AMPHIPHILIC MICROGELS FROM POLYMERISATION OF HYDROPHOBIC DROPLETS - NOVEL MICROGELS FABRICATED ON-CHIP

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ABSTRACT

We report the synthesis of microgels for drug delivery via on-chip droplet generation and downstream photo-polymerization which affords control over hydrophobicity/hydrophilicity and enables the synthesis of amphiphilic microgels from hydrophobic droplets. The amphiphilic microgels were found to be effective for encapsulation and release of a hydrophobic dye (Sudan red) as an analog of a drug molecule.

KEYWORDS: Microgels, Flow-focusing, Polymerization

INTRODUCTION

Microgels are microparticles consisting of three-dimensional cross-linked polymer networks [1]. Depending on the presence of functional groups, microgels can be responsive to stimuli such as temperature, pH and electric field, making them very attractive for use in drug delivery and oil recovery applications [2]. Conventional bulk synthesis of microgels leads to large size distributions (coefficient of variation (CV) typically 5-30 %), whereas droplet microfluidics allows for the generation of monodispersed droplets (CV around 3 %) that can be polymerized downstream to produce microgels. Several studies have reported hydrophobic or hydrophilic microgels by the polymerization of oil or water droplets [3]. To our knowledge, there are no studies for the on-chip production of microgels with tailored hydrophilicity/ hydrophobicity, and no studies on amphiphilic microgels that can be used for delivery of both hydrophobic and hydrophilic drugs. Amphiphilic microgels are usually prepared by modifying existing hydrophobic or hydrophilic microgels in a two-step procedure hampered by insufficient control over the hydrophilic/hydrophobic ratio and core-shell structures [4].

Here, we demonstrate the synthesis of microgels using a flow-focusing chip for the generation of monodispersed pre-polymer droplets followed by off-chip UV-initiated polymerization (fig. 1). We investigated the production of microgels of relatively hydrophilic poly(ethylene glycol) diacrylate (PEGDA), hydrophobic poly(propylene glycol) diacrylate (PPGDA), and amphiphilic acrylic acid-ethylene glycol dimethacrylate (AA-EGDMA) synthesized from tetrahydropyranyl acrylate (THPA) and EGDMA. By changing the ratio of these starting compounds, the cross-linking density of the AA-EGDMA microgels could be varied and thus their pH responsiveness. This was demonstrated with the release of Sudan Red dye.

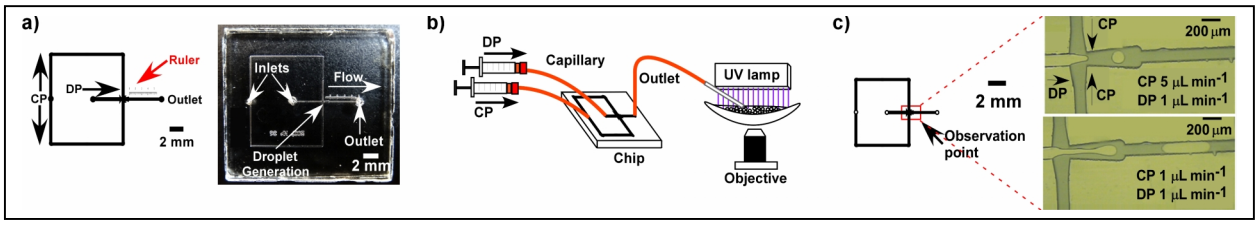

Figure 1: (a) Design and photograph of the flow focusing chip featuring a central channel for the organic dispersed phase (DP) and outer channels for the aqueous continuous phase (CP), merging into a 5 mm long outlet channel. (b) Experimental setup for droplet generation, off-chip collection and UV-initiated polymerization. (c) Examples of droplet generation in blue colored CP at different flow rates.

EXPERIMENTAL

A flow-focusing chip with inlets for the continuous phase (CP) and dispersed phase (DP), and a single outlet, each 100 μm wide, was used for droplet generation. The chip was fabricated in glass and etched to a depth of 50 μm (fig. 1a). Capillaries (150 μm i.d.) were glued into the inlet and outlet holes. The outlet capillary was connected to 5 cm long Tygon tubing (0.254 mm i.d.), which was placed onto a microscope slide or a Petri dish for droplet collection (fig. 1b). Glass syringes (500 μL) were interfaced to the inlet capillaries and placed onto two separate syringe pumps (PHD 2000, Harvard Apparatus). An inverted microscope (Eclipse Ti, Nikon) with a color CCD camera (MTV-63V1N, Mintron) was used for observation. Droplet size and color intensity were measured via Image J freeware.

Droplet generation studies were carried out using chloroform as DP and deionised water with 2 % sodium dodecyl sulfate (SDS), colored with blue printer ink, as CP (fig. 1c). The flow rates of CP and DP were varied from 1 μL min^{-1} to 50 μL min^{-1}.

In order to enable the simultaneous polymerization of the hydrophilic AA and the hydrophobic EGDMA crosslinker, a protected form of acrylic acid was used, specifically tetrahydropyranyl methacrylate (THPA). The THPA monomer was synthesized from AA and 2,3-dihydro-2H-pyran. PEGDA, PPGDA and EGDMA (Sigma Aldrich) were used as cross-linkers. 1-hydroxycyclohexyl phenyl ketone (HCPK) was used as initiator. 30 wt% PEGDA, PPGDA or THPA-EGDMA (30:4, 50:4 or 70:4 in molar ratio) with 4 wt% HCPK were dissolved in chloroform as the DP. An aqueous solution of 0.1 % SDS was used as CP. The droplets were collected off-chip and photo-polymerized for 30 min with a UV light source (15 W, 365 nm, UVP XX-15S). For the study of pH responsiveness, 1 M solutions of NaOH and HCl were employed. Sudan Red was used as hydrophobic dye and mixed in the DP to form microgels with 0.27 wt% drug content before polymerization for dye release studies.

RESULTS AND DISCUSSION

Droplet generation studies were carried out to investigate the influence of flow rate on the size of the droplets (fig. 1c). When the DP was kept constant at 1 μL min^{-1} and the CP was varied between 1 μL min^{-1} and 5 μL min^{-1}, droplets sizes ranged from 3.9 nL to 2.0 nL (580 μm to 205 μm in diameter, CV 2-7 %). As the flow rate of the CP was further increased to 50 μL min^{-1}, the size of the droplets decreased to 0.1 nL (48 μm, CV 8-14 %). On the contrary, when the DP flow rate was increased and the flow rate of CP was kept constant, the size of droplet increased. These findings were consistent with studies from other groups [5]. 0.5 μL min^{-1} for the CP and 5 μL min^{-1} for the DP were chosen for microgel fabrication since these conditions yielded droplets of small size (2.0 nL) with narrow size distribution (CV 2 %).

PEGDA and PPGDA were investigated as examples of more hydrophilic or hydrophobic microgels (fig. 2). The droplets were polymerized by UV irradiation (365 nm) to produce microgels. The relatively hydrophilic PEGDA microgels shrank somewhat (14 %) as some droplet material escaped into the aqueous CP. The more hydrophobic PPGDA microgels retained their size during polymerization.

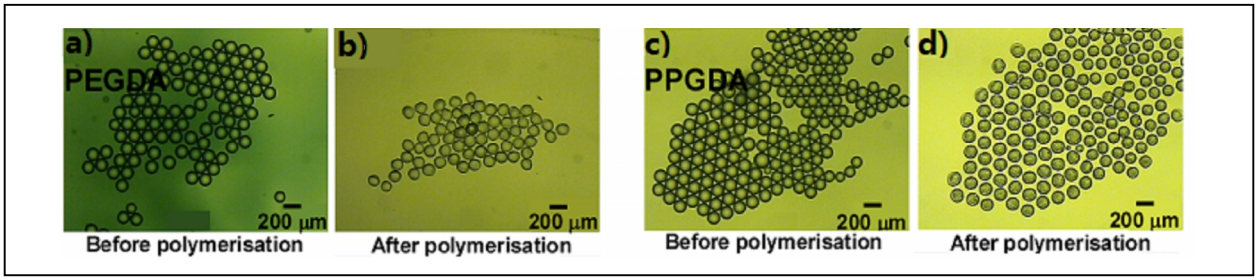

Figure 2: Examples of microgel fabrication by on-chip droplet generation and downstream photo-polymerization. (a/b) Polymerization of relatively hydrophilic PEGDA. (c/d) Polymerization of relatively more hydrophobic PPGDA microgels.

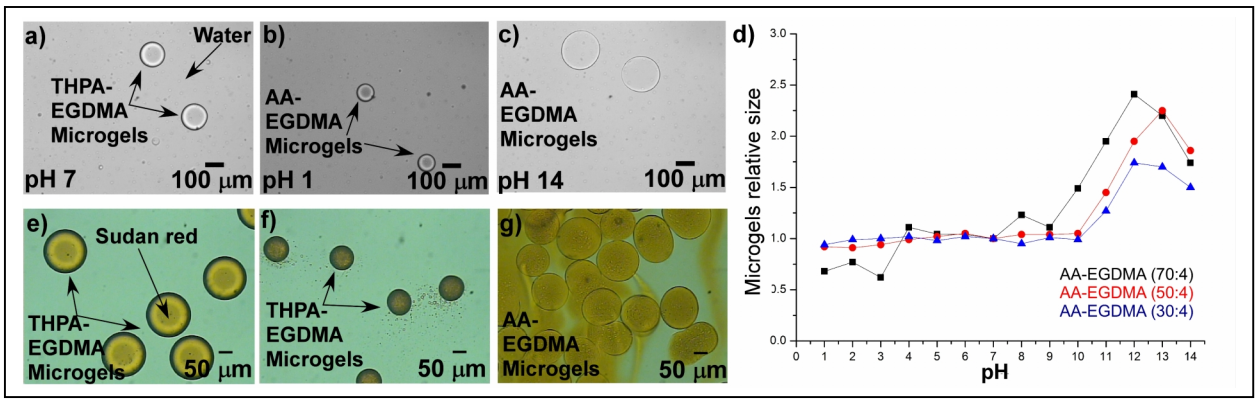

Figure 3: (a) THPA-EGDMA microgels (50:4 molar ratio) at pH 7. (b) Hydrolyzation of THPA-EGDMA to AA-EGDMA at pH 1. (c) Swelling of AA-EGDMA microgels at pH 14. (d) Relative size of three series of AA-EGDMA microgels (70:4, 50:4, 30:4 molar ratios at pH 1 to pH 14 compared to their size at pH 7. (e) Amphiphilic THPA-EGDMA microgels with hydrophobic Sudan Red dye encapsulated during droplet generation. (f) Gel particles after polymerization and (g) dye release at pH 14.

For amphiphilic microgel fabrication, droplets contained a hydrophobic crosslinker, EGDMA, and an in-house synthesized hydrophobic monomer (THPA), which is essentially a "protected" hydrophilic AA. Droplets were polymerized by UV to produce initially hydrophobic microgels and then hydrolyzed to produce amphiphilic microgels by "deprotecting" the THPA to form polyacrylic acid (AA). AA-EGDMA microgels of varying molar ratios (70:4, 50:4, 30:4) were prepared and their swelling/shrinking was studied at different pH values (fig. 3a-d). The 70:4-microgel with the lowest crosslinking density showed the highest degree of swelling at pH 12 (fig. 3d) and was chosen for release studies with Sudan Red as a model hydrophobic drug (fig. 3e-g). The dye was added to the oil phase during droplet formation to form microgel particles with 0.27 wt% drug content. As the pH was changed from low to high, the microgel swelled and Sudan Red was released, with only 0.05 wt% of dye remaining in the microgels after 10 min.

CONCLUSION

We have demonstrated the fabrication of microgels with controlled degrees of hydrophobicity as well as a first example of amphiphilic microgels elegantly synthesized from oil droplets with downstream polymerization and hydrolysis. The release of a hydrophobic model drug, Sudan Red dye, was also studied. The control afforded by on-chip microgel fabrication can now be further exploited for a range of drugs and microgel materials.

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