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Review Article

Nanotherapies for the treatment of ocular diseases

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ABSTRACT

The topical route is the most frequent and preferred way to deliver drugs to the eye. Unfortunately, the very low ocular drug bioavailability (less than 5%) associated with this modality of administration, makes the efficient treatment of several ocular diseases a significant challenge. In the last decades, it has been shown that specific nanocarriers can interact with the ocular mucosa, thereby increasing the retention time of the associated drug onto the eye, as well as its permeability across the corneal and conjunctival epithelium. In this review, we comparatively analyze the mechanism of action and specific potential of the most studied nano-drug delivery carriers. In addition, we present the success achieved until now using a number of nanotherapies for the treatment of the most prevalent ocular pathologies, such as infections, inflammation, dry eye, glaucoma, and retinopathies.

1. Barriers and constraints associated with ocular drug delivery

1.1. Ocular drug biopharmaceutical barriers

As illustrated in Fig. 1, drugs applied onto the eye need to bypass different biological barriers in order to reach the targeted ocular structures. Firstly, drug molecules are diluted on the precorneal tear film, with an approximate total thickness of 10 μm. It consists of an external lipid layer, an intermediate aqueous layer containing salts, secreted mucins, proteins and metabolic enzymes, and an inner layer, formed principally by lysozymes and cell surface mucins that form a layer known as glycocalyx, with a thickness of 500 nm [1,2]. The rapid renewal rate of the outer layers of this lachrymal fluid (1–3 μl/min) together with the blinking reflex, severely limits the residence time of drugs in the precorneal space (<1 min) and, thus, the ocular bioavailability of the instilled drugs (<5%) [3]. The glycocalyx is cleared in a slower manner and although its exact role is not yet fully understood, it is considered to be crucial on the regulation of cellular adhesion, hindering the permeation of molecules into the eye. Additionally, the metabolic enzymes present in this film may significantly degrade the drug molecules instilled onto the eye [4].

Depending on the target sites of the different ocular pathologies, drugs either need to be retained at the cornea and/or conjunctiva or cross these barriers and reach the internal structures of the eye. The entry of drugs through the conjunctiva is normally associated with systemic drug absorption and it is highly impeded by the sclera [5,6]. As a consequence, the cornea represents the main route of access for drugs whose target is in the inner eye. Unfortunately, crossing the corneal barrier represents a key challenge for many drugs. Indeed, the highly organized multilayer corneal epithelium and the hydrophilic stroma make the transport of drugs very difficult. Overall, this transport may occur by passive diffusion across the different compartments, although the presence of influx and efflux transporters may also play a significant role [7–10].

In addition to the above indicated barriers, for the treatment of pathologies associated with the back of the eye, drugs have to diffuse through the vitreous humor, a highly dense matrix formed by collagen fibrils and glycosaminoglycans [11]. Alternatively, drugs applied onto the eye can use the trans-scleral pathway, reach the choroids and then surpass the blood–retinal barrier [12].

Due to the complexity of these barriers, there is a clear need to rationally design delivery carriers that may help drugs overcome them. Although delivery strategies have been proposed for both, topical and intraocular administrations, this review will focus on the approaches explored until now for improving the ocular bioavailability of drugs applied topically onto the eye.

1.2. Influence of physicochemical properties on ocular drug bioavailability

Low molecular weight lipophilic drugs can diffuse by a transcellular pathway through the corneal epithelium. Then, the drug

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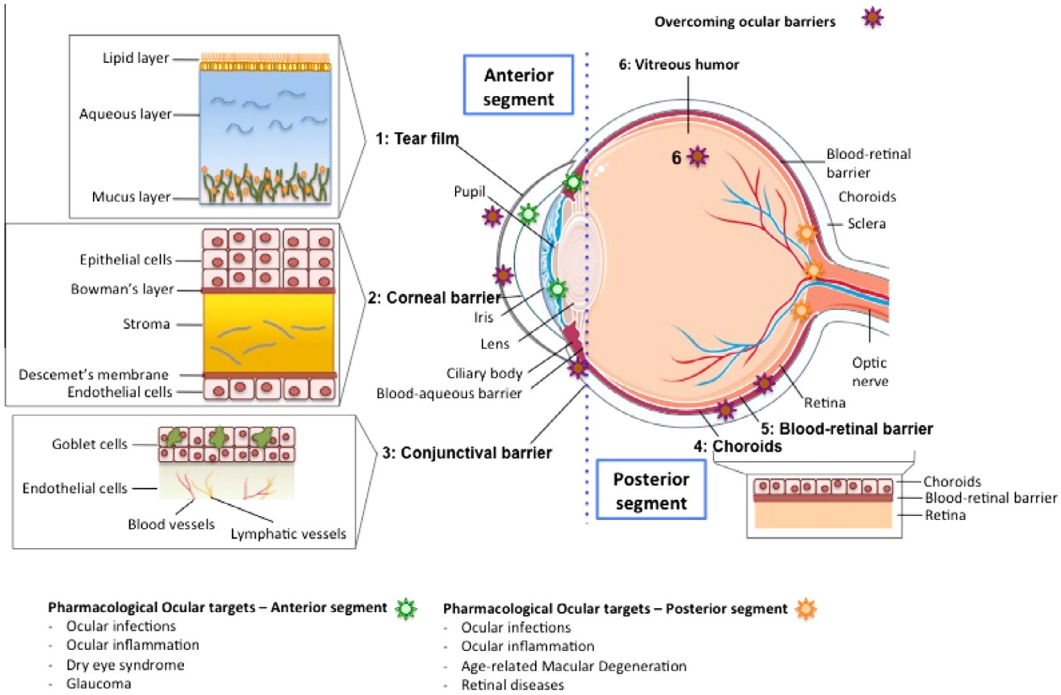

Fig. 1. Illustration that represents the different structures of the eye, divided in the anterior and posterior segments. The different barriers that drugs need to overcome after topical installation are indicated with a red star, and a detailed representation is also provided. The ocular targets to treat a specific disease are indicated with a green star, if they are in the anterior segment, or with a yellow star, if they are located in the posterior segment.

is retained in the stroma, forming a depot from which the drug is released into the aqueous humor. The biopharmaceutical problems of this type of drugs are related to their limited and slow access to the inner eye and also to the need of formulating them in the form of suspensions or emulsions, with the subsequent discomfort for the patient and drug loss.

Low molecular weight hydrophilic drugs, as it is the case of many antibiotics can be easily formulated as aqueous eye-drop solutions. However, they have a limited capacity to overcome the corneal epithelium, as they need to go through the paracellular route, a transport that is severely limited by the presence of tight junctions [13].

Large hydrosoluble molecules including nucleic acids, peptides, proteins, and antibodies, which are gaining increased attention in the ophthalmic field, constitute a particularly challenging type of therapies from the biopharmaceutical perspective. Indeed, these molecules are rapidly degraded by extracellular enzymes, and their entry, either by a paracellular or by a transcellular mechanism, is totally restricted [14–16].

In addition to the passive transcellular and intercellular transport there is increasing evidence of the presence of transporters, which may help the transport of specific molecules. However, in general, the contribution of this transport mechanism to the ocular bioavailability of drug is not expected to be very relevant [7–10].

In summary, most drugs exhibit great difficulties for overcoming the eye-associated barriers. Only drugs with a low molecular weight and a moderate lipophilic character can deal with these barriers, and they normally do it in a modest manner. As a consequence, other approaches besides the drug chemical modification appear to be necessary in order to improve the treatment of ocular diseases. In the next sections we present the nanotechnology-based formulation approaches reported so far for the formulation of lipophilic, hydrophilic and high molecular weight drugs.

2. Nanocarriers that may help overcome ocular barriers

In general it is accepted that nanotechnology offers the possibility to develop delivery systems particularly adapted to overcome the eye-associated barriers. Namely, ocular drug delivery nanocarriers have shown the capacity to (i) associate a wide variety of drugs, including large biomacromolecules, (ii) reduce the degradation of labile drugs, (iii) increase the residence time of the associated drugs onto the ocular surface, and (iv) improve their interaction with the corneal and conjunctival epithelia and consequently their bioavailability [17–20].

The use of nanocarriers for ocular drug delivery started in the 80s, being our group one of the pioneers in the field [21–26]. However, as shown in Fig. 2, it has only been in the last decade that this field has grown substantially, leading to a wide variety of nanostructures and providing an improved understanding of their potential for ocular drug delivery. Moreover, it is also possible to observe a shift from the initially most investigated delivery systems, liposomes, toward other types of nanostructures. This can be related to the advanced developmental state of liposomes, since they have already led to a substantial intellectual and industrial property and to several marketed products, and there is less room for innovation. In this section, we aim to provide an overview on the main features that characterize each specific type of nanostructure, and analyze the main factors that govern their interactions with the ocular surface after topical administration.

2.1. Liposomes and niosomes

Liposomes were evaluated for the first time in the 80s with the purpose of enhancing the corneal penetration of drugs [27,28]. Following this initial work, a great number of studies have been reported, most of them oriented to analyze the transport of drugs across the cornea [29–32]. Although these studies have generally