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Synthesis and characterization of nanoporous polycaprolactone membranes via thermally- and nonsolvent-induced phase separations for biomedical device application

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ABSTRACT

A constant and well-controlled drug release rate is of paramount importance to implantable drug delivery systems in finding the remedy against chronic diseases. This paper describes the synthesis and potential application of nanoporous poly(caprolactone) (PCL) membranes to achieve the zero-order release rate. Nanoporous PCL membranes were prepared via the combination of thermally- and nonsolvent-induced phase separations. In the membrane preparation, 1,4-dioxane and 2-methoxyethanol were used as solvent and nonsolvent, respectively, resulting in uniform nanoporous membranes and consistent lysozyme diffusion using a Teflon plate for membrane casting. Pore connectivity was improved significantly when coagulation bath temperature was lowered from 35 to 5 °C. By using a 5 °C water coagulation bath in the wet-process precipitation, the average pore size reduced from about 90 to 55 nm while increasing the casting solution concentration from 15 to 25 wt% PCL. Thus, by varying the polymer concentration of the casting solution, the lysozyme release rate was well controlled. The potential of nanoporous PCL membranes for an implantable drug delivery device to achieve the zero-order release rate was demonstrated in this study.

1. Introduction

Sustained and well-controlled release of protein- and DNA-based drugs has been an emerging therapy for the treatment of chronic diseases. For patients suffering from a chronic illness, it is preferable to deliver a drug of interest for a desirable period of time. In the case of endostatin, the constant release for a long period of time, other than bolus injection, enhanced therapeutic efficacy for pancreatic cancer [1,2]. An ideal controlled release system is able to maintain a drug concentration within the specific therapeutic window [3]. Several side effects, such as nausea and high fever, resulting from a drug concentration above the toxic level, can be prevented. Moreover, keeping drug concentration above the effective level can improve the efficient usage of a drug. Maintaining constant drug concentration in the body implies that the designed drug delivery system can offer a zero-order release rate over the entire treatment course. However, delivering a drug of small molecular size to the targeted tissues and cells in a safe, well-controlled, and patient-friendly manner remains a significant challenge [4]. Therefore, a novel method to engineer the release rate of such small molecules has to be developed.

For a membrane-based drug delivery system, the porous membrane structure, such as pore size, porosity and tortuosity, has a crucial effect on controlling the drug release rate [5–11]. The nanoporous structure is a determinant factor in the achievement of the zero-order release rate. Based on their experimental results and schematic model, Berg et al. showed and explained that a zero-order release rate can be achieved by using nanoporous polyelectrolyte films, instead of microporous films [12]. Paulose et al. displayed that a zero-order diffusion system can be obtained with utilization of the nanoporous TiO_2 membrane [13]. Ferrari et al. used nanoporous silicon membranes to deliver interferon-α with a zero-order release rate [10,14]. Moreover, a mathematical model was proposed to fundamentally understand the zero-order release behavior with the nanoporous membranes [15,16]. Therefore, a nanoporous membrane with tunable structure can offer a means to perform a versatile constant drug release rate during the entire medical treatment.

In medical and pharmaceutical fields, the drug or cell-loaded chambers sealed with a semipermeable membrane are capable of releasing the molecule of interest for a long period of time [17]. The nanoporous membrane can form a barrier between the

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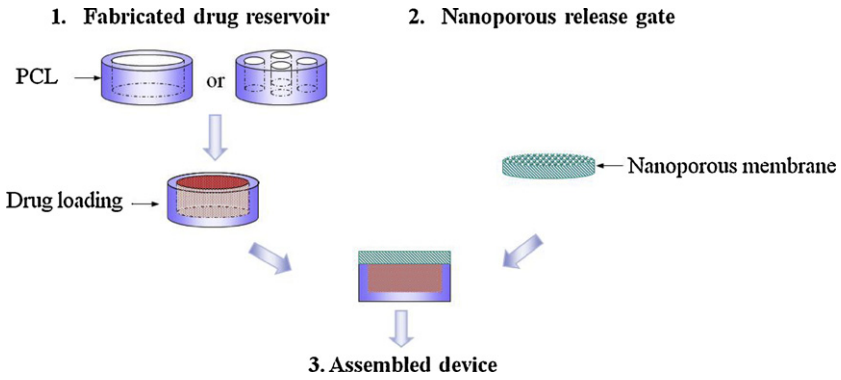

Fig. 1. Schematic design of the membrane-based reservoir-type drug delivery device.

surrounding and the inside of the chamber. When the pore size is small enough, a well-controlled drug release rate can be obtained. In our previous study, an implantable membrane-based drug delivery device was successfully developed, and its schematic design is shown in Fig. 1 [18]. Such a system can provide several potential advantages over microparticles and bulk materials for protein delivery, including high loading efficiency without use of any solvents with limited solubility of biomolecules, less denature of cells and/or protein drugs without exposure to organic solvents during assembling the device, availability of long-term release with the reservoir of a large volume, capability of loading optimized formulation [19], and a pre-designed release profile with an appropriate nanoporous structure [1]. Thus, the nanoporous membrane will be the key component to achieve the desirable constant release rate.

Silicon, alumina and titanium oxide-based nanoporous membranes are chemically inert and mechanically stable. They have highly uniform and well-defined pore structures [10,13,14,20]. However, if implanted, they must be surgically removed at the end of the medical treatment. Inexpensive polymers such as polycaprolactone (PCL), on the other hand, can be fully biodegradable, so a surgical retrieve is not necessary. Moreover, PCL is a U.S. Food and Drug Administration approved implantable material. Therefore, PCL is an excellent candidate to make implantable drug delivery devices.

Currently, porous PCL membranes have been prepared by a solvent-cast-leaching method [21,22], bi-axial stretching [23,24], thermally induced phase separation [25,26], nonsolvent-induced phase separation [27–29], and vapor-induced phase separation [30,31]. However, state-of-the-art porous PCL membranes which are prepared via above methods have a micro-scale pore structure. Due to the large pores, the mechanism governing diffusion phenomena may be Fickian diffusion, and the zero-order release rate will not be achieved [12]. Thus, a reliable and promising method is sought to synthesize the desirable nanoporous PCL membrane.

None of the studies so far have reported the synthesis of nanoporous PCL membranes for controlled drug release. In this study, nanoporous PCL membranes were successfully prepared via the combination of thermally- and nonsolvent-induced phase separations. A sufficient amount of nonsolvent was used to bring thermally induced phase separation into effect. Lysozyme was used as a model drug. The consistent lysozyme diffusion rate, indicative of uniform membrane structure, was obtained when a Teflon plate was used to prepare the free-standing nanoporous PCL membranes. The effect of varying coagulation bath temperature on the pore structure and lysozyme diffusion rate was investigated. Different polymer concentrations for the casting solution were used to control the lysozyme diffusion rate. The potential of nanoporous PCL membranes for the implantable drug delivery device (Fig. 1) to achieve the zero-order release rate was demonstrated in this study.

2. Experiments

2.1. Materials

Polycaprolactone (M_n ~80,000) was purchased from Aldrich Chemicals (Milwaukee, WI). 1,4-Dioxane was obtained from Mallinckrodt Chemicals (Philipsburg, NJ). 2-Methoxyethanol (ACS reagent, ≥93%) and lysozyme (from chicken egg white, lyophilized powder, ~95% protein, and ~50,000 units/mg) were purchased from Sigma–Aldrich (St. Louis, MO). Phosphate buffered saline solution (PBS) was purchased from Fisher Scientific Inc. All chemicals were used as received without further purification.

2.2. Preparation of nanoporous membranes by phase separation

Nanoporous polycaprolactone membranes were prepared using a combination of thermally- and nonsolvent-induced phase separations. In the preparation of the casting solution, PCL at a suitable concentration (e.g., 20 wt%) was dissolved in a diluent which consisted of 15 wt% 1,4-dioxane as solvent and 65 wt% 2-methoxyethanol as nonsolvent. The solution was well stirred and heated at 50 °C for approximately 2 h to ensure that it was clear and homogeneous. A general membrane preparation procedure is described below. The PCL solution at 50 °C was cast on a Teflon plate, and the cast film along with the Teflon plate was then immediately immersed into a coagulation bath. After 4–6 h, the newly formed membrane on the Teflon plate was removed from the bath. To remove the membrane from the Teflon plate, isopropanol was poured onto the membrane. After 20–30 min, the membrane was peeled off from the Teflon plate. The resultant PCL membrane was around 50 μm thick. In this study, nanoporous PCL membranes were prepared in four different ways.

1. *Different casting substrates*. The casting solution composed of 20 wt% polycaprolactone, 65 wt% 2-methoxyethanol and 15 wt% 1,4-dioxane was cast on a glass plate and a Teflon plate. Immediately, the cast film was immersed in a 5 °C water bath. Then, the membranes were peeled off and dried in air.
2. *Different coagulation bath temperatures*. The same casting solution described above was cast on the Teflon plate. Then, the cast film was immersed into 5, 15, 25 or 35 °C water.
3. *Different PCL concentrations in the casting solution*. Three casting solutions of 15, 20 and 25 wt% PCL were prepared in the diluents mixture of 2-methoxyethanol and 1,4-dioxane at the 65/15 weight ratio. Each of the solutions was cast on the Teflon plate and then immersed into 5 °C water.
4. *Thermally induced phase separation*. The 20 wt% PCL solution described earlier was cast on the Teflon plate, and the cast film was placed in a 5 °C close chamber to decrease the evaporation