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Paclitaxel/sirolimus combination coated drug-eluting stent: In vitro and in vivo drug release studies

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ABSTRACT

Paclitaxel and sirolimus are the two major drugs for the treatment of coronary arterial disease in current drug-eluting stents. The two drugs can effectively inhibit the in-stent restenosis through their independent pathways and show synergistic effect in preventing tumor tissue growth. We hypothesize that the combination of the two drugs in a drug-eluting stent (DES) can also effectively suppress the neointima growth in the stented artery. The present work was focused on the investigation of paclitaxel/sirolimus combination release profiles from a novel biodegradable polymer (poly (D, L-lactide-co-glycolide)/amorphous calcium phosphate, PLGA/ACP) coated stent both in vitro and in vivo. For the in vitro, the drug releasing profiles were characterized by measuring the drug concentration in a drug release medium (Dulbecco's phosphate buffered saline, DPBS, pH 7.4) at predetermined time points. For the in vivo, a rat aorta stenting model was employed. The results showed that both paclitaxel and sirolimus had a two-phase release profile both in vitro and in vivo, which is similar to the drug release profile of their individual coated DESs, and there is no evident of interference between two drugs. The data suggest that paclitaxel and sirolimus can be combined pharmacokinetically in a DES for the treatment of coronary arterial diseases.

1. Introduction

Coronary arterial stenting with drug-eluting stent (DES) is a major therapy for the treatment of coronary arterial diseases in present interventional cardiology practice. Currently, four DESs have been approved by the FDA for the U.S. market including: Cypher® stent (Cordis, Miami, FL), Taxus® stent (Boston Scientific, Inc., Natick, MA), Endeavour® stent(Medtronic Minneapolis, MN) and Xience® stent(Abbott Laboratories, Abbott Park, IL). Among four approved DESs, besides Taxus® stent which is coated with anti-microtubule drug—paclitaxel, all other three DESs are coated with either sirolimus (Cypher® stent) or its analogs zotarolimus (Endeavour® stent) and everolimus (Xience® stent) [1]. Though paclitaxel or sirolimus used alone in DESs can effectively inhibit the restenosis formation [2,3], restenosis in high risk patients such as small vessels, diabetes, and long segments of diffusely diseased arteries still remains unacceptably high (30–60% in bare metal stents and 6–18% in drug coated stents) [2–4]. Therefore, there still exists an unmet medical need for a more powerful anti-restenosis agent to curb the problem.

The in-stent restenosis (ISR) formation or the neointima growth in the stented arteries is a multiple factored sequential process involving smooth muscle cell (SMC) migration, extracellular matrix formation, macrophages recruitment, etc. over a period of several weeks [5–7]. This benign tissue growth process is similar to the tumor tissue growth [8], which had lead to the discovery of anti-tumor drugs such as paclitaxel and sirolimus as effective agents for the treatment of ISR [6,8]. Drug combination therapy is an effective, well-known regimen used in the daily treatment of tumors clinically. The similar approaches have been investigated previously in the treatment of ISR with anti-proliferative drugs such as sirolimus combined with anti-thrombotic agents (Glycoprotein IIB/IIIA inhibitor or heparin) [9] or paclitaxel com-

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