Fabrication of antibody-loaded microgels using microfluidics and thiol-ene photoclick chemistry

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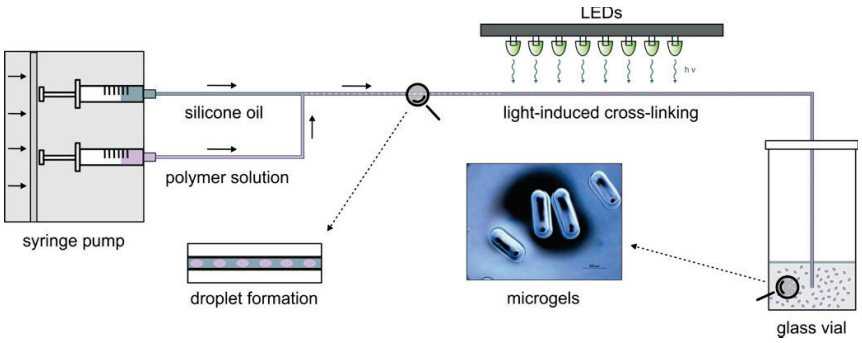
Graphical Abstract



Keywords

microgel, click chemistry, thiol-ene reaction, protein delivery, microfluidics, controlled release

Abstract

Reducing burst effects, providing controlled release, and safeguarding biologics against degradation are a few of several highly attractive applications for microgels in the field of controlled release. However, the incorporation of proteins into microgels without impairing stability is highly challenging. In this proof of concept study, the combination of microfluidics and thiol-ene photoclick chemistry was evaluated for the fabrication of antibody-loaded microgels with narrow size distribution. Norbornene-modified eight-armed poly(ethylene glycol) with an average molecular mass of 10,000 Da, 20,000 Da, or 40,000 Da were prepared as macromonomers for microgel formation. For functionalization, either hydrolytically cleavable ester or stable amide bonds were used. A microfluidic system was employed to generate precursor solution droplets containing macromonomers, the cross-linker dithiothreitol and the initiator Eosin-Y. Irradiation with visible light was used to trigger thiol-ene reactions which covalently cross-linked the droplets. For all bond-types, molecular masses, and concentrations gelation was very rapid (< 20 s) and a plateau for the complex shear modulus was reached after only 5 min. The generated microgels had a rod-like shape and did not show considerable cellular toxicity. Stress conditions during the fabrication process were simulated and it could be shown that fabrication did not impair the activity of the model proteins lysozyme and bevacizumab. It was confirmed that the average hydrogel network mesh size was similar or smaller than the hydrodynamic diameter of bevacizumab which is a crucial factor for restricting diffusion and delaying release. Finally, microgels were loaded with bevacizumab and a sustained release over a period of 30 ± 4 and 47 ± 7 days could be achieved *in vitro*.