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The gap between the need for novel retinal drug delivery methods, technologies in R&D phase, and approved ocular drug delivery technologies

Ron Neumann[1], neumann.ron@gmail.com and Dana Barequet[2]

The past four decades were marked by the realization that the delivery of drugs into the eye is a crucial step in the development and utilization of new ocular drugs. This realization led to vast efforts and investments in research and development (R&D) to improve and approve new technologies. The realization of intravitreal injections and the vast utilization of this methodology in retinal disease management deepened the need for new drug delivery methods for drugs already approved safe and effective. Yet, there are only a handful of technologies approved and in clinical use today. Here, we focus on this gap by highlighting bottlenecks and by encouraging creative thinking for solutions.

The medical need

The anatomy and physiology of the eye produce a huge challenge for drug delivery. The eye is affected by unique organ-specific diseases, hence the desire to deliver drugs directly to ocular tissues avoiding systemic exposure and adverse effects. The most common delivery route is topical administration by drops, but intravitreal and periocular and/or transscleral injection are now commonly used for posterior segment pathology.

A major limitation of eye-drop therapy for intraocular diseases is their low bioavailability at the site of action, with only 5–10% of the administered dose reaching the target tissue [1,2]. The rest of the drug is eliminated by lacrimation, reflex blinking, tear-film turnover, and nasolacrimal duct drainage [2,3]. As each layer of the cornea acts as a barrier, a drug must penetrate the lipophilic epithelium connected by tight junctions, the Bowman's layer, the hydrophilic stroma, the Descemet's membrane, and the endothelium, also connected by tight junctions. Another dynamic barrier that restricts drug transport across the cornea is the presence of transmembrane efflux pumps. Therefore, the external cornea is exposed to higher drug concentrations, and the delivery to the aqueous humor is dependent on contact time, molecular size, polarity, and the balance between the hydrophilicity and lipophilicity of the molecule.

The challenge is greater when posterior segment delivery is needed because of the longer diffusional distance, additional barriers, and dilution of the drug material in the vitreous body. Therefore, topical administration requires a high concentration of the drug material, with potentially extended external adverse effects because of exposure to higher drug concentrations. In fact, only corticosteroids and cyclooxygenase inhibitors of higher potency were shown to have therapeutic effects in the posterior pole, even though it is debatable whether the drug reached the posterior segment or had a major effect anteriorly that secondarily affected macular edema [4–6]. The need to apply high concentrations of eyedrops to achieve therapeutic concentrations in the posterior pole also presents the potential for higher systemic absorption and, hence, systemic adverse events.

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Another possible approach for delivering drug molecules to the back of the eye is systemic administration, although delivery is limited by blood dilution of the drug and the presence of inner and outer blood–retinal barriers. These require a high drug concentration circulating in the plasma to achieve therapeutic levels in the eye, and such high doses can result in systemic adverse effects [7]. Consequently, treating disorders that affect the posterior segment of the eye benefit from direct intravitreal and/or periocular injections and implants to the posterior ocular segment, and suprachoroidal space. Therapeutic tissue drug levels can be readily achieved, yet it is an invasive approach. Although such delivery methods are effective, they have ramifications, such as the need for semisterile 'injection parlors', accessibility of such facilities to rural populations, enormous economic burden on health organizations, as well as medical complications such as retinal bleeds, retinal detachment, and rare endophthalmitis [8]. Hence, effective retinal drugs that have revolutionized the way we treat common retinal diseases still require better modes of delivery to fully exploit their beneficial potential. Many research efforts are currently invested in developing new technologies that will fulfill this need. Here, we focus on delivery methods to the back of the eye, given that this appears to be one of the most challenging targets to achieve.

Currently available retinal technologies

At present, there are only a few delivery methods that aim to reach the back of the eye that have already reached the market and gained US Food and Drug Administration (FDA) approval (although some have been withdrawn for marketing reasons).

Vitrasert® (Bausch and Lomb Inc., Rochester, NY, USA) is a controlled-release intraocular implant of ganciclovir approved by the FDA for the treatment of AIDS-associated cytomegalovirus retinitis. It comprises a 4.5-mg ganciclovir tablet coated with polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) polymers, allowing drug release over an extended period of 5–8 months [9].

Retisert® (Bausch and Lomb Inc.) is approved by the FDA for the treatment of posterior noninfectious chronic uveitis and macular edema associated with retinal vein occlusion (RVO). It is the first marketed silicone-laminated PVA implant. It provides sustained release of fluocinolone acetonide 0.59 mg up to 3 years. The implant effectively controls inflammation, reduces uveitis recurrence, and improves visual acuity. However, adverse effects are cataracts and elevated intraocular pressure [10].

Ozurdex® (Allergan Inc., Irvine, CA, USA) was approved by the FDA in June 2009 for the treatment of macular edema. It use Allergan's NO-VADUR® technology to deliver dexamethasone 0.7 mg. It contains a poly(lactic-co-glycolic acid) (PLGA) polymer matrix that degrades slowly, resulting in the prolonged release of dexamethasone for up to 6 months. Randomized clinical trials have demonstrated its potency in reducing vision loss and improving visual acuity in eyes with macular edema associated with noninfectious uveitis, branch RVO (BRVO), or central RVO (CRVO) [11,12].

Iluvien® (Alimera Sciences, Inc., Alpharetta, GA, USA; pSivida Inc., 480 Pleasant St B300, Watertown, MA 02472, USA) is an implantable device for delivering fluocinolone acetonide 0.19 mg for up to 36 months [13]. It comprises a narrow cylindrical polyimide tube loaded with the drug, and PVA-based end caps provide rate-limiting drug delivery. A similar product, Yutiq (EyePoint Pharmaceuticals, 480 Pleasant St B300, Watertown, MA 02472, USA), a nonbioerodible intravitreal microinsert containing 0.18 mg fluocinolone acetonide, received FDA approval for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

Opinion

In this coming era of novel drug delivery systems, ocular treatment options will diverge not only between various drugs, but also the methods via which those drugs are delivered to ocular target tissues. Adopting intravitreal injections as a routine delivery method revolutionized the pharmacotherapeutic options to treat common retinal diseases. Yet, the invasive nature of this delivery method, the significant adverse event profile of the actual injections, and the huge economic burden, including the need for highly trained retinal staff, semi-sterile injection rooms, and so on result in a real unmet medical need for better delivery methods.

Novel retinal delivery methods aim to: (i) reduce injection burden, achieving fewer injection-related adverse events, increased patient comfort and compliance, and freeing up retinal specialist time and attention from the burden of seemingly endless injections; (ii) deliver the drug material specifically to the target tissue within the eye, leading to increased efficacy, reduced dose of the active ingredient, and reduced drug-related adverse events.

A comprehensive review of technologies is available in other papers in this special issue of *Drug Discovery Today*. To illustrate merely the **diversity of delivery systems** currently in development, we have selected three delivery systems that, in our opinion, demonstrate it.

The Genentech, Inc. (South San Francisco, CA < USA) 'refillable' Port Delivery System delivers ranibizumab to patients with wet age-related macular degeneration (AMD). This device is implanted utilizing a surgical procedure and can be refilled using a customized needle in a minimally invasive office-based procedure. The higher dose of 100 mg/ml was found to be effective in the LADDER study for 6 months without the need to refill the reservoir [14]. This was the first study showing such a dramatic reduction in treatment burden compared with monthly injections without compromising the treatment effect.

Coming from another angle, Clearside Biomedical, Inc. (Alpharetta, GA, USA) is developing an innovative suprachoroidal injection technology [15]. The aim is to deliver a smaller amount of steroid (triamcinolone acetonide) directly to the suprachoroidal space via a proprietary injection device. This technology allows the direct delivery of the drug compound to the actual target compartment within the eye, avoiding ocular tissue associated with corticosteroid-related adverse events, such as the eye angle and lens.

Another disruptive innovative example is being developed by Eyevensys, Inc. (Paris, France) inducing ocular target tissue cells to produce protein drugs via direct injection of a plasmid to the ciliary body [16,17]. This is intended to provide the sustainable production of the protein drugs by ocular tissue for a prolonged period of time.

Other technologies in development rely on PLGA-based (or other) microemulsions and nanoparticles, extended delivery time from polymers, dendrimers, and microspheres, or implanting cells engineered to produce proteins, such as anti-vascular endothelial growth factor (VEGF) and others.

It is unclear why there are only four major products in clinical use allowing drug delivery to the posterior segment of the eye (three of them evolve around corticosteroids) on the market when so much relevant research is occurring across the industry and academic centers. Are there any inherent blocks to completing the development of products or otherwise inhibit their introduction and acceptance by the market? Why do we not see more innovation in the clinic based on the productive field of research and technological advancement in formulation science?

Here, we highlight several issues that could explain this situation: (i) the technology is faulty. Although this is always an option, we assume that out of the many different technologies and research vectors available, there are more than only four technologies with real potentials to enter the market and bring innovation to patient care. We therefore believe that an un-

known number of delivery systems fail and are abandoned despite offering real capacity to deliver; (ii) the regulatory obstacle of 'first in human' (FIH) for delivering drugs that are already known to be effective in other indications or via other delivery systems (505b2 route of development[1]) [18]. Given that 505b2 typically relate to drugs that are already in use, the required toxicology package for FIH studies may be regarded as challenging. Considering that the full range of systemic and sometimes topical adverse events in humans is well known for the drug material and, given that the relevance of experimental animal eyes (mainly rabbits) to human eyes is in doubt, the value of some studies to address potential toxic effect(s) might be challenged. The appropriate level of preclinical animal studies needed for standard and nonstandard excipients included in the new drug delivery can be limiting for small organizations with a limited budget. Also, the balance between patient safety and developer financial capacity might be such that curtails further development efforts [19,20]. Surely patient safety must come first, but premature termination of good ideas with their potential benefit to patient should also be considered. Rough guidelines may not be the best practical choice here. The authors believe that specific evaluation of outstanding projects should be considered to enable some projects to proceed with less demanding requirements; (iii) although the patent life of a biotech invention is typically 20 years, usable patent life often does not exceed 10 years. Commonly, development takes 10 years and beyond, and sometimes development is halted because of the lack of investment despite solid technology and market needs. Projects might become futile once patent time does not allow development to be concluded in a timeframe that results in a financial reward to the developer and its investors [19,20]. Developers and investors should have enough time to realize profit from their investment. Unfortunately, research & development of some technologies is halted for more than a decade, whereas others never reach the clinical phase; (iv) to become a successful new drug delivery product, the developer needs to show a substantial clinical benefit of their product by payers such as countries and health insurance organizations [19,20]. Following approval by the regulator, a successful product needs to show real economic value for patient care, convincing payers to pay a premium price for a new technology delivering older (sometimes generic) products already on the market. Pharmacoeconomic modeling is crucial reflecting lower net patient care expenditure upon utilizing the new technology compared with the traditional product. This must be considered in the development program from the very beginning leading developers to acquire data that support such pharmacoeconomic assessment.

It follows that entrepreneurs and investors who are looking realistically at the difficulties of pushing a worthy product to the market might decide that their efforts will not have an economical reward and, therefore, good projects that have stalled for too long or whose development path is too costly or lengthy are abandoned. This might result in discarding of medically valuable projects that are not economically viable. It is our view that regulators and stakeholders should be allowed to grant such projects with particular considerations, similar to orphan indication, with a special status, for example with extended exclusivity even for patents that are soon to expire.

Concluding remarks

Although we do not offer a solution to the current situation, we have highlighted crucial issues in the development path of delivery systems and their success in the market. We believe that debate is needed to expedite more projects along the path of success. Many projects are already in development and we hope that their launch will enable current intraocular injection regimens to become more patient-friendly and introduce effective methodologies to the market that is thirsty for innovation.

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[1] 505b2 is related to an approval process focusing on a modified, already-approved technology: 'A 505(b)(2) application is one for which one or more of the investigations relied upon by the applicant for approval were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted' [XX].

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Ron Neumann[1,*]
Dana Barequet[2]

[1] *International Symposium of Ocular Pharmacology and Therapeutic and Maccabi Health Care Services*
[2] *Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Israel*

*Corresponding author.