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Recent Developments in Ophthalmic Drug Delivery Systems for Therapy of Both Anterior and Posterior Segment Diseases

Hao Chen[a], Yingying Jin[a], Lin Sun[a], Xi Li[a], Kaihui Nan[a,b], Huihua Liu[a,b], Qinxiang Zheng[a], Bailiang Wang[a,b,*]

[a] School of Ophthalmology & Optometry, Eye Hospital, Wenzhou Medical University, Wenzhou 325027, China
[b] Wenzhou Institute of Biomaterials and Engineering, Chinese Academy of Sciences, Wenzhou 32500, China

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ABSTRACT

Eye is a complex organ with unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Due to the special structure of the eye and the defects of the traditional medicine treatment, the search for a new type of ophthalmic drug delivery technology has drawn more and more attentions. Recently many kinds of ophthalmic drug delivery technologies with high drug delivery efficacy and good biocompatibility have been constructed to treat eye diseases. Hydrogels are generally used as a carrier of bioadhesive macromolecules to increase the viscosity of the drug formulation and prolong the residence time of the drug in the eye, thereby increasing the bioavailability of the drug. This review will discuss the recent progress in ophthalmic drug delivery systems and applications.

1. Introduction

Eye is an important human visual organ and > 95% of the daily information is obtained through the eyes. Due to the special physiological structure of the eye and the unique drug delivery barrier, the treatment of ocular diseases especially in the posterior eye segment is often not effective [1]. Pharmaceutical lipophilic drugs are difficult to dissolve into solution and oily or ointment formulations often cause blurred vision, eyelid adhesions and other discomfort. In the past, the treatment took repeated vitreous injection which easily led to intraocular infection, increased retinal detachment and other complications [2]. Due to the defects of ophthalmic drug delivery barrier and traditional drug delivery technology, more and more novel ophthalmic drug delivery technologies have been developed to treat eye diseases [3].

Considering the difference of ophthalmic anterior and posterior segment structures and barriers, it is urgent to construct appropriate ophthalmic drug delivery systems for the treatment of ocular diseases. Specifically, for the anterior segment, strong corneal penetrating drug technology can increase drug retention time [4]. While for the posterior segment, targeted and slow drug release nanoparticles, implants surface modified coatings and other drug delivery techniques can increase drug efficacy and reduce the times [5]. Based on the development of our laboratory research and related research reports, this article reviewed the recent ophthalmic drug delivery systems and applications based on physiological structure of the eye and the drug delivery barrier.

2. Eye Anatomy and Physiology and Eye Diseases

Eye is a complex organ with a unique anatomy and physiology. The structure of eye can be basically divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third of the eyeball while the remaining portion is the posterior segment. The anterior segment tissues include cornea, conjunctiva, iris, ciliary body, aqueous humor and lens structure [6], The posterior segment tissues include vitreous, retina, macular, optic nerve, choroid and sclera and other structures [2,8]. There are different physiological structure and barriers between anterior and posterior segments. Considering the disease at different parts of the eyeball, the administration way for disease therapy is not same. For the anterior segment, the major diseases are concentrated at cornea, conjunctiva, lens et al. For the posterior segment, the major diseases focus on the vitreous and the retina (Fig. 1).

The cornea is a clear, transparent, avascular tissue and nutrients and oxygen are supplied by the lachrymal fluid and aqueous humor. This layer consists of epithelium, endothelium and stroma three parts [9]. The epithelium is lipophilic which offers resistance to passage of hydrophilic molecules. The corneal stroma is hydrophilic which hinders rapid movement of hydrophobic molecules. The corneal epithelium possesses tight intercellular junctions that prevent uptake and

* Corresponding author at: School of Ophthalmology & Optometry, Eye Hospital, Wenzhou Medical University, Wenzhou 325027, China.
E-mail address: wangbailiang2006@aliyun.com (B. Wang).

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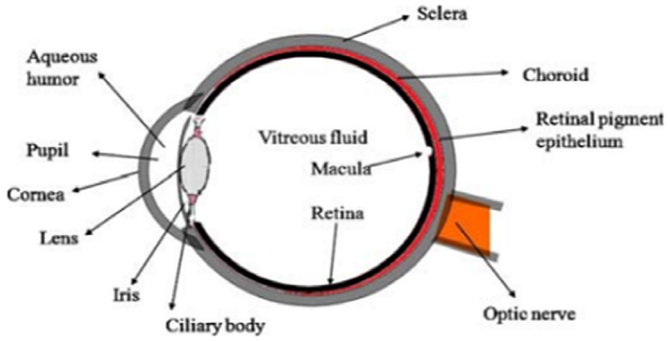

Fig. 1. The image of the different parts of each eye segment (anterior and posterior) [8].

paracellular permeation of polar molecules [10,11]. As the first important line of defense, the cornea resists foreign invasion through forming a corneal barrier, which reduces the penetration of drugs and drug utilization. Conjunctivitis, as a common eye disease, the main symptoms are mainly caused by foreign body sensation, burning sensation, heavy eyelids, increased secretions [11,12]. Antibiotics and corticosteroids are often used for bacterial conjunctivitis treatment. For allergic infections treatment, antihistamines and non-steroidal anti-inflammatory drugs are most common treated method. For these drugs effective delivery to cure the disease, more and more advanced materials such as nanoparticles, coatings and hydrogels have attracted a lot of attentions. For example, hydrogels have been widely used in ophthalmic applications such as in situ forming hydrogels for ophthalmic drug delivery, drug-eluting contact lenses and tissue adhesives for ocular wound repair and so on.

Lens is a biconvex transparent flexible tissue suspended by the suspensory ligament before the vitreous and behind the iris. Crystals is an important part of the eye curvature of the optical system which has the ability to regulate the refractive substance. However, the regulate capacity gradually decreased with age leading to the phenomenon of presbyopia formation [6]. Cataract is one of the most common blinding diseases of ophthalmology in clinical medicine. Clinically phacoemulsification combined with intraocular lens implantation method is often used for cataract treatment. What's more, posterior capsule opacification (PCO) has been the most common underlying complication after cataract surgery [13]. The development of PCO is attributed to the combination of adhesion, migration, proliferation, and trans differentiation of the residual lens epithelia cells (LEC) onto the surface of intraocular lens (IOL) material and lens posterior [14]. Therefore the material surface requires modification with antibacterial, anti-adhesion properties to reduce the lens posterior capsule turbidity and secondary cataract bacterial infection incidence.

Glaucoma leads to vision loss and even blindness. The progress of drug delivery systems provides more options of preservation and treatment of glaucoma. Drugs delivery systems have showed effective in drug bioavailability, sustained release time and low toxic effects [15]. Some traditional anti-glaucoma administrations are cooperated with nanomedicine approach to improve drug bioavailability and decrease drug dosage.

Retina is a thin transparent tissue which forms the innermost layer of the eye. Retina consists of tight junctions between the endothelial cells of the retinal blood vessels and the retinal-pigmented epithelium (RPE) [16]. The blood-retinal barrier (BRB) is composed of them both in the posterior segment which prevents the entry of drug molecules from blood circulation into the retina [17]. BRB is considered as a significant barrier for large molecules from systemic circulation penetrating the retina. The Age-Related Macular Degeneration (AMD) is the leading cause of blindness in people over the age of 50, which often results in severe loss of vision due to neovascularization derived from the choriocapillaris. The general treatment is intravitreal injection of anti-vascular endothelial growth factor substances, such as pegaptanib sodium, bevacizumab [18]. Intravitreal injections are limited by ocular pharmacokinetics and the frequent need for retreatment. Nanoparticles have been used for the treatment of post-ocular disease. There is currently no effective method for choroidal neovascularization (CNV) blindness treatment [19]. Therefore, targeted drug delivery systems are urgent need in therapies of these eye diseases.

3. The Drug Delivery Technology to Anterior and Posterior Segment

Due to the special anatomy and physiology of anterior and posterior segments, different routes of administration and appropriate anastomosis techniques are adopted for anterior and posterior segment disease treatment. The drug delivery technology in several important parts include anterior the cornea, lens and posterior vitreous and retinal are mainly introduced (Table 1).

3.1. The Administration Technology of Corneal

Targeting the cornea barrier and tear dynamic dosing barrier, local drug delivery techniques are mainly applied clinically. Taking into account drug adhesion to the cornea, viscosity, penetration, retention time and availability of the drug, drug delivery techniques used in corneal mainly contain hydrogels, nanosuspensions and liposomes.

3.1.1. Hydrogels of Drug Delivery Technology

Hydrogels are three dimensional networks composed of cross-linked hydrophilic polymer chains, which can be cast into practically any shape, size, or form and absorb up to thousands of times their dry weight in water. Hydrogels are polymeric materials distinguished by high water content and diverse physical properties [20]. Hydrogels may offer some favorable physicochemical properties, such as transparency, high water content, and mechanical flexibility. Hydrogels have already been approved useful in the treatment of the anterior segment of the cornea. For example, the mild preparation conditions and high water content of hydrogels are beneficial in preserving the activity of biopharmaceuticals. The commonly used hydrogel dosing technology makes use of bioadhesive hydrogels and in situ hydrogels. Bioadhesive hydrogels are generally used as a carrier of bioadhesive

Table 1
Advantages and disadvantages of different ocular formulations.

Drug delivery system	Advantages	Disadvantages
Hydrogels	Prolongs residence time and increases bioavailability	Depending on temperature, pH, ion trigger
Cyclodextrin Inclusion complex	Increases solubility, improves bioavailability, Increases permeability, and extends residence time	Limited to improve solubility in soluble drugs
Liposomes comfortable	Long-lasting, reducing the number of administration, controlled release, reducing the number of administration	Stability is poor, clear fast, conjunctival cell absorption problems
Nanoparticle	Small particle size, extended shelf-life, good stability, improved bioavailability, and reduced number of administration	Difficult to control the range of particle size distribution
Nano-suspension	Stability, prolonged contact time	Blurred vision poor patient compliance