Controllable Monodisperse Multiple Emulsions**
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Multiple emulsions, or “emulsions of emulsions,” are complex systems in which dispersed droplets contain smaller droplets inside. They are widely used to encapsulate active ingredients in myriad applications, including drug delivery,[1–3] foods,[4,5] cosmetics,[6,7] chemical separations[8,9] and syntheses of microspheres and microcapsules.[10–16] Monodispersity of size and accurate control of internal structure are critical for the versatility of such emulsions, because these attributes allow precise manipulation of the loading levels and the release and transport kinetics of the encapsulated substances.[10–21] Although there have been several reports on the preparation of monodisperse multiple emulsions,[10–13,17–23] concurrent and precise control over both the size and structure of the emulsions remains difficult to achieve, and current techniques are not scalable to higher-order multiple emulsions. Herein, we describe the fabrication of highly monodisperse multiple emulsions using capillary microfluidics to independently control both the size and the number of inner droplets. Importantly, our technique is easily scalable to higher-order multiple emulsions, which we demonstrate by making monodisperse, controllable triple emulsions. We illustrate the utility of the tight control afforded by this technique by fabricating a novel hydrogel microcapsule from a triple emulsion, and we demonstrate its use for simultaneous controlled release of two-phase (oil and aqueous phases) substances into the environment.

Multiple emulsions are typically formed through sequential bulk emulsification using shear, which usually results in polydisperse emulsions. Controlling the shear with constrained geometry,[24–28] porous membranes,[17,18] or micro-

channels[29] can produce emulsions that are nearly monodisperse; these can then themselves be emulsified to create multiple emulsions. However, although the volume fractions of both the initial and final emulsions can be controlled,[17–19,24,26–28] precise control over the number of inner droplets is difficult to attain with these techniques. There are, however, many cases where control of the number of inner droplets is more important than control of the volume fraction. For example, with accurate control of the number and size of inner droplets, transport kinetics of encapsulated substances can be precisely manipulated. Control of the number of inner droplets is also critical for structuring colloidal assemblies to produce nonspherical particles.[29] Furthermore, if the inner droplets are used as separate compartments for cell culture or evolution in the same large droplet, control of the number of inner droplets is essential.

Microfluidic devices offer an alternate route to produce monodisperse multiple emulsions. Cascading two T-junctions,[20,22] can produce monodisperse double emulsions with some control over the number and size of the inner droplets; however, the standard two-dimensional microfluidic channels require precise, localized modification of the surface chemistry to control the wettability to enable the production of multiple emulsions, which ultimately limits the utility of such channels. By contrast, coaxial flow-focusing geometries relax the wetting constraints but are still limited in the range of fluids that can be used and in the precise control afforded over the number and size of inner droplets. Moreover, current microfluidic methods cannot be scaled to make higher-order multiple emulsions, such as triple emulsions.

To overcome these limitations, we present a highly scalable microcapillary technique that simultaneously controls the droplet monodispersity as well as the number and size of the inner droplets (see the Supporting Information for experimental details). The first emulsification step is accomplished using a coaxial, co-flow geometry. It comprises the injection tube (a cylindrical capillary with a tapered end), which is inserted into the transition tube (a second cylindrical capillary with an inner diameter $D_2$), as shown in Figure 1a. Both cylindrical capillary tubes are centered within a larger square capillary; alignment is ensured by matching the outer diameters of the cylindrical tubes to the inner dimensions of the square ones. The other end of the transition tube is also tapered and is inserted into a third, coaxially aligned cylindrical capillary tube, the collection tube, of inner diameter $D_3$. We generate uniform monodisperse multiple emulsions in two emulsification steps. Droplets of the innermost fluid are emulsified in the first stage of the device by coaxial flow of the middle fluid (Figure 1b). The single emulsion is subsequently emulsified in the second stage through coaxial flow of the outermost fluid, which is injected in the outer stream through the square capillary (Figure 1a).

In both emulsification steps, droplets form immediately at the exit of the tapered capillary (Figures 1b and c); this dripping mechanism[30] ensures formation of highly monodisperse drops. The separation of the two emulsification steps affords independent control over each; we achieve this control by adjusting the device dimensions as well as the inner, middle, and outer fluid flow rates ($Q_1$, $Q_2$, and $Q_3$, respectively). The

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[6] The authors gratefully acknowledge support from the NSF (DMR-0602684), the Harvard MRSEC (DMR-0213805), the NSFC (20674054) and the Key Project of the Ministry of Education of China (106311). L.-Y.C. thanks the China Scholarship Council (2005851124). The authors thank Anderson Shum for discussions on polymerization in emulsions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.
Figure 1. Capillary microfluidic device and the formation of precisely controlled monodisperse double emulsions. a) Schematic diagram of the device geometry. The outer fluid must be immiscible with the middle fluid and the middle fluid must be immiscible with the inner fluid. b) and c) High-speed optical micrographs of the first (b) and second (c) emulsification stages. d) Optical micrographs of monodisperse double emulsions containing a controlled number of monodisperse single emulsions. e) Optical micrographs of monodisperse double emulsions showing controlled increase of the diameter of the inner droplets while the number is constant. All double emulsions were made in the same device and with the same fluids. The flow rates of the inner, middle, and outer fluids in (b) and (c) are \(Q_1 = 350\), \(Q_2 = 2000\), and \(Q_3 = 5000\) μL h\(^{-1}\), respectively. In (d), the flow rates of middle and outer fluids are fixed at \(Q_2 = 2000\) and \(Q_3 = 5000\) μL h\(^{-1}\), and those of the inner fluid are \(Q_1 = 20, 55, 70, 85, 150, 200, 225,\) and 240 μL h\(^{-1}\), from the left top to the right bottom. In (e), the variation ranges for the flow rates of the inner, middle, and outer fluids are \(Q_1 \approx 20–600, Q_2 \approx 1600–5000,\) and \(Q_3 \approx 2000–8000\) μL h\(^{-1}\) (in each case, \(Q_3\) is larger than \(Q_2\)). All scale bars are 200 μm.

number of innermost droplets can be precisely controlled, as illustrated by the double emulsions containing one to eight inner droplets (Figure 1 d). Similarly, the size of the innermost droplets can be precisely controlled, as shown by the three sets of double emulsions with different inner droplet sizes in Figure 1 e. In each case, all droplets are highly monodisperse. The coefficient of variation (CV, defined as the ratio of the standard deviation of the size distribution to its arithmetic mean) is used to characterize the size monodispersity of emulsion droplets. In all experiments, the CV values for diameters of internal droplets and for double emulsions are less than 2.3% and 1.6%, respectively. Furthermore, the coaxial structure of this capillary microfluidic device has the advantage that no surface modification of wettability is necessary, allowing the same device to be used to prepare either water-in-oil-in-water (W/O/W) or the inverse oil-in-water-in-oil (O/W/O) multiple emulsions.

The high degree of control and stability afforded by the dripping mechanism allows us to quantitatively determine the flow-rate dependence of the diameters of the inner and outer drops \(d_1\) and \(d_2\), respectively and to predict the number of inner droplets \(N_i\). For fixed device dimensions and solution conditions, the droplet diameter in coaxial flow is inversely proportional to the velocity of the surrounding flow \(v_0\) in the dripping regime. We calibrate the dependence of \(d_1/D_i\) on \(Q_1/Q_2\) and find the linear dependence depicted in Figure 2a. We find a similar linear dependence of \(d_1/D_3\) on \((Q_1 + Q_3)/Q_3\) (Figure 2b). Using these empirical relations, we can quantitatively predict the number of inner droplets as \(N_i = f_1/f_2\), where \(f_1\) and \(f_2\) are the formation rates of the inner and outer droplets. From mass conservation for each stream [Eq. (1)],

\[
N_i = \frac{f_1}{f_2} = \frac{Q_1/[(πd_1^3/6) - Q_1]}{Q_1/Q_2} d_1^2 = \frac{Q_1}{Q_1 + Q_2} \left(\frac{a_1}{Q_1/Q_2 + b_1}\right)^2
\]

using the linear fits to the experimental data in Figures 2a and b, we can predict the number of encapsulated droplets as a function of the flow rates [Eq. (2)], where \(a_1\) and \(a_2\) are the slopes, and \(b_1\) and \(b_2\) are the intercepts obtained from the fits in Figures 2a and b. The experimentally measured \(N_i\) values are well-described by Equation (2), with no free parameters, as shown by the solid line in Figure 2c; this correlation allows easy calibration of our device. When the number predicted is an integer, \(N_i\) can be precisely controlled; however, when the number predicted is between two integers, the operation is in a transition zone, and \(N_i\) takes either integral value. However, precise control over \(N_i\) can be achieved through correct adjustment of the flow rates.

This method for fabricating multiple emulsions has the significant advantage that it can be very easily extended, thus enabling us to generate additional hierarchical levels of multiple emulsions. We illustrate this concept by fabricating monodisperse triple emulsions, which consist of water-in-oil-in-water (W/O/W) drops. This preparation is accomplished by adding a second transition tube at the outlet of the first and injecting the outermost fluid to flow coaxially around this tube to form the third level of emulsification at its outlet, as shown in Figure 3a. The individual steps of drop formation leading to the triple emulsions are shown in Figures 3b–d. Although there are large deformations of the droplets during their formation as they flow through the tapered regions of the capillaries, the emulsification process remains stable. Again, both the diameter and the number of the individual drops at every level can be precisely controlled, as illustrated...
The simplicity of this method also enables us to incorporate alternate emulsification schemes. For example, we can inject a second fluid at the inlet of the transition tube to create double emulsions by flow-focusing of a coaxial stream\(^\text{[10]}\) with a subsequent emulsification step at the outlet of the transition tube to create triple emulsions, as shown in Figure 3 f. While only two drop-formation steps are required (Figures 3 g and h), the ability to independently control the number and size of innermost drops is reduced. Nevertheless, highly monodisperse triple emulsions can be fabricated, albeit with only a single innermost droplet (Figures 3 i and j).

The ability to precisely control the formation of multiple emulsions offers new opportunities to engineer novel materials. To illustrate this potential, we use the triple emulsion structure to fabricate a microcapsule made with a thermo-sensitive, poly(N-isopropylacrylamide) hydrogel that can be used for controlled release of active substances. Since each fluid layer is sandwiched between two immiscible fluids, we are able to perform a polymerization reaction in a specific device for generating triple emulsions.
layer. In this case, we form a W/O/W/O triple emulsion and add monomer, crosslinker, and initiator in the outer aqueous layer. We also add an accelerator to the inner oil phase, where it diffuses into the outer aqueous shell and speeds polymerization of the hydrogel. The result is a microcapsule consisting of a shell of thermosensitive hydrogel that encapsulates an oil drop containing several water droplets, all in a continuous oil phase, as shown in Figure 4a. Upon heating from 25°C to 50°C, the thermosensitive hydrogel rapidly shrinks by expelling water; however, because of the incompressibility of the outer oil, the hydrogel shell breaks, providing spontaneous, pulsed release of the innermost water droplets into the continuous oil phase, as shown in Figures 4b–e. This structure has a Trojan-horse-like behavior, protecting the innermost water droplets in the hydrogel shell until their temperature-induced release. This experiment demonstrates the utility of our technique to generate highly controlled capsules with multiple internal volumes that remain separate from each other; it also highlights the potential of this microfluidic device to create highly engineered structures for controlled release of active substances. Further refinements could adjust the thickness of the layers and the number of droplets, thus enabling fine control over diffusion of compounds contained within the innermost droplets, which would facilitate their highly controlled release.

The high degree of control and scalability afforded by this method makes it a flexible and promising route for engineering highly controlled multiple emulsions and microcapsules. The approach presented herein circumvents the difficulties in controllably forming multiphase structures. It can be used to optimize multiple emulsion systems for a broad range of applications in pharmaceutics, foods, cosmetics, and separations. Moreover, its generality will enable fabrication of novel materials containing complex internal structures. Future work must focus on refining methods proposed herein to allow the full potential of the technique to be realized. Moreover, applications of these devices to technological applications would require operating a large number of devices in parallel; this feat might best be accomplished through other fabrication techniques. Nevertheless, these results provide an essential guide to assess the utility of the structures that can be produced.

Received: March 29, 2007
Revised: July 15, 2007
Published online: September 11, 2007

Keywords: emulsions · gels · microfluidics · microreactors · template synthesis