NOVEL AMPHIPHILIC MICROGELS FABRICATED VIA ON-CHIP POLYMERISATION

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ABSTRACT

We report the on-chip polymerisation of hydrophobic microgels from precursor droplets, and their downstream synthesis to pH-responsive amphiphilic microgels for drug delivery. This elegant platform offers superior control over microgel properties, including size, crosslinking density and hydrophobic/hydrophilic properties. The encapsulation and release of hydrophilic (Trypan Blue) and hydrophobic (Sudan Red) dyes based on the microgel shrinking/swelling properties was also studied.

KEYWORDS: Amphiphilic microgels, On-chip polymerisation, Drug release, pH responsiveness

INTRODUCTION

Microgels are 3-dimensionally crosslinked polymer microparticles that can be used as drug delivery vehicles [1]. They can be responsive to specific stimuli such as pH, temperature and electric fields, depending on the types functional groups present. Conventional bulk synthesis methods yield microgels in large size distributions (coefficient of variation (CV) 5-30 %) and offer only limited control over the internal chemistry. Droplet microfluidics can overcome these issues by enabling the generation of monodispersed droplets (CV ~3 %) that, when loaded with precursors, can be polymerised downstream [2]. Nonetheless, the synthesis of amphiphilic microgels, useful for both hydrophilic and hydrophobic drug delivery, is typically achieved in a two-step modification that provides poor control over the hydrophobic/hydrophilic ratio and crosslinking density [3]. We have previously demonstrated the synthesis of amphiphilic microgels, based on hydrophilic chains and hydrophobic crosslinks, with controlled hydrophobicity from droplets generated on-chip followed by off-chip polymerisation [4].

Here, we report a far superior process for the synthesis of pH-responsive amphiphilic acrylic acid-butyl acrylate-ethylene glycol dimethacrylate (AA-BuA-EGDMA) microgels, in which hydrophobic droplets generated on-chip undergo immediate polymerisation within the microchannels. The microgels were rendered amphiphilic via a simple one-step hydrolysation process. This elegant platform offers superior control over microgel properties, including their size, hydrophilic/hydrophobic ratio, and crosslinking density. Furthermore, these microgels, unlike in our previous study, also contain hydrophobic groups in the backbone chains on the microgel and not only at the crosslinks.

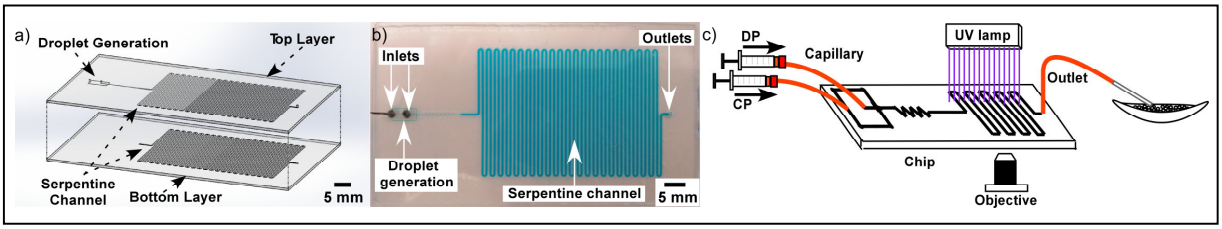

Figure 1: (a) Exploded schematic of the microfluidic device, featuring a flow focusing junction and serpentine channel in the top layer (10 μm deep, 30 μm wide), and the serpentine channel (50 μm deep, 800 μm wide, 2 m long) mirrored in the bottom layer. (b) Photograph of the microfluidic chip fabricated in glass. (c) Schematic showing the principle of droplet generation with in situ *UV polymerisation to form microgels.*

EXPERIMENTAL

A flow-focusing glass chip was used for droplet generation and polymerisation, which featured two layers (Fig. 1a,b): a top layer containing a flow-focusing junction and serpentine channel (30 μm deep, 10 μm wide), with the serpentine channel mirrored in the bottom layer (60 μm deep, 800 μm wide). The

flow-focusing junction contained two inlet holes for the introduction of continuous phase (CP) and dispersed phase (DP) solutions, while the end of the serpentine channel featured a single outlet hole. Fused silica capillaries (150 μm ID) were glued into the access holes, and glass syringes (500 μL) were interfaced to the inlet capillaries and placed onto two syringe pumps (PHD 2000, Harvard Apparatus). The outlet capillary was connected to 5 cm long Tygon tubing that was fed to a Petri dish for microgel collection. Visualisation of microgels was achieved using an inverted microscope with a colour CCD camera (MTV-63V1N, Mintron), with droplet size and colour intensity measured via Image J freeware.

Droplet generation studies were performed using chloroform as the DP (flow rate = 0.5 μL min^{-1}) and deionised water with 0.1 % sodium dodecyl sulphate (SDS) as the CP, which was varied from 0.5 to 5 μL min^{-1}. For amphiphilic microgel synthesis, droplets of chloroform DP were generated containing 30 wt% hydrophobic BuA monomer, hydrophobic EGDMA crosslinker, in-house synthesised hydrophobic monomer THPA (tetrahydropyranyl acrylate, a protected form of hydrophilic AA), and 4 wt% 1-hydroxycyclohexyl phenyl ketone (HCPK) as a photoinitiator. 0.1 wt% SDS in deionised water was used as the CP. Hydrophobic THPA-BuA-EGDMA microgels were thus polymerised in the serpentine channel via UV irradiation (12 W at 365 nm, UVP XX-15S) for 30 min (CP at 2 μL min^{-1}, DP at 0.5 μL min^{-1}), then collected and hydrolysed in pH 2 solution to yield amphiphilic AA-BuA-EGDMA microgels. The hydrophobic/hydrophilic ratios of the microgels were varied whilst maintaining the same crosslinking density. Sudan Red was employed as a model hydrophobic drug by adding 1 wt% to the DP during droplet formation, while Trypan Blue was used as a model hydrophilic drug by encapsulation following droplet polymerisation.

RESULTS AND DISCUSSION

The influence of flow rate on droplet size was first investigated by increasing the flow rate of the CP from 0.5 μL min^{-1} to 5 μL min^{-1}, while the DP flow rate was held at 0.5 μL min^{-1}, allowing droplet volumes to be controlled between 0.3 and 3.1 pL (CV 9 %) (Fig. 2a). For amphiphilic microgel fabrication, the flow rates of the CP and DP were 2 μL min^{-1} and 0.5 μL min^{-1}, respectively, allowing the droplets to be UV irradiated for 30 min as they passed through the serpentine channel, forming the THPA-BuA-EGDMA microgels (Fig. 3). Once the microgels were collected, the poly-THPA was deprotected with HCl (pH 2) to form poly-AA by hydrolysation. The resulting amphiphilic AA-BuA-EGDMA microgels consisted of a hydrophilic AA, hydrophobic BuA and hydrophobic EGDMA crosslinked internal network. Three types of AA-BuA-EGDMA microgel were prepared with different hydrophobicity/hydrophilicity ratios (21:49:4, 35:35:4, 49:21:4) but the same crosslinking density (70:4). The shrinking/swelling properties of these microgels were tested in different pH environments (Fig. 2b). In particular, the 49:21:4 AA-BuA-EGDMA microgels exhibited a greater degree of swelling at higher pH values due to the higher density of negatively charged AA groups.

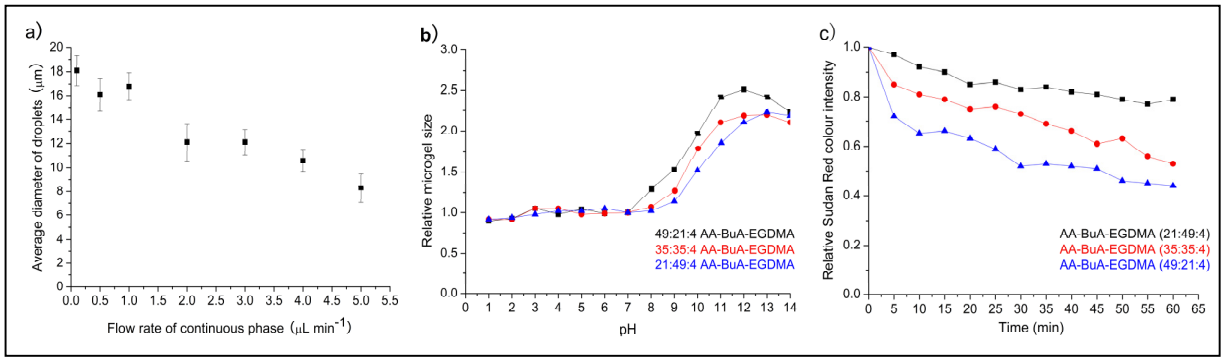

Figure 2: (a) Control of droplet size by varying the flow rate of the aqueous continuous phase, with the dispersed phase at 0.5 μL min^{-1}. (b) Effect of pH on the swelling/shrinking of the microgels by monitoring their size relative to their original size at pH 7. (c) Release of Sudan Red from the microgels over time while in a swollen state in pH 14 solution.

Drugs can be released in the swollen state, and tests were performed with Sudan Red as a model hydrophobic drug and Trypan Blue as a model hydrophilic drug. Sudan Red was added to the DP during droplet formation, encapsulating it during polymerisation. Conversely, hydrophilic Trypan Blue was encapsulated after polymerisation by first swelling then shrinking the microgels in dye solution. The release of Sudan Red into the surrounding environment was studied in pH 14 solution, with the colour intensity of the microgels reducing by 50 % after an hour (Figs. 2c and 4). The 49:21:4 AA-BuA-EGDMA microgel, having demonstrated the largest degree of swelling, thus yielded the faster dye release. Encapsulated Trypan Blue was released into the surrounding water phase at pH 7 solution due to its hydrophilicity, with most of the dye having been dispersed after an hour (Fig. 5).

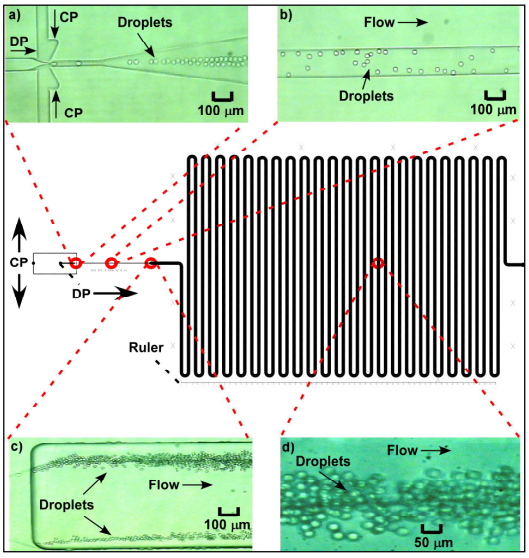

Figure 3: Photographs taken in the microfluidic channels of droplets (a) being generated by at the flow focusing junction, (b) in the 10 μm deep channel, (c) entering the 60 μm deep serpentine channel, and (d) inside the serpentine channel where they would undergo UV polymerisation.

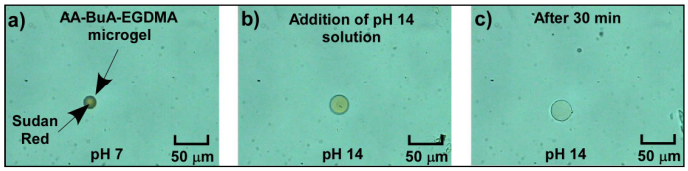

Figure 4: Photographs of hydrophobic Sudan Red model dye release from amphiphilic microgels. (a) In pH 7 solution, the shrunken microgels kept the Sudan Red contained. (b) When suspended in pH 14 solution, the microgels immediately swelled and started to release the dye. (c) After 30 min, most of the dye had dispersed into the surrounding environment.

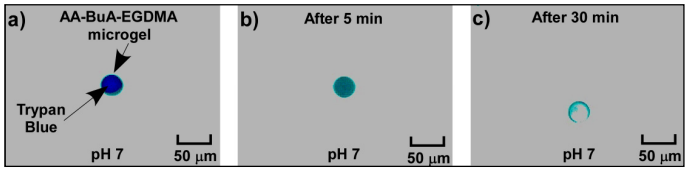

Figure 5: Photographs of hydrophilic Trypan Blue model drug release from amphiphilic microgels in pH 7 solution. (a) Immediately after encapsulation and washing of the microgels. (b) A clear decrease in colour intensity was observed after 5 min due to dispersion of Trypan Blue into the surrounding water. (c) After 30 min, most of the dye had been released.

CONCLUSION

We have demonstrated the elegant and efficient fabrication of microgels by on-chip polymerisation, enabling highly controllable sizes and hydrophobicity. Subsequent hydrolysis to pH-responsive amphiphilic microgels allows for encapsulation and release of both hydrophilic and hydrophobic model drugs, highlighting the potential as versatile drug delivery vehicles.

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