Fabrication of monodisperse thermosensitive microgels and gel capsules in microfluidic devices

Rhutesh K. Shah,[a] Jin-Woong Kim,[ab] Jeremy J. Agresti,[a] David A. Weitz*[ac] and Liang-Yin Chu*[ad]

DOI: 10.1039/b808653m

We use droplet-based microfluidic techniques to produce monodisperse poly(*N*-isopropylacrylamide) gel particles in the size range of 10--1000 μm. Our techniques offer exquisite control over both outer dimensions and inner morphology of the particles. We demonstrate this control by fabricating conventional microgels, microgels with embedded materials and voids, and gel microcapsules with single- and multi-phase cores. These techniques should be applicable for the synthesis of particles and capsules of a variety of chemical compositions and for the generation of higher order "supraparticles" by directed assembly of colloidal particles in droplets.

1.0 Introduction

Stimuli-sensitive microgels are cross-linked polymeric particles that swell or shrink reversibly by absorbing or releasing solvent in response to changes in the surrounding temperature, pH, ionic strength, electromagnetic field, or other conditions.[1,2] Their responsiveness to the external environment makes them attractive candidates for applications in drug delivery,[2–8] catalysis,[9–12] sensing,[13–18] and photonics.[2,19–21] Poly(*N*-isopropylacrylamide), PNIPAM, microgels are an example of thermosensitive microgels: their size change is triggered by changes in temperature. The polymer chains forming these microgels contain both hydrophilic amide groups and hydrophobic isopropyl groups. When dispersed in water at low temperatures, generally below 32 °C, the amide groups of the microgels interact strongly with water through hydrogen bonding and these strong interactions force water into the microgels causing them to swell. However, at higher temperatures, the hydrogen bonds between water and the amide groups are disrupted causing water to act as a poor solvent. As a result, water is expelled from the microgels, the polymer network collapses, and the particles shrink dramatically.[1] The transition is sharp and occurs at a relatively lower temperature (~32 °C) compared to other known thermosensitive microgels.[22]

Certain applications, such as controlled release of macromolecules, require microgels to have a narrow size distribution since the loading levels and release kinetics are directly affected by the polydispersity of the particles. Common synthesis techniques like emulsion polymerization[1,23–25] and solvent-free emulsion polymerization[26–29] can produce PNIPAM microgels with low polydispersity. However, these microgels are submicron in size. Synthesis of monodisperse PNIPAM microgels with dimensions of the order of several microns is more challenging. One method entails emulsification of monomer mixtures to form pre-microgel drops in

[a]*School of Engineering and Applied Sciences, Harvard University, CambridgeMassachusetts, 02138, USA. E-mail: weitz@seas.harvard.edu; chuly@scu.edu.cn*
[b]*Amore-Pacific R&D Center, 314-1, Bora-dong, Giheung-gu, Yongin-siGyeonggi-Do, 446-729, Korea*
[c]*Department of Physics, Harvard University, CambridgeMassachusetts, 02138, USA*
[d]*School of Chemical Engineering, Sichuan University, ChengduSichuan, 610065, China*

Rhutesh K. Shah

David A. Weitz

David A. Weitz is the Mallinckrodt Professor of Physics and Applied Physics and the director of the Materials Research Science and Engineering Center (MRSEC) at Harvard University. His current research involves developing new techniques to probe the mechanical properties of soft materials and engineering novel structures from colloids, polymers, and lipids, to encapsulate materials.

Liang-Yin Chu

a continuous phase followed by polymerization of the monomers in these drops; the method, thus, uses drops as templates for microgel fabrication. The key to monodispersity of microgels made using this method lies in the generation of highly monodisperse pre-microgel drops – a task that can be effectively accomplished using microfluidic techniques.[30–32] Drops in microfluidic devices are produced in series, in contrast to bulk emulsification methods where drops are formed in parallel under the influence of an external shear. The mechanism of drop formation is a balance of interfacial tension and the shear of the continuous phase acting on the dispersed phase. The interfacial tension is constant for a given pair of fluids, and the shear rate is precisely controlled using microfluidic devices. As a result, these techniques offer greater control over size and polydispersity of the emulsified drops compared to bulk emulsification methods. In addition, microfluidic devices allow execution of the two fabrication steps, emulsification of pre-microgel drops and monomer polymerization, to occur within the same device in a stepwise continuous fashion. This operational feature significantly reduces the possibility of droplet coalescence before polymerization, and thus, ensures that the monodispersity of the droplets is retained by the microgels.

Here we review and summarize methods to fabricate monodisperse PNIPAM microgels using microfluidic devices. We begin with a brief overview of particle fabrication in microfluidic devices and then transition to the specific example of PNIPAM microgels. The diameters of our microgels can be precisely controlled over a range of 10 to 1000 μm by tuning the flow rates of the fluids. We describe the fabrication of microgels in capillary microfluidic devices, as well as polydimethylsiloxane (PDMS) devices made using soft lithography. We also describe the generation of PNIPAM gel particles with different internal morphologies, created by modifying the microfluidic techniques.

2.0 Microgel fabrication in microfluidic devices

Microfluidic devices made from PDMS or polyurethane elastomers using soft lithography have been employed to fabricate monodisperse solid polymeric particles and microgels.[33–40] This is accomplished by forming monodisperse pre-microgel drops and polymerizing the monomers or crosslinking the polymers within these drops. To ensure monodisperse drop formation a flow-focusing geometry is patterned into these devices.[30] The mechanisms by which these drops gel are categorized[37,41] as chemical gelation,[40,42,43] temperature-change-induced gelation,[36] coalescence-induced gelation,[44,45] and ionic gelation using internal and external crosslinking.[46,47] Polymerization of monomers and/or gelation of polymers in these methods is initiated by ultraviolet (UV) irradiation, heat transfer, or chemical transport in and out of the droplets.

To date, microfluidic routes have not been explored for the formation of PNIPAM microgels. Since NIPAM polymerizes by free-radical polymerization, its polymerization can be effectively induced by heat, UV irradiation, or chemical means. The internal microstructure of PNIPAM gels, and thus, their swelling and deswelling kinetics are greatly affected by the choice of the reaction inducer and the polymerization conditions.[48–51] Gels prepared at temperatures higher than the phase transition temperature of PNIPAM exhibit a highly inhomogeneous internal microstructure. By contrast, those formed by chemical diffusion at low temperatures, below the phase transition temperature, reveal a microstructure with less inhomogeneity. The PNIPAM microgels described in this article are fabricated at room temperature through a redox reaction initiated or accelerated by chemicals introduced into the monodisperse droplets made in microfluidic devices.

3. PNIPAM microgel fabrication in capillary microfluidic devices

Capillary microfluidic devices were developed to fabricate monodisperse single and multiple emulsions.[31,32,52] These devices consist of coaxial assemblies of glass capillary tubes. The inner capillaries are circular in cross-section and are placed within square capillaries. Precision alignment of the coaxial geometry is achieved by matching the outer diameters of the inner circular capillaries to the inner dimensions of the outer square capillaries. The design of these devices was modified to convert them into micro-reactors for synthesizing monodisperse PNIPAM microgels. In one implementation,[53] a circular capillary is placed within two square capillaries such that one end of the circular capillary lies in one (left) square capillary while the other end lies in the other (right), as shown in Fig. 1(a). Prior to its placement in the square capillaries, the circular capillary is heated and pulled using a pipette puller to create a tapered geometry that culminates in a fine orifice. An aqueous solution containing the monomer, NIPAM, a crosslinking monomer, *N*,*N*′-methylenebisacrylamide (BIS), and initiator, ammonium

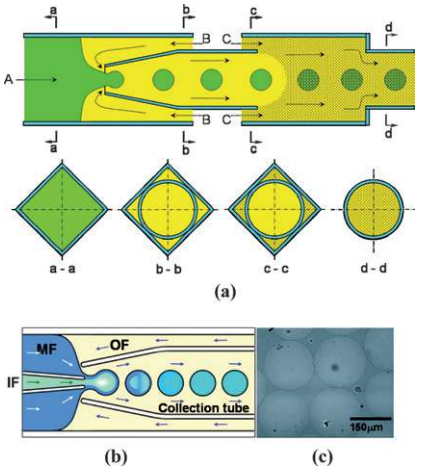

Fig. 1 (a) Schematic illustration of a capillary microfluidic device for making monodisperse PNIPAM microgels. Fluid A is an aqueous suspension containing the monomer, crosslinker, and initiator; fluid B is an oil, and fluid C is the same oil as fluid B but contains a reaction accelerator that is both water- and oil soluble. The accelerator diffuses into the drops and polymerizes the monomers to form monodisperse microgels. Cross-sectional views at different points along the device length are shown in the second row. (b) Schematic of an alternate device for making PNIPAM microgels. The outer fluid (OF) is an oil, the middle fluid (MF) is an aqueous solution containing the monomer, crosslinker, accelerator, and other functionalizing chemicals, and the inner fluid (IF) is an aqueous solution containing the reaction initiator. The drops of the inner and middle fluids coalesce to form microgels. (c) A bright-field microscope image of PNIPAM microgels in water. (Reproduced with permission from ref. 46and 48 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA.).

persulfate (APS), is pumped into the left end of the left square capillary. The continuous phase, kerosene, pumped through the right end of the left square capillary, flows through the region between the square and the circular capillaries and hydrodynamically focuses the aqueous phase into the tapered end of the circular capillary. The aqueous phase breaks into droplets at the entrance orifice of the tapered tube, forming monodisperse emulsion drops in the tube as shown in Fig. 1(a). The reaction accelerator, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED), dissolved in kerosene, is pumped through the left end of the right square tube. Since TEMED is soluble in both kerosene and water, it diffuses from kerosene into the aqueous droplets as the emulsion flows down the right square capillary. When the accelerator meets the initiator present in the aqueous droplets it triggers a redox reaction, polymerizing the monomers and resulting in the formation of monodisperse microgels. This chemical process is similar to the internal gelation process used to make alginate microgels,[37,46] where, the continuous phase contains a compound that diffuses into alginate containing droplets and triggers the release of cations that crosslink the alginate polymer chains causing gelation of droplets.

An alternate design of microfluidic devices consists of two internal cylindrical capillaries serving as injection and collection tubes coaxially aligned inside a square capillary.[54] The middle fluid (MF) is an aqueous solution containing the monomer (NIPAM), crosslinker (BIS), and accelerator (TEMED), whereas the outer fluid (OF) is oil. The reaction initiator (APS) is dissolved in water and injected in the droplets using the internal cylindrical tube shown on the left hand side of the device [Fig. 1(b)]. Since the inner and outer drops are both aqueous, they coalesce, bringing the accelerator in contact with the reaction initiator, thus causing the monomers to polymerize and gel as they flow down the collection tube. The injection tube is slightly inserted inside the collection tube to prevent clogging of either tube by premature gelation of drops. The result is a collection of monodisperse PNIPAM microgels as shown in Fig. 1(c). This process is similar to coalescence induced gelation described for biopolymers, where one drop containing a biopolymer solution is coalesced with another drop containing a crosslinker to form a biopolymer microgel.[37,45]

In both devices, the size of the microgels generated essentially follows the size of the pre-microgel drops, and can be effectively controlled by tuning the relative flow rates of the fluids or the size of the capillary orifices. The microgels exhibit an equilibrium volume change similar to that displayed by a PNIPAM bulk gel.[55] Upon heating from 20 to 40 °C, the microgel diameter decreases from ~95 to ~40 μm, which roughly corresponds to a thirteen-fold drop in particle volume [Fig. 2]. This temperature-dependent size change is sharp, reversible, and reproducible over several heating–cooling cycles. The equilibrium size change and response kinetics can be controlled by varying the crosslinker concentration, particle size, and by chemical modification. Microgels with a higher crosslinker concentration exhibit a smaller volume change as compared to those with lower crosslinker concentration. Also, since the response time of these gels is proportional to the square of their linear dimension, smaller microgels respond significantly faster to changes in temperature by comparison to larger microgels.

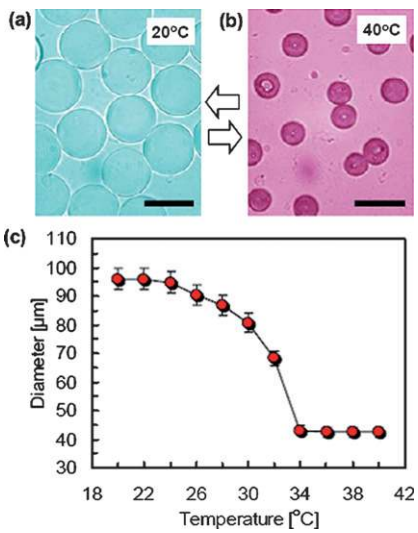

Fig. 2 Bright-field images of microgels prepared using a capillary microfluidic device in pure water at (a) 20 °C and (b) 40 °C. The scale bars represent 100 μm. (c) Diameter-change of these PNIPAM microgels plotted as a function of temperature.

4. PNIPAM microgel fabrication in poly(dimethylsiloxane), PDMS, devices

The microgel fabrication technique can be easily adapted to more conventional microfluidic devices made from a silicon elastomer of PDMS using soft-lithography methods.[56–58] As in capillary devices, the process involves two steps: formation of monodisperse pre-microgel drops and the polymerization of the monomers within these drops. In our system, the dispersed fluid is an aqueous solution containing the monomer (NIPAM), an initiator, and a crosslinker, while the continuous fluid is a kerosene solution containing a surfactant, polyglycerol polyricinoleate (PGPR 90) as shown in Fig. 3(a) and 3(b). The continuous fluid hydrodynamically focuses the dispersed fluid into a narrow channel, where monodisperse pre-microgel drops are formed as shown in Fig 3(c). A third fluid, kerosene containing both PGPR 90 and the accelerator, is added to the continuous fluid downstream of the drop generation as shown in Fig. 3(d). The accelerator diffuses into the drops and catalyzes gelation of the drops. The microgels formed by this method exhibit thermosensitive behavior similar to those formed using glass capillary microfluidic devices; their size can be controlled by controlling the relative flow rates of the fluids.[59]

An advantage of using these PDMS devices is the ease of production. Once a mask is designed, it is easy to produce a large number of devices. Moreover, these devices can be operated in parallel to produce microgels at a much higher rate than can be achieved with a single device.

5. Fabrication of monodisperse PNIPAM gel particles with different internal morphologies

PNIPAM gel microparticles with different internal structures can be fabricated by manipulating the microfluidic processes. For example, microgels can be fabricated with embedded materials and voids or as thin shells with aqueous or multi-phase cores.

5.1 Microgels with embedded materials

A variety of functional materials can be embedded in the PNIPAM microgels by

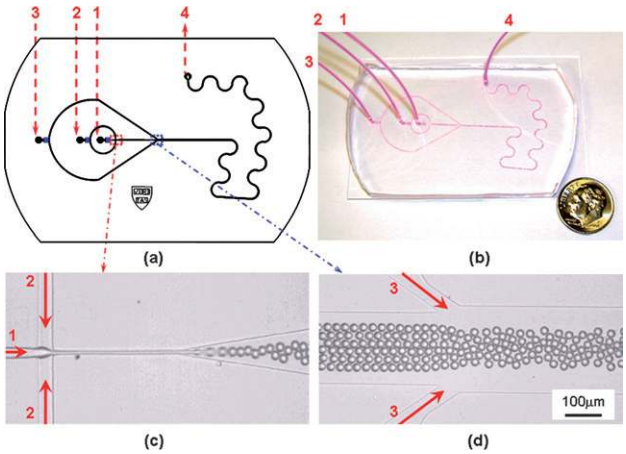

Fig. 3 (a) Schematic illustration of a PDMS microfluidic device for synthesizing monodisperse PNIPAM microgels. (b) Image of an actual PDMS microfluidic device. The polyethylene tubing and device-microchannels are filled with a dye containing aqueous solution for increased image contrast. Fluid 1 is an aqueous solution containing the monomer, initiator and crosslinker, fluid 2 is a kerosene solution containing a surfactant, and fluid 3 is a kerosene solution containing a surfactant and a reaction accelerator. The USA dime (17.9 mm in diameter) offers a visual perspective of the dimensions of the device and its microchannels. (c) Bright-field image of drop formation by flow focusing in the PDMS device (d) Bright-field image of the microchannel further downstream from the flow focusing junction. The image reveals an array of monodisperse droplets of the monomer solution in the region where the accelerator solution mixes with the continuous phase.

suspending them in the aqueous monomer mixture. These functional materials endow the microgels with specific chemical or physical properties for targeted applications. We demonstrate this by fabricating microgels with fluorescently labeled polymer microparticles, quantum dots, and magnetic nanoparticles [Fig. 4(a–c)].[54] The addition of functional materials has no detrimental effect on the thermosensitive behavior of the microgels. This is because of the fact that these materials are not chemically bonded to the polymer network but are only physically trapped within it.

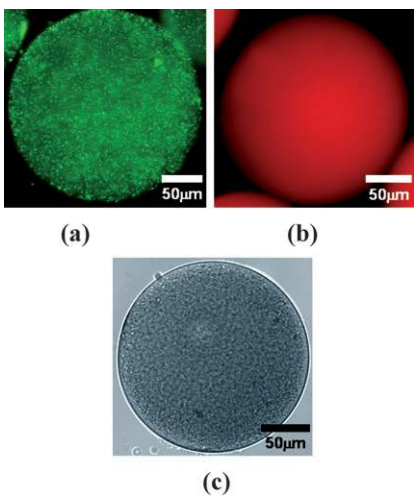

Fig. 4 Microgels with embedded materials. (a) A fluorescence microscope image of a microgel containing fluorescently labeled 1-μm diameter polystyrene particles. (b) A fluorescence microscope image of a microgel containing 19-nm quantum dots. (c) A bright-field microscope image of a microgel containing 10-nm magnetic particles. (Reproduced with permission from ref. 48 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA.).

5.2 Microgels with multiple voids

Monodisperse microgels with voids can be generated by using any of the microfluidic devices. Such microgels offer less resistance to the transport of water compared to those with a continuous core. Thus, the kinetics of swelling and deswelling, which are typically governed by the transport of water in and out of the microgels, can be effectively controlled by varying the number of voids inside the microgels. We make microgels with voids using a two-step process.[53] First, monodisperse PNIPAM microgels containing a number of solid polystyrene microspheres are synthesized in a capillary microfluidic device. Then, the embedded microspheres are chemically dissolved by immersing the polymerized microgels in xylene; this leaves voids inside the microgels. Microgels containing different numbers of 25 μm diameter polystyrene beads are shown in the top row of Fig. 5(a) while those with internal voids formed by dissolving such beads are shown in the bottom row of Fig. 5(a). The dynamics of shrinking and swelling of microgels with voids are more rapid than those of same-sized voidless microgels. When temperature is increased from 23 to 47 °C, the microgels with four voids shrink fastest, while the rate decreases with the number of voids, with the voidless microgels being the slowest, as shown in Fig. 5(b). The differences are more pronounced during swelling as the temperature is decreased back to 23 °C, as shown in Fig. 5(c). The inset in Fig. 5(c) clearly reveals a systematic decrease in the time required for the inception of swelling with an increase in the number of voids.[53] This difference is a result of the higher permeability of the voids, increasing the rate of water flow.

5.3 Gel microcapsules with an aqueous core

The device featured in Fig. 1(b) can also be used to produce monodisperse double emulsions by using inner (IF) and outer fluids (OF) that are immiscible with the middle fluid (MF).[32] Such double emulsions can serve as templates to create monodisperse PNIPAM gel "microcapsules" – spherical microparticles with a core–shell structure.[54] We generate oil-in-water-in-oil (O/W/O) double emulsions using an oil solution containing the accelerator TEMED as the inner fluid and an aqueous solution containing the monomer, crosslinker, and initiator as the middle fluid [Fig. 6(a)]. Once the double emulsions are formed, the accelerator diffuses into the MF, initiating the chemical reaction and resulting in the formation of uniform core–shell structured particles. After polymerization, the inner oil is removed by repeated washings with isopropanol, and subsequently, the microparticles are transferred into water. An image of a core–shell PNIPAM gel microparticle where the shell has been labeled with a fluorescent dye is shown in Fig. 6(b). The thickness and outer diameter of these gel shells can be tuned by controlling the relative flow rates of the fluids during drop formation.

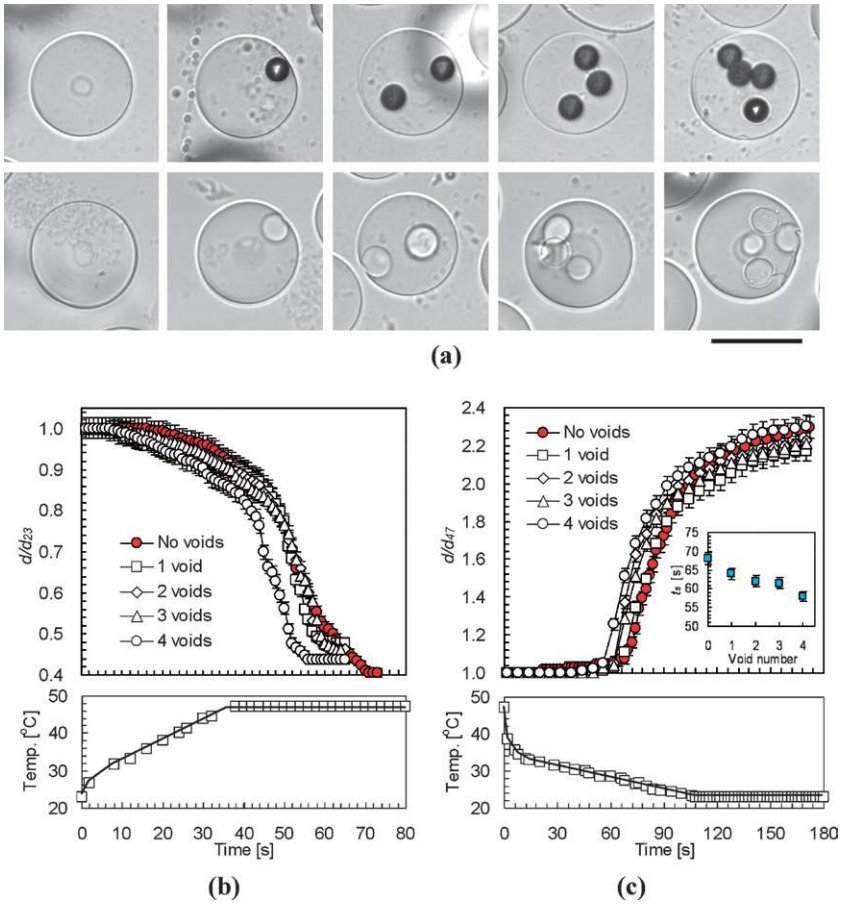

Fig. 5 (a) Microgels with different numbers of embedded polystyrene beads (top), and microgels with spherical voids formed by dissolving the embedded beads from such microgels (bottom). Scale bar represents 100 μm. (b,c) Effect of the number of voids on the dynamics of the shrinking and swelling behavior of microgels. The diameter of voids is 25 μm. The samples were (b) heated from 23 to 47 °C and (c) cooled from 47 to 23 °C; d_{23} and d_{47} are the microgel diameters at 23 and 47 °C, respectively, and t_s is the time elapsed before the microgels begin to swell. (Reproduced with permission from.ref. 46 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA.).

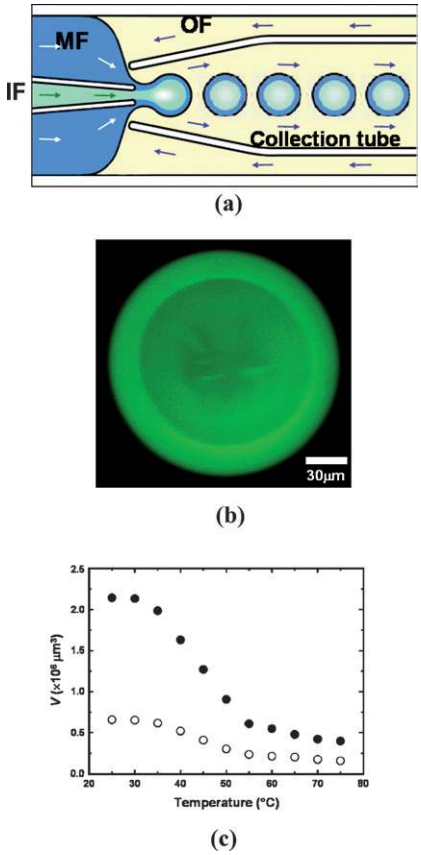

Fig. 6 (a) Schematic illustration of the capillary microfluidic device used for fabricating PNIPAM microcapsules. The inner fluid (IF) is an oil that contains a reaction accelerator, the middle fluid (MF) is an aqueous solution containing the monomer, crosslinker, and initiator, and the outer fluid (OF) is an oil. The accelerator diffuses from the inner drop into the MF and polymerizes the monomers therein to form a core–shell structure. (b) A fluorescence microscope image of a dye-labeled microgel shell. (c) Temperature dependence of the volume of the overall core–shell PNIPAM microgel (●) and its internal core (○). (Reproduced with permission from.ref 48 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA.).

When the temperature of a PNIPAM microcapsule with an aqueous core is increased from 20 °C to 75 °C, volumes of both the core and the polymer shell decrease as shown in Fig. 6(c), suggesting that the shrinking shell squeezes water out of the microcapsule. However, beyond 50 °C the core volume remains essentially unchanged while the shell volume continues to decrease. We believe this to be a result of the densification of the microgel shell, which reduces the permeability of water through it and eventually limits the degree to which the core-volume changes. Nevertheless, despite differences in volume change between the core and shell at high temperatures, the structural integrity of the microcapsule is maintained and the shell does not rupture.

5.4 Gel microcapsules with a multiphase core

Microcapillary devices used for making single and double emulsions can be further extended to make devices capable of fabricating higher order emulsions. The addition of two stages in series to a single emulsion device results in a device that is capable of forming monodisperse triple emulsions as shown in Fig. 7(a). The size and number of the internal drops can be precisely controlled by tuning the flow-rates of the fluids.[31,52] Such a triple emulsion device can be used to create monodisperse PNIPAM shells that encapsulate a multiphase core. To prepare these PNIPAM microcapsules, we use a water-in-oil-in-water-in-oil (W/O/W/O) emulsion system. The outermost fluid is a surfactant containing oil while the outer middle fluid (II) is an aqueous solution of the monomer, crosslinker and the initiator. The inner middle fluid (I) is silicon oil containing the reaction accelerator while the innermost fluid is water. Once the triple emulsions are formed, the accelerator in the middle fluid (I) diffuses into the outer aqueous shell containing the monomer and the initiator and catalyzes polymerization of NIPAM.

The resultant microcapsules consist of a shell of thermo-sensitive hydrogel,

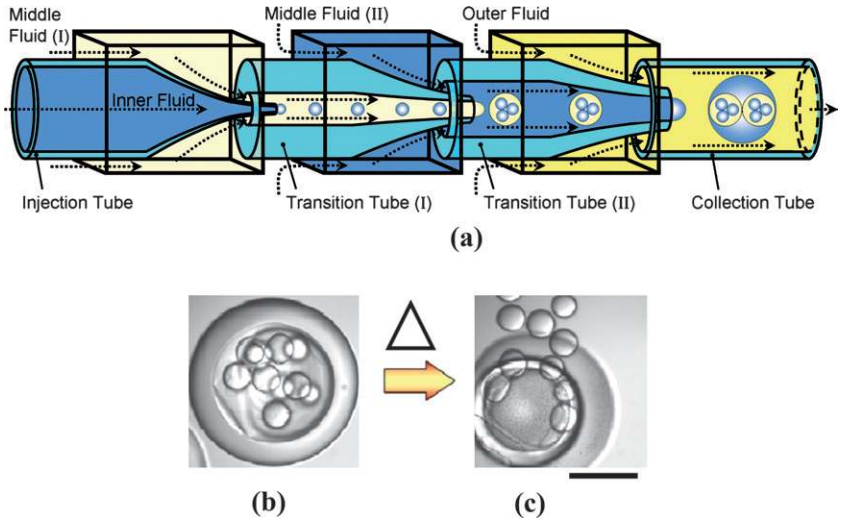

Fig. 7 (a) Schematic illustration of a capillary microfluidic device for generating controllable monodisperse triple emulsions. This device is used for generating monodisperse PNIPAM microcapsules each encapsulating a multi-phase core. The inner fluid is water, middle fluid (I) is oil containing a reaction accelerator, middle fluid (II) is an aqueous solution containing PNIPAM monomer, crosslinker, and initiator, while the outer fluid is oil. (b) Optical micrograph of the fabricated PNIPAM microcapsule at 25 °C. The shell is made of PNIPAM while the core contains monodisperse water droplets dispersed in oil. (c) Optical micrograph of the same microcapsule at 50 °C. When temperature is increased from 25 to50 °C, the PNIPAM shell shrinks by expelling water and eventually bursts under the stress exerted by its incompressible core, thus releasing the encapsulated contents into the outer continuous phase. The scale bar represents 200 μm. (Reproduced with permission from ref. 31 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA.).

which encapsulates an oil core containing several water droplets as shown in Fig. 7(b). When the temperature is increased above the phase transition temperature of PNIPAM, the thermosensitive hydrogel shell rapidly shrinks by expelling water. The incompressible oil in the core, for which the hydrogel shell has low permeability, exerts a counter-stress on the inner wall of the shell. As a result, the shell ruptures, and the encapsulated core of oil and water droplets is instantaneously released.[31] Such monodisperse multiphase capsules can be extremely useful in the simultaneous pulsed release of both water and oil soluble macromolecules.

6.0 Conclusion and outlook

We have highlighted here some novel techniques for producing monodisperse PNIPAM gel particles using microfluidic devices. These devices enable fabrication of the particles one at a time and offer robust and precise control over the external dimensions, which can range from ~10 to ~1000 μm. Moreover, the flexibility of the multiple emulsion technique can be used to finely control the internal morphology of the structures. We demonstrate this by fabricating conventional microgels, microgels with multiple voids, and gel microcapsules with single- and multiple-phase cores. Such particles have potential use in applications that require sequestering of macromolecules such as drugs or cosmetics and releasing them in a controlled fashion. We demonstrate the use of both capillary and PDMS microfluidic devices for making these gel particles. Although we have only discussed the fabrication of PNIPAM microparticles here, these techniques can be adapted to make similar structures of different chemical compositions. In addition, monodisperse emulsions generated using microfluidics can be used as templates to produce a variety of higher order structures or "supraparticles" – microparticles made up of smaller nanoparticles. For example microcapsules with selective permeability and high encapsulation efficiency can be fabricated by templating the assembly of nanoparticles with W/O/W double emulsions.[60] The permeability of these microcapsules can be effectively tuned by varying the size of the silica nanoparticles or by incorporating different materials such as polymers into the microcapsules. The ability to precisely control permeability and other physical properties of such capsules will enable the generation of novel and more versatile delivery vehicles suitable for different biomedical applications.

One of the challenges in the potential commercial production of particles and supraparticles using microfluidics lies in the low production rates generally achievable with these techniques. Depending upon the fluid flow rates and device geometry, a single device can produce a few grams to over a hundred grams of particles per day. Hence, in order to achieve commercially acceptable production rates, it will be necessary to operate many devices in parallel. Engineering such systems that incorporate extensive parallelization to increase production rates by several orders of magnitude remains a significant challenge.

Acknowledgements

The authors gratefully acknowledge support from the NSF (DMR-0602684), the Harvard MRSEC (DMR-0820484), Amore-Pacific, the NSFC (20674054), and the Key Project of the Ministry of Education of China (106131). We also thank Daeyeon Lee and Anderson Shum for useful discussions.

References

1 B. R. Saunders and B. Vincent, *Adv. Colloid Interface Sci.*, 1999, **80**, 1–25.
2 M. Das, H. Zhang and E. Kumacheva, *Annu. Rev. Mater. Res.*, 2006, **36**, 117–142.
3 N. Murthy, Y. X. Thng, S. Schuck, M. C. Xu and J. M. J. Frechet, *J. Am. Chem. Soc.*, 2002, **124**, 12398–12399.
4 S. V. Vinogradov, T. K. Bronich and A. V. Kabanov, *Adv. Drug Delivery Rev.*, 2002, **54**, 135–147.
5 V. C. Lopez, J. Hadgraft and M. J. Snowden, *Int. J. Pharm.*, 2005, **292**, 137–147.
6 L. Bromberg and V. Alakhov, *J. Controlled Release*, 2003, **88**, 11–22.
7 D. A. LaVan, D. M. Lynn and R. Langer, *Nat. Rev. Drug Discovery*, 2002, **1**, 77–84.
8 S. Nayak, H. Lee, J. Chmielewski and L. A. Lyon, *J. Am. Chem. Soc.*, 2004, **126**, 10258–10259.
9 Y. Lu, Y. Mei, M. Ballauff and M. Drechsler, *J. Phys. Chem. B*, 2006, **110**, 3930–3937.
10 D. E. Bergbreiter, B. L. Case, Y. S. Liu and J. W. Caraway, *Macromolecules*, 1998, **31**, 6053–6062.

11 A. Pich, J. Hain, Y. Lu, V. Boyko, Y. Prots and H. J. Adler, *Macromolecules*, 2005, **38**, 6610–6619.
12 C. W. Chen, M. Q. Chen, T. Serizawa and M. Akashi, *Chem. Commun.*, 1998, 831–832.
13 K. Iwai, Y. Matsumura, S. Uchiyama and A. P. de Silva, *J. Mater. Chem.*, 2005, **15**, 2796–2800.
14 G. E. Morris, B. Vincent and M. J. Snowden, *J. Colloid Interface Sci.*, 1997, **190**, 198–205.
15 G. Zenkl, T. Mayr and I. Khmant, *Macromol. Biosci.*, 2008, **8**, 146–152.
16 T. Hoare and R. Pelton, *Macromolecules*, 2007, **40**, 670–678.
17 V. Lapeyre, I. Gosse, S. Chevreux and V. Ravaine, *Biomacromolecules*, 2006, **7**, 3356–3363.
18 A. Jeenanong and H. Kawaguchi, *Colloids Surf., A: Physicochem. Eng. Asp.*, 2007, **302**, 403–410.
19 L. A. Lyon, J. D. Debord, S. B. Debord, C. D. Jones, J. G. McGrath and M. J. Serpe, *J. Phys. Chem. B*, 2004, **108**, 19099–19108.
20 D. Suzuki, J. G. McGrath, H. Kawaguchi and L. A. Lyon, *J. Phys. Chem. C*, 2007, **111**, 5667–5672.
21 S. Q. Xu, J. G. Zhang, C. Paquet, Y. K. Lin and E. Kumacheva, *Adv. Funct. Mater.*, 2003, **13**, 468–472.
22 R. Pelton, *Adv. Colloid Interface Sci.*, 2000, **85**, 1–33.
23 Y. Hirose, T. Amiya, Y. Hirokawa and T. Tanaka, *Macromolecules*, 1987, **20**, 1342–1344.
24 H. Kawaguchi, K. Fujimoto and Y. Mizuhara, *Colloid Polym. Sci.*, 1992, **270**, 53–57.
25 S. J. Mears, Y. Deng, T. Cosgrove and R. Pelton, *Langmuir*, 1997, **13**, 1901–1906.
26 M. J. Snowden and B. Vincent, *J. Chem. Soc., Chem. Commun.*, 1992, 1103–1105.
27 R. H. Pelton and P. Chibante, *Colloids Surf.*, 1986, **20**, 247–256.
28 B. R. Saunders and B. Vincent, *J. Chem. Soc., Faraday Trans.*, 1996, **92**, 3385–3389.
29 K. C. Tam, S. Ragaram and R. H. Pelton, *Langmuir*, 1994, **10**, 418–422.
30 S. L. Anna, N. Bontoux and H. A. Stone, *Appl. Phys. Lett.*, 2003, **82**, 364–366.
31 L. Y. Chu, A. S. Utada, R. K. Shah, J. W. Kim and D. A. Weitz, *Angew. Chem., Int. Ed.*, 2007, **46**, 8970–8974.
32 A. S. Utada, E. Lorenceau, D. R. Link, P. D. Kaplan, H. A. Stone and D. A. Weitz, *Science*, 2005, **308**, 537–541.
33 D. Dendukuri, D. C. Pregibon, J. Collins, T. A. Hatton and P. S. Doyle, *Nat. Mater.*, 2006, **5**, 365–369.
34 J. H. Jang, D. Dendukuri, T. A. Hatton, E. L. Thomas and P. S. Doyle, *Angew. Chem., Int. Ed.*, 2007, **46**, 9027–9031.
35 M. Seo, Z. H. Nie, S. Q. Xu, M. Mok, P. C. Lewis, R. Graham and E. Kumacheva, *Langmuir*, 2005, **21**, 11614–11622.
36 S. Q. Xu, Z. H. Nie, M. Seo, P. Lewis, E. Kumacheva, H. A. Stone, P. Garstecki, D. B. Weibel, I. Gitlin and G. M. Whitesides, *Angew. Chem., Int. Ed.*, 2005, **44**, 724–728.
37 H. Zhang, E. Tumarkin, R. M. A. Sullan, G. C. Walker and E. Kumacheva, *Macromol. Rapid Commun.*, 2007, **28**, 527–538.
38 D. Dendukuri, K. Tsoi, T. A. Hatton and P. S. Doyle, *Langmuir*, 2005, **21**, 2113–2116.
39 Z. H. Nie, W. Li, M. Seo, S. Q. Xu and E. Kumacheva, *J. Am. Chem. Soc.*, 2006, **128**, 9408–9412.
40 R. F. Shepherd, J. C. Conrad, S. K. Rhodes, D. R. Link, M. Marquez, D. A. Weitz and J. A. Lewis, *Langmuir*, 2006, **22**, 8618–8622.
41 J. K. Oh, R. Drumright, D. J. Siegwart and K. Matyjaszewski, *Prog. Polym. Sci.*, 2008, **33**, 448–477.
42 B. G. De Geest, J. P. Urbanski, T. Thorsen, J. Demeester and S. C. De Smedt, *Langmuir*, 2005, **21**, 10275–10279.
43 W. J. Jeong, J. Y. Kim, J. Choo, E. K. Lee, C. S. Han, D. J. Beebe, G. H. Seong and S. H. Lee, *Langmuir*, 2005, **21**, 3738–3741.
44 K. Liu, H. J. Ding, J. Liu, Y. Chen and X. Z. Zhao, *Langmuir*, 2006, **22**, 9453–9457.
45 S. Sugiura, T. Oda, Y. Izumida, Y. Aoyagi, M. Satake, A. Ochiai, N. Ohkohchi and M. Nakajima, *Biomaterials*, 2005, **26**, 3327–3331.
46 C. P. Reis, R. J. Neufeld, S. Vilela, A. J. Ribeiro and F. Veiga, *J. Microencapsulation*, 2006, **23**, 245–257.
47 H. Zhang, E. Tumarkin, R. Peerani, Z. Nie, R. M. A. Sullan, G. C. Walker and E. Kumacheva, *J. Am. Chem. Soc.*, 2006, **128**, 12205–12210.
48 Y. Hirokawa, H. Jinnai, Y. Nishikawa, T. Okamoto and T. Hashimoto, *Macromolecules*, 1999, **32**, 7093–7099.
49 A. Suzuki, Y. Kobiki and M. Yamazaki, *Jpn. J. Appl. Phys., Part 1*, 2003, **42**, 2810–2817.
50 X. J. Ju, L. Y. Chu, X. L. Zhu, L. Hu, H. Song and W. M. Chen, *Smart Mater. Struct.*, 2006, **15**, 1767–1774.
51 S. Takata, K. Suzuki, T. Norisuye and M. Shibayama, *Polymer*, 2002, **43**, 3101–3107.
52 R. K. Shah, H. C. Shum, A. C. Rowat, D. Lee, J. J. Agresti, A. S. Utada, C. L. Y., J. W. Kim, A. Fernandez-Nieves, C. J. Martinez and D. A. Weitz, *Mater. Today*, 2008, **11**, 18–27.
53 L. Y. Chu, J. W. Kim, R. K. Shah and D. A. Weitz, *Adv. Funct. Mater.*, 2007, **17**, 3499–3504.
54 J.-W. Kim, A. S. Utada, A. Fernández-Nieves, Z. B. Hu and D. A. Weitz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1819–1822.
55 E. S. Matsuo and T. Tanaka, *J. Chem. Phys.*, 1988, **89**, 1695.
56 Y. N. Xia and G. M. Whitesides, *Angew. Chem., Int. Ed.*, 1998, **37**, 551–575.
57 G. M. Whitesides and A. D. Stroock, *Phys. Today*, 2001, **54**, 42–48.
58 J. C. McDonald, D. C. Duffy, J. R. Anderson, D. T. Chiu, H. K. Wu, O. J. A. Schueller and G. M. Whitesides, *Electrophoresis*, 2000, **21**, 27–40.
59 L. Y. Chu and D. A. Weitz, unpublished data.
60 D. Lee and D. A. Weitz, *Adv. Mater.*, 2008, **20**, 3498–3503.