

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

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Received: 12 March 2019

Accepted: 8 July 2019

Published: 11 September 2019

Keywords: silicone oil; polydimethylsiloxane; low molecular weight components; dynamic viscosity; molecular weight distribution

Citation: Mendichi R, Schieronì AG, Piovani D, Allegrini D, Ferrara M, Romano MR. Comparative study of chemical composition, molecular and rheological properties of silicone oil medical devices. *Trans Vis Sci Tech.* 2019;8(5):9, <https://doi.org/10.1167/tvst.8.5.9>

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

Methods: We assessed the type of SiOil 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 $\leq 10,000$ g/mol. Due to the low MW, the content of LMWC with $M \leq 1000$ g/mol was determined by gas chromatography-mass spectrometry. The dynamic viscosity (η) was assessed by rotational rheometry.

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

Conclusions: Commercially available SiOils 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 SiOils may influence significantly their biocompatibility.

Introduction

Silicone Oils (SiOils) belong to the group of synthetic organosilicon compounds, made up of the repetition of $-\text{[R}_2\text{Si-O]-}$ group.¹ Structurally, SiOils 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 SiOil.^{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 SiOil are shear stress induced by eye movements, the presence of surfactants, SiOil 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 SiOil might be more resistant to emulsification. Also the linear or

Table 1. Findings of Silicone Oil products

Label	Brand Name	Producer Company	City, State or Country	Nominal η , mPa·s
A	PDMS	Micromed	Rome, Italy	1000
B	Silicone Oil	Teknomek	Istanbul, Turkey	1000
C	Mersilicon	Meran	Istanbul, Turkey	1000
D	Silikon 1000	Alcon	Fort Worth, TX, USA	1000
E	Sil-1000-S	DORC International	Zuidland, The Netherlands	1000–1500
F	OphthaFutur Sil	Pharmpur Ophtha	Königsbrunn, Germany	1000
G	Silicone oil	FCI	Paris, France	1000
H	Oxane 1300	Bausch + Lomb	Rochester, NY, USA	1000
I	RS-OIL ECS	AlChiMiA	Ponte San Nicolò, Italy	1000
J	Arciolane 1300	Arcad	Toulouse, France	1300

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 (η) 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) \leq 10,000 g/mol (low molecular weight components, LMWC), particularly linear or cyclic LMWC with $M \leq$ 1000 g/mol, and catalyst remnants.^{2,11} Indeed, the PDMS synthesis process produces siloxanes with different chain lengths and molecular weight.^{2,12} These manufacturing-related low molecular weight (LMW) impurities are not completely removed by purification and ultrapurification of SilOil.¹ Moreover, it has been demonstrated that part of these compounds are toxic and can diffuse into the ocular tissues.^{11,13}

Despite the importance of being aware about composition, physical properties, and purity of these medical devices, the package insert cannot contain such information.²

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 η 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 μ L of injection volume; \approx 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 μ m pores size polytetrafluoroethylene (PTFE) filters.

The MWD of SilOil samples was obtained with a

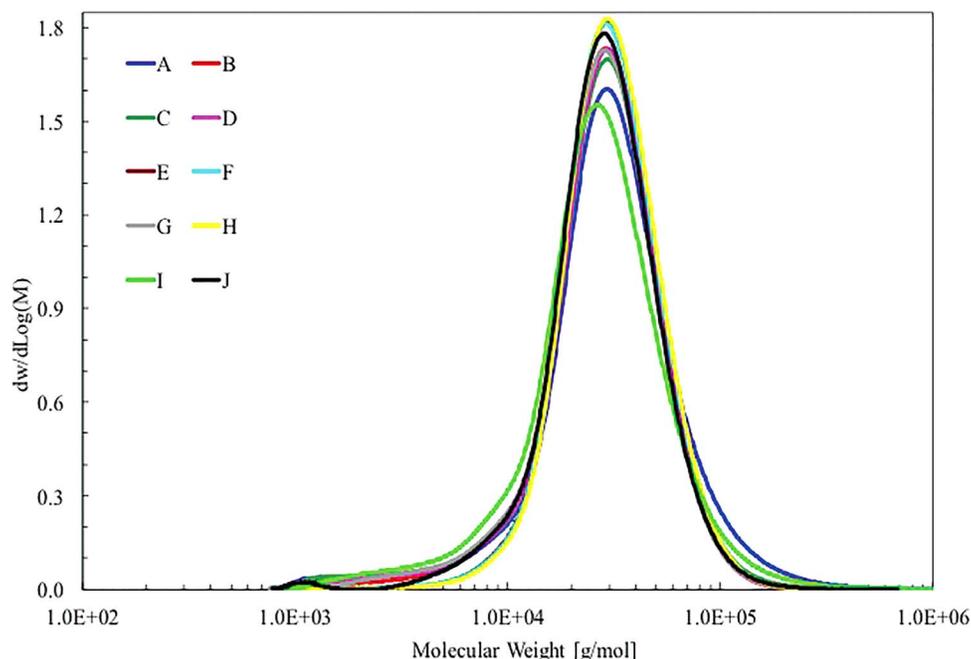


Figure 1. Comparison of the whole differential MWD of 10 SilOil products from a SEC-conventional SEC system using a relative calibration to polystyrene (PS) narrow standards.

relative calibration generated with PS standards with narrow MWD. The relative PS calibration (polynomial 3rd order) was generated by means of 16 PS standards with peak molecular weight (M_p) ranging from 1680.000 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 η 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 η 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 (η_0). The η 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 ≈ 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

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

molecular weight averages (numeric M_n , weight M_w , 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 : ≤ 2000 , ≤ 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).

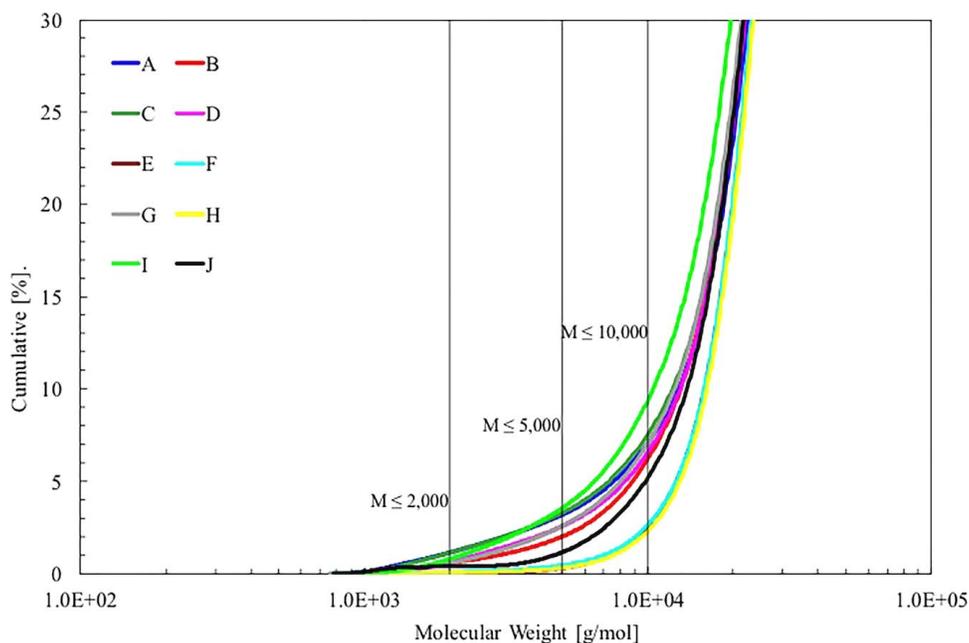
**Figure 2.** Comparison of a portion of the cumulative MWD of 10 SilOil products.

Table 3. Content of PDMS LMWC in 10 SilOil Products

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

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

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); decamethylcyclo-pentasiloxan (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 ($\dot{\gamma} > 100 \text{ s}^{-1}$) 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

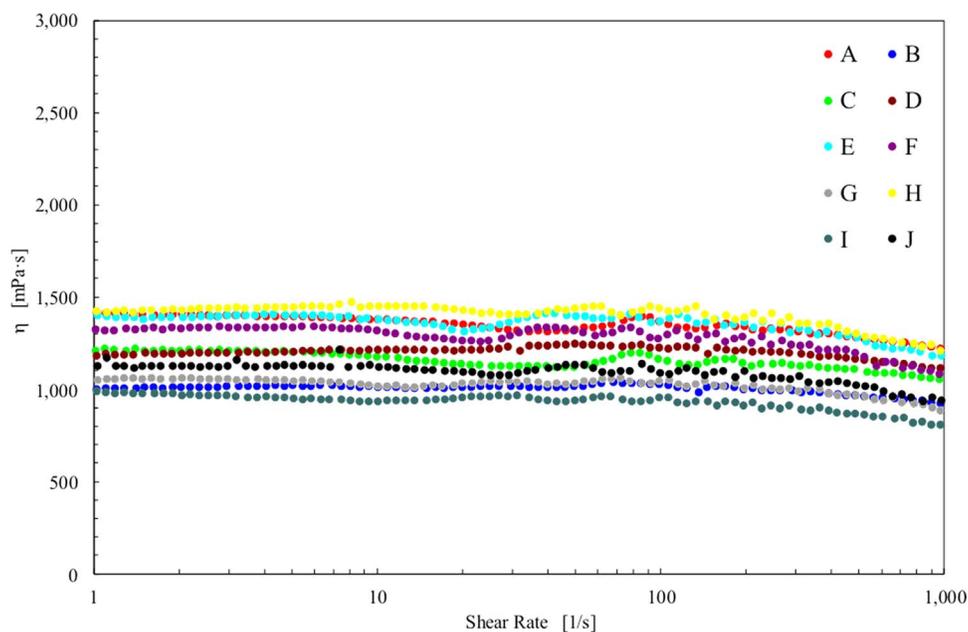
**Figure 3.** Flow curves for dynamic viscosity versus shear rate, $\eta = f(\dot{\gamma})$, of 10 SilOil products.

Table 5. Dynamic Viscosity Results of 10 SilOil Products

Label	η_0 , mPa·s	η (1 s ⁻¹), mPa·s	η (10 s ⁻¹), mPa·s	η (100 s ⁻¹), mPa·s
A	1396	1417	1376	1366
B	1010	998	1010	1024
C	1202	1207	1174	1164
D	1198	1180	1213	1220
E	1392	1396	1377	1364
F	1329	1324	1316	1271
G	1046	1046	1016	1040
H	1437	1423	1447	1439
I	959	985	933	954
J	1128	1121	1116	1084
Min	959	985	933	954
Max	1437	1423	1447	1439
Average	1210	1210	1198	1193

mPa·s, except in two products with declared η of 1000 to 1500 and 1300 mPa·s, respectively (Table 1). However, differences in η between the SilOils were meaningful and, for many of them, quite different from the declared nominal value (Table 5). The η_0 value of 10 SilOils ranged from 959 (sample I) to 1437 (sample H) mPa·s.

Discussion

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.¹⁴ Several physical properties make SilOil a suitable vitreous substitute, such as surface tension, specific gravity different from water, buoyancy, and transparency.^{2,14} 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).² This phenomenon has been associated not only with retinal inflammation, but also with ocular hypertension and other complications involving the anterior segment.¹⁵ 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.^{2,10} Safe surgery should aim to minimize all the known and editable factors potentially related to emulsifications.

The surfactants can be divided in two groups of molecules: biosurfactants (HDL-apolipoproteins, plasma lipoproteins, red blood cell membranes, growth factors, and cytokines) and SilOil impurities.² Low molecular weight components with $M \leq 1000$ g/mol are considered significant chemical impurities of SilOil.¹⁶ 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.¹⁷ 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.¹ 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,¹ 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.¹ 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 the analysis of SilOil on cyclic oligomers, in particular D4, D5, D6, and octadecamethylcyclo-

heptasiloxane (D7).^{11,16} A quiet high variability of their concentration in the original, purified SilOil has been reported.¹⁶ Nakamura et al.¹¹ 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.¹⁶ Based on these data, LMWC has been suggested to diffuse into surrounding ocular tissue. Nakamura et al.¹¹ also demonstrated severe inflammatory reactions in the anterior segment of rabbits following injection of LMWC, potentially relating these compounds with chronic ocular inflammatory reaction.¹¹ 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 $M \leq 10,000$ 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.^{17,18} Therefore, the inflammation associated with SilOil emulsification may be expected to worsen with time. Recently, Semeraro et al.¹⁹ 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.²⁰ 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 vinyl dimethyl-terminated PDMS with trimethylsiloxy-terminated PDMS of 100, 200, 5000, and 60,000 mPa·s ($M \sim 5700, 9430, 17,250, 116,500$ g/mol, respectively). They found an association between greater concentrations of LMW

silicones and increased protein denaturation as well as enhanced HSA solution turbidity, related to protein aggregates and SilOil-in water emulsions.²⁰ It has been supposed that LMW silicones, mobile and hydrophobic, may lead to more efficient contact with HSA and, consequently, protein denaturation and aggregation.²⁰

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.^{1,21} We found that the η_o 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,²² 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 η_o .²³ Therefore, the testing temperature may be not relevant to assess the differences between the SilOils analyzed in terms of η_o 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 $\leq 10,000$ 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.

Acknowledgments

Disclosure: **R. Mendichi**, None; **A.G. Schieroni**, None; **D. Piovani**, None; **D. Allegrini**, None; **M. Ferrara**, None; **M.R. Romano**, None

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