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Design and synthesis of an amphiphilic graft hydrogel having a hydrophobic domain formed by multiple interactions

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ABSTRACT

A novel hydrogel having hydrophobic oligo segments and hydrophilic poly(acrylamidoglycolic acid) (PAGA) as pH responsive polymer segments was designed and synthesized to be used as a soft biomaterial. Poly(trimethylene carbonate) (PTMC) as the side chain, for which the degrees of polymerization were 9, 19, and 49, and the composition ratios were 1, 5, and 10 mol%, was used as the oligo segment in the hydrogel. The swelling ratio of the hydrogel was investigated under various changes in conditions such as pH, temperature, and hydrogen bonding upon urea addition. Under pH 2–11 conditions, the graft gel reversibly swelled and shrank due to the effect of PAGA main chain.

The interior morphology and skin layer of the hydrogel was observed by a scanning electron microscope. The hydrogel composed of PAGA as the hydrophilic polymer backbone had a sponge-like structure, with a pore size of approximately 100 μm. On the other hand, upon increasing the ratio of trimethylene carbonate (TMC) units in the hydrogel, the pores became smaller or disappeared. Moreover, thickness of the skin layer significantly increased with the swelling ratio depended on the incorporation ratios of the PTMC macromonomer. Molecular incorporation in the hydrogel was evaluated using a dye as a model drug molecule. These features would play an important role in drug loading. Increasing the ratio of TMC units favored the adsorption of the dye and activation of the incorporation behavior.

1. Introduction

Polymeric hydrogels are widely researched biomaterials, which have attractive properties such as high water content, volume phase transition, and the capacity for drug incorporation. Hydrogels are typically applied as biomaterials in versatile fields such as soft actuators, wound dressing, and drug delivery systems [1–3]. In order to develop various applications, plenty of hydrogel designs were proposed to improve their properties. Moreover, hydrogel cross-linking methodology has played an important role in tuning hydrogel properties and the cross-linking method involves chemical, physical, and topological bond formation. On the other hand, various cross-linking structures are investigated in terms of chain entanglement, molecular interaction, and molecular weight between cross-link points. Double network gels, hydrogen bonding gels, and tetra-poly(ethylene glycol) gels are typically researched [4–6]. In this study, an amphiphilic hydrogel cross-linked via chemical interactions, such as hydrogen bonding and hydrophobic interaction, was designed and prepared. A hydrogel resulting from multiple cross-linking, without the use of potentially harmful chemical reactions, is relatively safe for biological applications. Therefore, we focused on the incorporation of a graft gel as a functional pendant segment into the hydrogel. For example, Kaneko *et al.* reported a poly(*N*-isopropyl acrylamide)-grafted hydrogel having a fast response rate to temperature [7]. Furthermore, a hydrogel based on an amphiphilic macromonomer was reported by Xu *et al.* [8]. This hydrogel was formed by the aggregation of micelles into the hydrogel upon temperature change.

The hydrophobic poly(trimethylene carbonate) (PTMC) segment is easily and precisely synthesized from trimethylene carbonate (TMC), a molecule containing the hydroxyl group, and catalyzed via the ring-opening polymerization (ROP) technique. A variety of ROP of the TMC monomer using different types of catalysts such as organic and organometallic compounds have been reported [9–11]. Additionally, PTMC has been widely investigated in the biomaterials field because of its biodegradability by lipase and its amorphous property [12–13].

In this study, we examined the graft gel that includes the amphiphilic polymeric hydrogel with the PTMC macromonomer as the hydrophobic graft segment (Fig. 1a). Graft hydrogels with a polymerization degree of PTMC ranging from 10 to 50 and a grafting ratio from 1 to 10 mol% were prepared. The hydrophilic–hydrophobic balance was controlled by altering the above two parameters. In addition, poly(2-acrylamidoglycolic acid) (PAGA) was selected as the hydrophilic main chain. PAGA has numerous advantages such as hydrogen bonding ability, pH sensitivity, and the presence of multiple reactive groups.

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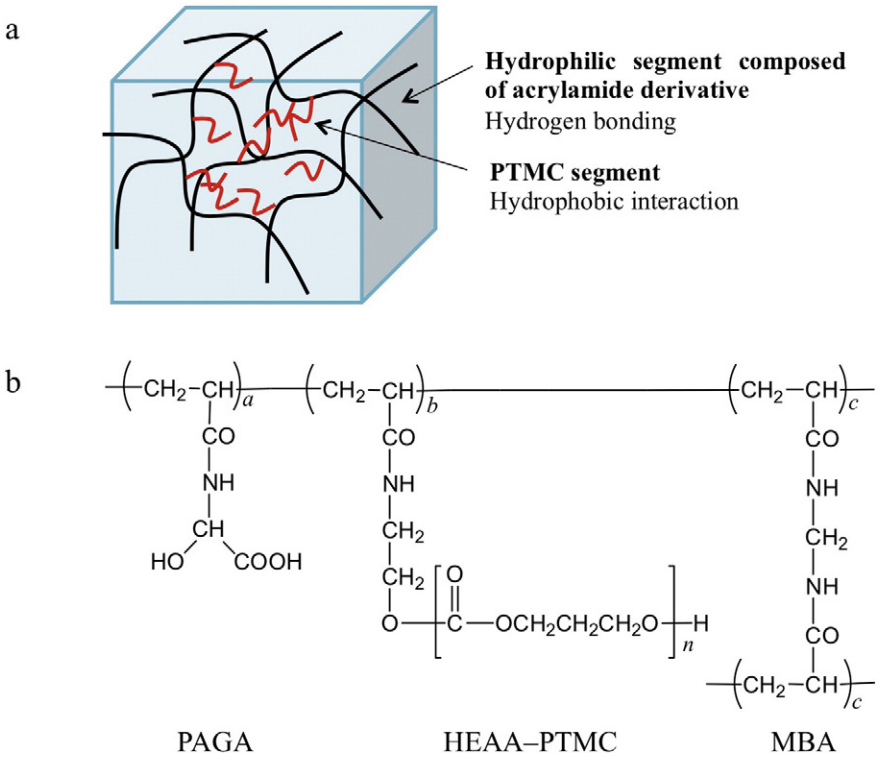

Fig. 1. (a) Illustration of the graft gel including PTMC segment. (b) Chemical structure of poly(AGA–*co*–HEAA–PTMC) graft gel.

We investigated the fundamental properties of the amphiphilic graft hydrogel. It spontaneously formed a three-dimensional structure via multiple interactions. Therefore, the favorable behavior of the hydrogel was changed by the hydrophobic effect and its physical properties were examined by swelling ratio measurement and scanning electron microscopy (SEM). The functional property of molecular loading was monitored by UV–Vis measurement using a model drug. The graft gel having PTMC segments is suitable for molecular adsorbent applications and this function is important for biomaterials and environmentally friendly materials.

2. Materials and methods

2.1. Materials

For ROP, 1,3-dioxan-2-one (trimethylene carbonate, TMC), as cyclic monomer, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), as organic catalyst, were purchased from Tokyo Chemical Industry, Co., Ltd., Tokyo, Japan. *N*-Hydroxyethyl acrylamide (HEAA) was kindly supplied by KOHJIN Co., Ltd., Tokyo, Japan. In order to terminate the polymerization, benzoic acid (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was used. For free radical polymerization, 2-acrylamidoglycolic acid monohydrate (AGA; Sigma-Aldrich Corp., St. Louis, MO, USA) was used as the monomer. 2,2′-Azobis(isobutyronitrile) (AIBN, Tokyo Chemical Industry Co., Ltd.) was used as the initiator for radical polymerization. *N*,*N*′-Methylenebis(acrylamide) (MBA, Wako Pure Chemical Industries, Ltd.) was used as a cross-linker. For confirmation of hydrogen bonding, urea was employed (Wako Pure Chemical Industries, Ltd.). Solutions with different pH values were prepared under the following buffer solutions: pH 3.0: glycine and HCl, pH 5.0: citric acid and NaOH, pH 7.1: phosphate buffered saline (PBS), pH 9.0: Na_2CO_3 and $NaHCO_3$, and pH 11.0: Na_2HPO_4 and NaOH. PBS (Dulbecco's PBS) was purchased from Life Technologies Corp., Waltham, MA, USA. The molarity of the buffer solution was 100 mmol/L except for PBS (10 mmol/L). The ionic strength of PBS was 150 mmol/L by NaCl. Other buffer solution was not adjusted by addition of NaCl. Other reagents were purchased from Wako Pure Chemical Industries. To investigate the drug incorporation function of the hydrogel, Basic Blue 7 (BB7) (Tokyo Chemical Industry, Co., Ltd.) was used as a model drug. All organic solvents were used as received.

2.2. Instruments for characterization

The chemical structure and degree of polymerization (DP) of the macromonomer were determined by ^{1}H NMR (Varian Unity INOVA AS 500 MHz). The solvent used was chloroform-*d* ($CDCl_3$) with tetramethylsilane. The chemical structure of the hydrogel was confirmed by FT–IR (FT/IR–4200, JASCO Co., Ltd., Tokyo, Japan). The surface and interior morphology of the hydrogel were observed by SEM (VE–9800, KEYENCE Co., Ltd., Osaka, Japan). The evaluation of molecular incorporation was monitored by UV–Vis spectroscopy (JASCO V–650, JASCO Co., Ltd.). Ultrapure water was produced by Direct–Q 3 UV MILLIPORE, Japan Millipore Co., Ltd., Tokyo, Japan.

2.3. Synthesis of HEAA–PTMC macromonomer

The HEAA–PTMC macromonomer was prepared according to a previously reported procedure [14]. We carried out ROP of TMC with the use of HEAA as the initiator. The chemical structure of the macromonomer was confirmed by ^{1}H NMR measurement. ^{1}H NMR spectra (500 MHz, $CDCl_3$) were assigned as follows; δ (ppm): 2.1 (m, 2H, –CH_2–CH_2–CH_2–), 3.6 (q, 2H, –CH_2–CH_2–O–), 3.7 (t, 2H, —NH–CH_2–CH_2–), 4.2 (t, 4H, –CH_2–CH_2–CH_2–), 5.6 (d, 1H, *H*–CH = CH–), 6.1 (q, 1H, CH_2 = *CH*–CO–), 6.2 (br, 1H, –CO–N*H*–CH_2–), and 6.3 (d, 1H, H–*CH* = CH–).

2.4. Preparation of poly(AGA–co–HEAA–PTMC) graft gel

To prepare the graft gel, free radical polymerization was carried out using AIBN, AGA, MBA, and HEAA–PTMC macromonomer (Fig. 1b). The reagents were each dissolved in *N*,*N*-dimethylformamide (DMF), and then, their solutions were mixed. The total concentration of initiator,