-Pacific, the NSF (DMR-1006546) and the Harvard MRSEC (DMR-0820484).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201102946.

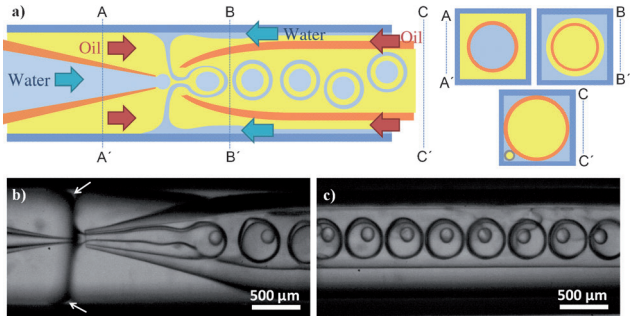

Figure 1. a) Microfluidic capillary device for preparation of W/O/W/O triple emulsion drops. The three cross-sectional schematics (A–A′, B–B′, and C–C′) are included for clarity. b,c) Optical microscope images showing triple emulsion generation and downstream motion. The white arrows in (b) denote the aqueous stream for the outer layers.

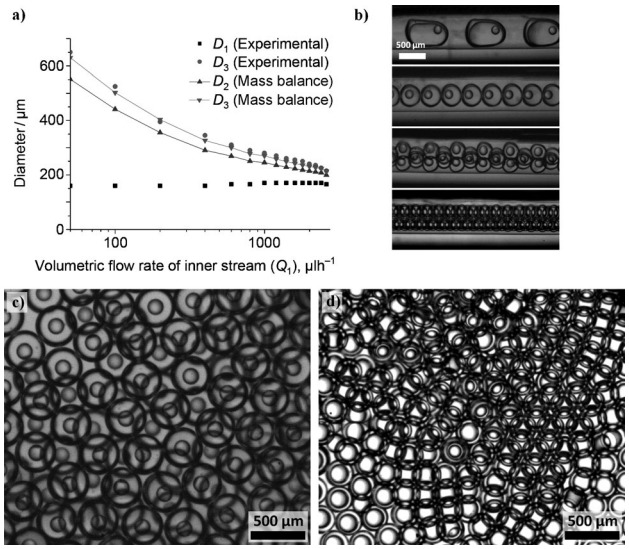

Figure 2. a) Diameters of the innermost drop (D_1), the middle shells (D_2), and the outer shells (D_3) in W/O/W/O triple emulsion drops as a function of the flow rate of the water for the innermost drops (Q_1) where the flow rates of the oil for the middle shells (Q_2), the water for the outer shells (Q_3), and oil as the continuous phase (Q_4) are kept at 2, 1, and 3 mL h^{-1}, respectively. Triangles and inverted triangles denote the calculated D_2 and D_3 values from mass balance equations. b) Optical microscope images of downstream motions at four different values of Q_1 equal to 50, 200, 800, and 2600 μL h^{-1} from top. c,d) Optical microscope images of monodisperse triple emulsion drops produced at two different values of Q_1 equal to 200 μL h^{-1} (c) and 1600 μL h^{-1} (d).

inject a second immiscible fluid, as shown in the schematic cross-section of C–C′ in Figure 1 a. An aqueous phase is injected through the center of the cylindrical injection capillary; this will ultimately form innermost drops. An oil phase is injected into the square capillary from the same side with an injection capillary as shown in Figure 1 a. Both water and oil are simultaneously injected into the channel between the cylindrical collection capillary and square capillary, with the oil being injected through the small additional capillary as shown in Figure 1 a. Because of the properties of the surfaces, the oil flows along the outer surface of the collection capillary, while the water shields the oil stream from the outer surface as shown in Figure 1 a. Thus, four immiscible fluids are simultaneously introduced into the orifice in the form of a coaxial flow. This results in the formation of triple emulsion drops with a single emulsification process.

To prepare the triple emulsion drops, we employ water (W_1) for the innermost drops, hexadecane with 1 wt % SPAN 80 surfactant (O_2) for the first oil shell, an aqueous solution of 3 wt % poly(vinyl alcohol) (PVA) and 1 wt % F108 surfactant (W_3) for the second water shell, and hexadecane with 1 wt % SPAN 80 (O_4) as the continuous phase. The water (W_1) and the hexadecane (O_2) flows into the orifice of the collection capillary from the left side while the aqueous (W_3) and the hexadecane solutions (O_4) form the coaxial interface and flow into the orifice simultaneously; therefore, the triple emulsion drops of $W_1/O_2/W_3/O_4$ are prepared in the collection capillary as shown in Figure 1 b,c. The outer three phases, consisting of O_2, W_3, and O_4, flow through the orifice of the collection capillary, forming two coaxial interfaces, one consisting of O_2/W_3 and the second consisting of W_3/O_4; the core water drops (W_1) are produced in dripping mode at the tip of the injection capillary,[7] and trigger the breakup of the coaxial interfaces. Therefore, the flow rate of the innermost aqueous phase (Q_1) determines the size of the triple emulsion drops as shown in Figure 2 a,b and Movie S1 in the Supporting Information. Since the innermost drops are formed in the dripping mode, as Q_1 increases, the frequency of their generation increases while their diameter (D_1) does not change significantly; therefore the frequency of the breakup also increases and this results in the reduction of the diameter of the middle (D_2) and the outer shells (D_3). We can calculate D_2 and D_3 using mass balance equations which describe the drop formation triggered by the innermost drops [Eq. (1)],

$$D_2 = D_1\left(1+\frac{Q_2}{Q_1}\right)^{1/3} \text{ and } D_3 = D_1\left(1+\frac{Q_2+Q_3}{Q_1}\right)^{1/3} \quad (1)$$

where Q_2 and Q_3 are volumetric flow rates of O_2 and W_3, respectively. The calculated diameter D_3 is in good accord with the measured one. The optical microscope images of the monodisperse triple emulsion drops produced at two different values of Q_1, 0.2 and 1.6 mL h^{-1}, are displayed in Figure 2 c,d, respectively.

As Q_2 increases, there is a concomitant decrease in D_1 because of the increased drag force on the innermost drops; at the same time, D_3 does not significantly change because of the compensation of the increase of Q_2 by the decrease of D_1 as seen in Equation (1). This effect of Q_2 on the size of drops is shown in Figure S1 in the Supporting Information. For large Q_2, the drop breakup mechanism changes from dripping, triggered by the innermost drops, to jetting. The coaxial interfaces form a long jet and produce pluglike drops containing the desired number of the innermost drops, as shown in Figure S2 in the Supporting Information. The number of core drops is controlled by Q_1, which determines the relative frequency of their generation and the interface breakup. The value of Q_3 affects the thickness of W_3, while Q_4 has insignificant influences on the size of any of the drops or

shells within the range of flow rates that produce the innermost drop-triggering mode, as shown in Figures S3 and S4 in the Supporting Information.

The opposite chemical modification of the device walls enables preparation of inverse triple emulsion drops (O/W/O/W) as shown in Figure 3a, where the injection and collection circular capillaries are treated to make them hydrophilic, whereas the square capillary is treated to make it hydrophobic. We make monodisperse microcapsules containing core particles from triple emulsion drops of O/W/O/W using a photopolymerizable monomer resin, ethoxylated trimethylolpropane triacrylate (ETPTA) as the oil phases. We show the generation of $O_1/W_2/O_3/W_4$ triple emulsion drops, where breakup of two coaxial interfaces consisting of W_2/O_3 and O_3/W_4 is triggered by the innermost oil drops (O_1), in Figure 3b and Movie S2 in the Supporting Information. The number of innermost drops can be controlled by the flow rate of the innermost fluid when operating in the jetting mode, in the same manner as the W/O/W/O triple emulsion drops. We polymerize the oil phases of triple emulsion drops by exposing them to UV illumination, and we show microcapsules containing a constant number of core particles in Figure 3c. Single-core triple emulsion drops ($N=1$) are produced in the dripping mode with values of Q_1, Q_2, Q_3, and Q_4 equal to 0.15, 6.5, 3.0, and 9.5 mL h^{-1}, respectively; while two- ($N=2$), three- ($N=3$), and four- ($N=4$) core triple emulsion drops are produced in the jetting mode, with values of Q_1 equal to 0.20, 0.23, and 0.26 mL h^{-1}, respectively, and with Q_2, Q_3, and Q_4, held constant at values of 6, 4, and 9 mL h^{-1}, respectively.

To make magneto-responsive core particles confined within the capsules, we add iron-oxide magnetic nanoparticles to the innermost oil drops of ETPTA before the microfluidic emulsification. The core particles sink to the bottom of the capsules and are aligned within the capsules upon application of an external magnetic field, as shown in Figure 3d and Movie S3 in the Supporting Information. A scanning electron microscope (SEM) image of a broken microcapsule containing a core particle is shown in the inset of Figure 3d. We demonstrate magnetic active inks by using these transparent microcapsules containing the movable magnetic cores and adding iron oxide and carbon black nanoparticles in the core drops and an aqueous suspension of 500 nm polystyrene particles in the inner space of the capsules as schematically illustrated in Figure S5a in the Supporting Information. The ink capsules are white in appearance because of Mie scattering of visible light by polystyrene particles; black dots appear when the core particles are aligned to the viewing side. This produces a black and white contrast of the ink capsules, controlled by the magnetic field as shown in Figure S5c,d in the Supporting Information. This type of active ink can potentially show faster response and lower energy consumption over conventional inks such as phoretic or rotation types when the density of the movable particles is matched with that of the scattering medium.[8] In addition, this geometry encapsulates the ink particles in self-contained microcapsules, which eliminates any migration of the ink particles, thereby providing improved resolution and robustness for the ink.

Monodisperse quadruple emulsion drops can also be prepared by a one-step emulsification process using a device of the same geometry but with different chemical modifications, as illustrated schematically in Figure 4a. Two biphasic streams, coming from both the left and right sides of the square capillary, form three coaxial interfaces and make quadruple emulsion drops by a breakup of the interfaces triggered by the innermost drops. To produce $W_1/O_2/W_3/O_4/W_5$ quadruple emulsion drops, the injection capillary and the collection side of the square capillary are treated to be hydrophobic, whereas the collection capillary and the injection side of the square capillary are treated to be hydrophilic as shown in Figure 4a. To modify the surface of the inner wall of the square capillary into two distinct regions, we separately

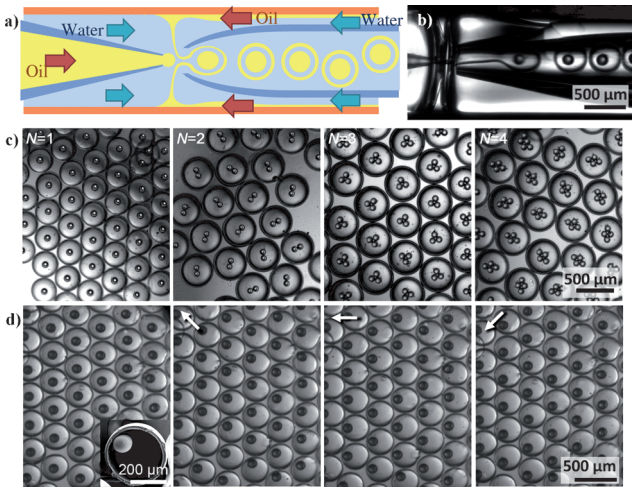

Figure 3. a) Microfluidic capillary device (and cross-sections) for preparation of O/W/O/W triple emulsion drops. b) Optical microscope images showing triple emulsion generation. c) Optical microscope images of monodisperse microcapsules containing single-, two-, three-, and four-core particles. d) Optical microscope images of microcapsules containing a magneto-responsive core particle. The core particles sink to the bottom of the capsule (first image) and are aligned upon application of an external magnetic field. The inset shows an SEM image of a broken capsule with magnetic core and the white arrows denote the direction of the magnetic field.

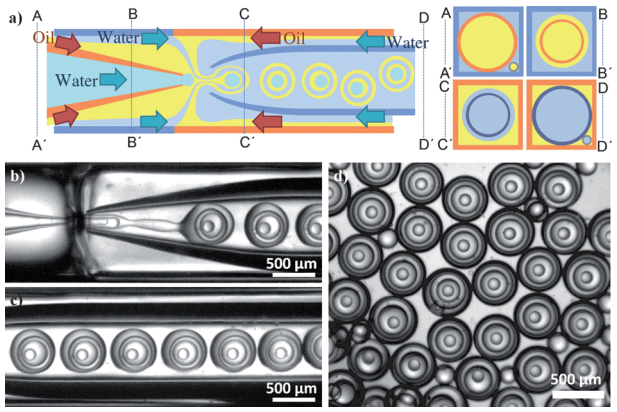

Figure 4. a) Microfluidic capillary device for preparation of W/O/W/O/W quadruple emulsion drops. b,c) Optical microscope images showing quadruple emulsion generation and downstream motion. d) Optical microscope image of monodisperse quadruple emulsion drops.

treat two square capillaries with different silane coupling agents and then connect them into a single capillary. The gap between two capillaries is sealed with an epoxy resin. The device and a schematic are shown in Figure S6 in the Supporting Information. The breakup of the three coaxial interfaces consisting of O_2/W_3, W_3/O_4, and O_4/W_5 is triggered by the injection of the innermost water drops (W_1), resulting in monodisperse quadruple emulsion drops with an onionlike configuration as shown in Figure 4b–d. The formation of quadruple emulsion drops and their downstream motion is shown in Movie S4 in the Supporting Information. The breakup occurs sequentially from the inner to the outer interfaces. Similarly, O/W/O/W/O quadruple emulsion drops can be produced using a device with the same geometry but with the opposite chemical modifications, as shown in Figure S7 in the Supporting Information.

Herein, we report a pragmatic microfluidic approach to create monodisperse multiple emulsion drops through one-step emulsification. The formation of stable coaxial interfaces and subsequent breakup can be achieved in simple capillary devices, providing a facile way to make monodisperse multiple emulsion drops of high order. This one-step emulsification approach is available for fluids with a wide range of viscosities and enables the full control of a diameter of each layer in the multiple emulsion drops through control of the flow rates of each of fluids. This class of multiple emulsion drops has great potential as advanced microcapsules. Herein, we have explicitly shown the production of active magnetic inks for display applications. Other examples of potential useful microcapsules include double microcapsules or microcapsules in microcapsules, which are both potentially useful for drug carriers, as they enable sequential release of multi-component drugs while avoiding cross-contamination; they could be valuable in growth-factor delivery and cancer therapy.[9] Furthermore, multiple emulsion drops can act as microreactors which can contain several different reagents. Therefore, this novel approach to make multiple emulsion drops is promising for a wide range of applications owing to its high degree of controllability, its stability, and its simplicity.

Experimental Section

Materials: To prepare multiple emulsion drops, hexadecane (Aldrich) with 1 wt% SPAN 80 (Aldrich) and an aqueous solution of 3 wt% PVA (M_w 13000–23000, Sigma-Adrich) and 1 wt% ethylene oxide-propylene oxide-ethylene oxide triblock copolymer (BASF Pluronic F108) are employed as the oil and water phases, respectively. In addition, ETPTA (Aldrich) containing 0.2 wt% photoinitiator (2-hydroxy-2-methylpropiophenone, Aldrich) is used to polymerize the oil phase. The photopolymerization of ETPTA is achieved by UV exposure for 2 seconds (Omnicure S1000). To make magneto-responsive black cores, iron oxide nanoparticles (α-Fe_2O_3, < 50 nm, Aldrich) and carbon black nanoparticles (Hiblack 420B, Degussa) are dispersed in the ETPTA at 0.2 and 1 wt%, respectively. Polystyrene particles with a diameter of 500 nm are dispersed in the aqueous solution of 0.1 wt% F108 as the scattering medium.

Device preparation and drop generation: Cylindrical glass capillaries of 1 mm in outer diameter (World precision instruments, Inc., 1B100-6) are tapered into the slope of approximately 0.4 and assembled in a square capillary of 1.05 mm in inner dimension (AIT glass). The surface modification of cylindrical and square capillaries is determined by the type of multiple emulsion drops as shown in Figures 1, 3, and 4, where capillary surfaces are treated with 2-[methoxy(polyethyleneoxy)propyl] trimethoxyl silane (Gelest, Inc.) and *n*-octadecyltrimethoxyl silane (Aldrich), making them hydrophilic and hydrophobic, respectively. During drop generation, flow rates are controlled by syringe pumps (Harvard Apparatus) and flow motion is observed using an inverted microscope equipped with a high-speed camera (Phantom V7.0 or V9.0).

Received: April 28, 2011
Published online: July 29, 2011

Keywords: emulsification · metal oxides · microcapsules · microfluidics · polymers

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