Rapamycin Drug Eluting Stent by Crystallization onto Stent Struts

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ABSTRACT SUMMARY

Surface crystallization onto metallic stent struts releasing rapamycin for weeks was developed. The process parameters were investigated in detail with regard to the coating morphology, drug loading and stability studies in different conditions. RM crystals coating onto stent gradually released the drug over a period of several weeks in buffer media and displayed stability. In vivo experiments did not raise any obvious safety concerns.

INTRODUCTION

Coronary stenting has revolutionized current perspective of coronary artery disease management. Intense work on stent development has successfully led to the introduction of DES in 2002, where usually the coated therapeutic agent is applied along with a polymeric carrier. The polymer coating is responsible for several functionalities, it holds the drug mechanically, preserves chemical stability of drug and regulates the release kinetics which highly needed to prevent the re-occlusion of the artery/in-stent restenosis.\(^1\)\(^2\)

This work presents a carrier free DES, where the drug is crystallized onto stent struts and being released for weeks without a polymer carrier. The drug, rapamycin, was crystallized onto metallic stent by placing the stent into a saturated solution of the drugs to form a “carpet” of drug crystals onto the stent struts (Figure 1A).

Additionally, the controllability of crystallization process enables the generation of a variety of morphologies, physical states and coating thickness. This process was further implemented using different drugs and supersaturated systems.

EXPERIMENTAL METHODS

Rapamycin was crystallized onto the metallic surfaces by two steps, seeding with nano-drug particles followed by crystal growth by immersing the stent in a solution of the drug. In order to direct the crystal deposition to the outer surface of the stent, the seeding process was performed while the stent was mounted on a coated needle with thin shrinkable tube to block the inner side of stent. Rapamycin crystallization onto metallic stents was carried out using three processes, differing mainly in the preparation and effectiveness of seeding layer. Amorphous rapamycin coating on stents was carried out by spray coating, using ultrasonic spray coating machine.

Stent coating was characterized using Scanning Electron Microscope (SEM). Cross section of crystalline coating was also analyzed for crystals carpet formation, including starting points (seeding crystals) crystals development, coatings developments, coating thickness and crystals humps. Coating thickness and roughness was studied by a P-15 profilometer. Coating topography was traced with Dimension 3100 scanning probe microscope (AFM) using Tapping Mode (TM). Crystallinity and phase of the developed rapamycin coatings was identified by X-ray diffraction (XRD). Storage stability for 6 months at 37°C, 4°C and -20°C followed by SEM and rapamycin release. In vitro release evaluation of both crystalline and amorphous coated stents loaded with ~100 μg per stent was carried out in PBS (pH 7.4) at
37°C. Rapamycin release was monitored by UV spectrophotometer at 277 nm.

Biocompatibility study of the developed coated stents was carried out in SD rats, 2 stents implanted subcutaneously per animal. At 7 and 28 days post implantation, animals were sacrificed and the implantation site was isolated for histopathology evaluation and the isolated stents were evaluated SEM.

RESULTS AND DISCUSSION
Crystal coating onto metallic stent was obtained under controlled crystallization. The drug loading, size of crystals and release profile was investigated.

![Figure 1. (A) Rapamycin crystals onto metal stent. (B) Crystals carpet illustration for ~100μg loading on stent.](image)

Rapamycin release profile showed continuous and controlled release for at least 90 days, were ~60 μg RM cumulatively released from crystalline coated stents. Amorphous coating showed burst release profile.

CONCLUSION
A surface crystallization methodology to generate a carrier-free DES for metallic stents was developed. Rapamycin crystals with a defined morphology and target drug load were applied using different procedures. A stable homogenous, continuous, uniform and easy to control and to prepare rapamycin crystal coating was developed. The developed crystallization process may have applications for other drugs for effective local drug delivery from surfaces of other implants.

REFERENCES