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The effect of solvents and hydrophilic additive on stable coating and controllable sirolimus release system for drug-eluting stent

Seong Min Kim [a,1], Sung-Bin Park [a,1], Tarek M. Bedair [a,b], Man-Ho Kim [c], Bang Ju Park [d], Yoon Ki Joung [a,e,*], Dong Keun Han [a,e,*]

[a] Center for Biomaterials, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul 02792, Republic of Korea
[b] Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt
[c] Advanced Analysis Center, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul 02792, Republic of Korea
[d] Department of Electronic Engineering & Institute of Gachon Fusion Technology, Gachon University, 1342 Seongnamdaero, Sujeong-gu, Seongnam-si, Gyeonggi 13120, Republic of Korea
[e] Department of Biomedical Engineering, Korea University of Science and Technology, Gajeong-ro 217, Yuseong-gu, Daejeon 34113, Republic of Korea

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ABSTRACT

Various drug-eluting stents (DESs) have been developed to prevent restenosis after stent implantation. However, DES still needs to improve the drug-in-polymer coating stability and control of drug release for effective clinical treatment. In this study, the cobalt-chromium (Co—Cr) alloy surface was coated with biodegradable poly(D,L-lactide) (PDLLA) and sirolimus (SRL) mixed with hydrophilic Pluronic F127 additive by using ultrasonic spray coating system in order to achieve a stable coating surface and control SRL release. The degradation of PDLLA/SRL coating was studied under physiological solution. It was found that adding F127 reduced the degradation of PDLLA and improved the coating stability during 60 days. The effects of organic solvent such as chloroform and tetrahydrofuran (THF) on the coating uniformity were also examined. It was revealed that THF produced a very smooth and uniform coating compared to chloroform. The patterns of in vitro drug release according to the type of organic solvent and hydrophilic additive proposed the possibility of controllable drug release design in DES. It was found that using F127 the drug release was sustained regardless of the organic solvent used. In addition, THF was able to get faster and controlled release profile when compared to chloroform. The structure of SRL molecules in different organic solvents was investigated using ultra-small angle neutron scattering. Furthermore, the structure of SRL is concentration-dependent in chloroform with tight nature under high concentration, but concentration-independent in THF. These results strongly demonstrated that coating stability and drug release patterns can be changed by physicochemical properties of various parameters such as organic solvents, additive, and coating strategy.

1. Introduction

Bare metal stents (BMS) are an initial model of the stent used in the coronary artery diseases treatment by implantation. However, long-term clinical results determined that more advanced stents were needed. During stent implantation, the artery walls can be damaged by stent ballooning, which can induce neointimal hyperplasia via the proliferation and migration of vascular smooth muscle cells inside the lumen [1,2]. Therefore, various drug-in-polymer coated drug-eluting stents (DESs) have been developed to prevent in-stent restenosis and inflammation after stent implantation [3–8].

The polymer/drug coated DES is an attractive therapeutic skill to achieve an effective local release of a drug within a desire period [9]. Sirolimus (SRL) is well known drug that reduces neointimal hyperplasia and thrombosis of human endothelial cells [10]. When a non-biodegradable polymer was used as a coating material for DES, late stent thrombosis and inflammation response occurred because of its permanent contact with blood and tissue in the vessel [11–13]. Therefore, recently biodegradable hydrophobic polymers with anti-proliferative drugs were used for DES coating system. Biodegradable poly(D,L-lactide) (PDLLA) is widely used in biomedical applications due to its good biocompatibility and excellent mechanical properties [14,15].

Many studies have been reported that drug release can be influenced by various factors, such as loading amount of drug, polymer-drug miscibility, and glass transition temperature (T_g) [16–18]. In particular, the properties of the organic solvent such as polarity and vapor pressure could affect the kinetic environment of polymer-chain mobility and control the interfacial interactions between polymer and drug [19,20]. Moreover, the particle size of SRL could be changed depending on the organic solvent. It has been known that the large particle size of SRL

* Corresponding authors at: Center for Biomaterials, Korea Institute of Science and Technology, Hwarangno 14-gil 5, Seongbuk-gu, Seoul 02792, Republic of Korea.
E-mail addresses: ykjoung@kist.re.kr (Y.K. Joung), dkh@kist.re.kr (D.K. Han).
[1] These authors contributed equally to this work.

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releases faster than smaller one in the polymer coating solution, after coating [21]. However, little is known about the concentration effect on the structure of SRL in organic solvents with similar polarity. Despite the development of DES, coating defect issues such as peeling and cracking of the polymer/drug coating layers still remain problems need to overcome [22,23]. In this aspect, our research has focused on optimizing the coating conditions such as polymer and drug ratio, type of solvent as well as the addition of hydrophilic additive in order to improve the stability of the polymer/drug coating surface and control the drug release. Additionally, we investigated the structure of SRL in chloroform and tetrahydrofuran (THF) with a respective polarity index of 4.1 and 4.0, using ultra-small angle neutron scattering (USANS) measurements.

2. Experimental section

2.1. Materials

A cobalt-chromium alloy (Co—Cr) plate (10×10 mm^2) was supplied from Minitubes Corp., (France). Stent-type stainless steel (SS) 316 L spring ($1.8 \times 0.25 \times 18$ mm^3) and Co—Cr alloy stent ($1.8 \times 0.17 \times 18$ mm^3) were obtained from Microspring (Korea) and Bioalpha Inc. (Korea), respectively. Poly(D,L-lactide) (PDLLA, RESOMER® R205S) was purchased from Evonik Industries (Essen, Germany). Sirolimus (SRL) was purchased from LC Laboratories (Woburn, MA, USA). Pluronic F127, chloroform and tetrahydrofuran (THF) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All reagents were used without further purification.

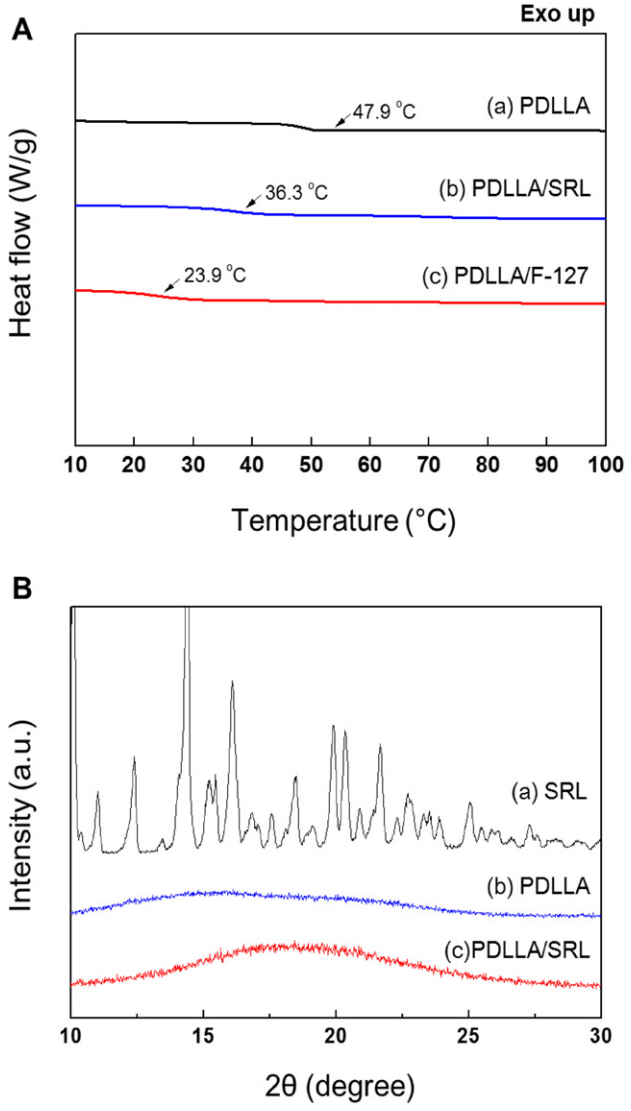

Fig. 1. (A) DSC curves of (a) PDLLA, (b) SRL-loaded PDLLA, and (c) F127-loaded PDLLA and (B) XRD patterns of (a) SRL, (b) PDLLA, and (c) SRL-loaded PDLLA films.

2.2. Pretreatment of Co—Cr substrate

The Co—Cr samples were immersed in acetone for 1 day. Thereafter, they were mechanically grinded using silicon carbide papers and polished using alumina suspensions (0.3 μm). The polished samples were bath sonicated in deionized water, ethanol, and acetone to remove the contaminants from the surface. Finally, the cleaned samples were dried under vacuum at 60 °C for 24 h.

2.3. Fabrication of SRL-loaded PDLLA matrix film

PDLLA, SRL-loaded PDLLA, and F127-loaded PDLLA films were prepared by solvent casting. Briefly, PDLLA was dissolved in organic solvent and the homogeneous polymer solution was poured into a Teflon mold. After 24 h, the dried films were further dried under vacuum at room temperature for 3 days.

2.4. Coating of SRL-loaded PDLLA matrix by ultrasonic spray system

PDLLA and SRL were dissolved in 10 mL of chloroform or THF to provide 0.3 wt% solution. Hydrophilic Pluronic F127 additive (10%) was added to PDLLA/SRL (90/10) solution and a homogeneous mixture

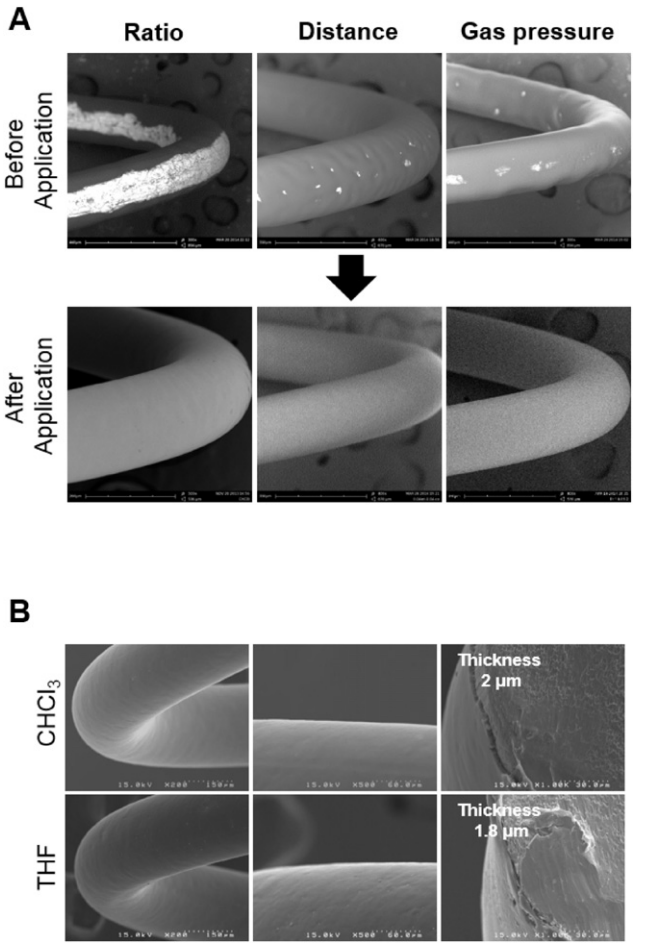

Fig. 2. Morphological observation of stent surface before and after optimal conditions applications: (A) The effect of polymer and drug ratio, distance, and gas pressure and (B) the influence of solvent type.