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Short communication

Measuring microgel swell ratio by cryo-SEM

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ABSTRACT

The swell ratio is a key parameter characterizing the structure and properties of a hydrogel. In macroscopic gels, the swell ratio can be determined by straightforward measurements of the gel weight in the dry and hydrated states. However, measuring the swell ratio characteristic of microgels (gel particles with dimensions of 0.1–100 μm) is substantially more challenging because of their small size and polydispersity. We use cryo-scanning electron microscopy (cryo-SEM) to measure microgel diameter both in the frozen-hydrated and fully dry states using pH-responsive poly(ethylene glycol)-co-acrylic acid microgels. The volume swell ratios characteristic of the various microgels are essentially the same as those measured from otherwise-identical macroscopic gels. Hence we can conclude that, at least in this case where the macroscopic gel and microgel synthesis methods are similar, the simple measurement of a macroscopic swell ratio provides a reasonable approximation to the microgel swell ratio.

Perhaps the most significant quantity characterizing a hydrogel is its swell ratio. The swell ratio is a macroscopic manifestation of the gel mesh size and crosslink density. These molecular-level parameters in turn control mechanical and transport properties critical to applications such as tissue engineering and drug delivery. The relationship between swell ratio and mesh size was initially developed by Flory and Rehner [1,2]. The volume swell ratio, Q, is given as:

$$Q = \frac{V_s}{V_d} \tag{1}$$

where V_s is the volume of swollen network at equilibrium and V_d is the volume of unswollen (dry) network. For a macroscopic hydrogel, determining the volume swell ratio is straightforward from measurements of the hydrogel weight in the dry, m_d, and water-swollen, m_s, states:

$$Q = 1 + \frac{\rho_p}{\rho_s}\left(\frac{m_s}{m_d} - 1\right) \tag{2}$$

where the polymer and solvent densities are ρ_p and ρ_s, respectively. The gel mesh size can then be calculated from the swell ratio using the Flory-Rehner theory, and this approach has been applied to a number of neutral polymer gel systems such as PEG and poly(vinyl alcohol) [3,4]. Peppas et al. [5] further modified the Flory-Rehner theory to address polyelectrolyte gel systems where issues of charge, pH, and ionic strength can contribute substantially to the gel-swelling behavior.

Microgels are gel particles with sizes in the range of 0.1–100 μm [6]. They are being used increasingly in a variety of colloid, drug-delivery, and surface-modification applications [7–10], which, just as in their macroscopic gel counterparts, require control of the mesh size. However, in contrast to a macroscopic gel whose dimensions enable reasonably easy and accurate measurements of the dry and swollen weights, the swelling behavior of microgels is much more difficult to characterize. Dynamic light scattering, for example, only provides the intensity-averaged hydrodynamic diameter and does so just for relatively small (sub-micron sized) microgels. Weight measurements can be made using samples containing a large number of microgels to mimic a macroscopic sample, but fully removing interstitial water between microgels is difficult and consequently can lead to errors in measuring the swollen weight.

Here we ask the simple question of how well a measurement of swell ratio from a macroscopic gel compares to that of a microgel synthesized under identical conditions - composition, solvent, UV exposure, etc. - except for the finely divided nature of the microgel. We use cryo-SEM to make direct measurements of microgel size in the frozen-hydrated (swollen) and dehydrated (dry) states, and, at

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least in the particular case involving poly(ethylene glycol)-co-acrylic acid (PEG-co-AA) gels and microgels, we find excellent agreement between the swell ratio characteristic of the macroscopic gels and the microgels.

PEG-co-AA gels and microgels were synthesized by free radical polymerization. The microgels were formed by membrane emulsification using a precursor solution of 2 mL PEG diacrylate (PEGDA; M_n = 575 g/mol; Sigma), 200 μL acrylic acid (Sigma), and 100 μL photo-initiator (Darocur 1173; Sigma) all dissolved in 10 mL dichloromethane. The precursor solution was dispersed as microscopic droplets in 100 mL deionized water (DI) by forcing the precursor solution through a Shirasu Porous Glass (SPG) membrane [11]. The resulting emulsion was exposed to 450 W UV light for 15 min. After solvent removal, the microgels were washed by repeated centrifugation and re-suspension in DI water. Macroscopic hydrogels with dimensions on the order of 1 cm were prepared by exposing 1 mL of precursor solution to 450 W UV light for 15 min. To better mimic the microgel synthesis conditions as well as prevent dichloromethane evaporation, the precursor solution was covered by 10 mL of DI water during photo-polymerization. The resulting gels were soaked in DI water and heated to 50 °C while dichloromethane was removed by vacuum. The gels were then soaked for 3 days in a large bath of DI water. The swollen weight was obtained after soaking the sample in either pH 3 or pH 9 0.01 M phosphate buffer for 48 h. The dry weight of the macroscopic gels was obtained by dehydrating the gels at 50 °C for 48 h. Prior to the hydrated weight measurement, excess surface buffer was removed by gently patting the gel surfaces with filter paper.

Cryo-SEM used frozen-hydrated samples prepared by high pressure freezing (HPF). 5 μL of microgels suspended in pH 3 or pH 9 buffer (0.01 M phosphate buffer) were frozen using a Leica EM HPM100 HPF system. High-pressure freezing promotes water amorphization while freezing by plunging in liquid nitrogen (LN2) at atmosphere pressure tends to create crystalline ice, which can induce artifactual specimen structure [12,13]. HPF microgel samples were cryo-fractured and cryo-transferred to a Zeiss Auriga Cross-Beam FIB-SEM equipped with a Leica VCT-100 cryo-transfer system. Frozen-hydrated samples were imaged using 1 keV electrons at a temperature of −135 °C and a vacuum of 2×10^{-6} mbar. Dried samples were imaged at room temperature. To remove water from the frozen-hydrated microgel suspensions, the sample temperature was raised to −95 °C to sublimate water into the

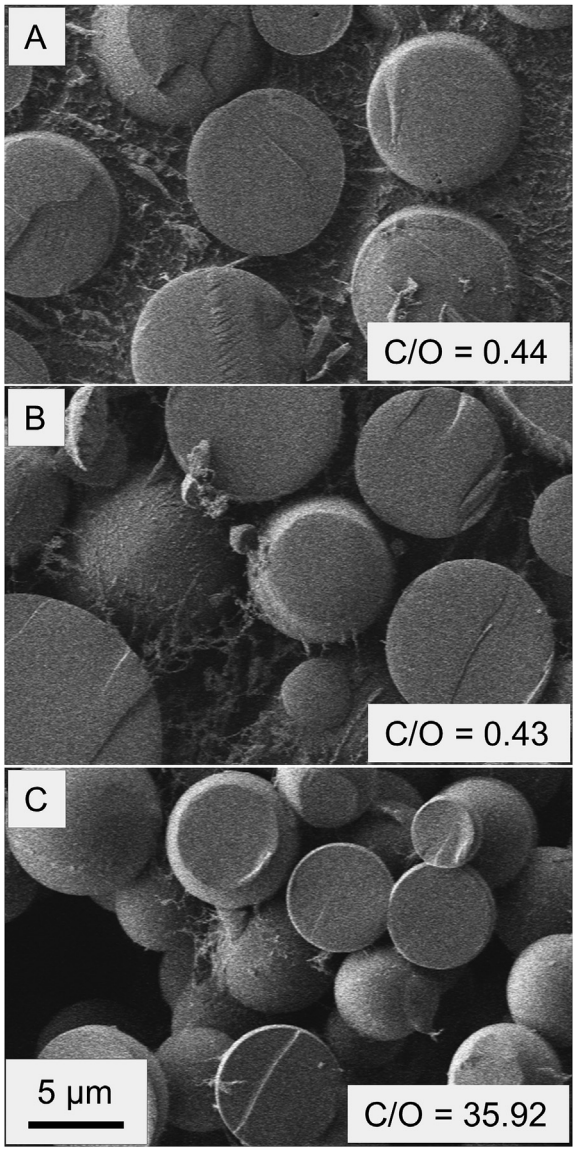

Fig. 1. Cryo-SEM (A, B) and room-temperature SEM (C) images of frozen-hydrated microgel suspensions (pH 3) after sublimation treatments of: (A) 10 min; (B) 40 min; and (C) 12 h. The insets indicate the ratios of carbon and oxygen X-ray intensities.

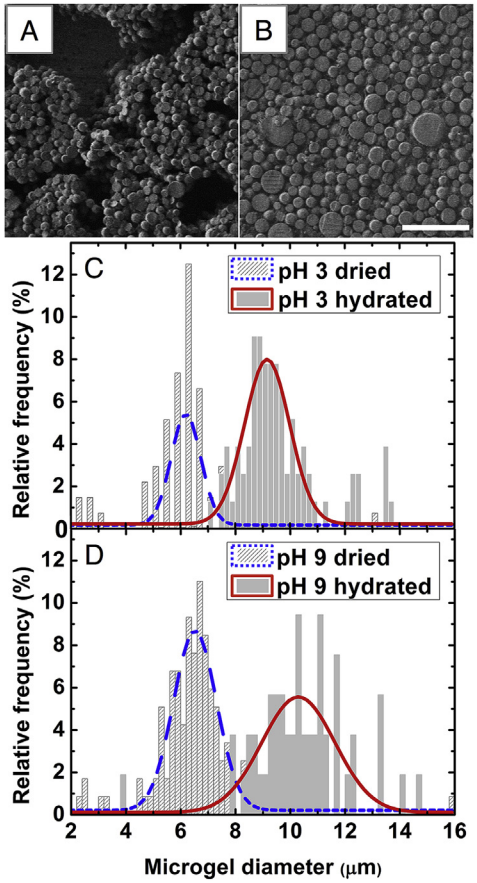

Fig. 2. (A) Room-temperature SEM image of dried microgels. (B) Cryo-SEM image of frozen-hydrated microgels after a 40 min sublimation treatment. The scale bar represents 50 μm for both A and B. Size-distribution histograms of dried (12 h sublimation) and frozen-hydrated (40 min sublimation) at: (C) pH 3; and (D) pH 9. The solid and dashed lines represent Gaussian fits to each data set (>100 measurements per data set).