Utilization of Nanoporous Titanium Dioxide Films on Drug-Eluting Stents

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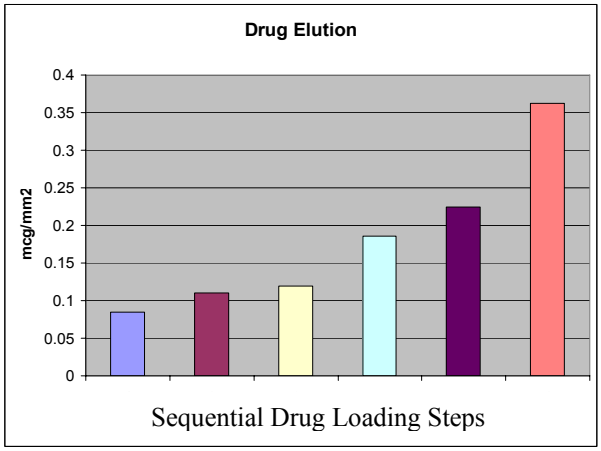
Statement of Purpose: Recently it has been shown that in patients with coronary artery disease, implantation of drug-eluting stents (Cypher™ and Taxus™) can dramatically reduce restenosis rates, and therefore the need for repeat procedures [0,0]. Stainless steel stents coated with polymers function as drug reservoirs and regulate drug delivery. However, the polymer approach is facing three recurrent problems; namely, (i.) the inflammatory reactions induced by all polymers, (ii.) the need to dissolve drugs and polymers in a common solvent and then coat the stents. This approach restricts the number of drugs available for polymer based drug-delivery; specifically, polymers are unable to carry proteins or genes as anti-restenotic agents. The last problem is (iii.) the fracture observed in certain polymer formulations during stent expansion. Therefore, a novel, robust and efficient scheme is needed to address the issues associated with presently available polymeric approaches. The development of drug eluting stents must overcome two major hurdles. First, a mechanism is needed by which the drug can be loaded onto a stent surface. A second major hurdle has been to control drug delivery. The biology of restenosis is such that the drugs need to be present for a period of 2-4 weeks after stent delivery to effectively inhibit neo-intima formation. Resolving this by loading the stent with more drug leads to a large and toxic quantity of drug being delivered to the vessel wall within hours of stent deployment [3]. A mechanism by which drugs can be delivered over a 2-4 week period, while avoiding local toxicity is ideal. The manuscript contained herein demonstrates the application of biocompatible, nanoporous titanium dioxide films that can serve as drug reservoirs and regulate drug delivery.

Methods: The next generation stent coating described in this manuscript is a metal-oxide nanoporous surface capable of retaining and releasing a variety of pharmaceutical agents. Surface modification to create the drug-eluting silicon surface for characterization purposes was achieved by spin-casting at 6000 rpm a solution containing a block-copolymer diluted in ethanol to which a titanium precursor had been added, After aging the coated surface and subjecting it to a calcination step to remove the surfactants it was possible to obtain the formation of a TiO_2 nanoporous films on a flat surface. Therapeutic elution rates from such a surface will depend, among other variables, on pore size, crystal orientation and surface energy [4]. The initial targeted pore size was 10-20 nm with a minimum depth of 200 nm. Experimental results indicate that these parameters can be controlled by varying the amount of block-copolymer diluted in ethanol, by the amount of titanium precursor added and by the thermal treatment subsequently applied. Observations indicated that drug dilution has to be tailored to minimize agglomeration and crystallization effects. Thus, the initial dilution was 1.2 mg of dexamethasone in 37.5 ml of ethanol. The samples were immersed in the solution for 48 hours, dried at 60°C for 1 hour to remove the solvent and immersed in 2 ml of ethanol for 24 hours to remove the incorporated drug prior to HPLC analysis.

Results / Discussion: Observations indicate that once agglomeration and crystallization effects are avoided the amount of drug that can be loaded in a single step in films whose thickness has been measured to be ~300 nm is drastically reduced to 0.07 mcg/mm^2. This value compares unfavorably with the targeted therapeutic value of 0.5 mcg/mm^2. However, the experimental observations indicate that by exposing the samples to sequential drug-loading steps it is possible to bring the total amount of drug loaded close to ideal values while at the same time precluding deleterious surface effects. Figure 1 presents the amount of dexamethasone measured employing HPLC analysis for samples that underwent six drug loading sequential steps. Additionally we have also observed the increase of drug loaded in a single step as a function of temperature. We therefore anticipate that the combination of thermal treatment with sequential drug-loading steps will enable us to reach the targeted dexamethasone value per unit area.



Conclusions: The loading of anti-restenosis drugs with targeted therapeutic values on nanoporous, biocompatible, titanium-dioxide films has been corroborated by employing a sequential-step approach. It is anticipated that additional medication could be loaded by applying appropriate thermal treatments.

References:

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