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Review

Implants for drug delivery to the posterior segment of the eye: A focus on stimuli-responsive and tunable release systems

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ABSTRACT

Efficient drug delivery to the posterior segment is a challenging task for the formulation scientist. Current treatment of chronic back-of-the-eye conditions requires frequent intravitreal injections of drug containing solutions due to the short half-life and limited tissue permeation of the administered molecules. Sustained release ocular delivery systems offering reduced administration frequencies have therefore gained popularity over recent years with a few implants already on the market and many more in the pipeline. However, current implants generally release drug at a predetermined rate without the ability to alter release rates. As required drug concentrations may change over the course of treatment due to the individual patient's clinical response, implants from which release rates can be tuned could optimize treatment efficacy. This article provides an overview of diseases of the posterior segment of the eye, describes currently available implants to treat such conditions and discusses advantages and disadvantages of various implant locations. Finally, stimuli-responsive drug delivery technologies that have been investigated for, or have the potential to be applied to, drug delivery to the back of the eye will be discussed. Emphasis is hereby placed on polymeric implants responsive to an electric current, light or a magnetic field to achieve tunable drug release.

Contents

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1. Introduction

With the 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 [1–6], with such systems also having great potential in the area of ocular drug delivery [7–9]. Effective and sustained drug delivery to the posterior segment of the eye is challenging as there are structural and physiological barriers which limit the penetration of topically or systemically administered actives into the ocular tissues. Thus, to treat ocular conditions of the posterior segment of the eye, invasive local therapy such as intravitreal injection of drug containing solutions is generally required. Since these injections have to be performed relatively frequently by a specialist they increase the burden on health care professionals. Moreover, they only provide modest relief and generally result in low patient adherence to the therapy [10]. Finally, they may result in unwanted ocular complication such as cataract formation or retinal detachment [11].

Ocular implants provide a platform for sustained release of drugs from either biodegradable or non-biodegradable polymeric systems over several months to years [12]. Currently, there are three ocular implants, Vitrasert®, Retisert® and Ozurdex®, approved by the FDA, with the first two being non-biodegradable systems anchored to the sclera while the latter is a biodegradable rod injected into the vitreous. Another non-biodegradable implant, Iluvien®, is currently awaiting FDA approval, but has already been approved in some EU countries [13–18]. However, while these systems can deliver the drug over long periods of time, the release rate cannot be altered. Thus, stimuli-responsive drug delivery systems (DDS) suitable for ocular implantation are of interest as they have the potential to provide tunable drug delivery to the affected areas [19,20]. Such systems offer fine control over drug release, helping to optimize therapeutic outcomes in individual patients [21] and could become particularly attractive for delivery of macromolecules in the treatment of ocular diseases [22].

Stimuli-responsive systems are considered 'intelligent' as they respond to a stimulus leading to the initiation, termination, increase or decrease in drug release. Such implants are generally divided into closed-loop and open-loop systems. Closed-loop systems are self-regulating where an internal stimulus, such as a rise in glucose concentration in the blood, increases drug release [23]. Open-loop systems require an external stimulus, such as application of an electrical current or a magnetic field, to achieve the desired response [24]. To date, only open-loop systems have been explored for the purpose of drug delivery to the posterior segment of the eye, although pressure responsive closed-loop systems may have great potential in the treatment of glaucoma. This article discusses the current treatment options for the most prominent chronic posterior segment conditions highlighting the need for stimuli-responsive drug delivery. It then provides an overview of various implant locations suggesting possible sites for stimuli-responsive tunable implantable systems. Finally, various types of implants are reviewed with a focus on systems responsive to an electric current, light or a magnetic field and their practical application for tunable drug delivery to the posterior segment of the eye.

2. Current pharmacological therapies for posterior eye conditions

Posterior segment diseases are a major health concern as these conditions directly impact on the patient's vision and therefore their quality of life. Around 285 million people are estimated to be visually impaired or blind with this number increasing by at least seven million per year [25]. The main vision threatening diseases affecting the posterior segment include age-related macular degeneration (AMD), diabetic retinopathy and uveitis. While a number of drugs are available to treat these conditions, only a few implantable devices exist to delivery these drugs efficiently and over extended periods of time. Table 1 gives an overview of implantable DDS approved by the FDA or in the pipeline for the treatment of posterior eye conditions with individual diseases described below and novel implantable systems further discussed in a later section.

2.1. Cytomegalovirus (CMV) retinitis

CMV is an opportunistic virus which can infect ocular tissues including the retina and is most prominent in patients with acquired immune deficiency syndrome (AIDS), affecting up to 25% of these patients [13, 40–42]. Without treatment CMV can lead to vision loss and is the leading cause of blindness in patients with compromised immunity [43]. Ganciclovir is the most studied drug for the treatment of this disease and is considered the first line of treatment [44]. Initially ganciclovir was given to CMV retinitis patients intravenously; however, this was associated with systemic side effects including neutropenia [45]. Later the intravitreal route was used to deliver the drug directly into the eye, which resulted in reduced systemic exposure. However, intravitreal injections are associated with low patient compliance and may cause cataract formation and retinal detachment [46]. These factors encouraged the development of an intravitreal ganciclovir implant (Vitrasert) which has shown good therapeutic outcomes in AIDS patients suffering from this eye condition, although raised intraocular pressure (IOP) and cataract formation have arisen as complications. Vitrasert releases 5 mg of drug at a predetermined rate over several months, achieving intravitreal drug levels of 4 μg/ml [15,46–48]. As some patients with compromised immunity (especially solid organ transplant patients [47]) have developed ganciclovir resistant CMV retinitis infection, another antiviral drug, foscarnet, either alone or in combination with ganciclovir, has been administered intravitreally to cure this infection. Therefore, an implant containing both drugs with the possibility to modify the release in response to a stimulus could offer an advantage over Vitrasert [49,50]. Cidofovir is another antiviral drug used for the treatment of CMV retinitis. It has a narrow intravitreal therapeutic index [51], thus a carefully designed controlled release implant would ensure therapeutic concentrations are maintained. Nevertheless, emerging resistance and treatment failures may limit this opportunity [52].

2.2. Age-related macular degeneration (AMD)

AMD is the leading cause of irreversible blindness in the population aged over 50 years with its prevalence projected to increase up to 50% in this age group by 2020 [53–55]. Early stage AMD is characterized by the presence of a few medium sized drusen in the retina as well as retinal pigment abnormalities. The advanced stage of AMD can be either dry (non-neovascular) or wet (neovascular). Wet AMD accounts for 10–15% of the overall prevalence of AMD but is responsible for over 80% of cases of legal blindness [56]. It is characterized by choroidal neovascularization and can lead to blindness in days to weeks as a result of hemorrhage or fluid accumulation. Anti-vascular endothelial growth factor (anti-VEGF) antibodies are the primary pharmacological course of treatment for wet AMD administered *via* the intravitreal route. These include FDA approved ranibizumab (Lucentis®) and off-label

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