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Enhanced solubilization of α-tocopherol by hyperbranched polyglycerol-modified β-cyclodextin

Motomi Kimura, Tooru Ooya*

Graduate School of Engineering, Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai-cho, Nada-ku, Kobe, 657-8501, Japan

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ABSTRACT

A hyperbranched polyglycerol-modified β-cyclodextrin (HPG-βCD) was examined as a solubilization agent of α-tocopherol (vitamin E). The HPG-βCD was prepared by anion polymerization of glycidol in the presence of β-CD. The HPG-βCD increased the solubility of α-tocopherol as compared with hydroxypropyl (HP)-βCD and HPG. Complexation efficacy (i.e., [complex]/[free host]) for HPG-βCD was 84 and 7 times higher than for HP-βCD and HPG, respectively. A 2D ROESY NMR data clearly indicate that α-tocopherol was encapsulated to βCD cavity of HPG-βCD with the intermolecular interaction with outer HPG moiety. These results suggest the solubilization enhancement was due to both inclusion complexation between βCD and α-tocopherol and hydrotropic solubilization by branched molecules of HPG. Therefore, the HPG-βCD is a good candidate as a solubilization agent of aliphatic compounds like vitamin E.

1. Introduction

Poorly water-soluble substrates such as lipophilic vitamins (e.g., vitamin A and E), polyphenols, curcumin, and paclitaxel (PTX) have been extensively studied for effective oral administration. However, low bioavailability of such the poorly soluble substrates as a solid dispersion-based dosage form has been still concerned due to insufficient dissolution rate in aqueous media. We have already found that branched structure of polyglycerol dendrimers enhanced the solubility of poorly soluble drugs [1,2]. However, molecular interaction between polyglycerols and the drugs was insufficient, so that precipitation was immediately observed when the solubilized solution was diluted in aqueous media. Inclusion complex formation between poorly soluble drugs and cyclodextrins (CDs) as well as the other solubilizing agents is thought to be one of good approaches to enhancing the solubility [3–7]. For example, PTX solubility was enhanced by methylated β-cyclodextrins (βCDs), although hydrophilic βCDs such as hydroxypropyl (HP)-βCDs did not show the enhancement [6–8]. Alternatively, Zarrabi and Vossoughi reported that hyperbranched polyglycerol-modified β-cyclodextrin (HPG-βCD; Fig. 1(a)) exhibited a significant enhancement in PTX solubility due to entropic driven complexation [9]. However, the possibility of HPG-βCD toward the other poorly soluble compounds has not been demonstrated so far. In this study, we demonstrated HPG-βCD on solubilization of α-tocopherol (Fig. 1 (b)) as compared with HP-βCD and HPG.

2. Materials and methods

2.1. Materials

α-Tocopherol, hydroxypropyl-β-cyclodextrin (HPβ-CD) were purchased from Sigma-Aldrich Japan (Tokyo, Japan). β-Cyclodextrin (βCD), Glycidol, and a microfilter (COSMONICEFILTER: 4 mm × 0.45 μm) were purchased from Nacalai Tesque Inc. (Kyoto, Japan). *N*,*N*-Dimethylacetamide (DMA) and sodium hydride was (NaH) were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). 1,4,7,10,13-Pentaoxacyclopentadecane (15-C5) was purchased from (Tokyo Chemical Industry Co., Ltd. Tokyo, Japan). A dialysis bag (MWCO: 3500 Da) was purchased form Spectrum Laboratories Inc.). Hyperbranched polyglycerol (HPG; M_n = 5 kDa) was purchased from nanopartica GmgH (Berlin, Germany).

2.2. Instruments and Measurements

^{1}H NMR spectra were measured by JEOL JNM-ECZS400FT NMR SYSTEM, and its data analysis were performed using a Delta NMR Processing and Control Software v5.0.4.4. ^{1}H NMR spectra were

* Corresponding author.
E-mail address: ooya@tiger.kobe-u.ac.jp (T. Ooya).

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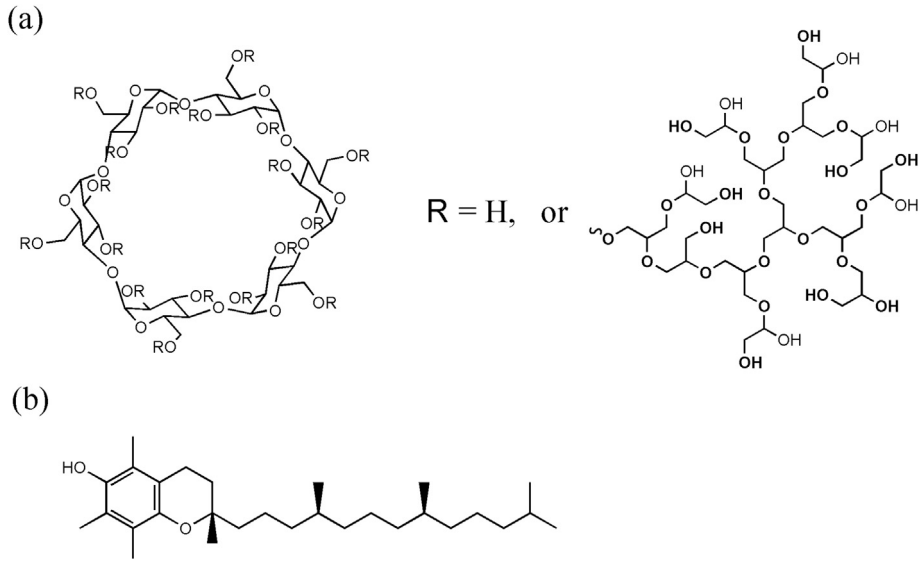

Fig. 1. Chemical structures of (a) hyperbranched polyglycerol-modified β-cyclodextrin (HPG-βCD) and (b) α-tocopherol.

measured using deuterium oxide (D_2O) as solvents. The chemical shifts were referenced to residual peaks of deuterated solvents: D_2O (4.70 ppm).

High-performance liquid chromatography (HPLC) was performed on a GILSON HPLC system (GILSON Inc., U.S.A.) with a COSMOSIL $5C_{18}$-MS-II (Φ 4.6 nm × 150 mm) column (Nacalai Tesque Inc., Japan) as stationary phase at r.t.. To determine α-tocopherol, a mixture of methanol and water (98:2) was used as mobile phase at a flow rate of 1.0 mL/min. All samples were injected by 20 μL, and detection was performed with a diode-array detector (Agilent 1100 DAD G1315B) at a detection wavelength of 292 nm.

2.3. Synthesis and characterizations of hyperbranched polyglycerol-modified β-cyclodextrin (HPG-βCD) [10]

The HPG-βCD was synthesized according to the anionic ring-opening multibranching polymerization method by using βCD as a multi-hydroxyl initiator. Solution of βCD (0.1984 g, 0.18 mmol) and 15-C5 (0.25 mL, 1.26 mmol) in dry DMA (10 mL) was added to a two-neck flask with NaH (0.0401 g, 1.67 mmol) and stirred for about 2 h at 50 °C. Then after the mixture was warmed up to 80 °C, solution of glycidol (1.5 mL, 22.6 mmol) in DMA (10 mL) was slowly added into the system, and then stirred for about 24 h. After the reaction the mixture was dialyzed using a dialysis bag (MWCO: 3500Da) against pure water for 5 days and then freeze dried *in vacuo*. The color of the final product was a transparent yellow, and the appearance was viscous liquid. The chemical structure and the molecular weight of was characterized by ^{1}H NMR, according to the report y Tao et al. [10]. Degree of polymerization (DP) of glycidol in the HPG-βCD was calculated by the following equation;

$$DP = \frac{(A_b - 6A_a)/5}{A_a/7}$$

where A_a is integrated areas of peak a (H1) and A_b (HPG and H2-H6 of βCD) (Fig 2). The number average molecular weight (M_n) was calculated to be 11,700 (g/mol).

2.4. Solubility tests

An excess amount of α-tocopherol was dissolved in ethanol (60 μL) (Solution A). The HPG-βCD (0.01, 0.05, 0.1, 0.15 and 0.2 g/mL), HP-βCD (0.001, 0.005, 0.01, and 0.02 g/mL), HPG (0.01, 0.05, 0.1, and 0.15 g/mL), or a physical mixture of HPG and HP-βCD (HPG concentration was 0.01, 0. 05, 0.1, 0.15 and 0.2 g/mL, respectively, and HP-βCD was mixed in equal amount.) was dissolved in water (240 μL), (Solution B), and then Solution A (60 μL) was added to Solution B (240 μL). The obtained suspension was stirred for 2 days at room temperature. Concentration of dissolved α-tocopherol, which was obtained by passing through a microfilter (0.45 μm), was determined by HPLC (The detailed condition was described in the section 2.2 **Instruments and Measurements**). Under the HPLC condition, a liner calibration curve was observed using α-tocopherol as a standard sample in the concentration range of 1 μg/mL – 10 mg/mL.

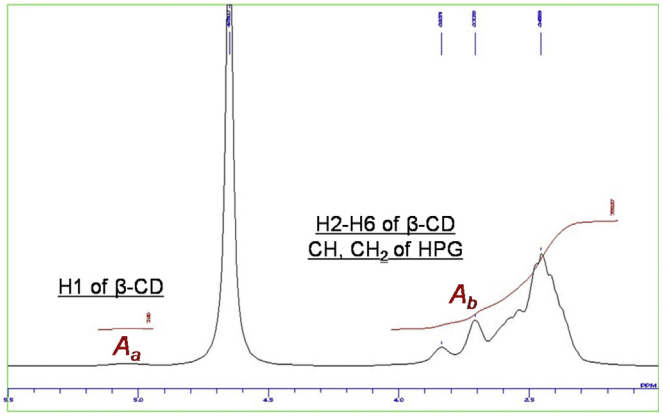

Fig. 2. A ^{1}H NMR spectrum of HPG-βCD in D_2O.

2.5. A 2D ROESY NMR measurements of the HPG-βCD/α-tocopherol mixture

In order to confirm whether the HPG-βCD forms the inclusion complex with α-tocopherol or not, a 2D ROESY NMR experiment was carried out at 400 MHz in D_2O on the JEOL JNM-ECZS400FT NMR SYSTEM at room temperature. The HPG-βCD was dissolved in D_2O, and then, α-tocopherol was suspended in the solution. Each