Development of a non-invasive ocular drug delivery device

Chapter 9.
Impact

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Aging of the population leads to an increase in age-related visual impairment and blindness.[1] According to the report by the World Health Organization (WHO), 2.2 billion people are suffering from vision impairment globally. One billion of the visually impaired patients could have been prevented or has yet to be addressed.[2] This includes moderate or severe distance vision impairment or blindness due to unaddressed refractive error (123.7 million), cataract (65.2 million), glaucoma (6.9 million), corneal opacities (4.2 million), diabetic retinopathy (3 million), and trachoma (2 million), as well as near vision impairment caused by unaddressed presbyopia (826 million).[1]

9.1. Clinical relevance of the ocular coil

Current patterns of topical ophthalmic drug delivery fail because low drug absorption due to short residence time on the ocular surface and high pre-corneal drug loss. This requires the need for frequent drug administration, which then again is causing low patient compliance.[3] To improve drug delivery, other routes than eye drops are used (**Chapter 2**). Implants or direct injections (*e.g.* subconjunctival, subtenon, intracameral, intravitreal) into the targeted site can be used but are invasive and only achieve suboptimal drug levels. For example, intravitreal injections of anti-VEGF for age-related macular degeneration need to be repeated regularly and have poor patient tolerance (pain and fear), significant risks (*e.g.* endophthalmitis), and increased costs (loss of working hours) and manpower requirements.

The ocular coil is a non-invasive drug delivery device. Ideally, it is put in place once by the physician and remains there for a prolonged period of time. As such, it would replace the need for self-administration of eye drops. This would be beneficial for *e.g.* aged persons that have difficulty to self-apply eye drops or patients with corneal ulcers who have to apply medication as often as once an hour. In both cases, eye drop administration is currently performed by a healthcare worker and comes with healthcare costs. The associated healthcare costs are significant.

Patient non-compliance with eye drops is prevalent, both for short-term use (*e.g.* after cataract surgery) as well as for chronic disease requiring lifelong use of eye drops (*e.g.* glaucoma). Reasons for non-compliance are forgetfulness, incorrect instilment, fear, and physical or cognitive limitations of aged persons. Consequences of poor compliance after cataract surgery are *e.g.* endophthalmitis (antibiotic eye drops) and cystoid macular edema (CME) (anti-inflammatory eye drops). Both complications can permanently impact vision. By bypassing patient compliance, the ocular coil may be able to reduce the incidence of those complications. In the end, this strategy may also be less expensive than the treatment of those complications.

9.2. The ocular drug delivery device market

In the treatment and prevention of ocular diseases, eye drops and ointments are often the first line of defense. Therefore, ophthalmic drug delivery represents a significant economic value. The global ophthalmic drugs market size was valued at $30.3 billion in 2018 and is expected to grow to $43.1 billion 2026 with a compound annual growth rate of 4.5%.[4] The US was the largest market for ophthalmic drugs, accounting for 40% of the global market. Five major EU countries (UK, DE, IT, FR, and ES) formed 18% of the global ophthalmic market.[5] Implementation of a new successful drug delivery method may have a significant impact on the field. Nevertheless, it is challenging for new drug delivery devices to enter the market. Tight rules and regulations of the Food and Drug Administration (FDA) and European Union's Public Health Division and European Medicine Agency (EMA) make it time consuming and expensive to bring a drug delivery device to the market. Hence, drug delivery devices can hardly compete with the low costs of eye drops. The advantage of drug delivery devices should considerably outweigh the total costs of the devices. One successful example is the ocular drug insert for preoperative pupil dilation (Mydriasert, TheaPharma), that is being used by 30% of Dutch cataract surgeons.[6] Benefits of this insert include the significantly decreased nurse time, number of gestures, and equal pupil dilation as compared to eye drops.[7] A recent cost-effectiveness study of different mydriatics before cataract surgery showed that intra-cameral injection is more expensive (€ 17) than eye drops (€ 5) or a mydriatic insert (€ 7) and results in the smallest pupil dilation. Due to the price, implementation could be considered when there is limited availability of nurses or physical space for perioperative care.[8]

Another drug delivery device that made it to the market is Dextenza™ (Ocular Therapeutix Inc. (Bedford, MA, US), a 0.4 mg dexamethasone loaded punctum plug that was FDA approved in November 2018.[9] Dextenza™ is injected at the end of cataract surgery and is the first punctum insert that can provide sustained release up to 30 days. Postsurgical treatment with Dextenza™ costs about € 409 ($ 450) and it takes about 25% of the postsurgical market since its release. A similar device is Dexycu® (EyePoint Pharmaceuticals, Watertown, MA, US).[10] Dexycu® is a 517 μg intracameral dexamethasone insert to be injected at the end of cataract surgery. The price of Dexycu® treatment is about € 541 ($ 595) and has proven to be more effective than 30 days eye drop therapy.[11]

Another potential alternative to postoperative eye drops is Omidria® (Omeros pharmaceutics). Omidria® is a drug combination of ketorolac and phenylephrine included in the irrigation fluid that is used during surgery. Thus far, results show less pain during and after the surgery [12,13] and a lower incidence in post-operative CME.[13] The price for one bottle of Omidria® is about € 470 (£ 400) [personal

communication]. However, the use of drugs for preoperative mydriasis is still needed and postoperative anti-inflammatory treatment is also advised.

9.3. Raman spectroscopy for (pre)clinical use

Tracking drugs through ocular tissue is a must in the field of ocular pharmacokinetics. It offers information on the achievable intraocular drug concentrations of a new drug delivery device. Raman spectroscopy is a non-invasive technique that is able to detect drugs *in vivo*. It is able to penetrate through ocular tissue and to provide detailed information on molecules and structures inside the eye.

Raman spectroscopy can be of significant value for drug related studies. Current methods include harvesting ocular tissues or fluids during surgery, but only provides information at a single point in time. Kinetic or real-time information can only be obtained from large cohorts of laboratory animals (*e.g.* rabbits, dogs, pigs, and monkeys).[14] This technique could therefore lower the number of animals used for pharmacokinetic experiments.

One example of clinical use of Raman spectroscopy could be used to identify the causative micro-organism in a patient with endophthalmitis. Currently, it takes a few days before this information is available (due to bacterial culture time) and the start of the correct treatment (*e.g.* specific antibiotic or antiviral) is delayed. Immediate identification on-site may increase the success-rate of the treatment. Other potential examples of clinical use of Raman spectroscopy include detection of inflammatory cytokine for corneal dystrophies [15] or insulin [16] for diabetes.

9.4. Quantification of ocular redness

The degree of ocular redness serves as an important diagnostic feature for the diagnosis and monitoring of ocular diseases. Furthermore, it is an indicator of the safety level of a new ocular drug. Objective scoring of ocular redness remains however difficult. In this context, a tool to quantify ocular redness can be of use in both clinical and research settings. In the future, it can be further optimized to determine other features, such as *e.g.* the severity of a hypopion, limbal redness and corneal neovascularization.

A (pilot) portable version of the tool has been developed for smartphones. This offers clinicians and researchers the possibility to monitor ocular redness of a specific patient over time. For example, after surgery it could be used to track recovery of the ocular tissue and the surgeon could adapt accordingly its treatment strategy to it. This tool may bring ophthalmology closer to personalized medicine.

9.5. References

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