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Analysis of drug coated polymer stents studied by XPS

Keywords
bioresorbable polymer, biomedical material, GCIS depth profile

Application Note MO441(A)
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Introduction

Cardiovascular interventional therapy with stents has emerged as the most effective method for coronary heart disease. However, thrombosis and hyperplasia are the usual pathological responses to the implantation of foreign devices. Originally stents were made of steel however in recent times these have been superseded by polymer stents. Recent developments have introduced a new range of stents made from bioresorbable polymers. However problems such as thrombosis and hyperplasia still remain as the pathological responses to the implantation of foreign devices.

To suppress this immune response and that of overgrowth and subsequent restenosis anti-inflammatory drugs are now loaded onto the surface of stent implants.

Here we investigate the surface of drug loaded polymer stents. The stents are made of polylactic acid (PLA) dosed with an anti-inflammatory drug with a molecular structure of $C_{51}H_xNO_{13}$. XPS yields quantitative information regarding drug distribution and using Argon cluster sputtering we can see the distribution of the drug into the stent structure. Analysis is also performed on stents submerged in buffer solution (PBS) to see the effects on ageing and the propensity for the drug to migrate into the solution with time.

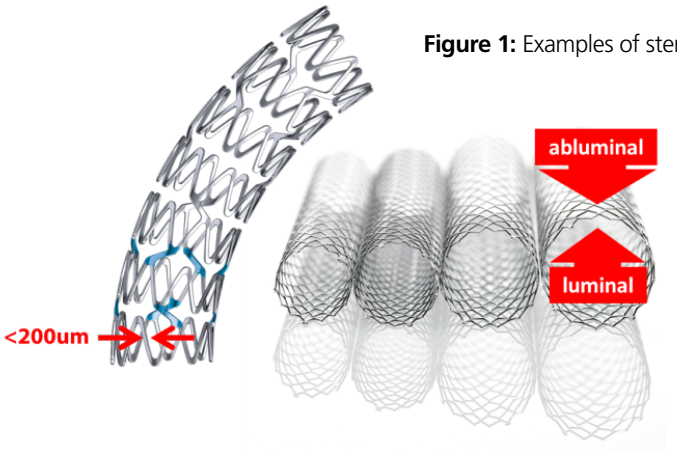

Figure 1: Examples of stent architecture.

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Experimental

XPS was performed using the state-of-the-art AXIS Supra spectrometer equipped with the gas cluster ion source (GCIS). Etch rates were calibrated with PLA thin-film standards.

Results

After introduction of the polymer stents into the analysis chamber spectra were acquired on the luminal (inner) and abluminal (outer) surfaces. A typical stent structure is shown in Figure 1. Due to the narrow nature of the stent scaffold structure (typically less than 200um) small-spot spectroscopy was employed with an analysis area of 110um. Both surfaces were analysed in three spots to evaluate evenness of coverage. The stent polymer and drug chemical structure mainly consist of carbon and oxygen atoms – here the differentiating marker atom used to evaluate drug concentration is Nitrogen. The concentration of Nitrogen in pure drug is 1.5 at.%. The 3-point atomic concentration of the two surfaces is shown below in table 1. with the derived drug concentration. Figure 2 shows a representative 110um diameter survey spectrum from the abluminal as received surface of the drug coated polymer stent. The average concentration is significantly higher on the abluminal surface which is consistent with the manufacturing process.

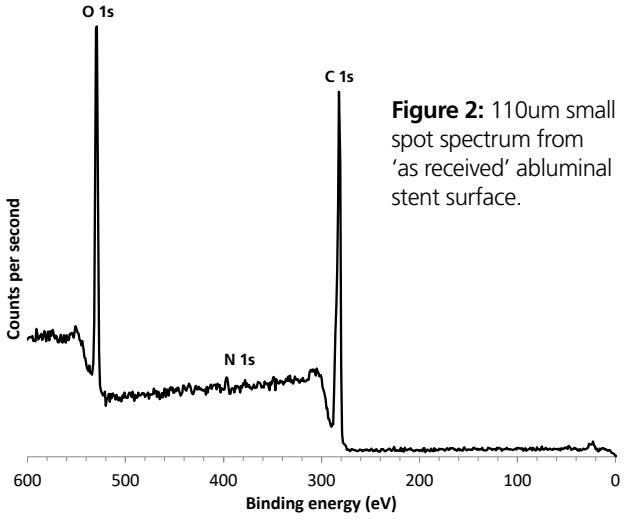

Figure 2: 110um small spot spectrum from 'as received' abluminal stent surface.

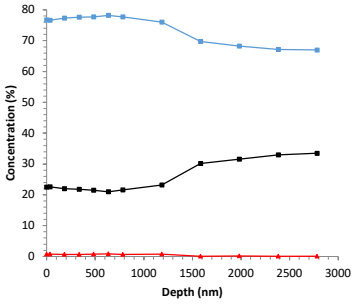

Figure 3a: 10kV Ar_{1000}^+ depth profile of abluminal surface; Carbon (blue), Oxygen (black) Nitrogen (red).

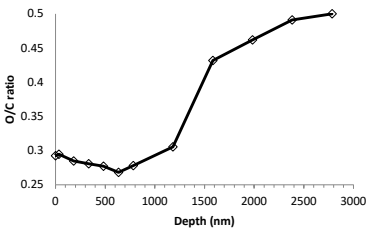

Figure 3b: C/O ratio.

To investigate the distribution of drug from the outermost surface into the stent conventional depth profiling techniques were applied using Argon cluster ions, Ar_n^+. The stent surface was etched with cluster ions to remove the upper layer and subsequently reanalysed. For this depth profile 10kV Ar_{1000}^+ ions were used as this etch mode allows for rapid etching and reduces experiment time, whilst retaining the chemical structure of the drug/polymer materials. The elemental concentration depth profile of the surface is shown in figure 3a. Figure 3b shows the step change in C:O ratio as a function of depth. N concentration can be seen in figure 3c where there is an even distribution of the drug in the top surface with a clear drop once the bulk of the stent is reached with the drug layer ~1.8microns thick.

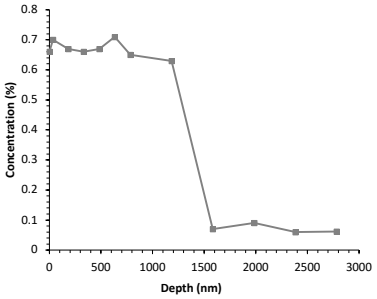

Figure 3c: Nitrogen concentration as a function of etch time.

Conventional methods to study the effects of ageing and drug mobility of stents involve immersion in buffer solution for varying time intervals. Subsequently the solution is analysed with HPLC to see the extent of drug dissolution form the stent surface [1]. Although this method is accurate in determining the amount of drug that has left the stent it is still unknown how much remains and how it is distributed. Here we will explore this by sputter depth profiling. The stents were immersed for 1-3 months (1M, 2M and 3M) in PBS and once dried reanalysed and depth profiled. Figure 4 shows a comparison of N concentration as a function of depth for the different immersion times. As expected for all stents immersed in PBS there was a significant decrease in the N concentration indicating significant drug dissolution. Depth profiling showed a sudden decrease in N concentration after the first etch cycle probably due to the removal of weakly absorbed N-containing contamination. The Nitrogen concentration of subsequent cycles was less than 0.1 atomic %. Surprisingly, after 100nm deep into the surface, the concentration of Nitrogen begins to rise again for all three aged stents indicating that despite significant depletion of the drug in the near surface region there is still a remaining fraction within the bulk. A similar profile shape to the as-received stent can then be seen with further etching with the Nitrogen concentration peaking and decreasing with depth. With increasing PBS exposure the Nitrogen maximum decreases as would be expected.

For the immersed stents the interface between the drug layer and the stent bulk is not as sharp – indicated by significant tailing of the profile – this is most likely due to pitting and corrosion of the stent structure, a well-documented effect of solution exposure. As would be expected the integral of the Nitrogen concentration with depth decreases with longer PBS exposure and the results of this shall be useful for future kinetic studies into the dissolution mechanism.

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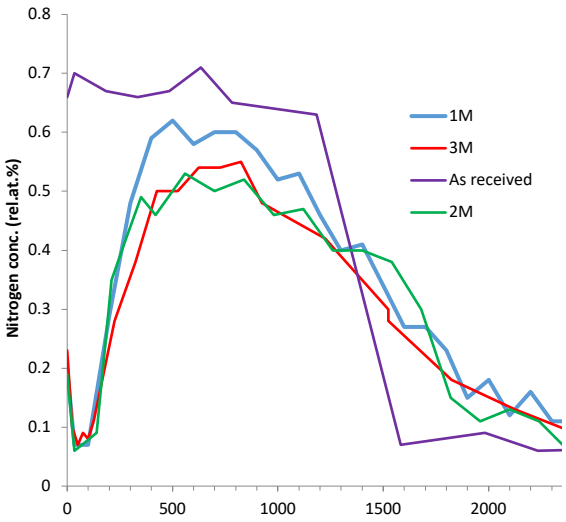

Figure 4: 10kVAr_{1000}^+ depth profiles of stents immersed in PBS for 'as received' (purple) 1M (blue) 2M (green) and 3M (red**).**

Table 1: surface analysis of aluminal and luminal stent surfaces.

SPOT	ELEMENT	ATOMIC CONC. [%]	
		Abluminal	Luminal
1	C 1s	74.78	73.17
	N 1s	0.84	0.73
	O 1s	24.2	25.33
2	O 1s	23.48	25.42
	N 1s	0.79	0.65
	C 1s	75.69	73.77
3	O 1s	25.34	22.07
	N 1s	0.83	0.41
	C 1s	73.3	76.16
mean N conc.		0.82	0.59
drug conc. %		52.5	37.8

Conclusion

Here we have used small area XPS and Ar_n^+ cluster depth profiling to investigate the distribution of anti-inflammatory drugs coated on the surface of bioresorbable stents. The abluminal surface of the as manufactured stent was fully characterised for drug concentration, layer thickness and drug distribution. Ageing experiments were performed to see the dissolution of the drug form the stent into PBS. XPS is an enabling technology allowing analysis of novel biomaterial devices. The high spectroscopic performance of the AXIS Supra allows low concentration elements to be detected with high precision. The use of cluster profiling allows delicate polymer materials to be analysed with confidence.

Acknowledgements

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References

1. **N. A. Lockwood et al.**, Journal of Biomaterials Science 21 (2010) 529–552

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