

Impact case study (REF3b)

<p>Institution: University of Liverpool</p>
<p>Unit of Assessment: 9 - Physics</p>
<p>Title of case study: New Silicon Oils for use in the Treatment of Retinal Detachment</p>
<p>1. Summary of the impact</p> <p>The University of Liverpool (UoL) has developed novel tamponade agents that are used to treat retinal detachments. These tamponades are modified silicone oils that have an increased extensional viscosity. This makes it easier for vitreoretinal surgeons to inject them into the eye and, experimentally, they have an increased emulsification resistance. The technology has been licenced to Fluoron GmbH, who manufacture these products under the name Siluron® 2000 and Siluron® Xtra. Siluron® 2000 has been on the market worldwide since 2008 and is used to treat retinal detachment patients, providing an impact to health by enhancing their clinical outcomes. Siluron® Xtra was launched in July 2013.</p>
<p>2. Underpinning research</p> <p>Retinal detachment is an important cause of blindness in the western world. It is the final common pathway for many disease processes including diabetic retinopathy and age-related macular degeneration. Treatment involves the removal of vitreous humour from the eye and its replacement with silicone oil to cause closure of the retinal tear. The emulsification of silicone oil-based tamponade agents, which are used in the treatment of complex retinal detachments, is a significant clinical problem. This causes clouding of vision and adverse biological responses, including inflammatory reactions and blocking of the fluid outflow from the eye, potentially leading to glaucoma. Currently, high shear viscosity oils are used to counter emulsification, but the higher the shear viscosity the more difficult the oils are to inject and remove from the eye. This project took a multidisciplinary approach to improving tamponades involving Dr Michael Garvey (a Senior Research Fellow in the Department of Physics, UoL) and Prof Rachel Williams (a senior lecturer in Department of Clinical Engineering, UoL) in collaboration with Prof David Wong, Consultant Vitreoretinal surgeon, University of Hong Kong and Honorary Professor (UoL) and Mr Theodor Stappler, Honorary Lecturer (Clinical, Royal Liverpool University Hospital) who provided strong clinical input. A highly qualified surfactant chemist (Dr Michael Day, Postdoctoral research associate, UoL), who was based in the Physics Department, studied the mechanisms involved in the formation of the emulsions in the eye. The physics-based team, following an idea of Garvey's, showed that the process of emulsification in the eye results from the oscillation of the silicone/water interface under a shear force which leads to the pulling out of filaments of the oil into the aqueous phase. which then snap, resulting in the formation of persistent satellite silicone droplets. Further, they demonstrated that the addition of very high molecular weight polymers to the oil increases its extensional viscosity and prevents filament snapping and satellite droplet formation. The increase in extensional viscosity was achieved by adding a range of high molecular weight additives at different concentrations to clinical grade silicone oil. The underpinning research was funded by EPSRC (EP/C546679-1) in 2005-2006 under the post-doctoral mobility scheme to allow Dr Day to use his expertise to address this cross-disciplinary problem.</p> <p>This project demonstrated that modification of standard clinical grade silicone oil tamponade agent (Siluron® 1000, Fluoron GmbH) with a low percentage of a very high molecular weight (423k) polymer of the same chemistry increased the extensional viscosity of the oil and reduced its emulsification [1, 2]. Furthermore, these silicone oil blends have a lower shear viscosity than Siluron® 5000 (Fluoron GmbH), the current high viscosity clinical grade silicone oil, and thus are advantageous in terms of ease of injection into and removal from the eye [3]. A patent [4] has been filed to protect these findings (WO 06/413269) in the EU, US and Canada and has been granted in Australia, China, Hong Kong and Japan (15/02/2013). Further funding was received from Fluoron GmbH (£58,629, 2007) to develop a product and the University has negotiated a licence deal with Fluoron GmbH that brings in annual royalty payments.</p>

3. References to the research

Key Outputs

1. Williams RL, **Day M**, **Garvey MJ**, English R, Wong D. Increasing the extensional viscosity of silicone oil reduces the tendency for emulsification. *Retina* 30(2):300-304, 2010 DOI: 10.1097/IAE.0b013e3181babe0c.
2. **Day M**, Blanchard RL, English R, Dobbie T, Williams R, **Garvey M** and Wong D, Shear and Extensional Rheometry of PDMS Tamponade Agents Used in Vitroretinal Surgery, AIP Conference Proceedings 1027, 1411 (2008); doi: 10.1063/1.2964592
3. Williams RL, **Day M**, **Garvey MJ**, Morphis G, Irigoyen C, Wong D and Stappler T. Injectability of silicone oil-based tamponade agents. *B. J. Ophthalmol.* 95: 273-276, 2011 DOI: 10.1136/bjo.2010.192344
4. **Garvey MJ**, Williams RL and **Day M**. Composition for treatment of a detached retina and method of production thereof WO 06/413269 May 2006

Original grants

2005-2006. **EPSRC**. Identification of colloid science routes to improve the clinical performance of tamponade agents, £65,717, PI RL Williams, Cols **MJ Garvey**, **M Day**

2007-2008. **Fluoron GmbH**. Producing novel tamponade agents, £58,629 PI RL Williams

4. Details of the impact

This interdisciplinary project developed a new tamponade agent to enhance the clinical outcome after treatment of retinal detachments. The medical team involved were faced with the problem that standard tamponade agents are based on silicone oils which can emulsify in the eye and cause adverse side effects. They discussed this with Garvey (Physics Department), who investigated the reasons for the emulsification. His underpinning research also suggested the solution to the problem and provided the required proof of principle that a silicone oil with an increased extensional viscosity had much higher resistance to emulsification. The increase in extensional viscosity was achieved by the addition of a low percentage of a very high molecular weight polymer of the same chemistry to the silicone oil. Following on from this, the UoL established that the extensional viscosity property of the blend also made the material easier to inject in comparison with an equivalent silicone oil with the same shear viscosity but without the high molecular weight additive.

An additional benefit of this approach is that since no chemically different material has been added to the clinical grade silicone oil, the regulatory requirements were easily met. In 2007, a collaboration was established with Fluoron GmbH, a silicone oil tamponade manufacturer, to develop the proof of principle prototype into a clinical grade product. Fluoron GmbH licensed the technology from the University and have since contributed a minimum payment of £10k per year and paid all patent costs.

Fluoron GmbH launched the product, named Siluron® 2000, in 2008 (EC certification: CE 575554) [5-7]. It accounted for 32% of Fluoron's sales by units in the period 2008-13 with 34,208 sales by 30th September 2013 [8]. A second product, named Siluron® Xtra, based on this technology, was launched for sale in July 2013 (EC certification: CE 575554). This product has 10% of the high molecular weight additive, further increasing the resistance to emulsification while maintaining the ease of injection within the range of current clinical products. Fluoron GmbH have brought this second product to market in response to requests from vitreoretinal surgeons [5] and have sold 1,145 units part way through its first year of introduction [8]. These products have enabled Fluoron to gain new customers and reduce complaint rates by 40% [8].

The ultimate beneficiaries of this development are patients. Current tamponade agents are either

made from 1000mPas silicone oil that is known to emulsify in the eye and cause adverse effects for the patient, or 5000mPas silicone oil that is very viscous and difficult to inject, making surgery more difficult. All silicone oils are currently removed after 3-6 months because of the risk of complications resulting from their emulsification. The new Siluron® 2000 has a shear viscosity of 2000mPas, making it easier to inject than 5000mPas oil, but because of the increased emulsification resistance, it is less likely to cause adverse effects to the patient [9-11]. Another major advantage of Siluron® 2000 is that its extensional viscosity makes it easier to inject than an equivalent oil, meaning that smaller gauge instruments can be used to inject and remove it causing a significant reduction in trauma to the patient's eye due to the surgery. This also fits very well with the general move within vitreoretinal surgery to the use of smaller gauge instruments. Siluron® Xtra has a shear viscosity of 5000mPas and can therefore be injected and removed using existing surgical equipment but has been requested by clinicians owing to its enhanced resistance to emulsification and thus improved clinical outcome for patients.

This development is important because the patients requiring this treatment would go blind if not treated. The incidence of retinal detachment is reported as 1 per 10,000 of population per year and of these 15-20% are treated with silicone oil tamponades. Some vitreoretinal surgeons have so far not used oil-based tamponades because of the related complications and therefore the availability of an oil with increased emulsification resistance is expected to increase the availability of this treatment option. This is the first product specifically designed to address the problem of emulsification. Fluoron GmbH has sold over 25,000 units of Siluron® 2000. In 2012 the units were sold in 37 different countries, with the largest numbers going to Germany and Egypt and substantial numbers going to Singapore, Italy, Belgium and Switzerland. They have recently (August 2013) received a licence to sell Siluron® 2000 and Xtra in China and believe this to be a substantial market, expecting to sell over 1000 units in the first year. An audit of the use of Siluron® 2000 in St Paul's Eye Unit at the Royal Liverpool University Hospital on 20 patients reported: "Clinically it proved easy to inject and remove in a small-gauge setup. Anatomical success rates were comparable to our experience with standard 5000cst silicone oil, so was its safety profile." [12].

5. Sources to corroborate the impact

5. Fluoron GmbH website description of Siluron® 2000 and Siluron® Xtra http://www.geuder.de/media/raw/RZ_Brochure_Siluron_GB_25072013.pdf demonstrating commercial promotion of the products.
6. Fluoron GmbH website user report on Siluron family of products http://www.geuder.de/media/raw/User_Report_Siluron_Xtra_by_Stappler_2013_E.pdf providing a clinical testimonial of the product.
7. EC-Certificate for Siluron® 2000 and Siluron® Xtra <http://www.fluoron.de/index.php?myID=56&sprache=en> demonstrating compliance with EU regulations.
8. Letter from the Vice President of Sales and Marketing, and Senior Product Manager at Geuder (Fluoron), and accompanying sales data.
9. Caramoy A. Schröder S. Fauser S. and Kirchhof B. (2010) In vitro emulsification assessment of new silicone oils. Br. J. Ophthalmol. 94(4):509-512 DOI: 10.1136/bjo.2009.170852 demonstrating emulsification resistance in comparison with other tamponade agents evaluated by a different research group.
10. Caramoy A. Hagedorn N. Fauser S. Kugler W. Groß T and Kirchhof B. (2011) Development of emulsification-resistant silicone oils: Can we go beyond 200mPas silicone oil. Invest. Ophthalmol. Vis. Sci. 52(8):5432-5436 DOI: 10.1167/iovs.11-7250 Further demonstration of emulsification resistance by a different group.
11. Yau Kei Chan, Chiu-On Ng, Paul Knox, **Michael Garvey, Rachel Williams, and David**

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Wong (2011) Emulsification of silicone oil and eye movements *Invest. Ophthalmol. Vis. Sci.* 52:9721-9727 DOI: 10.1167/iovs.11-8586 demonstrating emulsification resistance using a different model designed by scientists at the University of Hong Kong to mimic clinical eye movement and its influence on oil emulsification.

12. **Theodor Stappler**, Lazaros Konstantinidis and **David Wong** Siluron 2000 Novel-Generation Silicone Oil: Proof of Concept and One Year Clinical Results *Invest Ophthalmol Vis Sci* 2012;53: E-Abstract 5792 providing evidence of clinical acceptability. This is an audited clinical study that used the new oil and evaluated clinical outcomes.