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Drug-device combination approaches for delivery to the eye

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While the eye is readily accessible from the outside of the body, it is a rather isolated organ with a number of barriers and elimination mechanisms in place to protect it from the environment, rendering efficient treatment difficult. To enhance drug delivery to the eye, a number of drug-device combinations have been investigated over recent decades, increasing drug retention and permeation while also allowing for sustained drug release over prolonged periods. This article will summarize recent combination systems investigated for the treatment of anterior and posterior segment conditions.

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Introduction

Due to the accessibility of the ocular surface, topical drop application is the most common method for treating eye diseases. However, the unique ocular anatomy and physiology still render it difficult to achieve effective drug concentrations at the target site. This is mainly due to nasolacrimal drainage and high tear fluid turn-over limiting the formulation's precorneal contact time to less than 2 min [1]. Even when increasing this using viscosity enhancing [2], mucoadhesive [3•], particulate [4•] or *in situ* gelling systems [5–7], the poor permeation across the cornea further reduces the available drug amount. Thus, the bioavailability of conventional eye drops is generally less than 10% [8] leading not only to low efficacy, but also posing potential risks due to systemic absorption of the majority of the given dose. Finally, even when combining precorneal retention with permeation enhancing approaches using prodrugs [9], nanoparticles [10••], liposomes [11] or micelles [12•], topically applied formulations are generally unable to deliver sufficient drug to the back of the eye.

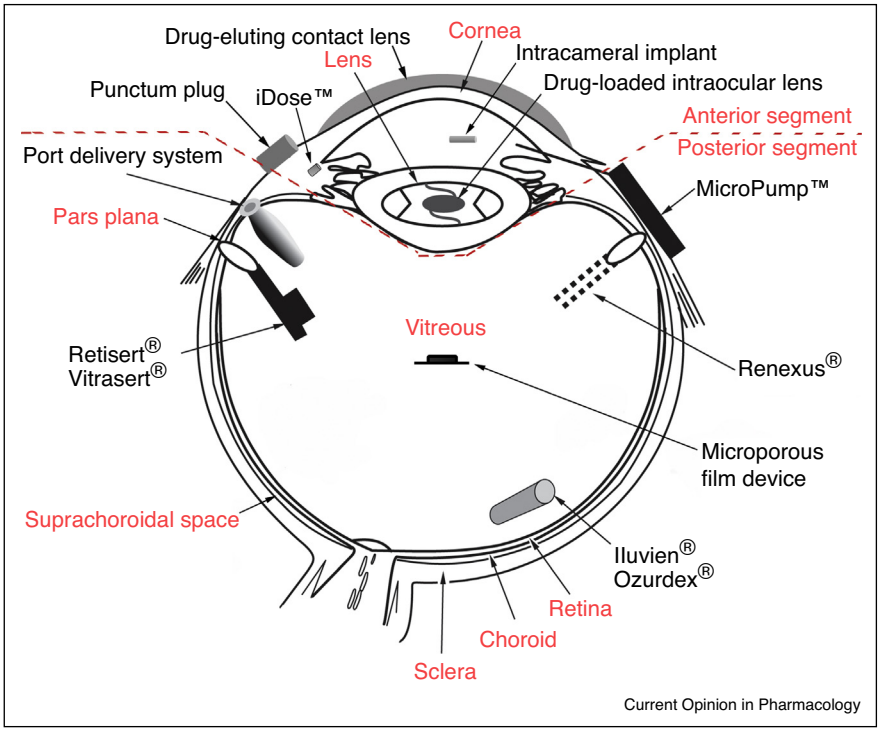
The gold-standard to treat posterior segment conditions thus remains injection of the drug-containing solution into the eyeball [13]. Although a relatively site specific application into a confined space, injected drugs face rapid elimination processes and need to diffuse through the vitreous, a dense network of collagen fibrils, before crossing the inner limiting membrane to reach the retina. Due to the limited vitreous half-life of drugs applied as solutions, injections need to be performed frequently to maintain efficient drug concentrations. In the case of age-related macular degeneration (AMD) treatment this means injecting solutions of anti-vascular endothelial growth factors (anti-VEGF), such as ranibizumab, bevacizumab or aflibercept, into the eyeball every four to six weeks [13]. While such intravitreal injections are generally considered safe, they can occasionally result in adverse events, but more importantly, they place an enormous burden onto patients and healthcare professionals with over 18 million injections given annually worldwide [14].

While many effective drugs exist to treat ocular conditions, the challenge remains to deliver them effectively and over prolonged periods of time with minimal side effects. This is where drug-device combinations offer great opportunities, especially when using already FDA approved drugs with well-known safety and efficacy [14] as is the case for most of the drug-device combinations discussed below. As such it is no surprise that the number of companies working on drug-device systems has skyrocketed over the past decade, with many combination products currently in clinical trials. However, to be marketed successfully such combination approaches need to achieve clear advantages over the drug alone especially with regards to therapeutic efficacy, lowered toxicity and increased patient compliance [15]. Figure 1 gives a schematic overview of ocular anatomy and drug-device combinations currently on the market or in (pre-)clinical studies which will be further discussed below.

Drug-device combinations for anterior segment delivery

Drug-device combinations for the front of the eye date back as far as the 1970s when Ocusert® (Alza) was approved for the treatment of glaucoma. This device was a membrane-controlled reservoir system containing

Figure 1



Schematic overview of ocular anatomy and drug-device combinations currently on the market or in (pre-)clinical studies. Modified with permission from [16].

pilocarpine in an alginic acid core, sandwiched between two transparent ethylenevinyl acetate membranes allowing drug diffusion for a period of seven days. However, difficulty of insertion, foreign-body sensation and inadvertent loss from the ocular surface ultimately resulted in its market withdrawal. Considering the rising incidence of glaucoma and the poor adherence to therapy due to the need of frequent drop administration, often as a combination of multiple products, to achieve sufficiently high drug concentrations, it is not surprising that a number of new drug-device combinations are currently in clinical trials for this condition.

One of these includes the bimatoprost containing Helios™ ring developed by ForSight VISION5, a multiple size silicon ring that sits under the eyelids and can release drug for up to six months (Figure 2). It is currently in Phase 3 clinical trials, but has shown good retention and efficacy in a Phase 2 randomized, double-masked controlled study [17]. Allergan, who acquired this periocular ring technology, is also currently performing Phase 3 clinical studies with bimatoprost SR, a biodegradable, intracameral implant based on the poly(lactic co-glycolic)acid (PLGA) NOVADUR™ matrix system, which has demonstrated favourable efficacy and safety for up to six months in a Phase 1/2 clinical study [18]. Another intracameral implant is being investigated by Envisia Therapeutics utilizing a Particle Replication In Non-Wetting Templates (PRINT®)-based PLGA rod for sustained travoprost delivery (ENV515; travoprost XR) [19], with a single rod administration having shown clinically meaningful reduction in intraocular pressure for 11-months (Phase 2 interim data).

Interesting combination products have also recently emerged using devices previously utilized solely for surgical applications. The iStent® by Glaukos, for example, is a trabecular micro-bypass stent and Glaukos' first Micro-Invasive Glaucoma Surgery (MIGS) device approved by the FDA in 2012. The device has since been tailored for drug delivery applications (iDose™) filled with a special formulation of travoprost and capped with a membrane designed for controlled drug elution into the anterior chamber. Travoprost has also been incorporated into a medicated punctum plug (OTX-TR, Ocular Therapeutix), which is currently moving into Phase 3 clinical trials, while the dexamethasone counterpart (Dextenza™) demonstrated preliminary efficacy and clinical safety in a Phase 2 chronic allergen challenge model [20] and met the primary endpoints in Phase 3 clinical trials for post-operative inflammation [21]. Punctum plugs were originally developed to reduce tear fluid drainage in patients with aqueous-deficient dry eye, but were adapted to contain micronized drug particles that slowly release as