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Strain-induced crack formations in PDMS/DXA drug collars

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ABSTRACT

Drug-eluting systems are currently used in cardiac leads in order to reduce inflammation and fibrosis at the lead–tissue interface. Drug release from these drug delivery systems can be modulated by the manufacturing processes used to create the drug systems and assemble them onto the cardiac lead. In this study, scanning electron microscopy, atomic force microscopy and Raman microscopy are employed to explore the material characteristics of a polydimethylsiloxane–dexamethasone acetate drug collar used on cardiac leads when varying the strain during collar assembly on the lead. A novel test fixture was created in order to investigate these drug collars under simulated stresses. Measurements of the collar while fitted to a rod revealed microcracks that are hypothesized to affect the drug release performance, resulting in increased drug elution. It was found that the strain that occurs during assembly of the collar onto the lead is a key factor in the formation of these microcracks. Results also suggest that cracks tend to form in areas of high drug particle density, and propagate between drug particles.

1. Introduction

When inserted into the endocardium for electrotherapy, cardiac leads may cause damage to the cardiac syncytium via inflammation and posterior fibrosis, resulting in increased threshold voltages [1,2]. However, the addition of a drug component on the distal end of the lead has been shown to lessen the inflammation and significantly diminish the formation of a fibrous capsule surrounding the electrode, ultimately resulting in a reduction of the threshold voltage [3,4]. This drug delivery system is typically composed of a two-phase system: for example, a continuous polydimethylsiloxane (PDMS) phase (a SiO_2-reinforced matrix) and a dispersed phase consisting of the drug dexamethasone acetate (DXA) [5,6].

Studies of similar drug matrices have been used to help explain how the drug is released. One such explanation is through an osmotic gradient [7], which is formed through the ingress of water into the pores of the polymer matrix because of the osmotic potential difference between the internal droplet solution and the external solution [8]. Swelling causes polymer tears, or ruptures, which occur initially at the surface of the matrix due to the low restraining force from thinner walls around the drug inclusions [5,9]. Furthermore, the osmotic pressure build up inside locations containing drug or salts can create microscopic cracks in the polymer matrix, thereby assisting in drug elution [8].

While these previous studies have employed similar combinations, currently no known drug elution work has involved PDMS and DXA, which is used in the drug collar manufactured by the Boston Scientific Corporation (BSC). The present work attempts to determine the effect that stretching (during assembly of a drug-containing component onto the lead) has on drug elution over time. The surface of the base of the drug collar is characterized by confocal Raman microscopy, atomic force microscopy (AFM) and scanning electron microscopy (SEM). These characterization tools may assist in understanding the mechanisms and pathways of drug elution for a drug collar in its realistic, stretched state, as it rests on the lead. Ultimately, developing knowledge of key factors that can influence drug elution time profiles, as well as the mechanisms of drug delivery, would be advantageous in guiding the design of refined devices.

2. Materials and methods

Samples were created by either combining micronized dexamethasone acetate with a two-part platinum-catalyzed, silica (SiO_2)-reinforced PDMS elastomer to a 33 wt.% drug loading followed by molding into drug collar components or molding the PDMS without drug incorporated into collar components. Each collar was assembled by stretching the component followed by placement onto the rod feature of a test structure fabricated out of a polycarbonate material. The test structure, illustrated in Fig. 1, was used to simulate placement onto a pacing lead and facilitate characterization of the drug collar in its stretched state.

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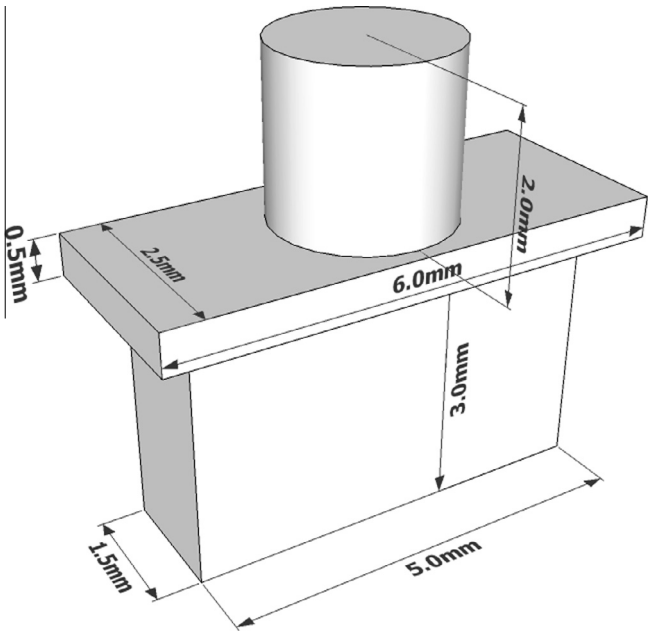

Fig. 1. Test structure with rod feature used for analysis of drug collar in stretched state, simulating drug collar assembled on a pacing lead. SEM and AFM imaging was performed on the top surface of the drug collar.

In order to assemble the drug collar onto the test structure, the collar is stretched. The inner diameter of the stretched collar during the assembly is d_s. This value is divided by the collar's original inner diameter, d_0, to find the strain as defined in Eq. (1):

$$\text{Strain}(\%) = \frac{d_s d_0}{d_0} \tag{1}$$

This is used as the strain value throughout this work. The duration of time that the collar was strained during assembly onto the test structure was approximately 30 s. The drug collar initial dimensions are: an inner diameter of 1.2 mm, an outer diameter of 1.9 mm and a height of 0.8 mm. While the collar rests on the lead structure, there is no residual strain. Emplacement strain values of 113, 159, 222 and 280% were employed throughout this study. It should also be noted that the practical lower limit is 146% strain in order to emplace the collar on the lead, but the process was modified in order to explore a lower amount of strain, namely 113%.

Elution testing of steroid drug from BSC leads is designed to provide quality and process control of the DXA eluting leads. In vitro testing includes agitation of samples at a constant rate in a 65% acetone and 35% water solution at 37 °C. At specific time points, aliquots of the solutions were removed and the drug concentration was determined by high-performance liquid chromatography. A drug elution–time profile was created by plotting percent cumulative eluted drug vs. time. Six samples for each strain of 113, 159, 222 and 280% were used for the drug elution experiments.

All drug collar samples imaged with SEM were sputter-coated with 10 nm of 60–40% gold–palladium using a Denton DV-502A high vacuum deposition system (Moorestown, NJ USA). Upon coating, two samples of each strain value were imaged with a Hitachi S-4700 cold field emission scanning electron microscope operated at 3 keV (Hitachi High Technologies America, Dallas, Texas, USA). Lens-to-sample distances from 5 to 15 mm and sample tilt angles from 0 to 45° were used. Before sputter-coating, some samples were microtomed using a Leica EM UC6 cryoultramicrotome (Buffalo Grove, IL, USA). Approximately 200 μm was removed using a glass knife, while maintaining a sample temperature of −120 °C, which was above the glass transition temperature of PDMS (−125 °C) [10].

Raman measurements were conducted on a WITec alpha 300R confocal Raman microscope (WITec Instrument Corp., Germany) equipped with a UHTS 300 spectrometer, a DV401 CCD detector and a piezo-driven, feedback-controlled scan stage that provides 4 nm lateral and 0.5 nm vertical positioning accuracy. A ×100 Nikon air objective with a numeric aperture of 0.90 was used. The excitation source was an Ar laser (CVI Melles Griot) operated at 514.5 nm wavelength and 10 mW power. The spatial resolutions in Raman imaging were tested to be ~0.30 μm laterally and ~0.60 μm vertically. Data processing was performed with WITec Project 2.08 software. Raman imaging was typically conducted over 10 μm × 10 μm sample areas wherein 50 × 50 Raman spectra were collected with an integration time of 0.2 s per spectrum. In the analysis of the unstretched sample, the collar was cut and mounted flatly on a glass slide using a piece of double-sided sticking tape. This facilitated obtaining reproducible data in the imaging measurements. In the analysis of the stretched sample, the collar was stretched on a stainless steel rod with a diameter of 2.74 mm and was secured on a glass slide. The measurements were conducted at the side of the stretched collar.

AFM was conducted with a Bruker Nanoscope V Multimode 8 (Santa Barbara, CA, USA), employing PeakForce QNM® (Quantitative Nanomechanical Mapping). This imaging mode executes fast force curves: essentially one approach–retract cycle (of tip to sample) via the Z scanner per measurement site (pixel) at a frequency of 2000 cycles s^{-1}. The method provides simultaneous measurements of several characteristic sample metrics, which are herein referred to as height, tip-sample adhesive force and "DMT modulus" per the proprietary instrument software. Height refers to the Z scanner displacement needed to reach the PeakForce setpoint (quantified below), and thus measures the surface topography to first approximation, but with possible higher-order effects due to differences of mechanical compliance (indentation) on rigid compared to soft surface locations. The tip-sample adhesive force is simply a measurement of the most negative deflection of the cantilever due to attractive forces sensed during retraction. Although the Bruker software outputs the so-called DMT modulus, a JKR adhesive contact mechanics model [11] would be more suitable for quantitative analysis of the soft polymeric system studied here, as described below.

In order to identify the possible appropriateness of either the DMT or the JKR model, a quantity known as the transition parameter λ is employed. The JKR or DMT models are strictly appropriate only for relatively large or small values of λ: $\lambda > 5$ (JKR) or $\lambda < 0.1$ (DMT) [12]. The transition parameter is defined as

$$\lambda = \frac{2.06}{S_0}\left(\frac{R\gamma^2}{\pi K^2}\right)^{1/3} \tag{2}$$

where R is the radius of the tip, estimated here to be 10 nm (per the manufacturer), ε_0 is the interatomic spacing, typically set to 0.16 nm [13], K is the system modulus and γ is the work of adhesion (defined below) [13]. The system modulus K, for the case of a rigid tip and a soft sample, relates to sample Young's modulus (E_{sample}) by $K \sim 1.5 \cdot E_{\text{sample}}$. For PDMS, $E_{\text{sample}} = 1.9$ MPa, and therefore the system modulus is ~2.8 MPa. Using Eq. (3), the work of adhesion γ can be estimated via the measurement of tip-sample adhesive force as defined above.

$$F_{\text{adhesion}} = -2\pi\gamma R \tag{3}$$

Prior to inputting a pull-off force into Eq. (3), however, one must first consider the appropriateness of these contact mechanics models; both the JKR and DMT models assume linear elasticity. This demands that the deformations produced be small compared to the

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