



Hydrophobically modified poly(vinyl alcohol) and boric acid-containing monoolein cubic phase as a glucose-responsive vehicle



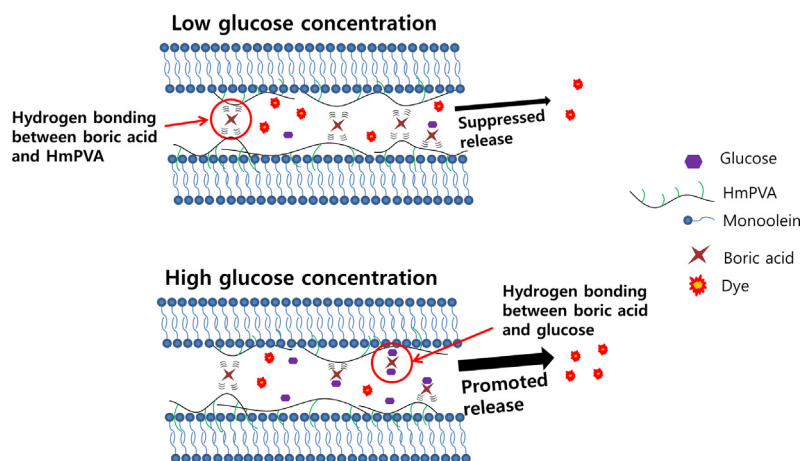
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HIGHLIGHTS

- HmPVA and boric acid were included in water channel of MO cubic phase.
- The cubic phase was glucose-responsive in terms of release.
- The release degree was higher at a higher glucose concentration.

GRAPHICAL ABSTRACT



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ABSTRACT

Glucose-responsive monoolein (MO) cubic phase was prepared by including hydrophobically modified poly(vinyl alcohol) (HmPVA) and boric acid in its water channels. The covalent attachment of hexanoyl chloride (a hydrophobic modifier) to PVA was confirmed by ^1H NMR and FT-IR spectroscopy. The viscosity of HmPVA/boric acid mixture solution (0.5% (HmPVA w/v)) in water/DMSO(1:1, v/v) increased significantly when the boric acid concentration increased to 3.2% (w/v). The viscosity of the HmPVA/boric acid mixture solution (0.5% (w/v)/0.8% (w/v)) decreased markedly when the glucose concentration increased to 400 mg/dL. The interfacial tension in the plateau region of HmPVA solution, about 42 dyn/cm, was lower than that of PVA solution, about 43 dyn/cm, suggesting that HmPVA was more surface-active than PVA. According to the polarized optical microscopy, the phase transition temperature was found to be about 49.8 °C. The release degree of amaranth (a dye) loaded in MO cubic phase containing HmPVA and boric acid was higher at a higher glucose concentration in the range of 0 mg/dL–400 mg/dL.

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1. Introduction

A cubic phase is formed when monoolein (MO) is hydrated with an adequate amount of water [1]. Either gyroid or diamond cubic

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phase is obtained, depending on the amount of water absorbed by MO molecules. For example, gyroid cubic phase and diamond one are formed, respectively, when MO molecules are hydrated at 23 °C so that the water content in cubic phase falls within 28%–32% and 32%–40% [2,3]. Two inter-crossing water channels are distributed evenly throughout the lipid matrix of MO cubic phase. The diameter of water channel is 1.8 nm to 3.5 nm, depending on the water content [4,5]. The cubic phase is in semi-solid state, and it is transparent due to its optical isotropic property [2]. Stimuli-responsive cubic phases have been developed by including stimuli-sensitive compounds either in the water channel or in the lipid matrix of MO cubic phase. Polymers exhibiting lower critical solution temperature (e.g. poly(*N*-isopropylacrylamide) and Pluronic F127) [6,7] and upper critical solution temperature (e.g. polyethyleneimine/cinnamic acid conjugate) [8,9] were included in the water channel of MO cubic phase to achieve temperature-responsive release property. The thermo-sensitive polymer chains change their conformation in response to temperature change, so the diffusivity of a diffusate through the water channel and the release rate strongly depend on the medium temperature. Silk protein together with alginate was included in the water channel of MO cubic phase to render the cubic phase responsive to medium pH change [10]. The complex coacervation between the protein and the negatively charged polysaccharide was postulated to control the release in response to the pH change. Recently, photo-responsive cubic phase were prepared by incorporating azobenzene in the lipid matrix of MO cubic phase [11]. The *cis/trans* transition of azobenzene under the irradiation of UV/visible light was claimed to fluctuate the MO bilayer and cause the load to release from the cubic phase. Recently, redox-responsive cubic phase was prepared by electrostatically immobilizing an 3,3'-dithiodipropionic acid compound in the water channel of MO cubic phase. The release was reported to be promoted in reducing environment due to the breakdown of disulfide bond.

In this study, glucose-responsive cubic phase was prepared by including poly(vinyl alcohol) (PVA) and boric acid in the water channel of MO cubic phase. Boric acid exists as tetrahydroxy borate anion in aqueous solution. Two hydroxyl groups of tetrahydroxy borate form hydrogen bonds with the diol unit of PVA chain, thus it can cross-link the polymer chains, leading to the formation of gel [12,13]. If PVA coexists with boric acid in the water channel of cubic phase, the diffusivity of a diffusate would be relatively low due to the cross-linking of PVA chains (i.e. gelation), leading to a suppressed release. On the other hand, tetrahydroxy borate can also interact with glucose through the hydrogen bonds. If glucose molecules diffuse into the water channels, they compete with PVA chains for interacting with tetrahydroxy borate molecule. Thus, the cross-linking density of cross-linked PVA chains can decrease and the release rate can increase with increasing glucose concentration (Fig. 1). The idea underlying the glucose-responsive cubic phase could be utilized in designing a self-regulated insulin carrier for the treatment of diabetes. PVA was hydrophobically modified using hexanoyl chloride in order to immobilize the polymer chains in the water channels of MO cubic phase, and the release profiles of dye (i.e. amaranth) loaded in the cubic phase were investigated at different glucose concentrations.

2. Materials and method

2.1. Materials

Poly(vinyl alcohol) (Sigma Aldrich product number 360627–500 G, MW 9000–10,000) (PVA), dimethyl sulfoxide (Sigma Aldrich product number 276855-1L, anhydrous $\geq 99.9\%$) (DMSO), *N,N*-dimethylformamide (Sigma Aldrich product num-

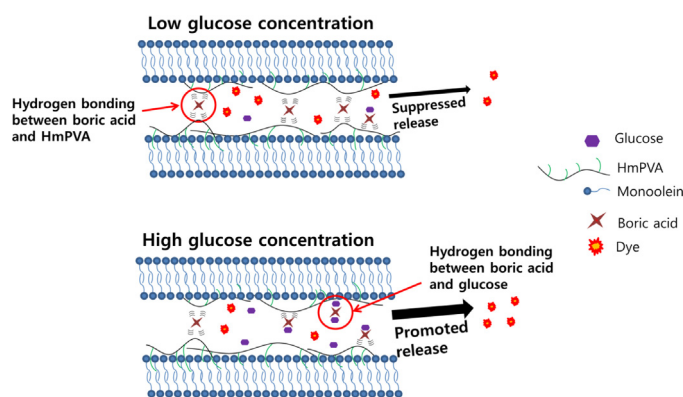


Fig. 1. Schematic representation of glucose-responsive MO cubic phase containing HmPVA and boric acid.

ber 227056-1L, anhydrous 99.8%) (DMF), hexanoyl chloride (Sigma Aldrich product number 156957–100 ml, 97%), boric acid (Sigma Aldrich product number B6768–500 G), monoolein (BASF Monomuls® 90-O18) (MO), D-(+)-glucose (Sigma Aldrich product number G5767–500 G), diethyl ether (DAEJUNG product number 4025-4410), filter paper (Whatman Catalogue number 1002-185 Filter paper No.2), deuterium oxide (Sigma Aldrich product number 151882–10 × 1 ML) (D₂O).

2.2. Preparation of hydrophobically modified poly(vinyl alcohol)

PVA was hydrophobically modified by a method described in a previous report [14]. PVA was put in 40 ml of DMF contained in a 100 ml two-neck round bottom flask, and it was heated to 140 °C using an oil bath under nitrogen atmosphere with reflux. Hexanoyl chloride was added to PVA solution so that PVA/hexanoyl chloride molar ratio was 1:3 and 1:5. The condensation reaction was performed at the same temperature for 2 min. The reaction mixture was cooled to a room temperature (23 °C), and it was poured in a 1 l beaker. 700 ml of diethyl ether was put in the beaker and the mixture was left at room temperature overnight to precipitate out hydrophobically modified PVA (HmPVA). It was filtered through a filter paper (Whatman No.2), washed with diethyl ether, and dried in a vacuum oven. HmPVA prepared from using the mixture solution whose PVA/hexanoyl chloride molar ratio was 1:3 and 1:5 was termed as HmPVA (1:3) and HmPVA (1:5), respectively.

2.3. ¹H NMR spectroscopy

HmPVA (1:3) and HmPVA (1:5) were dried overnight with P₂O₅ in a vacuum oven thermostated at 40 °C. Each of them was dissolved in D₂O, and the ¹H NMR spectra were taken on a NMR spectrometer (Bruker DPX 400 MHz, installed in Central Lab of Kangwon National University).

2.4. FT-IR spectroscopy

Each of PVA, HmPVA (1:3) and HmPVA (1:5) was grinded with KBr in a mortar, and the mixture powders were pelleted using a press. The FT-IR spectra were taken on a Fourier Transformed Infrared Spectrophotometer (FT-IR, FT-3000-Excalibur, Varian Inc., CA, USA).

2.5. Viscosity measurement of HmPVA/boric acid/glucose mixture solution

500 mg of each of PVA, HmPVA (1:3), and HmPVA (1:5) was dissolved in 100 ml of water/DMSO mixture solvent (1/1, v/v) so

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