In Vitro Modeling of Emulsification of Silicone Oil as Intraocular Tamponade Using Microengineered Eye-on-a-Chip

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Purpose. There is a lack of a standardized methodology or a physiologically realistic in vitro model to investigate silicone oil (SO) emulsification. In this study, we replicated the SO–aqueous interface within a microfluidic chip to study the formation of SO emulsion droplets in the eye cavity.

Methods. A chip made of poly(methylmethacrylate) was used to represent a cross-section of the posterior eye chamber. A retinal ganglion cell line was coated on the inner surface of the chamber to mimic the surface property of the retina. Silicone oil of different viscosities were tested. The SO–aqueous interface was created inside the chip, which, in turn, was affixed to a stepper-motor-driven platform and subjected to simulated saccadic eye movement for four days. Optical microscopy was used to quantify the count and size of SO emulsified droplets.

Results. Among SO of different viscosities, SO 5 centistokes (cSt) emulsifies readily, and a high number of droplets formed inside the chip. Silicone oil 100 cSt led to fewer droplets than 5 cSt, but the droplet count was still significantly higher than other SO of higher viscosities. There were no significant differences in the number of droplets among SO with viscosities of 500, 1000, and 5000 cSt. In all SOs tested, the number of droplets increased, whereas their size decreased with longer duration of simulated saccades.

Conclusions. The study platform allows quantification of the number and size of emulsified SO droplets in situ. More importantly, this platform demonstrates the potential of microtechnology for constructing a more physiologically realistic in vitro eye model. Eye-on-a-chip technology presents exciting opportunities to study emulsification and potentially other phenomena in the human eye.

Keywords: emulsification, eye-on-a-chip, silicone oil, tamponade, vitreoretinal surgery

Silicone oil (SO) tamponade is commonly used for the repair of complicated retinal detachment,[1] proliferative vitreoretinopathy,[2] ocular trauma,[3] and giant retinal tears.[4] It was first introduced in vitreoretinal surgery in 1962[5] and has since been widely used in combination with pars plana vitrectomy.[6]

Silicone oil emulsification is a significant complication that can affect the structures in both the anterior and the posterior segments.[7] Its occurrence is primarily due to the shear stress applied to the SO–aqueous interface in the eye induced by eye movements.[8] In the past decades, research has focused on reducing in vivo SO emulsification by modifying the chemical structure or the physical properties of SO.[9,10] Various kinds of SO with different densities and viscosities are currently available on the market. These new SOs include high-molecular-weight additives that claim to make the SOs easier to inject but more resistant to emulsification.[11] These SOs deserve thorough evaluation and comparison with existing SOs. There is, however, a lack of gold standard for comparison, because there is no widely accepted methodology for testing the propensity for SO to emulsify and for quantifying the droplets once they are formed.

Existing methods for testing emulsification rely on in vitro models that have limitations. Silicone oil tamponade inside a patient's eye consists of three phases in contact with one another, namely SO–retina, retina–aqueous, and SO–aqueous.[12] Up to now, simulation of the retina has been crude, relying simply on albumin coating of PMMA to render the surface more hydrophilic.[13,14] Different forms of mechanical agitation including vortex mixing,[15] sonication,[16] and homogenization[17] have been used to provide the energy input to induce emulsification. In the eye, however, such vigorous forces (or very high speeds) are inconceivable and, as such, are not a good mimic of the physiological conditions that give rise to emulsification. Lastly, quantification of emulsification inside the eye is probably very unreliable. Slit-lamp biomicroscopy can only detect large emulsified droplets.[18] Our group has recently shown that most droplets removed from patients' eyes are approximately 1 μm in diameter, well below the size that could be detected by the slit-lamp.[19] Counting and sizing of droplets involved collecting washings from patients during surgical procedures of silicone oil removal. Such attempts at ex vivo quantification are prone to errors due to droplets adhering to

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any vessel (or syringe) used to collect the washing and to any dilution effect from using infuscate to wash out the SO from the eye.

Recently, microscaled engineering technologies were applied to create the in vitro cell culture microplatforms that go beyond current cell culture models. These technologies provided unprecedented opportunities to recapitulate tissue–tissue interfaces, spatiotemporal chemical gradients, and dynamic mechanical microenvironments of living organs. The resultant platforms are often known as "organs-on-a-chip"[20]; examples include lung,[21] heart,[22] and kidney chips.[23] To date, relatively little work has been done on eye-on-a-chip. There is a cornea-on-a-chip that aims to provide a potential alternative to the standard transepithelial permeability assay (which normally uses live rabbits in testing corneal integrity).[24] To the best of our knowledge, the features of the posterior segment of the eye have not been previously modeled. Experiments concerning the vitreous cavity must rely on animal studies that are inherently costly in time and money. There may also be ethical considerations in using live animals, especially when the results may or may not be directly applicable to humans. There is, therefore, a compelling case for a good model that can screen tamponade and other agents before testing them in animal or humans.

In this study, we present an eye-cavity-on-a-chip platform that uses microengineered devices subjected to simulated eye movement to mimic both the mechanical and physiological microenvironments of SO tamponade. Mechanically, we mimicked saccadic eye movement. Physiologically, we used ganglion cells to line the cavity to recreate oil–aqueous–retina interactions. The whole chip is transparent, allowing quantification of droplets in situ, using optical microscopy.

Materials and Methods

Silicone Oil

Silicone oil with five different viscosities (5, 100, 500, 1000, and 5000 centistokes [cSt]) were used in this study. Silicone oil 5, 1000, and 5000 cSt (Alamedics GmbH, Dornstadt, Germany) were of medical grade, whereas SO 100 and 500 cSt (Aladdin, Shanghai, China) were of commercial grade.

Design of the Eye-Cavity-on-a-Chip

The inner structure of the eye-cavity-on-a-chip was designed using computer-aided design software (AutoCAD 2014; Autodesk, San Rafael, CA, USA) and fabricated by laser engraving (model VLS2.30; Universal Laser Systems, Scottsdale, AZ, USA) PMMA sheets (Fig. 1). The eye chip consisted of five 1-mm-thick engraved PMMA layers. The five layers were stacked and fused to each other by chloroform solution applied to the edges of the sheets. The middle layer was a 25-mm-diameter central chamber, which is analogous to the cross-section of the posterior segment of the eye. An indentation was designed to represent the shape of the lens. Fresh cell culture medium was exchanged daily by infusion, using a syringe pump (Longer Pump, Baoding, Hebei, China) via the perfusion channel that encircled the central chamber. Microscaled channels were designed to connect the perfusion channel with the central chamber. This allowed the exchange of nutrients from the perfusion channel to the central chamber, nourishing the retinal cells for the duration of the experiment.

There were four inlets/outlets placed at the corner of the topmost layer of the chip. Two of them were connected to the central chamber in the middle of the chip (Fig. 1, blue arrows) and the other two were connected to the outer perfusion channel (Fig. 1, red arrows).

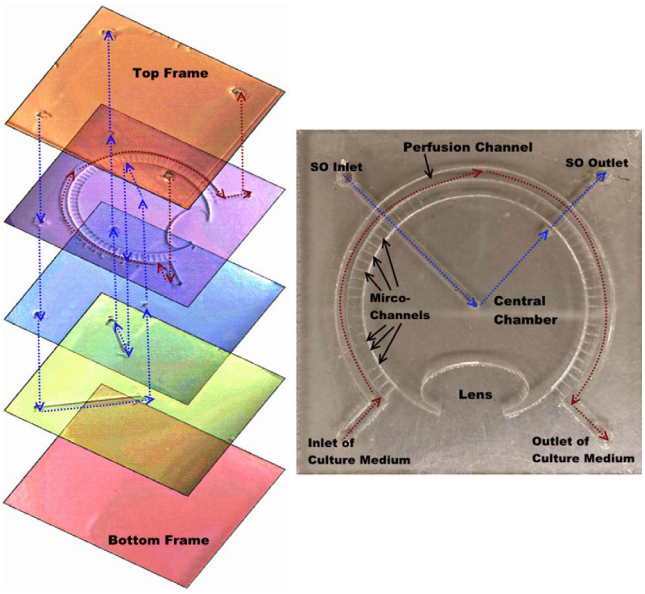

Figure 1. Microengineered eye chip mimicking the cross-section of the vitreous chamber of the eye. *Red arrows* indicate the routes of the culture medium within the chip. The nutrients in the culture medium enter the central chamber through the microchannels by diffusion. *Blue arrows* indicate the route of injection of SO into the chamber. This design separates the SO inlet and outlet from the microchannels, allowing infusion of SO directly at the center of the central chamber. Each layer here is given a different color to facilitate illustration. In reality, all layers are transparent.

SO–Aqueous Interface

A fibronectin solution (10 μg/mL in Dulbecco's modified Eagle's medium) was infused into the central chamber of the chip and incubated at 37°C for 4 hours. In this manner, the inner surface of the central chamber was coated with fibronectin, facilitating cellular attachment. A retinal ganglion cell line (RGC-5)[25] was then seeded and cultured until confluent, thus lining the entire inner surface, namely the wall, ceiling, and floor of the chamber. After successful cell attachment, the central chamber was filled with the cell culture medium. Then, 0.4 mL SO was infused into the central chamber. A SO–aqueous interface formed spontaneously. The layer of cells acted as a coating, preventing adhesion of SO to the inner surface of the central chamber.

Simulated Saccadic Eye Movement

We previously developed a stepper-motor-driven platform (Step Motor platform model C4/MD2; Arrick Robotics, Tyler, TX, USA) to simulate saccadic eye movements.[8] The shaft encoder (Baumer Electric, Frauenfeld, Switzerland) and data acquisition device (National Instruments, Austin, TX, USA) recorded the angular displacement, velocity, and acceleration of the actual motion executed.

Typical human saccadic eye movements have amplitudes between 5° and 15°, a maximum angular velocity between 300°/s and 400°/s and a duration of approximately 50 ms.[26,27] The simulated saccadic eye movements in our platform was set to an amplitude of 10°, an angular velocity of 390°/s, and a duration of 50 ms. We previously showed that the velocity profile of our system closely mimicked that of typical saccades

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in healthy adult humans.[8,28,29] The programmed motion was a continuous set of left and right saccades with a frequency of 0.5 Hz. The experiment was run continuously for 4 days. Each SO agent was tested on seven individual chips (i.e., $n = 7$ for each group).

Quantification of SO Emulsions

The emulsified SO droplets were assessed by light microscopy and digital photography daily for 4 days. The number and size of the droplets were counted and measured manually using the open-source ImageJ processing software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA). Data were presented using box and whisker plots.

Results

Replication of Conditions for Emulsification Inside Human Eyes

The retinal ganglion RGC-5 cell line not only lined the perimeter of the chip but also formed a confluent sheet on the wall, ceiling, and floor of the central chamber (Fig. 2a). With time, a significant change occurred in the color of the culture medium from reddish pink to yellowish orange. This was due to a drop in the pH of the culture medium. As such, the color change was an indicator of the viability of the cells. Byproducts of cell metabolism were slightly acidic and caused the color change (Fig. 2b). An obvious SO–aqueous interface was observed in the central chamber. The thickness of the aqueous film around the SO was roughly 500 μm (Fig. 2c). Silicone oil droplets of various sizes were observed in the aqueous layer (Fig. 2d).

Number and Size of Emulsified SO Droplets Observed in the Eye Chip

Number. Among all the different SOs tested, SO 5 cSt formed the largest number of emulsified droplets (Fig. 3a). Emulsification of SO 5 cSt was observed from day 1. Silicone oil 100 cSt had fewer emulsified droplets than the 5-cSt SO. The number of droplets associated with 5 and 100 cSt in turn was significantly higher than that observed with the more viscous SO (Fig. 3b). Flocculation (when droplets clumped together) of emulsified droplets was observed with both the SO 5 cSt and the 100 cSt (Figs. 4a, 4b). The number of droplets of SO 5 and 100 cSt increased with time over the 4-day period with continued motion. There were no significant differences between the other 3 SOs, namely, 500, 1000 and 5000 cSt, in terms of the number of droplets observed inside the chip (Fig. 3b). The number of droplets also increased with time in the 3 more viscous oils, but less dramatically than in the 2 less viscous oils.

Size. Generally, the more viscous the SO, the bigger the size of droplets formed. The median diameter of the droplets decreased with time for all SO. In addition, the range of droplet sizes also decreased with time such that the median size of droplets from SOs with different viscosities converged after 4 days (Fig. 5).

Discussion

The propensity to emulsify is the major drawback for SO long-term tamponade. The migration of emulsified SO droplets to various locations causes a number of postoperative complications such as secondary angle closure glaucoma in the anterior segment[30] or possible retinal toxicity with intraretinal infiltration.[31] For reasons mentioned above, accurate quantification of SO emulsification ex vivo is difficult and almost impossible in situ. In actual human eyes in patients, there are many confounding factors that influence SO emulsification. These include variations in surgical procedures among surgeons. We recently suggested that the presence of scleral buckle, the degree of fill, and the SO viscosity all influenced the propensity for oil to emulsify.[32] The availability of surfactants is another confounding factor. Fibrinogen, fibrin, gamma-globulin, glycoprotein, and lipoproteins and serum protein can all stabilize SO droplets.[33] In healthy patients, the amount of such surfactants in the aqueous is very small. In patients with retinal detachment and postoperative inflammation, the amount of such proteins in the aqueous increases[34,35] but each to a different extent due to blood ocular barrier breakdown, all of which make a fair judgment on the propensity or resistance of any SO difficult to make using clinical studies.

In vivo animal studies are not efficient for studying the emulsification resistance of various novel SOs because eye movements of animals cannot be controlled. Some animals, notably rabbits, do not change posture when they sleep, nor do they make large saccadic eye movements. However, rabbits are most often used for in vivo screening of novel silicone oils and other tamponades.[36,37] Droplets inside the animals' eyes cannot be easily monitored in situ. Emulsification in human often takes several months before they are obvious.[38] There are difficulties in conducting long-term animal studies. Animals may die or have other complications such as cataract and inflammation during the experimental period. Taken together, they provide good justification for a valid in vitro model to screen novel silicone oils.

We aim to use this in vitro eye-cavity-on-a-chip to answer clinically relevant questions about SO emulsification. Silicone oils with different viscosities and formulations are available on the market for various purposes in vitreoretinal surgery. Low-molecular-weight SO (e.g., 5 cSt) has been proposed for use as an infusion liquid to facilitate vitreous base shaving and drainage of subretinal fluid.[39] Our eye-cavity-on-a-chip enabled confirmation of the widely held belief that SO 5 cSt emulsifies readily. Many droplets were observed on day 1, and the number of droplets increased exponentially over the following 3 days. As expected, the average droplet size became smaller over time. In clinical situation, small droplets tend to migrate to the subretinal space and other locations, increasing the risks of various complications.[40] Therefore, SO 5 cSt should only be used with caution as an intraoperative tool and not as a tamponade to be left inside the eye even for a few days.

There has been a long-standing debate about the choice between 1000- and 5000-cSt SO for long-term tamponade. Silicone oil 1000 cSt is more user friendly and can readily be injected and removed even using small-gauge surgery. Silicone oil 5000 cSt is believed to be more resistant to emulsification.[15] The general and widely accepted concept is that SOs with a higher viscosity have a higher resistance against emulsification. This is supported by in vitro studies that used nonphysiological mechanical forces to induce emulsification.[11,12,15] The superiority of SO 5000 relative to 1000 cSt could be challenged. Certainly there is no clear evidence from randomized controlled clinical trials to strongly support the choice of SO 5000 cSt.[41] Our previous studies have shown that the increase in viscosity of SO decreased the average but not the maximum shear rate acting on the SO bubble.[8,32] The maximum shear rate may be more important in causing emulsification. Furthermore, it is believed that human saccadic eye movements are stereotypical, meaning that they have similar velocity profile and amplitude every time. The shear stress acting on the SO phase is derived from the equation [shear

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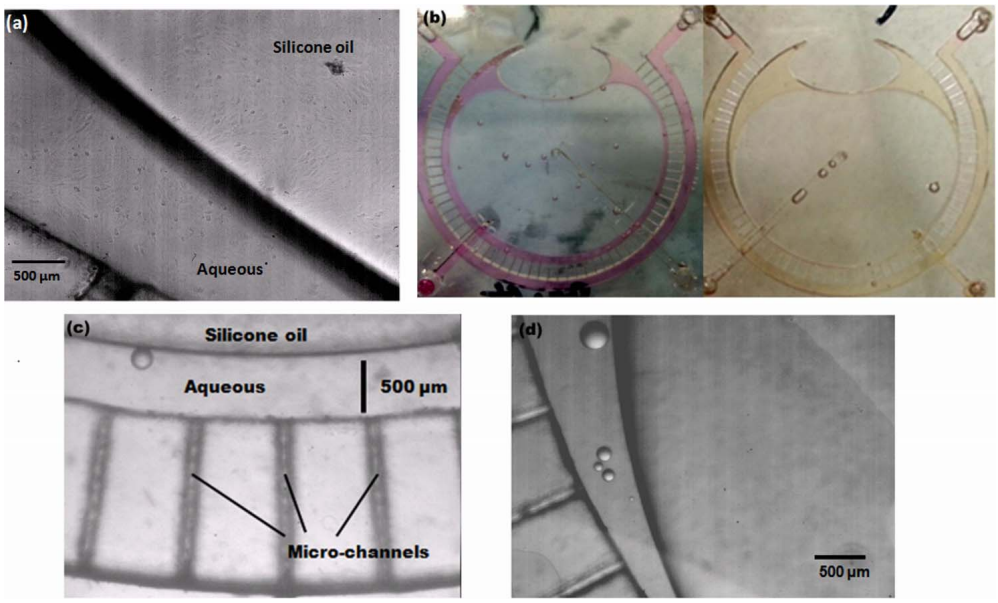

FIGURE 2. (**a**) Growth of the RGC-5 cell monolayer inside the central chamber. (**b**) The chamber seen at the start and after 1 day of the experiment. The color of the medium in the perfusion channel of the eye-chip is seen at the start of the experiment (*left*) and 1 day after the experiment (*right*). A significant change in color, from pink to yellowish orange, is observed. (**c**) The SO–aqueous interface at the central chamber. The aqueous film has a thickness of approximately 500 µm. (**d**) The emulsified SO droplets found within the eye chip.

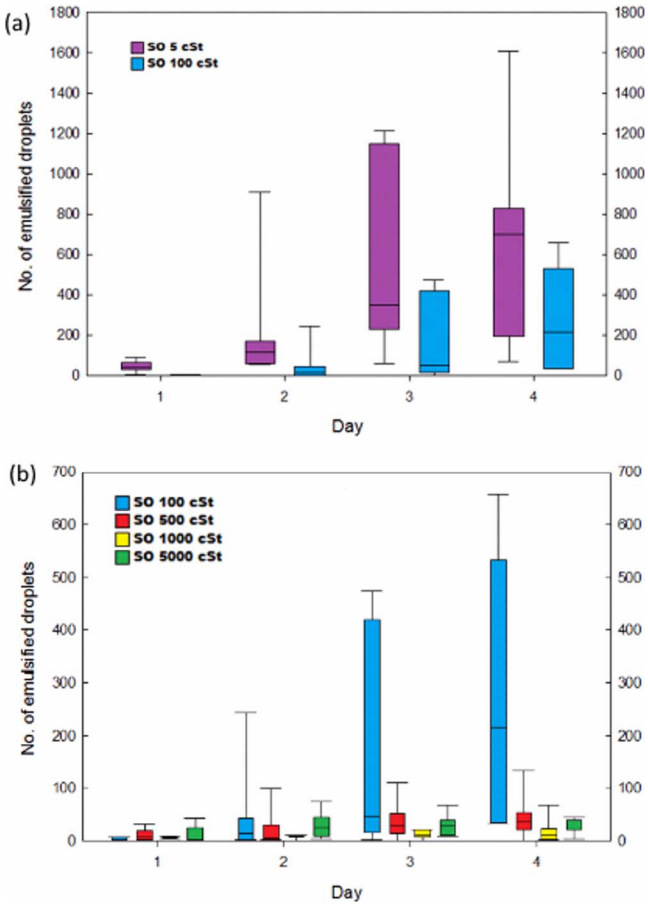

FIGURE 3. A box and whisker plot of the number of the emulsified droplets prepared with different SOs on days 1, 2, 3, and 4. (**a**) Comparison between SO 5 and 100 cSt. (**b**) Comparison among SO 100, 500, 1000, and 5000 cSt. $n = 7$ for each SO.

stress = shear rate × shear viscosity]. If human eyes moved with the same peak velocity, then an eye filled with an SO with a higher viscosity would be subjected to a higher shear stress. Therefore, any advantage gained from using SO with higher viscosity might be offset by the greater forces acting on the oil–aqueous interface. It might well be that beyond a certain viscosity, any further increase would not necessarily be advantageous.

In this study, we showed that the increase in shear viscosity of SO from 5 to 500 cSt decreased the number of emulsified droplets formed during saccadic-like eye motions. However, there were no significant differences between SO 500 and 1000 cSt or between 1000 and 5000 cSt in terms of both the number and the size of the emulsified droplets after 4 days (Fig. 3). Our results may explain why previous clinical studies failed

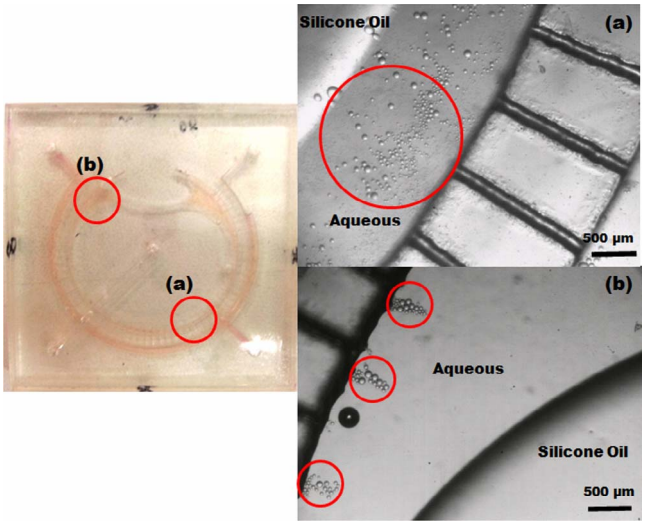

FIGURE 4. Flocculation of emulsified SO droplets in the aqueous phases of (**a**) 5-cSt SO and (**b**) 100-cSt SO.

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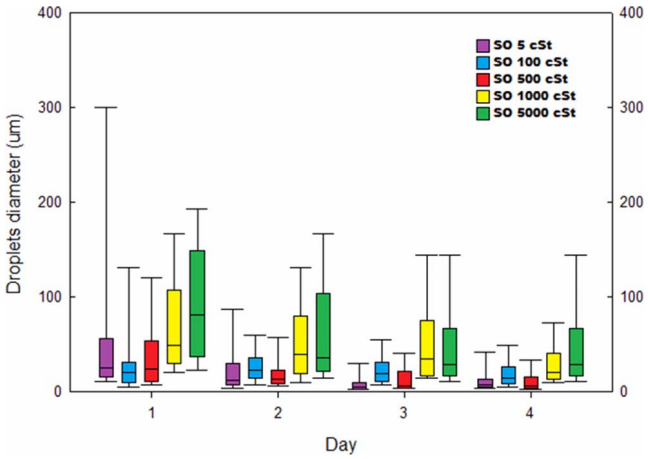

Figure 5. A box and whisker plot of the diameter of the emulsified droplets prepared with different SOs on days 1, 2, 3, and 4.

to show clear statistical differences between SO 1000 and 5000 cSt.

Vitreoretinal surgeons are often interested in the size of the emulsified SO droplets in vivo. Using measurements based on the Coulter principle, our group previously showed that most emulsified droplets from patients were approximately 1 μm.[19] In this study, however, the emulsified droplets at the SO–aqueous interface are examined only manually by light microscopy, which limits the observable droplet diameter to approximately 5 μm. Our results did not provide the full quantification of size or of number distribution of the emulsified droplets generated within the chip. Physical phenomena like coalescence[42] and Ostwald ripening[19,43] may have a significant effect on the size distribution of the in vivo SO droplets over a longer period of time. Our study only focused on emulsifications up to 4 days and therefore had not fully taken these phenomena into account. From our results, however, they showed a tendency for both the size and the range of sizes to decrease over the four-day period (Fig. 5).

The microengineered eye chip in this study is a two-dimensional (2D) platform that models the central cross-section of the eye cavity. The flow behavior of the SO in this 2D model may be different from that of 3D system inside an actual eye cavity. However, the rotational movement is in the plane of the chip. Similarly, most saccadic eye movements are horizontal. It might be said that our model tried to mimic the transverse cross-section of the eye. All the SO samples were tested in the same platform and thus subjected to the same motion that induces emulsification. Despite its limitation, we believe this platform is currently the best model for comparing different SOs.

Conclusions

This study is the first that aims to replicate the intraocular environment within an engineered chip. Our eye-cavity-on-a-chip platform successfully demonstrated the formation of the SO–aqueous interface during simulated saccadic eye movement and replicated the conditions for formation of emulsified droplets. We recognized that there are many aspects of the posterior segment of the eye that could be studied in future experiments using this platform, including the secretion of aqueous humor from the ciliary bodies,[44] the elasticity of scleral tissue,[45] and the regulation of vitreoretinal oxygen transport.[46] The current microengineered technologies offer an opportunity to integrate all these suggested features onto a single miniaturized chip. With advances in tissue engineering, we conclude that the eye-on-a-chip can offer much functionality and open up many opportunities for future research.

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