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The effect of heparin on the gellation of Pluronic F-127 hydrogel

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Abstract

The interaction between heparin and Pluronic polymer was characterized by the sol–gel transition temperature and the rheological properties of the heparin–Pluronic hydrogels. The decrease of the transition temperature was consistently shown in all media (distilled water, phosphate buffer, and PBS) as the added amount of heparin increased. In contrast, the addition of PEG produced the increase of the transition temperature. The order of phase transition with increasing temperature (heparin–Pluronic > Pluronic > PEG–Pluronic) obtained from the change in the storage modulus of the Pluronic solutions well coincided with the results obtained from the inverting vial method; a plateau of storage modulus in frequency sweep was developed at the lowest temperature for the heparin–Pluronic hydrogel, and the plateau modulus of the heparin–Pluronic hydrogel was higher than that of the pure Pluronic hydrogel near the sol–gel transition boundary. These results demonstrate that the interaction between heparin and Pluronic polymer exists, which promotes the Pluronic micelle–micelle association.

Keywords: Sol–gel transition; Pluronic F-127; Heparin; PEG; Hydrogel

1. Introduction

Pluronic F-127 (PF-127), an FDA-approved, commercially available biocompatible triblock copolymer, consists of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) blocks [1]. Aqueous solution of PF-127, at 20% or higher concentrations, exhibits the phenomena of reverse thermal sol–gel transition. During this transition PF-127 transforms from a mobile viscous solution to a semisolid gel on increasing temperature from 4 °C to body temperature (37 °C) and the gellation is reversible on decreasing temperature [2,3]. This sol–gel transition is attributed to the closed packed spherical micellar structure formed above the critical micelle temperature and can be characterized easily by the test tube inverting method [4,5]. The hydrogel formed by PF-127 have been studied extensively in biomedical applications, specifically as an injectable system using the sol–gel transition of PF-127. The PF-127 has been applied for the delivery of protein and peptide drugs, such as insulin [6], urease [7], interleukin-2 [8], growth factors [9–11], and typically it showed sustained release kinetics over several hours.

The sol–gel transition behavior of PF-127 is also affected by some solutes and polymers, which results in an increase or decrease in the sol–gel transition temperature. Solutes, such as *para*-hydroxybenzoate esters bind to PEO blocks of PF-127, promoting dehydration and causing an increase in entanglement of adjacent micelles, thus exhibiting transition at lower temperatures [5]. In contrast, the presence of poly(ethylene glycol)s hinders the PF-127 association, leading to an increase in the transition temperature [5]. The formation of cross-links or three-dimensional networks by interaction of PF-127 with polymers also leads to increased elastic characteristics in the rheological properties. For example, the formation of cross-links between the alginate and PEO blocks of PF-127 leads to the formation of a three-dimensional network, resulting in an improved shear stress response [12]. Similarly, the inclusion complexes formed by α-cyclodextrin and PEO blocks of PF-127 are thought to aggregate into microcrystals, which act as physical cross-links and induce formation of a supramolecular polymer network, consequently resulting in the gellation of the solutions even at low concentration of PF-127 [13].

Here, we characterized the effect of heparin on the gellation behavior of PF-127 aqueous solution. Heparin is a highly

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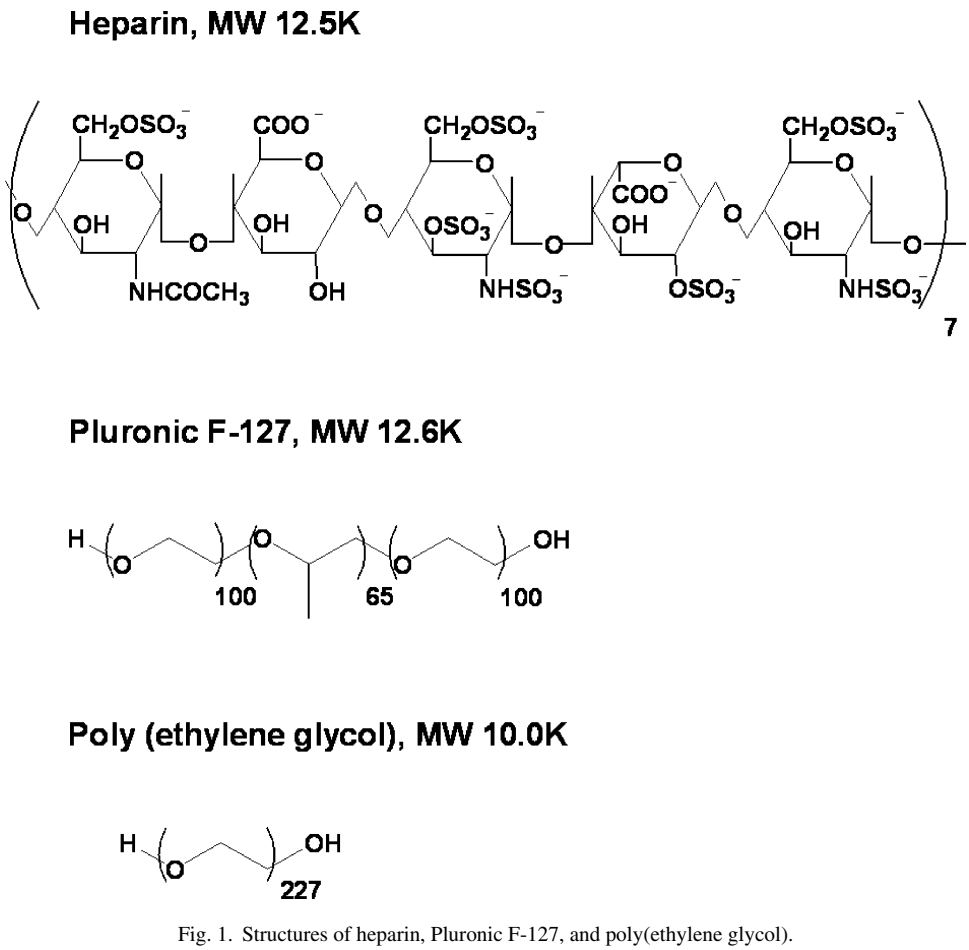

Fig. 1. Structures of heparin, Pluronic F-127, and poly(ethylene glycol).

sulfated, anionic polysaccharide composed of repeating disaccharides of 1,4-linked glucosamine and uronic acid residues [14]. Heparin interacts with a variety of proteins, such as antithrombin III (AT-III) and growth factors, and this association stabilizes proteins and protects them from proteolytic degradation [15,16]. Thus, the incorporation of heparin into the controlled release system is one of the most effective strategies for the delivery of growth factors [17–22]. The physically prepared heparin–Pluronic hydrogels were characterized by sol–gel transition temperature and rheological properties. We report the evidence of interaction between heparin and Pluronic polymer; a decrease in the sol–gel transition temperature and improved elastic rheological properties near the transition boundary compared to the pure PF-127 hydrogels.

2. Experimental

2.1. Materials

Pluronic F-127 ($E_{100}P_{65}E_{100}$, MW 12,600) was a gift from BASF Corp. (Seoul, Korea). Heparin sodium (189 IU/mg, MW 12,500) was obtained from Celsus Laboratories (Cincinnati, OH, USA). Poly(ethylene glycol) (PEG, MW 10,000) was purchased from Fluka (Ronkonkoma, NY, USA). The structures of three polymers are shown in Fig. 1. All reagents were used as supplied.

2.2. Sample preparation

PF-127 aqueous solutions (20–26%, w/w) were prepared by slowly adding Pluronic (25–35 g) into media (100 g), such as distilled water, 10 mM phosphate buffer (pH 7.4), and PBS (10 mM phosphate buffer and 100 mM sodium salts at pH 7.4) with vigorous stirring, and then stored in cold chamber at 4 °C overnight [23]. To prepare the heparin–Pluronic and the PEG–Pluronic solutions (0.0–4.8%, w/w), the required amount of heparin and PEG (0–50 mg) was added into 1 g of PF-127 aqueous solutions. The partially dissolved solutions were then transferred in cold chamber at 4 °C until thoroughly mixed.

2.3. Measurement of sol–gel transition temperature

The sol–gel transition temperature was determined by inverting the clear 1.7 ml microtubes, which contained 1.0 g of PF-127 solutions and additional amount (0–50 mg) of heparin and PEG, after keeping the sample at a constant temperature for 15 min to reach equilibrium [24]. Temperature increment was 1 °C per step and the average value and error bar of the sol–gel transition temperature were displayed in the phase diagram.

2.4. Measurements of rheological properties

Measurements of rheological properties with oscillatory shear deformation were carried out on heparin–Pluronic and