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# Cytotoxicity of Catalysed Silicone Resin Coatings for Smart Biomedical Devices

**Abstract:** Equipping medical devices with smart technologies holds great potential for the development of modern medical products. The development requires the identification of new integration strategies and the research of new material combinations due to the miniaturization of systems and increasing production figures. The realization of Smart Biomedical Devices requires a sufficient barrier effect (bioprotection) by appropriate encapsulation of the electronic components. Thinnest polymer coatings have proven to be suitable for conformal encapsulation. The aim of the study was to investigate the fundamental suitability of thin-film lacquers added with catalysts as coating materials for electronic systems with regard to their biological use. Due to long curing times of up to 14 days, eight different catalysts based on different chemical structures were added to the coating materials and their influence on a cytotoxic effect was investigated. A non-cytotoxic effect was observed for the organometallic catalysts based on tin, zirconium, titanium, bismuth, and tertiary amine. Most were resistant to steam sterilization. The curing time of the non-cytotoxic coatings could be significantly reduced by the addition of catalysts. The shortening of process times is an important economic aspect in the production of mass-produced Smart Biomedical Devices.

**Keywords:** Biocompatibility, bioprotection, silicone resin, coatings, catalysts, cytotoxicity, smart medical devices.

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## 1 Introduction

The use of electronic assemblies in contact with the biological environment requires barrier-acting and at the same time biocompatible protection of the electronics [1, 2]. In the narrower sense, this so-called bioprotection means that they must not exert any toxic effect on biological systems, in particular by releasing harmful substances from the electronics [3]. In the broader sense, however, this also means that integrated electronics must withstand the stresses caused by the biological system in its electronic functionality while guaranteeing maximum reliability [4, 5]. Reliability is synonymous with the multitude of requirements for medical devices that are described in numerous directives and legal regulations [6].

Metallic, ceramic, or polymeric material encapsulations are used as protective coatings [7]. In addition to protection against environmental influences [8], the task of these encapsulation materials is the electrical insulation of the integrated electronics [9]. Inorganic materials, such as metals and ceramics, fulfil the requirement to prevent functional failures due to the absence of moisture because of their hermeticity [7, 10]. Protection concepts based on metals and ceramics are increasingly reaching their limits with the growing demand for low-cost electronic components with short cycle times in production, but also in view of the continuous trend towards miniaturization [11]. By integrating electronic components into plastics, these developments can be countered much better. However, in the case of polymeric protective coatings there is a risk of moisture penetration [12, 13] due to their moisture absorption when the plastic is used carelessly, incorrectly or contaminated. Plastics, on the other hand, have good dielectric properties [10], which is why they will form the most important material group for the protection of smart systems in the future in the context of wirelessly communicating IoMT electronics [2].

Polymer coatings such as biocompatible parylene (CVD coating), lacquers, or pottings are used as standard to protect electronics [5]. Silicone-based coatings, such as silicone epoxides, are used for biomedical applications due to the biocompatibility of certain materials [14]. However, the availability of sterilization-resistant, biocompatible and at the same time barrier-effective coatings and pottings in humid environments is currently still very limited. In addition, depending on the polymer and curing mechanism, long curing times and thus long process times are required. Catalysts are used to accelerate the curing of polymer coatings. Various standard catalysts that have already been investigated have

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been classified as cytotoxic [15]. Tin catalysts are one of the most commonly used and versatile catalysts used in polymer production. This is mainly due to its high catalytic effect even in low concentrations, its high tolerance to other components of the coating materials, and its stability against environmental influences. Research is looking for possible alternatives to tin-free catalyst systems with a similarly good effect [16-18]. Bismuth carboxylates and zirconium chelates which promise a lower toxicity than tin complexes [18-21] are a main focus of the investigations.

The aim of the study was to investigate various protective coatings with the addition of catalysts to achieve shorter curing times. The core of the investigations was the suitability for medical use. These include in particular the resistance to disinfection and sterilization as well as the testing of biocompatibility [22]. A decisive criterion for the assessment of biocompatibility is the cytotoxicity of the materials in contact with the biological environment [23].

# 2 Materials and Methods

## 2.1 Coating Materials

Four two-component silicone-based protective coatings were selected to protect electronic assemblies from Evonik Industries AG (Essen, Germany) (see Table 1). In previous studies [24], these were found to be non-cytotoxic. The mixture from resin to hardener was based on the manufacturer's formulation. The optimum proportion of catalyst for manageable processing and despite its rapid curing reaction was determined in an experimental preliminary study within the specified range of the manufacturer.

The organometallic catalysts based on tin TIB KAT® 216 and 417, titanium TIB KAT® 519, zinc TIB KAT® 616, bismuth TIB KAT® 717 (TIB Chemicals AG, Mannheim, Germany), zirconium KAT® A209 (King Industries Inc., Norwalk, USA), and the tertiary amine Polycat® DBU (Evonik Industries AG) were investigated. Desmodur® N 3600 (Covestro AG, Leverkusen, Germany) was preferred to Vestanat® HT 2500 LV as the hardener for Silikotop® E 901 due to its lower cytotoxic effect in the tests without catalysts. To confirm this, both polyisocyanates were tested with the catalyst K-KAT® A209. In order to improve the electrical and mechanical properties of Silikoftal® ED and Silikopon® EF, the silane-modified polyurethane prepolymer modification resin Albidur® 1223 (Evonik Industries AG) was added to the coating compounds.

The casting of the test specimens for the experiments was carried out using a compressed air controlled dispenser in biocompatible silicone molds (Silpuran® 2430 A/B, Wacker AG, Burghausen, Germany). For this purpose, a cylindrical specimen geometry with a diameter of 9.2 mm and a height of 2 mm was determined. Due to the higher layer thickness than specified by the manufacturer, the specimens were cured for at least 14 days for complete cross-linking before testing.

**Table 1:** Investigated coating resins from Evonik Industries AG (Essen, Germany).

| Resin | Chemical name | Hardener | Modif. | Catalyst | Chemical name | Mixing batch (wt%) | Pot life without/with catalyst |
|---|---|---|---|---|---|---|---|
| Silikotop® E 901 | Solvent-containing OH-functional silicone polyester | Desmodur® N 3600 | - | TIB KAT® 216 | Dioctyltin dilaurate (DOTL) | 100 : 73.3 : 0,3 | 30 min / 15 min |
| | | | - | TIB KAT® 417 | Dioctyltinoxide silane blend | 100 : 73.3 : 0,3 | 30 min / 15 min |
| | | | - | TIB KAT® 519 | Titanium ethyl acetoacetate complex | 100 : 73.3 : 0,3 | 30 min / 15 min |
| | | | - | TIB KAT® 616 | Zinc neodecanoate | 100 : 73.3 : 0,3 | 30 min / 30 min |
| | | | - | TIB KAT® 717 | Bismuth carboxylate | 100 : 73.3 : 0,3 | 30 min / 15 min |
| | | | - | K-KAT® A209 | Zirconium chelate complex | 100 : 73.3 : 0.25 | 30 min / 20 min |
| | | Vestanat® HT 2500 LV | - | K-KAT® A209 | | 100 : 73.3 : 0.25 | 30 min / 20 min |
| Silikoftal® EF | Silicone epoxy resin | Dynasylan® Ameo | - | Polycat® DBU | Tertiary amine diazabicycloundecene | 100 : 23.4 : 3.7 | 8 h/ 15 min |
| | | | Albidur® 1223 | | | 100 : 18.5 : 23.4 : 4.3 | 8 h/ 15 min |
| Silikopon® ED | Silicone epoxy resin | Dynasylan® Ameo | - | Polycat® DBU | | 100 : 23.4 : 3.7 | 8 h/ 15 min |
| | | | Albidur® 1223 | | | 100 : 18.5 : 23.4 : 4.3 | 8 h/ 15 min |
| Silikophen® AC 1000 | Methylpoly-siloxane resin | - | - | Tego® Kat 1 | Tetra-n-butyl titanate | 100 : 3 | 2-3 h / 90 min |

## 2.2 Cleaning and Sterilization Process

The specimens were cleaned for five minutes each in dynamic full contact with acetone and isopropanol 70%. An optical inspection was then carried out. The samples packed in autoclave bags were steam sterilized at 121°C, 2 bar, 20 min for one cycle. Two independent casting batches ($r = 2$) of $n = 16$ test specimens each were tested.

## 2.3 Cell culture

Fibroblasts of cell line Hs 27 were used to test biocompatibility for *in vitro* cytotoxicity according to the standard DIN EN ISO 10993 by a CCK-8 assay. The cell culture medium used was Dulbeccos's Modified Eagle Medium (DMEM, without Na pyruvate, +3.7 g/l $NaHCO_3$, +4.5 g/l D-glucose). To this 5% fetal bovine serum (FBS) was added, as well as 1% each of the antibiotic penicilin and 1% each of the antibiotic amphotericin B. The incubation (37°C, 10% $CO_2$) was performed with eluates with an extraction time of seven days. The cells were inoculated and incubated for 72 hours. The vitality test to measure mitochondrial cell activity was performed with the tetrazolium salt WST-8. The proliferation rate was determined by measuring the colour change by photometry. Two independent test runs ($m = 2$) with $n = 3$ test specimens were performed and $i = 3$ eluate samples were taken from a sample with one test specimen each.

# 3 Results and Discussion

For the TIB KAT® 616 a reduction of the pot life could hardly be determined with a proportion of 0.3%. Furthermore, there was a massive development of gas bubbles in the test specimens, so that this catalyst was excluded for further investigations.

## 3.1 Cleaning and Sterilization

The test specimens of the tested material combinations proved to be resistant to cleaning with acetone and isopropanol in a dynamic full contact of 5 min each.

The coating materials Silikotop® E 901, Silikoftal® ED and Silikopon® EF proved resistant to steam sterilization. They only showed optically recognizable peculiarities, but no changes in haptics and hardness could be observed. Opacity of Silikotop® E 901 cleared within two weeks. Silikopon® EF with the modification resin Albidur® 1223 showed a clear white turbidity which remained stable. It should be added that the layer thickness of the test specimens cannot be compared with the usual layer heights of the lacquers of 60–80 µm.

Silikophen® AC 1000 proved to be unstable in steam sterilization. The material embrittled until it broke without mechanical force. After curing, the test specimens showed a concave curvature which was an indication of internal residual stresses. These stresses may have been increased by thermal expansion due to the application of temperature during the sterilization process [25]. In addition, the coating is suitable for a layer height of 20–25 µm. Silikophen® AC 1000 was only subjected to cleaning for further investigation with regard to cytotoxicity.

## 3.2 Cytotoxicity

The coating materials were tested for their non-cytotoxic properties in preliminary studies without the addition of catalysts [24]. Figure 1 shows the results of the eleven material combinations with catalysts.

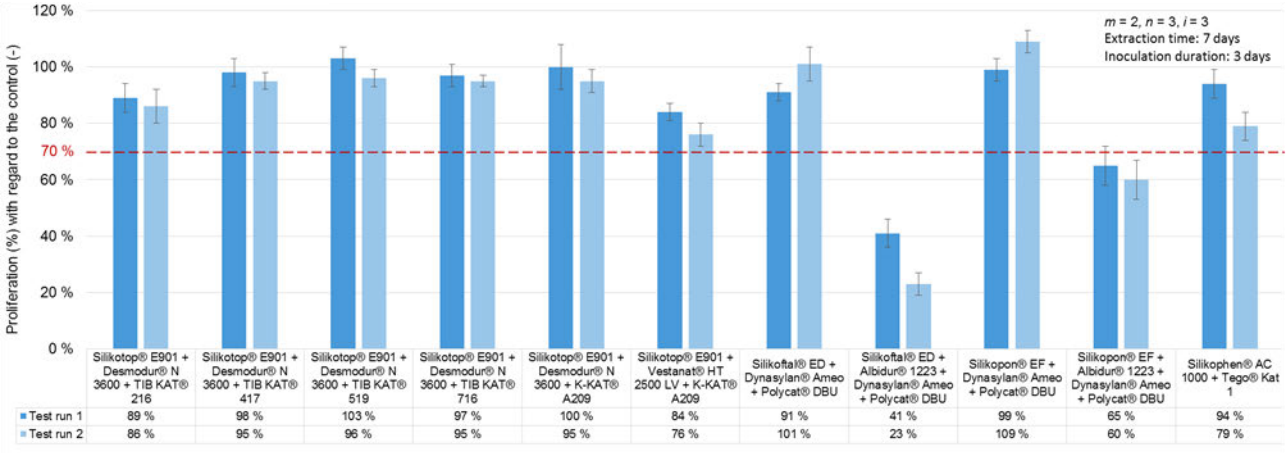


**Figure 1:** Result of the *in vitro* cytotoxicity tests according to DIN EN ISO 10993-5 and -12 in two independent test runs ($m = 2$).

The material combinations with Silikotop® E901 turned out to be non-cytotoxic with regard to the proliferation rates in comparison to the reference (≥ 70%, significant, $p << 0.05$). In particular, the catalysts TIB KAT® 417 (dioctyl tin oxide silane blend), TIB KAT® 519 (titanium), TIB KAT® 716 (bismuth) and K-KAT® A209 (zirconium) in combination with the polyisocyanate Desmodur® N 3600 each had a very low cytotoxic effect with proliferation rates of over 90%. Although the catalyst TIB KAT® 216 (DOTL) also showed no cytotoxic effect, the proliferation rates in both test runs were comparatively lower at 89% and 86%, respectively. In preliminary studies, Vestanat® HT 2500 LV in combination with K-KAT® A209 had a lower proliferating effect than Desmodur® N 3600 with K-KAT® A209, corresponding to the better non-cytotoxic effect of the hardener Desmodur® N 3600 (99%) without the addition of catalysts compared with the polyisocyanate Vestanat® HT 2500 LV (91%). The proliferation rates of both test runs differed by less than 10%. Compared to the first test run, the decrease in the proliferation rate in the second test run was not significant ($p > 0.05$) for Silikotop® E 901 with Desmodur® N 3600 and K-KAT® A209, TIB KAT® 216, 417, and 716. For Silikotop® E 901 with Desmodur® N 3600 and TIB KAT® 519 as well as Silikotop® E 901 with Vestanat® HT 2500 LV and K-KAT® A209 the decrease was significant ($p < 0.05$).

The material combinations based on Silikopon® EF and Silikoftal® ED also showed no cytotoxic effects without the addition of modifications (≥ 70%, significant, $p << 0.05$). This corresponded to the non-cytotoxic detection of the catalyst DBU at a concentration of 0.5 mg/ml [26]. There were significant fluctuations ($p < 0.05$) between the two test runs of 10% ($p < 0.05$). The modification resin Albidur® 1223 showed a significant reduction of the proliferation rate with Silikoftal® ED to below 70%. Silikopon® EF modified with Albidur® 1223 showed a not significantly lower proliferation rate of 65% ($p = 0.05987$) in the first test run. However, a second test run confirmed the cytotoxic effect.

Silikophen® AC 1000 showed no cytotoxic effect, however, a difference of 15% was observed in the proliferation rates of the two test runs. This was due, among other things, to the cleaning instead of sterilization that was carried out which, due to the lack of sterility level, can lead to problems caused by possibly remaining potentially toxic microorganisms in a biological environment. Since Silikophen® AC 1000 showed excellent properties for the realization of Smart Biomedical Devices (e.g. low viscosity, no cavities in the coating, thin walls), this material should be sterilized by other permissible methods [22].

In general, deviations may occur in *in vitro* experiments with cell cultures when sowing cells with deviations in cell count and due to variations in proliferation rates. Furthermore, minimal variations in the preparation ratio due to gravimetric weighing had to be taken into account. Complete mixing of the batch is absolutely necessary, as uncrosslinked monomers have a cytotoxic effect [27]. Especially with the modification resin Albidur® 1223, inhomogeneities may have occurred in manual mixing due to high viscosity (35,000 mPa•s at 23°C). Insufficient crosslinking using a DBU catalyst can lead to the release of a higher concentration of the DBU, resulting in a cytotoxic effect [26].

# 4 Conclusion

In this study, the silicone resin coatings Silikotop® E901, Silikophen® AC1000, Silikoftal® ED, and Silikopon® EF (Evonik Industries AG) were tested for their resistance to alcoholic cleaning with acetone and isopropanol, steam sterilization at 121°C, 2 bar, 20 min, and *in vitro* cytotoxicity according to DIN EN ISO 10993-5 and -12 by adding eight different catalysts to shorten the curing times. The eleven material combinations tested proved to be resistant to cleaning when stored for five minutes in full dynamic alcohol contact. With the exception of Silikophen® AC 1000, the lacquers and their combinations with the catalysts were resistant to steam sterilization. A non-cytotoxic effect was observed for the organometallic catalysts based on tin (TIB KAT® 216 and 417, TIB Chemicals AG), zirconium (KAT® A209, King Industries Inc.), titanium (TIB KAT® 519), bismuth (TIB KAT® 717), and the tertiary amine Polycat® DBU (Evonik Industries AG). In particular, Silikotop® E 901 crosslinked by Desmodur® N 3600 using these catalysts proved to be particularly promising for electronics encapsulation for medical applications. With the corresponding mixing ratios, particularly high proliferation rates compared to the reference could be demonstrated. Silikoftal® EF and Silikopon® ED also achieved the expected advantages. However, the modification resin Albidur® 1223 should not be used as the addition of this resin led to a cytotoxic effect according to our study.

The curing time of the non-cytotoxic coatings could be significantly reduced by the addition of catalysts. The shortening of process times is an important economic aspect in the production of mass-produced Smart Biomedical Devices.

**Author Statement**

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## References


[1] Werner VMK, Artmann L, Eblenkamp M. Protective Coat for Electronics and Body: Barrier Effect of Polymer Coatings for Encapsulation Smart Biomedical Devices. Kunststoffe international: 16–19.

[2] Suppa M, Peters W. Schutzlacke für elektronische Baugruppen: Anwendungsgebiete, Anforderungsprofile, Merkmale, Verarbeitung. 1st ed. Kempen: Lackwerke Peters 2010.

[3] Werner V, Eblenkamp M. Biokompatible Integration von IoT-Elektronik in Kunststoffbauteile. In: VDI Verlag GmbH, editor. Kunststoffe in der Medizintechnik: VDI Verlag GmbH; 2018: 45–65.

[4] Hassler C, Boretius T, Stieglitz T. Polymers for neural implants, 1 (49). Journal of Polymer Science Part B: Polymer Physics 2011: 18–33.

[5] Bartels O, Benedek C, Brennenstuhl W, et al. Leitfaden Anwendung und Verarbeitung von Vergussmassen für Elektronische Baugruppen 2010.

[6] Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI) und des Bundesinstitutes für Arzneimittel und Medizinprodukte (BfArM). Anforderungen an die Hygiene bei der Aufbereitung von Medizinprodukten. Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz 2012; 55: 1244–1310.

[7] Jiang G, Zhou DD. Technology advances and challenges in hermetic packaging for implantable medical devices: Implantable Neural Prostheses 22009.

[8] Teo AJT, Mishra A, Park I, Kim Y-J, Park W-T, Yoon Y-J. Polymeric biomaterials for medical implants and devices 4 (2). ACS Biomaterials Science & Engineering 2016: 454–472.

[9] Licari JJ. Coating materials for electronic applications. Polymers, processing, reliability, testing, William Andrew 2003.

[10] Lechleitner T, et al. Barriereschichten für med. elek. Implantate. VIP, Vol. 15 (5) 2003: 241–244.

[11] Qin Y, Howlader M, Deen MJ, Haddara YM, Selvaganapathy PR. Polymer integration for packaging of implantable sensors, (202). Sensors and Actuators B: Chemical 2014: 758–778.

[12] Osenbach JW. Corrosion-induced degradation of microelectronic devices, 2 (11). Semiconductor science and technology 1996: 155.

[13] Vanhoestenberghe A, Donaldson N. Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices, 3 (10). Journal of Neural Engineering 2013: 31002.

[14] Ma B, Liu S, Gan Z, et al. A PZT Insulin Pump Integrated with a Silicon Micro Needle Array for Transdermal Drug Delivery: 677–681.

[15] Tanzi MC, Verderio P, Lampugnani MG, Resnati M, Dejana E, Sturani E. Cytotoxicity of some catalysts commonly used in the synthesis of copolymers for biomedical use. J Mater Sci: Mater Med 1994; 5: 393–396.

[16] Florio J, Ravichandran R, d. Switala, Hsieh B. Non-Tin catalysts for alkoxy silane polymers. European Coating Journal 2016: 48–55.

[17] Schellekens Y, van Trimpont B, Goelen P-J, et al. Tin-free catalysts for the production of aliphatic thermoplastic polyurethanes. Green Chem 2014; 16: 4401–4407.

[18] Guhl D. Alternatives to DBTL catalysts in polyurethanes. A comparative study. Polyurethanes for High Performance Coatings, European Coatings Conference 2008: 119–137.

[19] Sardon H, Irusta L, Fernández-Berridi MJ. Synthesis of isophorone diisocyanate (IPDI) based waterborne polyurethanes: Comparison between zirconium and tin catalysts in the polymerization process. Progress in Organic Coatings 2009; 66: 291–295.

[20] Blank WJ, He ZA, Hessell ET. Catalysis of the isocyanate-hydroxyl reaction by non-tin catalysts. Progress in Organic Coatings 1999; 35: 19–29.

[21] Blank WJ. New Developments in Catalysis. Macromolecular Symposia 2002; 187: 261–270.

[22] Wintermantel E, Ha S-W, editors. Medizintechnik: Life Science Engineering; Interdisziplinarität, Biokompatibilität, Technologien, Implantate, Diagnostik, Werkstoffe, Zertifizierung, Business. 5th ed.

[23] Pizzoferrato A, Ciapetti G, Stea S, et al. Cell culture methods for testing Biocompatibility. Clinical Materials 1994; 15: 173–190.

[24] Werner VMK, Artmann L, Eblenkamp M. Schutzschild für Elektronik und Körper: Barrierewirkung polymerer Beschichtungen zur Kapselung von Smart Biomedical Devices. Kunststoffe: 45–48.

[25] Bonten C. Kunststofftechnik: Einführung und Grundlagen. 2nd ed. München: Hanser 2016.

[26] Havla JB, Lotz AS, Richter E, et al. Cartilage tissue engineering for auricular reconstruction: in vitro evaluation of potential genotoxic and cytotoxic effects of scaffold materials. Toxicology in vitro: an international journal published in association with BIBRA 2010; 24: 849–853.

[27] Goldberg M. In vitro and in vivo studies on the toxicity of dental resin components: a review. Clinical oral investigations 2008; 12: 1–8.