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Nanoparticle-loaded biodegradable light-responsive *in situ* forming injectable implants for effective peptide delivery to the posterior segment of the eye

Rohit Bisht, Jagdish K. Jaiswal, Ilva D. Rupenthal *

[a] *Buchanan Ocular Therapeutics Unit, Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1142, New Zealand*
[b] *Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1142, New Zealand*

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ABSTRACT

Diseases affecting the posterior segment the eye, such as age-related macular degeneration (AMD), are the leading cause of blindness worldwide. Conventional dosage forms, such as eye drops, have to surmount several elimination mechanisms and complex barriers to achieve therapeutic concentrations at the target site often resulting in low anterior segment bioavailability (ca. 2–5%) with generally none of the drug reaching posterior segment tissues. Thus, frequent intravitreal injections are currently required to treat retinal conditions which have been associated with poor patient compliance due to pain, risk of infection, hemorrhages, retinal detachment and high treatment related costs. To partially overcome these issues, ocular implants have been developed for some posterior segment indications; however, the majority require surgical implantation and removal at the end of the intended treatment period. The transparent nature of the cornea and lens render light-responsive systems an attractive strategy for the management of diseases affecting the back of the eye. Light-responsive *in situ* forming injectable implants (ISFIs) offer various benefits such as ease of application in a minimally invasive manner and more site specific control over drug release. Moreover, the biodegradable nature of such implants avoids the need for surgical removal after release of the payload. Incorporating drug-loaded polymeric nanoparticles (NPs) into these implants may reduce the high initial burst release from the polymeric matrix and further sustain drug release thus avoiding the need for frequent injections as well as minimizing associated side effects. However, light-responsive systems for ophthalmic application are still in their early stages of development with limited reports on their safety and effectiveness. We hypothesize that the innovative design and properties of NP-containing light-responsive ISFIs can serve as a platform for effective management of ocular diseases requiring long term treatment.

Introduction

Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide [1], with the number of people living with AMD expected to reach 196 million by 2020 and an estimated increase to 288 million by 2040 [2]. Effective drug delivery to the back of the eye is still challenging due to the presence of various elimination mechanisms (tear flow, nasolacrimal drainage, systemic absorption, protein binding and enzymatic degradation) and complex barriers (cornea, blood-aqueous barrier and blood-retinal barrier) which limit the entry of drug into the posterior segment following topical application (Fig. 1) [3–5].

After topical instillation of an eye drop, the majority of the drug is lost due to these elimination mechanisms resulting in low anterior segment bioavailability (2–5%) [6,7]. Moreover, the long distance between the site of application (cornea) and the target site (retina) make drug delivery to the posterior segment of the eye even more challenging [8]. To overcome these limitations, intravitreal (IVT) injections have become the gold standard for the management of posterior segment diseases. This involves direct administration of the drug solution into the vitreous thus overcoming the majority of the barriers and elimination mechanisms [9,10]. However, most drugs used in the treatment of posterior segment diseases have relatively short intravitreal half-lives. Therefore, to

* Corresponding author at: Buchanan Ocular Therapeutics Unit, Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.
E-mail address: i.rupenthal@auckland.ac.nz (I.D. Rupenthal).

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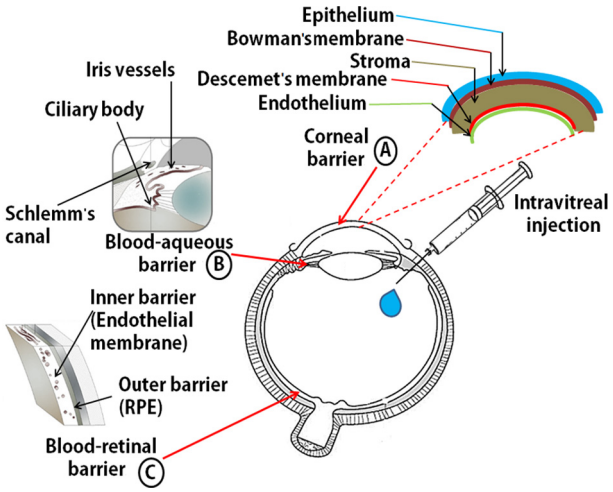

Fig. 1. Barriers to ocular drug delivery. (A) Corneal barrier; (B) Blood-aqueous barrier and (C) Blood-retinal barrier. RPE-Retinal-pigment epithelium.

maintain the required therapeutic drug concentration at the target site, injections are generally required every 4–8 weeks which may be associated with pain, risk of infection and high treatment costs [11]. Two of the currently marketed ocular implants for the management of posterior segment diseases (Vitrasert® and Retisert®) need surgical implantation and removal after the release of the loaded drug. And while they are able to deliver the drug over months to years, their implantation is still a rather invasive procedure that has been associated with various side effects and a high cost burden for patients and health care providers [12–14].

With recent advancements in the field of drug delivery technologies, formulation scientists and clinicians are looking for safer and more effective ways to deliver drugs to the posterior segment of the eye. To overcome the limitations associated with existing clinical interventions, nanoparticle (NP)-loaded light-responsive *in situ* forming injectable implants (ISFIs) may emerge as novel systems providing site-specific controlled drug delivery to the retina with great accuracy, safety and minimal invasiveness.

The hypothesis

Considering the impact of sight threatening diseases on a wide population globally, the focus of formulation scientists and clinicians has recently shifted from the anterior to the posterior segment of the eye. Irrespective of the immense development in the field of ocular therapeutics over the last decades, effective drug delivery to the retinal tissues remains challenging. Light-responsive systems are attractive for drug delivery to the back of the eye in a safe and effective manner as light of a certain wavelength can easily pass the transparent cornea and lens in a non-invasive manner. Thus, light can be used for site specific photocrosslinking of the system in the vitreous resulting in *in situ* implant formation and thus avoiding the need for surgical implantation.

Here, we propose NP-loaded light-responsive ISFIs as a platform for safe and effective drug delivery to the posterior segment of the eye. ISFIs are basically light-responsive liquids which can be injected into the vitreous in a minimally invasive manner and form a clear gel or solid depot quickly upon non-invasive photoirradiation through the cornea. Compared to other stimuli (pH, ions and temperature), light may result in more rapid sol-to-gel transformation lowering the diffusion rate of both the polymer and the entrapped drug. This would reduce the drug burst release from the polymer matrix and thus avoid any cytotoxicity related to free drug concentrations higher than the safety margins. The rapid sol-to-gel transformation would also result in improved physical properties helpful in maintaining the structural integrity of the system over longer durations, thus enhancing drug retention and bioavailability. In addition, the biodegradable nature of the ISFIs would avoid the need for surgical removal of the system after the drug release is completed. It is anticipated that incorporation of NPs into the light-responsive ISFIs will further reduce any burst release resulting in an even better safety profile. Due to the sustained release properties of this dual system the need for frequent IVT injections would be reduced. Therefore, biodegradable NP-loaded light-responsive ISFIs could have great potential as a sustained ophthalmic drug delivery platform for safe and effective management of posterior segment diseases.

Evaluation of the hypothesis

For conventional ocular dosage forms, such as topical eye drops, the majority of the instilled drug is immediately lost from the pre-corneal area due to lacrimal secretion and nasolacrimal drainage. Whatever remains on the ocular surface then has to be absorbed through corneal and non-corneal routes. The corneal route involves the permeation of the drug across the cornea and into the aqueous humor, from where it is distributed to the various intraocular tissues. The non-corneal route involves the absorption of the drug through the conjunctiva, from where it reaches the choroid and retinal pigment epithelium through the sclera [6,15]. The long distance between the site of drug administration and the retinal tissues including several complex barriers further limit the entry of drug into the posterior segment of the eye. Thus, conventional eye drops generally fail to deliver sufficient drug concentrations to the retinal tissues [16]. At present, the treatment of posterior segment diseases involves frequent IVT injections which have been associated with some side effects and high treatment costs. NP-loaded light-responsive ISFIs would therefore bring great benefit and innovation as advanced ocular drug delivery platform.

To date, various systems, such as colloidal formulations (polymeric nanocapsules, microparticles, liposomes and micelles) and polymeric implants have been developed or are under investigation for effective drug delivery to the posterior segment of the eye [17–21]. Hydrogels have been successfully marketed as artificial tears, corrective soft contact lenses [22] and foldable intraocular lenses [23]. Moreover, a few *in situ* gelling vehicles for topical administration, including Timoptic-XE®, have also made it onto the market with many more currently being investigated [24–27]. *In situ* gelling systems are three dimensional networks of soft materials containing a high percentage of water. They are free flowing liquids which transform into a gel or semi-sold depot in the presence of certain stimuli including pH, ions, temperature, light or specific biomolecules. Such systems have wide biomedical applications, such as tissue engineering, medical device development and drug delivery, mainly due to their structural similarities to body tissues [28–32].

Stimuli-responsive ISFIs offer various benefits for ophthalmic applications including (i) direct injection into the vitreous circumventing the majority of the penetration barriers (ii) ease of manufacturing; (iii) biodegradability avoiding the need for surgical removal; (iv) transparency and clarity important for unhindered vision; (v) ability to protect the incorporated therapeutics from degradation in the vitreous body, (vi) biocompatibility and (vii) ability to release drug in a sustained manner over prolonged periods of time thus avoiding the need for frequent IVT injections [33,34]. To date, various injectable stimuli-responsive *in situ* forming systems have been developed for drug delivery to the posterior segment of the eye [25,35–37]. However, many have suffered from a high initial drug burst release from the polymeric matrix due to