

Synthesis of Monodisperse Microparticles from Non-Newtonian Polymer Solutions with Microfluidic Devices

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Microfluidic devices can form emulsions that are highly uniform in size;^[1–3] they can also form compound emulsions, in which each supradroplet contains exactly the same number of internal droplets, packed in exactly the same configuration.^[4–6] Because the drops can be formed with a highly controlled structure and uniformity, they are useful as templates to synthesize monodisperse particles. In such a process, microfluidic devices are used to form droplets with the desired structure, which are then solidified to produce particles. This allows synthesis of particles with a variety of shapes, including Janus particles, nonspherical dimers, and core-shell capsules.^[7–10] However, the fluid precursors must be compatible with the formation of drops in microfluidic devices: this precondition limits the applicability of this technique. For example, this circumstance requires fluids with a low viscosity, negligible viscoelastic response, and moderate interfacial tension. If even one of these constraints is not met, it is difficult to achieve drop formation in the stable dripping regime. Instead, jetting occurs, resulting in the production of polydisperse particles.^[11] This represents a significant limitation, as the most useful materials for making particles typically have properties that do not meet these constraints. For example, lipid melts, due to their amphiphilic chemical properties, tend to be viscous and have low interfacial tension with oil or aqueous carrier phases. Solutions of long-chain polymers like poly(*N*-isopropylacrylamide) (pNIPAM)^[12] or polyurethane-polybutadienediol (pU-pBDO),^[13] form excellent particles, but tend to be viscous and have significant viscoelastic response at the shear rates needed for controlled drop formation.^[1,11,14] As a consequence, these fluids, and many others like them, cannot be used to synthesize particles in microfluidic devices, greatly limiting the applicability of this technique. To overcome the limitations with such fluids, a more robust drop formation mechanism is needed.

In this paper, we present a technique to create monodisperse particles from fluids that are normally incompatible with synthesis in microfluidic devices. We use one-step double emulsification,^[15] a recently-developed technique in which the difficult-to-emulsify fluid is surrounded by an immiscible chaperoning fluid that is easy to emulsify, forming a coaxial jet of the difficult fluid within the chaperoning fluid. The coaxial jet is introduced into a channel that widens horizontally and vertically, thereby creating a dripping instability in the chaperoning fluid. This instability causes the chaperone to pinch into equally-sized drops, which, in turn, pinches the inner fluid into equally-sized drops, thereby creating double emulsions in which drops of the difficult fluid are encapsulated within drops of the chaperoning fluid. We demonstrate the use of this microfluidic technique to form particles from fluids that, heretofore, have been incompatible with microfluidic synthesis. This is achieved using one-step double emulsification to form monodisperse droplets from several classes of difficult-to-emulsify fluids; the droplets are then solidified using polymerization, polymer cross-linking, or crystallization, thereby forming particles of the desired materials. Since one-step double emulsification is capable of forming monodisperse emulsions with a much wider variety of solutions than conventional drop formation techniques, this approach greatly broadens the kinds of particles that can be formed.

To synthesize particles with this process, we use microfluidic devices that form double emulsions.^[4,6,16] These devices consist of two cross-channel junctions connected in series, as shown in **Figure 1**. They are fabricated from poly(dimethylsiloxane) (PDMS) using the technique of soft lithography.^[17] We use channels that vary in both width and height to reduce the constraints of wettability patterning, thereby broadening the types of drops that can be produced. We fabricate these devices using multilayer photolithography to create multiheight channels.^[18] To make the height graduations symmetric in the vertical direction, we fabricate two PDMS replicas per device that are near-mirror images of each other. The bottom surfaces of these devices are aligned and bonded using plasma oxidation. Since some of the fluids used in these experiments contain organic solvents that would swell the PDMS devices, we coat the channels with parylene-c to increase their chemical resistance.^[19,20] When making water-in-oil-in-water (W/O/W) double emulsions, the devices must be hydrophobic: this is achieved with the parylene-c coating. To make oil-in-water-in-oil (O/W/O) double emulsions, we plasma-oxidize the devices after they are coated, and then flow-pattern^[21] the outlet with Aquapel (PPG, Pittsburgh, PA), a chemical that makes the channels hydrophobic. This makes the first junction hydrophilic and the second junction hydrophobic, as required to form these emulsions.

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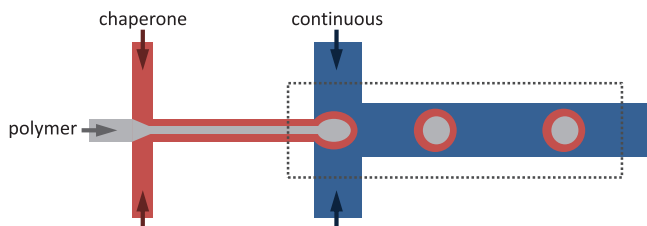


Figure 1. Schematic of a double emulsion drop maker consisting of two cross-channel junctions in series. The first junction has channel dimensions of $50\ \mu\text{m}$ in width and $50\ \mu\text{m}$ in height. The second junction widens horizontally and vertically to $200\ \mu\text{m}$ in width and $150\ \mu\text{m}$ in height. The difficult-to-emulsify polymer fluid (light blue) is injected into the central inlet of the first junction and surrounded by a chaperoning fluid (red) injected into the two side inlets. This creates a stable jet of the polymer fluid within the chaperone fluid. These fluids then enter the second junction, where the continuous phase (dark blue) is added from two more side inlets. Due to the widening of the channels, this also creates an absolute instability in the chaperoning fluid, causing it to narrow and pinch into drops: as it does so, it squeezes on the polymer fluid, pinching it into drops. The results are double emulsions having monodisperse polymer drops at their core. The dashed box demarcates the region pictured in the following figures.

To form drops in a microfluidic device, the flow conditions must be set such that the system operates in the dripping regime.^[1,11,14] For Newtonian fluids, this generally occurs for conditions in which the sum of the inner phase Weber number and the continuous phase capillary number is less than one: this allows formation of highly uniform drops over a wide range of flow rates. For non-Newtonian fluids, however, these conditions do not normally suffice, and generally it is extremely difficult to achieve monodisperse dripping. Instead, the extensional viscosity of the fluids resists the pinching needed to form drops, leading to the formation of long jets that break into drops of uncontrolled size due to the Rayleigh–Plateau instability, as shown in **Figure 2**, left. The difficulty of controllably emulsifying non-Newtonian solutions in microfluidics is a known and persistent problem,^[22] limiting the applicability of these techniques.

Our strategy for overcoming this limitation is not to rely on the inherent Rayleigh–Plateau instability of the viscoelastic jet, but instead to use a second, coaxial Newtonian fluid. The Rayleigh–Plateau instabilities in this second fluid induce drop formation, and this is transferred to the inner fluid, which also forms drops. This is achieved by injecting the viscoelastic fluid into the central inlet of a cross-junction device and the Newtonian chaperoning fluid into the side inlets. For the most controlled operation, the chaperoning fluid should have moderate viscosity, not much higher than $10\ \text{Pa s}$, and moderate-to-high surface tension, between 1 and $100\ \text{mN m}^{-1}$. The fluids are then introduced into a second junction, where the channels widen horizontally and vertically, and into which a third fluid, immiscible with the Newtonian fluid, is injected. These flow conditions create a coaxial jet in which the viscoelastic fluid is surrounded by the Newtonian fluid, which itself is surrounded by the continuous phase. Due to the widening of the channel, this also creates an absolute instability^[23] that generates oscillations in the interface between the middle and outer fluids, the wavelengths of which depend on the flow rate of the continuous

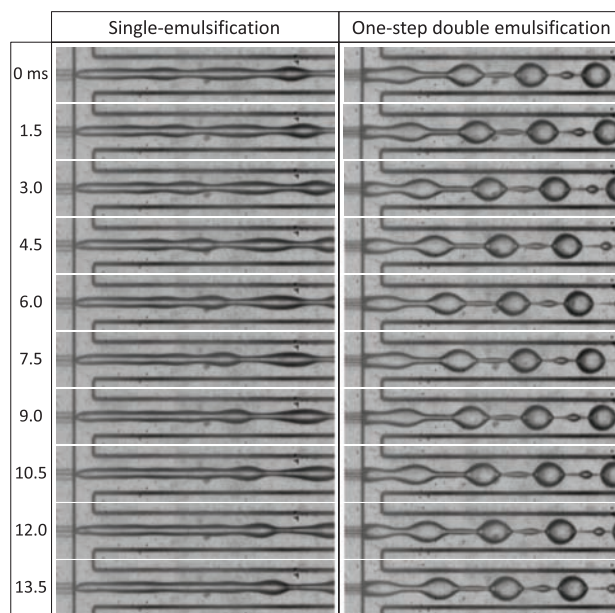


Figure 2. Fast-camera image sequence of the emulsification of a viscoelastic polymer solution failing (left), using direct single emulsification, and succeeding (right), using one-step double emulsification. For the single emulsion the fluids are heavy molecular weight pNIPAM for the droplet phase and mineral oil for the continuous phase, injected at $500\ \mu\text{L h}^{-1}$ and $3000\ \mu\text{L h}^{-1}$, respectively. For the one-step case the inner and middle phase fluids are unchanged, but the continuous phase is water with poly(vinylalcohol) at 10% by weight, with injection rates of $500\ \mu\text{L h}^{-1}$, $500\ \mu\text{L h}^{-1}$, and $2500\ \mu\text{L h}^{-1}$, for the inner, middle, and continuous phases, respectively. All images are at the same magnification, with final double emulsion drop diameters of $150\ \mu\text{m}$. Fast-camera videos of these processes are available in the Supporting Information.

phase. If the inner jet were not present, these oscillations would break the Newtonian fluid into monodisperse drops.^[11] However, the viscoelastic response of the inner jet resists this pinching, instead causing the oscillations to be convected downstream by the flow, as shown in **Figure 2**, right, and in movies available in the Supporting Information. Nevertheless, as the oscillations are convected downstream they grow in amplitude, squeezing on the inner jet and eventually pinching it into drops, thereby forming double emulsions. The outlet channel must be long enough such that the pinching has time to complete: if the time is too short, the outlet can be lengthened or the flow velocities reduced, both increasing pinch time. During the pinching, a thread forms between the two bulges that will become double emulsions. After the thread breaks, the remaining fluid is pulled into a sphere, becoming a small satellite double emulsion droplet, as shown in **Figure 2**, right. The satellites are thus byproducts of fluid getting trapped in the thread, due to its inability to drain faster than the pinch off occurs; they are, however, relatively small and are also quite monodisperse. We observe satellite drops with diameters ranging from 1 to $50\ \mu\text{m}$ in diameter, depending on the flow conditions and fluid properties. For a given set of conditions, we measure a coefficient of variation (CV) in the satellite drop diameter of about 5%.

To better understand the nature of the drop formation process, we estimate the forces involved in the coaxial pinching. There are two competing stresses in the process: the inward

squeezing of the interface due to the increased Laplace pressure, and the viscoelastic response of the thread. The squeezing stress can be estimated as $\Delta P = 2\sigma/r$, where σ is the interfacial tension and r is the radius of curvature of the interface. For example, for the smallest radius of the thread of fluid shown in Figure 2, the radius is estimated to be $r \approx 5 \mu\text{m}$, yielding a squeezing pressure of 2 kPa, for a surface tension of the chaperoning fluid of 10 mN m^{-1} . Opposing this is the viscoelastic response of the polymer solution. The pinching squeezes polymer out of the thread at a shear rate we estimate to be 100 Hz based on the fluid drainage velocity and dimensions of the thread. From linear viscoelastic measurements using oscillatory shear rheology, we measure the polymer solution loss modulus to be 0.3 Pa at a shear rate of 10 Hz. At these rates, the response is dominated by viscous effects, which increase linearly with the frequency. Thus, for the shear rates relevant to pinching, we estimate a total viscoelastic response of 30 Pa. This describes the pinching at one thread radius, however, these forces vary throughout the thinning of the thread: as the thread radius decreases, both the Laplace pressure and, through the shear rate, the viscoelastic response, increase. However, each force varies inversely with the radius of the thread, so squeezing stresses are always more than an order of magnitude larger than viscous stresses, ensuring that the interface can pinch the jet into drops. Moreover, because the oscillations are driven in the outermost Newtonian fluid, they have a constant wavelength and result in double emulsions which are monodisperse, with viscoelastic drops in their core.

To illustrate the utility of this approach, we use it to form particles from three classes of fluids that are normally incompatible with synthesis with microfluidic devices. The first fluid consists of a viscoelastic polymer solution that can be gelled by UV irradiation. We use chemically modified cross-linkable pNIPAM with weight-average molecular weight of 1700 kg mol^{-1} and polydispersity index 3.5, dissolved in water at 25 g L^{-1} . The overlap concentration of this polymer in water is $c^* = 2.8 \text{ g L}^{-1}$; thus, our solution is at nine times c^* , which is commonly associated with the semi-dilute entangled regime.^[24] This causes the fluid to respond elastically under shear. In addition, the fluid exhibits shear-thinning, covering a viscosity range of 2 Pa s at a shear rate of 0.01 Hz and 0.05 Pa s at 100 Hz. If single emulsification is used, a long, rippling jet is produced instead of drops, as shown in Figure 3a, top left. However, by surrounding this jet by a Newtonian fluid and using one-step double emulsification, we break it into drops of controlled size, as shown in Figure 3a, top right, and in movies available in the Supporting Information. We collect the double emulsions and expose them to UV light, thereby gelling the inner drops by cross-linking the polymer chains.^[22] The resultant particles are redispersed into a final carrier solvent by washing with water, isopropanol, 1,4-dioxane, and again water. The resultant soft microgel particles are monodisperse, with CV of 8%, as shown in Figure 3a, lower.

Viscous fluids are also difficult to emulsify, because their large dissipation resists the deformations needed for drop formation. To illustrate the applicability of this method to emulsify such fluids, we use a polymer mixture of pU at 24% and pBDO at 16% by weight, respectively, in toluene.^[25] This fluid exhibits a viscosity of 0.5 Pa s at a shear rate of 0.01 Hz, whereas its viscosity

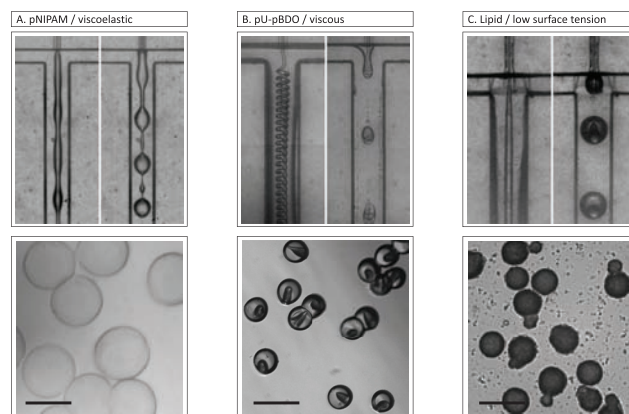


Figure 3. Demonstration of failing and succeeding emulsification using single and one-step double emulsification, respectively. A) Emulsification of a viscoelastic semidilute pNIPAM polymer solution and the resultant particles below. B) Emulsification of a viscous and viscoelastic polymer solution composed of pU–pBDO and the resultant particles below. The flow rates for the single emulsion case (left) are $1000 \mu\text{L h}^{-1}$, $1000 \mu\text{L h}^{-1}$, and $0 \mu\text{L h}^{-1}$ for the inner, middle, and continuous phases, respectively, and the one-step double emulsion case (right) $1000 \mu\text{L h}^{-1}$, $1000 \mu\text{L h}^{-1}$, and $10\,000 \mu\text{L h}^{-1}$ for the inner, middle, and continuous phases, respectively. The high viscosity of this inner phase prevents drop formation, instead leading to a coiling instability that forms a helix, unless one-step double emulsification is used. C) Emulsification of a low interfacial tension and viscous lipid melt and the resultant particles below. The flow rates are $500 \mu\text{L h}^{-1}$ for the inner phase, $1500 \mu\text{L h}^{-1}$ for the middle phase, and, for the one-step case, $10\,000 \mu\text{L h}^{-1}$ for the continuous phase. The melt is liquefied by heating it to $75 \text{ }^\circ\text{C}$ before introducing it into the microfluidic device. The drop formation channel width in all experiments is approximately $200 \mu\text{m}$. All scalebars in the lower panels denote $100 \mu\text{m}$.

is 0.05 Pa s at 100 Hz due to shear-thinning. Attempting to emulsify such a fluid by direct single emulsification produces very stable jets rather than drops, as shown in Figure 3b, left. Here, a helical jet is formed, because the widening of the channel creates a velocity difference between the jet and continuous phase. This imposes viscous drag on the jet that induces a coiling instability (see also movies available in the SI). However, by again surrounding this jet by a Newtonian fluid and applying one-step double emulsification, even this highly viscous fluid is broken into equal-sized drops, as shown in Figure 3b, right. Due to the high viscosity of this fluid, it takes a long time for the inner drop to relax into a spherical shape: it continues out of the device as an irregular, chiral shape. If desired, this shape can be locked-in by rapid solidification, which can be achieved, for example, by photoinduced cross-linking. Here, we solidify the pU–pBDO drops by adding dibutyltin dilaurate as a catalyst to the polymer mixture prior to drop formation. The resulting double emulsions are collected in a vial and heated to $65 \text{ }^\circ\text{C}$ for 12 h to complete the cross-linking. They are then redispersed in toluene. The particles are reasonably monodisperse, with CV of 5%, but have a patch on one side, possibly due to mechanical forces generated during gelation, as shown in Figure 3b, lower.

Lipid melts are another class of fluid that is difficult to emulsify, because the amphiphilic properties of the constituent molecules cause them to stick to channel surfaces and also to have

low interfacial tension with carrier solvents. Moreover, they must be liquefied by heating prior to emulsification, though even then they remain viscous. These properties make them especially difficult to emulsify in microfluidic devices: instead they produce smooth, stable jets, as shown in Figure 3c, left. In our experiments we use hydrogenated coco glycerides, heated to 75 °C prior to injection into the device. Even this fluid can be emulsified with one-step double emulsification, as shown in Figure 3c, right, and in movies available in the SI. The resulting lipid double emulsions are solidified by collecting them into an ice bath to freeze the melt, thereby producing particles, as shown in Figure 3c, lower. The particles have a CV of 10% in diameter.

There are several advantages of one-step double emulsification over single emulsification when making particles. The particle formation throughput is equal to the drop production rate: the maximum rate is limited by the dripping-to-jetting transition. The precise value of this transition depends on the fluid properties, including the mass, viscosity, and interfacial tension. Thus, the chaperoning fluid can be selected to have properties that maximize the production rate, independent of the particle-forming fluid, which can be chosen for the optimal properties of the target particles. This can be achieved, for example, by using a low-density middle-phase fluid and a middle/continuous-phase combination with high interfacial tension. Another advantage of one-step double emulsification is the ability to synthesize particles that are much smaller in diameter than the drop-forming channel. Normally this is not possible due to the physics of microfluidic drop formation.^[2] However, with one-step double emulsification this constraint is lifted, because the final size of the particle depends on the flow-rate ratio of the inner-to-middle phase during formation, $V_{in} = V_{db} \times Q_{in}/(Q_{in} + Q_{mid})$ where V_{in} is the inner drop volume, V_{db} the double emulsion volume, Q_{in} the inner-phase flow rate, and Q_{mid} the middle-phase flow rate. Even if V_{db} is fixed, D_{in} can be reduced by setting the flow-rate ratio small.

One-step double emulsification enables formation of mono-disperse particles from fluids that cannot normally be used in droplet-based microfluidics, including viscous or viscoelastic polymer solutions or low interfacial tension polymer melts. This is useful for synthesizing new kinds of particles, including particles that are made from waxy lipids and semidilute entangled polymer solutions. It should also be useful for synthesizing many other types of particles.

Supporting Information

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

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