A New Green Route to Prepare Stimuli-responsive Hydrogel Particles: Integrating Epoxy Chemistry with Thermal Induced Phase Separation

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Statement of Purpose

Hydrogel particles, on the micron or nanometer scales, are of great interests for biomedical applications. Currently, majority of the hydrogel particles are composed of monomers in the vinylic family, such as acrylates and acrylamides. In this work, we explore other monomers and reaction chemistry to enable the preparation of functional hydrogel particles in water. Specifically, we chose the nucleophilic ring opening of epoxide with amines, an efficient catalyst-free reaction sharing characteristics of click reactions and well-studied in the making of epoxy resins. We studied the effects of several reaction parameters on the size and distribution of the particles. Responsive properties of the particles were also characterized.

Materials and Methods

In a typical reaction, water soluble polyamines and epoxides were mixed in water with a certain amine to epoxide molar ratio. The solution was heated at 65 °C for up to 25 min before being diluted to 0.5%. The reaction continued for another 30 min. To collect the particles, the solution was firstly centrifuged at a speed of 3.0 k RCF for 5 min. The supernatant was again centrifuged at the speed of 16 k or 21 k RCF (depending on the size of the gel particles). The obtained pellet was dispersed in water, and further washed by repeated centrifugation and dispersion to remove unreacted monomers and free polymers.

The hydrogel particles were characterized for size, distribution, and charge density using a Zetasizer Nano-ZS. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) were used for structural characterizations of the particles. Responsiveness of the particles to pH was examined by measuring size at various pH.

Results and Discussion

The hydrogel particles were prepared based on epoxy chemistry and thermal induced phase separation. Only water was used as the solvent, no catalyst or stabilizer was needed, thus making it a green process. At 65 °C, the solution changed from clear to opaque as the reaction occurred, a result of the formation of intermediate polymer with temperature sensitive properties. The particles could be prepared with size ranging from ~100 nm to micron sized depending on the reaction parameter. Specifically, we studied the effects of (1) monomer ratios; (2) monomer concentrations; (3) reaction temperature; and (4) reaction time. As shown in Figure 1, particles prepared at a low temperature were much larger with a wide distribution than those at a high temperature. The influence of reaction time is also shown in Figure 1. Longer reaction time produced smaller size particles than shorter time, and gelation was observed beyond a certain time. The size can also be controlled by varying the reactant concentrations. As shown in Figure 2, the lower the concentration, the smaller the size. These hydrogel particles were spherical as revealed by TEM.

The hydrogel particles were pH sensitive, due to the presence of amine groups. It was found that as the pH increased, the particles became smaller and less stable. It was a result of deprotonation of the amine groups at higher pH. The responsive behavior could be useful for pH triggered drug release.

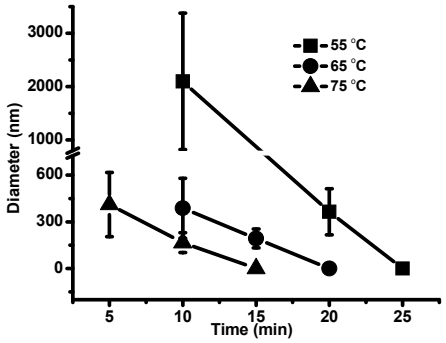

Figure 1. Particle size as a function of reaction temperature and time.

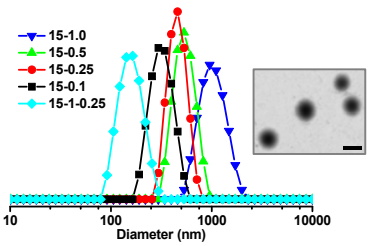

Figure 2. Size profile of particles prepared from various reactant concentrations and determined by dynamic light scattering. The TEM image showed the particles as spheres (scale: 250 nm).

Conclusion

We have demonstrated a new hydrogel particle system prepared from a very simple approach. The size of the particles can be easily varied via changing the reaction parameters. The responsiveness can be applied for drug delivery. In addition, these particles are positively charged and can be considered for gene delivery.