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Polymer-based Therapies for Posterior Segment Ocular Disease

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Ocular Diseases

In the United States, 36.8 million people over the age of 40 are affected by vision loss due to fourmajor ocular diseases: macular degeneration, diabetic retinopathy, glaucoma, and cataract [1]. The first two diseases affect the posterior segment of the eye, while the latter two affect the anterior segment. In macular degeneration, the macula of the retina is damaged by the abnormal growth of blood vessels and central, focused vision is damaged [2].While the exact cause is unknown, lack of nutrient supply for macula and UV exposure are believed to contribute to the progression. Similarly, diabetic retinopathy is indicated by new, abnormal blood vessels bleeding into the retina and vitreous [3]. It progresses in elderly patients with diabetes for over fifteen years. Therapeutic intervention is limited due to the physiological barriers of the eye as well aspotential routes of drug administration [4].

The Posterior Segment of the Eye

The posterior segment of the eye consists of the retina, vitreous, and choroid (Figure 1). While the anterior segment of the eye can be readily accessed for topical treatment, multiple physical barriers and clearance mechanisms prevent easy access to the posterior segment. The topical route is a convenient method of drug delivery; however, there is poor bioavailability due to nasolacrimal drainage and systemic absorption [5]. A model of transient diffusion has shown that less than 5% of a lipophilic drug and 0.5% of a hydrophilic drug reach the anterior chamber [6]. The amount of drug transported further decreases across the sclera, choroid, and retinal pigment epithelium (RPE) [7]. Permeability via sclera is reduced with cationic and lipophilic solutes and the RPE has tight intercellular junctions for hydrophilic molecules [7]. Additionally, the lymphatic system, blood vessels and active transporters all work to clear drugs administered through trans scleral routes. Drug delivery via systemic routes requires high doses to obtain a therapeutic concentration in the posterior eye due to the tight barrier of the RPE. Intravitreal injections circumvent physiological barriers and maintain therapeutic doses without damage to bystander tissues. However, frequent injections can lead to complications like retinal detachment, increase in ocular pressure, and hemorrhage [8]. Given the presence of these physiological barriers, the development of therapies that efficiently deliver drugs and extend drug release to the posterior segment of the eye would be beneficial to the progression of ocular disease treatment.

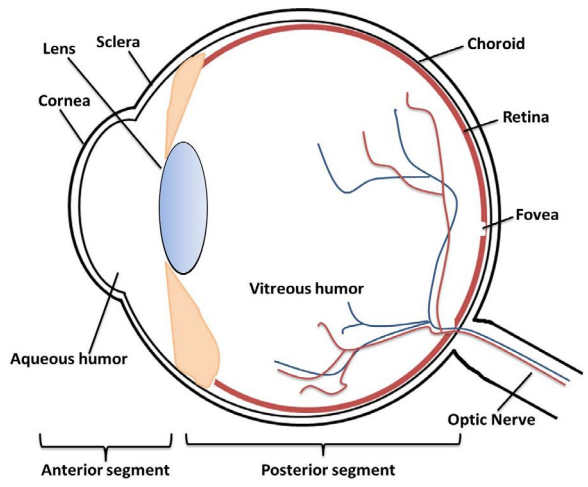

Figure 1: A model of the eye.`

Drug Delivery Systems for Posterior Segment of the Eye

While drugs are available clinically to attenuate the progression of posterior segment ocular diseases, they are limited by need for multiple dosing and consistent intravitreal injections to maintain the therapeutic dose. The development of new drugs is time consuming and expensive; therefore, more efficient and safer drug delivery systems would benefit disease treatment. More specifically, the development of polymers for use in drug delivery offers novel strategies for sustained ocular delivery. The limitations of topical delivery and adverse effects of more invasive techniques can be bypassed by manipulating the characteristics of polymers. By preparing drug/polymer ophthalmic formulations, drug release can be controlled over an extended duration [9]. For any DDS therapy to be effective, the drug delivery system must fulfill three major goals: (1) drug release must be targeted; (2) drug release should be controlled; and (3) the drug should maintain therapeutic efficacy at adequate dose levels [10].

Current Strategies for Posterior Segment-Targeted Deliveries

Thermo reversible hydrogels

Thermoreversible hydrogels are biodegradable, water soluble polymers that undergo phase transition upon temperature elevation [5,11]. The gel can be loaded with bioactive macromolecules and pharmacological agents irrespective of their solubility properties. Since the gel forms quickly in vivo, it can be used to achieve localized and sustained release. Studies have shown synthesis of an ABA-type block copolymer, poly (ethylene glycol)-poly (serinolhexamethylene urethane), to release bevacizumab. The drug release profile achieved a longer therapeutic window over 17 weeks in vitro. Such therapy treatment could potentially reduce intravitreal injection frequency [11]. Additional studies of thermo gels based on poly (DL-lactide-co-

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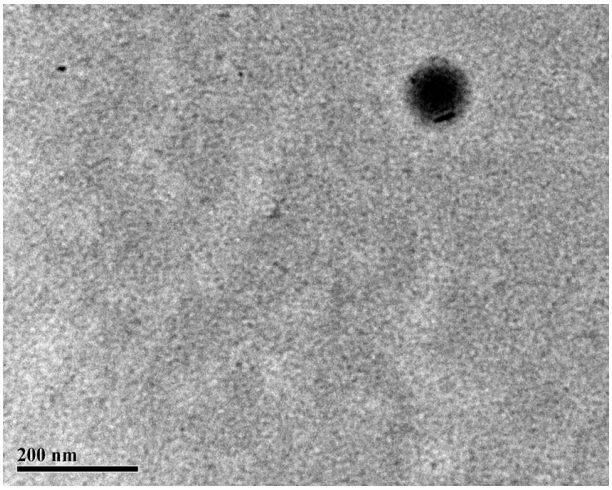

Figure 2: TEM image of triamcinolone acetonide-loaded PEGylated PLGA nanoparticles.

glycolide (PLGA) and polyethylene glycol (PEG) were able to deliver 45kDa protein across the sclera to the retina for up to 14 days [10]. An alternative formulation includes Pluronic F 127 as the thermoreversible polymer and methyl cellulose as a release controlling agent. This formulation has been used to deliver non-steroidal anti-inflammatory drugs for conjunctivitis [12] as well as selective inhibitors for glaucoma [13].

Biodegradable implants

Ocular implants also provide platforms for sustained release. They are implanted either into the vitreous or on the sclera for intravitreal or transscleral delivery. Biodegradable implants degrade in the eye and do not require surgical removal; however, the degradation process can result in inconsistent release profiles [14]. Ozurdex is composed of PLGA and releases dexamethasone intravitrealy over 4 to 6 weeks. Results have shown an improvementin intraocular inflammation for up to six months [14,15].

Non-biodegradable implants

Non-biodegradable implants provide more accurate control of drug release, but require surgical removal. Polymers such as silicone, polyvinyl alcohol and ethylene vinyl acetate are used in these implants. Several implants are in clinical use and clinical trials; however, studies have shown that while they reduce disease symptoms, they increase intraocular pressure and cataract progression [14].

PEG-PLGA nanoparticles

PLGA is an FDA-approved polymer that has been studied for biocompatibility and toxicity. Though biodegradable, the rate of degradation ranges from months to years and can be used to extend the release time of drugs. PEG also has a slow clearance from blood, allowing increased drug release. Nanoparticles have also been studied as drug carriers in ocular pharmaceuticals [15]. Particles at the nanometer range have shown increased solubility, surface area, and drug dissolution. When bevacizumab, an anti-VEGF antibody, was incorporated in PEG-PLGA,it showed sustained release for up to 60 days [16]. In another study, when corticosteroid triamcinolone acetonide was encapsulated by PLGA, inflammation associated with ocular diseases was reduced. The drug/polymer ratio was shown to effect the entrapment efficiency and release profiles [17]. Figure 2 shows a transmission electron micrograph image of triamcinolone acetonide encapsulated PEG-PLGA nanoparticles.

Conclusion and Future Considerations

There is a demand for newly repositioned drugs for posterior ocular diseases, because of the difficulty in gaining FDA approval for new therapies. There are a wide range of drug delivery systems including thermoreversible gels, implantable devices and drug-loaded nanoparticles that provide strategies to circumvent physiological barriers and provide sustained release with minimal systemic side effects. The polymer-based drug delivery system can expand current disease therapy and repurpose presently used drugs and extend their patent life.

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