Drug Delivery from Cardiovascular Stents, In Pursuit of a Non-Polymeric Approach

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ABSTRACT

Coronary heart disease (CHD) is the leading cause of death worldwide. The use of bare metal stents since 1990 has provided an alternative to bypass surgery but the treatment often results in restenosis. In 2002, stents that release anti-restenosis drugs from a polymeric coating were introduced and provided a drop in the restenosis rate to less than 10%. However, in 2006 studies showed that drug eluting stents (DES) caused an increased risk for thrombosis. The "permanent" polymers used on these original DES were widely blamed for this often fatal problem. Stent manufacturers continue to aggressively search for alternatives to the polymeric based DES designs. Six widely different approaches for a new drug eluting stent are described here and one, sputtered nanoporous columnar coatings, is examined in detail. Although many researchers believe that the primary benefits of nanoporous coatings come from their pore size scale and total pore space, arguments will be given that this is not necessarily true. Instead, new evidence points to the very high surface area of these coatings as an important factor in providing controlled long term release of anti-restenosis drugs from cardiovascular stents without polymers.

INTRODUCTION

CHD results from the buildup plaque on the walls of the coronary arteries (stenosis). As plaque builds up, blood flow is reduced. Partial restriction of blood flow can cause only pain, but if the restriction becomes more severe it can cause a heart attack. In addition to changes in lifestyle, treatments for CHD include both medicine and surgery. In 1960 coronary bypass surgery was developed. Although usually effective, bypass surgery is highly invasive. Balloon angioplasty was developed in the late 1970s to provide a much less invasive procedure than bypass surgery but it had a success rate of only about 50%. In this procedure a small balloon is positioned inside the diseased artery using a thin flexible guidewire. The balloon is then inflated to press against the plaque in an attempt to remodel the obstruction and improve blood flow. However, one of the primary risks associated with balloon angioplasty is that the artery will collapse when the balloon is deflated. Emergency bypass surgery is often required when this occurs.

Angioplasty with stenting was developed in the late 1980s. This procedure is essentially the same as balloon angioplasty except that a small wire mesh tube, or a stent, is placed around the balloon. When the balloon is inflated, the stent is expanded and positioned permanently against the vessel wall to keep it propped open after the balloon is removed. Cardiovascular stents are most commonly made from 316LVM SS or L605 CoCr and range in length from 8 to 38 mm and 2.5 to 4 mm in diameter. The individual struts that make up the open lattice design are typically between 0.07 and 0.16 mm in diameter. The strut network is produced by laser cutting seamless tubing. The stents are then electropolished [1] to remove burrs and then passivated by soaking in acid to grow a uniform oxide film.

Throughout the 1990's angioplasty with stenting grew in popularity because it offered quick relief of pain, eliminated the risk of vessel collapse, and was a minimally invasive procedure. However, stenting has the disadvantage that it causes injury to the vessel wall. Damage to the endothelial layer is for the most part unavoidable given the forces required to over expand the stent against the tissue to an extent that allows for elastic recoil. Upon injury, the response from the vessel is the growth of smooth muscle tissue out from beneath the endothelial layer in an attempt to heal the wound. In approximately 30% of the stenting procedures performed with these original stents, growth of smooth muscle tissue is severe enough to effectively reclose the artery to the extent that follow-up treatment is required. Restenosis is the term used to describe this occurrence.

FIRST GENERATION OF DRUG ELUTING STENTS

In 2002 Johnson and Johnson introduced the first DES called CYPHER. Several other companies followed with DES of their own over the next few years. These stents released cytotoxic drugs for approximately 30 days after implantation to prevent the growth of smooth muscle tissue. As a result, the rate of restenosis with these stents fell to less than 10%. In order to hold the drug onto the stent and provide long release times, polymer coatings were used. The drugs were first dissolved in a polymer solution and then the solution was coated onto the stent by spraying or dipping. The polymers that were used

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on early DES were all permanent or non-biodegradable; they remained on the stent after the drug was gone. In this application the polymers had to satisfy many requirements. They had to dissolve the drug up to a ratio of 60:40 polymer/drug and then form an elastic matrix on the stent that did not crack or delaminate during or after implantation. The polymers also had to provide diffusional resistance to control the release rate and also be biocompatible. This medical technology success provided rapid growth for DES sales. In 2006 the worldwide market for coronary stents was valued at $5.1 billion with much of this value coming from DES.

In 2006, studies showed that thrombosis and allergic inflammatory reactions were more likely with polymer coated DES [2]. Although the frequency of occurrence was low (< 1%) the risk of death from thrombosis was estimated to be as high as 60%. As a result of these findings, DES sales dropped by 40% in 2007 [3] and have remained at depressed levels since. DES involved two basic changes from the original bare metal stents (BMS): drug and polymer. Since the observed thrombotic events occurred after the drug was gone, the polymers were thought to be the source of the problem. As a result, aggressive efforts were begun by major stent makers, small companies, and university research groups to develop a DES platform that did not use permanent polymers.

ALTERNATIVE DES APPROACHES

A wide variety of approaches have been investigated to deliver drugs from stents without permanent polymers. These approaches can be grouped into those that use biodegradable polymers (BDP) instead of permanent polymers and those that do not use any polymers at all. One of the approaches with BDP is to simply replace the permanent polymers in the coating on the stent with BDP. BDP are already used in medical applications such as sutures, orthopedic fixation devices, and tissue engineered scaffolds; however, there are concerns with biocompatibility of BDP in a vascular application. Another approach is to place drug loaded BDP into holes or grooves that are cut into the individual stent struts. This idea was pioneered by Conor Medsystems and has the advantage of minimizing direct polymer-tissue and polymer-blood contact and hence a lower likelihood of biocompatibility problems. However, initial clinical trials for the Conor stent showed unspecified problems that have delayed its introduction in the US. Another approach is to make the entire stent out of BDP so that it disappears in about two years. The hope is that these bioabsorbable stents will enable the artery to heal before the stent dissolves. The major concerns with this concept are BDP biocompatibility and the structural integrity of the stent itself. Bioabsorbable stents are seen as highly desirable by many in the industry but commercialization appears to be several years away [4].

The completely polymer free approaches for DES can be grouped into three categories. The first is pure drug coatings on the stent. This was in fact an approach tried by several companies prior to the introduction of the CYPHER stent. The primary problem with this approach was that the drug film cracked and delaminated during balloon expansion. New attempts for the use of pure drug coatings are underway at Biosensors International and Nile. Both companies attempt to control drug delamination by roughening their stents by either etching or bead blasting prior to coating with drug. Clinical trials are underway for these stents. The second polymer free DES approach is to use non-polymeric materials to form a drug containing layer on the stent. Examples are glycocalix by Biosensors International and triglycerides by Ziscoat. Glycocalix is a synthetic form of glycocalyx, a material with the consistency of slime that is found on the surfaces of endothelial cells.

The third polymer free approach is to use nanoporous coatings. There are several ways to produce nanoporous coatings but only three have been investigated extensively for drug delivery from stents: anodic oxide films, dealloyed coatings, and sputtered porous columnar coatings. Anodic oxide films are made by anodizing a metal to grow a honeycomb-like oxide structure upward from the surface. The technique has been known for decades but has only recently been used to study drug release from nano-sized pores. These studies show that drug release from anodic oxide pores ranging in size from 20 to 200 nm in diameter is fast; the elution time for an amount of drug equivalent to that found on polymeric DES is less than two days. It is not yet known if this short elution time is sufficient for effective treatment. Additionally, these oxide films are brittle which requires that their thickness be held to less than a few microns to avoid film failure on a flexible medical device. Another way to make nanoporous coatings is by a dealloying process. Dealloyed coatings have also been known for decades but have only recently been studied for delivery of drugs. Setagon describes a process where a sputtered coating containing at least one structural material and one sacrificial material is applied to a stent [5]. The sacrificial material is dissolved using caustic agents to leave a tortuous nano-sized porous structure. Although these coatings have been promoted for drug delivery from stents, their drug elution rates have not been clearly reported. Like anodic oxide films, these films are also brittle.

Isoflux Incorporated has investigated sputtered porous columnar (PC) coatings for use in drug delivery. The remainder of this paper will describe this work. PC coatings are known as zone 1 structures on the Thornton coating zone diagram [6]. Zone 1 structures are promoted by low deposition temperatures and moderate to high gas pressures. The sputtered PC coatings described here were made using a cylindrical magnetron

cathode [7] operated under conditions that produced low homologous deposition temperatures and either low energy or oblique angle deposition at any given time [8]. Cylindrical cathodes have proven to be ideal for achieving good coating thickness uniformity on complex three dimensional shapes and for maximizing target material usage efficiency.

The PC coatings examined were made of either tantalum or chromium although other metals, oxides and alloys are possible. Figure 1 shows a side view SEM image of a Ta PC coating produced in a cylindrical magnetron cathode. The PC structure is clearly evident as is the approximate uniformity of the columns as a function of thickness. Typically, pore widths in Ta PC coatings range from 5 to 30 nm. The total porosity of these coatings is estimated to be approximately 20% while the column widths are around 200 nm. The number density of columns can be calculated using the following relationship, $n_c = (1-p)/a_c$ where p is the porosity and a_c is the cross sectional area of the column. For a Ta coating $n_c \sim 45\ \mu m^{-2}$. PC Cr coatings made under similar conditions have smaller columns of about 150 nm in width but have approximately the same total porosity. The number density of Cr columns is about twice that of Ta.

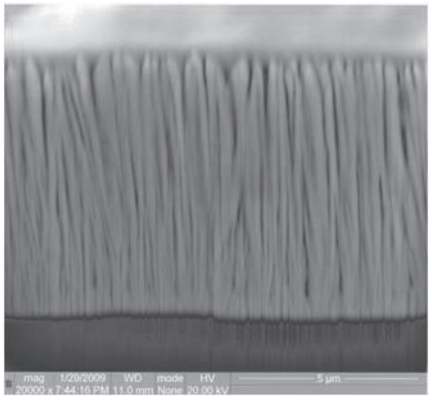

Figure 1: SEM image of a 7.5 μm thick Ta PC coating.

There are two important features that make PC coatings ideal for delivering drugs from flexible medical devices. The first is that they exhibit good adhesion when made in the manner described here. The second is that the coatings do not develop tensile stress when the substrate is flexed. This is because the coatings are made up of individual non-connected columns. As a result, the coating will not crack or delaminate from a stent when it is expanded.

INITIAL DRUG ELUTION STUDY WITH PC COATINGS

The nano-sized pore space in a PC coating provides an opportunity for drug delivery. The first attempt to examine this opportunity involved the use of a steroid drug, dexamethasone (DEX). PC coated stents were placed in a small chamber which was then evacuated to 150 mTorr. A solution of DEX in ethanol was then injected into the chamber to cover the stents. The chamber was then vented and drained and the stents were allowed to dry. The stents were then placed in test tubes with phosphate buffered saline (PBS) solution at 37 C. Measurements of the DEX concentration in PBS solution were taken periodically using UV spectrophotometry. Fresh PBS was added to the test tube after each measurement.

Figure 2 shows the cumulative DEX released as a function of time. As can be seen, there was a burst release during the first day. Furthermore, elution appeared to stop after a few days when the drug concentration in PBS dropped to levels below what could be reliably measured. This DEX release behavior indicated that the nano-sized pores in the PC coating did not offer enough diffusional resistance to extend the elution time to the 30 day performance of polymer coated DES. This agrees with predictions made using the Rankin equation [9]. The Rankin equation estimates the reduction in the diffusion coefficient of solutes in nanopores. Given the size of the drug molecules and the width of the pores, the Rankin equation predicts a 40% decrease in the diffusion coefficient from that seen in the bulk solution. This decrease is not enough to achieve the 30 day release target. The observed burst release has also been seen in drug elution studies made with other nanoporous coatings [10]. Examination of the PC coated stents with an optical microscope at 40x prior to placement in PBS showed a uniformly clean looking surface. This was an indication that the drug was indeed contained in the pore space and not only on the surface of the PC coating. It is important to note that in this initial study with PC coatings the total amount of drug released was in the range of that used for the CYPHER DES. However, comparison of gravimetric measurements of the PC coated stents before and after drug loading showed that approximately 40% of the total drug remained on the stents after ten days in PBS.

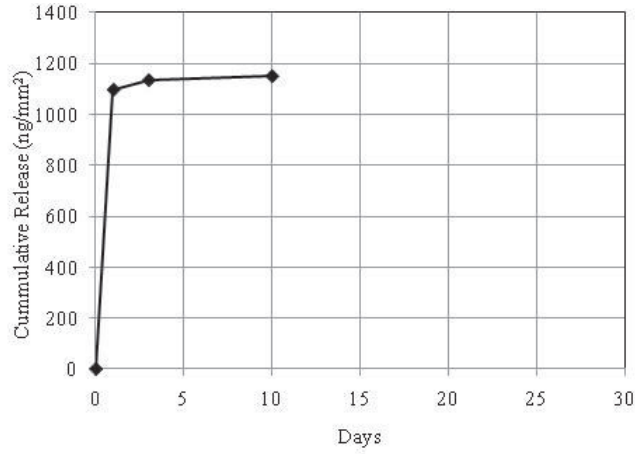

Figure 2: Dexamethasone release from a 10 μm Cr PC coating in PBS at 37 C.

HIGH SURFACE AREA

The sides of the columns in a PC coating provide a remarkable amount of surface area. The ratio of the surface area of a PC coating relative to the original smooth surface is given by $A^*/A = 1+n_c a_s$ where a_s is the surface area of the sides of a single column. Figure 3 shows the predicted surface area ratio for Ta and Cr PC coatings as a function of PC coating thickness. As an illustrative example, a 10 μm Cr PC coating increases the surface area of a stent by nearly 400 times. Since there is no need to limit the PC coating thickness to avoid film failure, higher surface area increases are possible.

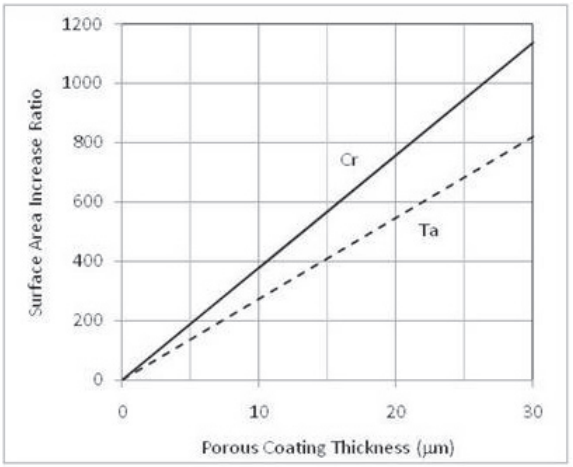

Figure 3: Surface area increase ratio for Cr and Ta PC coatings.

It is interesting to note that just a monolayer of drug molecules on the high surface area of a PC coating can represent a medically significant amount of drug. Furthermore, a monolayer of drug on a PC coating is equivalent to the amount of drug that was seen to remain on the coating after it was placed in PBS for ten days during the initial DEX elution study. Interestingly, Sridar et al. [11] observed and measured a slow release of doxorubicin from anodic oxide coatings for 14 days following the completion of the burst release. The authors pointed out the advantage of high surface area of nanoporous coatings for drug delivery.

FOLLOW-UP DRUG ELUTION STUDY WITH PC COATINGS

The original drug elution measurement apparatus was modified to allow the measurement of significantly lower drug concentrations (a 13x improvement). A second study was then performed to observe the release of sirolimus from PC coatings. Figure 4 shows a plot of sirolimus release from a 20 μm Cr PC coating in PBS out to 46 days. This plot clearly shows a slow post-burst release. The overall release profile can be explained by a dissolution controlled burst release phase followed by a longer and slower release phase that is controlled by desorption of the drug from the coating surface. Desorption controlled release begins once the drug film drops below a monolayer in thickness. Surface desorption rates depend on drug–surface forces; changing the drug or the coating surface can change the desorption rate. An important point with regard to the observed post-burst release of drug from PC coatings is that only because of the very high surface area is it practically important. A stent with a PC coating can achieve 30 day release of medically significant amounts of antirestenosis drugs without polymers. This is not the case with smooth stents.

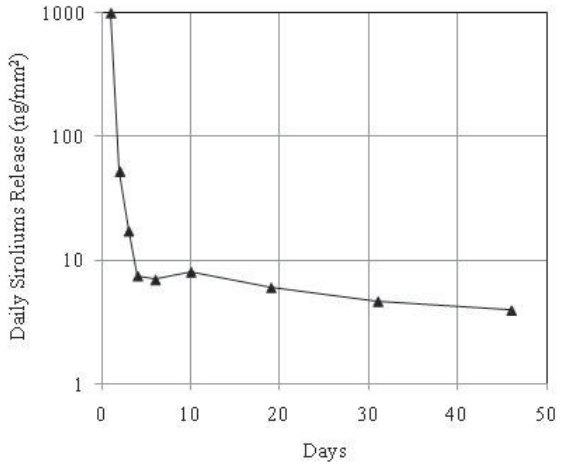

Figure 4: Sirolimus release from a 20 μm Cr PC coating in PBS at 37 C. Second study with a 13x increase in resolution of drug concentration.

CONCLUSION

Nanoporous coatings offer the opportunity for sustained release of drugs from cardiovascular stents without polymers. Drug release from a polymer free surface occurs in two stages: dissolution controlled burst release followed by desorption controlled slow release. Desorption controlled release occurs when the drug film thickness is a monolayer or less. Only nanoporous coatings provide enough surface area to contain a medically significant amount of drug in a monolayer. In particular, sputtered PC coatings show good adhesion and, because of their structure, do not crack or delaminate when the substrate is flexed. These features make sputtered PC coatings highly attractive for polymer free delivery of antirestenosis drugs from cardiovascular stents.

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