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Real-Time Confocal Raman Imaging of a Drug Delivery System on Cardiac Leads

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Abstract—**Drug delivery systems incorporated onto the end of cardiac leads are used to reduce inflammation and fibrosis at the lead-tissue interface and enable optimal lead performance. In this research, confocal Raman microscopy was used to capture chemical images of the drug delivery system on pacemaker leads in different elution media in real-time. Raman images in ambient air showed that drug was dispersed in the polymer matrix as discrete particles with size ranging from 1 to 3 μm. Upon immersion into an aggressive elution medium, drug near the surface dissolved immediately and solvent started to penetrate into the polymer matrix through channels from which drug was eluted. The drug depletion depth was a function of time, which was consistent with the drug release profiles obtained by HPLC. Comparing the drug elution in aggressive solvent and biorelevant solvent, a mechanism of drug release is proposed.**

I. INTRODUCTION

Cardiac leads, which connect medical devices such as pacemakers and defibrillators to the heart, are used to monitor the heart's rhythm and provide therapy when needed [1]. A drug delivery system is typically incorporated onto the distal end of cardiac leads to reduce inflammation and fibrosis at the lead-tissue interface and to enable optimal lead performance.

Figure 1 depicts preclinical pacing threshold data with and without the incorporation of a steroid system. This anti-inflammatory drug system reduces tissue inflammation and allows lower pacing energy requirements and increased device longevity [2]. Control of drug release from the drug system can directly impact the performance of the medical device.

In this research, a new imaging technical, confocal Raman microscopy (CRM), was employed to probe the chemical composition of a dexamethasone acetate (DXA)/silicone rubber drug delivery system. Confocal Raman microscopy was also capable of conducting real-time 3-D imaging in different elution media, which provides insight into the drug release mechanism.

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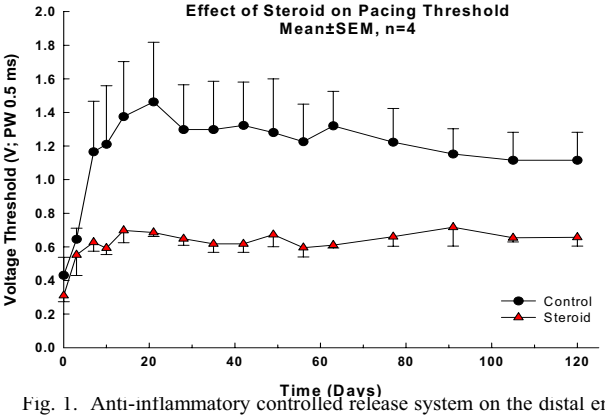

Fig. 1. Anti-inflammatory controlled release system on the distal end of cardiac leads can lower acute and chronic pacing energy requirements.

II. EXPERIMENTAL METHODS

Confocal Raman Microscopy

Raman scattering provides chemical fingerprints of a material irradiated by a laser. Combining high resolution confocal optical microscopy and Raman spectroscopy, a 3-D chemical map can be obtained from a material with ultimate resolution of 200-300 nm laterally and ~500 nm vertically. Raman spectroscopy and Raman chemical imaging have been widely used to characterize drug polymorphs and drug distribution in biomedical coatings [3]. In this research, Raman microscopy was employed to image the drug elution dynamics in real-time, to correlate to high performance liquid chromatography (HPLC) results.

A Witec (Ulm, Germany) Confocal Raman microscope equipped with an Ar-Ion laser (514.5 nm) was used to elucidate the spatial distribution of the steroid drug within the silicone rubber matrix. Raman imaging was performed by raster scanning a sample under the microscope objective. An array of spectra (i.e. 80×80 pixel scan for all images in Figure 4) was collected with the same integration time (0.05-0.2 s) at each pixel location. Raman images were generated by integrating one or more characteristic peaks from each component for all spectra and rendering the peak intensity as the brightness at each pixel location. The confocal capability allows imaging in both the vertical direction (cross section scan) and lateral direction at different focal planes. The intensity of the laser at the focal point was about 5-15 mW.

Drug Release

In vitro drug elution was characterized at different time points using a release rate tester in combination with HPLC.

The drug release profiles in two release media are shown in Figure 2. A fast release or burst release stage happened during the first few hours in the aggressive solvent.

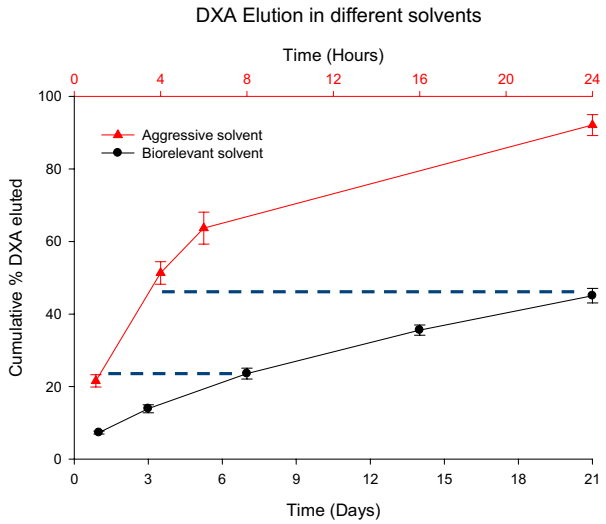

Fig. 2. Comparison of DXA elution in an aggressive solvent (an organic solvent that causes fast drug elution) and a biorelevant solvent (a solvent that simulates *in vivo* conditions). 1 and 4 hours of elution in aggressive solvent correspond to 7 and 21 days of elution in biorelevant solvent, respectively.

III. RESULTS AND DISCUSSION

Drug Distribution in the Polymer Matrix

Raman images were captured in ambient conditions to elucidate the distribution of the drug in the polymer matrix. Figure 3a reveals that the drug (dexamethasone acetate) forms discrete particles ranging in size from 1 to 3 µm. The polymer forms a continuous matrix. No drug signature was found in the polymer images, indicating insignificant mixing of the two components. Figure 3b shows Raman spectra of the individual drug and polymer constituents with characteristic peaks labeled, while Figure 3c shows a Raman spectrum of a random point on the composite drug collar system.

Imaging Real-Time Drug Release

The drug collar was mounted on a metal pin and was placed into a Petri dish. Upon adding solvent to the Petri dish, a liquid immersion objective (NA=0.9) was immediately brought into focus on the drug collar. Both vertical and lateral Raman scans were performed continuously over a set period of time. Drug, polymer and solvent images were generated using corresponding Raman peaks. Combination of all three images was also used to illustrate the distribution of the three components at specific time points.

Figure 4 depicts the Raman data collected in the aggressive solvent. Figure 4a is a vertical Raman scan with 1.5 hours of immersion. Penetration of solvent (red) can be clearly observed through vertical channels from which drug has eluted (yellow). A drug-depleted zone of ~ 6 µm below the collar surface has resulted from immersion in the solvent. Figure 4b is a lateral Raman scan of the collar surface collected at a later immersion time point. Most of drug seen in Figure 4a was replaced by the solvent. Some drug contrast appears to be present on the surface; however this is likely drug remaining below the surface. It is interesting to note that the solvent domains on this image are interconnecting, different from the drug particles in Figure 4a, in which all drug domains are well separated by the polymer matrix. This indicates that the aggressive solvent has strong penetration into the polymer, especially on the surface where sufficient interaction between the solvent and the drug is possible. This may explain why a burst release of the drug was observed at the early stage of the elution. No interconnection of the solvent channels was seen in Figure 4a

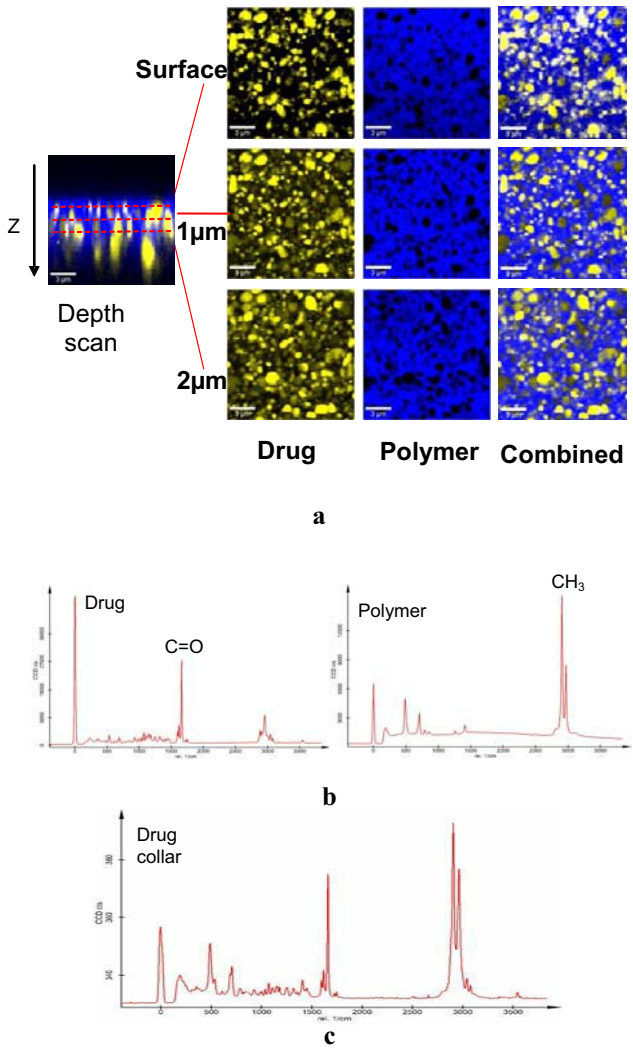

Fig. 3. Raman imaging on the drug collar under ambient condition. a) Raman images scanned in vertical and lateral directions: the image on the left is a vertical scan into the depth of the collar. The images on the right are from three focal planes (surface, 1 and 2 microns below the surface) of the collar. Drug is shown as yellow and polymer is shown as blue. b) Raman spectra from pure drug and polymer. c) A typical Raman spectrum from a random point on the drug collar. Characteristic peaks (i.e. the peak around 1650 cm^{-1} corresponds to

the C=O group in the drug, and the peak around 2900 cm^{-1} corresponds to the CH_3 group in the polymer) from the spectra are used to generate chemical maps of each component.

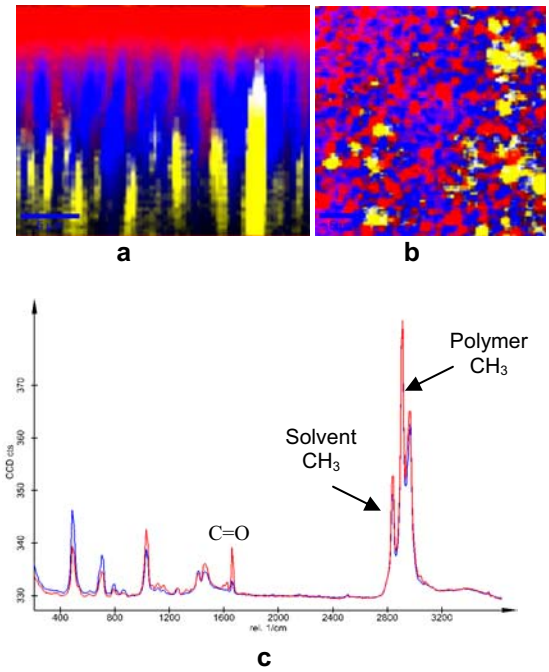

Fig. 4. Real-time Raman imaging reveals the interaction of elution medium and the drug-polymer system: a) vertical Raman scan showing the penetrating of the solvent into the collar; b) lateral Raman scan on the collar surface after immersing the collar into the aggressive solvent. (red: solvent; blue: polymer; yellow: drug); c) A typical Raman spectrum collected close to the collar surface after 10 min (red) and 180 min (blue) of immersion in aggressive solvent. Characteristic peaks from the drug (C=O group at 1665 cm^{-1}), polymer (CH_3 group at 2915 cm^{-1}) and solvent (CH_3 group at 2842 cm^{-1}) are observed on the spectra at the same time. Significant decrease of the drug peak during elution can be clearly seen.

Ex-situ Imaging on Eluted Drug Collar – Comparison of the Two Solvents

A series of drug collar samples were placed in either aggressive or biorelevant solvents, and then removed at progressive time points. Raman imaging was performed after the collars were dried. Figure 5 compares the chemical compositions of the collars from the two conditions. Figure 5a shows that in biorelevant solvent, after 21 days of elution, drug was depleted about 7 µm below the surface. However, in aggressive solvent (Figure 5b), after only 4 *hours* of elution, no drug was found more than 6 µm below the surface. In lateral scan images, holes that were left by the drug particles were found to be fewer than the number of drug particles in Figure 3a. This may be caused by the drying of the polymer and a resulting collapse of the voids left after drug release.

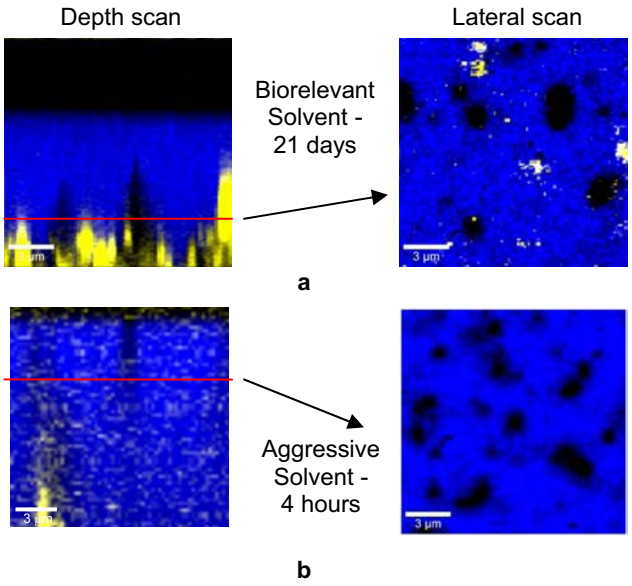

Fig. 5. Comparison of drug elution in two solvents. a) Raman images from collars eluted in a biorelevant solvent for 21 days; b) Raman images from collars eluted in an aggressive solvent for 4 hours.

Drug Release Process

From the above comparison, the drug release process may be proposed as the following: as the collar was immersed into the solvent, a burst release of drug occurred at the surface due to the direct interaction of drug particles and the solvent. The release of the drug created pores, which allows solvent to enter into the collar and dissolve drug at greater depths. Swelling of the polymer may also occur during elution, further enhancing release of drug due to pore expansion. During the drying of the collar, the evaporation of the solvent caused closing of the pores with a strong effect at the surface due to the surface tension. This may explain observations of smaller pores near the surface after drying (data not shown). Since the two solvents may swell the polymer differently, the drug release process may be different for the two conditions. Differences in the number of pores remaining on collars exposed to the two conditions supports possible differences in elution.

IV. CONCLUSION

Confocal Raman microscopy was used to image the drug elution from the drug collar from cardiac leads *in situ* (in elution medium) and *ex situ* (after the elution medium was removed). The use of chemical imaging to assess drug delivery systems can provide insight into drug release mechanisms and related raw material properties to guide drug delivery design.

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