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Review

Biological macromolecules for ophthalmic drug delivery to treat ocular diseases

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ABSTRACT

Development of newer drug carrier systems by the researchers has resulted in numerous breakthroughs in the development and manufacturing of ocular products. The ocular bioavailability of drugs at the posterior segment of the eye is a challenging task in the present scenario. Naturally derived macromolecular carriers are widely used to increase the efficacy of ocular drugs. They provide enhanced corneal permeability and retention effect at the surface of cornea for a prolonged period of time. In this regimen the present review focuses towards the major ocular diseases and their prevalence and development of efficient drug carrier systems utilizing various naturally derived macromolecules for improved delivery of drugs to treat ocular diseases.

Contents

Abbreviations: AMD, age related macular degeneration; VEGF, vascular endothelial growth factor; FGF, basic fibroblast growth factor; EGF, epithelial growth factor; RB, retinoblastoma; RGC, retinal ganglion cells; IOP, intra ocular pressure; AH, aqueous humour; ELAM-1, endothelial-leukocyte adhesion molecule; ET, endothelin-1; TM, trabecular meshwork; DR, diabetic retinopathy; HIF-1α, hypoxia-inducible factor; mTOR, mammalian target of the rapamycin; PEG, polyethylene glycol; CS, chitosan; NPs, nanoparticles; CAP, cellulose acetate phthalate; PLGA, polylactide co-glycolide; RES, resveratrol; QUR, quercetin; $^1O_2$, singlet oxygen; HB, hypocrellin B; ROS, reactive oxygen species; A549, human adeno lung carcinoma; h, hours; Ag NPs, nano silver; nm, nanometer; CAP, cellulose acetate phthalate.

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1. Introduction

Human eye is designed to gather visible information from the surrounding environment. It is segmented into two parts, anterior and posterior pole/segment. Orbit, lids and sclera are the protective structures of the eye. The anterior segment of the eye comprises cornea, aqueous humour, iris, ciliary body and crystalline lens, whereas the posterior segment includes retina and vitreous humour. The optic nerves, optic tracts and visual cortex are the visual signal pathways to the brain. Cornea is the delicate portion of eye and is composed of corneal epithelium, corneal stroma, and corneal endothelium layers. The structural integrity of the cornea is attained by corneal lamellar stroma. The tissue lining the inner surface of the eye and surrounded by vitreous cavity is the retina. The neural retina is composed of neurons, photoreceptors, bipolar cells, horizontal cells, amacrine cells and ganglion cells.

Cornea limits the diffusion of most hydrophilic/hydrophobic molecules and lowers the ocular bioavailability (1–7%) [1]. Tear turnover, nasolacrimal drainage, reflex blinking, and ocular static and dynamic barriers are the various anatomical and physiological constraints that limit the corneal drug permeation [2]. The presence of blood retinal barriers makes the systemic administration as an unfavorable approach for delivering drugs to the posterior segment of the eye. Occurrence of several ocular diseases also alters permeation or movement of the drug across the eye.

Vision loss is one of the most feared complications of human diseases other than death. Globally ocular diseases affect the patient's vision and quality of life. World widely an estimate of 285 million people are visually impaired, with an USA scenario of 3.4 million people over the age of 40 years [1]. The vision threatening diseases (Fig. 1) affect both the anterior/posterior segments of the eye which include age related macular degeneration, cataract, keratitis, glaucoma, diabetic retinopathy, retinoblastoma, allergic conjunctivitis and ocular trauma.

This review presents prevalence of different vision threatening diseases that are affecting the ocular globe and further focused on drug delivery systems developed using biological macromolecules as a carrier for the delivery of ocular drugs, so that the readers may utilize the information for design and evaluation of drug carrier systems based on macromolecules.

2. Ocular diseases

2.1. Age related macular degeneration

Age related macular degeneration (AMD) is a multifactorial degenerative disease affecting the posterior segment of the eye and it is one of the leading causes of blindness in developed countries with progressive loss of central vision in individuals over the age of 50 years. The development of AMD is characterized by abnormal growth of new blood vessels (angiogenesis) in the retinal pigment epithelium which leads to drusen, atropy, and detachment of bruch's membrane [3]. Still there is no cure for this disease, but the treatments may slow the progression [4]. Among two types of AMD, dry (atropic or nonexudative) and wet (neovascular or emulative), the wet form is characterized with the growth of new blood vessels, leakages of blood and fluid under macula, which leads to consequences of hemorrhage and scar formation (yellow or white spots) in the fundus [4]. Several cellular growth factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF) and epithelial growth factor (EGF) are elevated during the retinal angiogenesis due to the abnormalities associated with respective metabolic pathways. Alterations of multiple signaling pathways such as expression of VEGF, matrix metalloproteins, P13-K/AKt, and ERK1/2 are gaining importance for controlling retinal angiogenesis.

Globally around 8.7% of blindness is caused by AMD [4] and 30 million people are affected by AMD [5,6]. Among these the USA holds the highest risk position (11 millions). In the USA, a large percentage of people of age 50 (1.65 millions) and older are reported to have advanced stages of AMD, and this figure is expected to be doubled by 2020 [5]. The prevalence rate of late AMD in India is comparable to that of western populations. The major risk factors for AMD in India are population aging, and adaptation of western life style and diet [7]. It has been reported that improvement in diet, physical activity, maintenance of blood pressure and avoidance of smoking may decrease the prevalence of the AMD risks.

2.2. Cataract

Cataract, the formation of cloudiness/opacification of the crystalline protein in the eye lens, is a major leading cause of blindness globally. The different types of cataracts are cortical, nuclear, or posterior subcapsular. Crystallin (90%) protein is the mature component of lens which maintains the transparency of lens [8,9]. The early onset of cataract is associated with mutations in α, β and γ crystallin and its associated genes. Pathology of cataracts involves photooxidative stress, non- enzymatic glycation and exposure to hydrophobic drugs which may lead in to high molecular weight aggregates of crystallins and protein insolubilisation with elevated calcium levels in the lens [9,10]. Primarily the reactive hydroxyl radicals are responsible for the oxidative damage of lens. Oxidative stress is also mediated by hyperglycemia induced micro and macro vascular complications [11,12]. Factors such as race, heredity, smoking, UV exposure, nutritional inadequacies, diabetes, and aging lead to cataract formation [13].

Worldwide around 40–60% of the blindness is caused due to cataract and in India cataract is responsible for 50–80% of bilateral blindness. The current treatment options adopted for cataract is the surgical removal of the opaque lens. The current prevalence rate of cataract gets decreased (around 25%) in India due to increase in cataract surgeries [11]. An estimate of 10 year delay in cataract formation may reduce the need of surgery in 50% cases. However the development of a nonsurgical approach for cataract treatment may have beneficial impact on both human health and healthcare costs. In this strategy, multifunctional antioxidants were reported as anti-cataract agents due to their radical scavenging and chelation ability [8].

2.3. Fungal keratitis

Fungal keratitis (keratomycosis) occurs in the inflamed cornea by the attack of fungus such as *Candida albicans, Candida glabrata, Candida tropicalis, Candida krusei* and *Candida parapsilosis* [14]. A healthy cornea won't provide entry for fungus, whereas a traumatic cornea may provide way for fungal pathogens to enter. Fungal keratitis is characterized by corneal ulceration and stromal inflammatory infiltration [15]. The excessive corneal inflammation and

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