Acta Pharmaceutica Sinica B ▮▮▮▮;▮(▮):▮▮▮–▮▮▮

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

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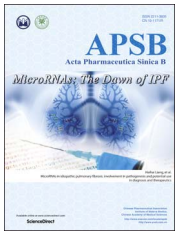

REVIEW

Nanotechnology-based strategies for treatment of ocular disease

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Received 20 March 2016; revised 24 May 2016; accepted 6 July 2016

KEY WORDS

Nanosystems;
Nanocarrier;
Eye;
Ocular disease;
Ocular drug delivery;
Therapy;
Diagnosis

Abstract Ocular diseases include various anterior and posterior segment diseases. Due to the unique anatomy and physiology of the eye, efficient ocular drug delivery is a great challenge to researchers and pharmacologists. Although there are conventional noninvasive and invasive treatments, such as eye drops, injections and implants, the current treatments either suffer from low bioavailability or severe adverse ocular effects. Alternatively, the emerging nanoscience and nanotechnology are playing an important role in the development of novel strategies for ocular disease therapy. Various active molecules have been designed to associate with nanocarriers to overcome ocular barriers and intimately interact with specific ocular tissues. In this review, we highlight the recent attempts of nanotechnology-based systems for imaging and treating ocular diseases, such as corneal d iseases, glaucoma, retina diseases, and choroid diseases. Although additional work remains, the progress described herein may pave the way to new, highly effective and important ocular nanomedicines.

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Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2016.09.001

Please cite this article as: Weng Yuhua, et al. Nanotechnology-based strategies for treatment of ocular disease. *Acta Pharmaceutica Sinica B* (2016), http://dx.doi.org/10.1016/j.apsb.2016.09.001

1. Introduction

Ocular diseases directly affect human vision and quality of life. A survey from 39 countries estimated that 285 million people suffer visual impairment. Of these, 65% are over 50 years old, and 82% of blind patients are over 50[1]. Significant achievements have been made in the discovery of ocular pathological mechanisms and management of ocular disease. However, due to the special physiological barriers and anatomical structures of the human eye, diagnoses and treatments of these disorders can suffer from low efficiency and lack of specificity. The current therapeutic methods seldom can completely restore vision loss or detect severe ocular diseases at an early stage[2]. Therefore, the development of improved diagnostics and therapeutics for ocular diseases is receiving intense attention.

Emerging nanotechnology and nanoscience methods are increasingly being applied to biopharmaceutics. Nanoscience is an interdisciplinary field that combines material science, physics, chemistry and biology, whereas nanotechnology involves the design and fabrication of different materials in nanometer scale at least in one dimension[3–6]. Several nanotechnology-based strategies have been developed and aimed at management of ocular diseases: bioadhesive enhancement, sustainable release, stealth function, specifically targeted delivery, and stimuli responsive release, etc[7–9]. Therefore, many attempts have been focused on fabrication of multi-functional nanosystems for ocular diseases therapy by improving drug (or gene) delivery to both the anterior and posterior segments of the eye.

In this review, we have focused on advances in development of nanotechnology-based systems for ocular diseases therapy and imaging. First, the specific anatomy and the attendant constraints in ocular drug administration are introduced. Some conventional and alternative drug administration routes are summarized and compared as well. Second, for a deeper insight of nanosystems mechanism, several examples of nanosystems for management of ocular disease are highlighted and reviewed. Then, some typical studies are summarized. Finally, we summarize the perspective of nanotechnology and existing challenges in ocular diseases therapy and diagnosis. This review will provide both inspiration and impetus for better design and development of intractable ocular disease managements.

2. Ocular anatomy and constraints to ocular drug delivery

The human eye is a globular structure organ with size of about 24 mm, and consists of two main parts: the anterior and posterior segments[10] (Fig. 1). The both parts have various biological barriers to protect the eye from foreign substances. The anterior portion includes the corneal, iris, lens, and aqueous humor. The posterior portion consists of the vitreous body, retina, choroid, and back of the sclera. The cornea is transparent and contains five layers: epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium[11,12]. The human corneal epithelium is the most important part of corneal barrier since it has multilayers of corneal epithelial cells which interconnect by tight junctions. These tight junctions can severely limit ocular penetration of drugs, especially many types of hydrophilic molecules. The corneal stroma is mostly composed of charged and highly organized hydrophilic collagen which hinders passage of hydrophobic molecules[13–15]. In recent studies, various efflux transporters on epithelial cells were proved to be of importance in preventing permeation of anti-viral and anti-glaucoma drugs[16–18].

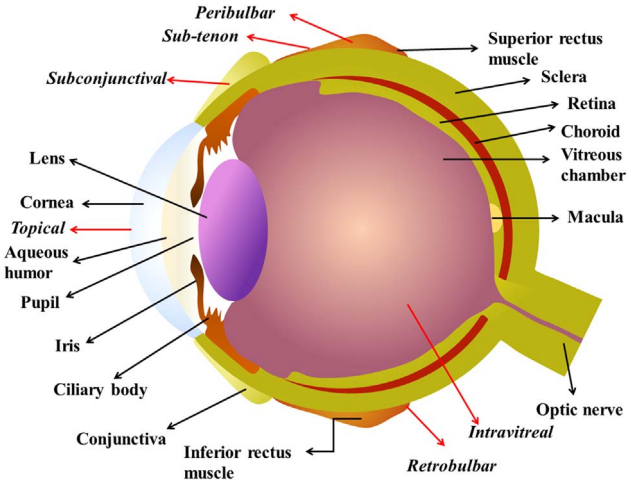

Figure 1 Ocular anatomy and administration routes of both traditional drugs and nanosystems: the black arrows show different eye structures and the red arrows show various administration routes.

The intraocular environment contains two main barriers: blood–aqueous and blood–retina barrier. The blood–aqueous barrier is composed of the nonpigmented epithelium of the ciliary body, which specifically includes the iris epithelium, iris vessel endothelium with tight junction, and Schlemm's canal endothelium. The tight junctions of cells control both active and paracellular transport[14,19,20]. The blood–retinal barrier is divided into inner and outer blood–retinal barriers. The former one is composed of retinal vascular endothelium with tight junctions. The latter includes a monolayer of retinal pigment epithelium (RPE) with tight junctions[19,21]. These two components restrict penetration of molecules into the intraocular chamber, resulting in inefficient therapy on intraocular tissues.

In addition, topical drug administration to the anterior segment of the eye is often limited by clearance mechanisms of the corneal surface and other precorneal factors, including eye blinking, tear film, tear turnover, solution drainage and lacrimation[22]. Human tear film has a rapid restoration time of only 2–3 min. Thus, most topically administered drugs are washed away within a few seconds after instillation. When topical drug solution volume is more than 30 μL (the upper limit volume that can be accommodated in the cul-de-sac), most of the drug is wasted by either nasolacrimal drainage or gravity-induced drainage[23]. Hampered by these factors and ocular barriers, the efficacy of the total administered drugs is less than 5%, suggesting the poor bioavailability of ocular drugs[23,24].

3. Benefits and limitations of ocular delivery routes

3.1. *Systemic administrations*

Intravenous injection and oral dosing are known systemic administration methods for ocular drug delivery. Since the choroid of the eye has a vascular choroid plexus structure, drugs can easily enter the choroid through blood vessels. However, the outer blood–retinal barrier of RPE cells governs the entry of drugs from the choroid into the retina. The tight junctions of RPE cells hamper most of the drugs and only 1%–2% of administrated drugs can

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