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Review

Non-invasive strategies for targeting the posterior segment of eye

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ABSTRACT

The safe and effective treatment of eye diseases has been remained a global myth. Several advancements have been done and various drug delivery and treatment techniques have been suggested. The Posterior segment disorders are the leading cause of visual impairments and blindness. Targeting the therapeutic agents to the anterior and posterior segments of the eye has attracted extensive attention from the scientific community. Significant key factors in the success of ocular therapy are the development of safe, effective, economic and non-invasive novel drug delivery systems. These specialized non-invasive ocular drug delivery systems revolutionized the drug delivery strategies by overcoming the limitations, provided targeted delivery to the ocular tissues by avoiding larger doses, and reducing the toxicity encountered by the conventional approaches. These non-invasive systems are fabricated by ingredients encompassing biodegradability, biocompatibility, mucoadhesion, solubility and permeability enhancement and stimuli responsiveness. The variety of routes are utilized to provide minimally invasive drug delivery to the patients without any discomfort and pain. This review is focused on the brief introduction, types, significance, preparation techniques, components and mechanism of drug release of non-invasive systems, including *in situ* gelling systems, microspheres, iontophoresis, nanoparticles, nanosuspensions and specialized novel emulsions.

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1. Introduction

The management and treatment of various disorders of the anterior and posterior segment of the human eye is a challenging task. The disorders associated with the posterior segment of human eye may lead to visual impairment, which ultimately may result in blindness (Araújo et al., 2011; Thrimawithana et al., 2011). The eye is an organ of sight and each eyeball of the human eye lies in a quadrilateral pyramid shaped bony cavity located on either side of the root of nose called orbit. The human eye measures antero-posteriorly about 24 mm in adults (Nema and Nema, 2011). Each eyeball can be classified into anterior and posterior segments. The portion behind the lens of the eye is called the posterior segment. The anterior segment of the eye contains cornea, pupil, iris, ciliary body, conjunctiva, anterior chamber, lens and aqueous humor whereas the posterior segment of the eye contains vitreous humor, sclera, choroid and retina (Aparicio-Blanco and Torres-Su &rez, 2015; Janagam et al., 2017). The disorders of the anterior segment of the human eye includes corneal infections and disorders like pterygium, Fuch's dystrophy, dry eyes, auto immune disorders *e.g.*, ocular cicatricle pemphigoid and cataracts (Ray, 2009). Similarly the disorders of the posterior segment includes glaucoma, cytomegalovirus retinitis (CMV), age related macular degeneration (Rokhade et al., 2007), diabetic retinopathy (DR), retinitis pigmentosa (RP), proliferative vitreoretinopathy (PVR), and inflammations of uvea (Azadi et al., 2007; Bastawrous, 2017; Thrimawithana et al., 2011; Yasin et al., 2014). A variety of drug delivery systems have been devised to overcome the limitations of conventional drug delivery systems regarding management of eye diseases (Del Amo and Urtti, 2008a). This review aims to discuss about various non-invasive strategies for the effective targeting of therapeutic agents at the posterior segments of the eye. The eye is a very sensitive organ and treatment of anterior and posterior segments of eye require surgical procedures and various invasive and painful techniques (Yasukawa et al., 2004). In addition to these issues the surgical procedures may cause retinal detachment, endopthalmitis and even. Although variety of advancements have been done in order to achieve effective ophthalmic treatments, but the reported literature describes about the invasive techniques, which require special medical assistance (Bourges et al., 2006). This review is based on advanced, safe and effective non-invasive treatment and drug delivery strategies that may effectively target the posterior segments of eye. This review focuses on the spreading of awareness to the general public and health care providers about the safe, effective, convenient and economic ophthalmic treatment techniques. The non-invasive strategies of drug targeting are presented and discussed in detailed in the next sections.

2. Challenges in ocular drug delivery approaches

Efficient drug delivery for the treatment of various anterior and posterior eye diseases has been a challenge due to the critical micro environment that exists in the eye and blood ocular barriers (blood aqueous and blood retinal barrier). The drug delivery targets in eye can be divided into four different parts, the pre-corneal area (conjunctiva, eyelids), cornea, anterior segment of eye (iris, cilliary body, and lens) and posterior segment of eye (retina, vitreous cavity) (Mandal et al., 2017; Ogunjimi et al., 2017). The cornea is a significant route for drug absorption which consists of five different layers (epithelium, Bowman's membrane, stroma, Descemet's membrane and endothelium). The corneal epithelium have a vital role in limiting *trans*-corneal drug absorption with a drug permeability rate of just 10^{-7}–10^{-5} cms^{-1}. After topical and *peri*-ocular administration, drug entry into the posterior segment of eye is mainly limited by the blood ocular barriers. The first challenge to delivery is tear drainage which occur in pre-corneal area (conjunctiva and eyelids) at almost 1.45 min^{-1}, which causes more than 100-folds higher elimination of topically applied drug or drug carrier compared to absorption rate. This problem is especially evident in case of hydrophilic nanocarriers. Some portion of unabsorbed drug may also get absorbed into systemic circulation (Shafaie et al., 2016). In some cases, absorption of drug remains less than 5%. Another barrier to absorption of topically applied drug delivery is the oily tear film which retards evaporation of water and prevents dryness of eye (Mun et al., 2014). Similarly, drug delivery to eye from systemic circulation is limited by a blood aqueous barrier present in the anterior segment of the eye (Lee and Pelis, 2016; Mandal et al., 2017; Patel et al., 2013). As different drug delivery systems show variability in performance, targeting of drug to the posterior segment of eye will require surface modification of drug delivery systems and administrations techniques.

3. Non-invasive strategies for drug delivery to the posterior segment of eye

The development of drug delivery systems to both the anterior and posterior segments of the eye is one of the most important