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Preparation of irritant polymer samples for an in vitro round robin study

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ABSTRACT

A round robin study using reconstructed human epidermis (RhE) tissues was conducted to test medical device polymer extracts for skin irritation potential. Test samples were four irritant and three non-irritant medical device polymers. Five of these polymer samples were developed and two were obtained commercially. The three non-irritant samples were comprised of 100% 80A polyurethane, one-part silicone, and polyvinyl chloride (PVC). The polyurethane samples were made using a hot-melt process, while the silicone samples were created by mixing and casting. The PVC samples were commercially produced sheets. The four irritant samples were comprised of one-part silicone and 25% heptanoic acid (HA), two-part silicone and 15% sodium dodecyl sulfate (SDS), PVC and 4% Genapol® X-100, and PVC and 5.8% Genapol® X-080. The HA, SDS, and Genapol® X-100 samples were produced using the mixing and casting method, while the Genapol® X-080 sheet samples were obtained commercially. During development, irritant polymer samples were extracted using polar and non-polar solvents that were subsequently analyzed chemically. Samples with sufficient levels of extracted irritants were tested on RhE tissues to confirm their irritation potential. Polymers that passed this screening test were used in the round robin study described elsewhere in this special edition.

1. Introduction

Biocompatibility assessment is an important aspect of the preclinical safety evaluation of medical devices. The globally harmonized ISO 10993 series of standards govern this process. As required by ISO 10993-1: 2009, dermal irritation is one of three biological effects that must be addressed for all medical devices regardless of the nature or duration of their body contact (ISO, 2009). Currently the Draize rabbit skin irritation test is used for this purpose (Draize et al., 1944; ISO, 2010).

This special edition of Toxicology In Vitro describes a round robin study designed to determine if reconstructed human epidermis (RhE) models are suitable replacements for the rabbit skin irritation test. Prior to this study, a proof-of-concept pilot project was conducted using medical device polymer extracts spiked with irritant chemicals and dosed on RhE tissues (Casas et al., 2013). Briefly, eleven medical device polymers were evaluated using EpiDerm™ EPI-200 tissues from MatTek Corporation (Ashland, Massachusetts, USA). Saline and sesame oil extracts were prepared for all polymers. Half of the extracts were spiked with two R-38 irritants, lactic acid in saline and heptanoic acid in sesame oil. The reduction of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was used to assess cellular viability in the RhE tissues. The authors reported that the EpiDerm™ EPI-200 tissues were able to accurately identify low levels of the two R-38 irritants in the dilute medical device extracts, which were complex mixtures. Casas et al.'s pilot project results were successfully reproduced by two labs in Europe (National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; MatTek In Vitro Life Science Laboratories (IVLSL), Bratislava, Slovakia). This prompted ISO Technical Committee 194's Working Group 8 (WG8), which is responsible for the ISO 10993-10

Abbreviations: DEHP, Diethylhexyl phthalate; DINP, Diisononyl phthalate; DPBS, Dulbecco's phosphate-buffered saline; ECVAM, European Center for Validation of Alternative Methods; EC_{50}, Effective concentration 50%; ESBO, Epoxidized soybean oil; HA, Heptanoic acid; IVLSL, In Vitro Life Sciences Laboratories; LA, Lactic acid; LC-MS, Liquid chromatography–mass spectrometry; NIHS, National Institute of Health Sciences, Japan; PTFE, Polytetrafluoroethylene; PU, Polyurethane; PVC, Polyvinyl chloride; RhE, Reconstructed human epidermis; RIVM, National Institute for Public Health and the Environment, The Netherlands; SA, Saline; SDS, Sodium dodecyl sulfate; SO, Sesame oil; WA, Water

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standard on irritation and sensitization, to sponsor an international round robin validation study. A key requirement of this study was that the test samples had to be medical device polymers that contained irritants that could be extracted according to ISO 10993-12 criteria (ISO, 2012).

When the round robin began, WG8 was unable to identify any commercially available medical grade skin irritating polymers. Consequently, two working group member companies volunteered to make the needed irritant polymers. These two medical device manufacturers, Medtronic plc (Minneapolis, Minnesota, USA) and Arthrex, Inc. (Naples, Florida, USA), both had polymer laboratories and Medtronic had an analytical chemistry laboratory with experience extracting and testing medical device materials.

This article summarizes studies that were performed to develop and test irritant polymer samples for the round robin validation study. Key findings are presented and discussed.

2. Materials

2.1. Medical device polymers

The test samples made for this study were comprised of the following medical grade polymers:

- A one-part, translucent, solvent-free silicone adhesive that cures at room temperature upon exposure to ambient moisture. Composition: 94% Silicone; 5% Silanetriol, ethyl-,triacetate; and 1% Silanetriol, methyl-, triacetate.
- A two-part, translucent, pourable silicone elastomer that features room temperature and heat accelerable curing. Part A composition: ≤60% Dimethyl siloxane, dimethylvinyl-terminated; and 15–40% Trimethylated silica. Part B composition: > 60% Dimethyl siloxane, dimethylvinyl-terminated; and 10–30% Dimethyl, methylhydrogen siloxane.
- A clear custom-made polyvinyl chloride (PVC) that contained diisononyl phthalate (DINP; 30–60%) as a plasticizer.
- A translucent 80A thermoplastic polyurethane elastomer polyether that may be processed by extrusion or thermoforming.

Due to confidentiality non-disclosure agreements, the brand names and commercial suppliers of these polymers are omitted. In addition, two other polymers were obtained from the National Institute of Health Sciences (NIHS), Division of Medical Devices in Tokyo, Japan. The first polymer, Y-1, was comprised of 61.3% PVC, 33.7% DEHP, and 4.9% EBSO [w/w]. The second polymer, Y-4, was comprised of 57.8% PVC, 31.8% DEHP, 5.8% Genapol® X-080, and 4.6% EBSO [w/w] (Haishima et al., 2014).

2.2. Irritant chemicals

The following irritants were used in the polymer test samples:

- Heptanoic acid (HA; CAS No.: 111–14-8; ≥99% purity; Sigma–Aldrich Company, St. Louis, Missouri, USA).
- Sodium dodecyl sulfate (SDS; CAS No.: 151-21-3; ≥99% purity; Sigma–Aldrich Company, St. Louis, Missouri, USA).
- Genapol® X-080 (X-080; ethoxylated isotridecanol; CAS No.: 9043-30-5; mixture; Sigma–Aldrich Company, St. Louis, Missouri, USA).
- Genapol® X-100 (X-100; ethoxylated isotridecanol; CAS No.: 9043-30-5; mixture; Sigma–Aldrich Company, St. Louis, Missouri, USA) (structurally similar to X-080).
- Reagent grade DL-lactic acid (LA; CAS No.: 50-21-5; 90–100% purity; Sigma–Aldrich Company, St. Louis, Missouri, USA). Composition: 61.5% lactic acid; 38% calcium lactate; 1.2% silicone dioxide; and 1.9% water.
- Food grade lactic acid powder (CAS No.: 50-21-5; 38% purity; Galactic, Milwaukee, Wisconsin, USA).

2.3. Extraction solvents

Physiological saline (NaCl; CAS No. 7647-14-5; liquid; 0.9%; Sigma-Aldrich Company, St. Louis, Missouri, USA) was used as the polar solvent. The non-polar solvent was Super Refined™ Sesame Oil NF-NP, USP grade (Croda, Inc., Edison, New Jersey, USA).

2.4. RhE tissues

The reconstructed tissue model EpiDerm™ Skin Irritation Test (EPI-200) (OECD, 2015) with Modulated Dose (100 µL) and exposure period (18 h, no post-incubation) (known as EpiDerm™ SIT-MD) was used in this study (MatTek IVLSL, Bratislava, Slovak Republic). SkinEthic™ RHE tissues (OECD, 2015) with Modulated Dose (100 µL) and exposure period (24 h) were also used (EpiSkin, Lyon, France).

3. Methods

The irritant and non-irritant polymer samples were prepared by the following processes.

3.1. Irritant samples

3.1.1. Heptanoic acid – one-part silicone

The first irritant polymer was made as follows: the silicone was placed in a 20 g polypropylene mix cup and then enough HA was added to make a final sample that contained 25% HA by weight. The cup was capped and placed on a Speed-Mixer DAC 150 FV (FlackTek, Inc., Landrum, South Carolina, USA) where the following sequence occurred: (1) mix at 1000 rpm for 30 s to initiate blending, and then, if needed, (2) use a metal spatula and mix by hand to facilitate better contact between the oily irritant and liquid silicone; and then (3) mix at 3500 rpm for 1 min. This process was repeated as necessary until the mixture appeared to be fully blended, which never exceeded four repeats. After the material was completely mixed, it was cast into uniform-sized samples. Large Teflon® casting blocks with a dozen surface cutouts measuring 1 cm × 1.5 cm × 1.5 mm deep were used for this purpose (Fig. 1). Enough HA-silicone was transferred with a metal spatula into the surface cutouts on a casting block so that it was flush with each block's surface. The blocks were placed in a laminar flow laboratory fume hood and allowed to cure overnight. Once cured, the samples were removed from the cutouts and any flash was trimmed off. The cured samples were placed into 20 mL borosilicate amber glass vials with hard plastic caps lined with PTFE (Part number: 02-993-253. Thermo Fisher Scientific, Waltham, Massachusetts, USA).

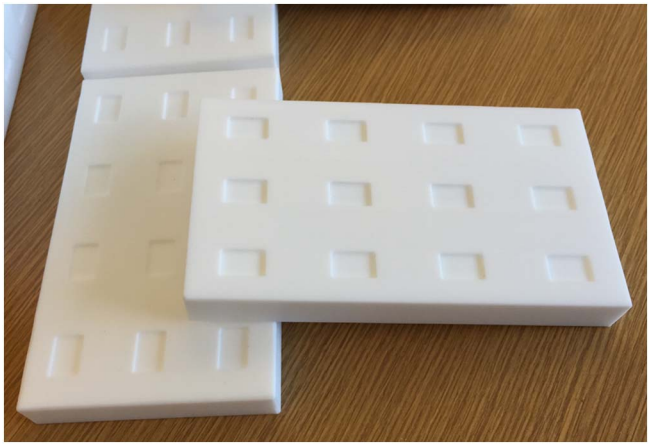

Fig. 1. Teflon® blocks for casting polymer samples.

3.1.2. Sodium dodecyl sulfate – two-part silicone

The second irritant polymer was made by first hand mixing powdered SDS into Part A of the two-part silicone, then adding Part B, so that the final SDS loading level was 15% by weight. Mixing was done with disposable medical tongue depressors in wax-lined food grade disposable cups. After the material was completely mixed, enough SDS-silicone was transferred with a metal spatula into the surface cutouts on each Teflon® casting block so that it was flush with the block's surface. The blocks were placed in a laminar flow laboratory fume hood and allowed to cure overnight. When cured, the samples were removed from the cutouts and any flash was trimmed off. The cured samples were placed into amber glass vials.

3.1.3. Genapol® X-100 – PVC

The third irritant polymer was made by hand mixing liquid Genapol® X-100 with PVC.

Mixing was done with disposable medical tongue depressors in wax-lined food grade disposable cups. After the material was completely mixed, enough X-100-PVC was transferred with a 50 mL pipette into the surface cutouts on each Teflon® casting block so that it was flush with the block's surface. To facilitate curing, the casting blocks were pre-heated to 177 °C in an oven. As soon as the polymer was loaded onto the blocks they were returned to the oven for 30 min, after which they were allowed to cool on a laboratory benchtop. When cured, the samples were removed from the cutouts and any flash was trimmed off. The cured samples were placed into amber glass vials.

3.1.4. Y-4 polymer

The Y-4 polymer was prepared by the NIHS. Briefly, PVC powder (100 g) was added gradually under stirring with a spatula to a mixture of DEHP (55 g) and ESBO (8 g) containing Genapol® X-080 (10 g) to yield a final composition of 57.8% PVC, 31.8% DEHP, 5.8% Genapol® X-080, and 4.6% EBSO [w/w]. Complete plasticization of the PVC was accomplished by stirring and heating to 100 °C (Haishima et al., 2014). The Y-4 polymer was provided in sheet form.

3.2. Non-irritant samples

3.2.1. Polyurethane elastomer

After considering the properties of the selected materials, it was concluded that the heat involved with forming thermoplastic polymers might degrade the chemical irritants, which, in turn, could result in extraction rate variability. Therefore, the 80A thermoplastic polyurethane (PU) elastomer was chosen to be a non-irritant sample. In brief, preparation was as follows: (1) PU pellets were dried in a 60 °C vacuum over for at least 16 h to remove any residual moisture, which could produce bubbles in pressed films; (2) The dried pellets were placed between two sheets of PTFE-coated release paper and covered by two 15 cm × 15 cm metal framing plates; (3) This sandwich assembly was placed between two 237 °C platens and compressed slowly for 45 s until the pellets melted and filled the 1.5 mm thick, 15 cm × 15 cm frame; (4) The melted sandwich was compressed to 6 metric tons and held for 1 min. After 1 min the pressure was increased to 18 metric tons and held for an additional minute; (5) The pressure was released and the assembly immediately moved to an adjacent room temperature press and placed in between the platens. This cools the assembly for 1–2 min and the polymer film (Fig. 2) is pulled from the release paper; and (6) a large paper cutter is used to slice the film into samples that are 1 cm × 1.5 cm × 1.5 mm thick.

3.2.2. One-part silicone

A second non-irritant sample was prepared using the room temperature vulcanized one-part solvent-free silicone adhesive. The large Teflon® casting blocks were used for this purpose. Briefly, the cutouts were filled with enough silicone so that it was flush with the casting block's surface. The blocks were placed in a laminar flow laboratory fume hood and allowed to cure overnight. Once cured, the samples were removed from the cutouts and any flash was trimmed off. The cured samples were placed in amber glass vials.

Fig. 2. Thermoplastic 80A polyurethane elastomer film use to create non-irritant polymer samples.

3.2.3. Y-1 polymer

The Y-1 polymer was prepared by the NIHS. Briefly, PVC powder (100 g) was added gradually under stirring with a spatula to a mixture of DEHP (55 g) and ESBO (8 g). Complete plasticization of the PVC was accomplished by stirring and heating to 100 °C (Haishima et al., 2014). The Y-1 polymer was provided in sheet form.

3.3. Chemical analysis

Preliminary samples of silicone and PVC irritant polymers were extracted for 72 h at 37 °C using saline and sesame oil per ISO 10993-12 (ISO, 2012). The irritants in the extract solutions were identified and quantified by LC-MS. The LC-MS consisted of a Waters Acquity LC separation module and an Applied Biosystem 4000 QTrap system. The specific irritant chemicals were used to tune the mass spectrometer to determine ionization conditions. Standard curves for each analyte were prepared for quantification.

3.4. RhE testing of irritant polymers

Polymer samples with sufficient levels of extracted irritants were tested on RhE tissues to confirm their irritation potential. These analyses were conducted in accordance with the OECD Test Guideline 439 on In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method (OECD, 2015). Both EpiDerm™ SIT-MD and SkinEthic™ RHE tissues were used in these studies, which were conducted by RIVM, MatTek IVLSL, and Nelson Laboratories, Inc. (Salt Lake City, Utah, USA). The apical surfaces of tissues were dosed with 100 µL extract aliquots. Positive and negative solvent controls were included. Tissues were kept in humidified incubators at 37 °C with 5% CO_2. Incubation times were 18 h (EpiDerm™ SIT-MD) and 24 h (SkinEthic™ RHE). After

incubation and rinsing with PBS, cell viability was determined by the colorimetric MTT reduction method. Cell viability reduction > 50% was indicative of skin irritation. This threshold is based on analyses conducted during ECVAM's international validation study of in vitro skin irritation assays, which determined that cell viability in RhE assays between 43% and 74% resulted in the maximum sum of sensitivity and specificity (Spielmann et al., 2007). Therefore, ECVAM selected a standard MTT-determined cell viability of 50% to provide reproducible and optimized test performance.

This EC_{50} level is now widely accepted as the standard threshold for skin irritation in RhE assays. In addition, the same cut-off value proved to work reliably in studies of cosmetic formulations with low irritation potentials. These studies were conducted under similar experimental conditions and overall design as the current medical device protocol (see Faller et al., 2002). Also in the current study, the 50% threshold proved to be indicative of correct prediction of irritation response. This cell viability was tested in a pre-validation study conducted between 2013 and 2016 whose data can be found in Kandárová et al. (TIV this issue).

4. Results

Table 1 provides a summary of LC-MS results for extracts from the final four irritant polymer samples.

Table 1
Extraction results for the final irritant polymer samples.

Polymer sample (form)	Extraction concentrations (ppm)	
	Polar (solvent)	Non-polar (solvent)
One-part silicone + 25% HA[a] (castings)	ND (SA)[c]	22,000 (SO)[c]
Two-part silicone + 15% SDS[a] (castings)	13,000 (SA)[c]	12 (SO)[c]
PVC + 4% Genapol® X-100[b] (castings)	3920 (WA)[d]	7840 (IPA)[d]
Y-4 (PVC + 5.8% Genapol® X-080) (sheets)	678 (SA)[c]	ND (SO)[c]

HA = heptanoic acid; SDS = sodium dodecyl sulfate; PVC = polyvinyl chloride; SA = saline; SO = sesame oil; ND = not detected; WA = water; IPA = isopropyl alcohol.

[a] Irritant loading levels represent weight percent [w/w].

[b] Irritant loading levels represent volume percent [v/v].

[c] Medtronic Materials Characterization Laboratory (2014–16); 72 h extractions at 37 °C ($n = 1$).

[d] DakkS (2017) Test Report on PVC Spiked Samples; 72 h extractions at 50 °C (n = 1).

Figs. 3–6 summarize the EpiDerm™ SIT-MD tissue testing results for the final four types of irritant polymer samples. Data for SkinEthic™ RHE tissues are not shown because they were very similar to the EpiDerm™ SIT-MD results.

5. Discussion

The goal of this project was to prepare irritant and non-irritant polymers for use as test samples in a round robin in vitro irritation study. Three irritant polymers and two non-irritant polymers were developed for this purpose, while one additional irritant and one non-irritant polymer were obtained from the NIHS.

5.1. Preliminary polymer studies

Initially, three irritants and four polymers were chosen for this project. The irritants: lactic acid (LA), HA, and SDS were selected because they were R-38 skin irritants with differing octanol-water partition coefficients (log Kow values of −0.72, 2.42, and 1.60, respectively). Moreover, LA and HA had been used successfully by Casas et al. (2013) during their proof-of-concept study, and SDS is widely used as a positive control for in vivo and in vitro skin irritation testing. Latter in the project, a fourth irritant, Genapol®, a polyethyleneglycol monoalkyl ether non-ionic surfactant, was added. Genapol® is the hemolytic agent in a reference material called Y-4, which is produced by the NIHS (Haishima et al., 2014). The polymers: one-part silicone, two-part silicone, PU and plasticized PVC were chosen because they're soft, easy to work with, and widely used in the medical device industry.

Early efforts to make irritant polymers were trial-and-error experiences that often led to failures. Such failures occurred with liquid LA in one-part silicone, PVC, and PU; powdered SDS in one-part silicone; irritant oils alone or in combination with SDS in two-part silicone; food grade powdered LA in one-part silicone; and “sugared doughnut” samples of food grade powdered LA on one-part silicone.

The key challenge faced during this process was being able to incorporate sufficient amounts of irritant into a polymer so that its extracts would contain enough irritant to cause a positive response in RhE tissues. Often, if irritant loading levels became too high (e.g., 25–35% [w/w]), then the polymer's physical integrity was impaired. When this happened, it would not cure properly, which led to materials with the consistency of yogurt or toothpaste that were not suitable for the round robin study. Differences in polarity between the polymers and irritants presented difficulties, as well. Lastly, incomplete mixing that produced inhomogeneous polymer/irritant materials may have been responsible for inconsistent results from samples of liquid LA in PVC, which led to their abandonment.

5.2. Final polymer studies

Typically, two or three loading levels of an irritant chemical were tried in a polymer to establish how much its matrix could accommodate. Then standard ISO 10993-12 extraction studies were completed with polar (saline) and non-polar (sesame oil) solvents that would be subsequently analyzed by LC-MS to determine irritant concentrations. Based on the irritant-RhE tissue effective concentration (EC_{50}) range-finding study done by Casas et al. (2013), plus human patch test and in vitro assay protocols, along with aqueous elution results reported by Haishima et al. (2014), the concentration ranges targeted were as follows: 2% for HA, 1% for SDS, and 0.1% for Genapol®.

If the extracted irritant concentrations were near their targeted levels, then an adequate number of samples would be cast and shipped for RhE testing to either Nelson Laboratories, Inc., MatTek IVLSL, or RIVM. These laboratories would extract the cured samples following the same ISO 10993-12 recommendations and use the extracts to dose RhE tissues. The objective of these screening tests was to confirm that enough irritant was present in one or both of the extracts to drive cell viability below 50%, the RhE threshold for irritation. Also, saline and sesame oil extracts from several non-irritant polymers were tested on RhE tissues to verify that they would not cause an irritation response. These studies found that the non-irritant polymers produced RhE tissue results that were comparable to the assay's negative control, which was Dulbecco's phosphate-buffered saline (DPBS) (data not shown).

Table 1 summarizes the results of LC-MS studies conducted on polar and non-polar extracts of the four final irritant polymers. Depending upon the polarity of the solvent and log Kow of the irritant, sometimes no irritant would be detected in one of the extraction solvents. For example, HA's log Kow is 2.42 and it was very soluble in sesame oil, but not detected in saline. Also, the discrepancy between the extract levels of Genapol® X-080 and X-100 may be due to their differing extraction temperatures (50 vs. 37 °C) and the fact that each contains different plasticizers. Additionally, extracts from non-irritant polymers were not analyzed by LC-MS because of their well-known biocompatibility and long-term use in medical devices.

Figs. 3–6 summarize the results of final RhE screening tests for the irritant polymers. All show mean tissue viability for saline and sesame oil polymer extracts, plus controls. Tissue viability during negative control dosing was consistently 100%, while positive controls always produced results considerably below the 50% tissue viability threshold

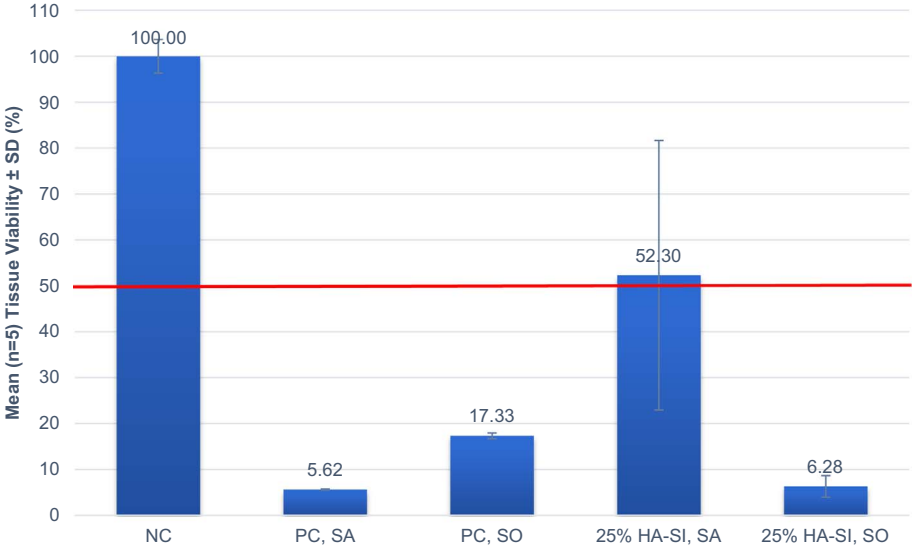

Fig. 3. EpiDerm™ SIT-MD tissue testing results for 25% HA in one-part silicone.
72 h extraction and 18 h exposure. NC = negative control of DPBS; PC, SA = positive control of 1% SDS in saline; PC, SO = positive control of 1% SDS in sesame oil; HA = heptanoic acid; SA = saline; SO = sesame oil; SI = silicone; and $n = 5$. Tissue viability below the 50% red line is indicative of an irritation response.
(Source: MatTek IVLSL and RIVM).

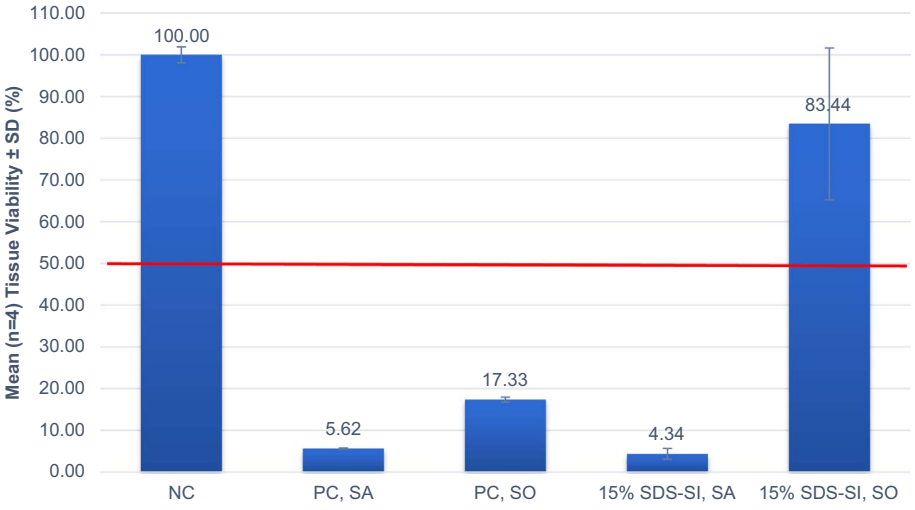

Fig. 4. EpiDerm™ SIT-MD tissue testing results for 15% SDS in two-part silicone.
72 h extraction and 18 h exposure. NC = negative control of DPBS; PC, SA = positive control of 1% SDS in saline; PC, SO = positive control of 1% SDS in sesame oil; SDS = sodium dodecyl sulfate; SA = saline; SO = sesame oil; SI = silicone; and $n = 4$. Tissue viability below the 50% red line is indicative of an irritation response.
(Source: MatTek IVLSL and RIVM).

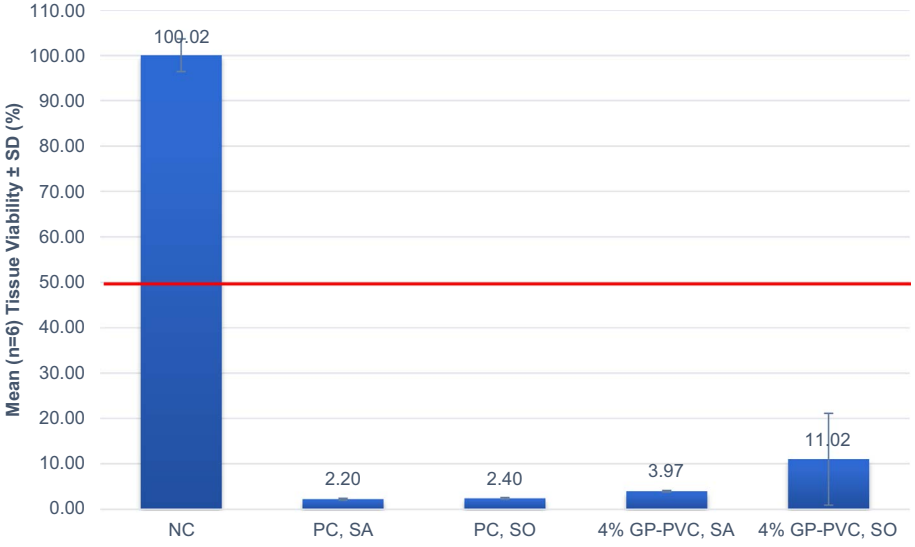

Fig. 5. EpiDerm™ SIT-MD tissue testing results for 4% Genapol® X-100 in PVC.
72 h extraction and 18 h exposure. NC = negative control of DPBS; PC, SA = positive control of 1% SDS in saline; PC, SO = positive control of 1% SDS in sesame oil; SA = saline; SO = sesame oil; GP = Genapol; and $n = 6$. Tissue viability below the 50% red line is indicative of an irritation response.
(Source: Arthrex, Inc. and Nelson Laboratories).

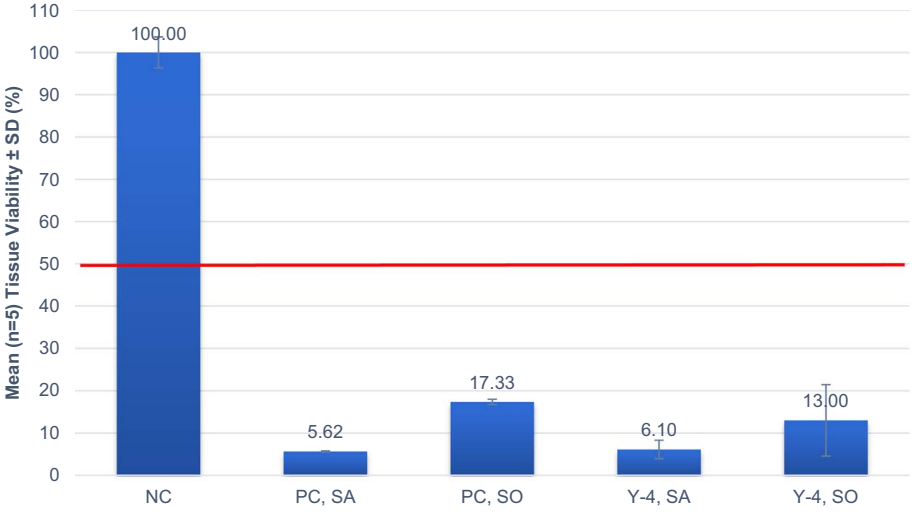

Fig. 6. EpiDerm™ SIT-MD tissue testing results for Y-4 polymer (5.8% Genapol® X-080 in PVC).
72 h extraction and 18 h exposure. NC = negative control of DPBS; PC, SA = positive control of 1% SDS in saline; PC, SO = positive control of 1% SDS in sesame oil; SA = saline; SO = sesame oil; and $n = 5$. Tissue viability below the 50% red line is indicative of an irritation response.
(Source: MatTek IVLSL and RIVM).

for irritation. In Fig. 3 (one-part silicone), HA's strong non-polar solubility is reflected by the low viability (6.28%) of sesame oil extract treated tissues and relatively high viability (52.30%) of the saline extract treated tissues. In Fig. 4 (two-part silicone), the situation is reversed as SDS's strong polar solubility drove viability very low (4.34%) for saline dosed tissues, while the viability of sesame oil treated tissues remained high (83.44%). In Fig. 5 (PVC), the amphipathic nature and strong irritancy of Genapol® X-100 significantly reduced tissue viability with saline (3.97%) and sesame oil (11.02%) extracts. Lastly, Fig. 6 (Y-4 polymer) depicts a similar story because Genapol® X-080 also appreciably reduced viability in both saline (6.10%) and sesame oil (13.00%) extract-treated tissues.

The RhE tissue screening consistently found that extracts of either saline, sesame oil, or both, drove tissue viability significantly below the 50% irritancy threshold for all four irritant polymers. These findings confirmed that the polymer samples were suitable for use in the round robin study.

6. Conclusions

The polymer preparation and testing process took almost three years to complete. Delays were caused by the high failure rate of irritant-polymer prototypes and competing priorities at the polymer development and testing laboratories. Nevertheless, after considerable effort four irritant and three non-irritant polymers were produced that were acceptable. Overall, Arthrex, Inc., Medtronic plc, and Japan's NIHS prepared and supplied over 2000 polymer samples for preliminary research and the round robin study.

Transparency document

The Transparency document associated with this article can be found, in online version.

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