Rational design and controllable fabrication of microparticles with tailored structures and functions via regulating meso-scale structures of droplet templates

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ABSTRACT

The hierarchical design of meso-scale structures based on integration of functional components like amphiphilic molecules, nanoparticles, and monomers in the interior and at the interface of droplet templates determines the integrated structures and functions of resultant microparticles. This review summarizes recent progress on the control of microfluidic emulsion templates for the synthesis of polymeric microparticles with advanced control over the desired functionality and internal structure. The strategies for the control of morphology and interfacial stability of emulsion templates by manipulating the meso-scale structures of interfacial amphiphilic molecules and nanoparticles for microparticle synthesis are first introduced. Then, the strategies for rational control of meso-scale structures of microparticles via manipulating the interfacial mass-transfer and reaction during the template synthesis are discussed. These strategies provide new opportunities for rational design and controllable fabrication of brand-new polymeric microparticles with predictable internal structures and functionality at a single particle level from emulsion droplet templates.

Keywords: Functional Microparticles; Emulsion droplets; Meso-scale structures; Microfluidics; Template synthesis

1. Introduction

Polymeric microparticles with specific structures and advanced functions (Wang, Zhang, & Chu, 2014) are widely used in myriad fields, such as drug delivery systems, microreactors, and diagnostic imaging agents (Canelas, Herlihy, & DeSimone, 2009; Edwards, et al., 1997; Kreft, Prevot, Möhwald, & Sukhorukov, 2007; Liu, Jin, & Ma, 2011; Yang, Zhang, Lan, & Zhang, 2010).   The meso-scale structures formed by integration of functional components such as amphiphilic molecules, nanoparticles, or functional monomers in the interior and at the interface of microparticles largely determine the macroscopic structures and integrated functions of the microparticles. Generally, polymeric microparticles can be fabricated by methods such as precipitation polymerization (De La Vega, Elischer, Schneider, & Häfeli, 2013; Sambe, Hoshina, Moaddel, Wainer, & Haginaka, 2006), and dispersion polymerization (Du & He, 2008; Xie, Zhang, Luo, Wu, & Li, 2003).   However, although these methods can create microparticles with uniform size, they still suffer from limited control of the spatial combination of functional components inside the microparticles for structure and function design.   Emulsion droplets with phase-separated morphologies provide excellent templates for synthesis of polymeric microparticles with advanced structures and functions (Choi, Weitz, & Lee, 2013; Deng, Mou, et al., 2014; Deng, Wang, et al., 2013; Zhao & Middelberg, 2009).   The separated phases and the interfaces between the phases can be used to incorporate different functional components for tailoring the meso-scale structures.   By controlling the spatial localization of each phase within the emulsion droplets, the meso-scale structures and functions of the functional components can be integrated for creating polymeric microparticles with diverse structures and advanced functions.   Compared with other techniques, such as membrane emulsification (Liu, Yang, & Ho, 2011; Piacentini, Drioli, & Giorno, 2014)

for emulsion generation, microfluidic techniques provide unique control on multiple microflows for engineering emulsion droplets with precise, controllable size, structure and composition (Chu, Utada, Shah, Kim, & Weitz, 2007; Shah, et al., 2008; Stone, Stroock, & Ajdari, 2004; Utada, et al., 2005; Whitesides, 2006). Multiple liquid phases containing different functional components such as functional molecules, polymers, cells, and nanoparticles can be precisely manipulated with microfluidics for creating multiple emulsions. These liquid phases can be accurately and spatially engineered inside single droplet entity to create hierarchically structured emulsion droplets. Their hierarchical structures offer flexible spatial combination and integration of the functional components for template synthesis of advanced functional microparticles via chemical/physical processes inside the liquid phase or at the interface. By precisely controlling the composition of each phase, it allows manipulation of the interfacial energies as well as the meso-scale structures of interfacial amphiphilic molecules. This leads to controllable evolution of spherical droplets into more diverse non-spherical droplets for template synthesis of functional microparticles (Deng, Wang, et al., 2013; Kim, Abbaspourrad, & Weitz, 2011; Lee, et al., 2012; Nisisako & Torii, 2007; Shum, Kim, & Weitz, 2008; Shum, Zhao, Kim, & Weitz, 2011; Wang, Zhang, Xie, et al., 2013; Yu, Wang, Ling, Chen, & Chen, 2012). Moreover, precise control of the phase compositions enables manipulation of the mass-transfer across the interfaces and reaction process at the interfaces for further controlling the meso-scale structures of the resultant microparticles (Deng, Wang, et al., 2013; Kim, et al., 2011; Lee, et al., 2012; Mou, et al., 2018; Nisisako & Torii, 2007; Shum, et al., 2008; Shum, et al., 2011; Wang, Zhang, Xie, et al., 2013; Yu, et al., 2012). Therefore, precise control of the meso-scale structures of functional components is crucial for design and fabrication of brand-new microparticles with advanced structures and functions.

In this review, recent progresses on control of the meso-scale structures of emulsion droplets from microfluidics for template synthesis of functional polymeric microparticles are highlighted. First, based on manipulation of the meso-scale structures of interfacial amphiphilic molecules and nanoparticles, the strategy for controlling the morphology and interfacial stability of emulsion droplets for microparticle synthesis are introduced. Then, based on manipulation of the interfacial mass-transfer and reaction during the template synthesis, the strategies for rational control of the meso-scale structures of microparticles are presented. These researches provide scientific guidelines for rational design and template synthesis of polymeric microparticles with tailored structures and functions from emulsion droplets.

2. Control of Meso-Scale Structures of Interfacial Amphiphilic Molecules for Regulation of Emulsion Morphology

When two immiscible liquid phases form an emulsion droplet system, amphiphilic surfactant molecules are arranged on the droplet surface to reduce the interfacial energy, thereby stabilizing the interfaces to create spherical droplets. When three immiscible liquid phases are involved for emulsion generation, droplets with more diverse morphologies can be formed. By regulating the interfacial energy between every two liquid phases in the three-phase system, the meso-scale structures of interfacial amphiphilic molecules can be well-manipulated to control the emulsion morphology (Deng, Wang, et al., 2013; Kim, et al., 2011; Lee, et al., 2012; Shum, et al., 2008; Shum, et al., 2011; Wang, Zhang, Xie, et al., 2013; Yu, et al., 2012). Based on this strategy for controlling meso-scale structure and the capability of microfluidics for generating

diverse emulsions, emulsion droplets with different morphologies can be developed for microparticle synthesis (Nisisako & Torii, 2007).   Kim et al (2011) separately co-flowed two immiscible oil phases in the two microchannels of a θ-shaped capillary in microfluidic device, which were then sheared by continuous water phase, to generate uniform Janus two-phase droplets for microparticle fabrication (Fig. 1a).   One oil phase was fluorocarbon oil (FC-77), while the other one was photo-curable monomer ethoxylated trimethylolpropane triacrylate (ETPTA).   By carefully changing the type and concentration of surfactants for interfacial energy manipulation, the meso-scale structures of amphiphilic molecules arranged at the droplet interfaces changed for controllable evolution of the two-phase droplets into core-shell morphology or acorn-like morphology.   In the microfluidic device, when the two oil phases were forced into contact by the shear of continuous aqueous phase at the end of θ-shaped capillary, the ETPTA phase immediately spread on the surface of FC-77 droplet.   This reduced the interfacial area with high surface tension between FC-77 and water, and formed a two-phase droplet.   The droplets finally evolved into a morphology with lowest interfacial energy.   This evolved morphology depended on the combination of three interfacial tensions in the three-phase systems.   Such a combination can be described by a spreading parameter, S ($S_i = \gamma_{jk} - (\gamma_{ij} + \gamma_{ik})$), where γ_{ij}, γ_{ik}, and $\gamma_{i=jk}$ were the interfacial tensions between fluids i and j, fluids i and k, and fluids j and k, respectively.   For example, for water phase with 3 wt% poly(vinyl alcohol) (PVA), $S_{ETPTA} > 0$, thus the FC-77 preferred to be wetted by ETPTA instead of water due to the reduced interfacial energy, resulting in two-phase droplets with core-shell morphology (Fig. 1b).   By contrast, for water phase with 1 wt% Pluronic F-108, $S_{ETPTA} < 0$, thus ETPTA dewetted on the surface of FC-77 and formed an acorn-like droplet (Fig. 1c,d).   Such an acorn-like morphology was further tuned by the balance of the three interfacial tensions at the

three-phase contact line (Fig. 1c). Upon UV-induced polymerization of the curable ETPTA part, microparticles with crescent-moon shape were formed. Based on the excellent flow manipulation by microfluidics, the size and shape of the microparticles were further tailored by precisely manipulating the volumetric flow rates of ETPTA (V_1) and FC-77 (V_2) (Fig. 1e and 1f). Similarly, Yu et al (2012) generated two-phase droplets, consisting of aqueous suspension of monodisperse polystyrene (PS) nanoparticless and photo-curable trimethylolpropane ethoxylate triacrylate (EO_3-TMPTA), in methylsilicone oil. By varying the surfactant concentration in the continuous oil phase, the combination of three interfacial tensions in the three-phase system was manipulated for control of the droplet morphology (Fig. 1g). After UV-polymerization, microparticles with different non-spherical shapes, similar to those of their droplet templates, were fabricated.

Besides the interfacial-energy-induced dewetting process, a wetting process induced by the interfacial energy can also be used to control the meso-scale structure of interfacial amphiphilic molecules for regulation of emulsion morphology. Deng et al (2013) generated two types of immiscible droplets (A and B) in microchannels for regulating the emulsion morphology via a interfacial-energy-induced wetting process. As shown in Fig. 2a, when $S_A = \gamma_{BC} - (\gamma_{AC} + \gamma_{AB}) > 0$, droplet A completely wetted on droplet B, with the B/C interface replaced by A/B interface, to create a B/A/C emulsion droplet (Fig. 2a3). By contrast, when $S_B = \gamma_{AC} - (\gamma_{AB} + \gamma_{BC}) > 0$, droplet B could completely wet on droplet A, with the A/C interface replaced by A/B interface, to create an A/B/C emulsion droplet (Fig. 2a4). As shown in Fig. 2b-e, when two different types of droplets were alternatively generated in the microchannels, they contacted with each other in the expanded chamber, and formed double emulsion droplets depending on the combination of interfacial energies among the three phases.

For $S_{A1} > 0$, droplet A1 completely engulfed droplet B, forming a B/A1/C emulsion droplet (Fig. 2b,d).   For $S_B > 0$, droplet B completely engulfed droplet A2 to create an A2/B/C emulsion droplet (Fig. 2c,e).   By controlling the volume of the droplet that wetted on another droplet, the shell thickness of the double emulsions was precisely manipulated in the range from nanometer-scale to micrometer-scale.   This allowed template synthesis of core-shell microparticles with shell of precisely-determined thickness.   Moreover, the wetting process was further applied for the engulfing between single emulsion droplets and multiple emulsion droplets.   This produced more diverse and hierarchical emulsion droplets for microparticle fabrication.

Alternatively, this interfacial-energy-based strategy can also be used to control the meso-scale structures of amphiphilic molecules at the interfaces of core-shell two-phase droplets for regulation of emulsion morphology.   For example, Lee et al (2012) generated W/O/W emulsion droplets with middle chloroform/toluene layer containing poly(D,L-lactic-co-glycolic) acid (PLGA) for interfacial stabilization and microparticle fabrication.   The chloroform in the middle oil layer was a good solvent for both the lactide and glycolide, while the toluene was a good solvent for lactide but a poor solvent for glycolide.   Upon evaporation of the chloroform, the quality of solvent in the oil phase became poor for the PLGA.   Thus, the PLGA at the two W/O interfaces preferred contacting with each other, instead of contacting with the poor solvent toluene. This produced an adhesion energy between the two W/O interfaces (Poulin & Bibette, 1999; Poulin, Essafi, & Bibette, 1999), and led to protrusion of the inner water droplet out of the middle oil layer (Fig. 3a).   Such a protrusion process led to self-assembly of PLGA molecules on the surface of inner droplets, and evolution of the W/O/W emulsion droplets from a core-shell morphology to an acorn-shaped morphology. Further evaporation of the chloroform in the oil phase resulted in hollow PLGA

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microparticles.   Similarly, Shum et al (Shum, et al., 2008) generated W/O/W emulsion droplets from microfluidics, with middle oil phase containing amphiphilic diblock copolymers poly-(ethylene glycol)-b-poly(lactic acid) (PEG(5000)-b-PLA-(5000)), a volatile good solvent and a less volatile poor solvent for the copolymers.   As the good solvent quickly evaporated, the copolymers at the W/O and the O/W interfaces were attracted towards each other, to form a copolymer bilayer (Fig. 3b,c).   Thus, the inner water droplet separated from the middle oil layer, resulting in a water droplet with copolymers self-assembled at the interface to form a bilayer membrane.   By precisely controlling the number of inner water droplets in the middle oil layer, the multiple inner water droplets adhered to each other due to the formation of self-assembled copolymer bilayers at the interface between every two droplets.   After further dewetting, polymersomes containing multiple droplets with controlled number, connected by copolymer bilayers were fabricated (Fig. 3d,e) (Shum, et al., 2011).

Wang et al (2013) accurately controlled the evolved morphology of W/O/W emulsion droplets via manipulation of the interfacial energies as well as the meso-scale structures of interfacial amphiphilic molecules.   Briefly, a mixture of benzyl benzoate and photocurable ETPTA, with surfactant polyglycerol polyricinoleate (PGPR), was used as middle oil phase for generating core-shell W/O/W emulsion droplets.   The poor solubility of ETPTA for PGPR reduced the solvent quality and led to adhesion of the PGPR layer at the inner W/O interface with the one at the outer W/O interface.   This process also resulted in formation of a bilayer film consisting of PGPR between the inner and outer water phases, and evolution of the W/O/W emulsion droplets into an acorn-shaped morphology (Fig. 4a).   This process was driven by an adhesion energy, $\Delta F = \gamma_{IM} + \gamma_{MO} - \gamma_{Film}$, where γ_{IM} and γ_{MO} were respectively the interfacial tensions of the inner and outer W/O interfaces, and γ_{Film} was the tension of the bilayer film.   By

controlling the volume fraction of ETPTA and benzyl benzoate in the oil phase, the adhesion energy ΔF was adjusted to make double emulsions evolving from a core-shell structure to desired acorn-shaped configurations (Fig. 4b-c). The controllably evolved acorn-shaped emulsion droplets were then used as templates for fabrication of hole-shell microparticles with versatile structures (Fig. 4d).

3. Control of Meso-Scale Structures of Interfacial Amphiphilic Molecules and Nanoparticles for Regulation of Emulsion Stability

The interface of emulsion droplets can be stabilized by amphiphilic molecules or nanoparticles. By regulating the assembling structure of amphiphilic molecules and nanoparticles at the interfaces, the interfacial stability of the emulsion droplets can be manipulated. This can provide emulsion droplets with stabilized interfaces for template synthesis of microparticles with shell consisting of amphiphilic molecules and nanoparticles, and coalesced droplets due to unstabilized interfaces for microparticles fabrication. The nanoparticles or amphiphilic molecules at the emulsion interfaces can be remained in the microparticles after template synthesis and used for tailoring the structures and interfacial functionalities of microparticles. For example, Lee & Weitz (2008) generated W/O/W emulsion droplets in microfluidic device, with middle oil phase containing volatile toluene/chloroform mixture and SiO_2 nanoparticles. The emulsion droplets were stably generated without the use of amphiphilic surfactants, since the interfaces were well-stabilized by SiO_2 nanoparticles. These SiO_2 nanoparticles at the interfaces and in the oil phase were further assembled into microparticles with shell consisting of assembled SiO_2 nanoparticles by evaporating the

volatile toluene/chloroform mixture (Fig. 5a-c).   However, for interfaces between water phases, use of nanoparticles for the interfacial stabilization usually remains difficult, due to their ultralow interfacial tensions.   Instead of nanoparticles, Song et al (2016) used protein nanofibrils to stabilize the W/W interfaces of all-aqueous emulsion droplets.   Due to the strong interface affinity and the high aspect ratio, the protein fibrils provided higher surface coverage on the interfaces for stabilization, as compared to spherical colloids.   The protein-fibril-stabilized droplets were further used for fabrication of microparticles with shell consisting of assembled protein fibrils (Fig. 5d-g).

Besides the stabilization of droplet interfaces, destabilization of the droplet interfaces can also be achieved by regulating the assembled structures of nanoparticles and amphiphilic molecules at the interfaces.   Such an interfacial destabilization enables controlled coalescence between two droplets, which can be used for triggered microreaction for microparticle synthesis.   Sun et al (2016) generated O/W emulsion droplets in microfluidic device, with thermo-responsive poly(N-isopropylacrylamide) (PNIPAM) nanoparticles covered at the droplet interfaces for stabilization (Fig. 6a). Upon temperature change, the wettability and volume of the PNIPAM nanoparticles were adjusted.   This controlled the meso-scale structures of PNIPAM nanoparticles aggregated at the droplet interfaces.   As shown in Fig. 6b and 6c, at 25 °C, below the volume phase transition temperature (VPTT) of PNIPAM (~32 °C), the PNIPAM nanoparticles in hydrophilic and swollen state were densely packed at the droplet interface for stabilization (Fig. 6b1, 6c1).   By increasing the temperature to 40 °C, higher than the VPTT, the PNIPAM nanogels became hydrophobic and shrunken, thus leading to aggregation of the PNIPAM nanogels and exposure of the droplet surface for destabilization (Fig. 6b2, 6c2).   When two droplets were brought into contact, such an

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exposure of the droplet surface led to coalescence of the two droplets (Fig. 6d1-d2). Based on this, continuous one-to-one coalescence of emulsion droplets stabilized with PNIPAM nanogels were achieved upon a thermo-triggering mechanism in the expanded chamber of microfluidic device (Fig. 6a).

The destabilization of interfaces stabilized by amphiphilic molecules can be achieved based on the wetting of a metal micro-lancet (Deng, Sun, et al., 2013). As shown in Fig. 7a and 7b, when pairs of emulsion droplets flowed across the metal micro-lancet, the droplet surfaces were wetted by the micro-lancet. This changed the meso-structures of amphiphilic molecules assembled at the interface for destabilization. Thus, controllable coalescence of the two droplets was achieved at the tip of the micro-lancet to minimize the total interfacial energies (Fig. 7c). Such a strategy was further applied for the coalescence of emulsion droplets with more diverse structures (Fig. 7d). Moreover, destabilization of the droplet interface can also be achieved by forcing two droplets into close contact via the interfacial-energy-based engulfing strategy. For example, as shown in Fig. 8a, the middle phase layer of a double emulsion droplet was used as a wetting layer to engulf another droplet (Deng, Sun, et al., 2014). When a double emulsion droplet, containing droplet B surrounded with a wetting layer A, contacted with the other droplet C, the wetting layer A preferentially wetted on droplet C as compared to the continuous fluid D. Thus, droplets B and C were engulfed by one wetting layer A. When the liquid phase between the two droplets was drained out, coalescence of the two closely contacted droplets was achieved (Fig. 8b,8c). Such controllable droplet coalescence can be used to trigger microreatcions for synthesis of microparticles (Deng, Sun, et al., 2014).

4. Manipulation of Mass-Transfer and Reaction at/across

Droplet Interfaces for Control of Meso-Scale Structures of Microparticles

The emulsion droplets with diverse structures provide advanced templates for synthesis of polymeric functional microparticles. Elaborate manipulation of the interfacial mass transfer and interfacial reaction during the template synthesis allows rational design and control of meso-scale structures of the resultant microparticles.

By controlling the transfer process of functional molecules based on the affinity partitioning in aqueous two-phase system, the meso-scale structures can be manipulated to produce microparticles with solid and hollow structures from water droplets (Ma, Song, Kim, Choi, & Shum, 2016). As shown in Fig. 9a, the partitioning coefficients of poly(allylamine hydrochloride) (PAH) and poly(sodium-4-styrenesulfonate) (PSS) in aqueous two-phase system were controlled by pH adjustment. Thus, the interfacial mass transfer as well as the distribution of PAH and PSS in the aqueous two-phase system containing water droplets were well manipulated for constructing microparticles with different structures. For example, when the polycations PAH in the water droplets and the polyanions PSS in the continuous water phase both transferred to the droplet interfaces, PAH and PSS assembled at the interfaces to form hollow microparticles with polyelectrolyte shell (Fig. 9a1,b). When only the PAH in continuous water phase transferred into the water droplets, complexation of PSS and PAH occurred inside the droplets to form solid polyelectrolyte microparticles (Fig. 9a2,c). These polyelectrolyte microparticles can be used for encapsulation and controlled release.

The mass transfer process during template synthesis can also influence the meso-scale structures on the surface of the resultant microparticles. For example, microparticles with wrinkled microstructures on their surface were fabricated from

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O/W emulsion droplets with mass transfer well manipulated (Liu, Deng, Li, & Zhu, 2012). As shown in Fig. 10a, O/W emulsion droplets containing chloroform, n-hexadecanol (HD) and polystyrene (PS) were generated from microfluidics as templates. The continuous aqueous phase contained sodium dodecyl sulfate (SDS) for stabilizing the droplets against coalescence. When chloroform diffused through the aqueous phase for evaporation, the interfacial tension decreased due to the increased HD concentration. Change of the height (h) of water phase in the container and the concentration of HD in the droplets allowed control of the diffusion process. The HD molecules moved to the droplet interface and interpenetrated to the interfacial SDS monolayer. This led to rearrangement of SDS molecules and reduced interfacial tension, which drove the interfacial roughening of the shrinking droplets. Fig. 10b shows the time-dependent evolution of the emulsion droplet into the PS microparticle during removal of chloroform at h=0.5 mm. Within ~ 1 min, the droplet first shrank due to chloroform removal, and then became PS microparticle with wrinkled surface. The degrees of wrinkles on the particles were further tuned by simply adjusting the HD concentration for regulating the mass transfer (Fig. 10c). These highly uniform dendritic microparticles can be potentially useful in drug delivery, catalysis, coating, cosmetics, and tissue engineering.

Moreover, by controlling the mass transfer process in double emulsion droplets for controllable evolution, the meso-scale structures of the resultant microparticles can be manipulated. By using W/O/W emulsions as templates, microparticles with highly interconnected hierarchical porous structures and controllable shapes were created via manipulation of interfacial mass transfer between the oil and aqueous phases and the reaction in the oil phase (Zhang, et al., 2015). As shown in Fig. 11a, the W/O/W emulsion droplets with methyl methacrylate, ethylene glycol dimethacrylate, and

surfactants as the middle oil phase, were generated from microfluidics for microparticle fabrication.   Based on the partially miscible property of the oil and water phases, the volume of middle oil phase decreased due to the mass transfer between oil and water phases.   This led to controllable deformation of the emulsion droplets into desired shapes depending on the packing structures of their inner water droplets (Fig. 11b). Meanwhile, the water molecules that diffused into the oil phase were stabilized by the excess surfactants to form water nanodroplets (Fig. 11e,f).   After UV-polymerization, microparticles with highly-interconnected hierarchical porous structures and controllable shapes were synthesized, with their micrometer-sized pores and nanometer-sized pores respectively templated from the inner water droplets and water nanodroplets (Fig. 11c,d,g).   Simply adjustment of the size, structure and composition of emulsion templates enabled individual and flexible manipulation of the pore size, porosity, functionality, and shape of the microparticles (Fig. 11h,i).   The microparticles that combined the enhanced mass transfer of micropores and large functional surface area of nanopores, allowed enhanced performances for oil removal and protein adsorption.   Besides control of the droplet morphology, fine control of the mass transfer process also allows manipulation of the interfacial stability for efficient conversion of droplet templates to microparticles.   For example, by using high concentration of Ca^{2+} in collection solution for crosslinking, fast mass transfer was achieved in θ-shaped droplets containing all aqueous phases for constructing multicompartmental calcium alginate microparticles (He, et al., 2016) (Fig. 12a,b). The fast mass transfer of Ca^{2+} into the alginate-containing phase quickly crosslinked the alginate; this avoided the mixing of contents in the two inner droplets, due to the unstable interface between water phases, for efficient conversion of the θ-shaped droplets into Ca-alginate microparticles with θ-shaped multicompartments.   Such a

strategy was also used for fabrication of Ca-alginate microparticles with more complex multicompartments (Fig. 12c). Moreover, by adjusting the viscosity, density and composition of each phase of O/W/O/W/O quadruple emulsions, the mass transfer and interfacial stability during the template synthesis process were manipulated to ensure efficient fabrication of Trojan-horse-like multicompartmental microparticles (Mou, et al., 2018) (Fig. 12d-i). These multicompartmental microparticles allowed synergistic co-encapsulation of distinct actives and diverse combination of release mechanisms for drug delivery and confined microreaction.

5. Conclusion and Outlook

In summary, this review highlights the strategies on control of the meso-scale structures in emulsion droplets from microfluidics for template synthesis of polymeric microparticles with tailored structures and functions. The droplet morphology can be finely tuned by regulating the assembling structures of surfactants at the interfaces based on interfacial energy manipulation for creating diverse morphologies. Meanwhile, emulsion droplets with diverse morphologies can also be created from coalescence of two droplets, by destroying the original assembling structures of surfactants and nanoparticles at interfaces via wetting phenomenon and volume phase transitions of the nanoparticles. These emulsion droplets benefit the template synthesis of versatile polymeric functional microparticles. Moreover, control of the mass transfer during the template synthesis enables manipulation of the interfacial reactions and the meso-scale structures for creating microparticles with flexible surfaces and interior structures. These strategies based on the control of meso-scale structures in emulsion droplet systems creates new opportunities for rational design and controllable fabrication of advanced polymeric microparticles. Future research

should focus on the scale-up of microfluidic systems for mass production of emulsion templates for industrial microparticle fabrication. Microfluidic systems based on multiplying the droplet-generating microchannels have been developed for high throughput production of emulsions and microparticles (Ofner, et al., 2017; Yadavali, Jeong, Lee, & Issadore, 2018). Recently, a silicon/glass microfluidic device with an array of 10260 droplet-generators has been developed for generating emulsion droplets at a rate of >1 trillion droplets per hour, and fabricating microparticles at a rate of 277 g per hour (Yadavali, Jeong, Lee, & Issadore, 2018). However, so far most of the microfluidic scale-up strategies are used for producing only single emulsion droplets. Further exploration of robust microfluidic systems for mass production of controllable multiple emulsions can benefit the fabrication of microparticles with more diverse structures and functions.

Acknowledgements

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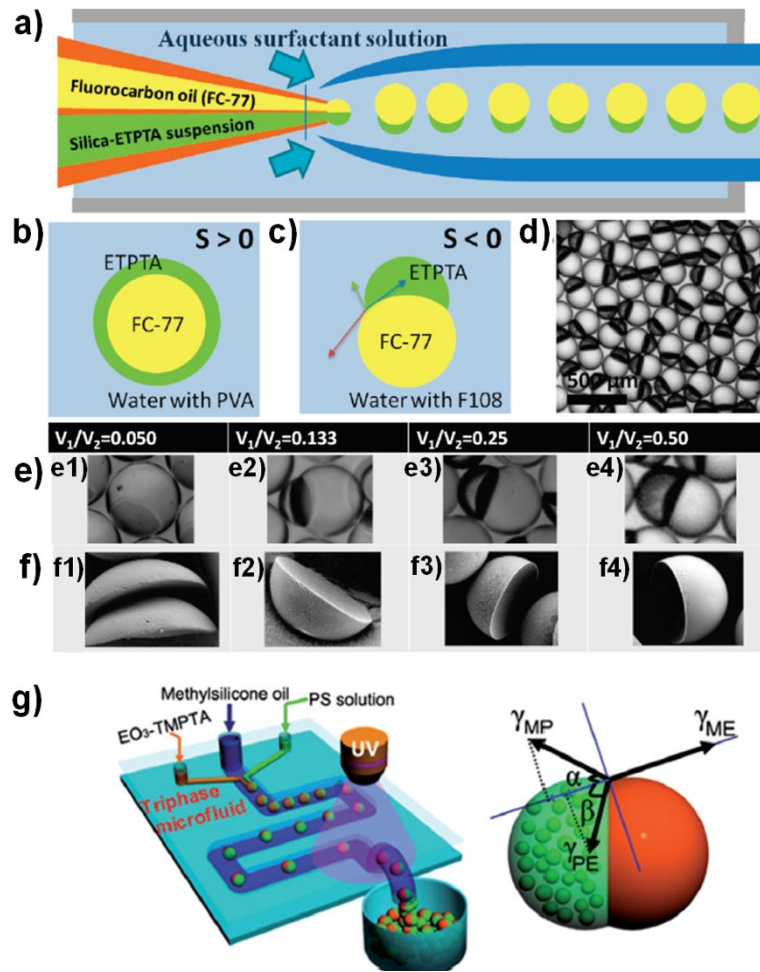
Fig. 1. (a-c) Microfluidic device with a theta (θ)-shaped capillary for generating emulsion droplets (a) with core-shell (b) and acorn-like Janus (c) morphologies depending on the interfacial-energy-based manipulation of interfacial amphiphilic molecules (Kim, et al., 2011). (d-f) Optical micrographs of acorn-like Janus droplets (d,e) with size and shape controlled by adjusting volumetric flow rates of ETPTA (V_1) and FC-77 (V_2), and SEM images of the resultant microparticles (f) (Kim, et al., 2011). (g) Microfluidic generation of Janus droplets with interfacial-energy-dependent morphologies for synthesizing photonic crystal microparticles (Yu, et al., 2012).
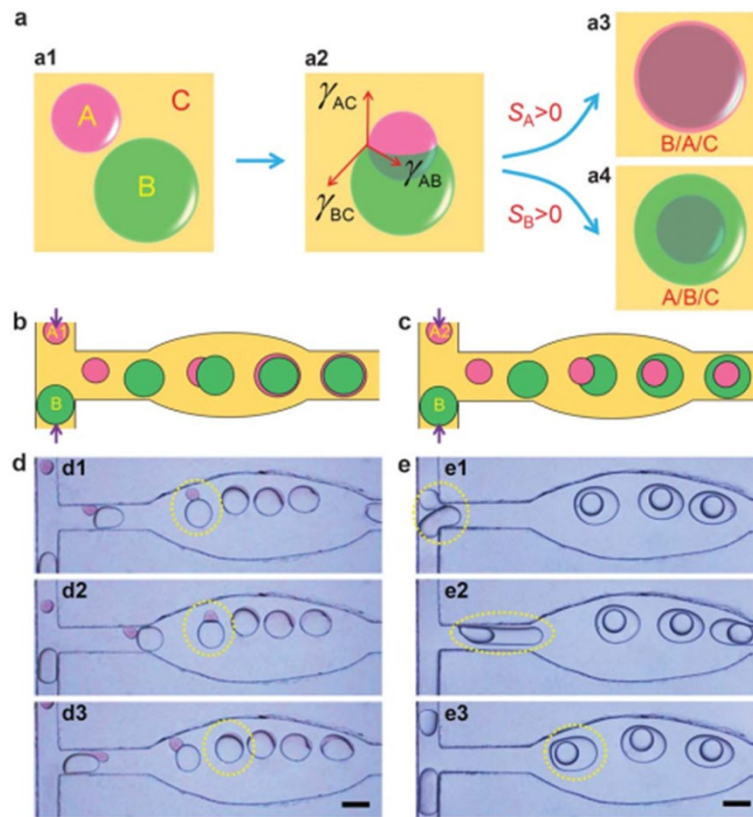
Fig. 2. (a) Interfacial-energy-based regulation of the meso-scale structures of interfacial amphiphilic molecules for formation of double emulsions from wetted droplet pairs. (b-e) Schematic illustrations (b,c) and high-speed snapshots (d,e) showing the formation processes of B/A1/C (b,d) and A2/B/C (c,e) double emulsion droplets via interfacial-energy-dependent droplet wetting (Deng, Wang, et al., 2013).
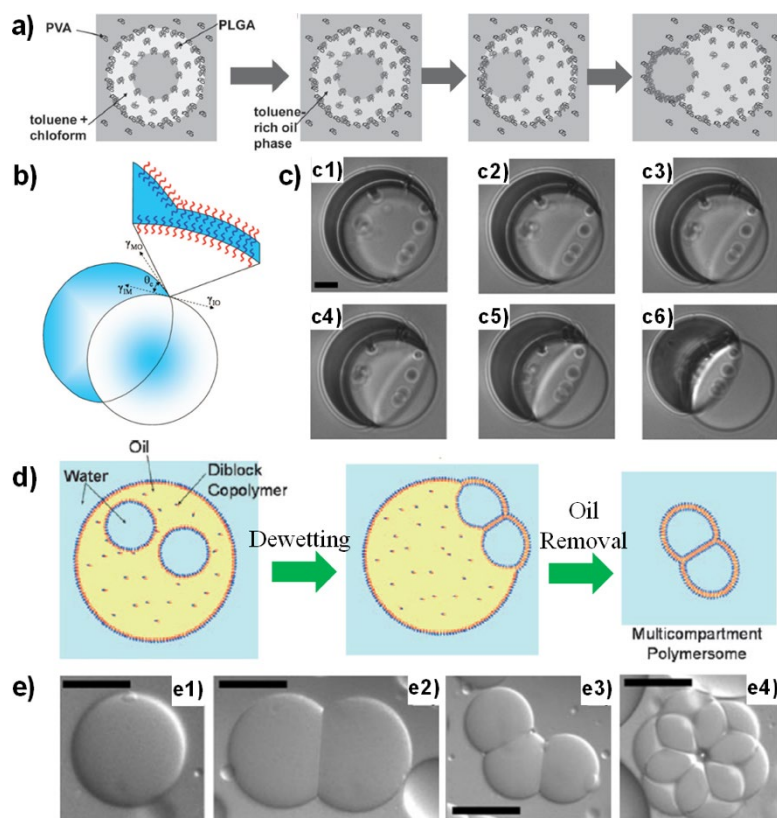
Fig. 3. (a-c) Template synthesis of hollow microparticles with assembled PLGA shell (a) and PEG(5000)-b-PLA-(5000) shell (b,c), from W/O/W emulsion droplets via interfacial-energy-based manipulation of the meso-scale structures of interfacial amphiphilic molecules for emulsion morphology control (a,b) (Lee, et al., 2012; Shum, et al., 2008). (d,e) Interfacial-energy-induced evolution of the multicore-shell W/O/W emulsion templates (d) for fabrication of multicompartmental microparticles with assembled PEG(5000)-b-PLA-(5000) shell (e) (Shum, et al., 2011).
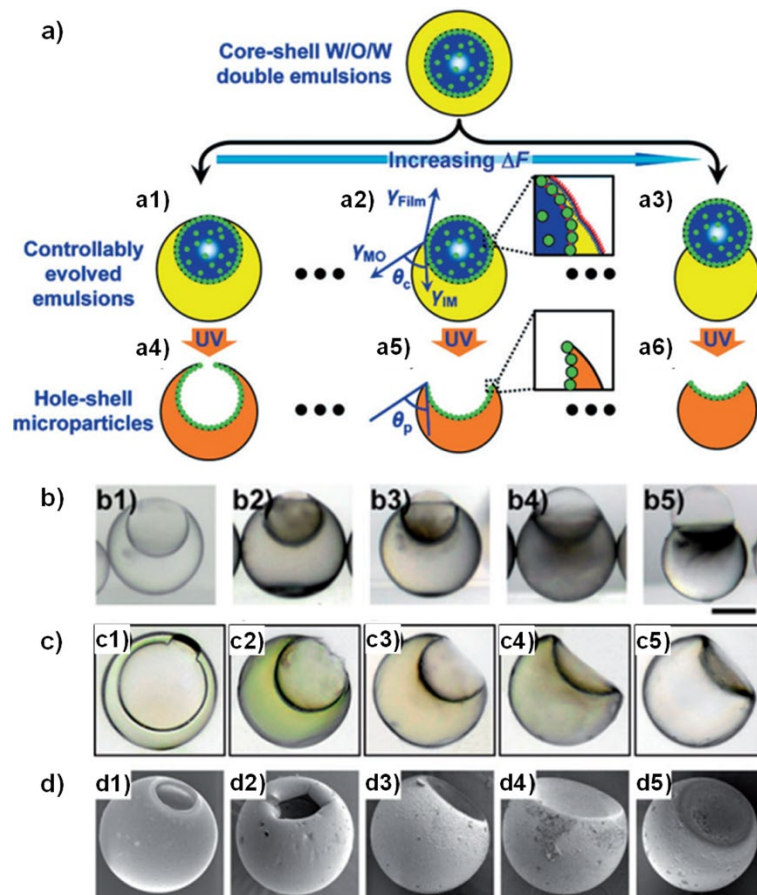
Fig. 4. (a) Template synthesis of hole-shell microparticles from controllably evolved W/O/W emulsion droplets via interfacial-energy-based manipulation of the meso-scale structures of interfacial amphiphilic molecules. (b-d) Optical micrographs (b,c) and SEM images (d) of the controllably evolved emulsion droplets (b) and the resultant hole-shell microparticles (c,d) (Wang, Zhang, Xie, et al., 2013).
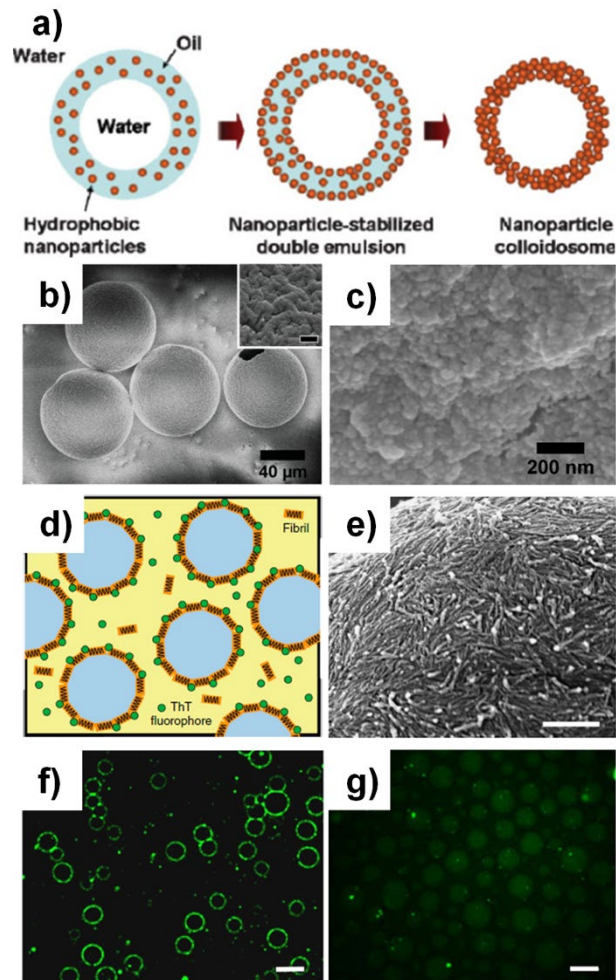
Fig. 5. (a-c) Controllable assembly of nanoparticles in W/O/W emulsion templates (a) for fabricating hollow microparticles (b) with shell consisting of assembled nanoparticles (c) (D. Lee & Weitz, 2008). (d-g) Controllable assembly of ThT-dyed lysozyme fibrils in W/W emulsion templates (d) for fabricating hollow microparticles (f,g) with shell consisting of assembled nanofibrils (e) (Song, et al., 2016).
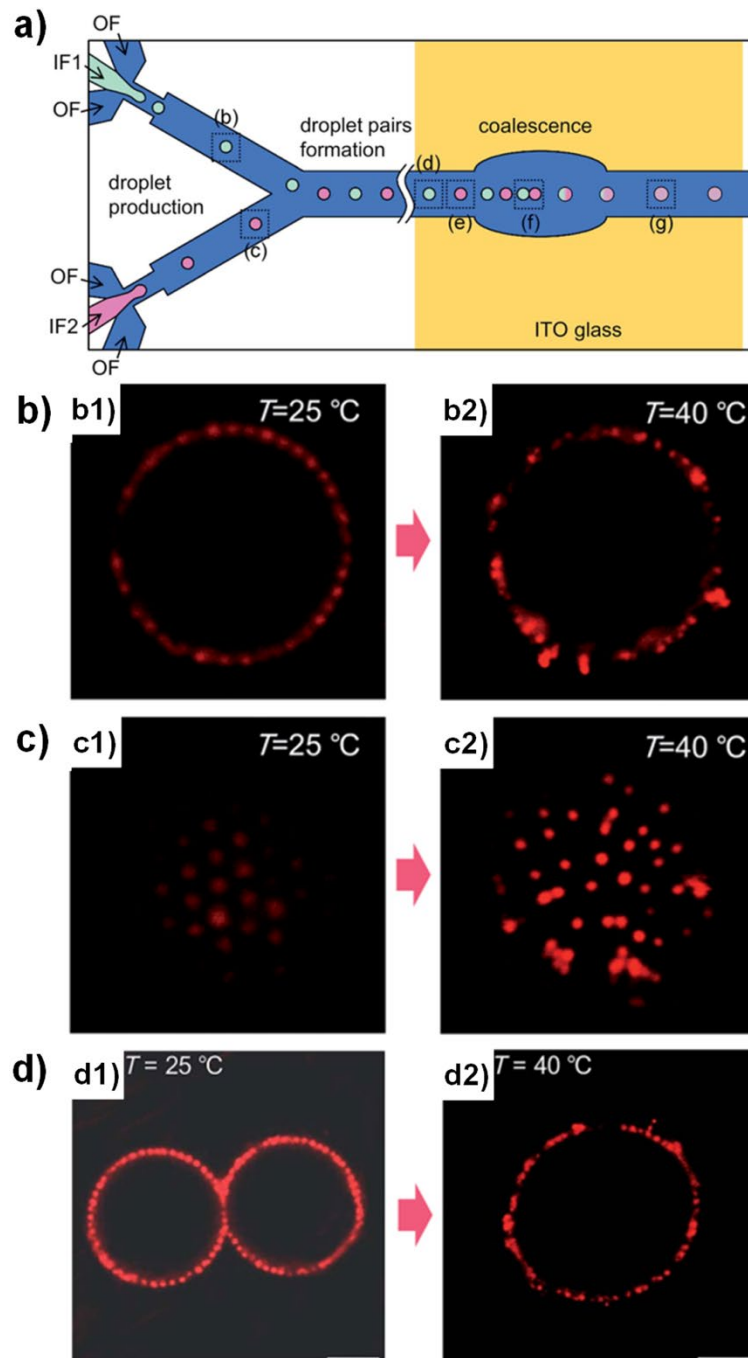
Fig. 6. (a) Schematic illustration showing the thermo-triggered coalescence of PNIPAM-nanoparticle- stabilized emulsion droplet pairs in microchip. (b,c) Assembling structure changes of PNIPAM nanoparticles on the equator (b) and top (c) of a droplet at 25 °C and 40 °C. (d) Assembling structure changes of PNIPAM nanoparticles on the droplet surface before (d1) and after (d2) thermo-triggered coalescence (Sun, et al., 2016).
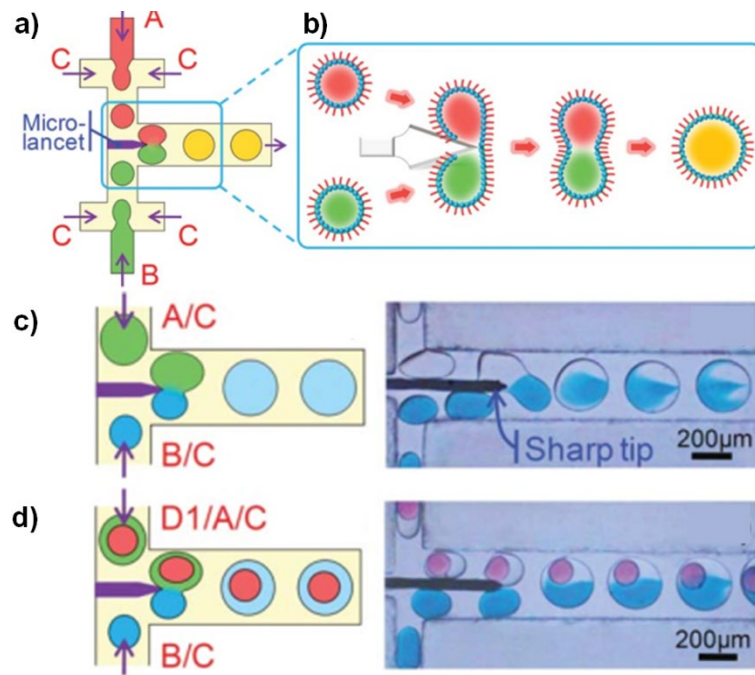
Fig. 7. (a,b) Schematic illustrations showing the controllable coalescence of two droplets in microchip (a) via micro-lancet-induced regulation of assembling structure of interfacial amphiphilic molecules (b). (c,d) Schematic illustration and high-speed snapshot showing the micro-lancet-induced coalescence between two W/O emulsion droplets (c), and between and W/O emulsion droplets and O/W/O emulsion droplets (d) (Deng, Sun, et al., 2013).
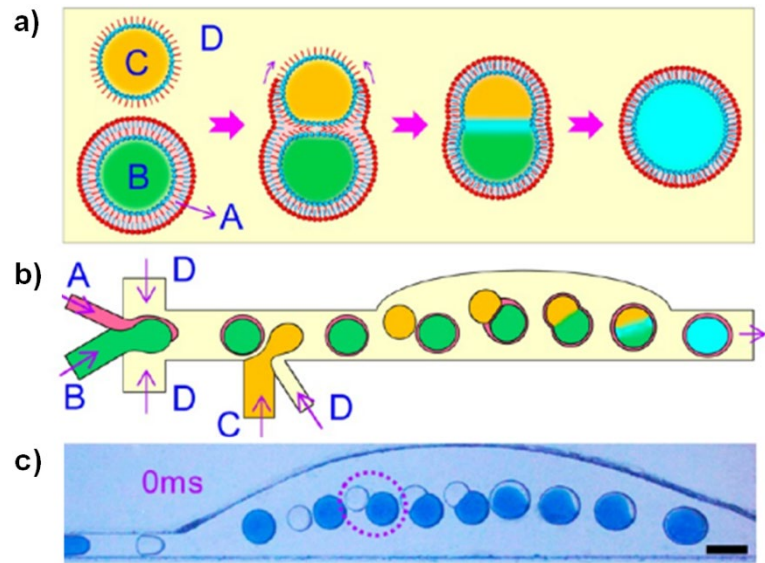
Fig. 8. (a) Schematic illustrations showing the coalescence of two droplets with a wetting liquid layer for regulating the meso-scale structures of interfacial amphiphilic molecules. (b,c) Schematic illustration (b) and high-speed snapshot (c) showing the controllable coalescence of two different droplets in microchip induced by a wetting liquid layer (Deng, Sun, et al., 2014).
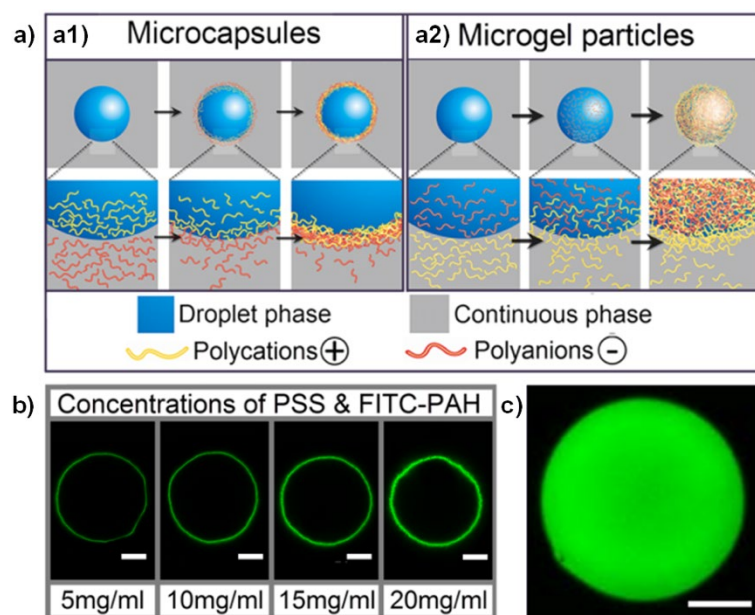
Fig. 9. Droplet-template synthesis of polyelectrolyte microparticles (a) with hollow (a1, b) and solid (a2, c) structures based on the affinity-induced mass transfer of polycations and polyanions in emulsion droplets (Ma, Song, Kim, Choi, & Shum, 2016).
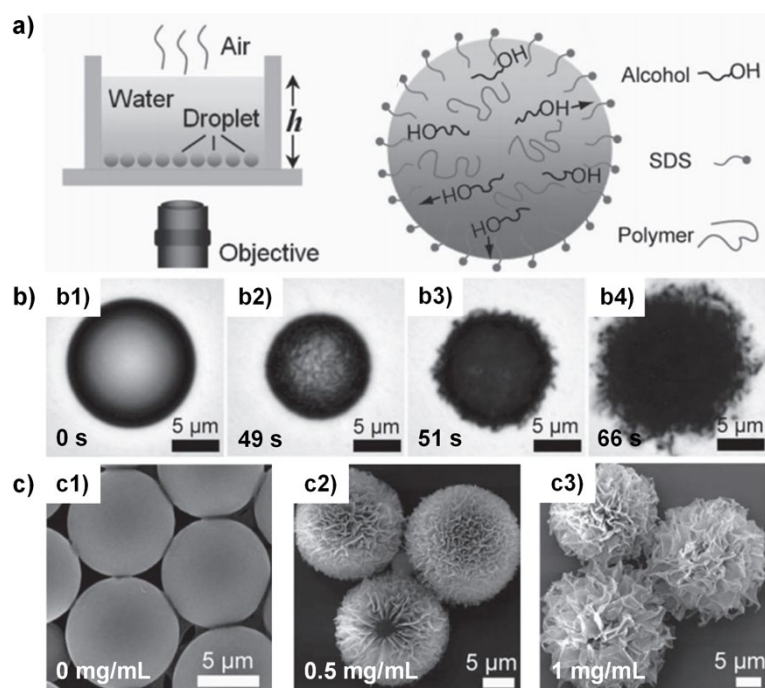
Fig. 10. Template synthesis of controllable PS microparticles with wrinkled surface structures (a) via mass transfer process controlled by height (h) of water phase (b) and HD concentration (c). The h in (b) is 0.5 mm, and the HD concentrations in (c) are 0 (c1), 0.5 (c2), and 1 mg/mL (c3) (S. Liu, Deng, Li, & Zhu, 2012).
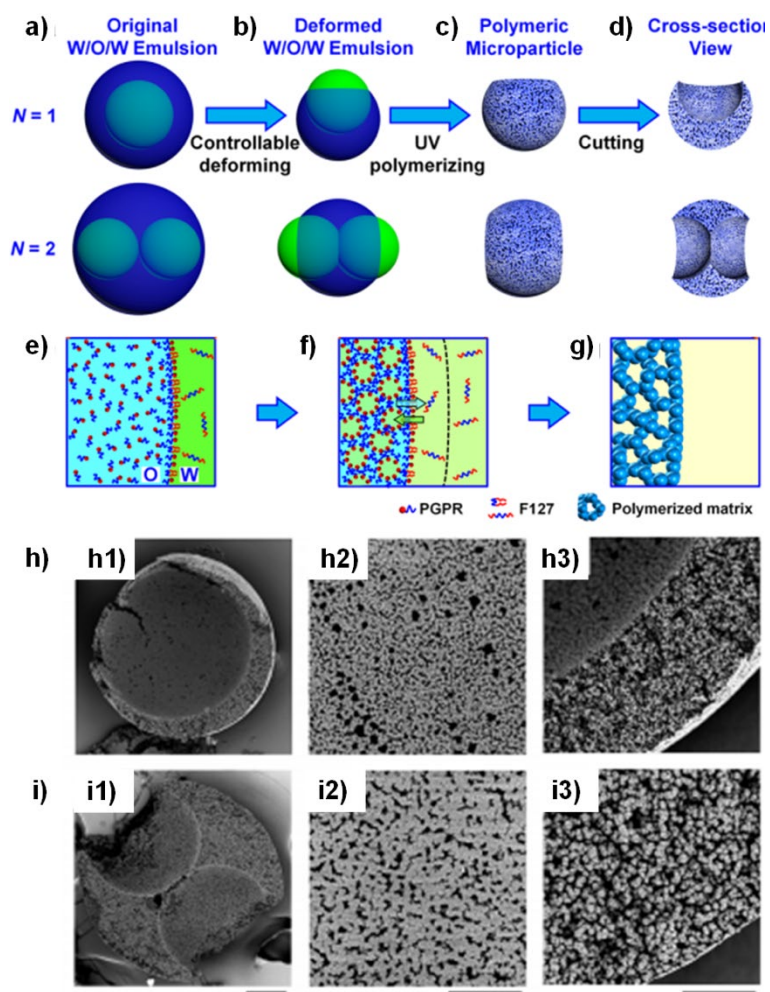
Fig. 11. (a-g) Mass-transfer dependent evolution of double emulsion droplets (a,b) for template synthesis of hierarchical porous microparticles (c,d), with micrometer-sized pores templated from inner droplets and nanometer-sized pores templated from nanodroplets formed during the mass transfer (e-g). (h,i) SEM images of ruptured hierarchical porous microparticles with one (h1) and two (i1) micrometer-sized pores, as well as their magnified outer surfaces (h2,i2) and cross sections (h3,i3) (Zhang, et al., 2015).
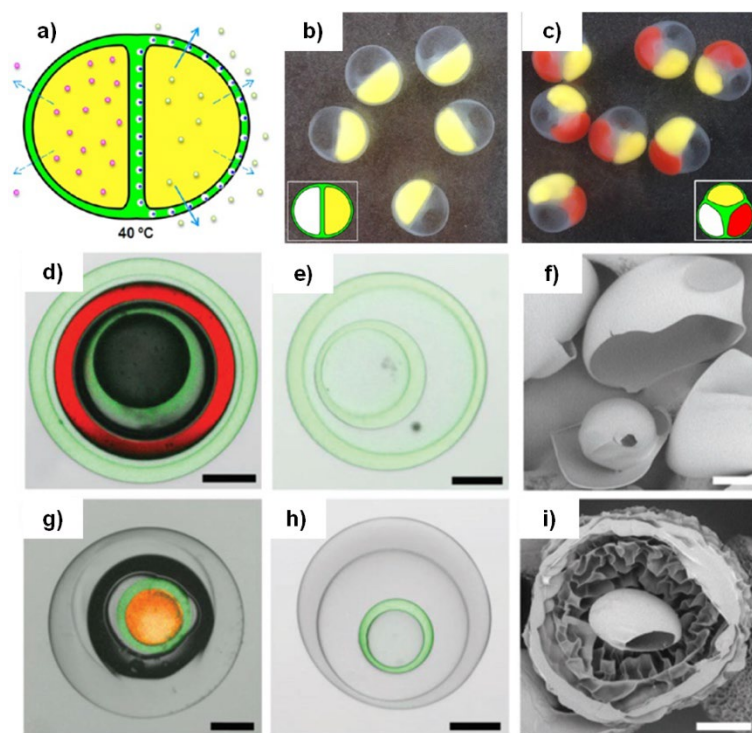
Fig. 12. (a-c) Ca-alginate microparticles with dual (a,b) and ternary (c) compartments synthesized via mass-transfer-dependent rapid crosslinking of double emulsion droplets (a,b) (He, et al., 2016). (d-i) Chitosan@chitosan microparticles (d-f) and chitosan@PNIPAM microparticles (g-i) with capsule-in-capsule structures synthesized from quadruple emulsion droplets via interfacial stability regulation (Mou, et al., 2018).