Comparative Study of Chemical Composition, Molecular and Rheological Properties of Silicone Oil Medical Devices

Raniero Mendichi¹, Alberto Giacometti Schieroni¹, Daniele Piovani¹, Davide Allegrini², Mariantonia Ferrara², and Mario R. Romano²,³

¹ Istituto per lo Studio delle Macromolecole (CNR), Milan, Italy
² Eye Center, Humanitas, Bergamo, Italy
³ Department of Biomedical Sciences, Humanitas University, Milano, Italy

Correspondence: Mario R. Romano, Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini, Pieve Emanuele, Milan 20090, Italy. e-mail: mario.romano.md@gmail.com

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Purpose: We evaluated chemical composition, and molecular and rheological properties in 10 commercially available silicone oils (SilOils), focusing on siloxane chains of low molecular weight (LMW components, LMWC) that are known to be “impurities” produced during the SilOil synthesis process.

Methods: We assessed the type of SilOil polymer and molecular weight distribution (MWD) by spectroscopy and conventional size exclusion chromatography, respectively. From the Cumulative MWD, we calculated the fractions of LMWC with molecular weight (M): ≤2000, ≤5000, and ≤10,000 g/mol. Due to the low MW, the content of LMWC with M ≤1000 g/mol was determined by gas chromatography-mass spectrometry. The dynamic viscosity (η) was assessed by rotational rheometry.

Results: For all SilOils, the polymer was polydimethylsiloxane. The samples differed significantly in terms of MWD and relative LMWC fractions. Specifically, the relative fraction of all LMWC (M ≤10,000 g/mol) ranged from 2.31% to 9.40% and the content of LMWC with M ≤1000 g/mol also varied significantly (range, 51–1151 ppm). The η values were different between the SilOils, and, for many of them, from the declared viscosity.

Conclusions: Commercially available SilOils differ significantly in molecular and rheologic features. These compounds contain a significant amount of LMWC, “impurities” generated during the synthesis process, acting as emulsifier, potentially inducing ocular inflammation and toxicity.

Translational Relevance: The amount of impurities in different SilOils may influence significantly their biocompatibility.

Introduction

Silicone Oils (SilOils) belong to the group of synthetic organosilicon compounds, made up of the repetition of [-R₂Si-O-] group.¹ Structurally, SilOils are polymers of polydimethylsiloxane (PDMS), characterized by low energy surface and chemical inertness.¹ Due to these safety properties, they have been used largely in vitreoretinal surgery as long-acting vitreous substitutes, mainly in complicated retinal detachments to stabilize the reattached retina.² However, despite their established biocompatibility,³ several serious complications have been reported following their use, such as glaucoma, optic neuropathy, and retinal toxicity.⁴–⁶ Some of these issues have been associated with the emulsification of SilOil.⁴,⁵,⁷ Indeed, it has been demonstrated that emulsification induces a macrophagic foreign body reaction, potentially leading to retinal inflammation and necrosis.⁸ Factors affecting the stability of SilOil are shear stress induced by eye movements, the presence of surfactants, SilOil surface tension, viscosity and composition, pH level, and heat.²,⁹,¹⁰

It should be noted that viscosity increases as the chain length increases and more viscous SilOil might be more resistant to emulsification. Also the linear or

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cyclic structure of the polymer chain influences viscosity and emulsifying properties of SilOil. However, among the commercially available vitreous tamponades, conventional SilOils with nominal (declared) dynamic viscosity ($\eta$) ranging from 1000 and 1500 mPa-s, are more easily managed, especially with smaller-gauge instrumentation.

The presence of surfactants/emulsifiers also has a major role in determining SilOil emulsification due to their ability to lower SilOil surface tension. They can be divided in two main categories: biosurfactants (plasma lipoproteins, high density lipoprotein [HDL]-apolipoproteins, red blood cell membranes, and so forth); SilOil “impurities,” such as PDMS chains with molecular weight ($M$) < 10,000 g/mol (low molecular weight components, LMWC), particularly linear or cyclic LMWC with $M$ < 1000 g/mol, and catalyst remnants. Indeed, the PDMS synthesis process produces siloxanes with different chain lengths and molecular weight. These manufacturing-related low molecular weight (LMW) impurities are not completely removed by purification and ultrapurification of SilOil. Moreover, it has been demonstrated that part of these compounds are toxic and can diffuse into the ocular tissues.

Despite the importance of being aware about composition, physical properties, and purity of these medical devices, the package insert cannot contain such information.

In this study, we performed an extensive analysis of different SilOil products, through three steps: characterization of the whole molecular weight distribution (MWD) of the PDMS polymer; composition analysis focusing on LMWC; determination of $\eta$ for a broad range of shear rate.

### Methods

We obtained 10 commercially available SilOils among the most used in ophthalmic surgery. For convenience, the products have been labeled with a letter from A to J (Table 1).

### Fourier Transform-InfraRed Spectroscopy

The type of polymer of SilOil products was checked by Fourier transform-infrared spectroscopy (FT-IR). This analysis was performed by a Tensor 27 spectrometer from Bruker (Billerica, MA) with 4 cm$^{-1}$ of resolution. The FT-IR spectrums were obtained on a potassium bromide (KBr) tablet.

### Molecular Weight Distribution

The MWD of PDMS polymer was obtained with a conventional size exclusion chromatography (SEC) system (Modular Alliance 2695 HPLC/SEC; Waters, Milford, MA) using a relative calibration to polystyrene (PS) standards and a differential refractometer (DRI) as concentration detector. The SEC experimental conditions were: tetrahydrofuran (THF) as mobile phase; four SEC columns (Polypore, Oligopore, PLgel 100Å, and 50Å; Polymer Laboratories, Church Stretton, United Kingdom); 0.6 mL/min of flow rate; 35°C of temperature; 150 μL of injection volume; ~6 mg/mL of sample concentration. Sample solutions were obtained by dilution of SilOil in THF solvent at the established concentration. All SilOil solutions before injection in the chromatography system were filtered by 0.2 μm pores size polytetrafluoroethylene (PTFE) filters.

The MWD of SilOil samples was obtained with a
relative calibration generated with PS standards with narrow MWD. The relative PS calibration (polynomial 3\(^{rd}\) order) was generated by means of 16 PS standards with peak molecular weight (\(M_p\)) ranging from 1,680,000 and 162 g/mol.

**Low Molecular Weight Components With \(M \leq 1000\) g/mol Content**

Since SEC using a differential refractometer as concentration detector is not sufficiently accurate for the quantitative analysis of LMWC with \(M \leq 1000\) g/mol in SilOil, the total content of these compounds was determined by means of the more accurate mass spectrometer detector on-line to a gas chromatograph (GC-MS) method. GC-MS analysis of SilOil was performed by a 7890A GC system coupled to a 5975 MS detector (Agilent Technologies, Santa Clara, CA). A Stabilwax (crossbond polyethylene glycol; Restek Corp., Bellefonte, PA) column was used. The experimental conditions were the following: (1) starting isotherm 37°C for 5 minutes; (2) from 37°C to 230°C using 10°C/min. heating rate, and (3) final isotherm 230°C for 10 minutes.

**Dynamic Viscosity**

The \(\eta\) of SilOil products was measured by an AR 2000 rotational rheometer (TA Instrument, UK) using a cone-plate rotor geometry (diameter D = 25 mm, angle \(\alpha = 1^\circ\), polymeric material). The temperature was 20°C maintained with a Peltier system. The \(\eta\) value of SilOil was determined by a flow curve \(\eta = f(\dot{\gamma})\), that is a shear rate (\(\dot{\gamma}\)) sweep from 0.1 s\(^{-1}\) to 1000 s\(^{-1}\).

For each SilOil, we have assessed the Newtonian (i.e., low shear rate plateau) dynamic viscosity (\(\eta_0\)). The \(\eta\) also was determined at three different shear rate values (1, 10, 100 s\(^{-1}\)) in simulating different flow rate and also shear oil stability.

**Results**

**Fourier Transform-Infrared Spectroscopy**

The FT-IR spectroscopy confirmed that the polymer was PDMS for all SilOil products.

**Molecular Weight Distribution (MWD)**

The whole differential MWD (Fig. 1) showed the relative content of various PDMS fractions with different molecular weights. The MWD was broad and the molecular weight ranged from slightly <1,000 to \(\approx 500,000\) g/mol.

From the whole MWD (Fig. 1), various molecular parameters have been extracted; specifically, molecular weight of chromatogram peak (\(M_p\)), three
molecular weight averages (numeric $M_n$, weight $M_w$, $z$ $M_z$), and polydispersity indexes, that is how MWD is broad ($M_w/M_n$ and $M_z/M_w$; Table 2). Differences in MWD between the SilOils were important. The $M_w$ ranged from 32,779 to 39,653 g/mol. The polydispersity index $M_w/M_n$ ranged from 1.34 to 2.05 (Table 2). In other words, the molecular weight of PDMS polymer is relatively high for a PDMS polymer and the MWD is broad.

The cumulative MWD shows the content of PDMS molecules with molecular weight lower or equal to the specific value. From the cumulative MWD, we can immediately calculate the fraction of PDMS molecules with $M$: $\leq 2000$, $\leq 5000$, and $\leq 10,000$ g/mol or any other $M$ value. Figure 2 shows the comparison of the cumulative MWD of samples to enhance the differences between 10 SilOil products specifically in the range of LMWC. We found substantial differences in LMWC content between 10 SilOil products, as clearly shown in Table 3. Specifically, the relative content of all LMWC with $M \leq 10,000$ g/mol ranged from a minimum of 2.31% (sample H) to a maximum of 9.40% (sample I).

Table 2. Molecular Findings of 10 SilOil Products

| Label | $M_p$, g/mol | $M_n$, g/mol | $M_w$, g/mol | $M_z$, g/mol | $M_w/M_n$ | $M_z/M_w$ |
|-------|--------------|--------------|--------------|--------------|-----------|-----------|
| A     | 30,584       | 19,354       | 39,653       | 77,851       | 2.05      | 1.96      |
| B     | 30,319       | 20,774       | 33,231       | 45,865       | 1.60      | 1.38      |
| C     | 30,714       | 18,691       | 34,201       | 52,337       | 1.83      | 1.53      |
| D     | 30,862       | 20,397       | 33,606       | 46,424       | 1.65      | 1.38      |
| E     | 30,702       | 26,300       | 35,313       | 47,241       | 1.34      | 1.34      |
| F     | 30,410       | 26,019       | 35,335       | 47,700       | 1.36      | 1.35      |
| G     | 29,986       | 19,709       | 32,779       | 46,278       | 1.66      | 1.41      |
| H     | 30,858       | 26,581       | 35,645       | 47,693       | 1.34      | 1.34      |
| I     | 27,612       | 17,978       | 34,868       | 71,269       | 1.94      | 2.04      |
| J     | 29,464       | 23,584       | 33,714       | 48,710       | 1.43      | 1.44      |
| Min   | 27,612       | 17,978       | 32,779       | 45,865       | 1.34      | 1.34      |
| Max   | 30,862       | 26,581       | 39,653       | 77,851       | 2.05      | 2.04      |
| Average | 30,151     | 21,939       | 34,835       | 53,137       | 1.62      | 1.52      |

Figure 2. Comparison of a portion of the cumulative MWD of 10 SilOil products.
Low Molecular Weight Components With M ≤ 1000 g/mol Content

For each SilOil, we assessed the sum of all types of LMWC with M ≤ 1000 g/mol determined by GC-MS, including hexamethyldisiloxane (HMDS); hexamethylcyclotri-siloxane (D3); octamethylcyclotetrasiloxane (D4); decamethylcyclopentasiloxan (D5); dodecamethylcyclohexasiloxane (D6; Table 4). Evidently, the content of LMWC with M ≤ 1000 g/mol in 10 SilOil products was very different ranging from a minimum of 51 ppm (sample E) to a maximum of 1151 ppm (sample C).

Dynamic Viscosity

The flow behavior of all SilOils was substantially Newtonian, as η value was constant at different shear rate; only in the higher shear rate range (j > 100 s⁻¹) there was a little pseudoplastic behavior, since η decreases when shear rate increases (Fig. 3).

The nominal value of the η of all SilOils was 1000

| Label | M ≤ 2000, % | M ≤ 5000, % | M ≤ 10,000, % |
|-------|-------------|--------------|----------------|
| A     | 1.14        | 3.20         | 7.09           |
| B     | 0.56        | 2.01         | 6.28           |
| C     | 1.12        | 3.29         | 7.58           |
| D     | 0.61        | 2.57         | 6.63           |
| E     | 0.05        | 0.29         | 2.57           |
| F     | 0.07        | 0.45         | 2.63           |
| G     | 0.56        | 2.59         | 7.05           |
| H     | 0.04        | 0.30         | 2.31           |
| I     | 0.78        | 3.57         | 9.40           |
| J     | 0.38        | 1.17         | 5.22           |
| Min   | 0.04        | 0.29         | 2.31           |
| Max   | 1.14        | 3.57         | 9.40           |
| Average | 0.53       | 1.94         | 5.68           |

Table 3. Content of PDMS LMWC in 10 SilOil Products

| Label | LMWC With M ≤ 1000 g/mol Content |
|-------|----------------------------------|
| A     | 556                              |
| B     | 293                              |
| C     | 1151                             |
| D     | 191                              |
| E     | 51                               |
| F     | 90                               |
| G     | 336                              |
| H     | 111                              |
| I     | 446                              |
| J     | 1004                             |
| Min   | 51                               |
| Max   | 1151                             |
| Average | 423                         |

Table 4. Quantitative Assessment of LMWC With M ≤ 1000 g/mol of Different SilOil

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Figure 3. Flow curves for dynamic viscosity versus shear rate, η = f(j), of 10 SilOil products.
Silicone oils are synthetic compounds considered biocompatible due to their hydrophobic and chemically inert properties, and have been used since the 1960s for intraocular long-term tamponade. Several physical properties make SilOil a suitable vitreous substitute, such as surface tension, specific gravity different from water, buoyancy, and transparency. However, several factors can lead to the loss of their stability and, consequently, emulsification (formation of smaller droplets of SilOil due to the breakdown of the original bubble). This phenomenon has been associated not only with retinal inflammation, but also with ocular hypertension and other complications involving the anterior segment. It has been demonstrated that the emulsification of SilOil is a multifactorial process, influenced by the presence of surfactants (surface-active substances able to lower the interfacial tension [IT] of SilOil), shear stress generated by the saccadic eye movements, changes in pH level, presence of scleral buckle, heat, degree of tamponade filling, as well as the physical properties of SilOil, such as surface tension, viscosity, and the homogeneity of their molecules. Safe surgery should aim to minimize all the known and editable factors potentially related to emulsifications.

The surfactants can be divided into two groups of molecules: biosurfactants (HDL-apolipoproteins, plasma lipoproteins, red blood cell membranes, growth factors, and cytokines) and SilOil impurities. Low molecular weight components with $M < 1000$ g/mol are considered significant chemical impurities of SilOil. These compounds are able to lower the IT of SilOil and, consequently, generate emulsification. There is evidence that retinal pigment epithelium cells can phagocytize SilOil droplets of emulsion inducing a foreign body reaction and inflammatory response. The SilOil viscosity also has a role, since lower viscosity has been associated with greater propensity to emulsification. Hence, with regard to surgical practice, the vitreoretinal surgeons’ knowledge of physical, chemical, and, consequently, potential inflammatory properties of SilOil is essential to optimize the safety and effectiveness of their surgical use. Aiming to perform an overall characterization of conventional SilOils, we analyzed 10 between the most used SilOils, checking the MWD of the polymer, composition, and dynamic viscosity.

We found that, as declared in the package insert of all commercially available conventional SilOils, the polymer was PDMS. However, it is known that the SilOil synthesis process generates a mixture of chains with the same structural unit (monomer) but different lengths, including a dominant fraction of the desired degree of polymerization and other linear and cyclic chains of different molecular weight. Therefore, labeling a compound as composed of 100% of PDMS is trivial and does not ensure the purity of the product. It has already been highlighted that toxicity should not be referred to the whole chemical group, but to a specific compound, even if, globally, the silicone’s safety decreases as the molecular weight decreases, as short-chain siloxanes can overcome biological membranes diffusing into the surrounding tissues. It follows that the knowledge of composition of SilOil and, in particular, the amount of LMWC is of crucial importance. We found a broad MWD and significant differences in MWD between the SilOils. Previous studies focused on the analysis of SilOil on cyclic oligomers, in particular D4, D5, D6, and octadecamethylcyclo-
A quiet high variability of their concentration in the original, purified SilOil has been reported. Nakamura et al. found that the concentration of LMWC up to D6 changed in SilOil recovered from human and rabbit eyes, with a significantly decline of D4, whereas the concentrations of heavier siloxanes remained stable. Significant time-dependent decrease in D4 concentration also has been detected recently in two different 5000 mPa·s SilOil. Based on these data, LMWC has been suggested to diffuse into surrounding ocular tissue. Nakamura et al. also demonstrated severe inflammatory reactions in the anterior segment of rabbits following injection of LMWC, potentially relating these compounds with chronic ocular inflammatory reaction. Moreover, the European Chemicals Agency (ECHA) recently has added D4, D5, and D6 oligosiloxanes to the Candidate List of Substances of Very High Concern for authorization due to their persistency, bioaccumulation, and toxicity (available in the public domain at https://echa.europa.eu/it/-/ten-new-substances-added-to-the-candidate-list). However, in our composition analysis D4, D5, and D6 oligosiloxanes represented only a small amount of “impurities” (Table 4), whereas significant differences were detected in the fraction of heavier LMWC, up to molecular weight M ≤ 10,000 g/mol (range, 2.31%–9.40%). It may be argued that these bigger molecules, remaining in the vitreous cavity due to the lower diffusion capability, could continue to perform their emulsifying action at the oil/water interface and in direct contact with the retina for the whole duration of SilOil tamponade. The inflammatory reaction associated with emulsified SilOil may, in turn, promote further SilOil emulsification and, consequently, further inflammation. Therefore, the inflammation associated with SilOil emulsification may be expected to worsen with time. Recently, Semeraro et al. reported the significant correlation between intraocular inflammation in SilOil-filled eyes and the tamponade duration. Moreover, with regard to the biological effects of LMW silicones, Nayef et al. evaluated their role on human serum albumin (HAS) denaturation/aggregation and the turbidity of protein/buffer/silicones solutions. SilOil of 1000 mPa·s with different molecular weight distribution were obtained mixing 1000 mPa·s vinylidimethyl-terminated PDMS with trimethylsiloxy-terminated PDMS of 100, 200, 5000, and 60,000 mPa·s (M ~ 5700, 9430, 17,250, 116,500 g/mol, respectively). They found an association between greater concentrations of LMW silicons and increased protein denaturation as well as enhanced HSA solution turbidity, related to protein aggregates and SilOil-in water emulsions. It has been supposed that LMW silicones, mobile and hydrophobic, may lead to more efficient contact with HSA and, consequently, protein denaturation and aggregation.

As stated previously, viscosity also influences the stability of SilOil. On one hand, SilOil with higher viscosity should be less prone to emulsification; on the other hand, lower viscosity should ensure greater purity of the silicones, since the longer the chain, the more “trapping” of LMW compounds. We found that the ηo value varied significantly, with poor agreement with the declared nominal value for some SilOil samples (Table 5). Arguably, it has been demonstrated that the dynamic viscosity of SilOil decreases as temperature increases, and our measurements were taken at 20°C instead of at body temperature (35–36°C). However, it also has been reported that the temperature-induced variation of viscosity is similar for silicone oils of different ηo. Therefore, the testing temperature may be not relevant to assess the differences between the SilOils analyzed in terms of ηo values.

In conclusion, the synthesis process of SilOil generates LMWC often, even if improperly, defined “impurities”, in form of linear or cyclic siloxanes of different molecular weight. Due to their properties, these “impurities” could influence the biocompatibility of SilOil inducing ocular inflammation. In this study, the relative content of PDMS LMWC with M of ≤ 10,000 and ≤ 1000 g/mol was significantly different in the samples analyzed. Also, the dynamic viscosity of 10 SilOil was significantly different. Since a SilOil with greater viscosity and less amount of impurities is potentially less prone to emulsification and, consequently, to the emulsification-related complications, it is worthwhile to highlight that the knowledge of SilOil properties can help surgeons in the choice of tamponade. Further studies could investigate the potential correlation between these siloxanes and the loss of biocompatibility of SilOil.

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