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Pacemaker Lead Insulations – Elaboration of an Oxidizing Test Solution for Comparative Assessment of *in vitro* Biostability

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Abstract: Conventional transvenous rhythm implants are still the treatment of choice for patients with cardiac arrhythmias. Complications are frequently associated with the polyurethane insulation of intracardially implanted pacemaker leads. For identification of insulation materials with improved properties, a suitable *in vitro* test setup is necessary. The present study focusses on the development of an *in vitro* oxidation model for analyzing the biostability of insulation materials under accelerated biochemical degradation mechanisms. A degradation of cylindrical Pellethane 80AE test specimens was conducted using three oxidizing test solutions (OS) of hydrogen peroxide and cobalt(II) chloride hexahydrate at 22°C, 37°C and 40°C. Surface morphological and structural changes of the insulation materials were analyzed in comparison to an untreated reference. Scanning electron microscopy showed degradation defects in the insulation surface of Pellethane 80AE, increasing with increasing concentrations of hydrogen peroxide and cobalt(II) chloride hexahydrate of the OS. Likewise confocal laser scanning microscopy revealed an increase of surface roughness with higher concentration and temperature of the OS. Evaluation of the chemical surface structure showed oxidatively induced changes in the soft segments representing known effects of polyurethane degradation. Thus, for a simulation of biochemically induced changes in the biostability of lead insulation materials such as Pellethane 80AE, an oxidizing test solution with a higher concentration of hydrogen peroxide at a test temperature of least 37°C is suitable to provoke significantly accelerated chemical degradation.

Keywords: pacemaker lead insulation material, polyurethane, *in vitro* biostability, oxidizing test solution.

1 Introduction

Accelerated *in vitro* test setups make a decisive contribution to the development of long-life pacemaker leads for particularly the identification of polymers with improved degradation properties. *In vitro* studies on the comparative investigation of the biostability of pacemaker lead insulation materials like Pellethane are already known from the literature [1-3]. The objective is to simulate the performance of an implanted pacemaker lead in the venous bloodstream, which is exposed to different degradation mechanisms, *in vitro*. Within the current study the composition and temperature of an *in vitro* oxidation model are optimized for investigating the degradation of insulation materials under oxidizing stress in an accelerated setup [4]. Targeted parameter adjustments are intended to achieve material degradation with clinically relevant damage patterns.

2 Materials and Methods

2.1 Test Specimen

Cylindrical test specimens of Pellethane 80AE (Lubrizol Corporation, USA) as an early insulation material for pacemaker leads with a length of 30 mm, an inner diameter of 2.25 mm and a wall thickness of 80 µm are used for *in vitro* testing.

2.2 Experimental Setup

Ten test specimens each were stored in six sealed glass vials with 60 ml of a respective test solution and incubated at temperatures of 22°C, 37°C and 40°C (Unimax 101 with Incubator 1000, Heidolph Instruments GmbH & Co. KG, Schwabach, Germany).

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To provoke oxidative degradation of the pacemaker lead insulation material, oxidizing test solutions were prepared using unstabilized hydrogen peroxide (H_2O_2) (AnalaR NORMAPUR 30%ig, VWR International, Radnor, PA, USA) and cobalt(II) chloride hexahydrate ($\text{CoCl}_2 \times 6 \text{H}_2\text{O}$) (Carl Roth GmbH & Co. KG, Karlsruhe, Germany) in three concentrations (OS-5, OS-10, OS-20), see **Table 1**. Ultrapure water (H_2O) (arium 611UV, Sartorius Stedim Biotech GmbH, Göttingen, Germany) were used to adjust the hydrogen peroxide concentration. An isotonic saline solution (NaCl 0.9%, B. Braun SE, Melsungen, Germany) was used as reference medium.

Table 1: Composition for 60 ml of the oxidizing test solutions for accelerated oxidative degradation of the lead insulation material, respectively [4]; based on DIN EN ISO 10993-13:2010-11 [5].

composition		Oxidizing test solution		
		OS-5	OS-10	OS-20
Concentration H_2O_2	[%]	5	10	20
Proportion CoCl_2	[M]	0.05	0.1	0.2
Volume of H_2O_2	[ml]	50	40	20
Volume of H_2O	[ml]	10	20	40
Volume of CoCl_2	[g]	0.70	1.43	2.85

OS = oxidizing test solution; H_2O_2 = hydrogen peroxide; CoCl_2 = cobalt(II) chloride hexahydrate; H_2O = ultrapure water

After 168 hours of storage in the respective test solution, the test specimens were removed, washed in ultrapure water at 22°C for 65 hours and then stored in a vacuum drying oven (Memmert GmbH + Co. KG, Schwabach, Germany) at 37°C and 5 mbar for 24 hours.

Three oxidizing test solutions and isotonic saline solution were used at a temperature of 22°C, 37°C and 40°C to investigate the influence of the composition and temperature of a test medium on the *in vitro* degradation behavior of Pellethane 80AE, see **Table 2**.

Table 2: *In vitro* analysis of Pellethane 80AE test specimens; test solutions are isotonic saline solution (NaCl 0.9%) and oxidizing solutions (OS) in three concentrations and at three temperatures.

Vial No.	Test specimen	Test medium
1	$n = 10$	NaCl 0.9%, 37°C
2	$n = 10$	Oxidizing test solution OS-5, 37°C
3	$n = 10$	Oxidizing test solution OS-10, 37°C
4	$n = 10$	Oxidizing test solution OS-20, 22°C
5	$n = 10$	Oxidizing test solution OS-20, 37°C
6	$n = 10$	Oxidizing test solution OS-20, 40°C

Subsequently, the surface morphological and structural changes of the lead insulation material were analyzed in comparison to an untreated reference.

2.3 Analysis of Changes in the Insulation

2.3.1 Scanning Electron Microscopy (SEM)

The polymer surfaces were imaged by means of scanning electron microscopy (Quattro S, Thermo Fisher Scientific Inc., USA) in low vacuum mode without any further preparation. The electron micrographs were obtained at a voltage of 6 kV using a secondary electron detector.

2.3.2 Confocal Laser Scanning Microscopy (CLSM)

For 3D visualization of the lead insulation surfaces, confocal laser scanning microscopy (LEXT OLS5000, Olympus, Japan) is used. Based on the acquisition of microscale features, the surface roughness is assessed by the area-related roughness values S_a and S_q via the arithmetic or quadratic mean of the topography height using the software Gwyddion (version 2.60, Český Metrologický Institut, Brno, Czech Republic).

2.3.3 Infrared Spectroscopy

Furthermore, investigations of changes in the chemical structure of the insulation materials (down to a depth of about 1 μm) are carried out using a spectrometer with diamond crystal (VERTEX70, Bruker Corporation, USA) for Fourier transform infrared spectroscopy under attenuated total reflectance (ATR-FTIR). For this purpose, wave spectra ($n = 5$) of the insulation surface of each test specimen is recorded between 500 cm^{-1} and 4000 cm^{-1} with a resolution of 4 cm^{-1} . Furthermore, a baseline correction is performed. For each measurement, 32 scans are averaged for a representative material spectrum. Subsequently, the signal heights are normalized with respect to the aromatic absorption peak at 1414 cm^{-1} for polyurethanes, as these peaks are described as stable for the respective material in the presence of an oxidative environment [1].

3 Results and Discussion

3.1 Surface Morphological Changes

Storage of the Pellethane 80AE test specimens in isotonic saline solution shows no morphological changes to the surface compared to the untreated reference. In contrast, storage of the test specimens in an oxidizing test solution shows an increased

occurrence of tiny defects and the appearance of superficial changes in the insulation surfaces with increasing concentrations of H_2O_2 and CoCl_2 , evenly distributed across the image section and increases further when the temperature of the test solution OS-20 is varied (see **Figure 1**). While the surface morphological changes are minor at a room temperature of approximately 22°C , when the test medium is heated to 40°C , pronounced insulation defects are evident on the entire insulation surface of the Pellethane 80AE test specimens.

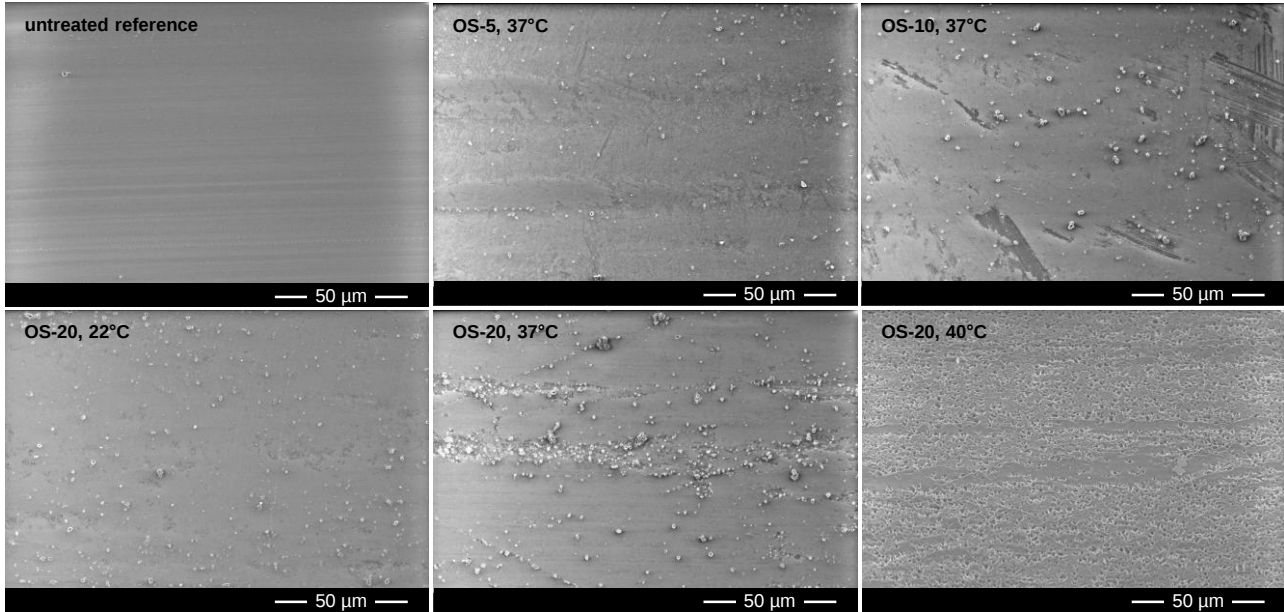


Figure 1: Comparative SEM images of the insulation surfaces of the Pellethane 80AE test specimens after 168 h of storage in oxidizing test solutions (OS) of different concentrations and temperatures compared to the surface of the untreated reference [4].

3.2 Comparison of Surface Roughness

Storage in physiological saline solution and OS-5 hardly leads to an increase in surface roughness compared to the untreated reference ($S_a = (24 \pm 3) \text{ nm}$, $S_q = (31 \pm 2) \text{ nm}$). However, the insulation surfaces of the test specimens show a higher mean arithmetic (S_a) and square (S_q) height value when exposed to an oxidizing test solution with a concentration that is increased further (see **Table 3**).

Table 3: Surface roughness of Pellethane 80AE test specimens; mean arithmetic (S_a) and square (S_q) height value for different compositions and temperatures of the oxidizing test solution (OS); mean value $\pm$ standard deviation ($n = 50$) [4].

roughness value	NaCl 37°C	OS-5 37°C	OS-10 37°C	OS-20 22°C	OS-20 37°C	OS-20 40°C
S_a [nm]	31 ± 4	19 ± 1	70 ± 2	33 ± 4	65 ± 6	169 ± 20
S_q [nm]	42 ± 5	26 ± 2	86 ± 3	43 ± 5	90 ± 8	224 ± 27

Furthermore, increasing the temperature leads to further increase in surface roughness according to the sequence $40^\circ\text{C} > 37^\circ\text{C} > 22^\circ\text{C}$. Changes in the surface microstructure of the test specimens stored in OS-20 are shown in **Figure 2**.

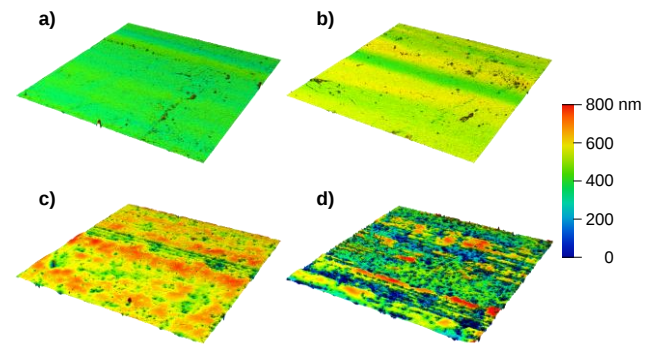


Figure 2: Exemplary height profiles of the surfaces of the Pellethane 80AE test specimens; untreated reference (a) and surfaces microstructures for OS-20 at 22°C (b), 37°C (c) and 40°C (d) [4].

3.3 Evaluation of Changes in the Chemical Surface Structure

Evaluation of changes in the chemical surface structure of the Pellethane 80AE test specimens is carried out by evaluating representative FTIR spectra with regard to additional absorption bands (peaks) and changes in the signal height for relevant wavenumbers (see **Figure 3**).

Oxidatively induced changes in the soft segment are reflected in a significant loss of the ether absorption at 1110 cm^{-1} and the methylene absorption at 1367 cm^{-1} , representing known effects of polyurethane degradation.

A decrease in the non-hydrogen-bonded carbonyl absorption at 1730 cm^{-1} and the urethane C-O-C absorption at 1080 cm^{-1} is characteristic for hydrolysis of the urethane bonds connecting the hard and soft segments. The change in the signal height of the urethane C-N absorption near 1220 cm^{-1} is less pronounced.

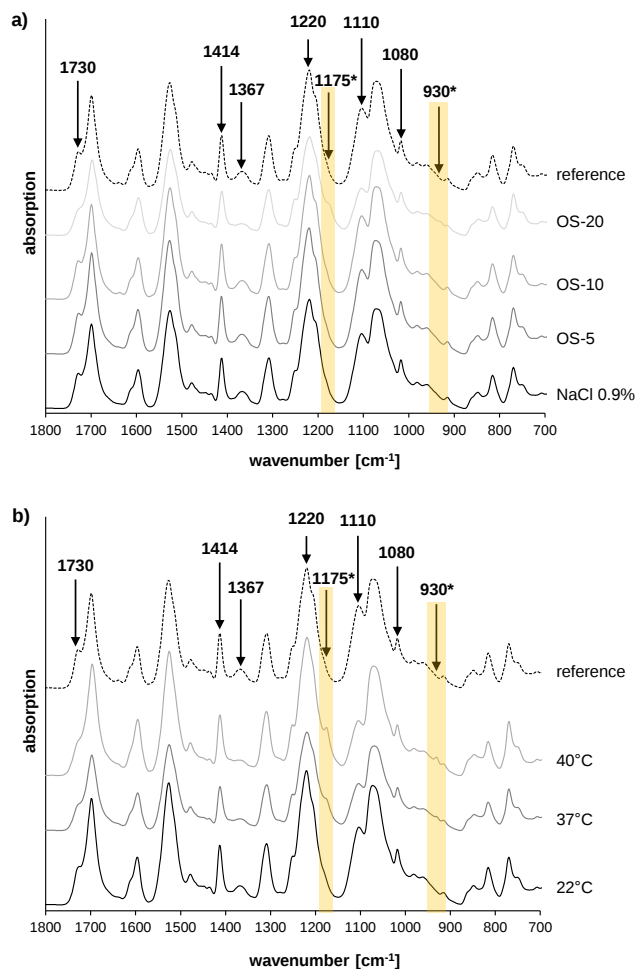


Figure 3: FTIR absorption spectra for Pellethane 80AE test specimens after storage (a) in different test solutions at 37°C and (b) at different temperatures of OS-20 in comparison to an untreated reference [4]. * marks additional peaks in the absorption spectrum

At the wavenumbers 1110 cm^{-1} , 1367 cm^{-1} and 1730 cm^{-1} the ratio of peak heights compared to the reference increases with increasing concentration and temperature of OS [4]. The additional absorption bands at 1175 cm^{-1} observed for OS-20 at 37°C and 40°C are attributed to branched ethers due to crosslinking of the polyether soft segment, while the bands at 930 cm^{-1} are attributed to either OH bending or aliphatic CO_2H associated with degradation of the soft segment [1].

4 Conclusion

Application of an *in vitro* oxidation model allows the physiological simulation of induced changes in the biostability of lead insulation materials, such as Pellethane 80AE. The studies conducted to establish the model show that future studies should be performed at least at 37°C in an OS-20 test solution to provoke significantly accelerated chemical degradation of the insulation. However, the surface morphological damage patterns obtained can only be compared to clinically occurring damage patterns to a limited extent. It was demonstrated that extending a biochemical *in vitro* oxidation model with biomechanical bending stress leads to damage patterns of pacemaker lead insulation materials such as Pellethane 2363-55DE comparable to clinically occurring insulation defects [2].

Author's Statement

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