PHYSICAL ELECTRONICS

3D IMAGING of a Pharmaceutical Coating Using TOF-SIMS

OVERVIEW

A feature of modern medical devices is the capability to deliver a pharmaceutical *in vivo*, and the occurrence of such devices is increasing in frequency. Examples include steroids on pacemaker leads to prevent inflammation, antimicrobials incorporated in catheters to reduce the occurrence of infection, and antiproliferatives on arterial stents to prevent re-blockage of the artery. In such drug containing systems, polymers are often used as a means to incorporate the pharmaceutical into the device and to control the pharmaceutical release, or elution rate. Therefore, understanding the chemical and physical properties of the pharmaceutical/polymer mixture is important. Moreover, understanding the "biointerface" at the surface of the device is crucial because this interface strongly affects the biocompatibility of the device.

Time-of-Flight SIMS (TOF-SIMS) was used to probe the top-most several microns of a drug-eluting stent coating. The coating consisted of 25 wt.% Rapamycin in a poly(lactic-co-glycolic acid) (PLGA) matrix. For the TOF-SIMS analysis, the pharmaceutical coating was sprayed onto a 1 x 1 cm^2 coupon to a target thickness of approximately 7 µm. A TOF-SIMS depth profile of the drug-eluting coating was aquired using a 20kV C_{60}^+ sputter ion beam in order to maintain molecular information of both the drug and the polymer matrix during the profile. The complete raw data stream was saved to facilitate 3D imaging. During post-acquisition processing, the raw data stream files are used to reconstruct an image stack, or 3D iso-surface, of any peak in the mass spectrum. A 3D iso-surface is a data cube produced at a defined mass-to-charge ratio using a uniform secondary ion intensity. The contrast and opacity of any iso-surface may be altered to view a hidden surface, and the iso-surface may be freely rotated to view the 3D molecular distribution from any angle.

EXPERIMENTAL

The following instrumental conditions were used to acquire the negative polarity (-SIMS) raw data stream depth profile and 3D images:

	Acquisition Phase	Sputter Phase
Ion Species	Au^+	C_{60}^+
Beam Energy	30 kV	20 kV
Beam Current	1.3 nA DC	300 pA DC
Raster Size	200 µm	400 µm

Analysis was performed with the sample at room temperature. Charge compensation was accomplished using 10 eV electrons. Each analytical cycle consisted of a 10 minute C_{60}^+ sputter and 5 minutes of data acquisition using a Au^+ ion source. The total profile depth of 3 µm occurred in 35 sputter cycles. The profile depth is estimated based on the sputter rate of poly(methyl methacrylate) (PMMA).

RESULTS

The molecular structures of Rapamycin and PLGA are revealed in Figure 1. The molecular ion of Rapamycin is observed at a nominal mass-to-charge *(m/z)* ratio of 913 in the negative polarity. The molecular ion and other relevant peaks in the negative polarity mass spectrum are indicated in Figure 2.

The 2D x-y images of Rapamycin and PLGA are presented in Figure 3. These images reveal that the drug, Rapamycin, is highly enriched within the first 0.5 µm of the surface. However, it is difficult to visualize sub-surface distributions without 3D imaging.

The 3D iso-surface models of Rapamycin (red, CN^-) and PLGA (green, $C_3H_5O_2^-$) are given in Figure 4.

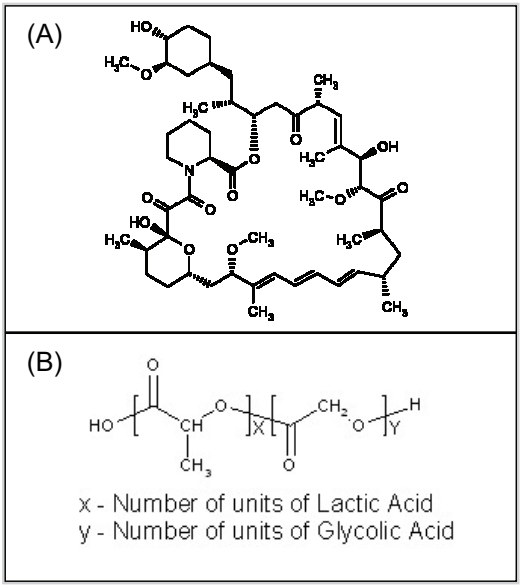

Figure 1: Molecular structures of Rapamycin (A) and PLGA (B).

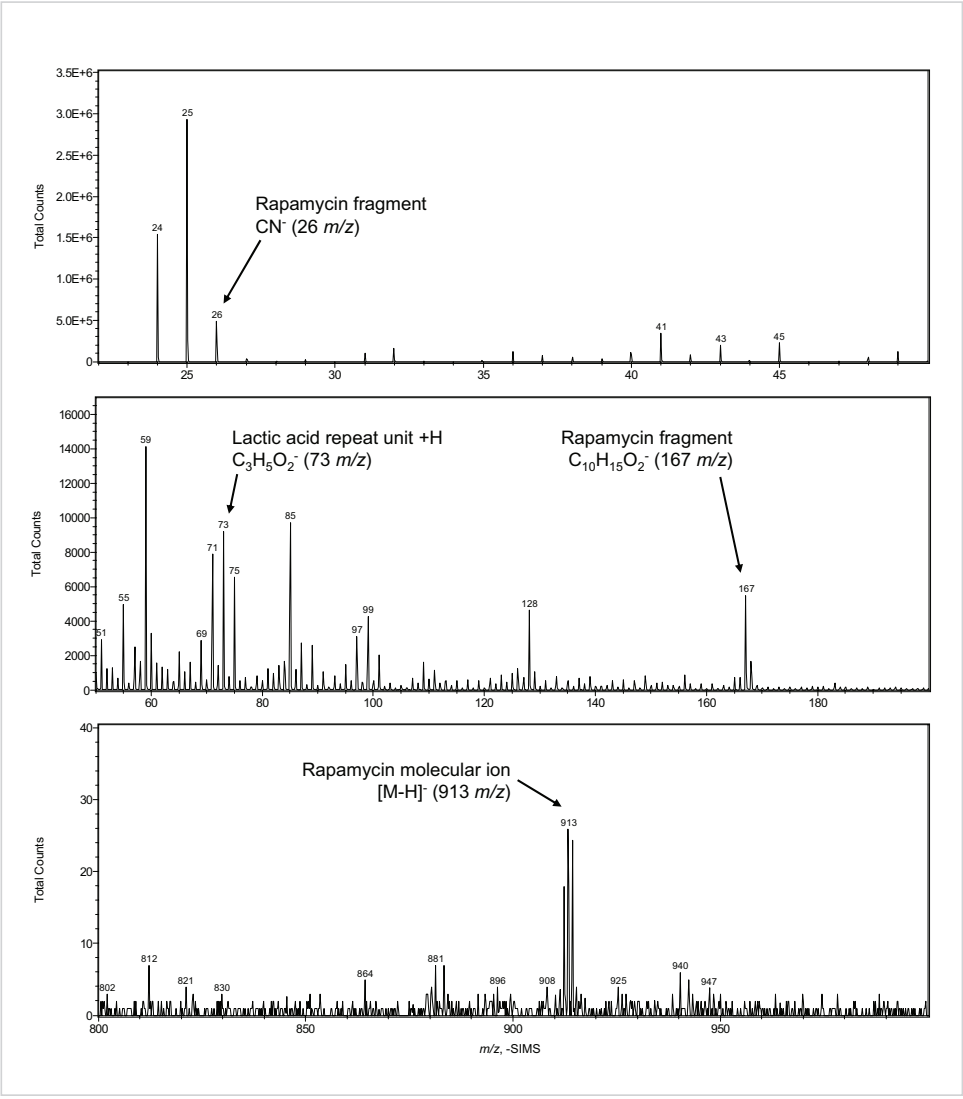

Figure 2: Negative polarity mass spectrum of Rapamycin/PLGA indicating the relavant peaks.

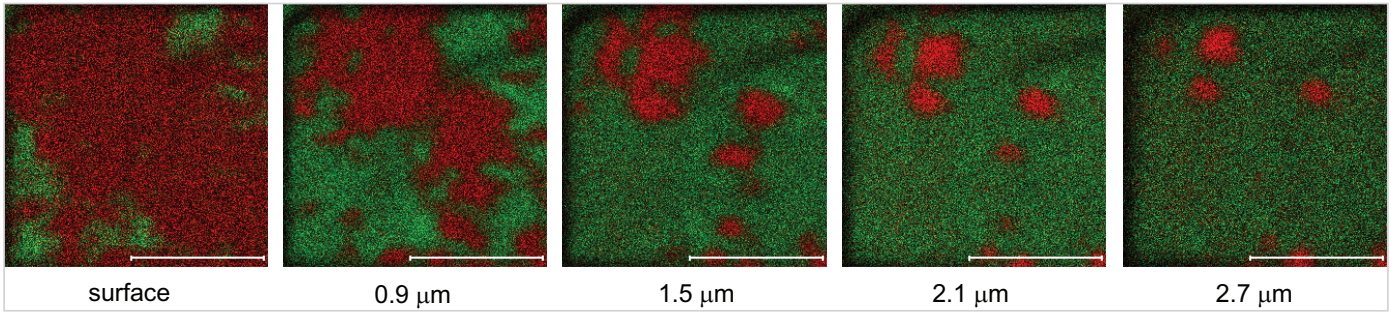

Figure 3: 2D x-y images-at-depth of Rapamycin (red, CN^-) and PLGA (green, $C_3H_5O_2^-$). The marker is 100 µm.

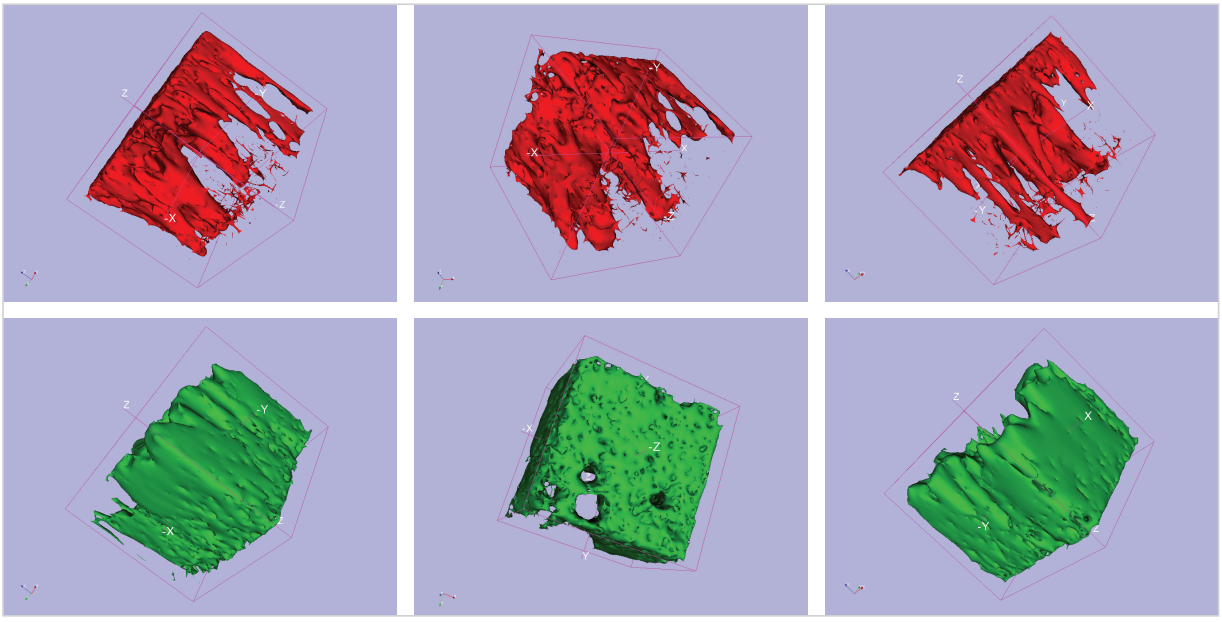

Figure 4. 3D iso-surface models of Rapamycin (red, CN^-) and PLGA (green, $C_3H_5O_2^-$). The marker is 100 µm.

The advantage of these displays is that the sub-surface distribution of each phase can be visualized. The iso-surfaces can be rotated to any orientation to study their 3D distributions. In order to better visualize how they relate to each other, it is often beneficial to overlay the iso-surface images. Figure 5 shows the iso-surface overlay of Rapamycin and PLGA. The opacity of an individual component or iso-surface may be altered, as shown in Figure 5B, so that subsurface domains within the matrix may be viewed.

The iso-surface models of Rapamycin and PLGA reveal, in a straightforward visual manner, the subsurface distributions of both the drug and the polymer matrix. It is clear that, while the drug is enriched at the surface, the sub-surface region contains a significant component of the drug as well. At approximately 2 µm below the surface, discrete domains of the drug, ranging in size from about 1- 20 µm, are observed to be disbursed throughout the polymer matrix.

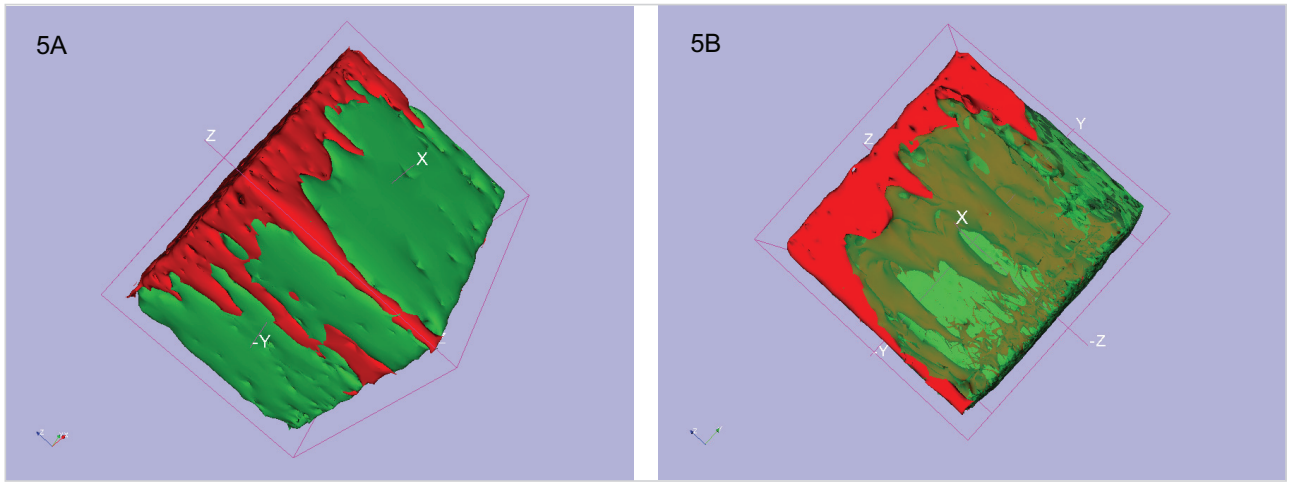

Figure 5: 3D iso-surface overlay of Rapamycin (red, CN^-) and PLGA (green, $C_3H_5O_2^-$).

CONCLUSION

TOF-SIMS can be used to probe several microns into the surface of an organic coating to study the structure and the 3D molecular distribution within the material. Because of the tremendous amount of data generated during this type of analysis, advanced data reduction and display technologies are required to interpret the data. The use of 3D iso-surface models can be successfully applied to TOF-SIMS data to visualize the subsurface distribution of molecular phases.

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