Scalable and Continuous Fabrication of Multifunctional Nanogels for Drug Delivery

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Statement of Purpose: Nanogels (NGs), a class of nanoparticles composed of crosslinked polymer networks, are particularly attractive in drug delivery due to the excellent in vivo stability in comparison to self-assembled nanoparticles such as liposomes, polymeric micelles, and vesicles.[1] Generally, NGs are prepared using two strategies, crosslinking of polymer precursors and microemulsion/inverse microemulsion, which allow post-crosslinking of reactive groups or polymerizable monomers in nanoparticles self-assembled from polymers and nanodrops formed by water in oil or oil in water emulsion respectively.[2] One significant drawback of these methods is the limited productivity and poor reproducibility, which hinders the industrialized production and successful clinical application of NGs. Herein, we developed a platform based on a multi-inlet vortex mixer (MIVM) for scalable and continuous production of uniform and multifunctional NGs. As shown in Figure 1A, the MIVM is composed of four inlets and a central chamber for mixing. Reactive polymers, crosslinkers, payload (drug, gene or protein) and targeting ligands or water can be subjected to different inlet of the MIVM. Then the four streams converge in the mixer and the confined impinging jet mixing and reaction between the polymers and the crosslinkers will produce uniform NGs in a continuous and reproducible way.

Methods: To verify the feasibility of this method, nanogels with different properties were prepared by using different polymers and linkers. As shown in Figure 1B, reactive oxygen species (ROS) responsive and positively charged NGs were obtained by using poly(amidoamine) dendrimer (PAMAM) and N-hydroxysuccinimide-functionalized thioketal (TK-NHS) as reactive polymer and linker. Specifically, PAMAM aqueous solution with a concentration of 1 mg/mL and TK-NHS with a concentration of 0.25 mg/mL in ethanol were mixed in the MIVM at an injection rate of 40 mL/min using syringe pumps. After removal of ethanol by rotary evaporation, the PAMAM/TK-NHS NGs were yielded. Similarly, sulfo-NHS functionalized hyaluronic acid (HA-SNHS) and cystamine (CA) were employed to fabricate reduction responsive and negatively charged HA-SNHS/CA NGs.

Results: As demonstrated in Figure 1C, the size distribution of PAMAM/TK-NHS NGs produced from 3 independent batches showed average sizes of 72.9, 77.3, 74.5 nm respectively with PDIs of 0.21, 0.21 and 0.23, indicating good uniformity and excellent batch-to-batch consistency. As we expected, the PAMAM/TK-NHS NGs are positively charged due to the positively charged PAMAM, which was proved by a zeta potential of 24.13±0.93 mV. The size distribution of the HA-SNHS/CA NGs was also narrow (Figure 1D), with a size of 288 nm and a PDI of 0.127, indicating uniform NGs were obtained. The zeta potential of the HA-SNHS/CA NGs was -22.53±1.92 mV, which is ascribed to the negatively charged HA.

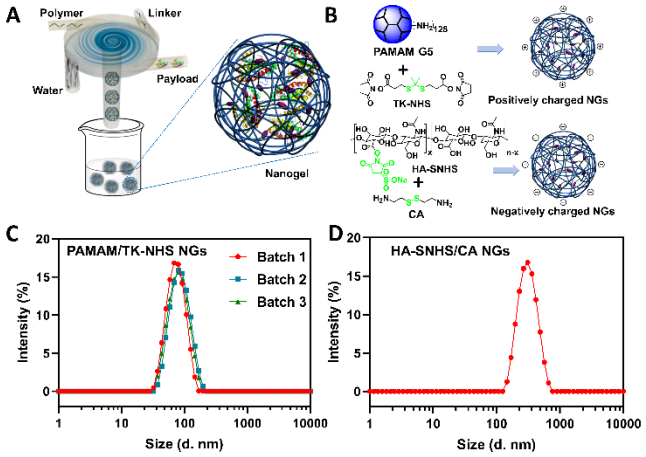

Figure 1. (A) Schematic illustration of the fabrication of NGs using the MIVM. (B) Synthetic routs of positively and negatively charged NGs. Size distributions of (C) PAMAM/TK-NHS NGs and (D) HA-SNHS/CA NGs.

Conclusion: The novel method based on MIVM enabled scalable fabrication of multifunctional and uniform NGs with good reproducibility. These stimuli-responsive NGs held great potential in developing smart drug delivery systems.

References:

[1] S. Hajebi et al, *Acta Biomaterialia*, **2019**, *92*, 1-18.

[2] I. Neamtu et al, *Int. Drug Delivery*, **2017**, *24*, 539-557.