Fluorocarbon Oil Reinforced Triple Emulsion Drops

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Emulsions have been widely used as vehicles for the delivery of various chemical and biological actives including food additives or nutriceuticals,[1–3] pharmaceuticals,[4] and cosmetics.[5] Their utility is due to their great capability for encapsulation and long-term storage of actives.[6,7] Multiple emulsions are of particular interest due to the compartments of these emulsion drops that can be enlisted to impart functionality;[8] for example, double emulsion drops with a middle phase that separates the innermost drop from the continuous phase enable highly efficient encapsulation of hydrophilic or hydrophobic actives.[9–11] Even more flexibility can be achieved by utilizing the middle phase in double emulsion drops as templates to form polymeric microcapsules,[12] vesicles,[13] and colloidosomes;[14] for instance, composition and the thickness of the polymeric shell in microcapsules can be modulated to fine-tune the permeability of encapsulated active as well as the mechanical stability of the capsule shell.[15–19] Although a variety of capsule shell materials capable of encapsulating chemical and biological small actives have been developed, leakage of encapsulated actives prior to release is typically observed; this drawback limits the versatile usage of capsule technologies in practical applications.[20] Undesired leakage of encapsulated actives from microcapsules results from the capsule fabrication process and the capsule shell material's inherent permeability to encapsulated molecules.[21] These limitations can be mitigated to some extent by fabrication of homogeneous, defect-free shell structures through covalent cross-linking of monomers or macromonomers. The resulting dense polymeric networks have reduced mesh size making them an attractive alternative to enhance the retention of encapsulated actives.[22] However, the monomers used for polymeric shells are mostly either hydrophilic or lipophilic facilitating leakage of actives that have strong affinity to the polymeric shell used;[23,24] this can substantially limit the types of cargoes which can be effectively encapsulated and retained within the microcapsules.[25] Moreover, for complex biomolecules such as proteins possessing hydrophobic entity, the 3D structure of proteins can be readily collapsed by adhesion of hydrophobic entities onto the polymeric membrane of capsules, thereby losing their bioactivity.[26] Therefore, there remains a need for a new type of microcapsule structure that enables highly efficient encapsulation and retention of small molecules as well as active biomolecules (protein).

In this work, we present a novel and pragmatic fluorocarbon oil reinforced triple emulsion drops to achieve highly efficient encapsulation and retention of small molecules and active biomolecules (protein) in microcapsules. Using a capillary microfluidic device, we produce monodisperse triple emulsion drops, enveloping an ultra-thin fluorocarbon oil layer in between the encapsulant and the photocurable oil, which transforms into a polymeric shell upon UV illumination. By utilizing the omniphobic property of the fluorocarbon oil layer,[27] we encapsulate a broad range of polar and non-polar cargoes in a single platform. In addition, we demonstrate that fluorocarbon oil act as an effective diffusion barrier as well as a non-adhesive layer, enabling highly efficient encapsulation and retention of small molecules and active biomolecules (protein) in microcapsules prepared from these emulsion drops.

To make these fluorocarbon oil reinforced triple emulsion drops, we use a glass capillary microfluidic device comprised of two tapered cylindrical capillaries, one for injection and the other for collection. We successfully align both tapered cylindrical capillaries by inserting them within a square capillary that has inner diameter slightly larger than the outer diameter of the cylindrical one, as shown schematically in **Figure 1**a. The injection capillary is treated to make it hydrophobic on the outer wall while the inner wall is treated to make it fluorophilic resulting in a Janus type cylindrical capillary as schematically illustrated in Figure 1b and detailed in Figure S1 (Supporting Information); the collection capillary is treated to make it hydrophilic. In addition, a small cylindrical capillary is inserted into the injection capillary to simultaneously inject two immiscible fluids, encapsulant and the fluorocarbon oil.

An encapsulant phase, which can be varied from water to organic solvents, is injected through the small cylindrical capillary to form the innermost drop. A fluorocarbon oil phase is injected through the injection capillary. The coflowing of these two immiscible fluids leads to stream of plug-like encapsulant drop due to preferential wetting of the fluorocarbon oil phase on the wall of fluorophilic injection capillary; the local confinement of encapsulant-in-fluorocarbon oil coaxial flow near the tip of the injection capillary reduces interfacial deformation between the plug-like encapsulant drop and the inner wall of the injection capillary, facilitating stable formation of the thin fluorocarbon oil layer.[28,29] We inject photocurable solution for the oil phase through the interstices of the square and injection capillaries. Additional aqueous continuous phase is injected through the interstices of the square and collection

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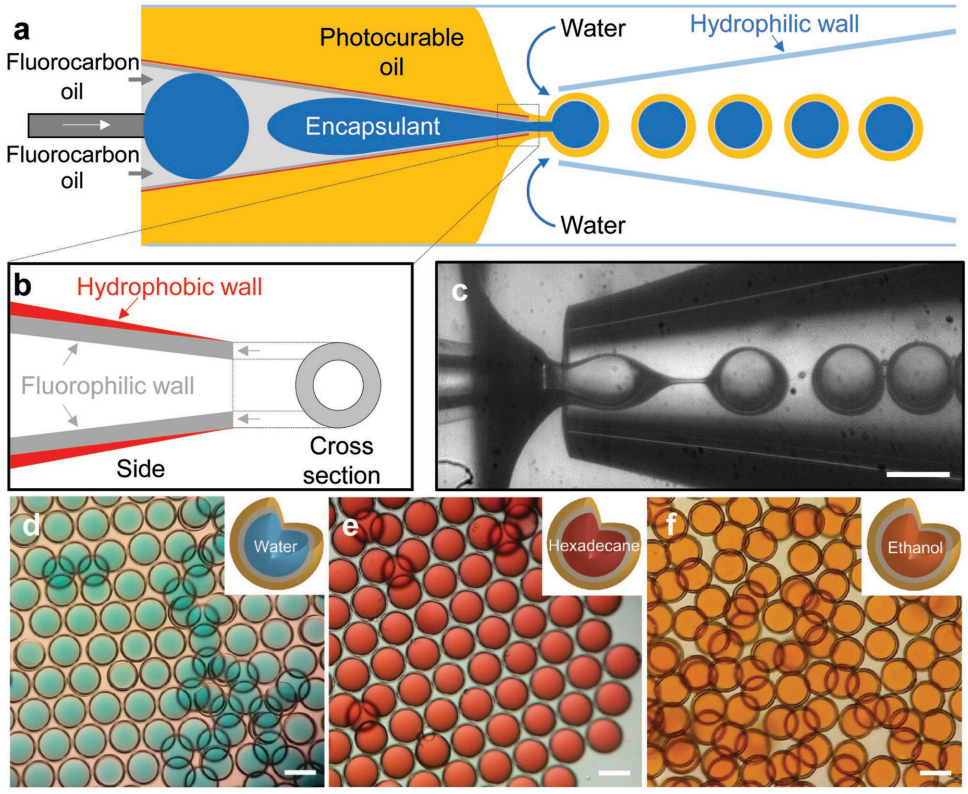

Figure 1. Encapsulation of various cargo materials using fluorocarbon oil reinforced triple emulsion drops. a) Schematic illustration of the microfluidic device used for preparation of fluorocarbon oil reinforced triple emulsion drops. b) Schematic illustration of a tapered Janus type capillary in which the outer wall is treated to make hydrophobic while the inner wall is treated to make fluorophilic. c) Optical image showing drop generation in a dripping mode. Scale bar represents 200 μm. d–f) Optical images of the triple emulsion drops encapsulating water (blue), hexadecane (red), and ethanol (orange). Scale bars represent 200 μm.

capillaries. The stream of plug-like encapsulant drops from the injection capillary coflow with the photocurable oil phase, which breaks up into monodisperse triple emulsion drops with the thin fluorocarbon oil layer by shearing of the aqueous continuous phase. The resulting emulsion drops then flow downstream through the collection capillary, as shown in the optical image of Figure 1c.

The omniphobic fluorocarbon oil layer in the triple emulsion drop separates the innermost encapsulant phase from the photocurable oil phase, enabling encapsulation of both polar and non-polar cargoes in a single platform. We use three types of solvents with different polarity as encapsulant phase; water (W_1), hexadecane (H), and ethanol (Et). We use FC-70 for the ultra-thin fluorocarbon oil layer (F), ethoxylated trimethylolpropane triacrylate (ETPTA) as the photocurable oil phase (P), and aqueous solution of 5% poly(vinyl alcohol) (PVA) as the continuous phase (W_2). All the cargo materials are successfully encapsulated within an identical emulsion drop with a fluorocarbon oil layer, as shown in the optical images of Figure 1d–f.

To successfully encapsulate various cargo materials surrounded by a fluorocarbon oil layer in an emulsion drop, it is essential to achieve stable triple emulsion drops. However, fluorocarbon oils inherently have high interfacial tension with other immiscible fluids[27] that preclude formation of a stable triple emulsion drop due to its unfavorable interaction with the adjacent phases. As a result, triple emulsion drops with a fluorocarbon oil layer undergo a dewetting transition followed by destabilization as shown in the series of photographs in Figure S2 (Supporting Information) without consideration of the interfacial tensions between the fluorocarbon oil and each of the other fluids that comprise the emulsion drop.

The stability of the multiple emulsion drop is determined by the relative values of these interfacial tensions which can be described using spreading coefficients, defined as

$$S_i = \gamma_{j,k} - \gamma_{i,j} - \gamma_{i,k} \quad (1)$$

where $\gamma_{j,k}$ is the interfacial tension between phase j and k.[30–34] The spreading coefficient (S_i) reflects the propensity of the middle fluid (i) to spread between the other two immiscible fluids, inner fluid j, and the outer fluid, k. Thus, fluid i completely engulfs a drop of the inner fluid j, forming a core–shell structure dispersed in a third immiscible fluid k when $S_i > 0$. This same principle can be extended for water/fluorocarbon oil/photocurable oil/water (W_1/F/P/W_2) triple emulsion drop where two middle fluids, fluorocarbon oil (F) and photocurable oil (P) completely engulf each inner drop to form a stable triple emulsion drop when the spreading coefficients of the fluorocarbon oil (S_F) and the photocurable oil (S_P), defined as

$$S_P = \gamma_{F,W2} - \gamma_{P,F} - \gamma_{P,W2} \quad (2)$$

$$S_F = \gamma_{W1,P} - \gamma_{F,W1} - \gamma_{F,P} \quad (3)$$

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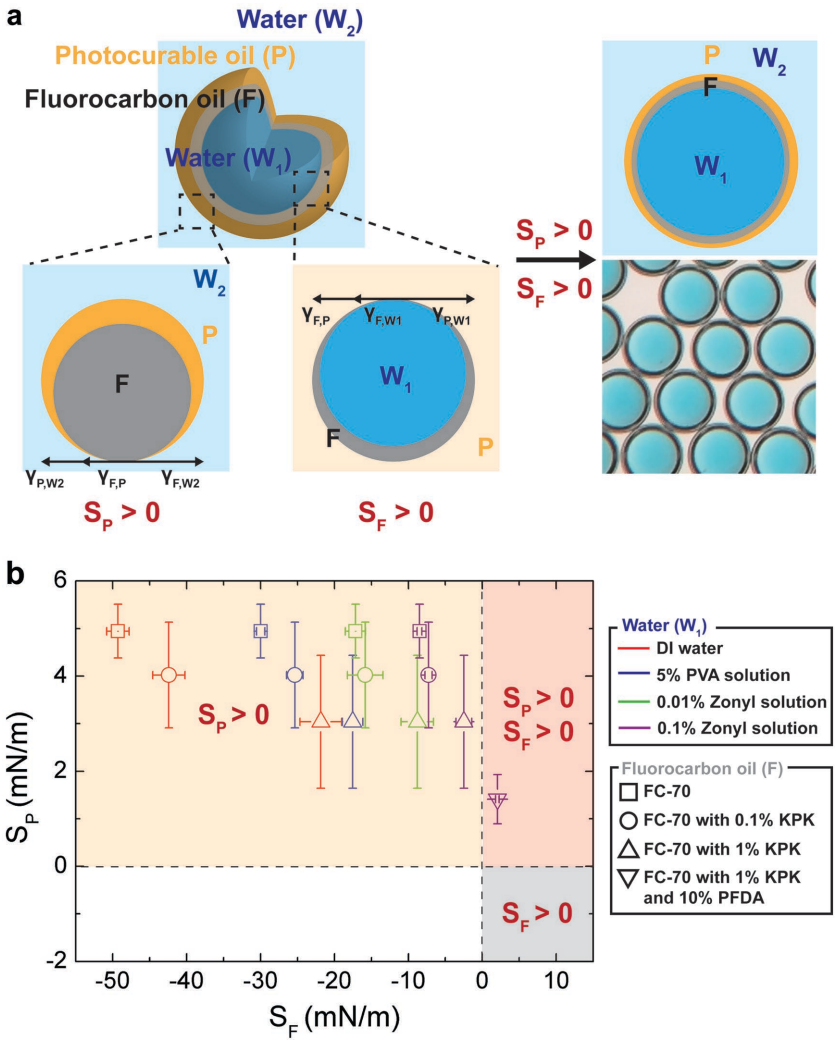

Figure 2. Tuning the spreading coefficients to generate stable triple emulsion drops. a) Schematic illustration and the optical image of stable triple emulsion drops. Both spreading coefficients, S_P and S_F, need to be positive to form a stable triple emulsion drop. b) Diagram showing DI water and fluorocarbon oil (FC-70) with or without surfactants and the corresponding spreading coefficients (S_P and S_F) investigated in this work. The regions in the diagram that satisfy the conditions $S_F > 0$ and $S_P > 0$ are highlighted with gray and beige, respectively. The surfactant composition located in the overlapping region highlighted with pink (both $S_F > 0$ and $S_P > 0$) results in stable triple emulsion drops.

are both positive as shown in the schematics and the optical image of **Figure 2**a.

These spreading coefficients can be modified by adding surfactants to each of the constituent phases to change the interfacial tensions.[35] To determine the effect of the surfactants, we measure the interfacial tensions using a pendant-drop method. For deionized (DI) water and FC-70, we measure the interfacial tension ($\gamma_{W,F}$) before and after adding surfactants in each fluid; 5% PVA or 0.1 % Zonyl FSO-100 (hereafter "Zonyl") is added to DI water while 1% Krytox-PEG-Krytox (KPK)[36] or 10% 1H,1H,2H,2H-perfluorodecyl acrylate (PFDA) is added to FC-70. This reveals that interfacial tension between DI water and FC-70 can be dramatically reduced from 45.0 ± 1.5 to 1.4 ± 0.2 mN m^{-1} by adding surfactants to each fluid, as shown in Figure S3 (Supporting Information). The detailed study of the effect of added surfactant on the interfacial tensions enables determination of conditions that allow both spreading coefficients, S_P and S_F, to be positive, as shown in the values of the interfacial tensions and the corresponding spreading coefficients tabulated in Table S1 (Supporting Information). We use ETPTA as the photocurable oil phase (P), and an aqueous solution of 5% PVA as the continuous phase (W_2); as a result, $S_P > 0$, and the photocurable oil completely engulfs the inner fluorocarbon oil drop, regardless of the surfactants added in the fluorocarbon oil phase. To visualize this behavior more effectively, we prepare a stability diagram as a function of the S_F and S_P values and plot each tabulated surfactant composition as a symbol in the diagram as shown in Figure 2b. The regions in the stability diagram that satisfy the conditions $S_F > 0$ and $S_P > 0$ are highlighted with gray and beige, respectively. Thus, the surfactant composition located in the overlapping region (pink with both $S_F > 0$ and $S_P > 0$) results in stable triple emulsion drops as shown in the optical image of Figure 2a.

Overall, these results indicate that spreading coefficients can be modulated to enhance the stability of the triple emulsion drops generated, enabling consistent production of microcapsules from these emulsion drops. Moreover, this concept is not limited to an aqueous solution (W_1) as the innermost encapsulant phase but can be extended to hexadecane (H) and ethanol (Et) as shown in the detailed analysis as well as the relevant stability diagram presented in the plots of Figures S4 and S5 (Supporting Information).

The ability to produce fluorocarbon oil reinforced triple emulsion drops offers new opportunities for encapsulation and retention of small molecules in polymer microcapsules. To validate this capability, we prepare two sets of emulsion templated microcapsules encapsulating fluorescein (green fluorescent dye, 332 Da, 0.05 mg mL^{-1}) as a representative small molecule; we compare the behavior of triple-emulsion microcapsules that have a fluorocarbon oil layer, with double-emulsion microcapsules without the fluorocarbon oil layer, as shown in the schematics of **Figure 3**a. To produce these emulsion templated microcapsules, we solidify the photocurable oil phase (ETPTA) in each set of emulsion drops by in situ photopolymerization to form polymeric shells. We characterize the retention of fluorescein by comparing the fluorescence signal from each of these samples. For the double-emulsion microcapsules, we observe fluorescence signal outside the microcapsules comparable to inside, indicating that the ETPTA polymer shell alone cannot prevent the leakage of fluorescein. In contrast, the triple-emulsion

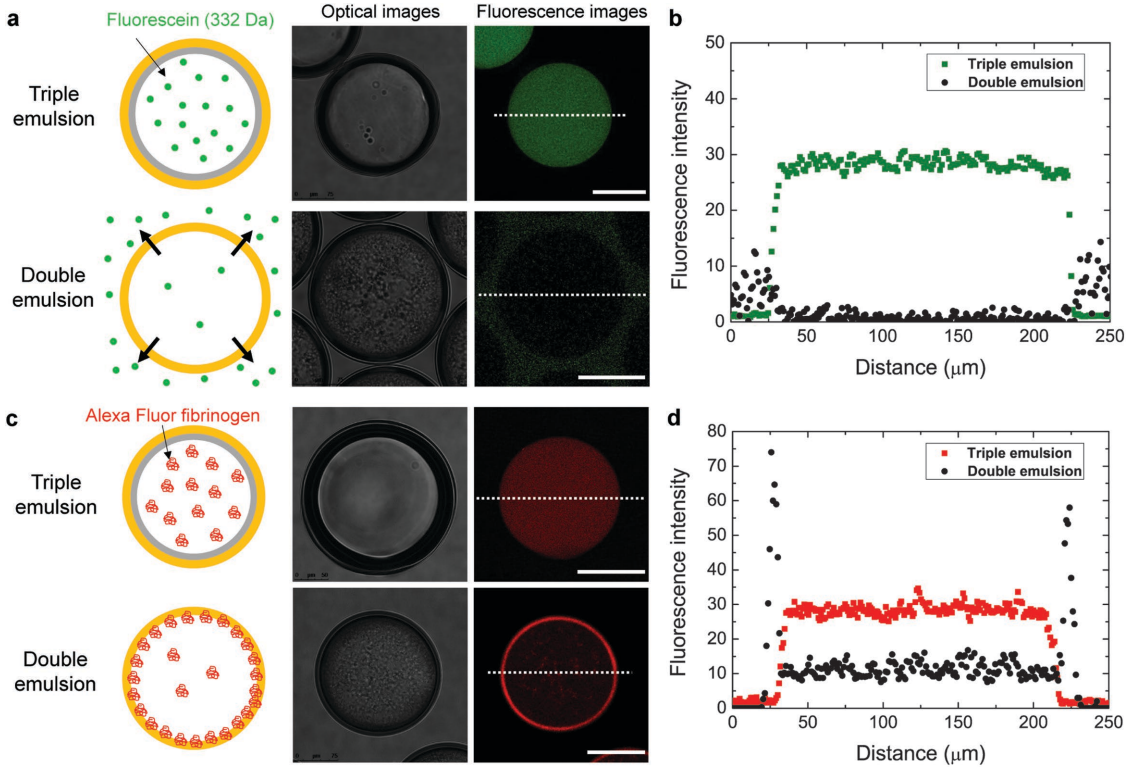

Figure 3. Microcapsules templated from multiple-emulsion drops. a) Optical and fluorescence image of triple- and double-emulsion templated microcapsules encapsulating fluorescein. The images were taken a day after they were prepared. Scale bars represent 100 μm. b) Spatially resolved intensity profiles of the green fluorescence in the microcapsules shown in (a) demonstrate that fluorescein readily leaks out for double-emulsion templated microcapsule while triple-emulsion templated microcapsule with a fluorocarbon oil layer have uniform distribution of fluorescein within the microcapsule. c) Optical and fluorescence image of triple- and double-emulsion templated microcapsules encapsulating Alexa Fluor fibrinogen. The images were taken 2 h after they were prepared. Scale bars represent 100 μm. d) Spatially resolved intensity profiles of the red fluorescence in the microcapsules shown in (c) demonstrate that fibrinogen adhere to the capsule shell for double-emulsion templated microcapsule while triple-emulsion templated microcapsule with a fluorocarbon oil layer have uniform distribution of fibrinogen within the microcapsule.

microcapsules do not exhibit any fluorescence signal whatsoever outside the microcapsule, and retain the full fluorescence signal within the capsule for more than a day, as evidenced by the fluorescence images of Figure 3a and the uniform distribution of fluorescence intensity profiles of Figure 3b. This demonstrates the effectiveness of the fluorocarbon oil layer in the retention of small molecules within the capsules.

To clearly verify the origin of this pronounced difference in permeability, we prepare two sets of water-in-fluorocarbon oil-in-water ($W_1/F/W_2$) double emulsion drops with two different types of fluorocarbon oil, FC-70 and a hydrofluoroether (HFE7500, Novec 7500 Engineered Fluid). We observe that fluorescein is fully retained within the double emulsion drop with FC-70 shell while equivalent fluorescence signal outside the emulsion drops compared to inside is observed for double emulsion drop with HFE7500 shell, as shown in the optical and fluorescence images of Figure S6 (Supporting Information). This indicates that FC-70 act as an effective diffusion barrier in preventing the leakage of fluorescein while HFE7500 does not. We attribute this behavior to the chemical composition of fluorocarbon oil: FC-70 is fully fluorinated while HFE7500 is partly composed of alkyl groups as shown in the chemical structures of Figure S6 (Supporting Information). To further confirm the effectiveness of this fluorocarbon oil (FC-70) layer compared to a solid fluorinated polymer membrane in preventing the leakage of small molecules, we produce perfluoropolyether (PFPE, Fluorolink MD-700) microcapsules.[25] We observe that fluorescein is mostly localized in the inner wall of the PFPE shell while the rest leaks out through the capsule membrane after a day as shown by the fluorescence images and the spatially resolved intensity profiles of Figure S7 (Supporting Information). These results demonstrate that introducing a thin liquid layer of FC-70 within the capsule shell can suppress the leakage of encapsulated small molecules.

The microcapsules with a fluorocarbon oil layer also enable highly efficient encapsulation of active biomolecules (protein). To validate this, we use an aqueous solution of fluorescently labeled fibrinogen (Alexa Fluor 647 fibrinogen, 0.05 mg mL^{-1} in phosphate-buffered saline), which is challenging to be encapsulated within emulsions or emulsion templated capsules due to strong adsorption at an oil–water interface followed by protein denaturation.[37] We encapsulate this solution as the innermost phase of a triple-emulsion microcapsule that has a thin fluorocarbon oil layer within a polymerized ETPTA shell. We also encapsulate this solution in a double-emulsion microcapsule without a fluorocarbon oil layer. We compare the behavior of the fluorescence signal for each of these microcapsules. While fibrinogen immediately adsorbs at the ETPTA–water

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interface of the double-emulsion microcapsules, fluorocarbon oil layer of the triple-emulsion microcapsules effectively prevents fibrinogen adsorption at the interface, as evidenced by the fluorescence images of Figure 3c and the spatially resolved intensity profiles of Figure 3d. We also note that the fluorosurfactant (Krytox-PEG-Krytox, KPK) in the fluorocarbon oil assembles at the water/fluorocarbon oil interface and stabilizes the innermost water drop; their PEG functional group may also contribute in preventing the adsorption of proteins as demonstrated previously.[36] Overall, these results confirm that incorporating a thin layer of fluorocarbon oil within the capsule shell is also effective at preventing proteins with hydrophobic entities from physically adhering to the hydrophobic capsule shell; this demonstrates the potential of encapsulation of proteins without the denaturation.

This concept of introducing a fluorocarbon oil layer within the capsule shell is not limited to ETPTA but is also applicable to other shell materials. To demonstrate this concept, we prepare two sets of microcapsules with a fluorocarbon oil layer encapsulating an aqueous solution in the core; we compare the mechanical responses of the microcapsules that have a polymerized ETPTA shell, with the other microcapsules with a photo-polymerized silicone shell (semicosil 949UV).[38] While ETPTA microcapsules placed between two glass slides easily rupture when compression force is applied, silicone microcapsules expand in projected surface area without rupturing and recovers back to its original morphology upon removal of the initial compression as shown in the schematics and the optical images of Figure S8 (Supporting Information). This significant difference in mechanical response of microcapsules from being brittle to elastomeric directly implies that broad spectrum of shell material can be utilized depending on the application needs.

Herein, we prepare monodisperse triple emulsion drops, enveloping an ultra-thin fluorocarbon oil layer with omniphobic property in between the encapsulant phase and the photocurable oil phase to achieve high loading efficiency of a broad range of polar and non-polar cargoes in a single platform. In addition, we polymerize the photocurable oil in these triple emulsion drops to form microcapsules, providing highly efficient encapsulation and retention of small molecules and active biomolecules. Furthermore, the strategies outlined in this work can be applied to other existing microcapsule systems to impart functionality; smart microcapsules that disintegrate upon external stimuli such as pH, temperature, and solvent can be modified to achieve significantly reduced permeability to practical actives by introducing a thin layer of fluorocarbon oil within the capsule shell. Also, introducing this omniphobic fluorocarbon oil layer enables simultaneous incorporation of hydrophilic and hydrophobic actives within the microcapsules. Such capsules may therefore prove useful for its versatility in multi-component drug delivery systems as well as applications that require encapsulation of complex fluid mixtures such as fragrances. Moreover, fluorocarbon oils are chemically inert, making them useful for encapsulation of reactive agents that easily deteriorate with time. We also expect this strategy of utilizing multiple emulsion drops, in which the physicochemical properties of each constituent phase can be precisely and quantitatively controlled through modulation of the interfacial tensions, to benefit even broader range of encapsulation applications requiring multiple functionalities in a single platform that was previously impossible to achieve.

Supporting Information

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

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