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Injectability of silicone oil-based tamponade agents

Williams RL¹, Day MJ², Garvey MJ², Morphis G³, Irigoyen C³, Wong D^{3,4} and Stappler T^{1,3}

¹Department of Eye and Vision Science, ²Department of Physics, University of Liverpool, Liverpool, UK

³St Paul's Eye Unit, Royal Liverpool and Broadgreen University Hospital Trust, Liverpool, UK

⁴Eye Institute, LKS Faculty of Medicine, University of Hong Kong, Hong Kong

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Corresponding author:

Dr Rachel L Williams

Department of Eye and Vision Science

Institute of Ageing and Chronic Disease

1st floor Duncan Building

Daulby Street

Liverpool L69 3GA

rlw@liverpool.ac.uk

tel: +44 151 7064205

fax: +44 151 7065803

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Abstract

Background/aims: High viscosity silicone oils are used as tamponade agents to increase the resistance to emulsification, however this makes the oils more difficult to inject. Increasing the extensional viscosity is one way to reduce emulsification. This study aimed to evaluate how silicone oils with increased extensional viscosity behave in terms of their ease of injection.

Methods: The shear viscosity and the length of time taken to inject 9mls of Siluron 1000™, Siluron 2000™, Siluron 5000™, SiliconMate™, a 56/44 w/w blend of Siluron 1000™/ Siluron 5000™ (Blend A) and a 90/10 w/w blend of Siluron 1000™/ PDMS M_w423k Da (Blend B) were examined.

Results: The shear viscosity of Siluron 1000™, Siluron 2000™ and Siluron 5000™ were within the expected ranges. The shear viscosity of Blend A was 2283 mPa.s, Blend B was 4710 mPa.s and SiliconMate™ was 995.3 mPa.s. Siluron 1000™ and SiliconMate™ had the shortest injection times as expected due to their lower shear viscosities. Comparison of Siluron 2000™ and Blend A demonstrated that Siluron 2000™ was easier to inject. Similarly, Blend B was easier to inject than Siluron 5000™.

Conclusion: Silicone oil blends containing small percentages of a high molecular weight additive are easier to inject than single grade oils of the equivalent shear viscosity.

Introduction

Silicone oils (PDMS) are well established long term intraocular tamponade agents particularly in the treatment of complex retinal detachments [1, 2]. Early improvements in the production of medical-grade silicone oils aimed at removing PDMS molecules with short chain lengths since the latter were thought to be one of the causes of postoperative ocular inflammation. Another reason for silicone oil-associated adverse reactions such as inflammation, glaucoma and even the development of proliferative vitreoretinopathy (PVR) has been the propensity of silicone oils to emulsify. Small droplets are formed due to shear forces acting at the interface between oil and water during eye movements. These satellite droplets may either coalesce back into the bulk oil or, if surfactant are available can become stable within the aqueous surrounding the bulk oil. These droplets remain in the patient's eye for life even when the bulk oil has been removed. Such considerations have led to the manufacture of silicone oils with even higher (shear) viscosities as in-vitro experiments indicate that such increased viscosity reduces emulsification [3]. The silicone oils currently on the market generally have a shear viscosity of either 1000 or 5000 mPa.s. The former type is easier to inject into the eye but is also believed to be more prone to emulsification, while the higher viscosity oil is perceived to be less prone to emulsification but is also more difficult to inject.

Such advances in the field of silicone oils now have to adapt to parallel advances in the field of microsurgical instrumentation. Since their inception [4], there has been a recognised trend towards small gauge surgery [5]. Complex procedures have now become accessible to such minimally invasive surgical techniques, including the injection of viscous silicone oil through the small gauge needles [6]. Furthermore, once injected, high viscosity silicone oils can prove equally difficult to remove from the eye [7].

There is, therefore, an accepted need for a product that is significantly easier to inject than 5000 mPa.s oil (ideally approaching 1000 mPa.s oil in this respect) whilst at the same time possessing

comparable resistance to emulsification. It has previously been shown that addition of a small (5-10% w/w) amount of a very high molecular weight PDMS polymer to 1000 mPa.s oil gives a composition with a greatly increased high strain rate extensional viscosity and consequently an enhanced resistance to emulsification (comparable to 5000 mPa.s oil) [8]. At the same time, the shear viscosity of such compositions remains lower than 5000 mPa.s thereby rendering them easier to inject than the latter. One such composition comprising 5% w/w 423,000 molecular weight PDMS polymer in 1000 mPa.s oil, having a shear viscosity of ca. 2000 mPa.s, has recently been introduced as a tamponade in Europe under the brand name Siluron 2000™.

In this study, the rate of injection of Siluron 2000™ using an Accurus Viscous Fluid Injection system (with both 20 and 23 Gauge cannula) was compared to that of 1000 and 5000 mPa.s oils along with the recently launched tamponade SiliconMate™ (Howard Instruments). The latter was included as it claims a similar shear viscosity to Siluron 2000™. Further, a particular aim of the study was to determine whether the high molecular weight PDMS polymer had any effect on injection rate over and above simply giving a particular composition shear rate. Siluron 2000™ was therefore also compared to a control blend of 1000 and 5000 mPa.s oils having a similar shear viscosity. Similarly, a composition comprising 10.0% w/w PDMS polymer having a shear viscosity close to that of 5000 mPa.s oil was examined.

Materials and methods

Siluron 1000™ mPa.s (MW 37 kDa) and Siluron 5000™ mPa.s (MW 65 kDa) were donated by Fluoron GmbH (Ulm, Germany). Poly(dimethylsiloxane) (PDMS) with a molecular weight of 423 kDa and a cited shear viscosity of 2,500,000 mPa.s (PS050) was purchased from Fluorochem Ltd. (Glossop, UK). Blends of 56/44 w/w Siluron 1000™ and Siluron 5000™ (Blend A), 90/10 w/w Siluron 1000™ and PDMS 423 kDa (Blend B) and 95/5 w/w Siluron 1000™ and PDMS 423 kDa (Siluron 2000™) were prepared. The Siluron 1000™ / high MW silicone additive blends were prepared as follows. The oil was added to a polystyrene container (Bibby Sterilin) followed by the additive. The mixture was

stirred on a roller mixer (model SRT2, Stuart Scientific) for 72 hours and then more vigorously mixed for 24 hours using an overhead stirrer. Blend A was prepared following the roller mixing step only. All mixing was performed at ambient temperature. A sample of SiliconMate™ 2000cS (Lot 200708 072013/ Howard Instruments Inc) was received from Fluoron GmbH.

Rotational (Shear) Rheometry:

For all samples, shear viscosities were measured at 25°C using a TA Instruments Advanced Rheometer AR500, using a cone and plate geometry (2°, 40 mm) at shear rates 10, 25 and 100 s⁻¹. In all cases, the average value of the viscosity measured at each of these three shear rates is quoted.

Injection tests:

In order to simulate real-life surgical situations the following setup was used: The Accurus Viscous Fluid Injection system (Alcon, USA) was used in conjunction with the original viscous fluid injection pack. The programme “viscous fluid injection” was chosen and the injection pressure was set to 80psi, the maximum for this type of machine. These also represent the injection settings in routine vitreoretinal surgery when silicone oils are being infused. The standard 20-gauge metal cannula provided as standard with every silicone oil injection pack was used. This is approximately 7.5 mm in length from the plastic hub to the tip of the cannula. The 23 gauge metal cannula was cut to be of the same length as the 20 gauge cannula so that the different lumen size was the only variable factor. Furthermore the same needles were used for all experiments in order to rule out further potential confounding factors. All injection tests were performed in triplicates and fresh oils were used for each run to avoid aeration effects. When the oil to be infused was changed, the cannulae were flushed with several ml of the new silicone oil to minimise cross-contamination. No detergents were used throughout the injection experiments to clean any piece of equipment. The time for each increment of 1 ml of the various silicone oils to be injected were measured using a stopwatch. The injection times for a total of 9 ml for each silicone oil were measured, again mimicking a real-life situation such as the volume of the eye.

Statistical analysis

One-way ANOVA analysis was performed using a Dunnett's T3 post-hoc test for small sample size pairwise comparisons on the injection times for 9 mls of each sample. Comparisons were made within the group of data for each needle size.

Results

Shear viscosity measurements

The shear viscosity measurements of the Siluron 1000™ and Siluron 5000™ were within the range expected at 1114 mPa.s and 4975 mPa.s respectively (Table 1). Siluron 2000™ was prepared in a standard ratio of Siluron 1000™ plus 5% of a high molecular weight additive and fitted into the expected range of shear viscosity at 2155 mPa.s. Blend A was made for comparison with Siluron 2000™ to match the shear viscosity without using the high molecular weight additive. The resultant shear viscosity was measured to be 2283 mPa.s. Blend B was made from Siluron 1000™ plus 10% of the high molecular weight additive and its resultant shear viscosity was measured to be 4710 mPa.s. The shear viscosity of SiliconMate™ was measured to be 995.3 mPa.s although it was labelled as 2000cS.

Silicone oil	Batch/manufacturer	Viscosity at 25°C /mPa.s
Siluron 1000™	Lot SIL1 121009/Fluoron GmbH	1114
Blend A (56/44 Siluron 1000™/ Siluron 5000™ w/w blend)	Lots SIL1 121009 + SIL5 230609/ Fluoron GmbH	2283
Siluron 2000™ (90/5 Siluron 1000™ /SO423k MW additive)	Tech grade SO1000/Fluoron GmbH; Additive/ Fluorochem Ltd.	2155
Siluron 5000™	Lot SIL5 230609/ Fluoron GmbH	4975
Blend B (90/10 Siluron 1000™ /SO423k MW additive)	Lot SIL5 230609/ Fluoron GmbH Additive/ Fluorochem Ltd.	4710
SiliconMate™ (2000 cs)	Lot 200708 072013/ Howard Instruments	995.3

	Inc.	
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Table 1 Shear viscosity measurements of Silicone oils presented at the average of three measurements taken at shear rates of 10, 25 and 100 s⁻¹

Injection rates:

It was possible to inject all the test silicone oils using the Accurus Viscous Fluid Injection system with a 20 gauge needle over a clinically relevant time period (Table 2). As expected the Siluron 5000™ was the most resistant to injection and took a total of 4 minutes to inject 9 mls. Blend B, which has a shear viscosity only marginally lower than Siluron 5000™ was significantly easier to inject than Siluron 5000™ and only took just over 2 minutes to inject 9 mls. If a similar comparison was made between Blend A and Siluron 2000™, both of which had very similar shear viscosities, it was demonstrated that the addition of the high molecular weight additive resulted in a reduction in the injection time for 9 mls (103 s to 71 s). The time taken to inject Siluron 1000™ was lower again as expected due to the lower shear viscosity. Similarly the time taken to inject the SiliconMate™ reflected the measured shear viscosity. Statistical analysis demonstrated that the injection times for 9mls of each fluid was significantly different from all others at the p<0.05 level. These data are presented graphically in Figure 1.

20 gauge	Siluron 1000™	Blend A	Siluron 2000™	SiliconMate™	Siluron 5000™	Blend B
0ml	0.00	0.00	0.00	0.00	0.00	0.00
1ml	6.00 ± 0.35	11.50 ± 0.00	8.00 ± 0.10	3.73 ± 0.20	26.37 ± 2.84	13.60 ± 0.44
2ml	11.40 ± 0.56	22.60 ± 0.35	15.70 ± 0.10	7.07 ± 0.11	52.50 ± 4.42	27.27 ± 0.15
3ml	16.77 ± 0.68	34.17 ± 1.12	23.80 ± 0.20	10.75 ± 0.12	79.30 ± 5.51	40.93 ± 0.40
4ml	21.97 ± 1.23	45.50 ± 0.95	31.90 ± 0.26	14.34 ± 0.35	106.20 ± 6.07	55.23 ± 0.25

5ml	27.67 ± 0.67	56.77 ± 1.29	39.67 ± 0.06	18.05 ± 0.33	132.97 ± 7.24	69.20 ± 0.60
6ml	33.07 ± 1.10	68.43 ± 1.29	47.60 ± 0.35	21.37 ± 0.29	160.17 ± 8.45	83.47 ± 0.55
7ml	38.73 ± 0.99	79.87 ± 1.50	55.47 ± 0.46	24.81 ± 0.30	186.70 ± 9.51	97.40 ± 1.06
8ml	44.40 ± 0.62	91.23 ± 1.58	63.53 ± 0.21	28.27 ± 0.35	213.13 ± 10.68	111.00 ± 1.32
9ml	50.07 ± 1.14	102.83 ± 2.04	71.23 ± 0.42	31.80 ± 0.50	240.07 ± 11.26	125.27 ± 1.42

Table 2 Injection time in s, presented as the mean ± SD of three measurements using the Accurus Viscous Fluid Injection system attached to a 20 gauge needle

Using a 23 gauge needle (Table 3) attached to the Accurus Viscous Fluid Injection system it was not possible to inject the Siluron 5000™. An attempt was made to inject the Blend B and it was demonstrated that this could be achieved with a total time to inject 9 mls in the order of 23 minutes. Multiple runs of this blend have not been run as it was considered that 23 minutes was too long to be clinically relevant. Comparison of the total injection time of Siluron 2000™ and the shear viscosity-matched Blend A demonstrated that the Siluron 2000™ with the high molecular weight additive was significantly easier to inject than the simple mixture of Siluron 1000™ and Siluron 5000™. The total times taken to inject 9 mls were approximately 11 and 17 minutes respectively. Shorter times for injection of 9mls of Siluron 1000™ and SiliconMate™ were measured as expected due to their lower shear viscosity. Statistical analysis demonstrated that the injection times for 9mls of each fluid was significantly different from all others at the p<0.05 level. These data are presented graphically in Figure 2.

23 gauge	Siluron 1000™	Blend A	Siluron 2000™	SiliconMate™
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0ml	0.00	0.00	0.00	0.00
1ml	54.37 ± 3.00	107.83 ± 6.89	74.13 ± 1.75	41.48 ± 1.75
2ml	109.40 ± 2.01	216.00 ± 2.59	152.33 ± 1.64	83.45 ± 2.19
3ml	162.60 ± 4.56	327.57 ± 1.61	229.57 ± 4.73	126.07 ± 3.71
4ml	217.57 ± 3.72	441.50 ± 3.44	303.83 ± 12.14	168.00 ± 3.03
5ml	272.43 ± 3.52	556.43 ± 2.99	379.20 ± 18.41	209.62 ± 4.31
6ml	326.37 ± 4.66	669.90 ± 5.54	454.90 ± 23.91	250.04 ± 3.58
7ml	378.00 ± 7.85	785.40 ± 4.98	531.17 ± 26.36	290.06 ± 2.92
8ml	431.87 ± 7.96	901.37 ± 3.81	605.00 ± 28.17	331.58 ± 3.18
9ml	485.23 ± 7.02	1017.83 ± 5.20	680.77 ± 30.99	370.79 ± 4.19

Table 3 Injection time in s, presented as the mean ± SD of three measurements using the Accurus Viscous Fluid Injection system attached to a 23 gauge needle.

Discussion

The behaviour of silicone oil tamponade agents in terms of their emulsification resistance and ease of injection will be influenced by their viscosity. Siluron 2000™ was designed to address the emulsification of silicone oil tamponades by increasing the extensional viscosity of the material while keeping the shear viscosity lower than Siluron 5000™ so that it is easier to inject than Siluron 5000™. Blend B is an experimental oil that takes advantage of the same rheological property of an increase in extensional viscosity. By adding a greater percentage of the high molecular weight additive it has the potential to increase the resistance to emulsification even further than Siluron 2000™ but has an increased shear viscosity and therefore is not expected to be any easier to inject than Siluron 5000™.

In general the shear viscosity of the oils will control their ease of injection, however, this study has shown that both Siluron 2000™ and Blend B were significantly easier to inject than their equivalent single phase oils Blend A and Siluron 5000™, respectively. This fact has also been reported by clinicians using Siluron 2000™ during surgery. Siluron 2000™ and Blend B were both produced by

taking Siluron 1000™ and adding 5% and 10% respectively of a high molecular weight PDMS polymer. The polymer is fully soluble throughout the Siluron 1000™ and increases the shear viscosity of the latter by enhancing the interpenetration of the molecular coils within the bulk oil and giving an increased resistance to shear flow. Although not observed from classical rheological analysis via cone and plate rheometry it would appear that when these composite oils are subjected to the pressure of the injection and the high shear rates in the narrow bore of the cannulae, less resistance to flow is experienced. This phenomenon is termed 'shear thinning' in the field of polymer science and is caused by the high molecular weight chains becoming elongated and aligned to the flow direction. In contrast the 56/44 w/w mixture of Siluron 1000™ and Siluron 5000™ did not behave in a similar way due to the comparable sizes of the molecular chains in the two components.

The SiliconMate™ silicone oil, although claiming to have a viscosity of 2000cS, was measured to have a viscosity of 995.3 mPa.s. This shear viscosity was also reflected in its injection behaviour where the injection times were very similar to those of Siluron 1000™. Owing to these data this oil would be expected to behave in a similar manner to Siluron 1000™ in terms of its emulsification resistance.

Conclusion

These data suggest that Siluron 2000™ and Blend B have a significant advantage for clinical practice in terms of their ease of injection as well as their expected emulsification resistance related to their increased extensional viscosity.

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Figure captions

Figure 1 Injection rates of the silicone oil tamponade agents using the Accurus Viscous Fluid Injection system attached to a 20 gauge cannula

Figure 2 Injection rates of the silicone oil tamponade agents using the Accurus Viscous Fluid Injection system attached to a 23 gauge cannula

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Competing interests: Authors RLW, MD and MJG are inventors on a patent related to the development of silicone oils with high molecular additives and the University of Liverpool have a licence agreement for this technology which includes royalties for the inventors. The other authors have no competing interests in this work.



