

# Flow Behavior of Heavy Silicone Oil During Eye Movements

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**PURPOSE.** Currently there are various heavy silicone oil (HSO) tamponade agents available for treating inferior retinal diseases. Most of these HSO agents are either homogeneous liquids or a mixture of two components. Variations in their emulsification rates in vivo have been reported. In this study, we investigated their flow behaviors during eye-like movements.

**METHODS.** A model eye chamber filled with various HSO agents was driven to perform eye-like movements. Five types of HSOs with different formulations together with 2 other tamponade agents were tested. Movements of various HSOs inside the chamber were captured by video recording and analyzed.

**RESULTS.** Oxane HD has a larger movement and higher velocity relative to the eye chamber than the less viscous Densiron 68. The behavior of Densiron 68 is similar to that of homogeneous HSO 1.07 and HSO 1.20. Both Oxane HD and 11% silica fluid show very different behaviors compared to the other HSO agents. In addition, 11% silica fluid shows behavior similar to that of F6H8, a low-viscosity tamponade agent.

**CONCLUSIONS.** The viscosity of HSO is not the sole parameter with which to determine the behavior of HSO during eye movements. Various HSOs that are manufactured by mixing different types of base SO and “heavy” additives show distinct flow behaviors. The solubility and stability of the heavy additives in the base SO alter its flow when subjected to eye movements, which may contribute to in vivo emulsification.

Keywords: emulsification, eye movements, heavy silicone oil, tamponade

Silicone oil (SO) has been used in vitreoretinal surgery for a long time to repair complicated retinal detachment.<sup>1</sup> Conventional SO has a specific gravity lower than water and thus provides a good tamponade effect for breaks or holes in the superior retina. There is also a group of SO that has a specific gravity higher than water. That type of SO is designed initially for treating proliferative vitreoretinopathy, which has a propensity to affect the inferior part of the retina.<sup>2</sup> Those types are commonly called heavy silicone oil (HSO). The first generation of HSO was made by substituting a few methylated groups of conventional SO to fluorinated groups in order to increase its specific gravity.<sup>3</sup> However, that type of fluorosilicone oil was found to be toxic to ocular tissues,<sup>4</sup> and it emulsified much more quickly than conventional SO.<sup>5</sup> In the early 2000s, the second generation HSO, consisting of a mixture of viscous SO with a low-viscosity fluorinated additive, was introduced.<sup>6</sup> The fluorinated additive contributes to the increase in specific gravity of the resultant mixture. Two commonly used examples of this type of HSO are Densiron 68 (mixture of SO and perfluorohexyloctane [Fluoron GmbH, Ulm, Germany])<sup>7</sup> and Oxane HD (SO and a partially fluorinated olefin, RMN-3 [Bausch & Lomb, Inc., Waterford, Ireland]).<sup>8</sup> They are well tolerated in human eyes and offer a satisfactory support for the inferior retina.<sup>9</sup> However, the fluorinated additives in HSO are associated with emulsification in vivo.<sup>10,11</sup> Segregation of the two components of HSO was proposed.<sup>12</sup> Very recently, another novel HSO was also introduced. This

HSO was made by mixing a low-viscosity SO liquid with nano-scale silica particles.<sup>13</sup> These nano-sized silica particles increase the specific gravity of the resultant mixture.

In this study, we studied the flow of various HSOs with different formulations during eye movements by using the dynamic eye chamber model. We compared the HSOs made of two-component mixtures with typical fluorosilicone oil. We hypothesized that the flow properties of these mixed HSOs are different from the typical silicone oil.

## MATERIALS AND METHODS

There were five types of heavy silicone oil, including Densiron 68 (Fluoron), Oxane HD (Bausch & Lomb), fluorosilicone oil 1.07 and 1.20 (Alamedics GmbH & Co. KG, Dornstadt, Germany), and 11% silica solution. This study also included the use of perfluorohexyloctane (F6H8; Fluoron) and sulfur hexafluoride (SF<sub>6</sub>; Arcadophta, Toulouse, France), which are short-term liquid and gas tamponades respectively. Physical properties and compositions of these agents are listed in the Table.

## Study of the Motion of HSO in an Eye Model Chamber

We used a study design and method similar to that published recently.<sup>14</sup> The eye chamber was made of poly(methylmetha-

TABLE. Compositions and Physical Properties of Various Tamponade Agents

| Tamponade Agent  | Shear Viscosity at 25°C, mPa · s | Specific Gravity, g/cm <sup>3</sup> | Composition  |
|------------------|----------------------------------|-------------------------------------|--|
| Densiron 68      | 1400                             | 1.08                                | 69.5% SO 5000 + 30.5% F6H8   |
| Oxane HD         | 3800                             | 1.02                                | 80.1% 5700 mPa · s SO + 11.9% RMN-3 (a partly fluorinated olefin)                        |
| 11% silica fluid | 2000                             | 1.11                                | 11% silica (Aerosil R972 Pharma silica) + 89% 22.5 mPa · s SO (556 cosmetic grade fluid) |
| HSO 1.07         | Not provided by the manufacturer | 1.07                                | Homogeneous fluorosilicone oil   |
| HSO 1.20         | Not provided by the manufacturer | 1.20                                | Homogeneous fluorosilicone oil   |
| F6H8             | 3.44                             | 1.35                                | Perfluorohexyloctane   |
| SF <sub>6</sub>  | 0.142                            | 0.006265                            | Sulfur hexafluoride  |

crylate) with a volume of approximately 6.3 mL. We estimated the volume of an eyeball by assuming that a human eyeball is a sphere with an axial length of 2.4 cm. Therefore, the volume of the eyeball would be approximately 7.2 mL. Published figures from magnetic resonance imaging studies in human gave the volume of the eyeball and vitreous cavity as  $6.013 \pm 0.449$  mL and  $5.482 \pm 0.440$  mL, respectively.<sup>15</sup> We chose 6.3 mL as a compromise. The inner surface of the chamber was coated with protein to achieve a hydrophilic surface property.<sup>16</sup> This coating is essential because it prevents adhesion of the SO onto the inner surface of the eye chamber and allows free movement of the SO inside the chamber during rotation of the chamber.

The eye model chambers were filled with 5 mL of each testing agent containing trypan blue-colored phosphate-buffered saline to avoid influx of air into the chamber. Eye chambers were then mounted onto the mechanical platform and subjected to preset large-amplitude eye-like movements (amplitude, 90°; angular velocity, 360°/s; duration, 300 ms) repetitively.

Movements of the HSO contained within the eye chamber during motion were recorded at a speed of 30 frames per second. We drew a chord for each HSO bubble in each frame and measured the gradient of these chords by using ImageJ software (US National Institutes of Health, Bethesda, MD, USA). The gradient was then converted to a value in terms of degrees. This value reflected the corresponding angular displacement of the HSO bubble in each photo frame. Angular velocity of the HSO bubble could then be calculated by the change of angular displacement within a certain time interval. The relative velocity between the wall of the model eye chamber and the HSO was also calculated by subtracting the velocity of the eye chamber from the velocity of HSO.

### Statistical Method

The unpaired *t*-tests were performed using Prism version 5 software (Graphpad, Chicago, IL, USA). *P* values of <0.05 were considered statistically significant. Sample size was  $n=8$  for all groups. All values in the graphs are means  $\pm$  standard deviations (SD).

### RESULTS

During rotation, Densiron 68 has the greatest angular displacement (Figs. 1a, 1b). The angular displacement of Oxane HD is between HSO 1.07 and HSO 1.20. The 11% silica fluid has the smallest displacement among all the HSO groups. F6H8 and SF<sub>6</sub> had minimum displacement compared with those of the other HSO agents. Similarly, Densiron 68 had the highest angular velocity profile. Oxane HD had a lower angular velocity profile than Densiron 68. Its behavior is similar to

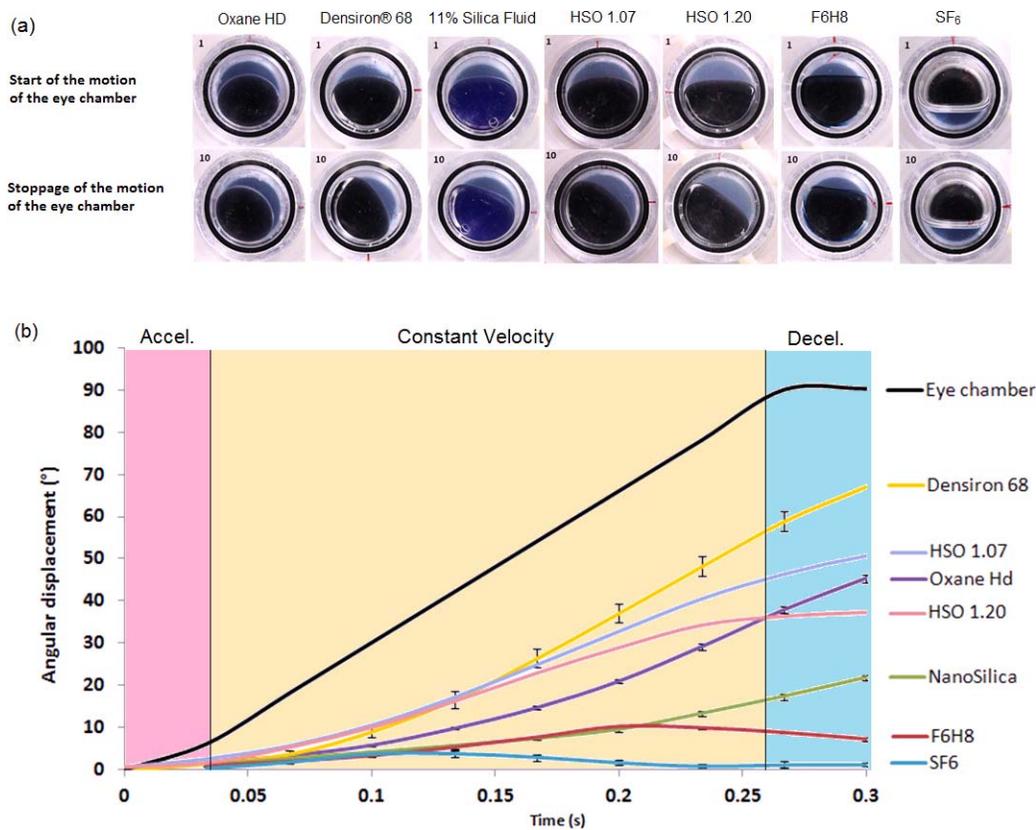
those of HSO 1.07 and HSO 1.20. The 11% silica fluid has the lowest velocity profile among all the HSO groups, and it is only slightly higher than that of F6H8 and SF<sub>6</sub> (Fig. 2a).

The angular velocity of HSO relative to the eye chamber indicates the relative motion between the HSO agents and the eye chamber during motion. Our data showed that Densiron 68 has the lowest angular velocity relative to the eye chamber among the agents (Fig. 2b). There is not much to separate Oxane HD from HSO 1.07 and HSO 1.20. The 11% silica fluid has a very high angular velocity relative to the eye chamber, which is also very similar to F6H8 and SF<sub>6</sub>.

The time required for the agents to come to rest inside the chamber after the chamber stopped also varied. After the chamber stopped (at time > 0.3 seconds), SF<sub>6</sub> and F6H8 were the earliest agents to come to rest (Fig. 3). The time needed for Densiron 68 to come to rest was similar to those required for HSO 1.07 and HSO 1.20. Both Oxane HD and 11% silica fluid needed a significantly longer time than Densiron 68 to come to rest.

### DISCUSSION

“Heavy” additives such as semifluorinated alkanes and alkenes are commonly used in the formulation of HSO such as Densiron 68<sup>7</sup> (SO and perfluorohexyloctane, F6H8) and Oxane HD<sup>8</sup> (SO and partially fluorinated olefin, RMN3). Densiron 68 and HSO 1.07 and HSO 1.20 show a similar fluidic behavior as conventional SO in a previous study.<sup>14</sup> On the other hand, Oxane HD shows a quite different flow behavior. Oxane HD needs a significantly longer time after the chamber stopped to reach maximum displacement than Densiron 68 and HSO 1.07 and HSO 1.20 (Fig. 3). Oxane HD has a smaller maximum angular displacement (Fig. 1b) and a higher relative velocity (Fig. 2b) than Densiron 68, given that Oxane HD has a shear viscosity (3800 millipascal seconds [mPa · s]) that is much higher than that of Densiron 68 (1400 mPa · s). This finding seemed to contradict the result in our previous study<sup>14</sup> that showed that SO with a higher shear viscosity tended to have a smaller relative angular displacement and lower angular velocity relative to the chamber wall during the chamber rotation. In the previous study, all oils tested were polydimethylsiloxane (PDMS). No mixtures or solutions of two or more different substances were tested. In the current study, Densiron 68 returned to its original position soon after the chamber stopped (Supplementary Video S1). This flow was similar to those of the homogeneous PDMS-based SO<sup>14</sup> and fluorosilicone oil (HSO 1.07 and HSO 1.20). However, Oxane HD needs a much longer time to return to its initial position after reaching the maximum position of displacement (Supplementary Video S2). This behavior is different to other HSO agents such as Densiron 68, HSO 1.07, and HSO 1.20.



**FIGURE 1.** (a) Angular position of various agents inside the eye model chamber at the start and end of the motion of the eye chamber. Images tagged with number 1 indicate start of the motion of the chamber, and those tagged with number 10 indicate the end of the motion of the chamber. (b) Angular displacement versus time of the eye chamber and different HSOs during 90° motion. The *pink region* indicates the period in which the chamber accelerates; *brown region* indicates the period in which the chamber rotates at a constant velocity; *blue region* indicates the period in which the chamber decelerates.

Differences in flow behaviors between Densiron 68 and Oxane HD suggested that the effects of the heavy additives on the fluidic properties of the base fluid should also be taken into account in the design of HSOs. Previously, it was demonstrated that RMN-3 in Oxane HD was not distributed homogeneously within SO, by using *in vivo* and *in vitro* nuclear magnetic resonance imaging.<sup>17</sup> Differences in the flow behaviors between Densiron 68 and Oxane HD may be due to differences in solubility and extent of segregation of the heavy additives in the base SO fluid correspondingly.<sup>12</sup> The heavy additive in Oxane HD, RMN-3, may not dissolve in SO as well as F6H8 does in Densiron 68, which alters the flow of the resultant mixture subjected to eye movements. The flow behavior of Oxane HD inside the eye chamber model might therefore be a combination of 1 of 2 distinctive flows. In addition to the latency of stopped motion after the eye-like motion, both the relative motion and the relative velocity increase in the case of Oxane HD compared with Densiron 68. The increase in relative velocity will lead to the increase in shear rate acting on the SO-aqueous and SO-eye wall interfaces inside the eye cavity during eye movements. As shear force is the product of shear rate and viscosity, the increase in shear rate would lead to a higher shear force acting on the SO. This results in a higher propensity of SO to emulsify.<sup>14</sup> In current clinical practice, most surgeons believe that Densiron 68 is more emulsification resistant than Oxane HD,<sup>12</sup> based on their experience. This clinical observation might be related to such a different flow behavior between the two compounds.

The base fluid among all commercially available HSOs varies, but most of the choices are SO with high viscosity. For

example, the base fluids of Densiron 68 and Oxane HD are 5000 mPa · s SO and 5700 mPa · s SO, respectively. The heavy additives of these two HSOs are of low viscosity. Clinical studies have shown the early emulsification of these HSOs.<sup>12,18,19</sup> The heavy additives are not viscous in nature, and therefore they are suspected of causing the early emulsification. The 11% silica fluid has a different design than either Densiron 68 or Oxane HD. The viscosity of its base fluid is very low, only 22.5 mPa · s. The dissolved silica particles significantly increase the resultant viscosity to 2000 mPa · s. The resultant mixture has a greater tamponade efficiency than Densiron 68 and Oxane HD.<sup>20</sup> However, 11% silica fluid shows a different flow behavior than the other HSO candidates. The 11% silica fluid does not flow like either Densiron 68 or Oxane HD and other viscous tamponade agents. Instead, the flow of 11% silica fluid is similar to that of the fluidic agent F6H8, with ripple-like flowing behavior observed during the movement (Supplementary Videos S3, S4). It also takes a longer time to reset to its initial position after the eye chamber stops moving. This phenomenon may also be due to a certain degree of segregation of the two components in 11% silica fluid. The base fluid of 11% silica fluid, 556 cosmetic grade fluid, is a polyphenylmethylsiloxane with low viscosity and specific gravity. The additive Aerosil R972 Pharma silica (Evonik, Essen, Germany) increases both the viscosity and specific gravity. If the two components segregate, the upper layer of 11% silica fluid in the chamber would be the less viscous base fluid, and the lower part would be more viscous, containing the silica. Under conditions of the eye-like motion, the lower viscous layer moves much

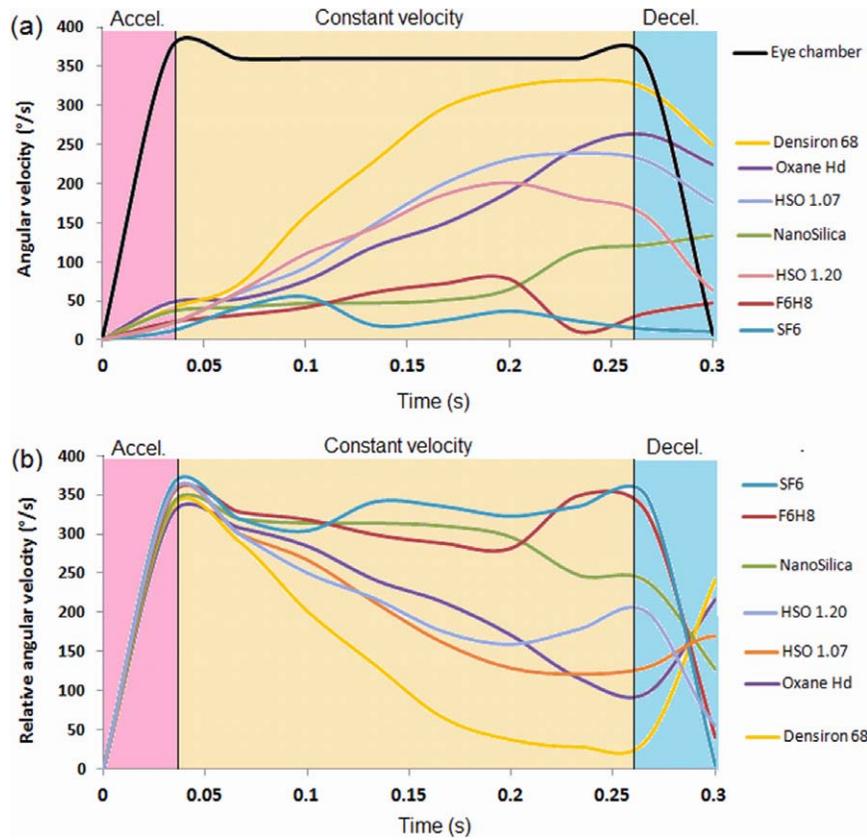


FIGURE 2. (a) Angular velocity profiles of the eye chamber and different HSOs and agents during 90° motion. (b) Angular velocity profiles of the eye chamber and different HSOs and agents relative to the chamber during 90° motion. The pink region indicates the period in which the chamber accelerates; brown region indicates the period in which the chamber rotates at constant velocity; blue region indicates the period in which the chamber decelerates.

faster than the less viscous upper layer due to differences in diffusion of momentum between the two layers. Therefore, ripples are observed in 11% silica fluid inside the chamber during the rotation of the chamber. This ripple-like behavior is similar to the flow of F6H8, which has a viscosity of only 3.4 mPa · s. Our results show that 11% silica fluid has a higher motion and velocity in the eye chamber relative to those of

Densiron 68 and Oxane HD. This might cause an increase in shear force between the 11% silica fluid phase and the water phase. This may trigger an earlier and more severe emulsification. On the other hand, the elasticity property of the resultant 11% silica fluid may hinder the emulsification. Because 11% silica fluid has not been involved in a clinical trial, its emulsification resistance in vivo remains unknown.

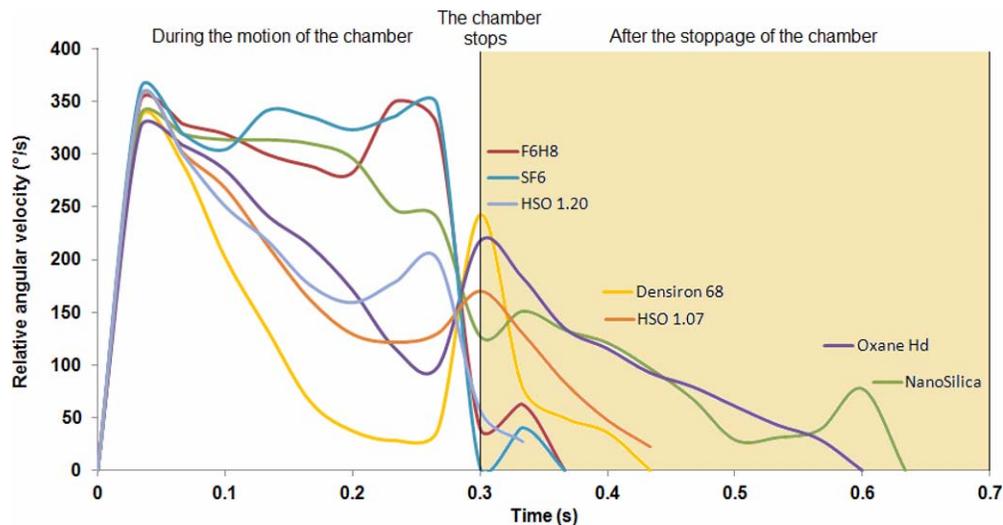


FIGURE 3. Angular velocity profiles of different HSOs and agents relative to the chamber during and after the motion of the chamber. The brown region indicates the period after the chamber stops.

There is a limitation in this study because the chamber was underfilled with tamponade agent. We chose to fill the model chamber to approximately 80% (5 of 6.3 mL). We appreciate that clinically, a degree of underfill could occur as a result of incomplete vitrectomy and gel compression by gas or silicone.<sup>21</sup> Nevertheless, a fill of 80% is not so realistic. Clinically, a much more complete fill is achieved especially when SO is injected after air exchange.<sup>22</sup> From the point of the experiment, filling beyond 80% led to difficulty. The shape of silicone inside the chamber was rounded, because it was hydrophobic. In the past, we have showed that when silicone filled a near-spherical cavity like the eyeball, the relationship between volume (percentage fill) and linear dimension of the bubble (height) was exponential.<sup>16</sup> When the fill was much more than 80%, the tamponade bubble “height” would be nearly the same length as the diameter of the chamber. In other words, it would be like visualizing a circle inside a circle. It was difficult to accurately measure the meniscus and the position of the bubble (relative to the chamber) using photographic means. In a recent publication, we showed that the relative movement and speed depended on a number of factors such as the presence of an indent, viscosity of SO, and extent of SO fill. Of these factors, the extent of SO fill was the least important.<sup>23</sup> Crucially, for this study, the method aimed at comparing like with like. All tamponade agents used were 5 mL in volume (approximately 80%). We therefore believe these results are valid.

## CONCLUSIONS

In this study, we showed that the viscosity of HSO is not the sole parameter with which to determine the behavior of HSO during eye movements. Densiron 68 has a flow behavior similar to that of the conventional SO as well as the homogenous fluorosilicone oil. Both Oxane HD and 11% silica fluid show flow patterns of a combined 1 of 2 distinctive flows. This could be explained by the segregation of the additives and the base oil. The solubility and the stability of the additives in the base SO alter its flow when subjected to eye movements, which may contribute to the emulsification in vivo.

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