

Synthesis and Characterization of Nanoporous PCL Membranes for Controlled Drug Release

Sustained release of protein drugs has been an emerging therapy, suitable for the treatment of a chronic disease. It is preferable to deliver a drug for a desirable period of time and avoid the need for continual administration. An ideal controlled-release system is able to maintain a drug concentration within the specific therapeutic window. A constant drug concentration in the body implies that the designed drug delivery system can achieve a zero-order release rate over the entire treatment course. Therefore, several side effects, such as nausea and high fever, can be suppressed [1].

Nanotechnology is a promising method to manipulate a substance at the molecular level [2, 3]. Nanoporous membranes can play an important role in the development of implant delivery devices. Furthermore, the nanoporous membranes have a potential for cell-based delivery devices. The nanoporous membranes have to offer immunisolation and must be capable of impeding the passage of immuno molecules, such as Immunoglobulin G (IgG) [4, 5].

Recently, polycaprolactone (PCL) has drawn lots of attention in biomedical applications. PCL has several advantages, including low cost, biocompatibility, and biodegradability. Moreover, PCL is an FDA-approved material for implantable devices. Thus, it is a superior material to fabricate affordable and implantable drug delivery devices.

The porous membranes play an important role in delivery systems. Several factors, including porosity, tortuosity, and pore size, have a crucial effect on controlling the rate of drug diffusion through the membranes. Currently, state-of-the-art, PCL porous membranes have pore sizes on the microscale [6-9]. The mechanism governing diffusion phenomena could be free diffusion. Therefore, microporous membranes might not be a proper means to achieve zero-order drug release rate. In this study, nanoporous PCL membranes can be prepared successfully via a combination of thermally and nonsolvent induced phase separations.

Biodegradable Drug Delivery Devices

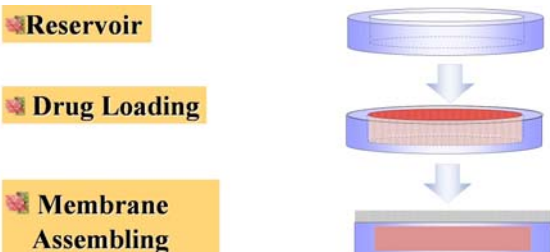


Figure 1. The procedure of producing the implantable delivery device.

Figure 1 shows how to make the implantable drug delivery device. The drug reservoir is fabricated via the

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hot embossing method, and the PLGA or PCL reservoir can be produced with different sizes, from millimeters to centimeters. Then, the drug can be loaded into the reservoir in the powder or solution form. Carbon-dioxide-assisted bonding can be used to assemble the reservoir and membrane at low temperatures. This technique can allow a drug not to suffer from denaturing during assembling. It can reach a drug loading efficiency of about 100%.

Thermally and Nonsolvent Induced Phase Separations (TIPS and NIPS)

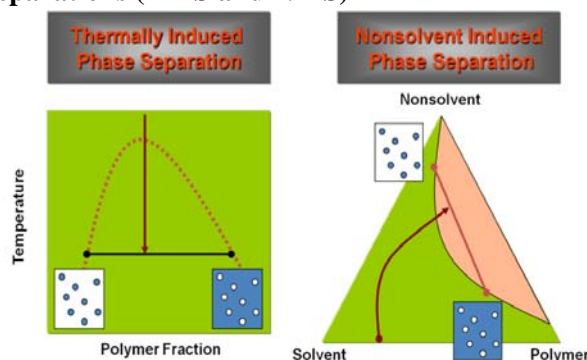


Figure 2. Illustration of thermally and nonsolvent induced phase separation concepts.

Thermally induced phase separation (TIPS) can help a homogeneous solution reach liquid-solid phase separation more quickly. It makes phase-separated solutions spend less time staying within the liquid-liquid separation region. Fast solidification can avoid pore coalescence [10]. Thus, TIPS can make porous membranes with high porosity. Moreover, nanoscale pore size can be obtained via nonsolvent-induced phase separation (NIPS). Therefore, nanoporous membranes with high porosity can be prepared via the combination of TIPS and NIPS.

Effect of Coagulation Bath Temperature on Porosity

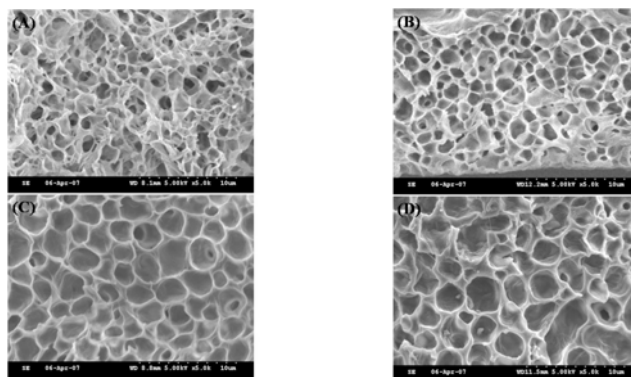


Figure 3. Cross sections of membranes prepared from a 20/65/15 w/w PCL/2-methoxyethanol/1,4-dioxane casting solution. Coagulation bath temperatures: (A) 5°C, (B) 15°C, (C) 25°C, and (D) 35°C.

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Cross sections illustrating the porous structures of the membranes that formed under various coagulation bath temperatures are shown in Figure 3(A-D). As can be seen, coagulation bath temperatures rising from 5 to 35°C would result in poor pore connections with isolated pores. At high coagulation bath temperatures, a polymer solution could not reach the solid-liquid phase separation region. Phase separations could stay within the liquid-liquid region. Pore coalescence would be significant in the slower solidification. Pore coarsening would lead to low porosity.

Effect of Polymer Concentration on Pore Size

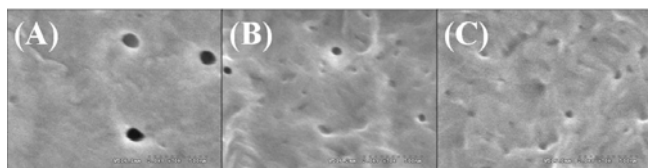


Figure 4. SEM pictures of nanoporous PCL membranes prepared by different polymer concentrations: (A) 15%, (B) 20%, and (C) 25%.

Figure 4 illustrates different pore sizes at the top side of membranes that were made from 15%, 20%, and 25% PCL in the casting solutions. As shown in this figure, increasing polymer concentration could give rise to smaller pore size. When the membrane was prepared from 15% PCL solution, its pore size was around 120 nm. However, the pore sizes were about 60 and 50 nm for the membranes produced from 20% and 25% PCL solutions, respectively.

Potential of Nanoporous PCL Membranes for Cell-based Drug Delivery Devices

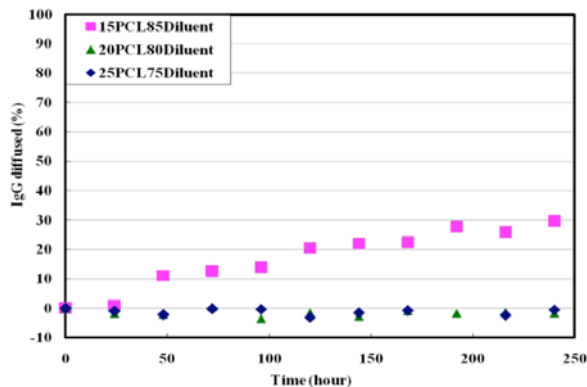


Figure 5. Diffusion of IgG through different nanoporous PCL membranes.

As shown in Figure 5, the membranes prepared from 20% and 25% PCL casting solutions could substantially retard IgG passage. It appears that these two PCL membranes were able to block IgG diffusion completely. At the permeate side, no fluorescent signal could be detected

above the baseline after 10 days. But the membrane prepared from 15% PCL casting solution would allow a considerable amount of IgG to pass through in the first 24 hours. These results suggest that nanoporous PCL membranes can achieve the desirable immunoisolation by varying the polymer concentrations.

References

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Presentations

- [1] Yen, C., He, H., Lee, L. J., and Ho, W. S. W., "Synthesis and characterization of polycaprolactone nanoporous membranes for liquid-phase controlled release", *AICHE Annual Meeting*, Salt Lake City, Utah, November 4-9, 2007, Paper 148b.
- [2] Yen, C., He, H., Lee, L. J., and Ho, W. S. W., "Synthesis and characterization of polycaprolactone nanoporous membranes for implantable drug delivery devices", *AICHE Annual Meeting*, Salt Lake City, Utah, November 4-9, 2007, Poster Paper 330o.