

Current Ocular Drug Delivery Challenges

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Dr Lambert is Vice President of Research and Development at Novagali Pharma. He began his career as a teacher and researcher, focusing on nanoparticles and nanocapsules applied to cancer treatment. His first assignment was to ensure proper transfer of cationic emulsion technology from the Hebrew University of Jerusalem to Novagali's laboratories. He then focused on developing this core technology from a research instrument into a state-of-the-art pharmaceutical development tool.

Introduction

The need for ophthalmic medications is continuously increasing as the populations of the industrialised nations age. The development of new products for treatment of ophthalmic diseases is facing a double challenge: pharmacology and drug delivery.

In addition to factors concerning the high tolerability/comfort requirements, the eye presents two difficult and challenging problems for drug delivery: the first is specific to hydrophobic NCEs, which usually lack suitable vehicles. Ointments must be used for lipophilic molecules, for example antibiotics. Usually these must be applied at night, just before sleep, since their viscosity makes them inconvenient and they disrupt vision to the extent that waking activities would be limited. The second obstacle is general to all ocular products: the low ocular bioavailability of topically applied drugs - a well-known and extensively-reviewed issue.

Drug delivery to the anterior segment of the eye

Whenever an ophthalmic drug is applied topically to the eye, only a small amount (<5%) actually penetrates the cornea and reaches the internal anterior tissue of the eyes. Rapid and efficient drainage by the nasolacrimal apparatus, non-corneal absorption and the relative impermeability of the cornea to both hydrophilic and hydrophobic molecules, all account for such poor ocular bioavailability.

The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories (Ding, 1998). The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs, such as implants, inserts and colloids. The second involves maximising corneal drug absorption and minimising

pre-corneal drug loss through viscosity and penetration enhancers, prodrugs and colloids.

One of the approaches recently developed is the drug incorporation into cationic submicronic vectors, which bind the anionic charges present at the corneal surface (negatively charged cell membranes and mucin) for increased residence time and penetration. In addition, their administration via conventional liquid dosage form is an attractive feature for patient acceptability and compliance.

Cationic compounds, because of this anionic surface, penetrate through the cornea easier than anionic species and cationic colloids also have longer residence time than negatively charged emulsions (Rabinovich-Guilatt, Couvreur *et al.*, 2004). Many studies performed in the last few years comparing cationic to anionic ocular drug delivery systems have confirmed the superiority of positively charged emulsions in delivering therapeutic agents to the eye.

Novasorb™ cationic emulsions provided significantly higher drug levels in the ocular tissues than the control solution or negative-charged emulsions. Furthermore, the spreading coefficient of the cationic emulsion on the cornea is four times higher than that of negative-charged emulsions (Figure 1). Therefore, cationic submicron emulsions have better corneal moisturising properties compared to either

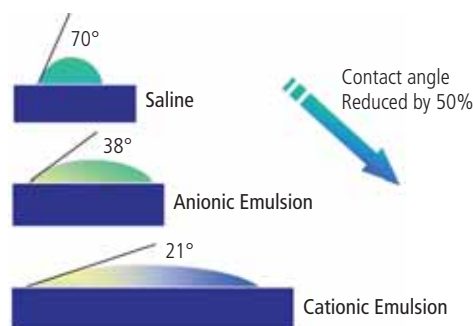


Figure 1 – Contact angles on the cornea.

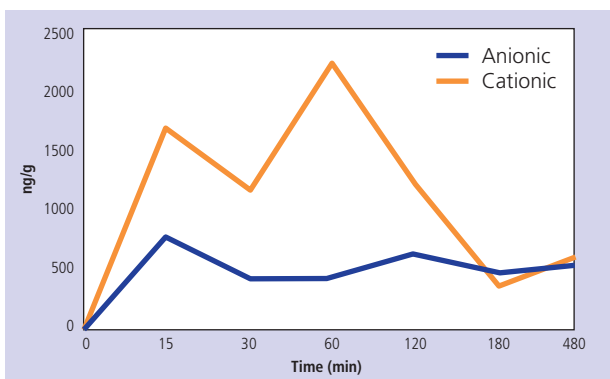


Figure 2 – Cyclosporin in conjunctiva after one single topical administration in anionic and cationic emulsion

saline or negative-charged emulsions. Piroxicam, vitamin E, indomethacin, cyclosporin, and other substances were successfully applied to rabbit eyes. For example, when anionic and cationic emulsions similar in size and composition containing cyclosporine (except the charged lipid) were administered to rabbits, the positively charged formulation produced significantly higher drug levels at the ocular surface (cornea and conjunctiva), and acted as a reservoir up to eight hours post-administration (Abdulrazik, Tamilvanan *et al.*, 2001) (Figure 2).

Delivery to the posterior segment

Drug delivery to the posterior eye, where 40% of main ocular diseases are located, is another great challenge in ophthalmology. To date, invasive treatments are used due to the lack of alternatives, requiring the most careful assessment in order to guarantee biocompatibility and lack of toxicity to the internal structures of the eye. While this concern may be easily resolved for hydrophilic molecules by administering a sterile isotonic aqueous solution (such as Foscavir® from **AstraZeneca**, Vitravene® from **Ciba Vision** or in-house formulated solutions), when the therapeutic agent is hydrophobic the ophthalmologist is obliged to inject unsuitable and potentially toxic products. The use of an emulsion (Eyeject™) as an intravitreal vehicle provides more simplicity and flexibility for clinical applications than an implant, especially concerning dose adjustment. In addition, its relatively short life span makes it ideal for use in diseases such as acute endophthalmitis or post-traumatic vitreous inflammation, achieving therapeutic concentrations for short though

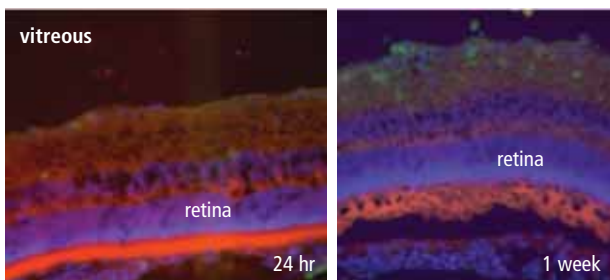


Figure 3 – Retinal distribution following intravitreal administration of a fluorescent cationic emulsion to animals.

significant periods of time (Figure 3). In addition to invasive approaches, topically-applied drugs were shown to reach the back-of-eye tissues through trans-conjunctival-scleral diffusion after multiple instillations (Koevary, 2003).

Conclusion

Thanks to the Novasorb™ electrostatic attraction occurring between the negatively charged droplets of ophthalmic emulsion and the negatively charged eye surface, there is a filmogenic 'bioadhesion' effect with product remanence onto the conjunctiva and cornea. This is followed by a strong penetration of the drug within these tissues further acting as reservoirs for diffusion of the drug to the back-of-eye tissues.

Novagali Pharma is a privately held biopharmaceutical company focused on ophthalmology that develops innovative drug formulations to treat eye diseases. Novagali's unique technology of cationic emulsion, Novasorb™, enables the delivery of drugs into all segments of the eye, safely and with optimal comfort for the patient. Novasorb™ cationic emulsions have been used in Phase I and Phase II clinical studies by more than one hundred patients and have demonstrated excellent comfort and promising features.

References

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