Novel Microgels Fabricated On Microfluidic Devices

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Abstract Microgels are micrometer sized particles consisting of a polymer network that show potential for the delivery of both hydrophilic and hydrophobic drugs. Microfluidic devices provide an excellent format for the generation of monodispersed droplets due to the precise manipulation of fluids and flow rates within the microchannels. Microfluidic droplet generation chips were therefore designed using T-junction and flow focusing geometries in glass. For microgel synthesis, monomers, crosslinker and initiator were added to the dispersed phase and water was used as the continuous phase. Controlled formation of monodisperse droplets was achieved with both geometries and droplets were collected off-chip for photopolymerisation. Three types of microgel were formed using this setup: poly(ethylene glycol) diacrylate, poly(propylene glycol) diacrylate, and tetrahydropyran acrylate - ethylene glycol dimethacrylate (THPA-EGDMA) microgels. THPA is a novel material for microgels that can be turned from hydrophobic to amphiphilic by hydrolysation. THPA-EGDMA microgels in particular demonstrated a strong response to pH changes due to the build-up of electrostatic force under high pH, showing potential for the encapsulation and release of drugs.

Keywords: Microgels, Microfluidics, Polymerisation, Droplets, T-junction, Flow focusing

1. Introduction

Microgels are a relatively novel and advanced functional polymer material (Baker, 1949; Staudinger and Husemann, 1935), consisting of particles with a size range of 1 to 500 μm that feature a three-dimensionally crosslinked polymer network as an internal structure. The gel particles are usually dispersed in a solvent such as water or chloroform. Microgels can be classified as being responsive and non-responsive, depending on the presence of functional groups on the polymer chains that respond to a specific stimulus, such as temperature, pH and an electric or magnetic field (Saunders et al., 2009). Microgels respond by changing their size or structure. Such microgels are desirable in many applications, including drug delivery and oil recovery, and have thus gained a significant scientific interest (Dadsetan et al., 2013).

Traditionally, microgels are synthesised by one of two methods: (i) emulsion polymerisation or (ii) precipitation polymerisation (Saunders and Vincent, 1999). The synthesis involves the use of monomer, crosslinker and initiator. Microgels synthesised by these methods normally feature a wide size distribution with coefficient of variation (CV) from 5 to 30 % and it is not possible to fabricate amphiphilic microgels since reagents may dissolve into the continuous phase (CP) before the polymerisation is complete (Ma et al., 2010; Lee et al., 2007).

Our aim is to synthesise microgels via the polymerisation of droplets generated within microfluidic channels. Droplet microfluidics has developed rapidly over the last decade or so. Common methods for droplet generation within microfluidic devices include the use of so-called “T-junction” and “flow focusing junction” designs (Zhao and Middelberg, 2011). These enable the generation of droplets with narrow size distributions (typically under 3 %) and allow precise tuning of size and shape by adjusting flow rates or microchannel geometry (Dang et al., 2012). Contrary to the conventional synthesis methods for microgels, each droplet can be controlled independently for synthesis and analysis.

In this paper, we report the on-chip generation of microgel precursor droplets followed by off-chip polymerisation using UV irradiation (Fig. 1). We were interested in tuning the hydrophobicity and hydrophilicity of microgels, and in particular the study of amphiphilic microgels, i.e. microgels that are based on both hydrophobic and hydrophilic functional groups. Such amphiphilic microgels can be used as drug delivery systems for both hydrophobic and hydrophilic drugs. Here, we report microgel synthesis with tetrahydropyran acrylate (THPA) as the monomer, while poly(ethylene glycol) diacrylate (PEGDA), poly(propylene glycol) diacrylate (PPGDA) and ethylene glycol dimethacrylate (EGDMA) were used as crosslinkers, and 1-hydroxycyclohexyl phenyl ketone (HCPK) was employed as the photoinitiator, by generating reagent containing droplets surrounded by an aqueous CP, followed by their photopolymerisation. The novel material THPA was used since it is a protected form of acrylic acid, which would allow the THPA-EGDMA microgel to be tuned from being hydrophobic to amphiphilic. We aimed to fabricate the microgels with diameters less than 200 μm to make them suitable for on-demand drug delivery and for realising fast polymerisation (Oh et al., 2009).

2. Experimental section

2.1 Chemicals

THPA, synthesised from 2,3-dihydro-2*H*-pyran and acrylic acid, was used as the monomer (Vohra et al., 2003). PEGDA, PPGDA and EGDMA were used as crosslinkers. HCPK was used as the initiator, They were purchased from Sigma-Aldrich. Dichloromethane (DCM) and chloroform, from Fisher Scientific, were used as solvents for the dispersed phase (DP). Double-filtered (0.05 μm) water with a resistivity of 18.2 MΩ cm at 25 °C was used as the CP, with the addition of 2 % sodium dodecyl sulphate (SDS, Fluka Biochemika) as surfactant. Cyan ink (Tesco Value) was used for visualisation of the aqueous CP in the channels during some experiments. To adjust the pH environment of the microgels, sodium hydroxide solution (1 M, Fisher Scientific) and hydrochloric acid solution (1.17 M, Fisher Scientific) were prepared by dissolving appropriate amounts of the stock material in double filtered water.

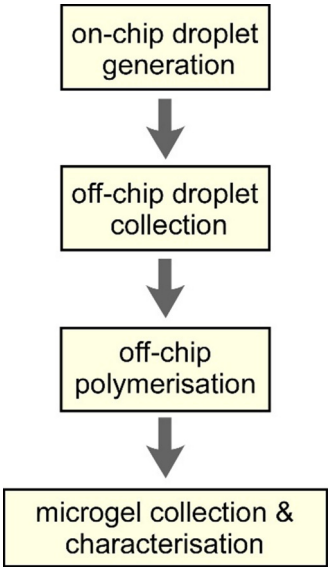

Fig. 1 Schematic of the procedure for microgel synthesis.

2.2 Chip setup and operation

Droplets were generated in glass microfluidic devices featuring either a T-junction geometry (Fig. 2) or a flow-focusing geometry (Fig. 3). Both chip designs featured one inlet for the continuous aqueous phase and one inlet for the reagent containing dispersed phase, as well as a single outlet. The channels were etched to a depth of 50 μm via photolithography and wet etching techniques, and had a width of 150 μm following the etching process (McCreedy, 2001). For interfacing, capillaries (150 μm i.d., CM Scientific, UK) were glued into the inlet and outlet holes with epoxy glue. A short section (5 cm) of Tygon tubing (0.254 mm i.d., 0.762 mm o.d., Cole-Parmer, UK) was connected to the outlet capillary and fed to either a microscope slide or a Petri dish (Fisher Scientific) that was used as a droplet collection vessel. Glass syringes (500 μL, SGE) were interfaced to the inlet capillaries via syringe adaptors (Idex Health & Science, UK) and placed onto two separate syringe pumps (PHD 2000/Pump 11

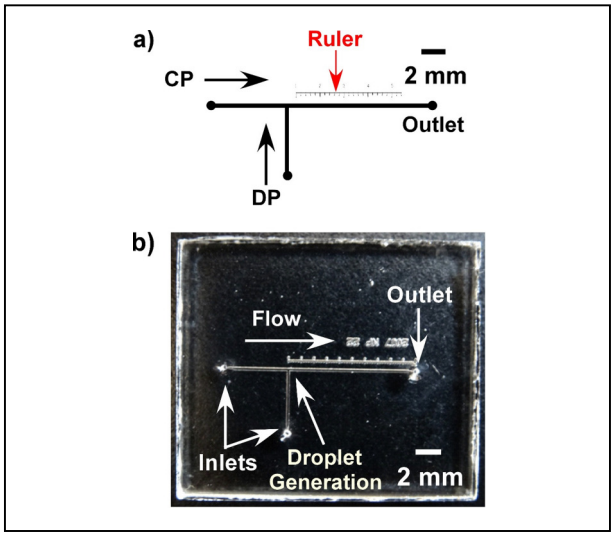

Fig. 2 (a) Layout and (b) photograph of the T-junction chip.

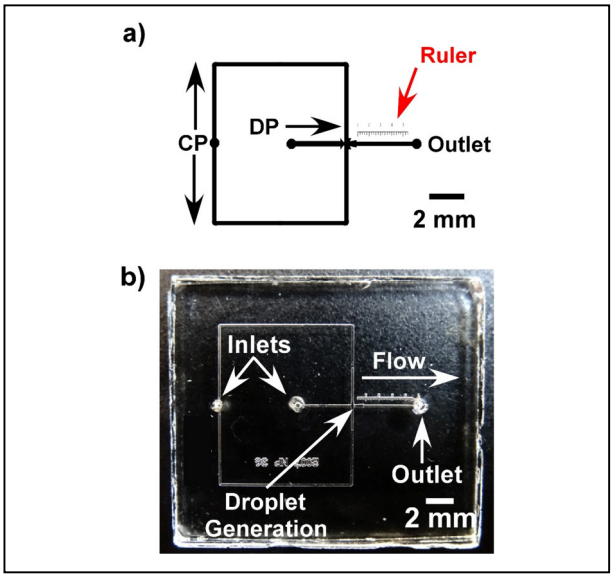

Fig. 3 (a) Layout and (b) photograph of the flow focusing chip.

Elite, Harvard Apparatus) in order to independently control the CP and DP flow rates. The chips were placed on the stage of an inverted microscope (Nikon Ti) with a colour CCD camera (MTV-63V1N, Mintron) to capture images inside the channels.

For droplet generation studies, the DP consisted of monomer, crosslinker and initiator dissolved in dichloromethane (DCM) or chloroform. An aqueous solution of 2 wt% SDS was used as the CP. Flow rates employed during experiments ranged from 0.1 µL min^{-1} to 5 µL min^{-1} as specified in the results section. The droplet formation was recorded on video and droplet sizes were measured via Image J.

30 wt% PEGDA (hydrophilic crosslinker) or PPGDA (hydrophobic crosslinker) with 4 wt% HCPK (initiator) were mixed with chloroform for the synthesis of hydrophilic and hydrophobic microgels, respectively. To synthesise amphiphilic microgels, 30 wt% THPA-EGDMA (50:4 mole ratio) with 4 wt% HCPK were mixed with chloroform before being transferred into the syringe. Droplets were generated on-chip and subjected to photopolymerisation off-chip by collecting them on a Petri dish or microscope slide and exposing them to UV irradiation at 365 nm. The synthesised microgels were then collected and characterised via microscopy. The concept is illustrated in Fig. 1. The setup for droplet generation followed by off-chip photo-polymerisation is shown in Fig. 4.

For droplet collection, the outlet capillary was inserted into a drop (~ 4 mL) of water that had been placed onto a microscope slide. After collecting the desired amount of droplets, the UV light source (15 W at 365 nm, UVP XX-15S) was turned on for 10 min polymerisation. Any changes in droplet size during this event were captured via the microscope camera. Chips and syringes were covered with aluminium foil to prevent reagents from polymerising before collection, and the entire setup was covered with a thick black cloth.

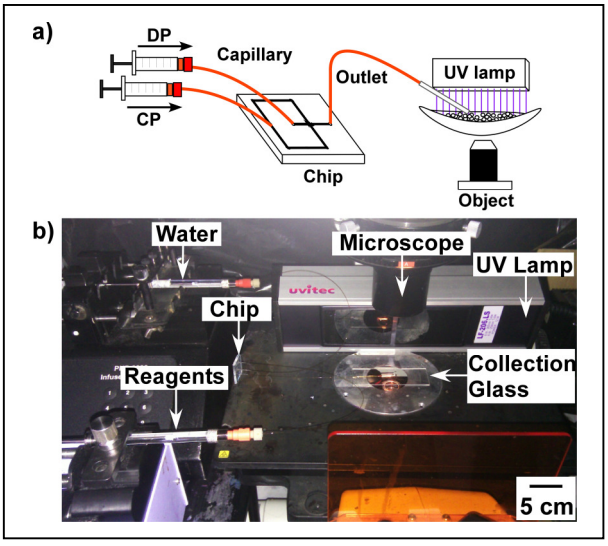

Fig. 4 (a) Schematic and (b) photograph of the setup for photopolymerisation showing the syringes, syringe pumps, chip, droplet collection glass, UV light and microscope.

3. Result and discussion

3.1 Droplet generation

T-junction and flow-focusing chips were used for droplet generation experiments in order to study the effect of relative flow rates of CP and DP on droplet formation behaviour and sizes. The DP used was pure dichloromethane. The continuous aqueous phase contained 2 wt% of the surfactant SDS, which stabilised the formation of spherical droplets and prevented droplet coalescence. Ink was added to improve visibility of the aqueous phase for observation via microscope.

For the T-junction chip (see Fig. 2), the effect of the CP flow rate on the size of the droplets was investigated when the flow rate of the DP was kept constant at 0.5 µL min^{-1}. Fig. 5 shows the droplet formation. The transparent dichloromethane broke into droplets at the T-junction by the shear force from the CP. At high flow rates of the CP the droplets were small and adopted a spherical shape (Fig. 5a). As the flow rate of the CP was decreased, the droplets became larger and adopted a more elongated shape (Fig. 5b). The length of the droplets increased gradually from 200 µm to 650 µm (equivalent to droplet volumes of 2.0 nL to 4.3 nL) and the frequency of droplet generation was reduced from 2.3 droplets s^{-1} to 1.8 droplets s^{-1} as the flow rate of the continuous aqueous phase was decreased from 5 µL min^{-1} to 0.5 µL min^{-1}. Since the 5 µL min^{-1} flow rate of CP yielded the smallest droplets, which would be more suitable for drug delivery and for enabling faster polymerisation, this value was chosen for the following series of experiments.

Droplet sizes were also studied by increasing the DP flow rate from 0.5 µL min^{-1} to 5 µL min^{-1}, with the CP being kept constant at 5 µL min^{-1}, and it was found that sizes decreased from 842 µm (5.2 nL) to 150 µm (1.8 nL) and the generation of droplets was increased from 2.3 droplets s^{-1} to 5.5 droplets s^{-1}. The size distribution of the droplets typically ranged from 4.7 % to 11.6 % (CV), which was generally better than that of traditional emulsion polymerisation (5 –30 %) (Ma et al., 2010; Lee et al., 2007). The narrowest size distribution (4.7 %) was obtained with a dispersed flow rate of 0.5 µL min^{-1} and a CP flow rate of 5 µL min^{-1}.

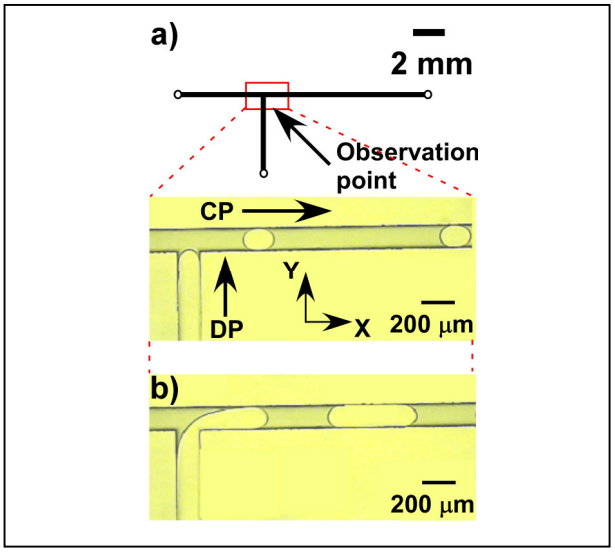

Fig. 5 Photographs of droplet generation in a T-junction chip, when the dispersed DCM phase was kept constant at 0.5 µL min^{-1} and the flow rates of CP were a) 5 µL min^{-1}, and b) 0.5 µL min^{-1}.

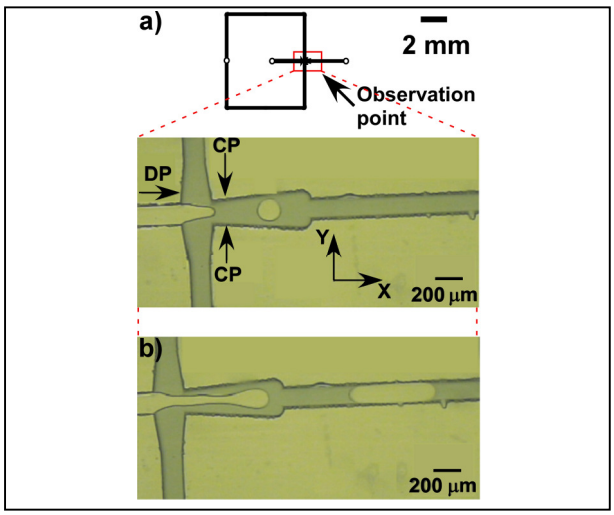

Fig. 6 Photographs of droplet generation in the flow-focusing chip, when the CP was kept constant at 5 µL min^{-1}and the flow rates of DP were a) 5 µL min^{-1}, and b) 0.5 µL min^{-1}.

Next, the effect of flow rates on the generation of droplets was studied for the flow-focusing chip (see Fig. 3) in the same way as for the T-junction chip. Fig. 6 illustrates droplet generation at a constant flow rate of 5 µL min^{-1} for CP, with DP flow rates ranging from 0.5 µL min^{-1} to 5 µL min^{-1}.

At low DCM flow rates, the tip broke off immediately at the junction into relatively small droplets (Fig. 6a). Under higher flow rates of the dispersed DCM phase, the tip of the DCM

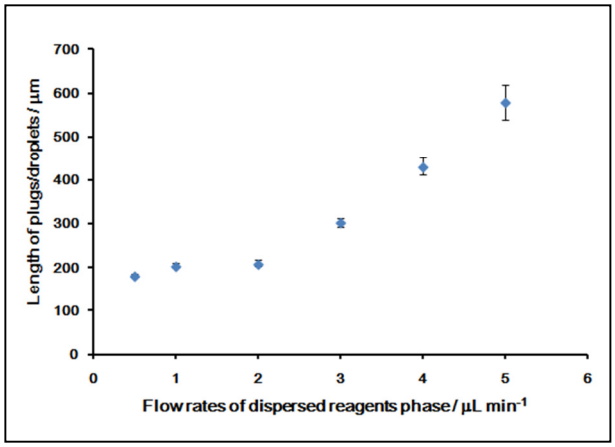

Fig. 7 The length of droplets generated in a flow-focusing device under flow rates of dispersed (reagent) phase ranging from 0.5 µL min^{-1} to 5 µL min^{-1}, with the CP flow rate kept constant at 5 µL min^{-1}.

extended into the widened region of the junction and broke off into a relatively large droplet that became squeezed and elongated in the outlet channel (Fig. 6b). The droplet lengths were measured in the narrow outlet channels and are plotted in Fig. 7. It was found that the size of the droplets increased from 182 µm to 580 µm (1.9 to 3.9 nL) and the frequency of droplet generation was reduced from around 6.5 droplets s^{-1} to 2.5 droplet s^{-1} as the flow rate of the dispersed droplet phase was increased. Larger droplets were produced since more DP was present due to the increased DP flow rate. Droplets with a length of 182 µm (1.9 nL) had a CV of 2.2 % and those with a length of 580 µm (3.9 nL) were 6.8 %, which indicated that the size distribution of droplets generated by the flow-focusing chip was narrower than those of the T-junction chip at the same flow rates.

Droplet sizes were also studied by increasing the CP from 0.5 µL min^{-1} to 5 µL min^{-1}, with DP at 0.5 µL min^{-1}, and it was found that droplet sizes were reduced from 652 µm (4.3 nL) to 205 µm (2.0 nL) and the generation of droplets was increased from around 1.5 droplets s^{-1} to 2.5 droplets s^{-1}. The trends demonstrated here under varying flow rates of the two phases were similar to those observed for the T-junction chip. This was to be expected since the flow rates of CP and DP affect the size of the droplets in the same manner when the dimensions of the channels and the physical properties of the fluids are fixed (Nie et al., 2008). For microgel fabrication, 0.5 µL min^{-1} for the CP and 5 µL min^{-1} for the DP were preferred in order to generate droplets between 150 µm and 200 µm (1.8 nL to 2.0 nL), since faster polymerisation could be achieved with reduced droplet sizes.

In summary, for the droplet generation in both the T-junction and flow-focusing chips, the size of droplets could be well controlled within a length range of 150 µm to 800 µm (1.8 nL to 5.0 nL). The increase in flow rate of CP and the decrease in flow rate of DP yielded a reduction in the size of the droplets in both chip designs, which is in line with findings reported by other research groups (Zhao and Middelberg, 2011; Dang et al., 2012). Furthermore, by increasing both the flow rate of CP and DP, the frequency of droplet generation could be increased. Compared to the T-junction chip, the flow-focusing device allowed the production of droplets with a narrower size distribution (2.2 %) under the same flow rate conditions, and so was used for all further studies here.

3.2 Microgel polymerisation

Microgel polymerisation was undertaken by collecting droplets outside the chip as detailed in section 2.2. An example of such an experiment is shown in Fig. 8.

Droplets were generated from 30 wt% PEGDA and 4 wt% HCPK in chloroform. The droplet sizes were similar to those obtained with pure dichloromethane as the DP, which were 200 µm (2.0 nL) on average when DP and

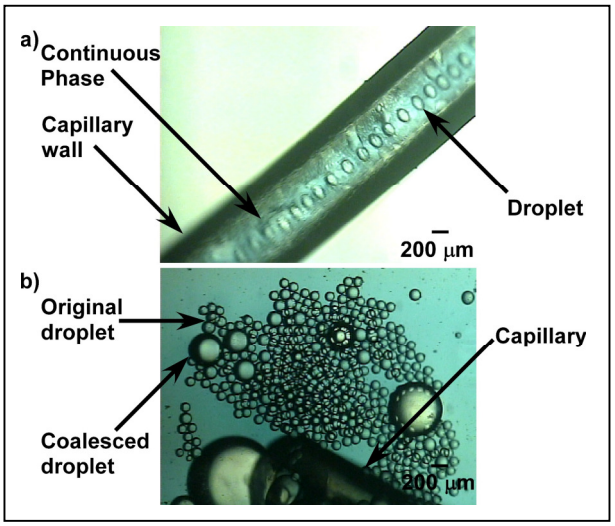

Fig. 8 Photographs of droplets a) inside the outlet capillary, and b) in the collection dish.

CP flow rates of 0.5 µL min^{-1} and 5 µL min^{-1} were employed, respectively, in the flow-focusing chip. As shown in Fig. 8a, droplets migrated through the outlet capillary one by one without adhering to the inner wall, before passing into a pool of water on a Petri dish (Fig. 8b). Droplets accumulated in the water on the external glass plate and adopted a spherical shape since they were no longer confined by the microchannel walls. The volumes of the elongated droplets inside the confined microchannel (2.0 nL) were larger than that of the spheres (1.6 nL) observed in the water collection pool. This showed that their volumes were reduced somewhat during their transfer from the chip to the water pool on the glass plate, the reason for which could be due to diffusion or dissolution of reagents into the surrounding water. Furthermore, due to a lack of SDS in the collection water in this experiment, some droplets coalesced into larger droplets as seen in Fig. 8b.

Photopolymerisation via UV irradiation was applied to fabricate hydrophilic PEGDA, hydrophobic PPGDA and functional THPA-EGDMA microgels, as described in section 2.2. Microgels were successfully prepared and collected, and underwent the polymerisation process while generally maintaining their original shape (Fig. 9). Gel particles were found to shrink or swell during polymerisation, depending on the reagents used. During polymerisation a rotational movement inside the gel particles could be observed, which would stop once the gelation was completed. Some microgels also changed their appearance from transparent to cloudy.

Droplets prepared from 30 wt% PEGDA (hydrophilic) and 4 wt% HCPK featured an average droplet length of 203 µm (2.0 nL) in the channel, and a diameter of 153 µm (1.9 nL) in the collection vessel before polymerisation. During polymerisation, the droplets shrank somewhat from 153 µm to 131 µm (1.9 nL to 1.2 nL). The shrinkage process could be caused by stronger elastic retraction forces generated by the establishment of the crosslinked network. A change in appearance from transparent to cloudy was also observed. This is likely to be due to the temperature during

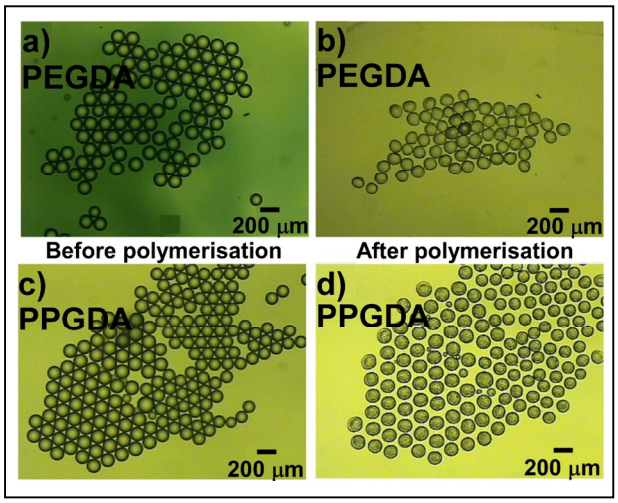

Fig. 9 Droplets prepared from 30 wt% PEGDA and 4 wt% HCPK (a) before and (b) after photopolymerisation. Droplets made from 30 wt% PPGDA and 4 wt% HCPK (c) before and (d) after polymerisation.

polymerisation reaching above the low critical solution temperature (LCST, the temperature below which the components of a mixture are miscible for all compositions, between 50 °C to 80 °C for PEGDA). At this point, the PEGDA would become hydrophobic and therefore would no longer be miscible with all of the droplet components (Ward and Georgiou, 2011). The rise in temperature may be caused by the heat generated by the polymerisation reaction itself, or from the UV light source. After about 10 min UV irradiation, the gelation was complete since the components inside the microgels stopped rotating. When the reaction stopped and the temperature generated from the reaction went below the LCST, the crosslinked PEGDA became hydrophilic and fully miscible in water again (Ward and Georgiou, 2011). As a result, the PEGDA microgels began to absorb the surrounding water and thus swelled to 135 µm (1.3 nL). They became transparent again after 30 min due to this absorption of water (Fig. 9 a,b). However, the surface of these microgels was not so smooth and their shape was not perfectly spherical. This may have been caused by inhomogeneous or inefficient polymerisation inside the droplets since the hydrophilic PEGDA may have been able to diffuse or dissolve into the water phase.

For droplets made from 30 wt% PPGDA (hydrophobic) and 4 wt% HCPK in chloroform, an average droplet diameter of 167 µm (2.4 nL)

was observed in the collection pool. During polymerisation, they swelled from 167 μm to 198 μm (2.4 to 4.1 nL), which may have been caused by the strong stretching forces from the crosslinked internal network or the thermoresponsiveness. They also changed from being transparent to cloudy due to the hydrophobicity of the PPGDA. Once the UV irradiation was stopped, the size of the droplets shrank from 198 μm to 165 μm (4.1 nL to 2.4 nL) within 30 min. The PPGDA microgels remained cloudy since PPGDA was unable to absorb water (Fig. 9c,d). The PPGDA microgels were much more spherical in shape and exhibited a smoother surface than the PEGDA microgels since their hydrophobicity meant that they were less easily dissolved into the surrounding water.

The droplets composed of 30 wt% THPA-EGDMA (50:4) with 4 wt% HCPK were observed to shrink from 180 μm (3.1 nL) to 123 μm (1.0 nL) following polymerisation. Their shape, however, remained quite spherical. Since both the THPA and EGDMA were hydrophobic, the cloudiness of the microgels persisted due to the droplet being unable to absorb the surrounding water during the polymerisation process.

It can be concluded that hydrophobic microgels were much easier to synthesise compared to the hydrophilic and amphiphilic microgels, since the hydrophilic part kept diffusing into the water phase in the latter cases. Therefore, in order to maintain the shape of the hydrophilic crosslinked microgels and prevent their dissolution, a much more efficient polymerisation method is required.

3.3 pH responsiveness of THPA-EGDMA microgels

The response of THPA-EGDMA microgels with changes in pH was studied, since they consisted of both hydrophilic acrylic acid groups and a hydrophobic EGDMA crosslinked polymer network. The results are shown in Fig. 10. Upon addition of HCl solution to reduce the pH to 1, the microgels shrank from 131 μm to 98 μm (1.2 nL to 0.5 nL). The shrinkage was caused by the hydrolysation of THPA into acrylic acid, which also altered the microgel

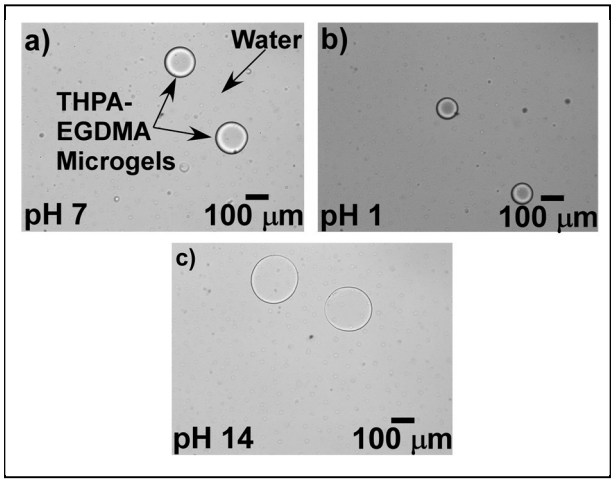

Fig. 10 Photographs of THPA-EGDMA microgels under different pH conditions: a) original microgels at pH 7, b) hydrolysed microgels at pH 1, and c) hydrolysed microgels at pH 14.

properties from hydrophobic to amphiphilic (Fig. 11). Upon addition of NaOH to give a pH of 14, the microgels swelled to 203 μm (4.4 nL) (Fig. 10c). They also changed from being cloudy to transparent due to the existence of ionised acrylic acid functional groups and subsequent absorption of water.

Since the acrylic acid functional groups were fully ionised at a high pH, the built-up electrostatic force established an internal repulsive force inside the microgels and resulted in their swelling. This pH responsiveness was fully reversible due to the reversible ionisation (Fig. 11). The addition of H^+ from the low pH solution suppressed the ionisation of acrylic acid groups and the addition of OH^- promoted the ionisation. The THPA prevented the hydrophilic acrylic acid group from dissolving into the aqueous CP. This swelling-contracting effect could be used to encapsulate and release drugs on-demand by controlling the pH of the surrounding environment, and this will be explored in future work.

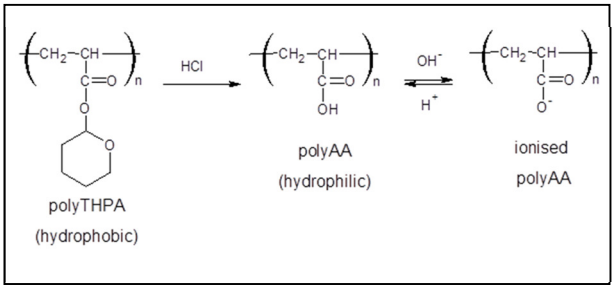

Fig. 11 The reaction scheme for the hydrolysation and ionisation of THPA.

4. Conclusions

A microfluidic approach was established for the fabrication of a new type of microgel. T-junction and flow-focusing microfluidic devices were tested for the generation of mono-dispersed droplets; the flow focusing geometry was found to give better control of the droplet generation, yielding narrow size distributions of 2.2 % under flow rates of 5 μL min^{-1} for the continuous phase and 0.5 μL min^{-1} for the dispersed phase. UV irradiation enabled gelation and polymerisation of the droplets to form microgels, which were prepared from a functional monomer (THPA) and different crosslinkers (PEGDA, PPGDA, and EGDMA). The various crosslinkers yielded different shapes and behaviours according to their hydrophilicity and hydrophobicity. Amphi-philic microgels were synthesised by hydroly-sation of the polymerised THPA-EGDMA microgel, which showed a strong response to different pH environments. For future work, a narrow channel network for on-chip droplet generation together with on-chip polymeri-sation can be studied to provide much more efficient and immediate polymerisation, This could prevent the diffusion of hydrophilic reagents into the water phase more effectively, while producing smaller droplets would be beneficial for drug delivery systems.

References

Baker, W.O., 1949. Microgel, A New Macromolecule. Ind. Eng. Chem. 41, 511-520.

Dadsetan, M., Taylor, K.E., Yong, C., Bajzer, Ž., Lu, L., Yaszemski, M.J., 2013. Controlled release of doxorubicin from pH-responsive microgels. Acta Biomater. 9, 5438-5446.

Dang, T.-D., Kim, Y.H., Kim, H.G., Kim, G.M., 2012. Preparation of monodisperse PEG hydrogel microparticles using a microfluidic flow-focusing device. J. Ind. Eng. Chem. 18, 1308-1313.

Lee, J., Hong, C.K., Choe, S., Shim, S.E., 2007. Synthesis of polystyrene/silica composite particles by soap-free emulsion polymerisation using positively charged colloidal silica. J. Colliod Inteface Sci. 310, 112-120.

Ma, J., Fan, B., Liang, B., Xu, J., 2010. Synthesis and characterization of Poly(N-isopropylacrylamide) / Poly(acrylic acid) semi-IPN nanocomposite microgels. J. Colliod Inteface Sci. 341, 88-93.

McCreedy, T., 2001. Rapid prototyping of glass and PDMS microstructures for micro total analytical systems and micro chemical reactors by microfabrication in general laboratory. Anal. Chim. Acta. 427, 39-43.

Nie, Z., Seo, M., Xu, S., Lewis, P., Mok, M., Kumacheva, E., Whitesides, G., Garstecki, P., Stone, H., 2008. Emulsification in a microfluidic flow-focusing device: effect of the viscosities of the liquids. Microfluid. Nanofluid. 5, 585-594.

Oh, J.K., Lee, D.I., Park, J.M., 2009. Biopolymer-based microgels/nanogels for drug delivery applications. Prog. Polym. Sci. 34, 1261-1282.

Saunders, B.R., Laajam, N., Daly, E., Teow, S., Hu, X., Stepto, R., 2009. Microgels: From responsive polymer colloids to biomaterials. Adv. Colloid Interface Sci. 147–148, 251-262.

Saunders, B.R., Vincent, B., 1999. Microgel particles as model colloids: theory, properties and applications. Adv. Colloid Interface Sci. 80, 1-25.

Staudinger, H., Husemann, E., 1935. Über hochpolymere Verbindungen, 116. Mitteil.: Über das begrenzt quellbare Poly-styrol. Ber. Dtsch. Chem. Ges. 68, 1618-1634.

Vohra, V., Schmidt, D., Ober, C., Giannelis, E., 2003. Deintercalation of a chemically swichable polymer from a layered silicate nanocomposite. J. Polym. Sci. 41, 3151-3159.

Ward, M., Georgiou, T., 2011. Thermorespon-sive polymers for biomedical applications. Polym. 3, 1215-1242.

Zhao, C.-X., Middelberg, A.P.J., 2011. Two-phase microfluidic flows. Chem. Eng. Sci. 66, 1394-1411.