Keratose as a Novel Drug Carrier for Drug Coated Balloons

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Statement of Purpose: Although stents remain the most effective minimally invasive treatment option for coronary atherosclerosis, their effectiveness to treat peripheral artery disease (PAD) are significantly reduced due to high strut fracture rates. Balloon angioplasty has thus become the prevailing treatment in PAD but is limited by high restenosis rates. To overcome this limitation, drug coated balloons (DCB) employ an antiproliferative drug coating on the balloon to limit restenosis. Thus DCB deliver anti-proliferative drug without the need of a metallic stent platform. With only 1-2 minutes to interact with the artery, drug transfer from the balloon to the artery dictates the success of DCBs. In this study, we propose the use of keratose as a drug carrier/excipient for a novel DCB design. Our group has shown that keratose hydrogel is capable of long-term release of various factors and drugs and capable to act as a drug carrier [1]. Here we demonstrate the feasibility of the keratose coating to develop a novel DCB.

Methods: Lyophilized keratose-alpha (KOS-α) was combined with 1x phosphate buffered saline (PBS) to form a 4% weight to volume mixture of KOS-α. Commercially available balloon catheters were coated with 4% KOS-α solution using a dipping method. The balloon was coated with a second layer following a drying time of 20 minutes. To evaluate coating thickness, KOS-α coated balloons were embedded in O.C.T. compound, sectioned at 15 microns, and stained by Hematoxylin. Coating thickness was evaluated by light microscopy with Micron imaging software (Westover Scientific, Mill Creek, WA).

Four coating compositions were prepared and coated on commercially available balloon catheters: 1) 4% KOS-α, 2) 6% KOS-α, 3) 2:1 6% KOS-α and iopromide, and 4) 6% KOS-α followed by iopromide. Balloons were coated with a dipping method and after 20 minutes of drying were subjected to subsequent dips into a vial of distilled water. Loss of coating was determined by color threshold technique. Number of dips to loss-of-coating was recorded. Rate of degradation of keratose hydrogel was evaluated. A 12% and 15% KOS-α hydrogel was prepared in 1x PBS. In a 2 mL Eppendorf tube, 350 µL of the hydrogel was injected into the bottom of the tube with a syringe. The hydrogel was gelled overnight at 37°C and 500 µL of 1x PBS was added on top of the hydrogel. At various time points, the PBS was collected and replaced with 500 µL of fresh 1x PBS. KOS-α degradation was determined at each time point by DC Protein Assay (Bio-Rad Laboratories, Hercules, CA) read at 750 nm absorbance.

Results: The 4% KOS-α balloon coating demonstrated circumferential uniform coating with KOS-α crystallization (Fig. 1A and 1B). Hematoxylin stained sections showed a thickness ranging from 4 to 7 microns (Fig. 1C). This thickness is comparable to other DCB products which range from 3 to 7 microns.

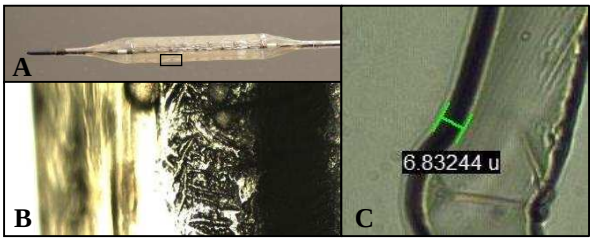

Fig. 1. 4% KOS-α coating. A) Balloon after coating, B) Crystallization at 10x mag., C) Coating thickness.

Coating retention results demonstrated increased retention of 6% KOS-α in comparison to 4% KOS-α (Table I). The disproportional increase in retention from 4% to 6% KOS-α suggests the ability to fine-tune keratose concentration in order to establish optimal coating retention for clinical applications. Greatest retention was achieved with 6% KOS-α coating followed by a layer of hydrophobic iopromide. This result gives insight into the importance of coating hydrophobicity and provides an option for significant increase in retention – 58.8% in this case.

TABLE I. Coating Retention

Coating	Dips to coating loss
4% KOS-α	40
6% KOS-α	133
2:1 6% KOS-α and iopromide	63
6% KOS-α followed by iopromide	226

Cumulative keratose release from a 12% and 20% KOS-α hydrogel reflects previous findings from our group that keratose concentration alters keratose degradation (Fig. 2). Increased concentration leads to slower degradation.

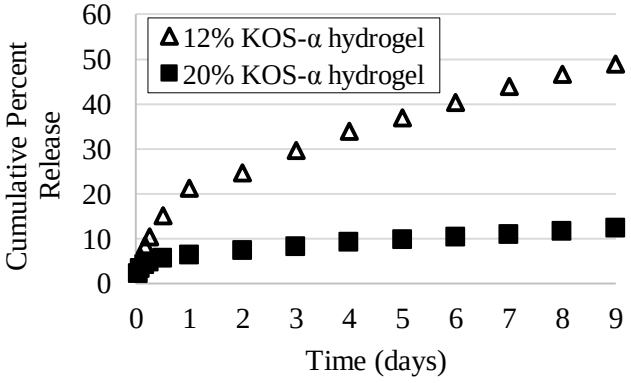

Fig. 2. Keratose release from hydrogels.

Conclusions: This research demonstrates the ability of keratose to coat angioplasty balloons at a thickness relevant to commercially available DCBs. The development of a retention test will allow us to comparatively evaluate the relative lifetime of various coatings in future tests. In addition, replication of the hydrogel release study further describes the tunability of keratose and its promise in the application of controlled drug-release.

References: [1] Saul JM. J Biomed Mater Res A. 2011; 98A: 544-553