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EDITORIAL

# Ocular drug delivery—eye on innovation

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The estimated number of people visually impaired in the world is 285 million, 39 million blind, and 256 million having low vision, with 65 % of visually impaired and 82 % of all blind people being 50 years and older. The major blinding disorders currently include age-related macular degeneration (AMD), diabetic retinopathy/macular edema (DR/DME), and glaucoma, and while there are many effective medications to treat these conditions, the challenge remains to deliver them effectively with a sustained release profile and with minimal side effects. One would think that a small organ such as the eye, which is readily accessible from the outside of the body, would be easy to treat. However, the eye is a rather isolated organ with a number of barriers in place to protect it from the environment posing major challenges to effective drug delivery. Therefore, achieving sufficiently high concentrations at the target site and maintaining these over prolonged periods of time with minimal side effects offers great opportunities for new product development, especially when using already FDA approved drugs with well-known safety and efficacy.

Topical eye drops are still the most common method of treating anterior segment diseases; however, generally less than 5 % of the applied drug reaches the ocular tissues. This is mainly due to the fast nasolacrimal drainage and the poor permeation of the remaining drug across the sandwich-like structure of the cornea, with the lipophilic corneal epithelium being the main barrier to ocular entry for most drugs. Therefore, to develop more efficient drug carriers for topical ocular delivery, reliable models are required in the early stages of formulation development to avoid failure in clinical trials. The first review article of this special ocular drug delivery issue by Agarwal and Rupenthal discusses in vitro and ex vivo models currently used to study corneal penetration and evaluates their advantages and limitations with a focus on diffusion cell assemblies and their adequate set-up to simulate in vivo conditions. To enhance topical ocular drug delivery, researchers have predominantly focused on two strategies: (1) to increase the corneal residence time using viscosity enhancers, mucoadhesive, particulate, and/or in situ gelling systems and (2) to increase the corneal permeability using penetration enhancers, prodrugs, and colloidal systems such as nanoparticles and liposomes. In this issue, Jamard et al. report on self-assembling nanogels based on poly(N(*tert*-butylacrylamide) and methylcellulose intended for topical application showing sustained release of the loaded cargo while also being biocompatible with human corneal epithelial cells. As with any novel formulation, it is imperative to test its biocompatibility with the ocular tissues. However, as in vivo toxicity studies of topical ocular formulations can be unethical due to the involvement of invasive tissue sampling, suitable in vitro models are of high demand. The review by Rönkkö et al. summarizes human corneal models ranging from simple monolayer cell cultures to three-dimensional structures that have been developed for toxicological prediction. The in vitro bioassay model reported by Chen et al., on the other hand, can be useful for evaluating the efficacy of ocular delivery systems, with their reported two-layer

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contact-independent three-dimensional neuronal co-culture model being able to evaluate nanoparticle-based neurotrophic factor gene delivery to astrocytes.

Nano- and microparticles have generally found great application in the area of ocular drug delivery whether for topical application or injection into the vitreal or suprachoroidal space. The review article by Bravo-Osuna et al. gives an excellent overview about the use of nanoparticles, liposomes, niosomes, dendrimers, microemulsions, and microparticles in the treatment of ophthalmic diseases with an emphasis on their clinical translation. And while so far only a limited number of particulate systems have reached the market, including a non-medicated liposomal spray and a medicated nanoemulsion for dry eye treatment, many pre-clinical and clinical studies are currently underway. Reimondez-Troitiño et al., for example, report on the successful preparation of polyarginine and protamine nanocapsules with adequate properties for topical ocular administration, which exhibited enhanced precorneal residence time and improved wound healing after photorefractive keratectomy surgery. The article by Butt et al., on the other hand, discusses the potential use of an anti-microbial fatty acid-based microemulsion for the treatment of neonatal conjunctivitis, which could have great implications considering the increasing risk of antibiotic resistance and the need for alternative treatment options.

Understanding ocular barriers and pharmacokinetics is of great importance when developing efficient ocular drug delivery systems. The review article by Agrahari et al. gives a comprehensive overview of ocular pharmacokinetics and the various models used, while the following two research articles explore the development of novel in vitro and ex vivo pharmacokinetic models. In order to account for the small tear volume and flow rates found in vivo, for example, Pimenta et al. developed a microfluidic cell to mimic the continuous, volumetric flow rate of the tear fluid, thus offering a valuable in vitro tool to optimize drug-loaded contact lenses. Bisht et al., on the other hand, established an ex vivo model for intravitreal drug sampling by the microdialysis technique and found this to be a useful tool to investigate intravitreal kinetics and ocular disposition of therapeutic molecules delivered via the intravitreal route, which remains the gold standard to treat posterior segment conditions. And while intravitreal injections deliver the drug directly into the eye, currently injected formulations are based on simple drug solutions with short half-lives; thus, frequent injections are generally required. To overcome this issue, Lance et al. have developed an exciting new device composed of twin nanoporous polymer thin films surrounding a drug reservoir which provided release of ranibizumab over 16 weeks in vitro and 12 weeks in vivo, without showing any signs of immune response when implanted into rabbit eyes. This device therefore presents a potential solution to the challenge of delivering protein therapeutics to the vitreous and retina for sustained periods of time. Nevertheless, although confined to the relatively small vitreal space, released drug still faces elimination processes and needs to diffuse through the vitreous before crossing the inner limiting membrane to reach the retina with the retinal pigment epithelium and Bruch's membrane posing yet another permeation barrier for delivery into the choroid. Thus, another option to sustain drug release and enhance retinal tissue permeation is the use of lipid-based carriers. These are reviewed as promising delivery systems for the treatment posterior segment diseases by Du et al. with a particular emphasis on lipid on-demand delivery systems allowing for dose individualization which may have great potential to overcome current limitations.

In fact, all the marketed implants so far as well as the majority of systems currently in clinical trials may achieve sustained release, but their release rate cannot be altered if the condition worsens or aborted in the case of serious side effects. Thus, with advances in polymer science and nanomaterial development for biomedical applications over recent years, there has been a paradigm shift from conventional to stimuli-responsive or tunable devices, with such systems also having great potential in the area of ocular drug delivery. Du et al. elaborated on a lyotropic stimuli-responsive liquid crystalline system in their review with drug release being stimulated by light. Other suitable stimuli could include a small electrical current as reported in the article by Ramtin et al. proposing an electro-responsive implant based on conducting polymer films which could have great potential for tailored treatment of posterior segment diseases. Besides intravitreal injection, the periocular route offers another delivery opportunity with the sclera allowing molecules up to 20 kDa to permeate (compared to ≤5 kDa across the cornea) as well as the possibility to inject larger volumes (≤1 ml compared to ≤100 μl intravitreally). Even more localized are suprachoroidal injections via precise microneedles which allow the drug solution to spread between the sclera and choroid around the eye ball. Besides using such microneedles for precise drug application into the ocular tissues, they can also be used as physical means to overcome the ocular barriers. This has been explored in the final article of this special issue, with Thakur et al. reporting on the design and fabrication of minimally invasive rapidly dissolving polymeric microneedle arrays which were able to deliver macromolecules into the eye via the intrastromal or intrascleral routes.

In summary, this issue incorporates advances in ocular drug delivery technologies for both anterior and posterior

segment delivery, while highlighting the current challenges faced with regards to the ocular barriers present as well as the establishment of suitable models to reliably test the developed systems and thus avoid failure in clinical trials. We therefore hope that our readers will find this volume comprehensive and highly resourceful for developing novel ocular delivery systems. This theme issue would not have been possible without the timely submission and revision of articles by the authors, critical evaluations by the reviewers, and the editorial assistance provided by Ms. Belle Mojado, Mr. John Rafael Patricio as well as other staff at Springer who ensured that papers were carefully processed, reviewed, and published to their deserved high standard. We are also thankful to Prof. Vinod Labhasetwar, Editor-in-Chief, for providing us the opportunity to develop this theme issue. We hope you enjoy this special ocular drug delivery issue—it is more than meets the eye!