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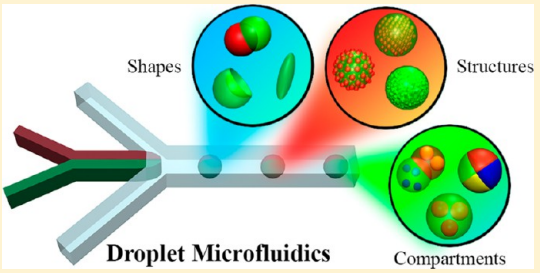
Droplet Microfluidics for Producing Functional Microparticles

Ju Hyeon Kim,[†,‡] Tae Yoon Jeon,[†,‡] Tae Min Choi,[†] Tae Soup Shim,[†,‡] Shin-Hyun Kim,*[,†] and Seung-Man Yang[†,‡,§]

[†]Department of Chemical and Biomolecular Engineering and [‡]National Creative Research Initiative Center for Integrated Optofluidic Systems, KAIST, Daejeon 305-701, South Korea

ABSTRACT: Isotropic microparticles prepared from a suspension that undergoes polymerization have long been used for a variety of applications. Bulk emulsification procedures produce polydisperse emulsion droplets that are transformed into spherical microparticles through chemical or physical consolidation. Recent advances in droplet microfluidics have enabled the production of monodisperse emulsions that yield highly uniform microparticles, albeit only on a drop-by-drop basis. In addition, microfluidic devices have provided a variety of means for particle functionalization through shaping, compartmentalizing, and microstructuring. These functionalized particles have significant potential for practical applications as a new class of colloidal materials. This feature article describes the current state of the art in the microfluidic-based synthesis of monodisperse functional microparticles. The three main sections of this feature article discuss the formation of isotropic microparticles, engineered microparticles, and hybrid microparticles. The complexities of the shape, compartment, and microstructure of these microparticles increase systematically from the isotropic to the hybrid types. Each section discusses the key idea underlying the design of the particles, their functionalities, and their applications. Finally, we outline the current limitations and future perspectives on microfluidic techniques used to produce microparticles.



INTRODUCTION

Colloids and granules are useful for the preparation of a variety of artificial products. Polymeric particulate materials have been prepared using emulsion or dispersion polymerization in a highly controlled manner. Emulsion polymerization, in which monomers are dispersed in an aqueous phase, provides monodisperse particles with a size range of 50−1000 nm. Dispersion polymerization techniques, in which monomers are dissolved in an organic solvent, provide monodisperse particles with a size range of 1−10 μm. Conventional synthesis methods produce spherical particles under interfacial energy minimization constraints. A variety of innovative approaches have been developed to produce nonspherical or chemically patterned particles, thereby opening up new applications of colloidal materials.[1] For example, spherical colloids embedded in a matrix are stretched to produce ellipsoidal particles. Polymerization-induced phase separation in monomer-swollen particles produces snowmanlike particles. Larger microparticles are produced using suspension polymerization techniques or evaporation-induced consolidation. Emulsion droplets containing monomers or polymers are prepared in a dispersion medium that is submitted to bulk shearing forces. The monomers then polymerize or the volatile solvent is evaporated to produce solid microparticles. Although the average microparticle size can be roughly controlled according to the shear rate during the emulsification process, the size distribution is relatively broad compared to the distribution of particles prepared using emulsion or dispersion polymerization methods. Appropriate methods for achieving the functionalization of such large microparticles have not yet been developed.

Microfluidic techniques provide some of the most promising approaches to producing and functionalize monodisperse microparticles.[2,3] Microfluidic emulsification techniques have enabled the preparation of highly uniform droplets with a wide range of sizes from a few hundred nanometers to a few millimeters. The consolidation mechanism used in suspension polymerization methods is applied to prepare monodisperse spherical microparticles directly from the droplet templates. The microparticles are further functionalized by employing creative strategies in droplet microfluidics. Such steps are difficult to achieve using conventional suspension polymerization methods. Figure 1 provides a schematic illustration of the various types of microparticles that can be prepared using droplet microfluidics. Three distinct aspects of the microparticles are controllable, including the shape, compartment, and microstructure. Two or all three of these aspects can be simultaneously tuned to design microparticles having advanced functionalities. This feature article reviews and discusses the key contributions to this field of droplet microfluidics for the design and synthesis of microparticles over the past few years; more general approaches to microparticle synthesis with novel techniques are reviewed in previous papers.[2,3] We first introduce the microfluidic techniques used to produce isotropic microparticles, including the effects of droplet type and consolidation method. We then discuss methods for engineering the microparticle shape, compartment, and microstructure,

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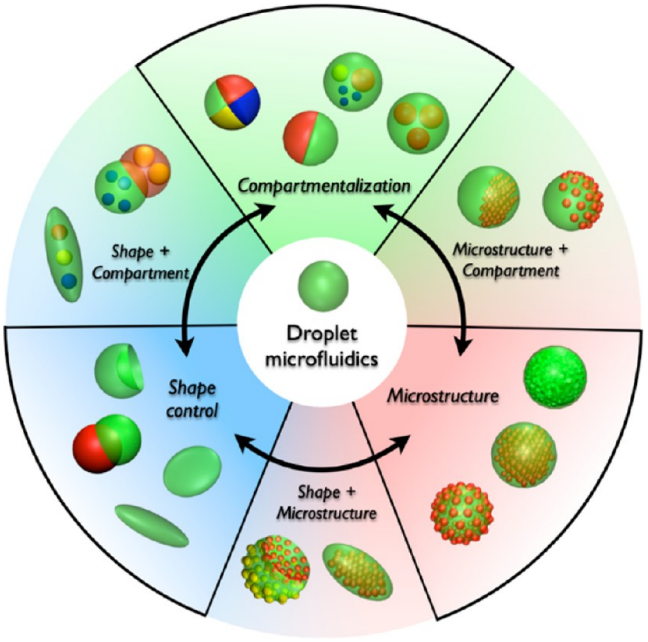

Figure 1. Classification of microparticles prepared by droplet microfluidics: three main aspects of shape, compartment, and microstructure can be independently or simultaneously incorporated into microparticles.

each of which requires distinct microfluidic approaches and provides different functionalities and applications. The third section describes the preparation of advanced microparticles having a higher level of complexity. Hybrid microparticles have been systematically designed to enable the use of microparticles in specific applications. Finally, we outline the current challenges and outlook on the microfluidic technique-based design of microparticles.

■ ISOTROPIC MICROPARTICLES

Emulsions are intrinsically unstable because the interfacial energy at the mobile boundary between the two immiscible fluids is nonzero. Surfactants or nanoparticles stabilize an emulsion over finite periods of time to prevent coalescence. The stabilizers reduce the interfacial energy and form a barrier at the immiscible fluid interface. Stable emulsion droplets favor a spherical shape with a minimized interfacial area and the retention of a uniform Laplace pressure over the whole interface. Therefore, emulsion droplets provide useful templates for producing isotropic microparticles by employing appropriate solidification processes. Three distinct types of emulsion droplets are prepared using microfluidic emulsification of one fluid in another immiscible fluid: oil-in-water (O/W), water-in-oil (W/O), and water-in-water (W/W) emulsions. Each emulsion type provides microparticles having distinct properties. The wettability of the microfluidic device surfaces, the effects of the emulsion stabilizer, and the dynamics of the consolidation process must be carefully considered in using each of the emulsion types.

O/W Emulsion Templates. Microparticles composed of hydrophobic materials have been prepared using O/W emulsion droplets containing hydrophobic precursors, polymers, or nanoparticles. Microparticles prepared using an O/W emulsion have a controlled composition and size; any polymer dissolvable in an organic solvent can be used to make particles. The microparticles can be used in a wide range of applications including micromechanical systems (MEMS), diagnostic assays, and adsorbent of toxic materials such as heavy metals and oils. The microparticles can encapsulate lipophilic drugs while retaining the ability to form a stable dispersion in water. These qualities are very important for drug delivery applications. O/W emulsions are produced in microfluidic devices using a variety of emulsification-promoting device geometries such as the T-junction or the cross-junction.[3] In these geometries, the channel walls are rendered hydrophilic to enable the continuous flow of the aqueous phase along the walls while avoiding wetting the device wall surfaces with oil droplets. The oil droplets are stabilized against coalescence by surfactants. Water-soluble surfactants having a hydrophilic−lipophilic balance (HLB) of 8−18 are generally used for this purpose. The surfactants are usually introduced into the continuous phase, as illustrated schematically in Figure 2a, in agreement with the Bancroft rule.

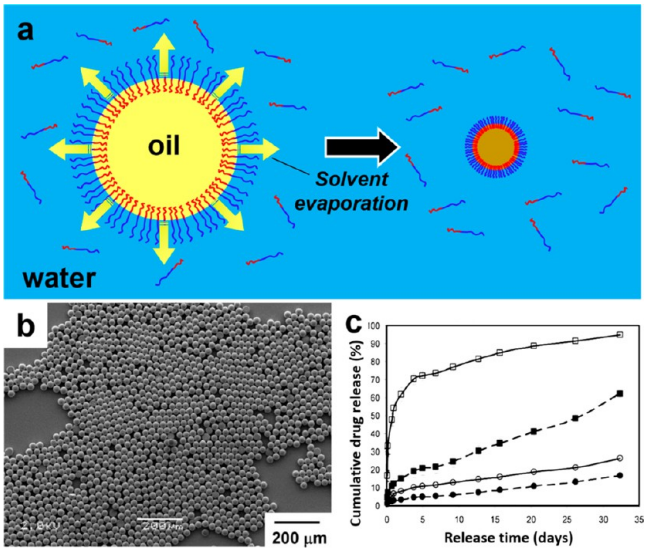

Figure 2. (a) Schematic illustration of the fabrication of microparticles from the template of the oil-in-water (O/W) emulsion system; evaporation of solvent in oil drop consolidates the drop to microparticles. (b) Scanning electron microscope (SEM) images of microparticles made of poly(lactic-*co*-glycolic acid) (PAA).[4] (c) Drug release profiles of PLGA microparticles, where squares and circles denote microparticles of 11 and 41 μm diameter, respectively, and the unfilled and filled symbols denote microparticles made by conventional and microfluidic methods, respectively.[4] Reproduced with permission from ref 4. Copyright Wiley-VCH.

Among various applications of the microparticles prepared using an O/W emulsion in microfluidics, drug delivery applications have been most intensively developed using a variety of biocompatible and biodegradable polymers, including poly(lactic-*co*-glycolic acid) (PLGA),[4] polycaprolactone (PCL),[5] and polylactide (PLA).[6] These polymers are typically dissolved in a volatile organic solvent, and the solution is emulsified to form O/W emulsion droplets that form microparticles during solvent evaporation. The microparticle size is controlled according to the initial droplet size and polymer concentration. For example, dichloromethane (DCM) containing PLGA and a hydrophobic drug, bupivacaine, is emulsified in a 1% poly(vinyl acrylate) Tris buffer solution using flow-focusing microfluidic device geometry to form a

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monodisperse microparticle dispersion in water after the evaporation of DCM, as shown in Figure 2b.[4] The diameter of the uniform PLGA microparticles can be controlled over the range of 10−40 μm. The particles enable the sustained release of bupivacaine, whereas polydisperse microparticles made by bulk emulsification methods frequently exhibit an initial burst release of the drug due to the heterogeneous internal distribution of the drug as shown in Figure 2c. The microparticle size can be decreased to the submicrometer scale by diluting the polymers in the droplets. For example, toluene droplets 20 μm in diameter containing 0.005 g/L polyfluorene are transformed into microparticles 150 nm in diameter by evaporating the toluene.[7] Hydrophobic nanoparticles such as magnetic nanoparticles[5] and quantum dots (QDs),[8] which usually form poorly stable dispersions in an aqueous phase, can be incorporated into the microparticles dispersed in water without modifying the nanoparticle surfaces. These nanoparticles provide magnetic and optical functionalities.

W/O Emulsion Templates. Microparticles composed of hydrophilic materials are prepared using W/O emulsion droplets containing water-soluble precursors or water-dispersible nanoparticles. Aqueous droplets can incorporate additional water-soluble ingredients or living organisms to provide a useful means of encapsulating bioactive agents. Such W/O emulsions are produced and stabilized in microfluidic devices having hydrophobic channel walls and with the addition of oil-soluble surfactants having an HLB of 3−6. The W/O templates form hydrogel microparticles or microgels that provide biocompatible and hydrophilic microcarriers. Hydrogel precursors for alginate,[9] chitosan,[10] and poly(acrylamide)[11] have been dissolved in water droplets and polymerized to create microgels, as shown in Figure 3a. Finally, the microgels are transferred into the water phase.

Polymerization is performed via two distinct mechanisms: physical gelation by forming microcrystals or ionic cross-links and chemical polymerization by forming covalent bonds between prepolymers. Because physical gelation does not involve cross-linkers or polymerization initiators, which are usually harmful to living organisms, it is widely used to prepare an artificial extracellular matrix for cell growth. Cells show good viability when encapsulated, and they can survive for long periods of time in a biocompatible and highly permeable gel matrix. The cell viability in a microgel is comparable to that observed in a bulk gel.[12] Therefore, microgels prepared by physical gelation can provide a 3D cell-culturing medium for individual cells or colonies of cells. Microgels are particularly useful for analyzing the biological behaviors of cells in a controlled environment. For example, cells are encapsulated in a microgel by cooling cell-laden droplets of agarose, as shown in Figure 3b.[13,14] Upon cooling, agarose forms a stable microcrystalline phase that forms a gel. Cells grow and mutate in agarose microgel particles, which then are readily sorted using fluorescence-activated cell sorting (FACS) techniques using minimum reagents and time as a result of the very small volume, several picoliters, of the microgel particles. Ionic gelation provides another approach to preparing physical gels. As ions diffuse from a continuous phase into water droplets, the precursors are cross-linked by the ions present in the droplets. This principle has been used to prepare a variety of microgels from alginate,[9] chitosan,[10] peptides,[12] and pectin.[15] Ionic gelation also provides a high cell viability when used in cell culture applications.

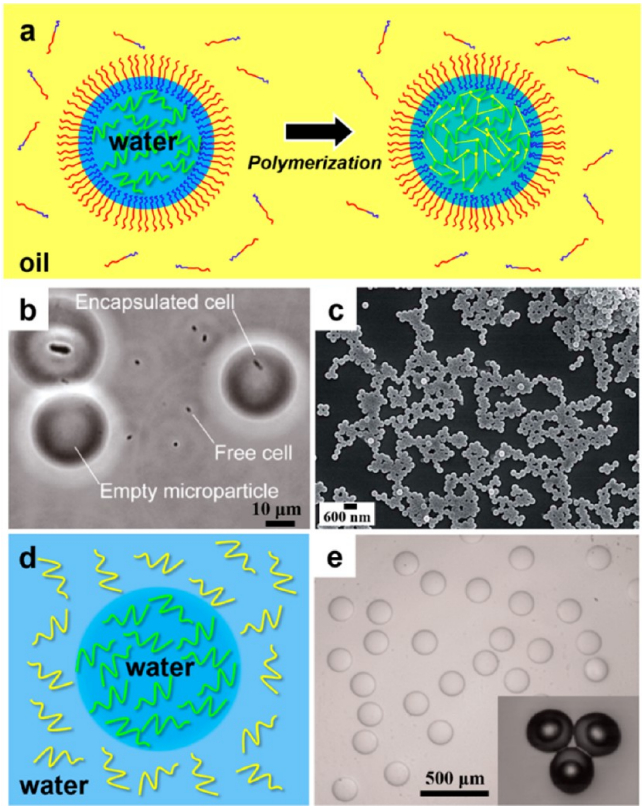

Figure 3. (a) Schematic of the polymerization of aqueous droplets in microgels using the W/O emulsion system. Prepolymers in aqueous droplets can be either physically or chemically cross-linked to form gel structures. (b) Optical microscope image of agarose microparticles containing *E. coli* cells. Aqueous agarose droplets at 40 °C were cooled in a collection chamber to form cell-laden microparticles.[13] (c) SEM image of polymerized PEG particles. Aqueous PEGDA drops (4 wt %) were generated in tip-streaming mode, and subsequent UV polymerization results in submicrometer PEG particles with a diameter of 360 nm.[18] (d) Schematic illustration of the W/W emulsion system. Two dissimilar polymer solutions with sufficiently high concentrations are phase separated to form aqueous two-phase systems. (e) Optical microscope image of 17 wt % aqueous PEGDA drops dispersed in a 16 wt % aqueous dextran solution. PEG microparticles were polymerized to maintain their spherical shapes as shown in the inset of e.[21] Reproduced with permission from refs 13, 18, and 21. Copyright American Chemical Society (b), Royal Society of Chemistry (c), and AIP Publishing LLC (e).

Although free radical polymerization reactions can include compounds that are detrimental to cell culture growth, these reactions provide a simple and rapid gelation of precursors within a microfluidic chip. This method has been used intensively to encapsulate drugs or other chemicals; there are few reports that show the encapsulation of live cells through free radical polymerization. A variety of precursors having unsaturated hydrocarbon chains may be used, such as acrylate and amide groups, and free radicals may be formed using thermoinitiators[16] or photoinitiators.[17,18] For example, microgels composed of poly(*n*-isopropylacrylamide) (PNIPAAm) are prepared through photopolymerization.[18] PNIPAAm microgels can include small hexadecane droplets in the gel matrix to enable the simultaneous encapsulation of both hydrophobic and hydrophilic drugs. Submicrometer-sized microgels composed of poly(ethylene glycol diacrylate) (PEGDA) are prepared through photopolymerization in aqueous nano-

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droplets prepared using tip-streaming methods of droplet generation, as shown in Figure 3c. The microgels can include sodium dodecyl sulfate (SDS)-coated iron oxide nanoparticles to provide magnetic functionality.[18] Although chemicals for free radical polymerization are toxic to live cells, they can sometimes be employed to improve the mechanical strength of microgels that are preformed by physical gelation; the enhancement of the mechanical property can result in the long-term viability of cells.[19]

Isotropic microparticles can be prepared by evaporating water droplets containing nanoparticles. The nanoparticles form spherical aggregates held together through van der Waals interactions upon completion of the consolidation step. Monodisperse aqueous droplets containing silica nanoparticles produce uniform microspheres after the evaporation of water. The droplets can include a binary mixture of silica and titania nanoparticles, which produces composite microspheres. The composition may be determined by the mixing ratio of the two nanoparticles. This enables control over the microsphere properties, including the effective refractive index and average density.[20]

W/W Emulsion Templates. Aqueous dispersions of microparticles are frequently required for biological applications. Although O/W emulsions provide microparticles that are directly dispersed in water, it is difficult to encapsulate delicate biological materials in oil droplets. By contrast, W/O emulsions can capture cells and bioactive materials, but the resultant microparticles must be transferred from the oil to the water phase. A delay in transfer can reduce the cell viability. To address this problem, W/W emulsion systems have been proposed. W/W emulsion systems use aqueous solutions of two chemically dissimilar polymers that undergo phase separation at sufficiently high concentrations, as shown in Figure 3d.[21] An extremely low interfacial tension between the two aqueous phases makes a stable jet instead of a droplet. The jet breakup may be triggered by applying a mechanical perturbation to the dispersed phase with a controlled frequency. W/W emulsion droplets are then generated at this frequency.[22] This method has been used to prepare an aqueous solution of 17 wt % PEGDA emulsified in an aqueous solution of 16 wt % dextran to form monodisperse droplets, as shown in Figure 3e. The precursors present in the droplets were subsequently photopolymerized to produce a monodisperse microgel dispersion in water.

■ ENGINEERED MICROPARTICLES

Microparticles are functionalized to produce other microparticles with enhanced complexities relative to homogeneous isotropic particles. To this end, the microparticle shape, compartment, and microstructure are engineered, as shown in Figure 1. New features of engineered microparticles expand the scope of applications to which microparticles are applied.

Compartmentalized Microparticles. Microparticles prepared from uniphasic droplet templates are usually homogeneous in their material composition. Biphasic droplets, which consist of two separate domains, can produce biphasic microparticles. Biphasic particles are referred to as Janus particles because they display two different faces in a single particle. Bi- or multiphasic microparticles are used as microcarriers of multiple ingredients, building blocks for secondary assemblies, and field-responsive microparticles for advanced applications. Template droplets having multiple compartments are prepared by designing microfluidic devices to inject several distinct fluids in parallel simultaneously and concurrently emulsify these fluids into single droplets. The general device design used to prepare biphasic droplets is schematically illustrated in Figure 4a. In such a microfluidic

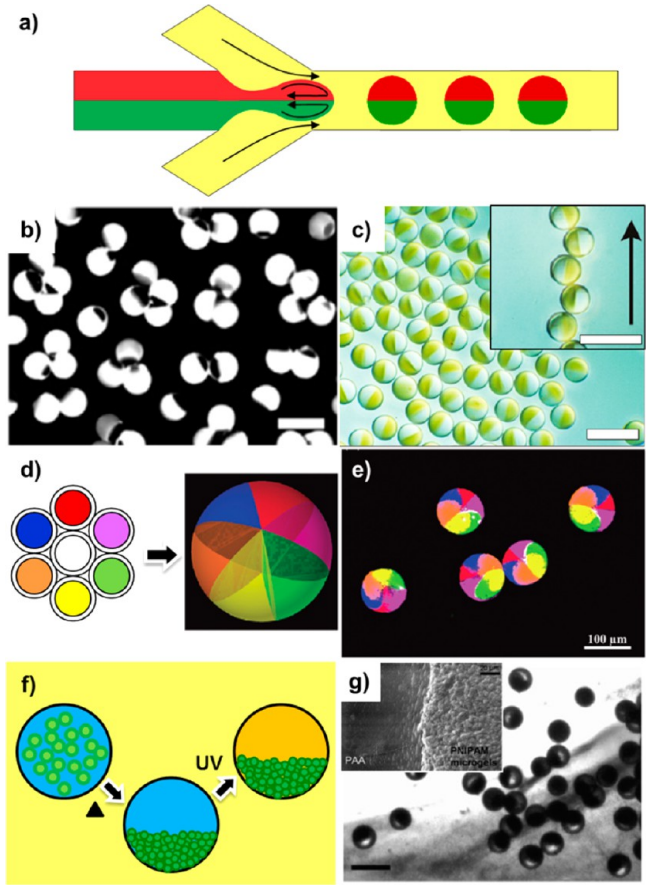

Figure 4. (a) Design of a microfluidic device for the generation of Janus droplets. Two parallel streams are coemulsified into a continuous phase at a junction while maintaining two distinct domains. (b) Fluorescence microscope image of clusters of Janus particles in a mixture of water and methanol.[23] (c) Optical microscope images of magnetoresponsive Janus microparticles. The inset shows the formation of chainlike structures under an external magnetic field.[25] (d) Scheme of the cross-section of a septuple-barreled capillary and axisymmetric microparticles with six compartments; the central channel of the capillary is not used for injection.[27] (e) Confocal microscope image of microparticles with six compartments.[27] (f) Scheme for phase-separation-induced formation of Janus microparticles; thermoresponsive nanoparticles are shrunken and compacted above their lower critical solution temperature. (g) Janus microparticles made by phase separation. The inset shows the domain boundary. Scale bars are (b, c, e) 100 μm, (g) 200 μm, and (g, inset) 20 μm.[28] Reproduced with permission from refs 23, 25, 27, and 28. Copyright American Chemical Society (b, c) and Wiley-VCH (d, e, g).

device, the flows are usually laminar as a result of the large viscous force relative to the inertia. These flows produce small Reynolds numbers. Therefore, the fluids maintain parallel streamlines, and convective flow does not influence the interstream mixing; the streams mix slowly by diffusion alone. Two miscible fluids form two parallel flows in a microfluidic channel and can be emulsified into droplets at a junction at which a third continuous phase exerts a drag force on the parallel streams. Although vigorous rotational flows can be

generated during the formation of droplets at the junction as a result of external shear forces, the centerline symmetry of the device gives rise to a rotational flow confined within its own hemispherical domain to produce twin circulatory flows that produce negligible convective mixing, as depicted in Figure 4a. The droplets maintain the compartments for some distance as they flow through symmetric channels; however, tortuous channels or a density mismatch between the droplets and the continuous phase can rapidly mix the two phases. Therefore, the droplets should be solidified in the channel prior to mixing to retain the clear boundary and distinct compartments within the microparticles.

Symmetric and asymmetric Janus microparticles are prepared by emulsifying two parallel oil flows of a photocurable resin into a continuous water phase in which the droplets are solidified by in situ photopolymerization. The relative sizes of the domains are controlled by the relative flow rates.[23] The use of two different monomers in each hemisphere yields an amphiphilic Janus particle. One hemisphere will be hydrophilic, whereas the other will be hydrophobic. The hydrophobic surfaces of the amphiphilic microparticles attract each other via hydrophobic interactions in a polar solvent to form clusters, as shown in Figure 4b. Such site-selective interactions provide promising means for controlling the self-assembly of the structures. Similarly, Janus microgels are prepared from aqueous droplet templates in a continuous oil phase. Janus microgels composed of two distinct biopolymers are fabricated via diffusion-induced gelation on a microfluidic chip.[24] Enzymatic hydrolysis can preferentially degrade a specific biopolymer in one hemisphere to enable the sequential release of two encapsulants in a desired fashion.

Janus microparticles can be further functionalized to be field-responsive. For example, Janus microgels having one hemisphere that contains magnetic nanoparticles are generated, as shown in Figure 4c. Magnetic nanoparticles provide an anisotropic superparamagnetic susceptibility that enables the manipulation of particle motion by the application of an external magnetic field. Therefore, these microgels are assembled to form chainlike structures under a magnetic field, as shown in the inset of Figure 4c.[25] Janus microparticles having an anisotropic distribution of charging materials are responsive to an electric field. For example, electroresponsive Janus microspheres have been prepared in which one hemisphere contains carbon black nanoparticles and the other contains titania nanoparticles. These particles will align under an electric field and have been used as an active pigment in Gyricon display devices, which are a type of electronic paper based on rotating Janus balls.[26]

Conventional 2D microfluidic devices provide multiphasic droplets configured in a side-by-side geometry. Triphasic microparticles with side-by-side geometry are prepared by injecting three distinct flows in parallel into a 2D microfluidic device.[23] Multiphasic droplets with a 3D axisymmetric geometry are prepared using capillary microfluidic devices in which multibarreled capillaries are used to inject distinct fluids in parallel with an angular distribution.[27] For example, triple-barreled capillaries produce triphasic droplets having fan-shaped domains that span 120°, with a central axis. Similarly, quintuple- and septuple-barreled capillaries produce four and six compartments in a single droplet, respectively, in which the central barrel of the multibarrel droplet remains unused to retain its axisymmetry. These 3D capillary devices produce microgels having multiple compartments. Distinguishable aqueous solutions of alginate are injected into each barrel. The alginate solutions are then concurrently emulsified in air under centrifugation. The droplets fly through the air and arrive at an aqueous solution of $CaCl_2$, in which they rapidly gelate while preserving the compartments. For example, a cross-sectional view of a septuple-barreled capillary device and a resulting axisymmetric droplet are schematically illustrated in Figure 4d. The resultant microgels having six compartments are shown in Figure 4e. Such microgels having multiple compartments are useful as microcarriers that can encapsulate the cells and magnetic nanoparticles within their own compartments. Therefore, cells can be isolated from toxic magnetic particles while rendering the microgels magnetoresponsive.

Without multiphasic droplet templates, compartments can be prepared by phase separation in droplets. For example, single aqueous droplets containing cationic nanoparticles of amine-modified PNIPAAm, anionic poly(acrylic acid) (PAA), and photocurable hydrogel precursors exhibit phase separation within the droplets as the temperature increases beyond the lower critical solution temperature (LCST) for PNIPAAm, 32 °C. Aggregates of the weakly associated nanoparticles and PAA, held together by electrostatic attraction, shrink and compact on one side of the droplets above the LCST. The phase separation can be permanently captured by the photopolymerization of the hydrogel precursors, resulting in Janus microgels.[28] Each fabrication step is shown in Figure 4f. The emulsion droplets having compacted aggregate domains are shown in Figure 4g, and the boundary between the two domains is shown in the inset.

A compartment can be formed in the core−shell structure of a droplet-in-droplet, which is called a double-emulsion droplet. Such a hierarchical structure may be produced using a distinct microfluidic device design. Conventional microfluidic devices connect two droplet makers in series, as shown in Figure 5a. Droplets generated in the first junction are then nested in the second junction to form a droplet-in-droplet. Each junction must be rendered to have a different surface wettability to prevent the dispersed phase from wetting the wall. In capillary microfluidic devices, two tapered capillaries are assembled coaxially, and double-emulsion droplets are generated in a single step, as shown in Figure 5b. Three-dimensional flow-focusing enables the formation of stable core−shell structures in the capillary device. The two capillaries must be rendered to have different wettabilities.

Although double-emulsion droplets have an isotropic outer surface, an eccentric core can provide anisotropic properties. For example, oil-in-water-in-oil (O/W/O) double-emulsion droplets composed of a magnetic monomer core and a hydrogel precursor shell have been used to produce microgels containing eccentric magnetic cores, as shown in Figure 5c. The shell is photopolymerized, whereas the core is thermopolymerized.[29] The rotating external magnetic field exerts a torque on the core of a microgel to produce eccentric rotation of the microgel. The isotropic outer surfaces of the core−shell structures can be useful for avoiding direct exposure of the core to the environment, especially if the core is toxic. For example, QDs and magnetic nanoparticles are separately dispersed in photocurable resins, and the suspensions can be injected to form two separate oil cores in a single hydrogel precursor shell. Subsequent photopolymerization solidifies the core−shell structures, one core of which will deliver the optical information from the QDs and the other core of which provides magnetoresponsiveness. The biocompatible hydrogel

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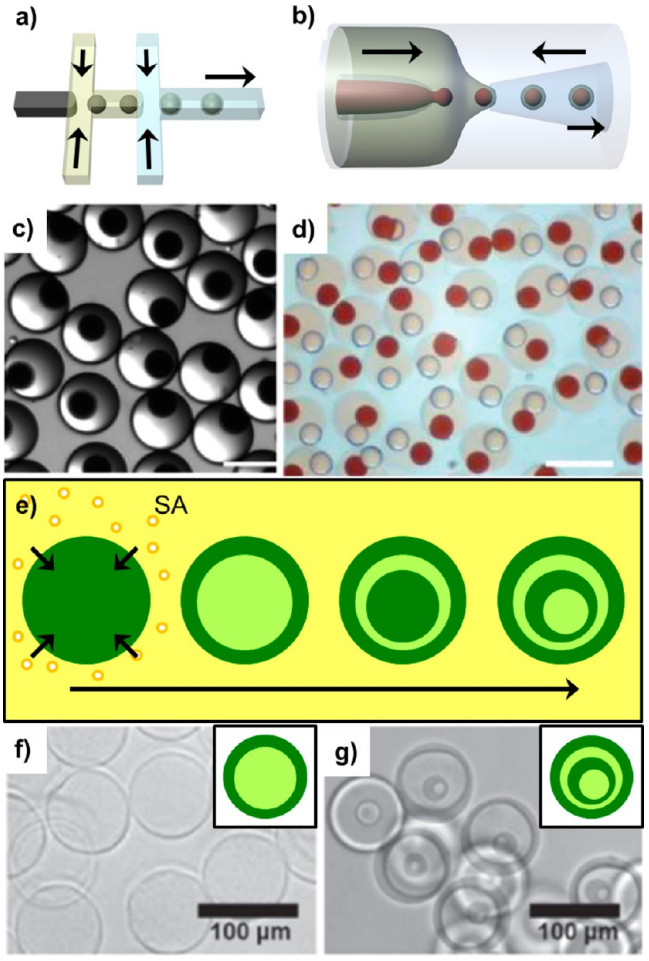

Figure 5. (a, b) Designs of a 2D microfluidic device and a 3D capillary microfluidic device for the preparation of double-emulsion droplets, respectively. (c) Optical microscope image of microgels containing eccentric magnetic cores.[29] (d) Microgels containing two cores: one magnetic- (red dots) and the other quantum-dot-loaded (gray dots).[30] (e) Schematic diagrams of the formation of a multiple-emulsion droplet from a single-emulsion droplet by diffusion-induced phase separation. (f, g) Optical microscope images of capsules and capsule-in-capsules composed of hydrogels, respectively.[31] Insets show templates of double- and quadruple-emulsion droplets used for the structures, respectively. Scale bars are (c) 50, (d) 200, and (f, g) 100 μm. Reproduced with permission from refs 29, 30, and 31. Copyright Wiley-VCH (c, f, g), and American Chemical Society (d).

shell prevents exposure of the toxic nanoparticles. Microgels containing dual cores are shown in Figure 5d.[30]

Phase separation can produce core−shell structures as well as Janus structures. For example, aqueous droplets containing PEGDA exhibit phase separation as a separating agent diffuses into the droplets. This process results in a core−shell structure, as shown in Figure 5e.[31] Interestingly, phase separation produces multiple emulsion droplets with a high order if the PEGDA concentration is sufficiently high. Triple- or quadruple-emulsion droplets are generated from droplets containing 60 or 80% PEGDA, respectively. These double- and multiple-emulsion structures provide capsules and capsule-in-capsules through the selective polymerization of the hydrogel precursors, as shown in Figure 5f,g.

Shape-Controlled Microparticles. Stress-free emulsion droplets always adopt a spherical shape to minimize the interfacial energy while retaining a uniform Laplace pressure. Microparticles templated from an emulsion droplet are typically spherical. Nonspherical microparticles can be produced using a variety of approaches. The simplest means of preparing nonspherical microparticles involves the physical confinement of the droplets.[32,33] As droplets pass through a channel having dimensions that are much larger than the size of the droplet, the droplets will maintain a spherical shape and produce spherical microparticles, as shown in Figure 6a. However, as droplets are injected into a channel having a height that is smaller than the diameter of the droplet, the droplets will deform to form flat top and bottom surfaces and curved side walls, yielding circular microdisk particles by in situ polymerization. Droplets injected into a narrow square channel produce rod-shaped microparticles, as shown in Figure 6c. Physical confinement approaches provide simple and effective methods for controlling the microparticle shape, although only convex or flat surfaces are available.

Sharp-edged microparticles can be produced using paired droplets in which two immiscible dispersed phases are coemulsified into a third continuous phase. The paired droplets can form a variety of equilibrium structures depending on the spreading parameters and relative volume of the droplets. The spreading parameter in paired droplets, S, is expressed as $S = \gamma_{CA} - (\gamma_{CB} + \gamma_{AB})$ where γ_{CA} and γ_{CB} are the interfacial tensions of dispersed phases A and B with continuous phase C, respectively, and γ_{AB} is the interfacial tension between dispersed phases A and B. For positive value of S, dispersed phase B engulfs a droplet of A to form a core−shell structure. By contrast, negative values of S result in partial engulfment and form dumbbell- or acorn-shaped droplets. The structural details are determined by the minimum total interfacial energy. Such paired droplets can be captured to produce nonspherical microparticles. Full polymerization of the two dispersed phases or selective polymerization of one dispersed phase may be used to prepare such microparticles, as shown in Figure 6d. For example, paired droplets having two bulbs composed of two immiscible photocurable precursors produce dumbbell-shaped microparticles through photopolymerization, as shown in Figure 6e.[34] Two immiscible oil phases of a photocurable precursor and an inert oil produce microparticles composed of convex and concave surfaces through the selective polymerization of one bulb in the paired droplets, as shown in Figure 6f,g. In this example, two different shapes were made from the same combination of fluids by tuning the relative volume of the photocurable oil to that of the inert oil.[35] Similarly, two immiscible water phases—one containing polymerizable PEGDA and the other containing dextran—can be coemulsified in a continuous fluorinated oil phase to produce sharp-edged microparticles. The dextran-rich phase forms a core to avoid its exposure to the oil phase, and the PEGDA-rich phase forms a shell encapsulating the dextran core. Upon UV illumination, the PEGDA molecules are selectively polymerized and the dextran molecules migrate into the polymerized PEGDA shell. During this polymerization, the thinnest part of the PEGDA shell opens because of the inhibition of polymerization from the oil−water interface; this leads to the formation of an open socket in each microparticle.[36]

Interestingly, doughnut-shaped microparticles can be fabricated from emulsion droplets. Droplets usually undergo isotropic shrinkage as a dispersed phase diffuses into the continuous phase in a free suspension. However, the droplets flowing through a microfluidic channel provide anisotropic diffusion and odd shrinkage. As droplets with a high solubility

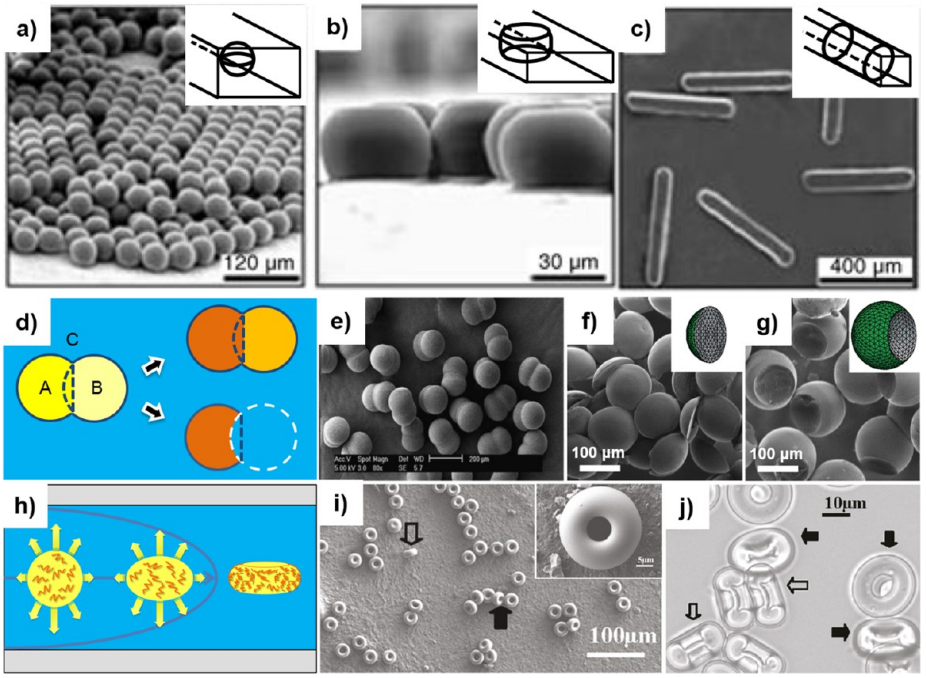

Figure 6. (a–c) SEM images of microparticles with spherical, circular disk, and rod shapes, respectively. Insets show the physical confinement of droplet in each case.[32] (d) Scheme for the fabrication of dumbbell-shaped particles and crescent-moon-shaped particles from a template of paired droplets. (e) SEM image of dumbbell-shaped microparticles of which bulbs are made from two different monomers.[34] (f, g) SEM images of microparticles produced from the selective polymerization of one bulb of paired droplets, where the relative volume of the polymerizable bulb to the nonpolymerizable bulb is controlled. Insets show the shapes of the polymerizable bulb, respectively.[35] (h) Schematic illustration of the formation of doughnut-shaped microparticles through the anisotropic shrinkage of droplets flowing through the center of a microfluidic channel. (i, j) SEM and optical microscope images of doughnut-shaped microparticles composed of silica nanoparticles. (i, inset) A magnified view.[37] Reproduced with permission from refs 32, 34, 35, and 37. Copyright Wiley-VCH (a–c, e–g) and American Chemical Society (i, j).

in the continuous phase flow through the center of a microfluidic channel, the droplets anisotropically diffuse into the continuous phase. Diffusion toward the side-channel wall is preferred over diffusion along the flow direction as a result of the rapid rate at which the continuous phase is refreshed by the shear flow. If the droplets contain nanoparticles or polymers, then the concentration of these species increases at the droplet interface as a result of solvent-diffusion-induced material flux after initial isotropic shrinkage. The concentration gradient forms an elastic membrane. Anisotropic diffusion continues to drain the solvent, which deforms the membrane, causes buckling in the lateral direction, and produces a doughnut-shaped microparticle after consolidation has been fully completed, as shown in Figure 6h. This mechanism was used to fabricate doughnut-shaped microparticles with a central thin membrane from aqueous droplets containing silica nanoparticles in a continuous phase of dimethylcarbonate, as shown in Figure 6i,j.[37] Similarly, doughnut-shaped polymer particles have been fabricated from flowing droplets of *N*,*N*-dimethylformamide in a continuous phase of poly(dimethylsiloxane).[38] The size and curvature of the doughnuts are controllable according to the flow rate of the continuous phase, which influences the solvent diffusion rate.

Microstructured Microparticles. Microparticles can be designed to have surface or internal microstructure. Regular surface structures have been prepared by particle adsorption at the droplet interface. Emulsions in which the droplets are stabilized by colloids are known as Pickering emulsions. Colloidal particles having an intermediate wettability reduce the interfacial energy through adsorption, thereby spontaneously anchoring and forming arrays at the interface. The energy reduction by a single particle adsorption event is expressed as $E_b = \pi R^2\gamma(1 - |\cos\theta|)^2$, where R is the radius of a particle, γ is the interfacial tension, and θ is the contact angle measured from the phase in which the particle originates.[39] Because this energy reduction is much larger than the thermal energy for a particle more than tens of nanometers in size, adsorption is irreversible. Emulsification of a monomer suspension of colloids into an immiscible continuous phase results in the migration and adsorption of the colloids in the droplets to the interface. These processes stabilize the interface by reducing the interfacial energy and forming an interfacial barrier. The anti-Bancroft-type adsorption provides shorter diffusion lengths than are observed in particles prepared via Bancroft-type adsorption, thereby leading to rapid stabilization, and it can minimize the consumption of particles.[40,41] The adsorbed colloids form hexagonal arrays along the spherical surface due to interparticle repulsion induced by the charges on the surfaces exposed to the water phase. Polymerization of the monomers captures the structure and yields spherical microparticles having surfaces that are decorated with a hexagonal array of colloids. Each step of the production process is illustrated schematically in Figure 7a. This approach yields microparticles decorated with an array of colloids, as shown in Figure 7b,c.[41]

The surface structures can be further tailored by applying additional chemical treatments. For example, microparticles are decorated with a hexagonal array of silica particles, the exposed surfaces of which provide active sites for material formation. Negative charges on the surfaces of silica particles enable the selective deposition of silver nanoparticles through the silver mirror reaction, as shown in Figure 7d.[42] The hierarchical silver

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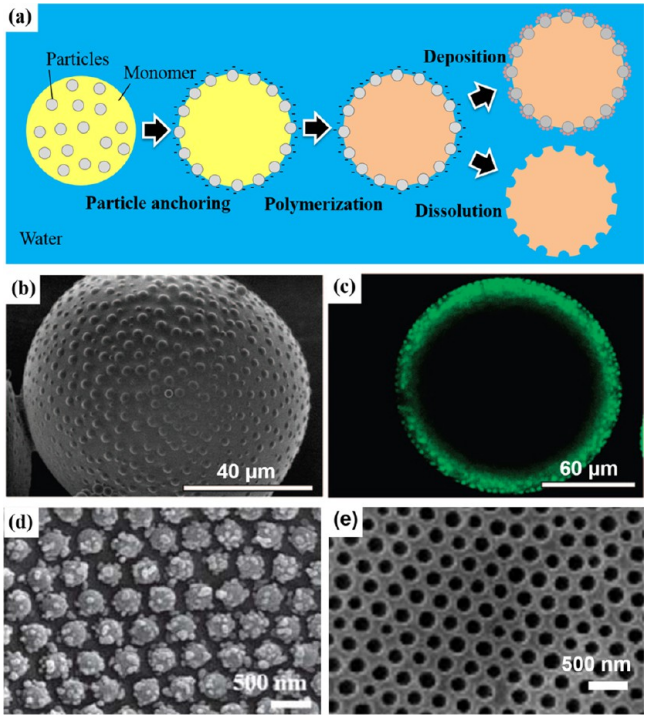

Figure 7. (a) Schematic illustration of the preparation of microparticles with surface structures. Particle-stabilized emulsion droplets are polymerized into a solid sphere to make colloidal arrays. The surface can be further functionalized with two distinct methods of selective material deposition and particle removal. (b, c) SEM and confocal microscope images of a microparticle whose surface is decorated with polymer particles.[41] SEM images of microparticle surfaces: (d) a hexagonal array of silver-nanoparticle-decorated silica particles[42] and (e) a hexagonal array of dimples templated from silica particles.[40] Reproduced with permission from refs 40, 41, and 42. Copyright Wiley-VCH (a–c, e–g), Royal Society of Chemistry (d), and IOP Publishing (e).

nanoparticle-on-silica particles-on-polymer microparticle structures are useful in molecular sensor applications. Dense arrays of silver nanoparticles in each silica dome provide hot spots for surface-enhanced Raman scattering, and microparticles provide beneficial rapid binding kinetics relative to film-type structures. Rather than relying on the deposition of a material, silica particles can be selectively dissolved to form a polymeric matrix that leaves an array of dimples on the microparticle surface, as shown in Figure 7e.[40] The golf-ball-like structures can then be subjected to additional treatment for the preparation of superhydrophobic surfaces.

The microparticles can be designed in several distinct ways to have internal structure. For example, O/W emulsion droplets composed of a homogeneous mixture of monomers and solvents are transformed into porous microparticles through polymerization-induced phase separation and the subsequent removal of the solvent, as illustrated schematically in Figure 8a.[43] Although the monomer is miscible with the solvent, an increase in the degree of polymerization will decrease the solubility over the course of polymerization to induce phase separation. Phase separation occurs irregularly but on the length scale of the separation distance. Therefore, removing the solvent leaves pores having a consistent size within the interior of the microparticles. The solvent is referred to as the pore generator, or porogen. Porous microparticles prepared from the glycidyl methacrylate or ethylene glycol dimethacrylate

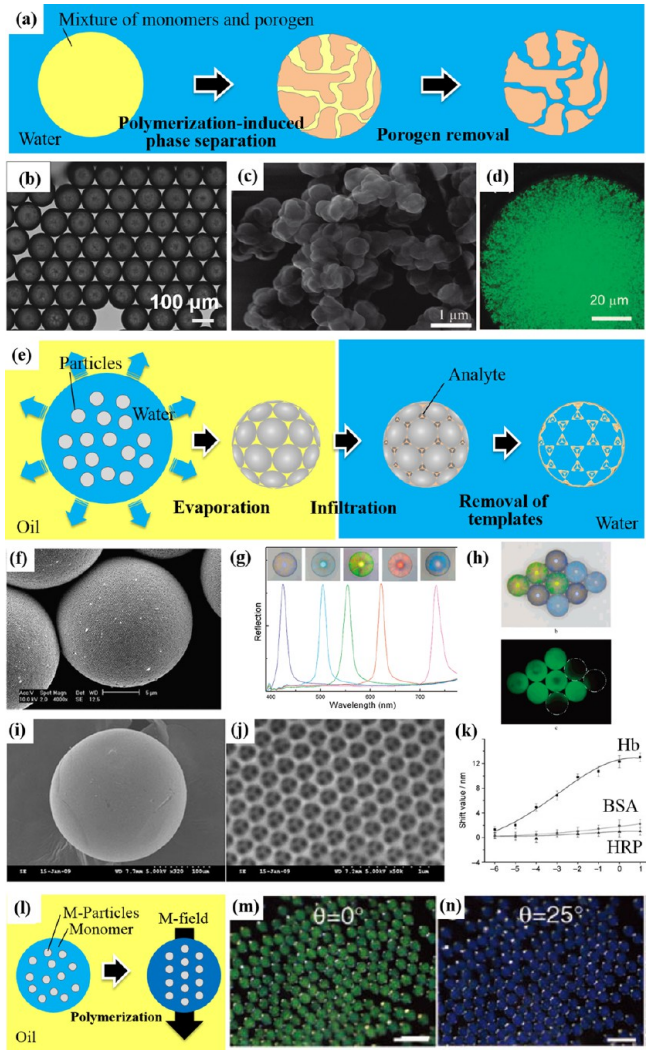

Figure 8. (a) Schematic illustration of the preparation of microparticles with continuous internal pores. Polymerization-induced phase separation in emulsion droplets and subsequent removal of porogen leaves continuous pores in the resultant microparticle. (b–d) Microparticles with internal pores made from a mixture of photocurable monomers and porogen.[43] (b) Optical microscope image showing high size uniformity of the microparticles, (c) SEM image of the surface pores, and (d) confocal microscope image showing internal pores. (e) Schematic illustration of the preparation of microparticles with regular arrays of colloids or cavities. The evaporation of a droplet containing colloids yields a dense packing of particles with spherical symmetry; these are called photonic balls. The infiltration of monomers and analytes into the interstices between the colloids forms a composite structure, and subsequent removal of the colloids and analytes leaves porous structures with molecular imprints. (f) SEM image of photonic balls, which is an assembly of silica particles.[51] (g) Reflectance spectra and optical microscope images of photonic balls, each of which is composed of silica particles of different sizes.[54] (h) Demonstration of suspension arrays with three distinct photonic balls, where three balls are treated with different IgGs and selective binding produces fluorescence only from two of the three.[54] (i, j) SEM images of inverse photonic balls imprinted with bovine hemoglobin (Hb).[56] (k) Reflection peak shift as a function of protein concentration, where three different proteins of bovine Hb, bovine serum albumin (BSA), and horseradish peroxidase (HRP) are used; only bovin Hb shows a significant peak shift.[56] Reproduced with permission from refs 43, 51, 54, and 56. Copyright American Chemical Society (b–d, f, g, h) and Wiley-VCH (i–k).

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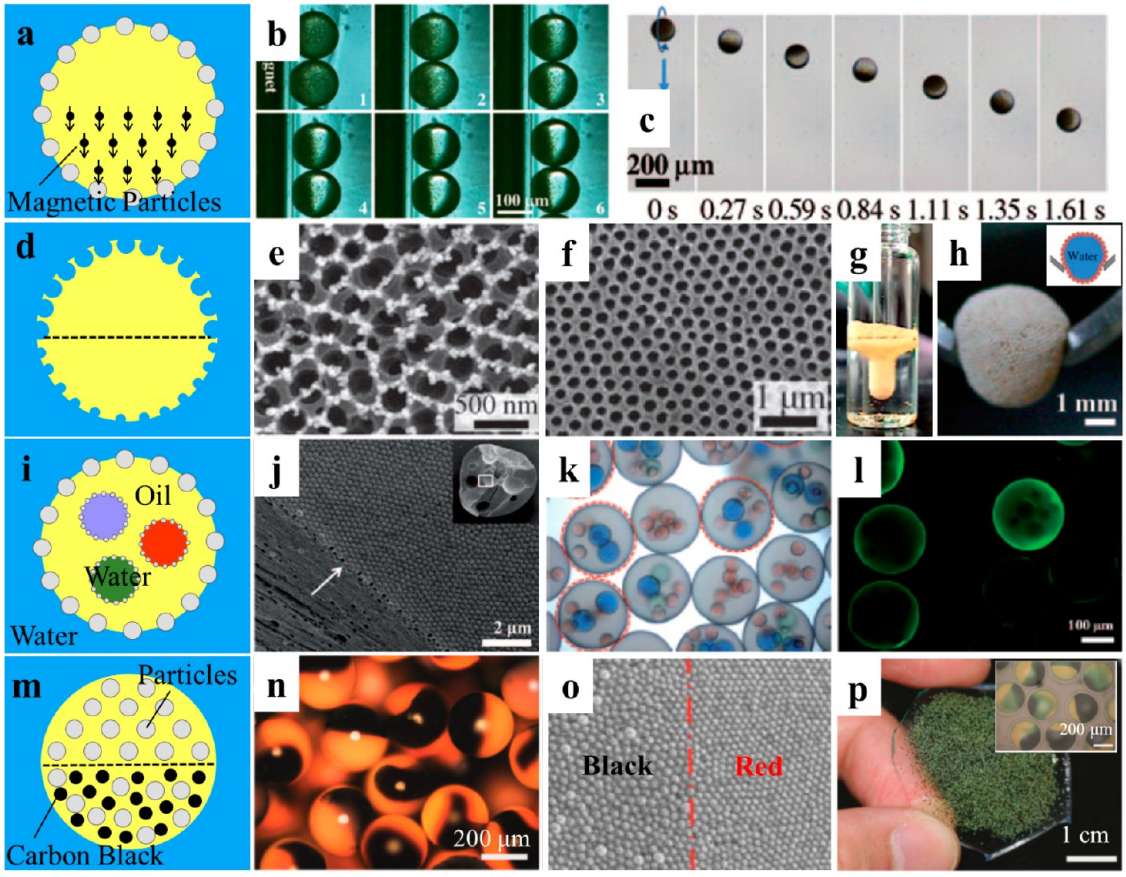

Figure 9. Compartmentalized microparticles with microstructures. (a–c) Microparticles with surface nanostructure, of which one hemsperical domain contains aligned weakly ferromagnetic nanoparticles:[58] (a) schematic diagram, (b) series of optical microscope images showing the magnetophoretic movement of nanoparticles, and (c) a series of optical microscope images showing rotation-induced translational motion. (d–h) Amphiphilic Janus microparticles composed of a superhydrophobic surface and a hydrophilic surface:[59] (d) schematic diagram, (e) SEM image of a superhydrophobic surface, (f) SEM image of a hydrophilic surface, (g) microparticle-stabilized water drop that is picked up by a pair of tweezers, and (h) microparticle-stabilized interface between air and water that is highly flexible and impregnable. (i–l) Microparticles with surface nanostructure containing multiple internal compartments:[60] (i) schematic diagram, (j) SEM image showing a hexagonal array of silica particles on the surface, and (k, l) optical and fluorescence microscope images showing a mixture of three distinct microparticles, where microparticles containing two blue and five red cores display only fluorescence. (m–p) Janus microparticles with regular internal nanostructure:[61] (m) schematic diagram, (n) optical microscope image showing Janus microparticles with red structural color from one hemisphere and black color from the other, (o) SEM image showing a boundary between two domains, and (p) an oil-swollen elastomer film that contains a single Janus microparticle in each cavity. Reproduced with permission from refs 58–61. Copyright Wiley-VCH (b, c, e–h, j–l, and n–p).

monomers and the porogen dioctyl phthalate are shown in Figure 8b–d. Microparticles are highly uniform and have macropores throughout their volume.[43] The resultant microparticles have a wide surface area on the order of a few m^2/g, making them useful in a broad range of applications such as ion-exchange resins, catalyst supports, and biomedical applications. Similarly, W/O emulsion droplets composed of gellable biopolymer mixtures provide phase separation. For example, aqueous droplets containing gelatin and maltodextrin exhibit phase separation upon cooling. The degree of separation and domain size are controlled by the cooling rate.[44]

Isolated pores can be prepared using small droplet templates, bubbles, and particles. For example, oil droplets composed of an organic solution containing the polymer and a phase change material (PCM) exhibit phase separation of the PCM as the organic solvent evaporates, resulting in the formation of PCM droplets in the oil droplet. After complete evaporation of the solvent, the removal of the PCM yields isolated pores in the interior of polymer microparticles.[45] The evaporation process, which is slow relative to the polymerization process, provides sufficient time for phase separation and leads to the formation of isolated macropores instead of pore networks. Microbubbles stabilized by fluorous compounds also serve as porogens. Perfluoro alkyl chains stabilize air bubbles dispersed in an organic solution containing a polymer, and the stable bubbles form isolated pores in the polymer microparticles after evaporation of the solvent.[46] Small droplets of a continuous phase can be engulfed in the interior of an emulsion droplet in the presence of a high concentration of surfactants in the continuous phase. The droplets act as porogens and produce pores in the microparticles after complete drying.[47] Thermoresponsive nanogels composed of PNIPAAm can be used to create tunable pores in microparticles formed from W/O emulsion droplets. The nanogels shrink as the temperature increases beyond the LCST, thereby creating pores.[48] The templating droplets or bubbles can be incorporated into the main emulsion droplets in a microfluidic device having two serial droplet makers to produce relatively large pores.[49] The templates are prepared in the first junction and are then encapsulated into the outer droplets in the second junction to

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form structures similar to those of the double-emulsion droplets. In these structures, the number of templates is determined by the frequency of template formation relative to outer droplet formation.

Highly ordered internal structures can be prepared via the self-organization of monodisperse colloidal particles in emulsion droplets.[50] As W/O emulsion droplets containing monodisperse silica particles evaporate, the concentration of particles increases to produce dense packing in spherical colloidal crystals, as shown in the first half of the schematic diagram shown in Figure 8e and the SEM image shown in Figure 8f.[51] The regular arrays of colloids exhibit the selective reflection of light at specific wavelengths, yielding photonic ball properties. An alternative method for producing photonic balls involves interparticle repulsion within the droplet rather than evaporation. The repulsive forces induce the particles to assemble into regular structures to minimize the repulsive energy.[52,53] The photonic balls have distinctive colors and reflection peaks, depending on the constituting particle diameter and concentration, as shown in Figure 8g. These features provide useful codes for microparticle identification.[54] The photonic balls are then used for biological analysis. Biological arrays based on the encoded microparticles are referred to as suspension arrays. For example, microparticles of a given color may be independently pretreated with specific biomolecules, and a mixture of the microparticles is used as a suspension array rather than as a conventional planar array. As the mixture is exposed to fluorescently labeled biomolecules, the microparticles having specific binding affinities toward the biomolecules in the suspension will display fluorescence, as shown in Figure 8h. The fluorescence signature then is used to identify the unknown biomolecules. The colloidal structure of the photonic balls can be inverted to form a porous structure. Infiltration of the materials into the interstices between particles and the subsequent removal of the particles leaves behind regular arrays of cavities.[55] During the inversion process, specific proteins can infiltrate the matrix materials to leave a molecular imprint after the removal of the proteins, as shown in the second half of the schematic diagrams shown in Figure 8e. SEM images of the inverse photonic balls are shown in Figure 8i,j.[56] The molecular nanoholes selectively accept specific proteins that were used to form imprints, and the binding events induce shifts in the reflection peaks. The peak shifts are proportional to the concentration of the specific protein but are not affected by the concentrations of the other proteins, as shown in Figure 8k. Evaporation-induced or interparticle-repulsion-induced crystallization always produces regular arrays of colloids in a face-centered cubic (fcc) structure. By contrast, the application of an external field can align colloids to form regular chains. For example, magnetic particles dispersed in a photocurable resin form regular chains in a droplet under an external magnetic field. The structures of these chains are captured by photopolymerizing the resin. The interparticle distance in each chain is determined by the intensity of the applied magnetic field. The resultant microparticles have rotation-dependent colors due to their special chainlike structures.[57]

■ HYBRID MICROPARTICLES

The shapes, compartments, and microstructures of microparticles prepared using emulsion droplets can be engineered, as discussed above. Desired functionalities for specific applications are obtained by simultaneously tuning one or more of these properties in a single microparticle, as shown in Figure 1. Such microparticles are referred to as hybrid microparticles here. This section discusses the synergetic effects of the hybrid microparticles, their properties, and their applications. This section is divided into four subsections that address different combinations of the particle features: compartments plus microstructures, microstructures plus shapes, shapes plus compartments, and all three features.

Compartments and Microstructures. Compartmentalized microparticles with surface or internal microstructures have been prepared for a variety of practical applications. Four representative examples of these hybrid particles are summarized in Figure 9. The simplest example is the magnetoresponsive microparticle with a surface nanoarchitecture as shown in Figure 9a. Such particles are produced using photocurable O/W emulsion droplets containing monodisperse colloidal particles and magnetic nanoparticles. Monodisperse colloids form hexagonal arrays at the interface, whereas weakly ferromagnetic nanoparticles may be aligned and transported to one side of a droplet under a magnetic field, as shown in Figure 9b.[58] The droplets are solidified by photopolymerization, resulting in microparticles having surfaces that are decorated with colloidal particles and interiors that are compartmentalized according to the local concentration of magnetic particles. The aligned magnetic nanoparticles embedded in the polymerized resin produce a net magnetic moment that enables the rotational motion to be controlled by an external rotating magnetic field. When the rotational axis is parallel to the substrate, the microparticles exhibit rotation-induced translational motion through coupling between the microparticle surface and substrate, as shown in Figure 9c. The nanoarchitecture on the microparticle surface enhances the coupling efficiency through mechanical interactions to facilitate translational motion. Remote control of the particle locomotion is potentially useful in microrobots, microfluidic pumps, and mixers.

Colloidal arrays on the surfaces of microparticles can be etched away to leave behind an array of dimples. Dimpled surfaces are further treated using dry etching techniques to increase the porosity and implant chemical compounds on the surfaces. Directional dry etching produces two distinct hemispherical surfaces, as shown in Figure 6d. Unidirectional reactive ion etching using hexafluoride produces a highly porous fluorinated top surface, as shown in Figure 9e. By contrast, the bottom surface remains intact, as shown in Figure 9f. The resultant top surface becomes superhydrophobic as a result of the high porosity and the presence of fluorine atoms, whereas the bottom surface remains hydrophilic. These properties provide amphiphilicity.[59] Amphiphilic Janus particles are useful for stabilizing the interfaces between air and water. Microparticles align at an interface when the superhydrophobic surface faces the air. A dense array of microparticles at the interface forms a highly flexible and impregnable water-repelling interface. For example, microparticle arrays prevent direct contact between a hydrophilic glass rod and the underlying water, as shown in Figure 9g. Microparticle-stabilized water droplets, that is, liquid marbles, can be picked up using a pair of tweezers, as shown in Figure 9h. Stable interfaces between air and water are difficult to achieve using conventional molecular surfactants or microparticles.

Microfluidic devices can be used to incorporate distinctive multicores into double-emulsion droplets in a controlled fashion, and these multicore droplets are transformed into

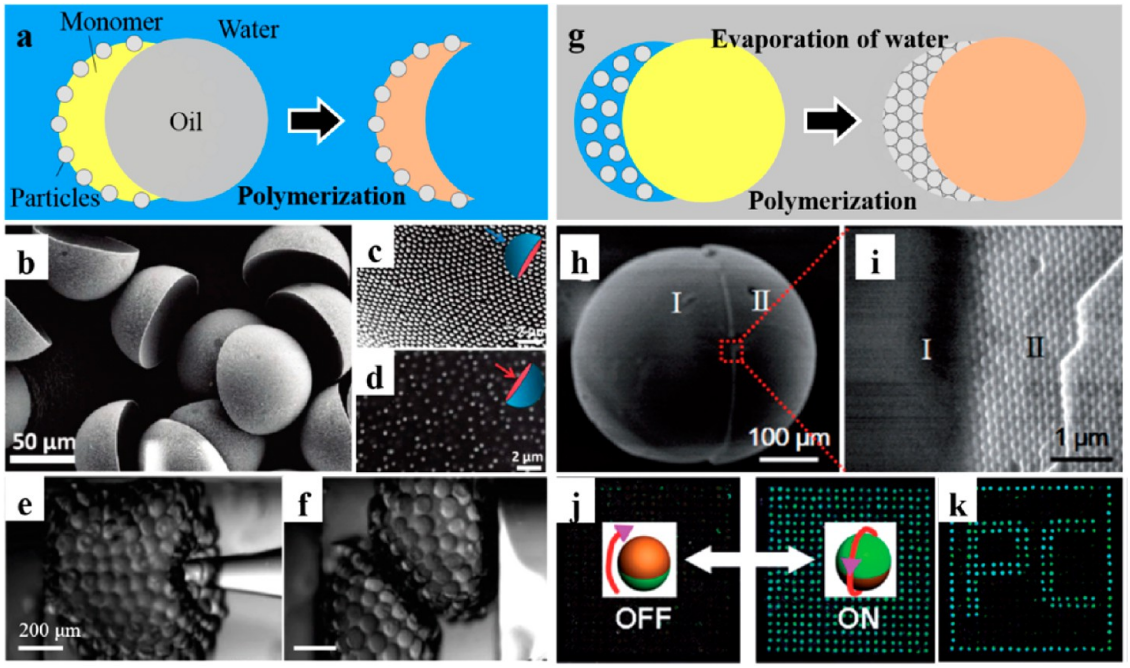

Figure 10. Nonspherical microparticles with microstructures. (a–f) Crescent-moon-shaped microparticles composed of a convex surface with nanostructure and a bare concave surface:[63] (a) schematic diagram for the preparation of the microparticles, (b–d) SEM images of the microparticles, convex surface, and concave surface, and (e, f) optical microscope images of the microparticle-stabilized oil droplets in a polar medium. (g–k) Acorn-shaped microparticles with a colloidal crystal cup:[64] (g) Schematic diagram for the preparation of the microparticles, (h, i) SEM images of the microparticle and magnified view of the edge line of the acorn cup, and (j, k) images of the microparticle array showing two different states of on and off and displaying letters "PC". Reproduced with permission from refs 63 and64. Copyright American Chemical Society (b–f) and Wiley-VCH (h–k).

microparticles, as schematically illustrated in Figure 9i. Microparticles having distinctively labeled multicores are optically identified and used as encoded microparticles in suspension arrays. The microparticle surfaces can be decorated with partially exposed colloids, as shown in Figure 9j, to provide reaction sites for molecular binding. Three distinct microparticles have been used to demonstrate a biological immunoassay. Each of the three microparticles is treated with a specific protein, and a mixture of these treated microparticles is mixed with a fluorescently labeled protein that can selectively bind to one of the proteins on the microparticles. The microparticles that present two blue and five red cores, indicated by the dotted circles, exhibit only fluorescence after binding, as shown in Figure 9k,l.[60] These results permit the identification of the fluorescently labeled protein.

Microparticles having regular internal structures can provide structural colors, as shown in Figure 8. The selective introduction of the internal structure into one hemispherical domain yields microparticles with Janus optical characteristics. The Janus microparticles are further functionalized to display electroresponsive properties by adding charged materials to the other hemisphere. For example, Janus microparticles in which one hemisphere contains a regular array of silica particles and the other contains both silica particles and carbon black nanoparticles are prepared, as shown in Figure 9m,n.[61] The templating droplets are prepared using microfluidic devices having two parallel injection channels, similar to the one shown in Figure 4a. The resulting microparticles exhibit color from one domain whereas the other domain is black. The particles are electroresponsive as a result of the anisotropic distribution of the carbon black. The boundary between the two domains is clearly observed at the surface of the microparticle, as shown in Figure 9o. These Janus microparticles are aligned under an electric field to enable switching between the two states: colored hemisphere up or carbon black hemisphere up. These microparticles have been used as the active color pigments in Gyricon display devices operated in reflection mode. Devices are implemented by embedding the microparticles in an elastomer film that is then swollen with oil to produce a microparticle-filled cavity, as shown in Figure 9p.

A photocurable suspension of magnetic particles is used to prepare compartmentalized microparticles with structural colors using a single-emulsion droplet template.[62] Under an external magnetic field, magnetic particles form chainlike structures within single emulsion droplets in a suspension. Here, the interparticle distance and chain direction are determined by the field intensity and direction, respectively. A digital micromirror array is used to select part of a droplet for polymerization under UV exposure, thereby capturing the chain structure. The unexposed part of the droplet then remains unfixed. The unexposed part is subsequently polymerized under a magnetic field having a different magnitude, resulting in a similar chain structure but with a different interparticle distance. Two or more domains having distinct structural colors can then be integrated into a single microparticle. These microparticles are potentially useful as display pigments and encoded microparticles for use in suspension arrays.

Microstructures and Shapes. Designed surfaces or internal microstructures can be incorporated into nonspherical microparticles. For example, polymeric microparticles with a crescent-moon-shape are prepared such that the convex surface presents a hexagonal array of silica particles. The array of silica particles can then render the convex surface hydrophilic relative to the concave surface to provide amphiphilic properties.[63]

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Such microparticles are produced by coemulsifying photocurable monomers containing silica particles and fluorinated inert oil in a continuous water phase to form paired droplets. A negative spreading parameter creates a dumbbell-like configuration, as shown in Figure 10a. Silica particles dispersed in the droplets of the photocurable monomers are then selectively anchored at the interface between the droplet and water, whereas the interface between the photocurable droplet and the fluorinated oil droplet remains intact as a result of the hydrophilic nature of the silica particles. Photopolymerizing the monomers and removing the inert oil yields crescent-moon-shaped microparticles having two different surfaces, as shown in Figure 10b. The hexagonal array of silica particles on the convex surface is shown in Figure 10c, and the intact concave surface is shown in Figure 10d. These microparticles efficiently stabilize oil droplets in a polar medium because of their amphiphilic properties and nonspherical shapes. The hydrophobic concave surfaces cover the oil droplet whereas the hydrophilic convex surfaces are directed toward the polar medium to prevent direct contact between the oil droplet surface and the external glass stick, as shown in Figure 10e, or with the surface of a neighboring oil droplet, as shown in Figure 10f.

Nonspherical microparticles with internal microstructure can be prepared by coemulsifying an aqueous suspension of polystyrene particles and a photocurable monomer containing magnetic nanoparticles in a continuous oil phase, as shown in Figure 10g. After the water molecules are fully evaporated from a droplet, polystyrene particles form a crystal structure in the shape of an acorn cup. The monomer droplet is then polymerized to form an acorn-shaped microparticle, as shown in Figure 10h. The edge line of the acorn cup of colloidal crystals is shown in Figure 10i. These microparticles are aligned under an external magnetic field to provide field-controlled switching of the structural color, as shown in Figure 10j. The array of microparticles displays a monocolored image under selective filliping, as shown in Figure 10k.[64]

Shapes and Compartments. Nonspherical shapes and compartments can be prepared simultaneously in a microparticle. The simplest such form is the Janus microdisk having two hemicircular domains. Microdisks are produced by injecting two distinct photocurable precursors of a hydrogel into parallel channels, followed by coemulsification in a continuous oil phase. When the height of the channel is low enough to deform the droplet into a disk shape, Janus microdisks are produced by in situ polymerization, as shown in Figure 11a. Each compartment of the Janus microdisk can include a different material. For example, magnetic nanoparticles are captured in one compartment, whereas palladium (Pd) nanoparticle-decorated tobacco mosaic virus (TMV) is captured in another compartment, as shown in Figure 11b.[65] TMV provides a nanotemplate for producing Pd nanoparticles, and the hydrogel acts as a carrier of a uniform distribution of Pd nanoparticles. The Pd nanoparticles in the microdisks are used as catalysts to facilitate the dichromate reduction reaction, as shown in Figure 11c. The conversion rate is faster for a higher loading of Pd nanoparticles. It should be noted that microparticles aged for 1 week exhibited conversion rates comparable to the rate obtained from the newly prepared microparticles. This result is attributed to the high stability of the Pd nanoparticles on the TMV substrate. However, the magnetic nanoparticles introduced magnetoresponsive properties into the microdisks. The microdisks are readily separated

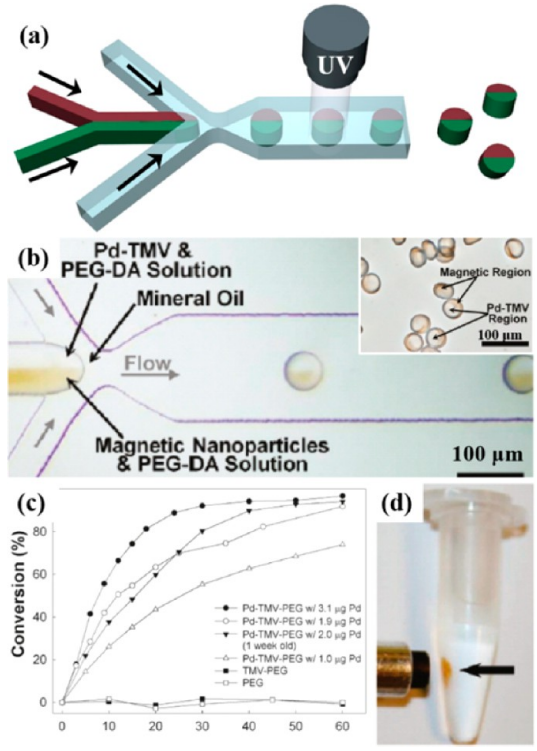


Figure 11. (a, b) Schematic illustration and optical microscope image of a microfluidic device for the production of Janus microdisks. The inset of b shows Janus microdisks containing magnetic nanoparticles in one compartment and palladium (Pd) nanoparticle-decorated tobacco mosaic virus (TMV) in the other. (c) Time dependence of conversion in the dichromate reduction reaction depending on the condition of Janus microdisks. (d) Images of Janus microdisks that are concentrated by an external magnetic field.[65] Reproduced with permission from ref 65. Copyright American Chemical Society (b–d).

under an external magnetic field, as shown in Figure 11d, and reused for the catalytic reaction.

Another type of nonspherical microparticles with multiple compartments can be prepared by double-emulsion templates.[66] When the small volume of thermopolymerizable aqueous outer droplets confine both of the photocurable oil droplet and the microgel, the outer envelope becomes nonspherical. The inner oil droplets are photopolymerized, and then the outer aqueous droplets are thermally polymerized. This results in the formation of snowmanlike microparticles; one bulb has a microgel and the other has a polymerized sphere from the oil droplets, where both of them are covered with a polymerized hydrogel layer. These anisotropic microparticles are further designed and potentially useful for the simultaneous delivery of hydrophilic and hydrophobic materials.

Shapes, Compartments, and Microstructures. All three structural features can be tuned in a single microparticle design. For example, rod-shaped microparticles containing spherical compartments with distinct structural colors have been prepared from O/W/O double-emulsion droplet templates. A capillary microfluidic device permits multiple distinct oil cores of a photocurable suspension of silica particles or magnetic nanoparticles to be generated in an aqueous solution containing a photocurable hydrogel precursor. This phase is then emulsified in a continuous oil phase, and the inner diameter of the collection capillary channel is selected to be comparable to the diameter of the cores. This device then forms cylindrical

droplets of the aqueous solution containing spherical cores, as shown in Figure 12a. In situ polymerization solidifies the

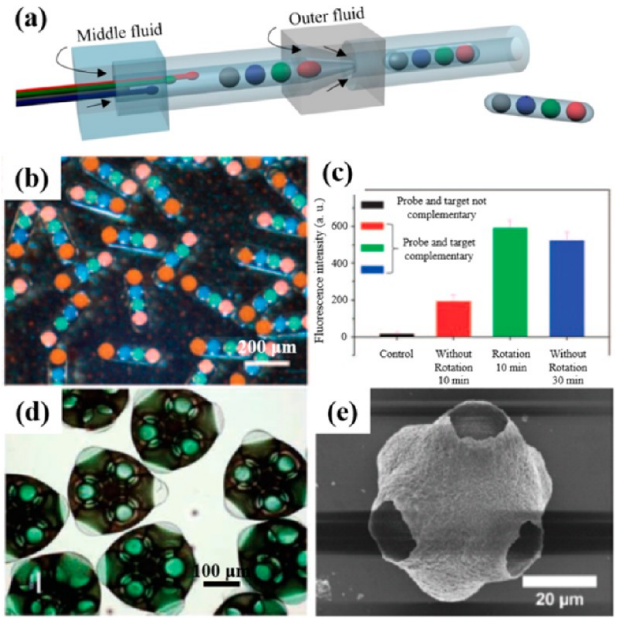


Figure 12. Nonspherical microparticles with compartments and microstructures. (a, b) Schematic illustration of a capillary microfluidic devce for the production of rod-shaped microgels containing four distinctive cores and an optical microscope image of the resultant microgels.[67] (c) Fluorescence intensity from the microgels, where the microgels are pretreated with a specific sequence of DNA and then applied to fluoresently labeled DNA. Only complementary DNA binds on the surface of microgels, and the binding efficiency is enhanced by rotating the microgels.[68] (d) Optical microscope image of triangle-shaped microparticles containing nine cores.[69] (e) SEM image of octahedron-shaped microparticles containing six cores, where the shell is composed of aggregates of silica nanoparticles; very thin parts of the shell are deconstructed during the drying of the microparticle, resulting in large windows.[69] Reproduced with permission from refs 67–69. Copyright Nature Publishing Group (b, c) and Wiley-VCH (d, e).

structure, yielding rod-shaped microgels that contain multiple cores arranged in series. For example, rod-shaped microgels containing three colored cores and one magnetic core are shown in Figure 12b. The colors arise from regular arrays of silica particles in the cores. The microparticles are used as encoded microparticles in suspension arrays. Distinct color cores arranged in series provide abundant numbers of codes. Treating the microgels with a specific sequence of DNA results in binding only to complementary DNA, where the DNA binding is much more efficient on the rotating microgels under an external magnetic field than on the stationary microgels, as shown in Figure 12c.[67]

Nonspherical microparticles can be obtained using a double-emulsion droplet template in which multiple cores are encapsulated by a small volume of a middle phase. Multiple cores are densely packed within the nonspherical envelope of a middle phase to form unique configurations that are determined only by the number of cores. For example, microparticles prepared from double-emulsion droplets having nine cores are shown in Figure 12d.[68] The middle phase drains out of the films between the outer envelope and the overhanging surfaces of the core droplets, resulting in an ultrathin film. Single colloidal particles simultaneously anchor to the interfaces formed by the ultrathin middle layer with either the core or continuous phases. After polymerization of the middle layer, the particles are etched away to create regular pores on the shell membrane. These nonspherical microparticles are composed of multiple cores and perforated shell membranes. They may potentially be useful as microcarriers for the controlled release of a drug. Similarly, nonspherical multicore microparticles can be prepared using the middle phase of an organic suspension of hydrophobic silica nanoparticles. Nanoparticles anchor at both interfaces, thereby stabilizing the nonspherical droplets. After evaporation of the organic solvent, the silica nanoparticles form nonspherical shells, as shown in Figure 12e. The regular pores of these shells are size-selectively permeable.[69]

■ SUMMARY AND OUTLOOK

Microfluidic emulsification technologies have progressed significantly over the past 10 years. Assisted by advances in technology, new classes of microparticles have been prepared and utilized, as we discuss above. Novel microparticle shapes, compartments, and microstructures have provided new opportunities to apply the microparticles in a wide range of applications. These microparticles serve as microcarriers for drugs and cells, encoded particles for biological assays, building blocks for secondary assembly, active display pigments, microsensors, interface stabilizers, and catalyst substrates. These properties are very difficult to achieve using conventional bulk emulsification methods. One obstacle to the practical use of functional microparticles is their low-throughput preparation. Although microfluidics platforms provide very uniform emulsion droplets with highly controlled compositions and structures, the platforms essentially offer droplet-by-droplet production, which limits the production rate. Recent advances in microfluidics have partially overcome this barrier by parallelizing droplet fabrication and enhancing the production rate by a factor of 100.[70] These results constitute huge progress, although the progress is not yet sufficient to facilitate the use of the microparticles in the full range of applications. Microfluidics cannot completely replace bulk emulsification methods. In fact, replacement is not necessary because not all applications require high-quality uniform microparticles. Even at the current throughput levels, microfluidics devices can provide sufficient quantities of functional microparticles for high-end applications, such as microcarrier applications of drugs or cells and microsensor applications. Enhanced throughput using parallelization will provide larger quantities at a lower price. In addition, particles designed using microfluidic devices can provide tools for optimizing systems because the uniform properties of microparticles provide the key features required for specific applications. From this optimization, some key features can be reproduced in particles produced by the bulk method, thereby providing a large quantity of functional particles for bulk applications. The design of functional microparticles using microfluidic devices continues to progress to meet the needs of a wide range of old and new applications.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kim.sh@kaist.ac.kr. Tel: +82 42 350-3911. Fax: +82 42 350-3910 (S.H.K.).

Notes

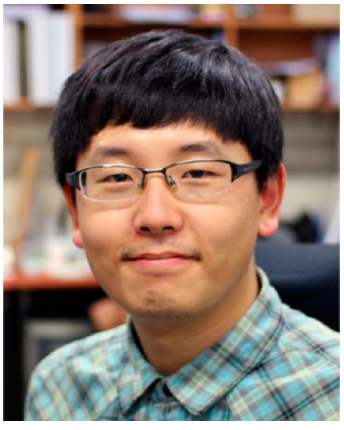
The authors declare no competing financial interest.

Biographies

Ju Hyeon Kim received his B.S. degree in chemical and biomolecular engineering from KAIST, Korea, in 2011. He is currently a Ph.D. candidate in the same department. His research interest is droplet microfluidics for reconfigurable photomasks.

Tae Yoon Jeon received his B.S. degree in chemical and biomolecular engineering from Sogang University, Korea, in 2011. He is currently a Ph.D. candidate in chemical and biomolecular engineering at KAIST. His research interest is the patterning of polymeric and metallic nanostructures using interference lithography.

Tae Min Choi received his B.S. degree in chemical and biomolecular engineering from KAIST, Korea, in 2013. He is currently a Ph.D. candidate in the same department. His research interest is microfluidic encapsulation of colloidal photonic crystals.



Tae Soup Shim received his B.S. in chemical engineering from Yonsei University, Korea, in 2007 and his Ph.D. in chemical and biomolecular engineering from KAIST, Korea, in 2013. He is currently working in chemical and biomolecular engineering at KAIST as a postdoctoral researcher. His research interests lie in biomimetics, colloidal self-assembly, microfluidics, and the fabrication of responsive biopolymers.

Shin-Hyun Kim received his B.S. in chemical engineering from Yonsei University, Korea, in 2004 and his Ph.D. in chemical and biomolecular engineering from KAIST, Korea, in 2009. Following this, he worked as a postdoctoral researcher at Harvard University. He is currently working at KAIST, Korea, as an assistant professor of chemical and biomolecular engineering and KAIST Institute for the NanoCentury. His major research interests include colloidal self-organization in confined geometry, droplet-based microfluidics, and the synthesis of functional microparticles and capsules.

Seung-Man Yang earned his Ph.D. degree in chemical engineering from Caltech in 1985. He subsequently joined KAIST as a professor in chemical and biomolecular engineering. His principal contributions have been in theories and experimental methods for fabricating smart

soft matter. He has authored over 250 peer-reviewed papers and books and patents in related areas. He received the 2007 DuPont Science and Technology Award, the Man of the Year 2008 of KAIST, and the 2009 Kyung-Am Prize for Sciences and Arts. He passed away on September 26, 2013.

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■ DEDICATION

[§]Professor Yang passed away unexpectedly on September 26, 2013. We dedicate this work as a memorial to him.

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