Isopropyl Myristate Modified Silicone as a Potential New Encapsulating Material for Implantable Devices

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ABSTRACT: A new modified silicone was obtained by the physical entrapment of a hydrophobic lipid, isopropyl myristate (IPM), to improve the encapsulation properties and corrosion resistance of medical electronic implants. Differences between the water transport for films in contact with water vapor versus those in contact with liquid water were identified; they showed increased permeability to water vapor, which was possibly the result of differences in the water organization at the hydrophobic film interface. Improvements, including enhanced scratch resistance and adhesion, in the mechanical properties of the modified material was also achieved. The incorporation of IPM further resulted in a significant improvement in the cell biocompatibility compared with the unmodified polymer; this suggested that the IPM combination could be a viable basis for implant device packaging. © 2010 Wiley Periodicals, Inc. J Appl Polym Sci 119: 2917–2924, 2011

Key words: biocompatibility; coatings; silicones

INTRODUCTION

Silicone elastomers are widely used as biomaterials for the coating of medical devices and implants because of their well-known and commonly accepted biocompatibility and bioinertness. Nevertheless, basic materials properties could still be further optimized.[1] The generic advantage of these elastomers, however, is that they can, respectively function as durable dielectric insulators, a barrier against matrix-induced contamination and as stress relieving shock/vibration adsorbers over a wide range of humidities and temperatures.[2] The production of catheters, stents, cardiac leads, tracheal intubators,[3] soft contact lenses,[4] and plastic surgery implants[5] is commonly silicone based, and now, silicones have become the industry standard for the encapsulation of implantable electronic devices.[6] However, a major concern in these applications is the resistance to water transport, particularly through relatively thin barrier layers; this leads to device reliability issues through hydration, corrosion, and degradation processes, which are compounded by possible delamination.[7] Thus, it was reported that the main failure of a visual prosthesis is attributable to the ingress of moisture; such moisture could originate as water vapor or as condensed water[8] and could cause a failure of adhesion between the encapsulant and the microelectronic device, in which the creation of voids and condensation could occur.[9] Eventually, when enough water diffuses through an encapsulant to create a continuous water path at the device interface, the presence of entrained ions and any electrical bias promotes electrocorrosion.[10] This accelerates the surface degradation, which puts at risk device functionality over the longer term.

Several solutions at the molecular level exist to reduce the water permeability through polymeric membranes. First and most important is control through modification of the chemical structure of the polymer, influencing, for example, the chain polarity and hydrophobicity.[11–13] The permeability of polymers toward gases decreases with increasing polymer polarity, largely because of the higher activation energy for diffusion in a polar polymer.[14] Conversely, polar polymers are poor water barriers because water is soluble in such polymer phases.[15]

Polymer stereoregularity promotes closer chain packing and crystallinity, both of which also decrease permeability.[16,17] The orientation of polymer molecules has a further effect on permeability,[17] the extent of which depends on the type of polymer and the degree of orientation. This can also lead to

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anisotropic permeability behavior. Interchain crosslinking can also reduce permeability,[18] especially where the original noncrosslinked phase can be swollen by the penetrant. Finally, the addition of a plasticizer to a polymer causes increased segmental mobility, which effectively lowers the glass-transition temperature and causes a reduction in the barrier properties.[19]

The entrapment of an additional hydrophobic agent, a synthetic lipid, as part of a silicone membrane to mimic human skin[20] has proved a useful means of testing drug transport. In particular, it appears that for skin, it is an intercellular lipid matrix that is essential to the barrier properties of skin, and drug permeation is radically altered after the extraction of skin lipid.[21]

It was considered, however, that the incorporation of the highly hydrophobic isopropyl myristate (IPM) into a silicone matrix would not only increase the surface water repellency but, through reduced water solubility in the bulk phase, reduce water transport.

A further possible benefit of lipid incorporation into silicone is a slower aging of the material *in vivo.* One cause of aging of silicone breast implants, for example, has been identified to be lipid infiltration from tissue; this results in a loss of the mechanical properties and failure of the elastomer.[22] Pre-entrapment of a synthetic lipid should saturate the matrix with a defined, controlled agent and help to reduce the further impact of body lipid ingress, thus slowing any effect on aging.

A further concern with regard to the development of new materials for biomedical applications is the regulatory approval process.[23] Although synthetic polymer chemistry is a powerful and convenient materials modification tool, this leads to major regulatory challenges when any new chemistry is applied. Concerns would exist, for example, about the residual synthetic side products, their bioeffects, and the longevity of any facile surface chemical modification in the face of a chronic tissue degradative response at the implant locus. Both medical-grade silicones and IPM have the advantage that they are already approved for clinical use, and the use of physical entrapment eliminates the problems of covalent binding, with its uncertainty of unknown reaction side products. Such a modified material should, thus, experience a shorter approval pathway.

EXPERIMENTAL

Sample preparation

Medical-grade, unrestricted (for >30 days *in vivo* contact) silicone rubber (MED-4211) was used for this study, except for the scratch and delamination studies, which also used unrestricted silicone rubber (MED-6215). Both silicone systems were two parts platinum-catalyzed commercial products of Nusil Technology (Bakersfield, CA). The materials are both used routinely for medical device packaging, although for the handling and formation of surface films, MED-6215 is more satisfactory because it is less viscous before curing; it also generates a marginally harder coating.[24]

In the preparation process, part A of either MED-4211 or MED-6215 was dissolved in heptane (VWR International, United Kingdom) at a concentration of 20% (w/v) and was stirred until solution homogeneity was obtained (2–3 h). Next, IPM (Fluka, Gillingham, UK) was added (with stirring) in various amounts as required (specified with the results). For preliminary studies, the following lipids were added: cholesterol (CH), behenyl oleate (BO), and 4-methylumbelliferyl stearate (4MB). All of these were purchased from Sigma-Aldrich (Gillingham, UK) and were used without further purification. Finally, part B of the relevant system was added to give a ratio of 10 : 1 (A : B) and subsequently stirred to give a homogeneous mixture. After 1 h, the material was ready to be used for sample preparation. The material (4 mL) was cast on to a polystyrene Petri dish followed by incubation at 65°C for 4 h. After that, silicone films were gently removed from the Perti dish and placed on a glass plate for further heat treatment at 100°C for 2 h and then at 150°C for 45 min.

METHODS

Contact angle

Contact angle measurements were performed by a contact angle rig (CAM 200, KSV Instruments, Helsiniki, Finland) set up with at least five readings for each sample, with water as a wetting agent by the sessile drop method.

Water-vapor transport

We determined the water-vapor transmission by fixing a silicone membrane over the open mouth of a 50-mL glass conical flask containing a known amount of water (~ 10 mL). Membranes were additionally sealed at the sides with Parafilm. Measurements of the water-vapor transport, based on the gravimetric determination of vaporized water,[25] were taken after 1 week of exposure to ambient air. All samples were run in parallel so that all samples were subject to identical changes in the ambient relative humidity.

Liquid-water-transport measurement

A specially designed device was used to determine water transmission from liquid water through the

silicone membranes. It consisted of two parts: a screwed, open circular upper clamp ($r = 22.5$ mm) and a lower component of a known amount of hygroscopic agent (anhydrous $CuSO_4$, ~ 2 g, Fluka) in a weighing boat. A silicone membrane was mounted between the two parts with paste sealant to ensure a leak-proof seal. After 1 week of immersion of the construct in distilled water at a temperature of 37°C, the weight of $CuSO_4$ was remeasured to determine the hydrate formation and, therefore, the water transport through the membrane.

Membranes both for water-vapor and liquid-water transport measurements were vacuum-dried at 60°C for 4 h to remove any residual water before the studies.

Mechanical tests

Scratch test

A silicon wafer coated with a single layer of Nusil MED-6215 silicone (used as a control sample) was coated with additional layers of either unmodified or 1% IPM-modified silicones (MED-4211 or alternatively MED-6215). The scratch resistance of such laminates was then determined by the following experimental setup: (1) a wafer was attached to a steel plate by double-sided adhesive tape; (2) a specially designed device with a beveled stainless steel needle was mounted on a tensile tester, such that the needle pushed into the wafer with a constant force; and (3) the device was moved with a constant vertical velocity of 25 mm/min to make a scratch. The scratch resistance was determined by measurements taken with an optical microscope of the width of the created fissure.

Adhesion test

The same samples described in the scratch test were cut into 50×10 mm^2 rectangular pieces, and then, a silicone layer strip was removed up to about 20 mm and clamped onto the upper part of a tensile tester. The remaining silicon adherent sample was clamped to the lower surface. Once the sample was mounted, increasing force was applied and measured at the moment when the additional silicone flap started to delaminate. The value of this force was a direct indicator of the strength of adhesion.

Biocompatibility

The test chosen was the direct cell contact assay and was carried out in conformity with ISO10993-5:1999 with 3T3 mouse fibroblasts. Because the end point of the standard test is a relatively subjective observation of the cell morphology, it has become common practice to supplement this with a quantitative evaluation of cell proliferation. Here, we used the resazurin-based AlamarBlue dye reduction assay.

Samples of 10×10 mm^2 were cut for testing. Both positive- and negative-toxicity polymer samples were included in the test. The negative-toxicity controls were 13-mm Thermanox cover slips (Nalgene Nunc, type 174950, lot 551810, Roskilde, Denmark). ISO 10993-5 standard organotin-plasticized poly(vinyl chloride) (Portex, type 499/400/000 lot 30375, Ashford, UK) was used for the positive-toxicity controls. Cell growth in the presence of the test and control materials was compared to growth in standard multiwell tissue culture plates.

Cell culture

The Swiss albino murine fibroblast cell line 3T3 (ECACC reference number 93061524) was obtained from mycoplasma-free stocks held within the Institute of Cell and Molecular Biology. The cells were cultured in Eagle's minimal essential medium (D5546, Sigma, Gillinham, UK) supplemented with a 1% penicillin/streptomycin solution (10,000 U/mL of each antibiotic, Gibco Invitrogen, type 15140-122, lot 1268409, Paisly, UK) and 10% heat-inactivated calf serum (Biosera, Ringnver, UK South American origin, catalog number S 1810/500).

Toxicity test

The test materials were immersed overnight in 100% ethanol (analytical-reagent grade, Fisher Scientific, code E/0605 DF/17, batch 0613664) in a Petri dish and kept overnight within a class II laminar flow cabinet. The materials were then washed three times in phosphate buffered saline and subsequently washed with Eagle's minimal essential medium containing 3% (w/v) penicillin/streptomycin.

The test and control materials were placed into 24 well plates, each containing three replicates for the three test materials and the negative and positive controls. Each test material was used in two replicate cell culture plates so that a total of six replicate determinations were carried out for each material. Once the test and control materials were positioned in the plate, 1 mL of cell culture medium containing 3T3 cells at a density of 1×10^4 cells/mL was added to the wells. The tests for this group of materials were carried out in two parts, with duplicate cell culture plates used in each part.

A 10% solution of AlamarBlue (1 mL, Biosource, type DAL1100, lot 146581SA, Paisly, UK) in cell culture medium was added to each well. The plates were placed back into the incubator for 4 h at 37°C to allow the reduction of the dye. A sample of the medium was then removed from each well, and its optical density was measured with a fluorescence

plate reader (Bio-TEK Synergy HT, Potton, UK) with excitation filters at 530–560 nm and emission at 590 nm. The resulting fluorescence signal was proportional to the amount of AlamarBlue dye that had been converted to the reduced form by the metabolic action of the cells and so was a measure of the number of metabolically active cells.

At the end of each dye incubation period, the dye-containing medium was removed, the cells were washed once, and then, 1 mL of fresh cell culture medium was added. The cells were then returned to the incubator until the next measurement point.

RESULTS AND DISCUSSION

Preliminary lipid screening

The strategy for creating a new material with potential use as a coating for implantable microdevices was centered here on a modified commercially available silicone. Lipids were selected as modifiers with the possibility of creating a water-impermeable barrier through a shift to hydrophobic properties, the aim being to extend the coated implant lifetime.

Four lipids, IPM, CH, BO, and 4MB, were investigated.

Contact angle measurement was used for a preliminary assessment of the modified material water repellency.[26]

The contact angle measurements for the Nusil MED-4211 silicone modified with various lipids at 1% (w/v) are shown in Figure 1. All of the lipids, except CH, gave high contact angles, which confirmed a hydrophobic effect when they were incorporated into the silicone. CH actually significantly reduced the contact angle, presumably because of the surface exposure of its hydrophilic hydroxyl

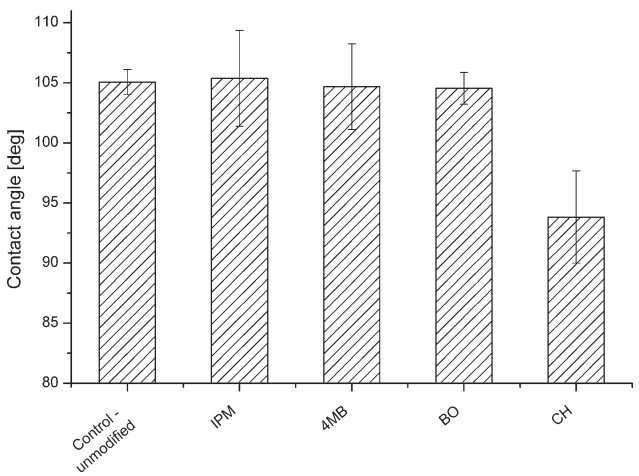

Figure 1 Water–polymer surface contact angle measurements of lipid [1% (w/v)]-modified MED-4211 silicone membranes with water. The data are expressed as the mean value plus or minus the standard deviation ($n = 5$).

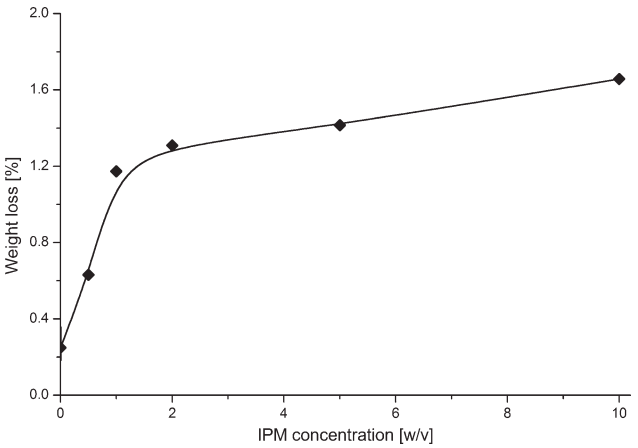

Figure 2 IPM-modified silicone membranes immersed in phosphate buffer with BSA solution for 30 days at pH 7.0.

group. Although any effect of IPM was marginal and not statistically significant, it was an attractive lipid within this group because of its prior use in biomedicine. For example, it was reported not to cause significant inflammatory change to outer human stratum corneum in a comparative study with rat skin.[27] Also, it is widely used in deeper dermis layers to enhance drug flux through the skin, for example, of estradiol.[28] The hydrophobicity of the material gives a good basis for reducing device surface wetting through its inner surface contact with that device; liquid-water tracking along the silicone–substrate interface would be less likely to occur.

IPM behavior in the polymer matrix

Modified silicone membranes were exposed to phosphate buffered saline (pH 7.4) and bovine serum albumin (BSA; 40 mg/mL) solution at 37°C for 30 days to evaluate any protein influence on the IPM stability. Figure 2 shows that with increasing IPM concentration, the weight loss of the silicone membranes immersed in BSA increased. We concluded that BSA had an additional effect and that as an amphiphile, it appeared to solvate the IPM, assisting its release from the silicone matrix. It is known that BSA has surfactant properties and that it can penetrate a polymer matrix, particularly a loosely packed polymer layer, regardless of its thickness, provided there is sufficient polymer chain flexibility.[29] The diminishing leaching effect at higher IPM loadings was possibly due to a saturation of the BSA-mediated removal process because of the finite concentration of BSA available for solubilization.

Water permeability

The most important feature of an encapsulating material, and the primary aim of the silicone IPM

modification, is water resistance. One aspect to this is water uptake, that is, water residing within the polymer at saturated equilibrium; the other is water transport through the silicone membrane phase, a more direct indicator of the membrane barrier properties. A further contributor to water resistance is the strength of adhesion to the substrate;[8] adhesion should be strong enough to prevent the problem of condensed-water tracking alone between the coating and the device after delamination.

Water-vapor transport

The permeation of a gas or vapor through a polymer film is thought to involve the following stages: adsorption of the permeating species onto the polymer surface, solubilization in the polymer matrix, diffusion through the film down a concentration gradient, and desorption from the opposite surface.[10]

Remarkably, an upward trend of increased water-vapor transport with increasing IPM concentration was observed (Table I).

As far as water-vapor transport through a membrane is concerned, two phenomena, nucleation and clustering on the hydrophobic surface, contribute to the diffusion process.[30]

In this case, nucleation could probably be neglected because the availability of any hydrophilic sites for water molecule nucleation was extremely low because the polymer and lipid were hydrophobic and the likelihood of hydrophilic impurities, for example, in the form of ionic salts is practically zero.

Clustering on the other hand, can occur when mutual penetrant–penetrant interactions at the surface are stronger than those of the penetrant–polymer, which certainly appeared to be the case for the hydrophobic poly(dimethyl siloxane) (PDMS).[31] Hence, water clusters were likely to have been created on the hydrophobic surface. However, from a modeling study,[32] it would appear that the chances of significant penetration of the water clusters from the surface to bulk PDMS and cluster formation within the PDMS were highly improbable.

Therefore, it seemed reasonable to conclude that transport involved nonaggregated water transport through the membrane.

TABLE I
Effect of the IPM Concentration on the Water-Vapor Transport Through the Modified Silicone Membranes over 7 Days

Material	Water transport (mg/cm^2)
Control: Aluminum	1.653 ± 0.0
Unmodified silicone	49.992 ± 0.010
0.5% w/v IPM-modified silicone	55.566 ± 0.011
1% w/v IPM-modified silicone	55.687 ± 0.023
2% w/v IPM-modified silicone	59.122 ± 0.016
5% w/v IPM-modified silicone	63.065 ± 0.005

The data are expressed as the mean value plus or minus the standard deviation ($n = 3$).

TABLE II
Liquid-Water Transport Through the IPM-Modified Silicone Membranes: IPM Concentration Dependence

Material	Water transport (mg/cm^2)
Aluminum	2.096 ± 0.114
Unmodified silicone	65.924 ± 0.460
0.5% w/v IPM-modified silicone	63.263 ± 0.520
1% w/v IPM-modified silicone	61.785 ± 0.183
2% w/v IPM-modified silicone	62.327 ± 0.184
5% w/v IPM-modified silicone	62.633 ± 0.116

The data are expressed as the mean value plus or minus standard deviation ($n = 3$).

Liquid-water transport through modified silicones

Compared with the reference aluminum foil film, the silicones allowed substantial water transport. The nominal amount seen for the aluminum indicated the experimental error during measurement due to transient $CuSO_4$ exposure to ambient air during apparatus assembly. Improved water resistance was observed (Table II) with increasing IPM concentration up to 1% (w/v), but a further increase in the IPM concentration had no apparent effect on the water transmission through the membranes; however, any observed effect with IPM was small in any case.

The results were quite the reverse of the water-vapor trends; this may have been because, with liquid-water interfacial clustering, known to be prevalent in such membranes,[33] this precluded initial water uptake. On the silicone membrane, liquid water was exposed to the repelling action of IPM molecules across all of the available surface area. However, although IPM at the membrane surface might have repelled water aggregates in the liquid state, it evidently did not sufficiently suspend the flux of monomeric water vapor. This may have been because of the availability of microchannels for the transport of water vapor that were not available to liquid water, for example, because of wall effects at hydrophobic surfaces. The presence of such open structures suggested on the basis of these findings would be difficult to confirm structurally by a high-resolution vacuum or other technique because of the liquid nature of the IPM.

Mechanical endurance

The reason for the tested use of an additional layer of silicone (either MED-4211 or MED-6215) over the

TABLE III
Scratch Test Results of Various Double Silicone Layers Measured as the Average Value of the Created Fissures

Material	Average width (mm)
Control	174.06 ± 13.72
MED-4211	107.24 ± 15.14
MED-4211+1% w/v IPM	42.76 ± 11.20
MED-6215	129.36 ± 6.28
MED-6215+1% w/v IPM	132.81 ± 12.02

The data are expressed as the mean value plus or minus the standard deviation ($n = 5$).

standard microelectronic silicone wafer coated with MED-6215 was to enhance the water repellency of the coating and to further optimize the mechanical properties of the eventual coating, as applicable to specific implanted devices. The dual-layer approach allowed for both the incorporation of a more resistive IPM and the prevention of direct adhesion problems of this layer on the silicon substrate. This principle of dual function or laminate layers is one that will allow for a combination of specialist properties that are unlikely to be met by a single material.

Scratch test

The introduction of any additional overlaying silicone layer significantly improved the scratch resistance of the substrate, as reflected in the observed lower scratch width (Table III). Also, modification of the MED-4211 silicone with IPM had the greatest effect on the scratch resistance. Improved scratch resistance is accompanied, with some advantage, by an increase in elasticity in a modified material.[20] The greater scratch resistance of MED-4211 was consistent with its more elastic nature, as a less hard material. A more elastic material would also conform more readily to natural tissue mechanics and follow the irregularity of any device surface. Another advantage of increased elasticity is that such materials are less vulnerable to mechanical damage during the implantation process itself, for example, to scratching by surgical instruments or during handling.

Adhesion

The results of the adhesion strength determination between the silicone base MED-4211 material and either unmodified or 1% (w/v) IPM-modified additional silicone layers are shown in Figure 3. Modification for both kinds of silicone resulted in a lower strength of adhesion, but when a double coating was used (with a silicone first layer), the adhesion was at least as good as that with a control single silicone adherent layer, that is, the standard coating. Therefore, a double layer had advantages, and if delamination did occur, it took place at the silicon substrate and silicone–polymer interface rather than between the two polymeric silicone layers.

The good adhesion between the two silicone layers, regardless of IPM inclusion, was likely to have resulted from polymer chain intercalation between the two layers; past the initial curing stage, some remodeling of the matrix occurred. Adhesion to the impermeable silicon would have been limited to weaker adsorption forces only.

In conclusion, the introduction of an additional layer of silicone improved the mechanical properties of the coating, and moreover, when IPM-modified silicone was used, the coating was further improved in terms of water repellency, as stated previously.

Biocompatibility

A quantitative assessment of cell growth in each well as a whole was provided by the AlamarBlue dye reduction test. The test produces a fluorescent signal of arbitrary units that is proportional to the number of viable cells in each well. The comparative effect of these materials on cell growth is best assessed if growth is normalized to that in the negative-toxicity (no material present) control. From this, the mean background fluorescence without cells (coefficient of variation <5%) was subtracted from all other measurements, and cell growth was expressed as a proportion of the matching cell-only control in the subsequent analysis.

The comparative cell growth at 96 h is shown in Figure 4, and effectively summarizes the findings.

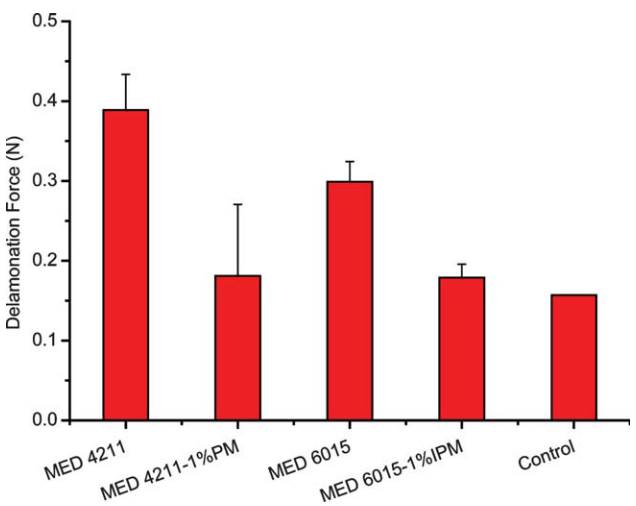

Figure 3 Adhesion test results of various double silicone layers measured as the minimum force required to start a single-layer pealing process. The data are expressed as the mean value plus or minus the standard deviation ($n = 3$).

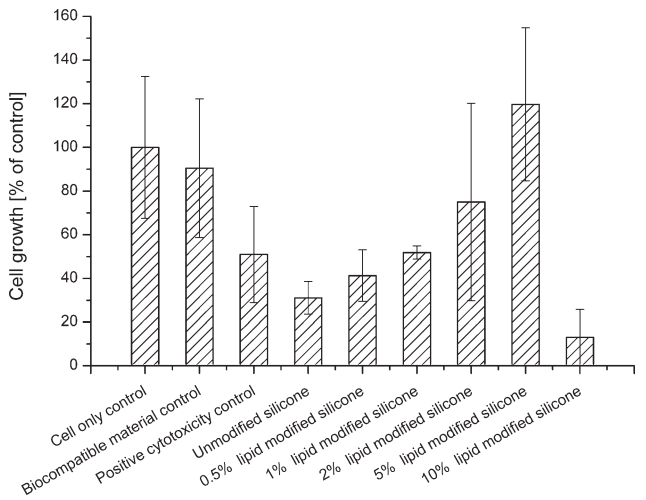

Figure 4 Relative cell growth at 96 h. The data are expressed as the mean value plus or minus the standard deviation ($n = 12$ for the controls and 6 for the test materials). An indicative statistical analysis was performed for the 96-h incubations with a one-way analysis of variance coupled with Bonferroni's multiple comparison test[34] to evaluate the differences between the materials (GraphPad Prism version 4.02, La Jolla, CA). The significance was taken at $p < 0.05$.

The biocompatible control performed better than the tested materials, and despite the nominal reported acceptability of silicones as a biocompatible implant material, the silicone formed here performed less well than this, except the MED-4211 with 5% IPM. However, there was no statistical difference between the biocompatible material control and all of the test incubations other than the MED-4211 with 10% IPM, which had significantly less growth than all of the other incubations.

The evident cytotoxicity effect strongly suggests that there were retained leachables in the material, despite the use of the standard forming and curing processes. Further studies are warranted to analyze both the nature of these components and the time course of their loss from the material. The latter is, in any case, likely to be greater in protein-loaded growth medium than in simple buffer because of the surfactant properties of protein. This finding also indicates the need to critically evaluate individual silicone coatings to determine the degree of cytotoxic material leaching; a universal assumption about silicone inertness for medical implants may not be appropriate in all situations, unless batch-by-batch cytotoxicity testing is done. The evident *in vivo* biocompatibility of commercially prepared silicones may be due to proprietary, extensive prewash processes. Even with this, however, residual leachables will exist at low levels, unmasked by long terms of the hydration of silicone. Accordingly, a thorough quantitation is warranted of explanted materials to determine the extent of the ongoing release of leachables. Nevertheless, it is evident that there was a dose-dependent improvement in the silicone biocompatibility as the IPM concentration was increased up to 5% (w/v) IPM. This may have been the result of the partial masking of the surface by the IPM or by the IPM serving as a sink for organic, lipophilic leachable agents. The very poor biocompatibility seen with 10% (w/v) IPM suggested a quite different process; it was likely here that the high relative amounts released had a direct adverse effect on the cells. The interactivity of released IPM as a reservoir of toxic leachables also warrants analysis. The optimum level of IPM with regard to biocompatibility was at least 5% (w/v) on the basis of these results, however, because of the need for mechanical integrity of the layers, long-term stable retention of the IPM, and a better hydration resistance of films, 1% (w/v) would be a safer starting point.

In conclusion, the results show that the unmodified MED-4211 used in this study, as prepared, had a substantially lower biocompatibility than the biocompatible control, but the incorporation of IPM resulted in a dose-dependent increase in cell growth on the material up to a concentration of 5%. The inclusion of 10% IPM resulted in much less cell growth than that which occurred in the unmodified material. Thus, it appears that IPM up to 5% increased the short-term biocompatibility of this silicone rubber to a significant degree.

CONCLUSIONS

A potentially useful candidate material was established as possible packaging material and laminate for passive microelectronic device surfaces. The preliminary coating of a range of microelectronic devices with IPM-modified silicone showed promising results for its functionality and *in vitro* compatibility.[35] Furthermore, some reduction in the water permeability of the modified material, although not evident to a major degree, offered an improved protection barrier against water ingress that may be of cumulative importance over extended periods of implantation. In combination with the better biocompatibility, the material would be of potential use for *in vivo* devices.

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