Zordera

ZERO-ORDER SUSTAINED DRUG DELIVERY TO THE RETINA FROM A NANOPOROUS FILM DEVICE

This article describes how a team of senior UCSF researchers, including Daniel Bernards, PhD, Robert Bhisitkul, MD, PhD, and Tejal Desai, PhD, are developing a nanoporous membrane-based implant which can significantly improve drug delivery to the back of the eye. Zordera, Inc, is the company set up to take the device through commercial development.

An increasing number of biologics and the emergence of biosimilars have focused attention on the development of advanced drug delivery technologies. This industry is expected to reach US$51 billion (£30 billion) by the year 2015, primarily driven by the introduction of new biologics, uptake of delivery platforms, and utilisation of controlled release systems.

Despite recent successes in the treatment of ophthalmic diseases, delivery of such therapeutics remains a challenge. To this end, in the laboratory of Tejal Desai and in collaboration with retina specialist Robert Bhisitkul at UCSF, a proprietary nano-engineered polymer film technology platform has been developed for long-term delivery of small and large molecule therapeutics.

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To further the commercialisation of this technology, Zordera, Inc, has been founded. Zordera's bioerodible nanotechnology platform is designed to enhance the utility and bioavailability of hard-to-deliver compounds by allowing continuous, sustained zero-order release of therapeutics, which can improve patient compliance and contribute to superior clinical and economic outcomes.

Currently, treatments for macular degeneration are typically injected into the eye, often monthly. On average patients receive 7.7 injections per year. Since these frequent injections are often required for many years, there is an increased risk of infection, retinal detachment and cataracts. A portion of the injected dose is broken down or cleared through the circulation before it even reaches its target, the retinal tissue. This low bioavailability is compensated for by increasing the initial administered dose, increasing the risk of toxicity. A proportion does reach the retina but during the two or three weeks following injection, the drug is present at the target tissue in steadily declining amounts.

Zordera's core technology is a nano-engineered device that allows transport of drug molecules from a reservoir through a nanometre-sized porous biodegradable polymer thin-film.

The thin film is manufactured by first creating an oxide mould, which has millions of nanowires each approximately the size of the intended drug molecule. A polymer solution is applied to the mould and once solidified, the oxide mould is chemically dissolved leaving just the polymer, with nanopores where the nanowires had been. The drug in pellet form is sealed in between two membrane layers to give a resulting device that is around 40 µm thick (see Figure 1).

By matching a target drug's molecular diameter to the pore size, drug molecule

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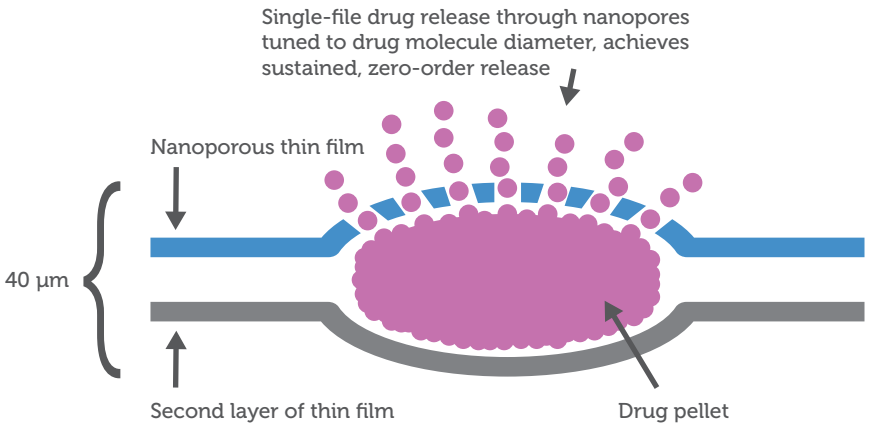

Figure 1: Schematic diagram showing the configuration of Zordera's nanoporous film device.

release from the membrane can be constrained to single-file – i.e. only one drug molecule at a time can leave through any given pore. This, together with decoupling drug release from subsequent device degradation, means that a precisely controlled release profile can be achieved throughout the life of the device. The device itself degrades safely later on, after the drug payload has been completely delivered.

Unlike many sustained delivery technologies, these nano-engineered polymer films are functionally tuneable to achieve a zero-order release profile such that drug concentration falls within a narrow range over the course of several months. This technology was also designed to address several key development issues that have prevented commercialisation of competing technologies. For example, to mitigate potential safety risks, the device is made of materials that are widely used in approved medical products and can be removed from the eye using standard surgical procedures, if necessary.

To support provider and patient adoption, the device is designed to be deployed with a standard gauge needle. To enable cost-effective and streamlined fabrication, sterilisation and packaging, its design is based on proven large-scale manufacturing processes.

To date, much of the development has taken place at the University of California, San Francisco (UCSF) under the support of the US National Institutes of Health (NIH) as well as grants from the Rogers Foundation (CA, US) and the Wallace H. Coulter Foundation (FL, US). Numerous *in vitro* and *in vivo* studies using model and therapeutic compounds have demonstrated safety and performance of the technology.

Sustained, zero-order delivery has been shown in excess of seven months with model therapeutic albumin, through four months with AMD therapeutic Lucentis®, and two months with rapamycin. *In vitro* stability of antibodies, such as Lucentis and IgG, has been demonstrated to be excellent, with no appreciable degradation over several months.

Safety in a rabbit model has been demonstrated over nine months with no inflammation, no increase in ocular pressure and no adverse effects. No device-related reports of iritis, cataract, endophthalmitis, vitreous haemorrhage or retinal detachment/degeneration have been observed. Histology similarly showed a lack of long-term adverse effects.

A number of aspects differentiate these devices from competing technologies. Tuning the design and properties of the nanostructured thin film device, it is possible to deliver therapeutic at a constant rate that is optimised for the desired drug delivery profile. Because of their thin film nature, these biodegradable devices can be furled to fit inside and be deployed by syringe. This provides more reliable drug levels in the eye, simplifies the administration of the product and minimises the potential for infections.

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Although initially under development for AMD, the device is also being tested for the treatment of increased intra-ocular pressure and inflammation. It also has potential in the treatment of glaucoma and uveitis.