Drug Eluting Stents: Controlled Drug Release Using Magnesium Alloy Coatings

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Statement of Purpose: Drug eluting coronary stents have been shown to be effective at reducing the rate of restenosis compared to bare metal stents. Paclitaxel is commonly used in drug eluting stents (DES) for its ability to inhibit smooth muscle cell proliferation and therefore, prevent restenosis. However, despite their short term success, DES have been associated with late stent thrombosis which has been linked to hypersensitivity to the polymeric coatings containing the drug[1]. Therefore, there is a need to develop DES without polymer coatings. Recently, several groups have produced fully-resorbable magnesium stents. Success has been limited due to the early loss of mechanical stability as the magnesium degrades in the body[1]. However, magnesium is a potential candidate to substitute for polymer coatings because it is biodegradable as well as biocompatible and does not produce toxic degradation byproducts. Here, we propose to use a nanoscale coating of magnesium on Paclitaxel physically deposited on cobalt chromium surfaces. We investigated the release kinetics of two different coats: pure magnesium and AZ31 magnesium alloy. AZ31 (Al 3%, Zn 1%) has been shown to degrade slower than pure magnesium due to the presence of aluminum[2].

Methods: Cobalt Chromium alloy (L605 grade) was purchased from High Tech Metals, Inc (Sylmar, CA). Paclitaxel (>99% purity) was purchased from ChemieTek (Indianapolis, IN). CoCr was cut into 1cm by 1 cm coupons and cleaned by sonicating twice for 10 minutes at a time in soap water, ethanol, acetone, and methanol, respectively, then dried under argon gas. Paclitaxel (PAT) was dissolved in ethanol to make a 1 mg/mL solution. 25 µL of PAT solution was placed on the surface of clean CoCr and allowed to dry under ambient conditions for 3 hours following a method previously reported by our group[3]. Pure magnesium target was purchased from Goodfellow Corporation (Oakdale, PA). Magnesium Alloy AZ31 was purchased from A Metal Source LLC (Cleveland, OH) and custom machined by ITM (Schertz, TX) to form a sputter target. Pure magnesium and AZ31 targets were sputtered using Denton Vacuum Desk II TSC sputter coater (Moorestown, NJ) at 100% power, 10mTorr pressure to create 20 nm and 100 nm coatings on the substrate. Seven different sets were prepared:

	PAT (µg)	Coating
Set 1	0	100 nm Mg
Set 2	0	100 nm AZ31
Set 3	25	None
Set 4	25	20 nm Mg
Set 5	25	100 nm Mg
Set 6	25	20 nm AZ31
Set 7	25	100 nm AZ31

Specimens (n=3) were incubated in 2mL of PBS + 0.05% tween20 at 37ºC. At specified time intervals (0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 12, 16, 20, 24 h) the specimens were removed and immediately transferred to fresh PBS-tween20. 1mL of ethanol was added to each vial of collected PBS-tween20 prior to HPLC testing to enhance Paclitaxel solubility. Waters 2695 separations module with Waters 2487 Dual λ absorbance detector (Milford, MA) was used for HPLC analysis at 227 nm wavelength using a Nova-Pak C18 column (3.9mm x 150mm) at 1 mL/min with a water and acetronitrile 45:55 v/v mobile phase at 35 ºC.

Results: Sets 1 and 2 (controls) did not release PAT as expected. Uncoated PAT (Set 3) specimens released all of the drug by 12 h with 50% of the drug being released in the first 30 min. Set 4 released 33% of the drug in the first 15 min. Set 5 took 75 min to release this same amount of drug. Set 6 released 33% of the drug in 105 min and Set 7 released the same amount in 3h. After 24h, Set 3 release 100% of the drug; whereas Set 4, 5, 6, and 7 released 64, 50, 46, and 46% respectively.

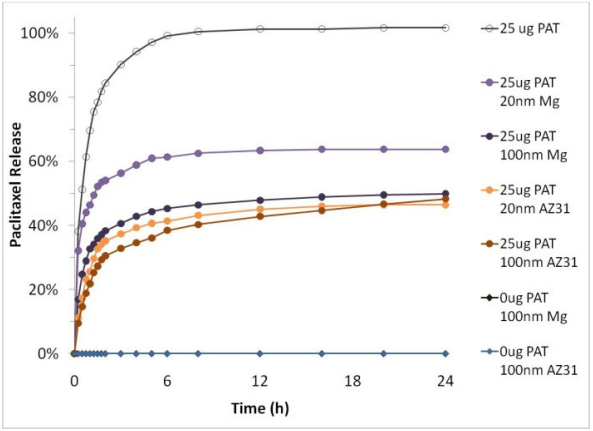

Figure 1. PAT release from CoCr. Release is controlled by magnesium and magnesium alloy coating

Conclusions: We have been able to sputter coat pure magnesium and magnesium alloy AZ31 on the surface of paclitaxel-covered cobalt chromium. The sputtered pure magnesium coat slowed down the release rate of paclitaxel from the surface. Sputtered magnesium alloy AZ31 further reduces the release rate. There is a significant difference ($p<0.05$) in the Paclitaxel release from the different coat thicknesses. Thicker coats of both pure magnesium and magnesium alloy slow down PAT release in the first 2 h.

References:

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