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# A Scalable Platform for Functional Nanomaterials via Bubble-Bursting

Jie Feng, Janine K. Nunes, Sangwoo Shin, Jing Yan, Yong Lin Kong, Robert K. Prud'homme, Luben N. Arnaudov, Simeon D. Stoyanov, and Howard A. Stone\*

There is strong interest in the utilization of nanoemulsions and nanoparticles for drug delivery, material science, biology, functional foods, and nutraceuticals.<sup>[1–3]</sup> Because of the small size, large surface area to volume ratio, and high reactivity, nanomaterials overcome some of the limitations found in conventional emulsions and particles. When certain functional materials are required to be incorporated into nanoemulsions to increase their utility, the fabrication process is typically more complicated since physicochemical interactions need to be considered. A low-cost and energy-efficient system with versatility remains the focus of research. To our best knowledge, such a facile platform to produce nanoemulsions encapsulating various functional materials is not available. Furthermore, many laboratory fabrication processes are not readily scaled up.<sup>[4]</sup>

Recently, bubble bursting at an air/oil/water-with-surfactant compound interface was found to disperse sub-micrometer oil droplets into the water column.<sup>[5]</sup> This setup differs from ultrasound emulsification, which generates cavitation bubbles that produce extreme shear needed to break up droplets.<sup>[6]</sup> In some cases, the cavitation might lead to undesirable sonochemical drawbacks such as lipid phase oxidation.<sup>[7]</sup> Inspired by our previous report,<sup>[5]</sup> in this communication we propose a new top-down platform to generate functional oil-in-water nanoemulsions. We demonstrate scaled-up synthesis of nanoemulsions with stability for days, which offers the flexibility of further treatments and functionalization. By placing functional materials in the appropriate phase, we also document that the bubbling system has the capability to produce nanoemulsions encapsulating functional materials, such as quantum dots, silica nanoparticles, and lipid molecules. Considering the simplicity and energy efficiency of the new bubbling platform, together with the diversity of products and the potential for mass production, our one-step encapsulation system offers a

J. Feng, Dr. J. K. Nunes, Dr. S. Shin, Dr. J. Yan, Dr. Y. L. Kong, Prof. H. A. Stone Department of Mechanical and Aerospace Engineering Princeton University Princeton, NJ 08544, USA E-mail: hastone@princeton.edu Prof. R. K. Prud'homme Department of Chemical and Biological Engineering Princeton University Princeton, NJ 08544, USA



Dr. L. N. Arnaudov, Prof. S. D. Stoyanov Unilever Research and Development 3133AT Vlaardingen, The Netherlands

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new toolbox for generating (multi)functional nanoemulsions and nanoparticles.

The experimental system for fabrication of nanoemulsions is sketched in **Figure 1**a,b. After continuous bubble bursting at an air/oil/water-with-surfactant interface, oil droplets with the radius of 50–400 nm and a moderate polydispersity index (see the Experimental Section for definition) are dispersed in the water column,<sup>[5]</sup> as shown in Figure 1b. It is significant that this dispersal system outperforms typical nanoemulsion fabrication methods in several important aspects relevant to industrial applications. Its energy efficiency is between 1% and 10%,<sup>[5]</sup> which is at least one order of magnitude greater than the efficiency of classical high-shear-rate methods.<sup>[8]</sup> Also, our system avoids the negative thermal effects often exhibited in such high-energy emulsification methods.<sup>[9]</sup>

Furthermore, our system works even when the interfacial tensions are of the order of tens of mN m<sup>-1</sup>, while spontaneous emulsification requires an ultralow interfacial tension between compounds, which is achieved with a large amount of emulsifiers.<sup>[10]</sup> Finally, bottom-up approaches, such as dispersion polymerization, are often used to obtain sub-micrometer particles, but they require the dispersed phase to be soluble in the continuous phase.<sup>[11]</sup> Our top-down system is not constrained by this limitation as the solvent-insoluble liquid phase, here oil, can be directly dispersed in water (the solvent) in the form of sub-micrometer droplets.

The idea for encapsulating functional nanomaterials is shown in Figure 1c-f. We first disperse the functional lipophilic/ amphiphilic materials in the oil phase, which solves the issue of poor water solubility for many functional groups (Figure 1c). After a bubble approaches the interface, it bursts<sup>[12]</sup> (Figure 1d), and the bubble's cavity collapses (Figure 1e). During this collapsing stage, oil spreads on the inner surface of the bubble, leading to the formation of sub-micrometer lenses in a wetting state called pseudo-partial wetting (see the Supporting Information).<sup>[5]</sup> Then the associated fluid motion during bubble collapse entrains these lenses, encapsulating them with the functional materials into the bulk water (Figure 1e). Hence we obtain functional oil-in-water nanoemulsions, with lipophilic materials inside the oil droplets and amphiphilic molecules at the oil/water interface (Figure 1f). We refer to our recent paper<sup>[5]</sup> for more details about the dispersal mechanism.

First, we highlight the opportunity for scaling up this system to produce nanoemulsions in a large volume. Here we directly apply the scattering intensity of the dynamic light scattering (DLS) measurements as a representative parameter for the concentration comparison of different nanoemulsions. When a sample has a higher concentration of oil droplets, the scattering





**Figure 1.** Schematic of bubble bursting at a compound interface to generate functional nanoemulsions. a) Sketch of the experimental system. We refer to the configuration of a thin layer of oil on the surface of a water column as a compound interface. Inset: Close-up of the deformed compound interface. b) After bubble bursting, we observe sub-micrometer oil droplets dispersed in the water phase. c–f) Demonstration of the idea for encapsulating functional materials with the bubbling platform. c) Initially, functional materials, such as amphiphilic molecules and lipophilic chemicals, are dispersed into the oil layer. When a bubble reaches the interface, the oil layer and a water film will be pushed up, forming a bubble cap, and drainage occurs under the action of gravity and surface tension. d) Eventually the films rupture when they become thin enough that intermolecular forces dominate. We observe that the oil film ruptures before the water film in the experiments.<sup>[5,12]</sup> e) After rupture of the films, a spray of polydisperse droplets is entrained from the cavity wall into the bulk. The functional materials will be encapsulated into these droplets during this process. f) Finally we obtain functional nanoemulsions in the water phase.

intensity of the sample increases with other measurement parameters fixed (see the Supporting Information for more discussions).<sup>[13,14]</sup> When the mean droplet size is constant, the scattering intensity can be used for a direct comparison of the droplet concentration.

The increase of the bubble diameter,  $d_b$ , does not affect the mean droplet diameter,<sup>[5]</sup> while it increases the scattering intensity, *I*, as shown in **Figure 2a**. When  $d_b$  doubles from 1.9 to 4.0 mm, *I* increases by almost a factor of 4, and *I* also increases if more bubbles are generated per unit time (increasing the bubbling frequency, Figure 2b).

The increasing trend with the bubbling frequency for  $d_b = 4.0$  mm has a larger slope than that for  $d_b = 2.8$  mm (Figure 2b), and reaches a plateau at  $I \approx 4000$  kilo-counts per second (kcps) (see the Experimental Section for definition), which we believe is because the detector may be saturated around this value.

A convenient way to increase the bubble size and bubbling frequency simultaneously is by using porous nozzles, such as glass, since the pore size of the glass frit affects the bubble size while the bubbling frequency can be controlled by the injection air pressure. Indeed, the production rate of the bubbling system increased with the application of a glass frit, as indicated by temporal trends of the scattering intensity in Figure 2c. After 2d of bubbling, the system with a glass frit has a scattering intensity that is almost twice that of with a single needle, showing that the concentration is increased significantly, while the mean droplet diameter remains approximately constant (Figure 2c). Therefore, tuning the bubbling parameters offers a simple straightforward path for scaling up our system, which also avoids affecting the produced droplet size.

In addition, we investigated the emulsion stability. The intensity distribution in Figure 2d indicates the mean droplet diameter is constant at least for 5d, while the stable value of the scattering intensity shows that the concentration of the oil droplets does not change by an observable extent. Thus, our evidence is that the nanoemulsions are stable for at least 5d, which provides appropriate time and flexibility for further treatments before the nanoemulsions lose their functionality. In Figure 2e, we further verify the capability for mass production with our platform by generating 60 mL of hazy nanoemulsions.

Following the study of scaling up, we focus on the utilization of functional materials in our bubbling system to show potential for the encapsulation capability. For demonstration purposes, we choose single species of a model cargo in each example, which exhibits properties that are either lipophilic (quantum dots) or amphiphilic (silica particles and lipid molecules). Note that when the amphiphilic materials are



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**Figure 2.** Scaling up of the bubbling system. a) Influence of the bubble diameter on the scattering intensity (left Y-axis) and the mean oil droplet diameter (right Y-axis). b) Influence of the bubbling frequency on the scattering intensity (left Y-axis) and the mean oil droplet diameter (right Y-axis) for two different bubble diameters ( $d_b$ ). Circle:  $d_b = 2.8$  mm, triangle:  $d_b = 4.0$  mm. In the above experiments, oil phase: tridecane, aqueous phase: [hexadecyltrimethylammonium bromide ( $C_{16}TAB$ ] =  $0.09 \times 10^{-3}$  M, oil layer thickness = 1 mm, detector attenuation = 11 (see the Experimental Section for the definition of detector attenuation). For (a), the bubbling frequency is  $0.32 \text{ s}^{-1}$ . c) Relationship between the scattering intensity and the experimental time using a glass frit or a single needle. Each setup has been performed three times to check the reproducibility. Oil phase: tridecane, aqueous phase: [ $C_{16}TAB$ ] =  $0.09 \times 10^{-3}$  M, oil layer thickness = 1.2 mm, detector attenuation = 11. PDI is short for polydispersity index from DLS measurement (see the Experimental Section). d) Intensity distribution (bottom X-axis, left Y-axis) of DLS, D, and the scattering intensity (top X-axis and right Y-axis) for one sample after bubble bursting. Oil phase: hexadecane, aqueous phase: [ $C_{16}TAB$ ] =  $0.09 \times 10^{-3}$  M, oil layer thickness = 1 mm, detector attenuation = 8. Inset: Time evolution of the mean oil droplet diameter and PDI for 5 d. e) Images of the aqueous phase in two glass storage bottles before and after bubbling. We have produced 60 mL of nanoemulsions (as shown by the capacity scale on the wall of the bottle) and the solution after bubbling is hazy compared with the original solution. Oil phase: hexadecane, aqueous phase: [ $C_{16}TAB$ ] =  $0.09 \times 10^{-3}$  M, oil layer thickness = 1 mm, bubbling frequency = 1 s<sup>-1</sup>. The bubbling time is 48 h for all the above experiments. The error bars are defined as the standard deviation of three measurements.

saturated at the interface, they may also be present in the bulk oil phase. In all cases, the aqueous phase contains hexadecyltrimethylammonium bromide (C<sub>16</sub>TAB) with a concentration of 0.09  $\times$  10<sup>-3</sup> M. None of the above additives affect significantly pseudo-partial wetting between the oil and water phases.

We begin with quantum dots (QDs), which have unique optical properties that make them appealing as in vivo and in vitro fluorescent probes in various biological investigations, while traditional fluorescent labels with organic molecules fail to provide long-term stability nor do they allow simultaneous detection of multiple signals.<sup>[15–18]</sup> One of the most prominent materials for life science applications, cadmium selenide, needs further treatments to be water-soluble. As a solution to avoid such treatments, oil-in-water nanoemulsions have been proposed as a bioimaging carrier for QDs.<sup>[19,20]</sup> QDs were first dispersed into the oil phase, and we observed the fluorescent signal of one sample water droplet from the aqueous phase after bubbling (**Figure 3**a). We further demonstrate the integration of

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#### а C 18 Green QDs 15 Green and red QDs 12 (%) D 9 6 Green QDs 3 Oil phase Red QDs 0,∟ 10 100 10000 1000 d (nm)

**Figure 3.** Functional nanoemulsions using QDs. a) Sample image from experiments using green QDs (QSP540-10). The scale bar is 1 µm. Inset: Illustration showing the structure of the functional nanoemulsions encapsulating green QDs. b) Simultaneous sample images from experiments using green and red QDs (QSP630-10), with detectors limited in different wavelength ranges. The left panel indicates the signal from green QDs (emission wavelength =  $530 \pm 10$  nm) and the right panel shows the signal from red QDs (emission wavelength =  $640 \pm 10$  nm). The scale bar is 500 nm. Inset: Illustration showing the structure of the functional nanoemulsions encapsulating both green and red QDs. c) The intensity distributions of DLS for samples in (a) and (b). The mean oil droplet diameter using green QDs is 214 nm with a PDI of 0.374. The mean oil droplet diameter using both QDs is 232 nm with a PDI of 0.258. Oil phase: hexadecane, aqueous phase:  $[C_{16}TAB] = 0.09 \times 10^{-3}$  M,  $d_b = 2.8$  mm, oil layer thickness = 1 mm, bubbling frequency = 0.32 s<sup>-1</sup>, bubbling time = 48 h.

two different QDs in the same nanoemulsion, as we identified the fluorescent signals of two emission wavelengths simultaneously from the same water sample (Figure 3b). Such an integration is useful in improving the clarity of imaging, particularly in the case of bioimaging when one of the emission wavelength may be interfered by other emission sources. Our results verify that QDs are successfully encapsulated into these sub-micrometer droplets (Figure 3c), while no fluorescent signals in the water were observed in the control experiments without bubble bursting.

After using lipophilic QDs, we test amphiphilic nanomaterials in our system. Surface-modified silica particles with intermediate hydrophobicity have proved to be good emulsifiers for Pickering emulsions,<sup>[21,22]</sup> which are stabilized by solid particles in place of surfactants, and hence there is a high resistance to droplet coalescence.<sup>[23]</sup> We qualitatively estimated the wettability of the nanoparticles by immersion experiments (see the Supporting Information),<sup>[24]</sup> and we find that R816 is less hydrophobic than H30 (see Table S1 in the Supporting Information).

We chose linear alkane (hexadecane) and UV-curable polymers (Norland Optical Adhesive (NOA)89) as the oil phases. No nanoparticle aggregates were observable since the bulk oil remained transparent after dispersing the nanoparticles. However, we note that the DLS measurements for the bulk oil indicated that there may be a broad size distribution for nanoparticles in the oil phase, from one single nanoparticle to clusters of several hundred nanometers. After bubble bursting, for the combination of hexadecane and H30, the environmental scanning electron microscope (ESEM) image of one oil "droplet" (Figure 4a) shows that the silica nanoparticles sit on the aggregate's surface, which has a roughness on the order of the nanoparticle size, 5-30 nm of H30. For the combination of NOA89 and R816, we first cured the sample with UV light to obtain solid sub-micrometer particles. With ESEM, we examined the surface morphology of a typical aggregate (Figure 4b), which is evidence that we obtained solid nanoparticles coated by smaller silica particles. The DLS results for these two samples show the mean particle diameters remain in the sub-micrometer range (Figure 4c). The larger polydispersity of the UV-cured sample may come from the curing process, which heats the solution and possibly influences the droplet interactions, such as the coalescence. The above results demonstrate the capability of our bubbling system to produce Pickering nanoemulsions and highlight the opportunity to tune the interfacial properties of the functional nanoemulsions.

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Next, we utilize the bubbling system for encapsulating lipid molecules to form lipid nanoemulsions, which are considered as nanocarriers for lipophilic materials, such as lipids themselves and drug components with poor water solubility; also, the lipid molecules coating the oil droplets may help protect the droplet and its contents from hazardous environments during delivery.<sup>[25-27]</sup> We checked the oil phase after the lipid molecules were dispersed, and obtained a homogeneous fluorescent signal from the confocal microscope, showing that there were no large aggregates in the experimental concentration range. Figure 4d shows a typical confocal image for a water sample after bubbling. The fluorescent signal from the lipid molecules indicates that the lipids, originally in the oil phase, have been encapsulated into the sub-micrometer oil droplets dispersed into the water (mean droplet diameter  $\approx$  140 nm as shown in Figure 4e). We note that since an excess amount of lipids was deposited into the oil phase, there may be lipid molecules on the surface of the oil droplet and also inside the oil droplets.

Furthermore, for the case where oil is undesirable, we can remove the oil phase by evaporation (see the Experimental Section). The DLS result for the water sample after heating shows a smaller mean droplet diameter (Figure 4f), which suggests one way to eliminate the oil phase in the lipid nanoemulsions. The inset of Figure 4f is a schematic for the lipid aggregates, but whether the oil phase has been completely removed or replaced partially by water molecules has yet to be studied. Also, more bio-friendly and nonionic surfactants are also applicable to generate nanoemulsions in the bubbling platform (see the Supporting Information). We note that the mean droplet size changes slightly with different encapsulating materials while remaining at the sub-micrometer scale. Since the formation of the sub-micrometer lens in pseudopartial wetting results from the competition of the van der Waals interaction of the air/oil/water system and capillary pressure of the oil (see ref. [5] and the Supporting Information for details), the dispersed nanomaterials may influence such interactions and thus the mean droplet size is shifted to some extent.



**Figure 4.** Functional nanoemulsions using amphiphilic nanomaterials. a–c) Functional nanoemulsions using nanoparticles. a) ESEM image of an oil droplet coated with surface-modified silica particles (Wacker-Chemie H30) in the bubbling system. The scale bar is 100 nm. Inset: Illustration showing the structure of an emulsion coated with nanoparticles. Oil phase: hexadecane. b) ESEM image of a solid particle coated with surface-modified silica particles (Wacker-Chemie H30) in the bubbling system. The scale bar is 100 nm. Inset: Illustration showing the structure of a coated solid particle. Oil phase: UV-curable polymers (NOA89). c) The intensity distribution of DLS for samples in (a) and (b). The mean droplet diameter in (a) is 144 nm with a PDI of 0.399. d–f) Functional nanoemulsions using phospholipids. d) Fluorescent image of the lipid-encapsulated nanoemulsion. The scale bar is 500 nm. Inset: Illustration showing the structure of a lipid nanoemulsion. e) The intensity distribution of DLS for sample before and after evaporation. Before evaporation, the mean droplet diameter given by DLS is 391 nm with a PDI of 0.289 (see the Supporting Information for size estimation). After evaporation, the mean droplet diameter given by DLS is 172 nm with a PDI of 0.179. Inset: illustration showing the structure of a lipid nanoemulsion after the evaporation experiment. Oil phase: hexane. In all the above experiments, aqueous phase:  $[C_{16}TAB] = 0.09 \times 10^{-3}$  m, bubble diameter = 2.8 mm, oil layer thickness = 1 mm, bubbling frequency = 0.32 s<sup>-1</sup>, bubbling time = 48 h.

In summary, we report a continuous and scalable bubbling system for functional nanoemulsions. Scaling up this low-power system can be achieved by simply increasing the bubble diameter and bubbling frequency. As demonstrations for the wide applicability, QDs, silica particles and lipid molecules are encapsulated successfully with our system, which is also compatible with a variety of other nanosized materials, such as magnetic nanoparticles, as long as they are dispersible in the bulk oil phase or preferentially absorb to the oil/water interface. The encapsulation and dispersion of functional nanoemulsions are realized by bubble bursting at the compound interface. As we emphasize in the Introduction, in cases where conventional methods have unavoidable disadvantages such as low-energy efficiency or strict requirements for the composite solubility for functional nanoemulsion generation, we believe our bubbling system offers a new and versatile way for encapsulating various functional materials in nanoemulsions in one step.

### **Experimental Section**

*Experimental System*: The experimental system is shown in Figure 1a. For each experiment, a thin layer of the dispersed phase, e.g. a nonpolar oil, was deposited on an aqueous solution containing an ionic surfactant  $C_{16}$ TAB. Air bubbles were formed at the tip of a tube located at the bottom of the tank. The bubbles rose to the interface because of buoyancy. We changed the size of the bubbles by adjusting the injection pressure

and the diameter of the tube. The bubbling frequency was adjusted to 0.1–1 Hz and we made sure that there were at most a few bubbles at the interface without forming a bubble column. Each experiment ran for 48 h to produce enough sub-micrometer droplets to be detected. To reduce the influence of dust, the container was cleaned before each experiment. During the experiment, we reduced the contamination of the interface and the bulk by covering the tank. We collected samples deep in the bath and far from the interface. Samples were analyzed with DLS 8 h after sampling without any further treatment. For Figure 2a,b, the container is a glass beaker of 50 mL (89000-198, VWR), and the volume of the water phase was 20 mL. For Figure 2c, the container is a self-made acrylic plastic box with dimensions of 0.14 m in length, 0.08 m in width, and 0.09 m in height, and the volume of the water phase was 500 mL. The glass frit is a glass dispersion tube with fritted glass at the end (CG203-03, Chemglass Life Science).

The UV-cured experiments were carried out using a UV oven (IntelliRay 400, Uvitron) to crosslink the particles. The UV wavelengths were within the range 320–390 nm and the exposure time was 15 s. For the evaporation experiments, since the boiling point of hexane is 68 °C, we heated the sample at 70 °C for 24 h to remove the hexane phase. For the immersion experiments, 70 mg of powders was placed carefully and evenly on the surface of a liquid phase (pure water or 1:1 (v/v) methanol/water) and we measured the time for all the powders to flow on the liquid surface before sinking into it.

*Materials*: An aqueous surfactant solution was used as the continuous phase. Ultrapure water (resistivity = 18.2 M $\Omega$  cm, Millipore MilliQ) was used to prepare all solutions. We used C<sub>16</sub>TAB (hexadecyltrimethylammonium bromide, Sigma–Aldrich, BioXtra, ≥99%) as the surfactants. For the oil phase, we used *n*-hexadecane (Sigma–Aldrich, anhydrous, ≥99%), and *n*-tridecane (Sigma–Aldrich,





 $\geq$ 99%). Also, we used *n*-hexane (Sigma–Aldrich, anhydrous, 95%) in the evaporation experiments with lipids.

Quantum dots (QSP540-10 and QSP630-10) were purchased from Ocean Nanotech and used as received. They came in powder form and were mixed with hexadecane directly. The emission wavelength is 540  $\pm$  10 nm and 630  $\pm$  10 nm for QSP540-10 and QSP630-10, respectively. For Figure 3a, the concentration of QSP540-10 in the oil phase is 1 mg mL<sup>-1</sup>. For Figure 3b, the concentrations of QSP540-10 and QSP630-10 are 0.05 and 0.1 mg mL<sup>-1</sup>, respectively.

Silica particles were purchased from Wacker-Chemie and Aerosoil and used as received. For Figure 4a, 10 mg of the nanoparticles was dispersed into a hexadecane layer of 1.2 mL on top of a solution of 25 mL with [C<sub>16</sub>TAB] = 0.09 × 10<sup>-3</sup> M. For Figure 4b, 10 mg of the nanoparticles was dispersed into an UV-curable liquid layer of 1.2 mL on top of a solution of 25 mL with [C<sub>16</sub>TAB] = 0.09 × 10<sup>-3</sup> M. We dispersed the nanoparticles in the oil phase with a vortex mixer for 5 min before each experiment. The UV-cured material in Figure 4b is Norland Optical Adhesive 89 which can be cured by UV light with maximum absorption within the range of 310–395 nm.

The lipid solution was prepared by depositing 1 mg of lipid mixture on the walls of a glass vial, and then drying overnight under vacuum. The lipid mixture, which was dissolved in chloroform, consists of 1,2-dioleoyl-sn-glycero-3-phosphocholine and 1,2-dipalmitoyl-sn-glycero-3phosphoethanolamine-*N*-(lissamine rhodamine B sulfonyl) (ammonium salt) mixed at a ratio of 99.5:0.5 mol%. Then, 3 mL of hexadecane was added to the dried lipid mixture to obtain final lipid solution. All lipids were purchased from Avanti Polar Lipids. Chloroform and hexadecane were purchased from Sigma–Aldrich. All chemicals were used as received.

*Image Techniques*: Fluorescence images were obtained using a Leica TCS SP5 confocal microscope, and the ESEM images were taken by a FEI Quanta 200 field-emission-gun ESEM. Images were processed using Fiji Software.

Dynamic Light Scattering: The size of the sub-micrometer droplets was determined by DLS using a Malvern Zetasizer Nano ZS. The measurements were performed at 173° scattering angle with 4 mW He-Ne laser producing light with wavelength of 633 nm. The unit of the scattering intensity is kilo-counts per second (kcps), representing how many photons are received by the detector per unit time. For all the DLS measurement for size, the DLS instrument automatically optimized the detector attenuation and measured position. For intensity comparison, the measured position was fixed at 4.65 mm from the wall of the cuvette, and the detector attenuation was also manually set. The detector attenuation is a parameter which represents a fixed ratio between the real detected intensity and the shown intensity. It ranges from 1 to 11 in the zetasizer, and a larger number indicates a smaller attenuation. When the detector attenuation is 11, there is no signal attenuation for the detector. DLS data were processed with Malvern's software using a distribution analysis based on a cumulant model to fit a single exponential to the correlation function to obtain the cumulant mean size and size distribution of the sub-micrometer droplets. The cumulant analysis is defined in International Organization for Standardization (ISO) standard document 13321. The calculations of PDI are defined in the ISO standard document 13321:1996 E.

## **Supporting Information**

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

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