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# Loading of vitamin E into silicone hydrogel by supercritical carbon dioxide impregnation toward controlled release of timolol maleate

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ABSTRACT

Supercritical $CO_2$ impregnation was applied to loading of vitamin E into silicone hydrogel for development of controlled release system of timolol maleate, hydrophilic ocular drug for glaucoma. Vitamin E was loaded into the silicone hydrogel to reduce the diffusivity of timolol maleate. Supercritical impregnation accomplishes the large amount of loaded vitamin E into the silicone hydrogel at the low concentration in supercritical $CO_2$ compared with that by ethanol liquid solution. The loading of vitamin E 0.49 g $g^{-1}$-hydrogel by the supercritical impregnation results in the significant reduction of the diffusivity of timolol maleate in the silicone hydrogel to $1.4 \times 10^{-5}$ $mm^2$ $min^{-1}$ much smaller than of that without vitamin E, $13 \times 10^{-5}$ $mm^2$ $min^{-1}$. The release system of timolol maleate in silicone hydrogel with the low diffusivity is obtained from the effective loading of vitamin into the silicone hydrogel using the supercritical impregnation.

## 1. Introduction

Ocular drug release system using hydrogels as soft contact lenses has attracted much attention because of a higher bioavailability of ocular drug than a conventional eye drop [1–4]. An administration by eye drops causes an insufficient therapies and serious side effects [5,6]. The drug releases via the hydrogel lenses are expected to achieve sustainable and controlled release of the ocular drug and the bioavailability more than 50% [7]. Moreover, the drug release from hydrogel lenses allows to an administration to patients with the ocular diseases during their sleep. Fabrication techniques of the ocular drug release system with hydrogel lenses are categorized to the two methods; a polymerization of hydrogel containing drug and an impregnation of hydrogel with drug. The former techniques have been investigated in various approaches, such as a new composite of polymer and drug [8–10], hydrogel modified by surfactant [11–13] and nanoparticles loading to hydrogel [14,15]. However, there are problems on difficulties of extending to its actual applications of these polymerization processes that requires a long time and high cost to investigate the process design for optimization of the hydrogel composite for achievements of controlled drug releases. Impregnation techniques with drug have been studied toward developments of a simple fabrication of ocular drug delivery systems using synthesized hydrogels [16–18] and commercial soft contact lenses [19–26]. Hydrophilic monomer, *N*, *N*-dimethylacrylamide and hydrophobic monomer, Methaacryloxypropyltris (trimethylsiloxy) silane were used for the synthesis of the silicone hydrogel [16]. Chauhan's group has studied the diffusivity of ocular drug in silicone soft contact lenses containing Vitamin E as an agent reducing the diffusivity of the drug. [23–26]. Vitamin E in the hydrogel does not affect much to the oxygen permeability and transmittance [25]. The ocular drug was loaded into the hydrogel in aqueous solution after the impregnation with Vitamin E. The fabrication of the hydrogel containing Vitamin E requires a long time, 1–7 days for loading the ocular hydrophilic drug into the hydrogel [23,25,26].

Supercritical $CO_2$ is a potential solvent for fabrication techniques of drug delivery systems because of its properties of non-toxic, high solubility, high diffusivity, low surface tension and low critical temperature leading to a mild operation condition. Some research groups have reported possibilities to fabricate composites of the hydrophobic drug and polymer for development of the drug delivery systems because of the high solubility of hydrophobic drugs in supercritical $CO_2$ [27–32]. While, it is quite difficult to apply the supercritical $CO_2$ impregnation to the ocular drug salt, such as meloxicam sodium salt and sodium L-Ascorbate because the solubilities in supercritical $CO_2$ are much lower than those of hydrophobic drugs [33,34]. Supercritical $CO_2$ impregnation has a possibility to be applied for loading vitamin E into the hydrogel due to the high solubility of vitamin E in supercritical $CO_2$ as reported the extraction process [35–37]. In the literature [23,25,26], the ocular drug salt needed to be loaded into the hydrogel in the aqueous solution after loading vitamin E in ethanol solution in order to prevent the loss of the drug salt into ethanol. This fabrication technique

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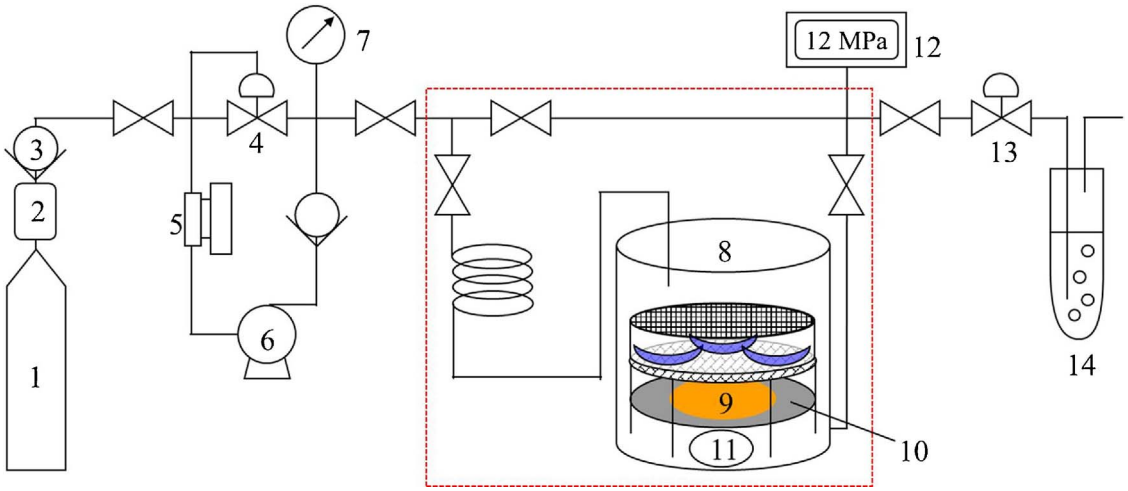


**Fig. 1.** Setup for supercritical impregnation. 1: $CO_2$ cylinder, 2: silica gel cell, 3: check valve, 4: back pressure regulator, 5: chiller, 6: double plunger pump, 7: pressure gauge, 8: high-pressure vessel, 9: vitamin E, 10: aluminum foil, 11: stirrer bar, 12: precision pressure gauge, 13: metering valve, 14: ethanol trap, red line: controlled temperature. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

causes a low diffusivity of the drug salt in the hydrogel containing Vitamin E and the long time required on its loading process. Using the supercritical $CO_2$ impregnation for loading vitamin E, the drug salt can be loaded into the hydrogel in advance. The fabrication method using supercritical impregnation allows to loading the ocular drug salt into the hydrogel without vitamin E and then the hydrogel with the drug can be impregnated with vitamin E in supercritical $CO_2$.

In this work, we developed an impregnation technique of Vitamin E into the silicone hydrogel using supercritical $CO_2$ for fabrication of the release system of timolol maleate as hydrophilic ocular drug. Timolol can be used for the treatment of glaucoma with reduction of intraocular pressure [38]. Vitamin E has been applied for the inhibition of some eye diseases after surgery [23]. The loading of vitamin E into the silicone hydrogel was conducted in supercritical $CO_2$ after loading timolol maleate in the aqueous solution in order to reduce the fabrication time of the release system. The release profile of the timolol maleate from the silicone hydrogel with vitamin E was evaluated by in vitro release test. The diffusivity of the timolol maleate in the hydrogel is determined from the release profile. The hydrogel with vitamin E from the supercritical impregnation were analyzed by a differential scanning calorimetry and a thermogravimetry. The molecular interaction between the timolol maleate and vitamin E with the polymer network of the hydrogel is studied by a Fourier transform infrared spectroscopy.

## 2. Experimental

### 2.1. Chemicals

Ethylene glycol dimethacrylate (EGDMA), *N*,*N*-dimethylacrylamide (DMAA), 2,4,6-trimethylbenzoyl diphenylphophine oxide (TPO) from Wako Pure Chemical Ind. Ltd., 3-methacryloxypropyltris(trimethlyfiloxy)silane (TRIS) from Alfa Aesar and acryloxy terminated ethyleneoxide dimethylsiloxane-ethyleneoxide ABA block copolymer (DBE-U12) from Gelest were used for the synthesis of the silicone hydrogel. The purities of EGDMA, DMAA and TRIS are over than 97.0 98.0 and 98.0%, respectively. Timolol maleate and ethanol with purities over than 97.0 and 99.5% were supplied from Wako Pure Chemical Ind. Ltd. *d*-α-tocopherol (vitamin E) with purities over than 97.0% was from Tokyo Chemical Ind. Co. Ltd. Phosphate buffer solution (PB) with pH 7.4 from Wako Pure Chemical Ind. Ltd. was used for the release test of timolol maleate. Carbon dioxide with the purity over 99.5% was supplied from Fujii Bussan Co. Ltd. Ultra-pure water with the resistivity 18.2 MΩ cm was produced by Direct-Q UV3 Water Purification System from EMD Millipore Corporation.

### 2.2. Synthesis of silicone hydrogel

Silicone hydrogel was synthesized by the polymerization of TRIS (hydrophobic monomer), DMAA (hydrophilic monomer) using DBE-U12 as macromer and EGDMA as cross-linker [16]. The mixed solution of these compounds were prepared in a glass tube capped with an aluminum foil in weight ratio, 2.00: 2.35: 0.74: 0.19 for TRIS, DMAA DBE-U12 and EGEMA. Nitrogen gas was flowed into the solution for 15 min for removing the oxygen dissolved in it. And then, the initiator TPO was added to the solution. The weight fraction of TPO in the solution was 0.022. The solution with TPO was installed into a mold with two glass plates separated by a glass spacer in the thickness 0.13 mm. Ultraviolet (UV) light with 365 mm was irradiated to the solution inside the mold for 50 min. After the UV irradiation, the solution in the mold was immersed in the ultrapure water heated to 373 K for the smooth separation of the synthesized silicone hydrogel from the glass plate. The synthesized silicone hydrogel was cut to the circle shape in diameter 1.4 cm and stored in the ultrapure water at the room temperature for the loading of vitamin E as described at the next section.

### 2.3. Loading of vitamin E into silicone hydrogel

#### 2.3.1. Supercritical impregnation after loading of timolol maleate

Before loading vitamin E into the silicone hydrogel, timolol maleate was installed into the hydrogel in the phosphate buffer (PB) aqueous solution with pH 7.4. The dried silicone hydrogel synthesized at the previous section was soaked into 2 mL of the PB aqueous solution with timolol maleate at the room temperature for 12 h. The initial concentration of the timolol maleate in the PB solution was 5.0 mg $mL^{-1}$. After the soaking, the silicone hydrogel with timolol maleate was removed from the PB solution and dried at 313 K for 1 h.

Vitamin E was loaded into the silicone hydrogel with timolol maleate by a supercritical impregnation in high-pressure $CO_2$. A schematic diagram of setup of the supercritical impregnation is given in Fig. 1. Carbon dioxide from a gas cylinder was dehydrated by passing through a silica gel column and liquefied on a chiller. The liquefied $CO_2$ was pressurized by a double plunger pump (NP-D-321 from Nihon Seimitsu Co., Ltd.). The pressurized $CO_2$ achieved to the supercritical state in pre-heating coil and was fed into a high-pressure vessel. The high-pressure vessel was inside an air thermostatic bath for controlling the temperature. The pressure in the system was controlled by a back pressure regulator. In advanced, the silicone hydrogel with timolol maleate and vitamin E were installed into the high-pressure vessel with 0.08 L. The amount of vitamin E loaded in the high-pressure vessel was