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Diffusion of guest molecules within sensitive core–shell microgel carriers

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ABSTRACT

The diffusion of payloads within core–shell carrier particles is of major relevance for drug-delivery applications. We use spatially resolved two-focus fluorescence correlation spectroscopy to quantify the diffusivity of different dextran molecules and colloids within carrier particles composed of a temperature-responsive poly(*N*-isopropylacrylamide) (PNIPAM) shell that surrounds a temperature-insensitive polyacrylamide core. The deswelling of the shell that occurs upon heating above the lower critical solution temperature of PNIPAM slightly slows down the diffusion of these tracer oligomers near the core–shell interface. By contrast, the mobility of the tracers inside the core is not affected by deswelling of the shell. This finding assures absence of artifacts such as adsorption of the guests to the amphiphilic shell polymer, supporting the utility of these microgel carriers in encapsulation and controlled release applications.

1. Introduction

Microgels are small particles with size in the range of 10 nm–100 μm [1]. They consist of polymer networks swollen by solvent, typically water. These particles have the capability to incorporate guest molecules or colloids within their interior; this makes microgels interesting for a variety of applications [2], including those in catalysis [3], separation procedures [4], and in drug delivery [5–12]. These and other applications are particularly excelled when the microgels exhibit environmentally responsive swelling and deswelling, which is achieved if they consist of environmentally responsive polymer gels. One of the most popular polymers exhibiting such responsivity is poly(*N*-isopropylacrylamide) (PNIPAM) [13]. Water-swollen PNIPAM networks have a lower critical solution temperature (LCST) of 33.6 °C [14–16]. Above this critical temperature, the polymer becomes less soluble in water, and the size of a PNIPAM microgel markedly decreases, entailing volume changes of up to 1000% [17].

There are two different classes of microgel particles: small, colloidal-scale microgels with sizes of a few micrometers to some few micrometers [18,19], and bigger, non-colloidal microgels with sizes of several tens or hundreds of micrometers [20]. Depending on their targeted application, both these classes of microgels have their specific advantages. For example, whereas colloidal-scale microgels can penetrate cells or capillary tubes, above-colloidal microgels cannot, which may both either be desired or undesired in inter- or extracellular drug delivery applications. For both these different classes of microgels, a particularly useful morphology is that of a core–shell particle, because this morphology intrinsically resembles that of a microcapsule [19,20]. Such core–shell particles allow active compounds to be encapsulated within their core, whereas the shell can be tailored such to allow for triggered, controlled release of the actives [19,21,22]. However, to make this truly useful, it must be understood how the shell swelling and deswelling affects the diffusive mobility of the active payload within the microgel core, because it is this mobility that eventually determines the rate of release of the active in an application [23,24].

In this work, we study the mobility of different dextran tracer molecules and colloids inside above-colloidal core–shell microgel particles through the use of spatially resolved two-focus fluorescence correlation spectroscopy (2fFCS) [25] as shown in Scheme 1. The microgels consist of a core of polyacrylamide (PAAM) surrounded by a shell of PNIPAM that slightly interpenetrates the PAAM core at the core–shell interface. Despite this interpenetration, the core shows no change of size and shape upon variation of temperature around 34 °C in aqueous media, whereas the shell does [21]. This mechanism can be used to incorporate guest

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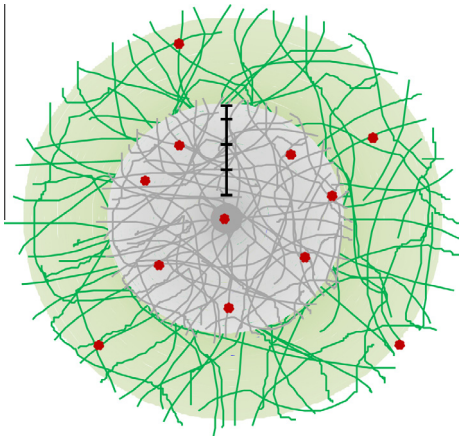

Scheme 1. Schematic of a core–shell particle as studied in this work. The gray center indicates a temperature insensitive and unlabeled PAAM hydrogel core. The green layer indicates a temperature sensitive, AlexaFluor488-labeled PNIPAM hydrogel shell. The red dots indicate labeled tracer particles. In this work, the diffusive mobility of these tracers is probed by 2fFCS at positions indicated by the black scalar. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

molecules or colloids inside the core: at elevated temperature, the shell deswells and the guest molecules are trapped within the particle core but still freely diffuse within it, while reswelling the shell by temperature decrease allows the guests to be released [21]. In solvents different than water that are non-solvents or poor solvents for PAAM and PNIPAM, both the core and the shell deswell completely or partially. In both the above scenarios, we find that it is the core degree of swelling or deswelling that determines that of the interpenetrating part of the shell polymer network, independent of the shell degree of swelling or deswelling itself. In neither case, however, we find marked effect of the shell swelling or deswelling on the diffusivity of dextran tracers within the core. This finding assures absence of artifacts such as adsorption of the guests to the amphiphilic shell polymer, supporting the utility of the microgel carriers in encapsulation and controlled release applications.

2. Materials and methods

2.1. Microgel synthesis

Core–shell particles as sketched in Scheme 1 are obtained by two-step droplet-based microfluidic templating [21]. In the first step, 60-μm polyacrylamide (PAAM) hydrogel core particles are prepared. In the second step, these particles are wrapped into 30-μm hydrogel shells of poly(*N*-isopropylacrylamide) (PNIPAM) labeled with AlexaFluor488. To allow for rapid shell gelation at room temperature, a photochemical polymer-analogous approach is employed: instead of using monomer polymerization, the shell hydrogel is prepared from pre-polymerized PNIPAM chains that carry small percentages of photoreactive moieties, dimethylmaleimide. These moieties can be rapidly dimerized by UV-induced [2 + 2] addition without marked heat of reaction, thereby ensuring a homogeneous, non-porous polymer gel layer to be formed at high reaction rate [26].

2.2. Tracer entrapment

We probe two kinds of labeled dextran tracers that diffuse within the core–shell microgels: a 3000 g mol^{-1} dextran labeled with AlexaFluor647 (Invitrogen) with a hydrodynamic radius of R_h = 1 nm and a 70,000 g mol^{-1} dextran labeled with Rhodamine (Invitrogen) with a hydrodynamic radius of R_h = 6.5 nm. Whereas the first tracer resembles a typical molecular active compound, the second tracer resembles a typical colloidal active. The hydrodynamic radii of both these tracers are calculated via the Stokes–Einstein equation from their diffusion coefficients determined at infinite dilution. To load these tracers into the microgels, an aqueous (LiChroSolv water, Merck) solution of both dextrans is mixed with an aqueous microgel suspension and then left to equilibrate for 24 h, allowing the tracers to penetrate the microgels by diffusion. The samples are then transferred into a temperature controlled sample cell [27] that allows the sample temperature to be varied between 5 and 60 °C. At low temperature, both the PAAM core and the PNIPAM shell are swollen in aqueous medium, whereas the shell deswells at elevated temperature.

To supplement contrary experiments with particles with deswollen core and partially swollen shell, methanol (MeOH) is added to the water to serve as a precipitation agent for PAAM. When this is done, the co-nonsolvency effect of water/MeOH on PNIPAM [28–32] allows the shell degree of swelling to be determined by the water/MeOH mixing ratio [33]. To quantify this, we measure the swelling ratio of a PAAM gel with the same composition as the core of the core–shell particles, along with the swelling ratio of plain PNIPAM microgels with the same composition as the shell of the core–shell particles in different water/MeOH mixtures, as shown in Fig. 1. To realize the PAAM-gel control experiment, a macroscopic PAAM gel with a radius of 50 mm and a height of 7 mm is prepared by photo-crosslinking similar to the procedure of the core microgel gelation. This gel is stored for 24 h and then cut into discs of equal size each (radius 10 mm). The gel discs are dried at room temperature for 16 days until no further mass changes are measurable. The dried discs are then immersed in water/MeOH mixtures with compositions as detailed in Fig. 1 (left) and stored in these media for 7 days to reach equilibrium-swollen states. The mass-swelling ratios are calculated from the masses of the discs before and after swelling.

2.3. 2fFCS

To probe the diffusivities of fluorescently labeled dextran tracers within the microgels in a spatially resolved fashion, we use two-focus fluorescence correlation spectroscopy (2fFCS). The simpler one-focus variant of this technique (FCS) is often used to determine tracer diffusion in hydrogels [34–37], and the two-focus extension allows us to conduct these experiments in complex environments, solving potential problems due to refractive-index mismatch between the immersion medium and the microgel

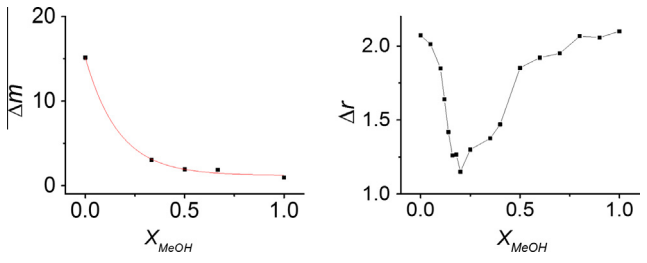

Fig. 1. Comparison of the deswelling of a PAAM hydrogel (left) and the co-nonsolvency of a PNIPAM microgel [30] (right) in mixtures of water and methanol (MeOH) at 20 °C. The red line in the left diagram indicates a single exponential fit. Δm is the mass ratio of the PAAM hydrogels with respect to the mass in dry state (before dissolving in the water/MeOH mixtures). Δr is the ratio of the PNIPAM microgel radii in swollen and deswollen states, referenced to the particle size in water at 40 °C. x_{MeOH} is the mol fraction of MeOH in the solvent mixture. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)