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Drug Release Mechanisms of Steroid Eluting Rings in Cardiac Pacemaker Lead Electrodes

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***Abstract*— This paper reports on the drug release mechanisms of silicone structures with embedded steroids applied in pacing leads. Different derivatives of the steroid dexamethasone, which is associated with the reduction of acute stimulation thresholds, were evaluated together with different matrix based release control mechanisms with the target to potentially match optimal drug release rates during the first month after implantation. By incorporating dexamethasone-21-dihydrogen phosphate in silicone matrices in combination with release rate adaption layers, almost continuous release rates were obtained under physiological test settings.**

I. Introduction

Implantation of endocardial pacing leads into the heart can cause inflammatory immune response of the surrounding cardiac tissue. After implantation, the formation of fibrous connective tissue around the electrode surface is believed to cause rising stimulation thresholds over time. The two basic fixation types that are supplied by most pacemaker manufacturers are (i) helix screws as active-fixation mechanism and (ii) tines on the tip end that catch onto muscular trabeculations as a passive fixation mechanism. While active fixation allows an optimal contact to the endocardial tissue, trauma that is associated with implantation of the active-fixation leads is known to temporarily raise stimulation threshold levels [1] as depicted in Fig. 1A. This directly impacts and hinders the optimization of the stimulation parameters of the pacemaker right after implantation. By delivering therapeutic drugs such as glucocorticosteroids directly at the implantation site either by passive or active fixation (see Fig. 1B), acute stimulation thresholds can be minimized and chronic thresholds are lowered in comparison to conventional non-eluting leads [2]. There are multiple studies on steroid eluting leads which proved good or better performance in comparison to non-eluting leads, e.g. ventricular active-fixated [3], atrial active-fixated [4;5], double chamber active fixated [6], ventricular passive-fixated [7-9], or epicardially fixated rings [10-12].

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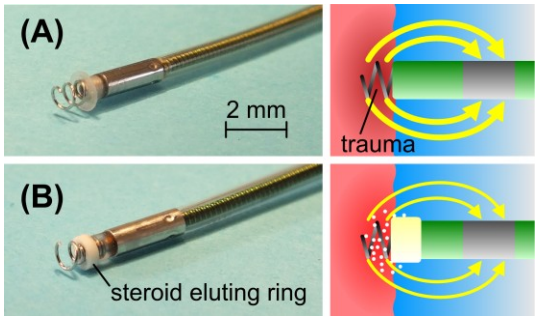

Figure 1. (A) Conventional actively fixable pacemaker lead electode (type KY-5, Osypka, Rheinfelden-Herten, Germany) with screw on distal tip end. (B) Actively fixable pacemaker lead electrode with additional steroid eluting ring for reduced trauma (type KY-5X).

The two most commonly used glucocorticosteroid derivatives for pacemaker leads are dexamethasone acetate (DexA) and dexamethasone sodium phosphate (DexP) [13].

However, while steroid release is reported from stents [14], contact lenses [15;16], or microspheres [17], there is no information available in literature that describes the controlled release mechanisms and quantifies the amount of drug released from such rings over time. The physiochemical properties of the mentioned glucocorticosteroid derivatives are quite different. While DexA can be practically not dissolved in water, DexP is easily dissolved. When incorporating both derivatives into silicone matrices, different release kinetics may be expected. In the case of lipophilic DexA in a hydrophobic silicone matrix, release will be diffusively controlled as described by the generally accepted Higuchian matrix model [18]. In contrast, highly water soluble drug particles in the hydrophobic silicone matrix such as DexP can follow a non-diffusive osmotic model that was first introduced by Gale et al. [19], in order to obtain constant (zero-order) release kinetics.

DexA and DexP eluting rings are fabricated and tested for one month under physiological settings. Release profiles are determined by quantitative high performance liquid chromatography (HPLC) analysis. For further investigations, scanning electron microscopy (SEM) micrographs of cross sections are taken.

II. Materials and Methods

A. Fabrication of Steroid Eluting Rings

Steroid eluting rings were fabricated by mixing (i) dexamethasone-21-acetate and (ii) dexamethasone-21-dihydrogen phosphate (Sanofi-Aventis, Frankfurt am Main,

Germany) with silicone rubber elastomer (NuSil, Carpinteria, CA, USA) at a 1:2 weight ratio in each case. The compound was molded into hollow cylindrical shapes with an external diameter of 1.65 mm, a height of 0.9 mm, and an internal diameter of 0.6 mm. Declared agent load for both steroid ring types is 0.7 mg ± 0.1 mg.

B. *Physiological test setup*

As depicted in Fig. 2 three different configurations are prepared by rings with homogeneous drug concentration profile (DexA, DexP) and rings with an additional release rate adaption layer (inhomogeneous drug concentration profile, DexPX). In order to raise the amount of delivered drug and thus the accuracy of the release rate measurement, 5 steroid eluting rings were applied onto a stainless steel rod and evaluated in parallel three times for each case. The resulting 9 assemblies were immersed into glass bottles containing 50 mL isotonic saline solutions considered to be a sufficient concentration sink for the steroids. Afterwards, the bottles are stored in an oven at 37 °C while agitated at heart frequency (60 min^{-1}) using a standard orbital shaker (3500 orbital shaker, VWR, Darmstadt, Germany). Samples of 1 mL test solution were then taken after day 1, 2, 5, 12, 22 and 30 in case of DexA and after day 1, 7, 15, 22, and 28 in case of DexP and DexPX. The drug concentration of the individual samples was quantified at the last sampling day by using an HPLC analysis method as described in the next section.

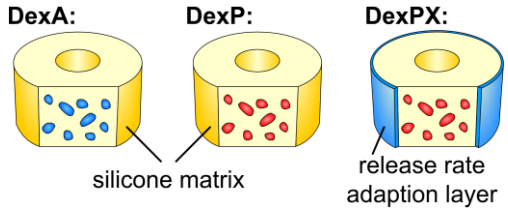

Figure 2. Three different ring configurations DexA, DexP, and DexPX.

C. *HPLC Analysis Method*

A quantitative HPLC analysis method was developed, validated, and performed on a Varian system consisting of a ternary solvent delivery module ProStar 230, a photodiode array detector ProStar 335, and an autosampler ProStar 410 with a 20 µL loop attached.

Isocratic chromatographic separations were carried out in a stainless steel Pursuit 5 Diphenyl 150 x 4.6 mm column at room temperature with a degassed acetonitril-water mobile phase (40:60 v/v, both with 0.1% (v/v) trifluoroacetic acid) and a flow rate of 1.0 mL/min. The quantitative analysis of DexA and DexP was performed with the detector set at 243 nm wavelength. Peaks of DexP and DexA arrive at the detector at 3.55 min (see Fig. 3A) and 8.00 min (see Fig. 3B), respectively. The detector was then calibrated in the range between 100 µg/mL down to the detection limit determined with 0.1 µg/mL. Precision by the method was validated down to 1 µg/mL with relative standard deviations (RSD) smaller than 1.5%. Linearity of the calibration curve is given with a regression coefficient R = 0.9999.

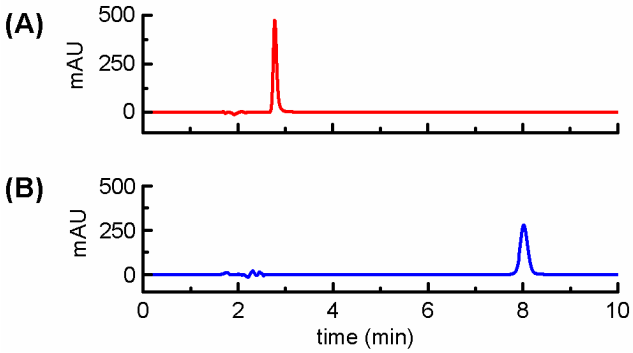

Figure 3. (A) Chromatogram of 0.1 mg/mL DexP, (B) chromatogram of 0.1 mg/mL DexA.

Due to the practical insolubility of DexA in water, calibration standards as well as test samples are extracted by 40% (v/v) ethanol before quantitative HPLC analysis was performed. As depicted in Fig. 3, this result in smaller peaks for the same concentration (0.1 mg/mL calibration standards are shown). DexP samples are used unmodified.

III. Results

A. *HPLC Analysis*

The determined release profile of DexA eluting rings indicates that 53.3 µg ± 2.1 µg are released after test period of one month as depicted in Fig 4A. This equates to approx. 7.6 % of the declared agent load of 0.7 mg. The data can be fitted according to the Higuchi equation $Q = 2Ac_0(Dt/\pi)^{0.5}$ by calculating the curved surface area of the hollow cylinder as $A = 4.67$ mm^2 and the initial drug load per volume c_0 as 0.42 mg/mm^3. By this, the diffusion coefficient of DexA within the silicone matrix is determined as $2.31 \cdot 10^{-10}$ mm/s ± $0.12 \cdot 10^{-10}$ mm^2/s.

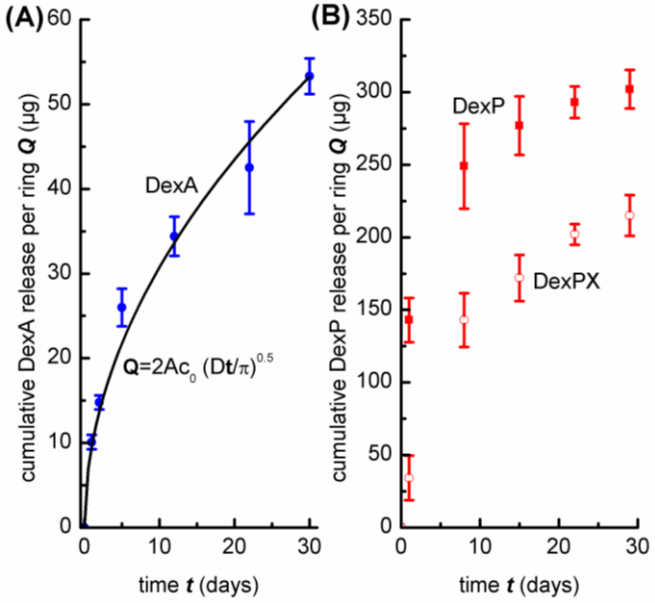

Figure 4. (A) Cumulative released amounts of DexA per ring. (B) Cumulative released amounts of DexP and DexPX per ring.

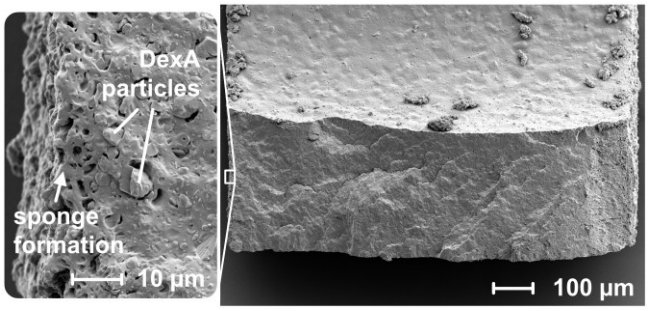

Figure 5. SEM micrograph of a DexA eltuting ring after 12 days incubated within a physiological conditions.

On the other hand, DexP eluting rings show initially an increased agent release of 143 µg ± 15 µg after 1 day as well as a higher agent release of 302 µg ± 13 µg after the test period of one month. The totally released drug equals 43.1% of the declared agent load of 0.7 mg (Fig. 4B). By use of the additional release rate adaption layer (DexPX), the initial release can be decreased to 34.2 µg ± 1.5 µg after one day and to 215 µg ± 14 µg after one month. For both types, a diffusion coefficient according to the Higuchi equation cannot be determined. This assumes that the release mechanism is different and might be osmotically controlled for DexPX.

B. Characterizations with SEM/BSE micrographs and EDX

For taking SEM micrographs, the steroid eluting rings are immersed into liquid nitrogen and broken into two parts to obtain cross sectional views. As depicted in Fig. 5, the inner part of the cross section of a DexA eluting ring is homogenous while a 10-µm-deep sponge-like area is seen at the outer surface after 12 days of physiological settings. The sponge-like area is expected to be the part of material where depletion has already occurred.

For characterization of DexP eluting rings, the detection of back-scattered electrons (BSE) provides additional contrast information with respect to the allocation and size of agent particles (see Fig. 6A), while punctual energy dispersive X-ray (EDX) spectroscopy can specify the detection of DexP and the silicone matrix by peaks of the elements phosphor and silicon, respectively.

Native DexP eluting rings show exposed drug particles at all surface areas (Fig. 6A2). The exposed drug could be responsible for the initially higher drug release rate. Thereby, the distribution of particle sizes could additionally cause non-uniform release rates by comparing individual rings. After immersion into the physiological liquid, steroid particles at the surface can be dissolved directly without being retarded by the silicone matrix. In addition, the sizes of individual drug particles appear to decrease towards the center of the silicone matrix (see Fig 6B2).

IV. CONCLUSION

Release kinetics and mechanisms of three different configurations of steroid eluting rings where observed to be significantly different. The differences can be attributed (i) to the different solubilities in water of the steroid dexamethasone derivatives, and (ii) to additional release rate adaptive layers.

From application point of view, the release of DexA from the silicone matrix might be too slow for an acute treatment of a trauma associated with actively fixated pacing leads, but might be probably a good choice for chronic passively fixated pacing leads. The release from rings with DexP is initially too high and might therefore be ineffective for treatment of the acute trauma. DexPX with an additional release adaption layer slows down the initial release and is therefore considered to be the best alternative for the treatment of the acute trauma.

Nevertheless we have further to investigate strategies to completely deplete the ring with constant (zero-order) kinetics.

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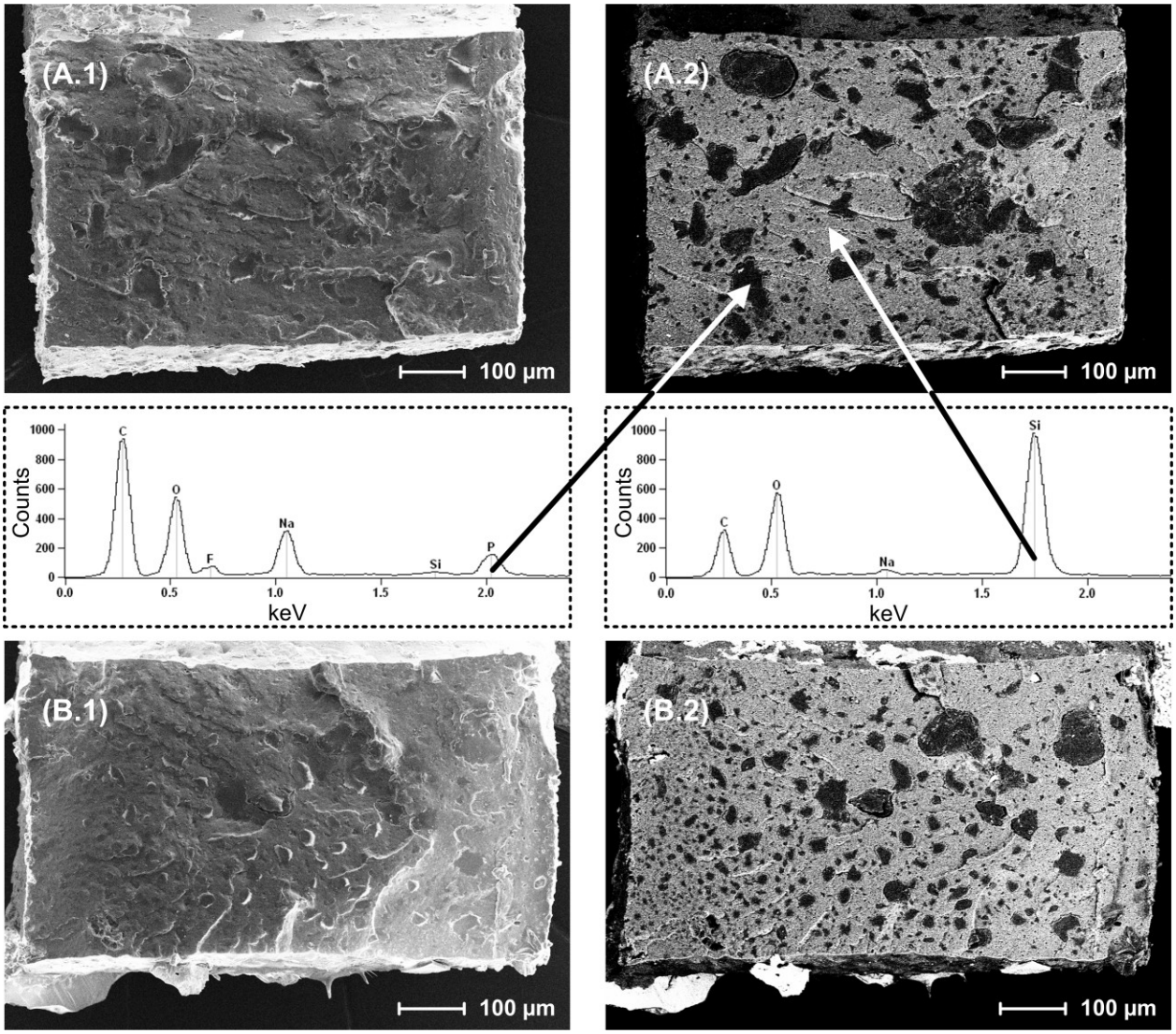

Figure 6. (A.1) SEM and (A.2) BSE micrograph of a native DexP eltuting ring before introduction into physiological settings. (B.1) SEM and (B.2) BSE micrograph of a DexP eluting ring after 12 days incubated in physiological settings.

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