**INTRODUCTION**

Delivering therapeutics to specific sites in the eye whilst also achieving effective drug concentrations is a difficult task, due to a number of inherent anatomical and physiological ocular barriers, including the cornea, the sclera, Bruch’s-choroid complex and the blood-retinal barrier. These barriers not only protect the eye from invasion by foreign substances, but also regulate the intraocular milieu, which is essential for the eye’s physiological function. However, these barriers also pose a major obstacle to efficient drug delivery, overcoming which remains a major challenge to improve ocular drug bioavailability, with various strategies having been investigated over recent decades.

Formulation-based approaches include chemical penetration enhancers, prodrugs and drug delivery carriers such as liposomes and nano- or microparticles able to penetrate the ocular barriers. Physical force-based methods, initially utilised in transdermal drug delivery, generally require a power-driven physical device to deliver energy to the barriers, thereby enhancing transient drug transport. Compared with formulation-based approaches, physical force-based strategies may allow greater control over the drug dosage whilst also offering the possibility to record parameter information. Here follows a brief overview of physical methods (Figure 1), including iontophoresis, sonophoresis and microneedles, which can enhance drug penetration by transiently disrupting the ocular barriers in a minimally or non-invasive manner.

**IONTOPHORESIS**

Iontophoresis, application of a low-intensity electrical current, enhances drug delivery across biological membranes by causing electrorepulsion and electro-osmosis of the drug molecule. Electrorepulsion primarily applies to the movement of ionic drugs, while electro-osmosis can enhance the transport of both neutral and charged molecules by convective solvent flow. The relative contribution of electrorepulsion and electro-osmosis depends on both the physicochemical characteristics of the drug (e.g. size, charge and charge to molecular-weight ratio) and the electrical properties of the biological membrane. Iontophoretic permeability enhancement of small, charged molecules is mainly governed by electrorepulsion, along with a minor contribution by electro-osmosis, whereas for macromolecules the mechanism is highly dependent on the charge to molecular-weight ratio.

The basic design of ocular iontophoretic devices consists of a power source and two electrodes: the donor electrode (an ocular applicator or eye cup) and the

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**Di Huang, PhD Candidate, Erica Chen, PhD, Postdoctoral Research Fellow, and Ilva Rupenthal, PhD, Senior Lecturer and Director, all of the Buchanan Ocular Therapeutics Unit of the University of Auckland, discuss the possibilities offered by physical force-based methods of enhancing the efficacy of ophthalmic drug delivery by providing a way past the eye’s natural barriers.**

“This piece reviews a 2017 article the authors published in Advanced Drug Delivery Reviews.”

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**Expert View**

The drug is filled into the applicator and the return electrode is placed on the forehead to form an electrical circuit. The EyeGate® II Delivery System (EyeGate Pharma, MA, US), an annular shaped silicone probe with a 0.5 cm² contact area and a 13 mm inner diameter used for transscleral iontophoresis, for example, is currently being investigated in a number of clinical trials for delivery of a sustained release dexamethasone formulation (EGP-437) in the treatment of anterior uveitis, dry eye and macular oedema, as well as for prevention of ocular inflammation in patients who have undergone cataract surgery.

**SONOPHORESIS**

Sonophoresis, also called ultrasound, involves the application of a sound field at frequencies higher than 20 kHz to improve drug transport across biological membranes, including ocular barriers. It has been utilised in the field of ophthalmology for decades but primarily as a diagnostic imaging tool. However, therapeutic ultrasound has recently emerged as an option to treat glaucoma by cyclocoagulation or to enhance ocular drug uptake. The mechanisms for ultrasound enhanced drug delivery take into account non-thermal (e.g. cavitation, acoustic streaming and mechanical stress) and thermal effects with ultrasound parameters, co-administration of microbubbles and drug characteristics, all having an effect on delivery efficacy. Cavitation is generally considered the predominant factor for enhanced drug delivery and is defined as the formation of microbubbles due to an acoustic pressure gradient within the coupling medium. Continuous pulsation of cavitation microbubbles over many pressure cycles without any collapse is considered stable cavitation, while the growth and collapse of microbubbles within a few pressure cycles is associated with inertial cavitation.

Corneal permeability enhancement is generally a result of stable cavitation at low ultrasound intensities, whereas both stable and inertial cavitation play important roles at higher ultrasound strengths. Transsclerally applied ultrasound results in the formation of transport channels and the modification of the proteoglycan fibre morphology, without significantly disturbing the collagen network. Here, low intensity ultrasound produces sufficient acoustic pressure to generate stable oscillating microbubbles, resulting in microstreaming with higher intensities being required to achieve inertial cavitation.

Due to the sensitivity of the ocular tissues, it is incredibly important not to sacrifice patient safety, even if doing so could potentially achieve greater treatment efficacy. The eye’s temperature increase due to absorption of sound waves is of particular concern; the thermal safety requirements for diagnostic ultrasound allow a maximum temperature increase of 1.5 °C.

The majority of studies published to date have investigated transcorneal ultrasound in combination with microbubbles; however, a limited number of studies also exist on the application of ultrasound for enhanced drug delivery to the posterior segment of the eye. Recently, transscleral ultrasound has also been combined with the use of nanocarriers, in order to enhance the vitreous diffusion and retinal permeability of peptide loaded nanoparticles following intravitreal injection, thus achieving higher retinal drug concentrations. However, so far, there has been no evidence that ultrasound can enhance retinal permeability upon extraocular administration in large animal models or humans.

**MICRONEEDLES**

Microneedles (MNs) are micrometre sized needles, or arrays of such, fabricated by adapting microelectronics tools. Applying MNs to biological membranes can create tiny transport pathways, thereby allowing drugs to permeate across these barriers. To
date, numerous MN fabrication approaches have been utilised, resulting in a variety of shapes, sizes, materials and configurations.11

According to their delivery mechanism, ocular MNs can be categorised into four types:

1. Solid MNs, able to create micropores in the ocular surface through which therapeutics can diffuse after MN removal.
2. Drug-coated MNs, with the drug coating dissolving and diffusing into the eye after insertion.
3. Dissolving MNs, which disintegrate over time, thus releasing the matrix encapsulated drug into the ocular tissues.
4. Hollow MNs, able to infuse pressure-driven liquid drug formulations.

Enhanced drug delivery into the cornea and anterior segment of the eye can be achieved by insertion of MNs across the corneal epithelium, the main barrier to penetration encountered after topical eye drop administration, to deposit drugs directly into the corneal stroma. Solid stainless steel MNs, coated with different compounds ranging from small drugs to macromolecules, were inserted into rabbit corneas in vivo providing up to 60-fold higher bioavailability compared with the topically administered drugs.12 However, in vivo application is still challenging due to the corneal curvature and lack of a supporting pressure during MN insertion.

Various polymeric MNs have found great use in intrascleral drug delivery. Unlike solid or hollow MNs, dissolving MNs minimise accidental retinal damage, whilst also remaining as a depot for sustained drug delivery. Thakur, et al,13 developed a simple and cost-effective mouldcasting method for fabrication of rapidly dissolving MNs, using polyvinylpyrrolidone, which efficiently penetrated the outer scleral layers, thus enhancing intrascleral permeation of macromolecules.

Currently the most advanced ocular MN application includes drug delivery into the suprachoroidal space, a potential space between sclera and choroid. Drug solutions injected into this space can flow circumferentially around the eye, with suspensions of particles up to 1 μm having been successfully delivered into the suprachoroidal space of rabbit, pig and human eyes.14 Clearside Biomedical (GA, US) initially evaluated the efficacy of suprachoroidal delivery using hollow MNs for the treatment of acute posterior segment uveitis by injecting triamcinolone acetonide into the suprachoroidal space of living pigs.15 The company subsequently completed a Phase II clinical trial to determine the safety and efficacy of suprachoroidally administered, proprietary, non-preserved triamcinolone acetonide (Zuprata™) via 1000 μm long MNs in subjects with macular oedema associated with non-infectious uveitis. Currently participants are being recruited for a Phase III study for further efficacy evaluation. Clearside Biomedical also completed a Phase II clinical trial in subjects with macular oedema following retinal vein occlusion and is currently investigating suprachoroidal application of a small tyrosine kinase inhibitor (Axitinib™) in the treatment of wet age-related macular degeneration.

CONCLUSION

Safe and effective treatment of ocular diseases is a challenging task due to the presence of various protective ocular barriers and elimination mechanisms. A vast number of novel strategies have been utilised to overcome these barriers and improve drug delivery to the target site, thereby enhancing drug bioavailability and avoiding potential side effects. The enhancement of drug permeability, ease of application and minimally or non-invasive delivery characteristics render physical force-based methods an exciting option for the treatment of both anterior and posterior segment disorders.

Iontophoresis is the most extensively investigated approach among these physical techniques so far, with numerous therapeutic agents (such as low molecular weight drugs, macromolecules and nanocarriers) already having been successfully delivered to various ocular tissues. Although the number of studies on ultrasound and MN mediated ocular drug delivery is still limited, both have specific advantages, including site-specific drug delivery to the ocular tissues as well as the possibility to combine them with sustained release particles. Further in vivo studies are required to understand the contribution of dominant mechanisms, optimise device design and parameter settings, and evaluate the feasibility and safety of repeated and long-term application of such methods in the clinical setting.

ABOUT BOTU

The Buchanan Ocular Therapeutics Unit aims to translate ocular therapeutic related scientific research into the clinical setting, whether pharmaceutical, cell or technology based. Projects include the development of stimuli-activated systems investigating implants responsive to ultrasound, light or a small electrical current. Dr Rupenthal’s team, including five PhD candidates

ABOUT THE AUTHORS

Di Huang obtained a BSc in Pharmacy from Central South University in Changsha, China (2011) and an MSc in Pharmaceutics from Sun Yat-sen University in Guangzhou, China (2014), which focused on transcleral ultrasound for protein loaded nanoparticle delivery. She has been a PhD student within the Buchanan Ocular Therapeutics Unit since 2015 and is currently investigating ultrasound-mediated delivery of peptide-loaded nanoparticles for efficient treatment of diabetic retinopathy.

Dr Erica Chen is a postdoctoral research fellow within the Buchanan Ocular Therapeutics Unit and the co-supervisor of Di Huang’s PhD project. Dr Chen obtained a BPharm from Kaohsiung Medicine University, Taiwan (2004) as well as a Postgraduate Diploma in Pharmaceutical Sciences (2008) and a MHSc (2009) from the University of Auckland, New Zealand. In 2014, she completed her PhD investigating intravitreal peptide delivery for the treatment of optic neuropathies.

Dr Ilva Rupenthal is a Senior Lecturer in the Department of Ophthalmology, University of Auckland, and the inaugural Director of the Buchanan Ocular Therapeutics Unit established in 2013. She currently also holds a Sir Charles Hercus Health Research Fellowship and received the 25th Anniversary Emerging Researcher Excellence Award from the Health Research Council of New Zealand in 2016. Dr Rupenthal is an author on over 50 peer-reviewed journal articles and has attracted over NZ$5 million in research funding.

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and two postdoctoral research fellows, is also investigating other ocular therapeutics in the area of dry eye, diabetic retinopathy and age-related macular degeneration management.

REFERENCES


