A Novel Dual-Functionalized Polycaprolactone : Synthesis, Surface Properties, and Its Controlled Release

張, 宇澄

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氏　　名　：張　宇澄

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論 文 内 容 の 要 旨

Recently, the drug-eluting stent (DES) implantation has emerged as an excellent treatment for cardiovascular disease. Since the drug-eluting coating contacts with blood vessel immediately, anti-proliferation drugs can be accurately delivered to the lesion. This approach shows good performance on inhibiting proliferation and migration of smooth muscle cells which are widely accepted as the principal mechanism underlying in-stent restenosis. In this thesis, a novel PCL-based drug eluting coating was developed, which is consisted three layers including the top phosphorylcholine (PC)-based rate-controlling membrane, middle drug reservoir, and bottom PC thin film. The top PC-based rate-controlling membrane could control the diffusivity of the drug in the second layer and improve the surface biocompatibility. The drug reservoir used PCL and dopamine-modified PCL to immobilize drugs via hydrophobic interaction. The bottom PC thin film endow stainless steel sheet with a good biocompatibility, after the degradation of polymer.

In Chapter 1, the background, purpose, and the content of this thesis were introduced.

In Chapter 2, graft-functionalization and end-functionalization are applied for PCL. A new method on the basis of nucleophilic substitution provided a high conversion rate without any undesirable side reactions (i.e. degradation). The end-functionalization of this dopamine-modified PCL using 2-methacryloyloxyethyl phosphorylcholine (MPC) via atom transfer radical polymerization (ATRP) was carried out to obtain polymers designated as PMPC-*block*-poly(α-dopamine-ε-caprolactone)-*block*-PCL-*block*-poly(α-dopamine-ε-caprolactone)-*block*-PMPC (PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$) and (PCL-*co*-PCL-DOPA)-*b*-(PMPC)$_2$.

In Chapter 3, the formation of PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$ film onto stainless steel by "graft-to"

method is discussed. Polymer concentrations showed a significant influence to the formation of polymer thin film. Low concentrations induced insufficient but smooth and uniform adsorption. High concentrations showed aggregate adsorption that led to rough and thick polymeric films. The optimized coating formation was obtained at 50 mg/mL. The resultant surface showed strong hydrophilicity, good stability, and excellent anti-biofouling properties.

In Chapter 4, the surface reorganization of PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$ and (PCL-*co*-PCL-DOPA)-*b*-(PMPC)$_2$ is evaluated, since it shows significant influence to the performance of PC-based coating. Surface reorganization is the switching between hydrophobic and hydrophilic segments under different condition to reduce the surface free energy. The crystalline PCL segments existing in PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$ were able to suppress the surface reorganization due to its low mobility polymer chain. (PCL-*co*-PCL-DOPA)-*b*-(PMPC)$_2$ without crystallinity is reorganized under hydrophilic and hydrophobic conditions.

In chapter 5, biodegradable PCL-*b*-(PCL-DOPA)$_2$/PCL/drug films with different ratios of PCL and PCL-*b*-(PCL-DOPA)$_2$ including 2:1 (wt:wt), 1:1 (wt:wt), and 1:2 (wt:wt) are prepared. Due to the strong inter- and intra- molecular interactions existing in PCL-*b*-(PCL-DOPA)$_2$ and PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$, these polymers are able to serve as drug-eluting coating. Results indicated that the introduction of PCL-*b*-(PCL-DOPA)$_2$ enhanced the drug capacity, however, the inherent hydrophilicity of PCL-*b*-(PCL-DOPA)$_2$ induced higher diffusion rate and faster drug release. Moreover, a rate-controlling membrane was prepared using PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$. The resultant film provided a better controlled-release that is accordance with the Higuchi Model.

In the Chapter 6, we summarize this thesis and give some additional idea about the application of PCL-*b*-(PCL-DOPA-*b*-PMPC)$_2$.