Nanotechnology in ophthalmology

Dr Douglas Clarkson looks at how breakthroughs in nanotechnology are helping to treat eye disease

The concept of things at the small scale was first described by Richard Feynman in 1959 in his famous lecture on the theme of 'There's plenty of room at the bottom'. It was not until ground-breaking work by physicists at IBM who developed the atomic force microscope around 1990 that the concept of manipulating individual atoms was shown to be possible.

Today nanotechnology is generally accepted as the branch of science which deals with things in the range between 0.1nm (10^{-10} metres) and 100nm (10^{-7} metres). Individual atoms have sizes in the range 0.1nm to 0.3nm. Microelectromechanical systems (MEMS) devices exist on a slightly larger scale of things – typically between 10µm (10^{-5} metres) and 100µm (10^{-4} metres). A useful reference to identify the range of size of objects from nanotechnology upwards is provided by the National Nanotechnology Initiative (www.nano.gov/html/facts/The_scale_of_things.html).

A specific feature relevant to nanotechnology is that, as sizes of systems approach the nanotechnology range, component assemblies of atoms begin to exhibit different characteristics compared with larger scale associations of atoms.

The need for drug delivery at the small scale

Management of retinal disease is currently dominated by drug therapy using the delivery mechanism of intravitreal injection. This is not only time-consuming for clinical management but certainly distressing for the patient. It is also susceptible to the continuing risk of complications such as endophthalmitis, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.

It is likely that future research will more strongly focus on the mechanism of drug delivery into the eye as well as the composition and effectiveness of such anti-vascular endothelial growth factor (VEGF) drugs. In the drive for improved drug delivery systems for the eye, especially to the posterior chamber, increased use will be made of both nanotechnology and microelectromechanical systems. Options for use of nanotechnology have been variously reviewed.[1, 2, 3]

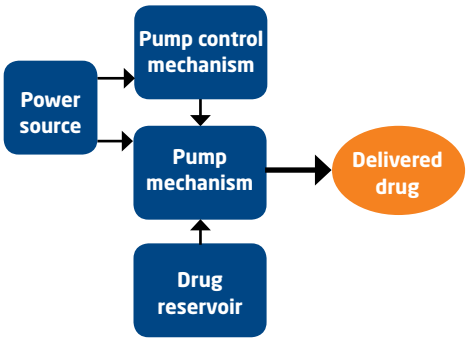

Figure 1 Schematic of pump delivery system

Currently, Allergan has developed the Ozurdex product 4 which is a biodegradable implant containing the corticosteroid dexamethasone and which uses Novadur technology. While the development of more effective drug delivery techniques will require additional investment, there is the potential for reductions in overall cost of anti-VEGF treatments and improved clinical results based on improved medication compliance.

There is also the possibility of making such devices 'smart' so they can be remotely controlled or even, in a more advanced scenario, be self-regulating. Further review of drug metabolism in the posterior chamber is provided by Choonara *et al.*[5]

Designs for micro pumps

The rapid development of microelectronics, however, has changed the levels of function and control of possible implanted miniature pump devices. Some initial developments have already been reported.[6] Figure 1 indicates the generic structure of such an implanted pump delivery system.

At the simplest level, the miniature pump would be self-contained, with its own power source, drug reservoir and no external control over drug delivery rates. The device would be limited by the capacity of the power source and the level of drug able to be contained in the reservoir. At the end of the device's life it would have to be explanted from the eye and possible insertion of another similar unit be considered.

An increased level of sophistication would allow external control of the device by, for example, light-modulated control signal. This level of control could stop and start a device and alter the drug delivery rate. In a development of this communication function, it would also be possible to interrogate the device by activating a 'talkback' mode, where data could be read back from the device using optically coded techniques.

Encoded data could include, for example, details of the equivalent volume of the drug dispensed and the status of the power source. Modern electronics is certainly more than capable of providing this level of functionality. A key element of the design of such a system would be the resilience of the software.

Ideally, power sources should be able to power the application without the requirement to top-up or replace the source. Materials technology used for battery function require high energy/volume factors. Energy transfer into energy source using microwaves and electromagnetic induction are also possible. Such systems have already been developed for larger implant systems by Mussivand *et al.*[7] High energy density rechargeable batteries, integrated into silicon circuits for biomedical implantation applications, are also described by Notten *et al.*[8]

A range of technologies have been identified as having potential for miniature pump delivery systems. In particular, MEMS technology[9] is identified as a viable approach. The core element of such a pump-driving system is indicated in Figure 2, where alternate voltage pulse (positive and negative) causes deformation of membrane in opposite senses.

On the inlet phase, fluid is drawn into the pump chamber with outlet value closed. On the outlet phase, fluid is driven into the outlet channel with

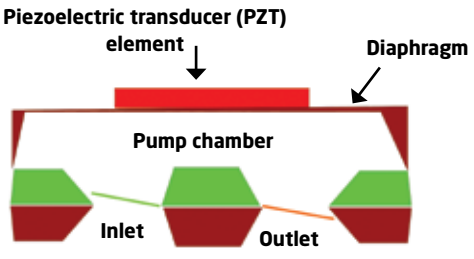

Figure 2 Detail of MEMS technology pump device

the inlet channel closed. Such pump systems tend to have an optimum frequency for drug delivery rates. A key design element is to minimise the operating stress on the diaphragm material to prevent its failure.

Advanced design techniques of extensive numerical simulation are used to optimise design configurations. Electro wetting, electrochemical and ion conductive polymer film (ICPF) actuator micro pumps are further described by Nisar *et al.*[10] Provided sufficient energy and also sufficient volume of drug is available, existing micro pump technology can deliver this function.

Drug reservoir options

In association with the capacity of the power source, the issue of volume of drug reservoir is another key issue and, if the issue of energy transfer to micropumps can be achieved, is the key limiting factor of the technology.

In terms of Lucentis administration, the initial loading regime is 0.05ml in the first three months and then 0.05ml administrations at monthly intervals if required. In the first year a typical dose could be 0.6ml per year. It is also relevant to note that the mode of drug administration is intermittent and not continuous within the conventional administration pattern.

While further research on drug diffusion is required, it may only be required to deliver an initial loading dose of 0.05ml, followed by daily equivalent doses of around 0.0015ml over a year. In this mode, the pump device is essentially dormant and is activated for a short time for each daily administration. The dominant power requirements of the device may therefore be for a hibernation mode in the monitoring electronics.

The volume of the micro pump system, however, needs to be considered in relation to the total volume of the eye, which is typically in the range 7.00ml to 8.00ml. Also, the emptying of 1ml of fluid into the eye requires the filling with an equivalent volume of displaced fluid. Where would this come from? Also, the stability of the injected drug is another relevant issue. Lucentis has a short active half life and may be an unsuitable choice for micro pump delivery, since the drug would presumably have to retain efficacy over a period of at least a year.

The technology of micro pumps does offer, in their time line of development, future exciting capabilities. Drugs from separate reservoirs can be delivered as a 'cocktail' – with the proportion of drug mix as well as separate drug rates part of the selectable options.

Conclusion

Technologies already exist to enable drug delivery to the posterior chamber of the eye using micropump technology. Careful thought, however, must be given to the long-term stability of any drug selected for such delivery.

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Bigger picture

Two new low vision aids caught **Bill Harvey's** attention at Optrafair

More and more patients are asking about the ever increasing numbers of electronic low vision aids now available. I am glad to see that the cost of these is slowly reaching levels one might reasonably expect, and there have been definite improvements in reliability and robustness.

Optelec had a wide range of products on show at its stand. The one which caught my eye was the ClearReader+ which looks like a small desktop shredder (Figure 1). The instrument is positioned over a piece of text and the scanning camera pulled out of the main unit so it is pointing towards the writing. By use of a simple array of well contrasting buttons, the user may then select a voice to read out the text. Ease of use, good design and effective and rapid text recognition make this an exciting product in my view. Cost is around the £2,000 mark.

Bierley was promoting its latest product, the MPD-12-mono (Figure 2). This is a MonoMouse combined with a 12-inch screen, allowing magnified scanning of text. The screen also displays a large character clock and can be used as a digital frame for photos of family and friends. This is an interesting combination that is proving popular with patients who might find prefer this to the more stigmatised appliances one often associates with the low vision world. It is priced around £300.