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One Step Formation of Controllable Complex Emulsions: From Functional Particles to Simultaneous Encapsulation of Hydrophilic and Hydrophobic Agents into Desired Position

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An emulsion is a dispersion of droplets of one type of fluid in a second fluid. Recently, complex emulsions with different geometries, including multiple emulsions,[1,2] Janus emulsions,[3,4] or multilayered emulsions,[5] have been the focus of research interest because of their significant potential in many applications, including foods,[6] pharmaceuticals,[7] cosmetics,[8] materials,[9] and chemical separations.[10] However, the preparation remains one of the most challenging issues although there have been several studies on the preparation of multiple emulsions and precise control over both their size and structure. Conventional approaches for the generation of complex emulsions are limited because of the multi-step nature of the emulsifications. Additionally, the hydrodynamic and physicochemical heterogeneities of fluids pose further scientific and technical obstacles for generating complex emulsions in a controlled manner.[11–13]

Recently, microfluidic approaches for preparing emulsions have been rejuvenated by important contributions from leading groups[14–16] because of design emulsions with a high degree of flexibility and control. Utada et al. have opened a new avenue for double emulsion design by introducing the combination of flow focusing and a capillary system,[17] Deming and colleagues have focused on the stabilization of double emulsions using single-component block copolypeptides,[18] Middleberg et al. have prepared a double emulsion in a microfluidic channel using mass transfer,[19] and Huck et al. have presented a way to form a double emulsion with controllable shell through phase separation of aqueous two phases.[20] Although double emulsions can be prepared by precisely controlling the flow, they still depend on sequential multi-step emulsifications in a series of single droplet makers.[21–26] The complicated fabrication method and complex procedures involved, including synchronizing the frequencies used to generate the droplets, are prerequisites for the successful development of complex emulsions. Therefore, a simple preparation method for complex emulsions remains one of the most important emerging technologies because the emulsion is applied to simultaneously encapsulate multiple active ingredients without cross-contamination and used for the synthesis of novel functional materials as a template.

We report the principle of generation of complex emulsions based on the phase separation of a droplet. The basic principle involves diffusion of the separating agent, which provides control over the formation of multiple emulsions in a confined microfluidic system; it is a first report for generating complex multiple emulsions in a single step and provides precise control over droplet size and efficient encapsulation and compartmentalization of the active ingredient into the desired position in a emulsion droplet. In general, two immiscible fluids are used to generate emulsions. Here, a disperse fluid consists of a monomer and a D-solvent (a good solvent for the monomer), whereas the mixture of a separation agent (SA) and a C-solvent (a good solvent for the SA) plays role in a continuous fluid. The transformation of a single droplet into complex emulsion droplet follows the concept of phase separation based on the diffusion of molecules at an interface (Figure S1). First, we create discrete droplets in a flow-focusing geometry when two immiscible fluids are introduced (Figure S1a and **Figure 1**a). Immediately after formation, the disperse droplets, which are composed of the monomer and D-solvent, appear as a single phase. The SA molecules, which are dissolved in the continuous phase, can diffuse through the interface between the continuous and disperse phases (Figure S1b). Lastly, multiple emulsions, including double, triple, and quadruple emulsions, can be generated by varying the rate of phase separation (Figure S1c).

Based on this principle, we produce monodisperse water-in-oil (W/O) emulsions (Figure 1b); the disperse fluid consists of polyethyleneglycol diacrylate (PEG-DA) and water with different mixing ratios, and the continuous oil phase consists of n-hexadecane and 2, 2-diethoxyacetophenone (DEAP, photoinitiator), which is a separating agent (SA). The diffusion of SA molecules from the continuous to disperse fluid initiates phase separation of the disperse droplets. Once they have diffused into a droplet, transient separation between a complex of SA and PEG-DA (water-poor region) at the shell region and a partially separated region (water-rich region) at core readily occurs (Figure 1b). Sufficient diffusion time for the equilibration of the SA in the continuous phase into the disperse phase completes phase separation of the disperse droplets, thereby transforming the single droplet into multiple emulsions such as double, triple, and quadruple emulsions. Diffusion is significantly influenced

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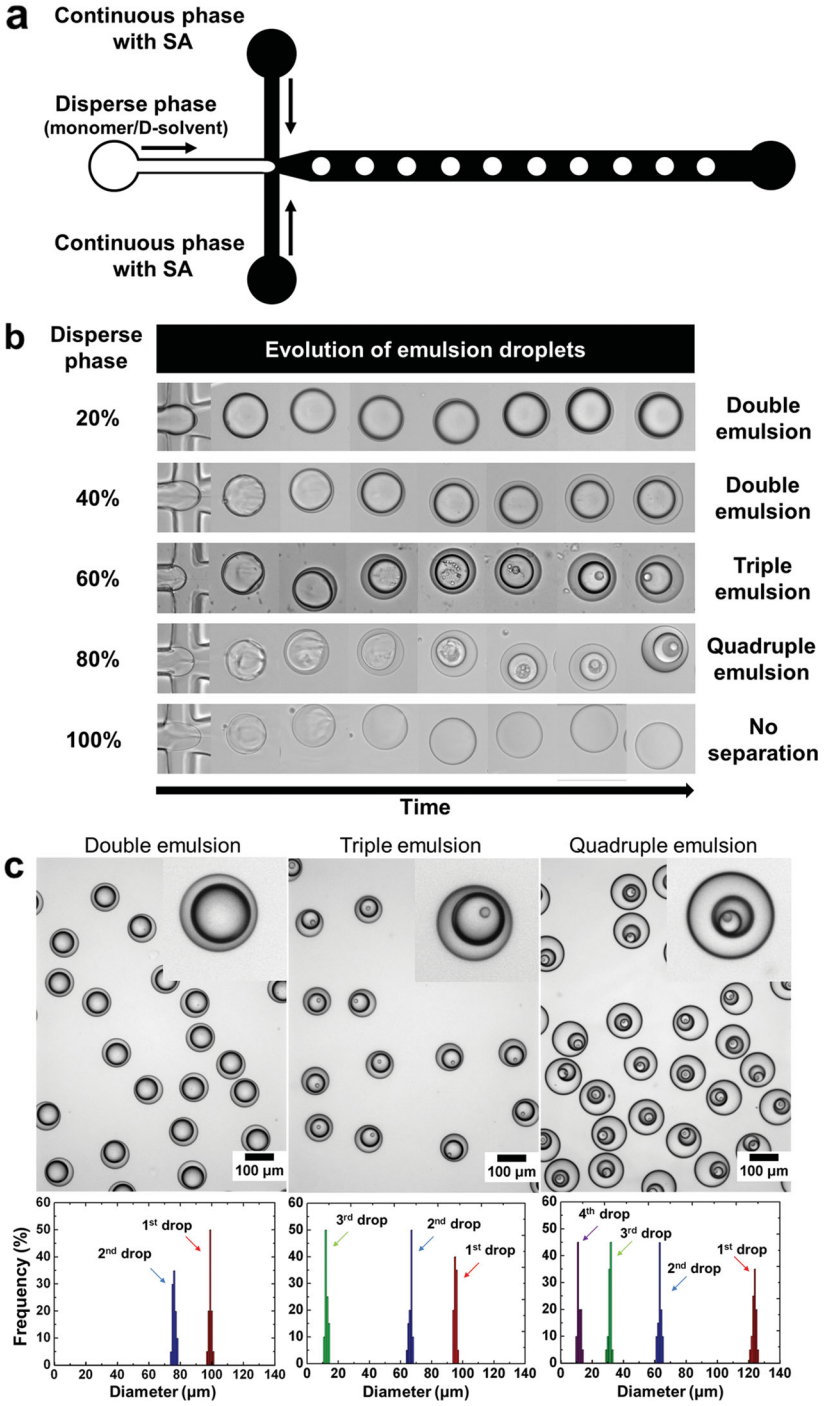

Figure 1. Generation of multiple emulsions from a single droplet in a microfluidic channel. (a) Design of the flow-focusing microfluidic device. The phase separation of disperse droplets requires that the continuous fluid (a mixed solution of n-hexadecane and 2, 2-diethoxyacetophenone (DEAP) (7:3, v/v)) is immiscible with the disperse fluid (aqueous PEG-DA solutions from 20 to 100%). (b) Sequential evolution images showing the change in the morphologies of the droplets as the concentration of PEG-DA in the disperse phase is varied. When relatively low concentrations of PEG-DA (20–40%, v/v) are used, double emulsions are produced that have a core-shell structure. Increasing concentrations of PEG-DA (60-80%, v/v) result in the sequential evolution of phase separation, thus forming triple and quadruple emulsions. Pure PEG-DA droplets do not exhibit any phase separation. (c) Multiple emulsions in the collection reservoir. All of the emulsions are produced using the same device. DEAP dissolved in n-hexadecane was used as a separation agent (SA) because of its solubility with PEG-DA in the disperse phase.

by the viscosity of the solvent.[27,28] High concentrations of PEG-DA increase the viscosity of the droplet (Figure S2) and is obstructing the diffusion of DEAP (the separating agent; SA). This process results in the slow rate of phase separation and permits several separation steps of the droplet. For example, in cases where greater than 60% PEG-DA is used, we observe the interesting features of high-order triple or quadruple emulsions. These emulsions first create the outermost shell, which is composed of PEG-DA/DEAP, and the thickness of which is determined by the diffusion coefficient of DEAP. The core primarily contains water and a small fraction of PEG-DA/DEAP. Both phases are immiscible, and polydisperse tiny droplets occur. These droplets instantly coalesce into a single drop, finally forming the triple emulsions. Additional separation creates a second shell and forms the quadruple emulsion, which is produced in an 80% PEG-DA aqueous mixture (Figure 1b and c). Based on the measurement of the characteristic time for complete phase separation, we find that it takes approximately 1.5 sec for double emulsion, 2 sec for triple emulsion, and 3 sec for quadruple emulsion, respectively. Thus, control over the morphology of the multiple emulsions strongly depends on the rate of phase separation rather than more complex hydrodynamic or mechanical control parameters, providing new insight for the design of emulsions. This property can be used to control the morphologies of the droplets, supporting the hypothesis that the diffusion time of the SA molecules to reach equilibrium controls the formation of multiple emulsions because the higher concentration of monomer in the disperse phase retards the diffusion of SA molecules, inducing sequential phase separation (Figure 1b). The droplet appears as a single phase during the initial stage. In all cases, the later growth stages of the phase-separated regions are visible (Figure 1c). Complete phase separation clearly indicates that the formation of multiple emulsions is prominent without requiring the use of a complex microfluidic device design. We present only one step emulsification; surprisingly, this achieves a high degree of control over the formation of multiple emulsions and varying the morphologies obtained. Furthermore, we can produce uniform double emulsions whose drop diameter and shell thickness can be controlled. Thus, we can form drops with extremely thin shells; the ratio of shell thickness to the radius of the outer drop can be as low as 1% (Figure 1b, c; 20% PEG-DA). Alternatively, we can increase the shell thickness of the double emulsion

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and quadruple emulsion up to 36% and 60% of the drop radius, respectively (Figure 1b, c; 40% and 80% PEG-DA). A collection of multiple emulsions, including double, triple, and quadruple emulsions, also demonstrates high monodispersity (Figure 1c).

These results obviously confirm a primary advantage of the microfluidic system; it provides a confined chemical space so that we can develop a facile and efficient platform that opens new research opportunities. In addition, it supplies considerably larger interfaces for transferring the SA molecules and even minimizes the total mass required to reach the equilibrium state, achieving highly efficient mass transfer.[29] For example, unlike the evolution of complex multiple emulsions in a microfluidic channel, the phase separation cannot be observed in bulk systems. To examine this hypothesis, we have monitored the phase separation of a mixture of aqueous PEG-DA solution (lower phase) and n-hexadecane containing DEAP (upper phase) (Figure S3). The mixture of aqueous PEG-DA phase separates into two phases (water-rich and -poor) without any external force, and complete separation requires more than 2 days. We also form a pendant drop to mimic the phase separation in a relatively small volume (approximately 0.7 μL). The resulting phase separation is identical to the result obtained in an Eppendorf tube described above. Reaching the equilibrium state requires approximately 600 sec (Figure S4). This result proves that phase separation in bulk solution is completely different from that in a microchannel and the microfluidic approach can controllably and rapidly create homogeneous mixtures at the commencement of a reaction, which is a desirable feature.

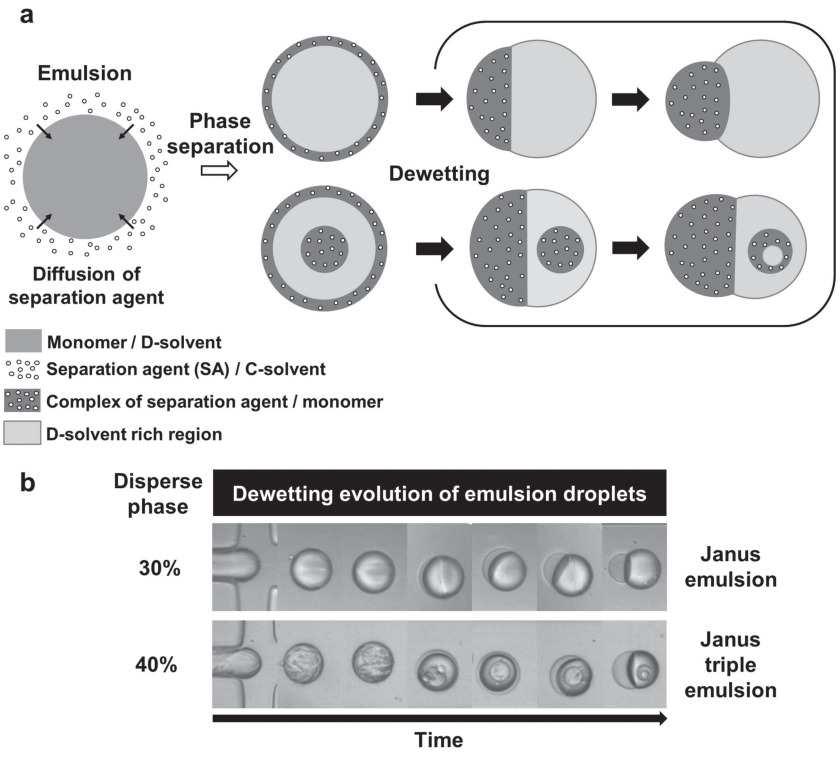

Figure 2. Generation of Janus emulsions from a single drop. (a) Schematic diagram for the formation of Janus emulsions based on phase separation and the dewetting transition. (b) Sequential optical images of double and triple emulsion drops undergoing the dewetting transition. The emulsion drop consists of a water-rich drop surrounded by a shell of a NIPAm-rich fluid. At the end of the transition, the drop adopts an acorn-like structure with two distinctive compartments (a Janus emulsion).

One of the interesting scientific issues is the formation of complex emulsion with various architectures by combining mutually insoluble compounds in the disperse phase.[3,4] Conceptually, the formation of emulsions requires the existence of a separated compartment to load each compound within the disperse phase. One of the promising emulsions is Janus emulsion[4,30,31] with the anisotropy of the drop interface because it has been utilized to prepare Janus particles,[32,33] anisotropic particles of advanced complexity and refinement,[34] multidrug carries,[35] and even for direct use as catalysts.[36] Thus, we examine the feasibility of generating a Janus emulsion within each compartment by combining phase separation and dewetting phenomena. Based on a previously studied principle, the disperse droplet can be transformed into a double or triple emulsion (**Figure 2**a). When surfactants are dissolved in a continuous fluid, they play a role in decreasing the surface free energy at the interface of the double or triple emulsion drop, subsequently initiating a dewetting transition at the interface of the inner drop and collecting on one side of the inner drop, thereby forming an acorn-like shape (Figure 2a). The shell phase remains attached to the drops, which induce segregation of the single droplet into two compartments. Therefore, we can obtain Janus emulsions that have two primary compartments. To demonstrate the formation of Janus multiple emulsions, an aqueous disperse droplet composed of N-isopropylacrylamide (NIPAm; 30, 40%), N,N′-methylenebisacrylamide (5%, cross-linker), methanol (5%, cosolvent), and water under an n-hexadecane continuous fluid containing Span 80 surfactant (5%) and DEAP (5%, SA) is applied. The resulting disperse droplets are transformed into double or triple emulsion drops, depending on the concentration of NIPAm. The NIPAm-rich layer at the shell region of the double or triple emulsion, which initially wets the entire inner drop, dewets from the inner drop (water-rich phase), thereby producing an acorn-like structure (Janus emulsion) (Figure 2b).

The ability to produce complex emulsions provides great opportunity for fabricating novel functional materials with monodispersity, shape control, and flexibility of material composition. Here, we are able to use complex multiple emulsions as a template for the formation of anisotropic particles including hollow microcapsules, microcapsules-in-microcapsules, and hemispheres. Unlike conventional approaches for forming complex particles,[37–40] our approach utilizes a simple single emulsion, which is formed in microchannel without the need for elaborate device design, fabrication, or surface modification. The emulsions generated through phase separation

and dewetting can be transformed into anisotropic particles by photopolymerization. The successful synthesis of anisotropic particles is summarized schematically (**Figure 3**). The first and second row represents a schematic diagram, and optical images of the complex emulsions generated in the microfluidic device (Figure 3a). The experimentally matched results are shown in the third and fourth row, respectively (Figure 3b). The spherical double and quadruple emulsion precursors are converted to monodisperse anisotropic particles. When templating Janus emulsions, Janus particles are not fabricated; only monomer rich lobes in the Janus emulsion are polymerized. In this way, hemispheric particles derived from Janus double emulsions or both hemispheric and hollow microcapsules that have a thick shell derived from the Janus triple emulsions, respectively (Figure 3a, b). This study clearly demonstrates that the use of complex emulsion template provides an alternative and efficient method for an excellent tool in designing particles.

In practical applications of microcapsules for carrying chemical payloads, it is important that they can be stored in a dry state for extended periods and sequentially rehydrated without the loss of their properties. This behavior should be confirmed by drying and rehydrating the microcapsule; on contact with water, the dried and shrunken microcapsule instantly returns to the swollen hydrated state, and the microcapsule-in-microcapsule structure is perfectly restored (Figure 3c). The temperature sensitivity of the microcapsules on swelling and contracting is also confirmed. Initially, we monitor the change in volume of the microcapsules while increasing the temperature (Figure 3d). As expected, the volume of the NIPAm microcapsule decrease as the temperature is increased because it becomes hydrophobic and expels water above a lower critical solution temperature (LCST, approximately 32 °C). This result indicates that the microcapsule-in-microcapsule preserves the inherent thermosensitivity of PNIPAm, and the morphologies of the two types of microcapsules resulting from the triple and quadruple emulsions do not affect the thermo-responsive capability. In summary, these studies demonstrate a high degree of compatibility regarding the evolution of complex emulsions and more complex particles could easily be created.

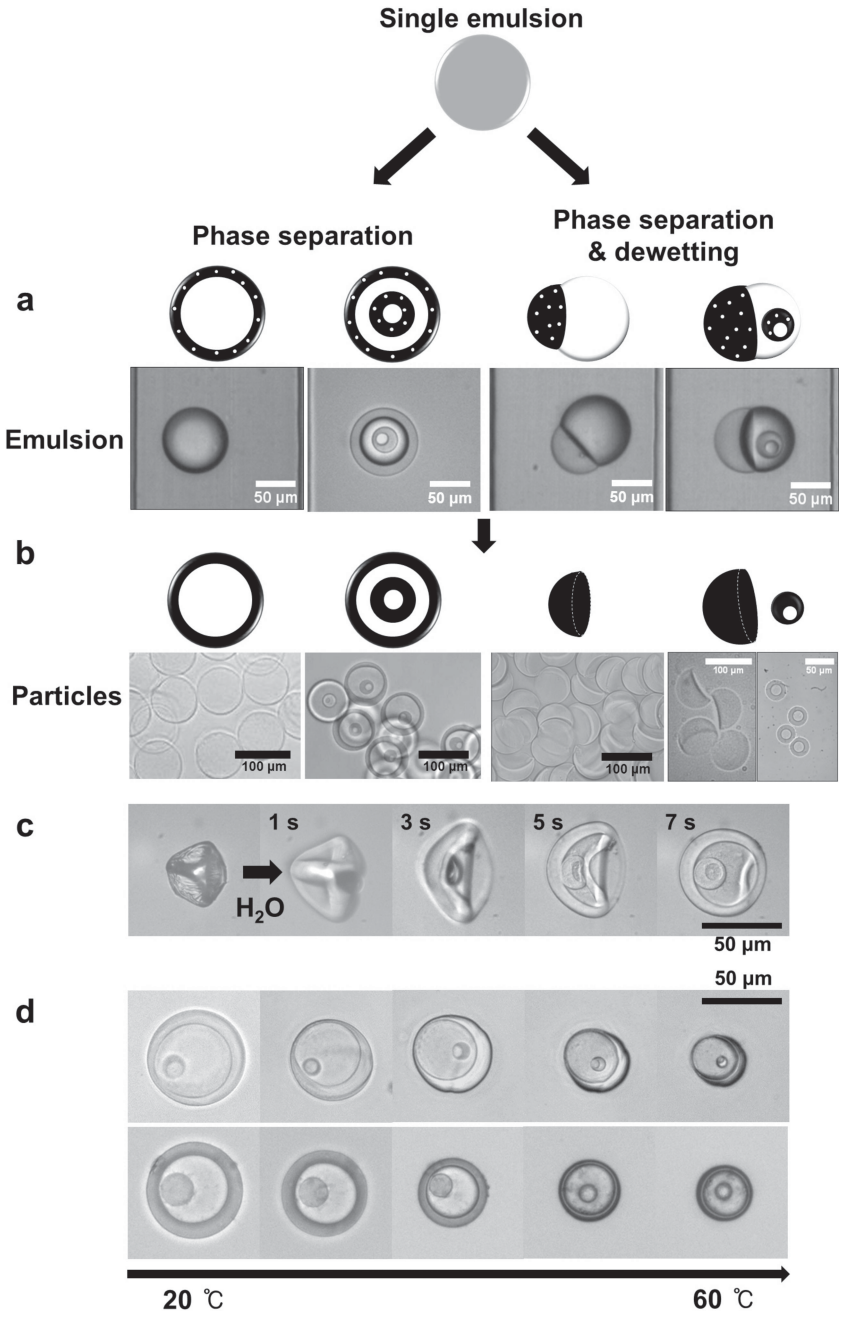

Figure 3. Synthesis of anisotropic particles with complex geometries. (a) Schematics and optical images of the possible formation of multiple emulsions through phase separation and the dewetting transition in a confined microfluidic system. (b) Optical images of the polymerized structures produced through photopolymerization (from left, a hollow microcapsule that has an ultra-thin shell, an onion microcapsule, a hemisphere, and a hollow microcapsule that has a thick shell). (c) Rehydration of the dried onion microcapsules (microcapsules-in-microcapsules); rapid recovery toward the original structure after the addition of water. (d) Thermosensitivity of the onion microcapsule when the temperature is increased from 20 to 60 °C.

Recently, anisotropic materials, including emulsions, gels, particles, and capsules with multiple compartments, have been investigated for their great potential to efficiently encapsulate active agents and for use as an intelligent delivery system because the storage of different functional agents separately reduce the risk of cross-contamination.[35,41,42] The versatility and flexibility of these systems also allow simultaneous encapsulation of multiple types of drugs for cocktail

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therapies.[43] Although recent advancements in micro/nano-carrier engineering are obvious, technological challenges in encapsulating different compounds in single capsules remain when hydrophobic and hydrophilic compounds are simultaneously loaded.[44,45] Thus, precise and simultaneous encapsulation can open exciting new opportunities for the treatment of serious diseases. Furthermore, multiple compounds that are separately encapsulated can induce or mediate reactions on demand. Here, we extend our approach to explore simple, simultaneous, and selective encapsulation because complex emulsion droplets can potentially be used to simultaneously encapsulate hydrophobic and hydrophilic compounds into a desired position. First, we load a hydrophobic fluorescence dye (Nile red) into the disperse phase (aqueous PEG-DA solution) and produce multiple emulsions, such as double, triple, and quadruple emulsions, in accordance with the basic principle of phase separation. Total fluorescence (upper row in **Figure 4**a) and corresponding confocal fluorescence images (lower row images in Figure 4a) clearly indicate that the hydrophobic dye strongly interacts with the complex PEG-DA/DEAP fluid, but it is repelled by water, thereby achieving successful selective encapsulation in the multiple emulsions (Figure 4a). Next, we investigate the flexibility of one-step multi-component encapsulation. As a proof of concept, we use two dyes, hydrophilic Erioglaucine disodium salt (blue) and hydrophobic TERATOP RED HL-S (red). When these dyes are introduced into the disperse phase in an Eppendorf tube, we can clearly observe a purple color due to the mixing of the two colors (Figure 4b; top-right). The addition of a separation agent (DEAP) creates two segregated compartments; therefore, each dye is selectively localized (Figure 4b; bottom-right) into the top or bottom layer. We can create purple drops in a microfluidic channel, which transform into double emulsions or Janus emulsions with multi-compartments (Figure 4b; left). Optical images confirm that the blue and red dyes are successfully encapsulated in the hydrophilic (core) and hydrophobic (shell) regions, respectively (Figure 4c, d). Furthermore, we also load both water-soluble (sulforhodamine B) and oil-soluble (fluorescein) dyes into the disperse fluid. We can clearly observe the position of both fluorescent dyes in the double and Janus emulsions, and the fluorescence signals provide the loading uniformity; the lack of loading uniformity may reduce encapsulation efficiency and control over the desired release characteristics. (Figure 4e and f). The double emulsions exhibit compartmentalization of hydrophilic dyes (red) into the inner core region and hydrophobic fluorescein dyes into the shell. In the Janus emulsions, the hydrophilic and hydrophobic dyes are placed into the small and large lobes, respectively. In addition, the sharp interface between the two halves of the emulsions indicates negligible mobility of the encapsulated active compounds within the complex emulsion matrix (Figure 4e and f). These results confirm that we can load the active agents into the desired compartments and only simple mixing can induce the simultaneous encapsulation of hydrophilic and hydrophobic species. To the best of our knowledge, this method for the simple, simultaneous, directed, homogenous, and reproducible loading of two distinctive chemicals outperforms existing techniques that are based on common multiple emulsions or droplet microfluidics.

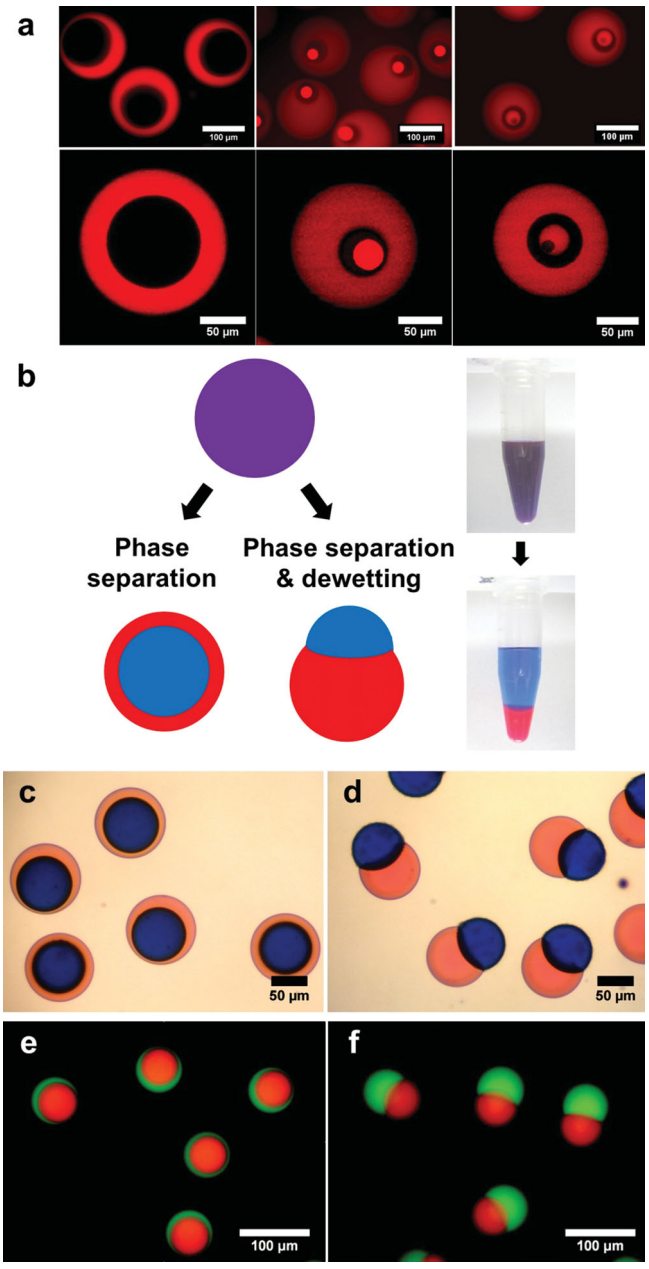

Figure 4. Regioselective and simultaneous multi-component encapsulation. (a) Fluorescence image and corresponding confocal images of multiple emulsions, which clearly shows the selective encapsulation of a hydrophobic dye (Nile red) into the shell region. (b) One-step encapsulation of multi-components at each desired position. Upon loading of Erioglaucine disodium salt (blue) and TetratopRedHL-S (red), the aqueous PEG-DA solution becomes purple. After inducing the phase separation through the addition of DEAP to the mixture, the blue and red dyes move into the hydrophilic region (core) and the hydrophobic region (shell), respectively. Bright-field images of the double emulsion (c) and the Janus emulsion (d). We used a 40% aqueous PEG-DA solution as a disperse phase and hydrophobic hexadecane to dissolve 20% DEAP (w/w) and 1% Span 80 (w/w) for the phase separation and dewetting process, respectively. Fluorescence images of the double emulsion (e) and the Janus emulsion (f) when hydrophilic (red) and hydrophobic (red) dyes are simultaneously introduced.

Our approach is the only one-step process that can provide 100% encapsulation of an active compound.

In summary, we present the one-step fabrication method of a complex emulsion, providing a versatile route toward new material platforms for anisotropic particles and functional emulsions. The use of complex emulsions overcomes a critical limitation of conventional single or double emulsions by allowing the straightforward preparation of stable droplets. To the best of our knowledge, this is the first demonstration of simultaneous encapsulation of two distinct compounds into desired compartments achieved by simple mixing with a disperse solvent. Further studies of these complex emulsions involving extension of the active components used to more relevant therapeutics and nutrients as well as rational control of the particle microstructures to tune the release kinetics will aid in further understanding their capabilities in a wide range of applications, including pharmaceuticals, multi-drug chemotherapies, and cosmetics.

Supporting Information

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

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