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Transmission behavior of pNIPAM microgel particles through porous membranes

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ABSTRACT

Microgels used for biomedical applications have to be purified to remove unreacted monomer, linear polymers and other impurities, some of which could be toxic. Purification is generally carried out by repeated dialysis against fresh water, which is extremely slow, or by ultracentrifugation, which is labor-intensive and expensive. Microfiltration and ultrafiltration are convection-driven, membrane based techniques which offer the potential for fast and scalable purification of microgel particles. Factors such as deformation of microgels and their responsiveness to environmental conditions such as pH and salt concentration would need to be considered while developing membrane-based purification processes. In this study, a model poly (N-isopropylacrylamide) or pNIPAM microgel was covalently tagged with Rhodamine B to enhance its detectability. The effects of salt concentration in the feed, membrane pore-size, and permeate flux on microgels transmission through different membranes were investigated. Both, the properties of the microgel particles, and operating conditions were found to significantly affect membrane filtration of pNIPAM microgel.

1. Introduction

Microgels are spherical cross-linked polymer networks having size in the micron to submicron range [1,2]. Poly (N-isopropylacrylamide) or pNIPAM microgels are thermo-responsive and can undergo volume phase transition around 32 °C in aqueous medium, this phenomenon being analogous to the lower critical solution temperature (LCST) phase transition behavior of linear pNIPAM [3]. Given the proximity of this transition temperature to the physiological temperature in humans, a variety of applications including their use as controlled drug delivery vehicles and as biosensors have been proposed [4]. Microgels for biomedical and pharmaceutical applications need to be purified to remove, as completely as possible, unreacted monomers, crosslinker, initiator, oligomers and linear polymer chain fragments, since these impurities are frequently toxic or in some cases may interfere with sensing and detection [5]. Currently, post-synthesis purification of microgels is generally carried out by repeated dialysis against fresh water [6]. Although dialysis gives acceptable purity for product development grade material, it is a diffusion-driven, equilibrium-limited process and so small amounts of impurities could be left behind [7–9]. This raises doubts as to whether clinical-grade microgel could indeed be produced by dialysis. An alternative approach for microgel purification is based on repeated cycles of ultracentrifugation where at the end of each cycle, the supernatant is removed and replaced with distilled or deionized water till the conductivity of the supernatant is $< 5\ \mu S/cm$ [10]. The purity obtained depends on the equilibrium distribution of the various impurities between the microgel precipitate and the supernatant phases. Moreover, running multiple ultracentrifugation cycles is labor intensive; a factor that is likely to affect the cost-effectiveness and productivity of the purification process.

Membrane filtration processes such as microfiltration and ultrafiltration are pressure-driven, where convective mass transport predominates. Membrane filtration has been widely used for the separation and purification of biopharmaceutical products such as therapeutic proteins and DNA [11,12]. Compared to dialysis, membrane filtration offers the potential for a much higher rate of impurity removal, significantly lower water or buffer usage, and more complete removal of impurities, particularly those with larger molecular weights which diffuse very slowly through dialysis membranes. To the best of our knowledge, the direct use of either microfiltration or ultrafiltration for the purification of microgels has not yet been reported in the literature. While there have been some reports on the deformability of microgels in nanopores, these studies have looked at the phenomenon from the point of view of renal elimination, i.e. transport through glomerular membrane [13–15].

Physical properties of microgels such as their stimuli-responsiveness and deformability make the design and development of

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membrane filtration-based purification processes quite challenging. Microgels are flexible spheres which can undergo changes in both size and elasticity in response to changes in temperature, ionic strength, and pH [16]. Some previous studies have shown that microgels can deform quite significantly under shear, leading to their translocation through nanoporous structures [13–15]. When soft microgel slurries are subjected to shear, their microstructure is altered [17], and this affects their colloidal stability, often leading to shear-induced aggregation [18]. Membrane selection for micro- and ultrafiltration processes is usually guided by retention behavior of synthetic polymers such as polyethylene glycol, or biopolymers such as dextran. The extent of macromolecule retention is commonly expressed in terms of the so called molecular-weight cut-off or MWCO value. However, MWCO, as determined based on the retention of these polymers would have very little practical value in selecting membranes for micro-, or ultrafiltration of microgel particles due to their tendencies to deform and change in size. Moreover, other complicating factors such as electrostatic charge, surface properties of the membrane commonly observed during membrane filtration processes in general are also expected to influence microgel filtration processes [11,12]. Particularly, as the volume phase transition temperature (VPTT) of pNIPAM relies on the temperature-dependent interactions between the microgel and water, the swelling of pNIPAM microgel particles will depend on the type and concentration of ions present [19].

This study examines the effects of salt concentration, membrane pore-size, and permeate flux on the transmission of model poly (N-isopropylacrylamide) or pNIPAM microgel particles through different micro- and ultra-filtration membranes. Microgel particles are hard to detect and quantify when present at dilute concentrations, making them difficult to track them during a membrane filtration process. The pNIPAM microgels used in this study were therefore prepared by co-polymerization with a methacrylate co-monomer bound to fluorescent Rhodamine B in order to enhance their detectability when present in extremely low concentrations in permeate samples. The results obtained are discussed.

2. Experimental

2.1. Materials

N-isopropylacrylamide (NIPAM, 99%, 415324-50G, Sigma-Aldrich, St. Louis, MO, USA) was purified by recrystallization from 60:40 toluene:hexane mixture. N, N-methylene-bisacrylamide (MBA, 99+%, 146072-100G, Sigma-Aldrich) and ammonium persulfate (APS, 99%, 215589-100G, Sigma-Aldrich) were used as received. Methacrylate-Rhodamine B (MA-RhB, 80 mol% RhB) was synthesized by reacting methacryloyl chloride (97%, stabilized with ~200 ppm monomethyl ether hydroquinone, 523216, Sigma-Aldrich) with Rhodamine B (R6626, 95%, Sigma-Aldrich). The water used in the synthesis and characterization steps was of Millipore Milli-Q grade. Sodium chloride (SOD002.205) was purchased from BioShop Canada Inc., Burlington, ON, Canada. Sodium chloride solutions used in the microgel filtration experiments were microfiltered and degassed prior to use. Isopore membranes (0.22 μm pore size, GTTP04700) were purchased from Millipore, Billerica, MA, USA. Cellulose acetate microfiltration membranes (0.8 μm pore size, LOT #: 0589700522M11407-13P) was purchased from Sartorius, Gottingen, Germany. The 3 kDa (OT003SHEET) and 50 kDa (OT050SHEET) molecular weight cut off (MWCO) ultrafiltration membranes were purchased from Pall Corporation, Port Washington, NY, USA. All membranes were used as received.

2.2. Synthesis of p(NIPAM-co-MA-RhB) microgels

Microgel particles were prepared by precipitation polymerization in a two-necked round bottom flasks attached to a condenser unit and continuously purged with nitrogen. NIPAM (1.4 g), MA-RhB (0.01 g), and MBA (0.02 g) were dissolved in water (150 mL) in the flask. The content of the flask was stirred with a magnetic stirrer bar (250 rpm) and heated at 70 °C with nitrogen purging for 30 min. Subsequently, the initiator (0.1 g APS in 5 mL water) was injected into the flask and the reaction was allowed to continue overnight. The reaction mixture was then cooled to room temperature and dialyzed using cellulose membrane tube (14 kDa molecular weight cut-off) for 7 cycles of dialysis against fresh water. The dialyzed microgels were lyophilized, weighed, and stored at room temperature.

2.3. Microfiltration and ultrafiltration of microgels

Microgels were re-dissolved in deionized water to obtain a concentration of 2.4 mg/mL. A custom-fabricated stirred-cell membrane module made of Delrin® and having a working volume of 1.2 mL was used to carry out membrane filtration. Delrin is a good thermal insulator and this guaranteed that the temperature inside the module was unaffected by temperature outside. The membrane was held in place within the membrane module using a pair or O-rings held under pressure to provide compression seal. The membrane was attached facing downward and a free-spinning magnetic stirrer placed within the feed compartment below kept the content well mixed and provided the hydrodynamic conditions needed to prevent microgel accumulation on the surface of the membrane. The stirring speed was measured with an open module containing 0.1 mg/mL microgel solution and was found to be ~600 revolutions per minute (rpm). The effective area of the membrane was ~1.89 cm^2. The experimental setup used in this study (see Fig. 1) was similar to that used for pulsed

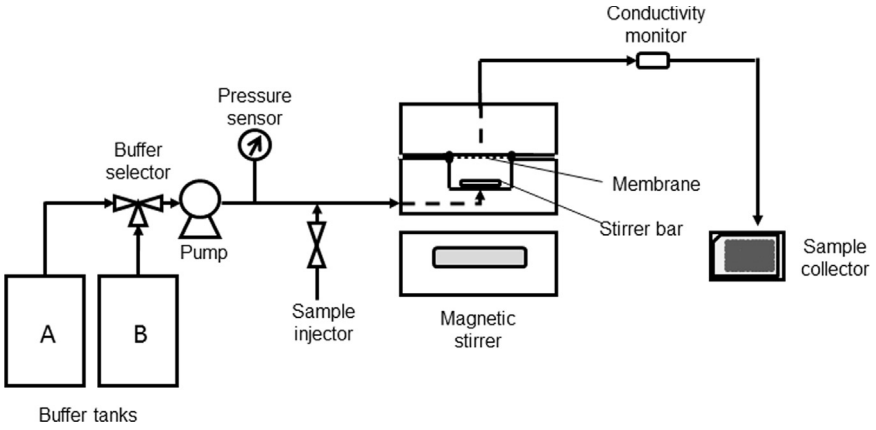

Fig. 1. Experimental setup used for pulsed injection and parameter scanning membrane filtration (Pump: HiLoad P-50, sample loop volume: 50 μL; membrane module volume: 1.2 mL, membrane area: 1.89 cm^2).