



## Research paper

## Design of nonionic micelle-laden polysaccharide hydrogels for controlled delivery of hydrophobic drugs



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## ARTICLE INFO

## Article history:

Received 17 December 2016

Received in revised form 24 April 2017

Accepted 25 April 2017

Available online 27 April 2017

## Keywords:

Cloud point

Diffusion

Polyelectrolyte

Structure/performance

Phase behavior

Mesh

## ABSTRACT

The incorporation of micelle self-assembly in hydrogels has been used to produce self-healing materials, materials with tunable mechanical properties, and hydrophilic or hydrophobic drug delivery systems. However, little is known about the connection among formulation – structure – properties (particularly transport) in these systems. This connection is explored in alkyl ethoxylate micelle-laden gellan gum hydrogels used as delivery system for the hydrophobic drug dexamethasone. Phase behavior maps and rheological characterization of the micelle-laden hydrogels indicate that their properties are largely dominated by the concentration and cloud point (CP) of the alkyl ethoxylate nonionic surfactant. The sol-gel temperature of the hybrid hydrogels was found to be close to the CP of the surfactant, and their storage modulus ( $G'$ ) was found to increase with increasing surfactant concentration. A detailed analysis of the phase behavior maps, and evaluations of the mesh size of the hybrid hydrogels suggest a novel mechanism whereby micelles associate with gellan gum strands during high temperature hydration, hindering the double-helix assembly of the strands upon cooling. This increases the number of single strands and the density of physical cross-links, reducing the mesh size of the hydrogel. This mesh size reduction led to a decrease in the effective diffusion coefficient of micelles in the gel, and extended the release time of dexamethasone from 2 h in surfactant-free hydrogel to more than 2 days in the micelle-laden hydrogel.

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## 1. Introduction

Recent work introducing micelle or micelle-like assemblies in hydrogel networks has been largely driven by three reasons, the introduction of self-healing materials, the introduction of environment-sensitive properties, or the introduction of hydrophobic solubilization sites in an otherwise hydrophilic environment (Can et al., 2016; Friedrich et al., 2010; Pekař, 2015). Hydrogels with micelle-like assemblies can be synthesized as copolymers containing surfactant-like monomers, block copolymers, conventional hydrogel backbones grafted with lipophilic moieties, or they can be obtained via physicochemical interactions between surfactants and conventional hydrogels (Baldwin and Kiick, 2010; Pekař, 2015; Yang and Alexandridis, 2000). Mixtures of micellar surfactant solutions with polymer hydrogels or micelle-laden hydrogels, are of particular interest because of the simplicity in producing these systems, the versatility in the selection of surfactants and

hydrogel-forming polymers, the flexibility in surfactant-polymer ratios, and the easier regulatory path for approved polymers and surfactants (Baranovskii et al., 2011; Bengani and Chauhan, 2013; Hoare and Kohane, 2008; Kapoor and Chauhan, 2008; Kapoor et al., 2013; Liu and Li, 2005; Marras-Marquez et al., 2014; Paulsson and Edsman, 2002; Pekař, 2015). The first attempts at producing these micelle-laden hydrogels used highly irritating surfactants, such as sodium dodecyl sulfate (SDS), which limited their use (Paulsson and Edsman, 2002). Recent work avoided this limitation using alkyl ethoxylated surfactants, producing formulations suitable for ophthalmic applications (Baranovskii et al., 2011; Kapoor et al., 2013; Marras-Marquez et al., 2014). Some of these hydrogels used polysaccharides such as gellan gum and agarose as their polymer backbone (Marras-Marquez et al., 2014; Paulsson and Edsman, 2002).

Polysaccharide hydrogels are promising alternatives in biological applications such as drug and food delivery carriers and tissue scaffolds (Coviello et al., 2007; Zuidema et al., 2011). Polysaccharide hydrogels are three-dimensional networks formed by swelling of sugar-based polymers that can be chemically or physically crosslinked. Physically crosslinked hydrogels formed via ionic bonding, hydrogen bonding, or hydrophobic interactions can be

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used to design smart delivery systems because of their sensitivity to environmental conditions (Langer and Peppas, 2003). Anionic polysaccharides, such as gellan gum, have certain advantages over their nonionic counterparts since they are fully water soluble, resistant to biological fluids containing electrolytes, and stable at high temperatures, decreasing the possibility of phase separation. Moreover, they have more rigid backbone structures and a lower charge density compared to synthetic polyelectrolytes which facilitates the formation of micellar aggregates along the polysaccharide chains (Chiappisi et al., 2013).

The interactions of polysaccharides with surfactants have also been studied to identify combinations that can provide improved stability and rheology control for specific applications (Goddard et al., 1991; Kwak, 1998). These interactions give rise to distinctive surfactant-polymer complexes. For instance, the interactions of nonionic synthetic polymers such as polyethylene oxide (PEO) with ionic surfactants promote a considerable increase in viscosity due to the formation of micellar aggregates on the polymer that facilitate the entanglement of subsequent polymer chains (Brackman, 1991). Moreover, the interactions of surfactants and polymers of opposite charge have been shown to induce the formation of necklace type structures where polymer chains are wrapped around surfactant micelles which increase chain entanglement and thus, the viscosity of the mixture (Kwak, 1998). In case of mixtures of ionic synthetic polymers such as hydrophobically modified polyacrylates and nonionic surfactants, viscosity increments at high temperature have been associated to the binding of surfactant on the hydrophobic sites of the polymer acting, as crosslinks in the polymer network (Sarrazin-Cartalas et al., 1994). Unfortunately, the interactions between charged polysaccharides with nonionic surfactants, a combination of interest in this work, under some circumstances promote phase separation at high surfactant concentrations at room temperature (Fijan et al., 2007).

The anionic polysaccharide gellan gum is of particular interest because of its safety and compatibility in food and drug delivery applications, as well as mechanical stability under physiological conditions (Paulsson et al., 1999). Gellan gum is a bacterial polysaccharide produced by *Sphingomonas elodea* with an average molecular weight  $M_w \sim 500$  kDa which undergoes gelation in the presence of cations (Morris et al., 2012). Gellan gum hydrogels have been used for the delivery of hydrophobic drugs, for example, the commercial in-situ forming gel Timoptic-XE<sup>®</sup> designed to be dosed as a liquid drop that once in contact with the electrolytes in the tear fluid forms a gel (ionotropic gelation) that produces an extended release of timolol maleate, a beta blocker designed to reduce the intraocular pressure in glaucoma patients (Feke et al., 1996). Liposome-laden gellan gum hydrogels have also been introduced to for the ophthalmic delivery of timolol, using concentrations of about 0.4% gellan gum in the liquid solution, without any adverse reaction (Yu et al., 2015). In this case, the micelle-like assembly of liposomes improved the distribution of the drug throughout the eye.

Compared to liposome-laden hydrogels, nonionic surfactant micelle-laden hydrogels require a much simpler preparation protocol. However, as indicated earlier, identifying the appropriate combination of surfactant and polymer is a challenge, particularly because of the complex phase behavior of these systems. Previous studies have shown the influence of nonionic surfactant properties, namely their cloud point (CP) and concentration, on the performance of surfactant-polysaccharide mixtures. For instance, mixtures of hydrophobically modified hydroxyethyl cellulose and low concentrations of penta and hexaethylene glycol monododecyl ethers (C12E5, and C12E6) had lower CPs than the CP of the surfactants. For these systems, the viscosity only increased close to the CP of the gel, and phase

separation was observed at high surfactant concentrations (Zhao et al., 2005; Zhao and Chen, 2006). Similarly, the addition of the nonionic surfactant polysorbate 80 to gellan gum hydrogels (3% in water) improved the gel mechanical properties in concentrations of up to 30% of polysorbate 80, while concentrations above 30% weakened the hydrogel (Fasolin et al., 2013). The significant influence of surfactant molecular structure and surfactant/polymer ratio on the rheological properties has also been reported for chitosan (cationic polysaccharide)-nonionic sorbitan esters (Grant et al., 2006).

Although the previous paragraphs may suggest that micelle-laden hydrogels is a mature field, a review by Pekař (2015) highlights that further understanding of the gel structure-property relationship, especially transport, is “needed badly”. Our work explores the broader question of formulation-structure-property relationship, including surfactant selection, surfactant/polymer ratio, phase behavior, hydrogel structure, and drug transport. To this end, combinations of gellan gum with n-octyl tetraethylene glycol monoether (C8E4), polyethylene glycol-6 caprylic capric glyceride (C9GE6), and n-dodecyl hexaethylene glycol monoether ( $\sim$ C12.5E6) were considered. Phase behavior, rheological and solute transport properties were evaluated for surfactant-polymer combinations that produced single phase hydrogels. Micelle size and self-diffusivities were determined for selected surfactant-gellan gum combinations. Structure-performance relationships were subsequently established to predict the phase behavior and microstructure of nonionic surfactant-gellan gum hydrogels, as well as their impact on the release profile of dexamethasone used as a model hydrophobic drug.

## 2. Materials and methods

### 2.1. Materials

Nonionic surfactants C8E4 (Dehydol OD5<sup>®</sup>, 100% active), C12.5E6 (Novel<sup>®</sup> S23E-6, 100% active) were kindly donated by BASF North America and C9GE6 (Softigen 767, 100% active) was kindly donated by Sasol North America. Low acyl gellan gum polysaccharide Kelcogel<sup>®</sup> was kindly donated by CP Kelco San Diego, CA. USP grade dexamethasone (99%), reagent grade sodium chloride, and calcium chloride dihydrate (99%) were purchased from BioShop Canada. Magnesium chloride (98%), sodium bicarbonate (99.5%), potassium chloride (99%), and deuterated water D<sub>2</sub>O (99.9 atom% D) were purchased from Sigma Aldrich Canada. All chemicals were used without further purification.

### 2.2. Artificial tear fluid preparation

Simulated tear fluid was prepared considering the electrolyte concentrations in the tear film of normal patients measured by Gilbard et al. (Gilbard, 1994), briefly, 0.61 mM of Mg<sup>2+</sup>, 0.80 mM of Ca<sup>2+</sup>, 24.0 mM of K<sup>+</sup>, 32.8 mM of HCO<sub>3</sub><sup>-</sup>, 133.2 mM of Na<sup>+</sup>, equivalent to 0.059 g of magnesium chloride, 0.09 g of calcium chloride dihydrate, 1.79 g of potassium chloride, 2.75 g of sodium bicarbonate, and 5.87 g of sodium chloride per liter of solution. The solution pH was adjusted to a value within the pH of human tears (7.14–7.82) with HCl 6N.

### 2.3. Phase diagrams

Mixtures of each C8E4, C12.5E6, C9GE6 nonionic surfactant with gellan gum were prepared by adding specific amounts of surfactant and polymer to deionized water or simulated tear fluid solution in a tear fluid ratio (TFR = ions present in the sample/ions present in the tear fluid) of 0.25, to give a final concentrations of

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