Anatomy and Barriers of Ocular Drug Delivery

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Ocular diseases profoundly impact patients' vision and overall quality of life globally. However, effective ocular drug delivery presents formidable challenges within clinical pharmacology and biomaterial science, primarily due to the intricate anatomical and physiological barriers unique to the eye.

ocular barriers ocular drug delivery nanocarriers nano-based drug delivery system

1. Introduction

The normal human eye measures approximately 22 to 27 mm axially and 69 to 85 mm in circumference [1]. It can be divided into two segments: anterior and posterior, separated by the ciliary body and lens. The anterior segment comprises the cornea, conjunctiva, iris, ciliary body, and lens, while the posterior segment contains the vitreous humor, retina, choroid, sclera, and optic nerve. The eye's intricate anatomy and protective barriers pose challenges for drug administration. It shares characteristics with immune-privileged organs like the brain, isolating it from the body's circulation with a blood–retinal barrier, making systemic therapy difficult, particularly for posterior segment disorders.

2. Barriers of the Anterior Segment

2.1. Tear Film Barrier

The tear film on the ocular surface forms an initial barrier, impeding drug delivery, while drainage through the nasolacrimal system can dilute and remove drugs, affecting their efficacy. This tear film, around 3 μm thick and 3 μL in volume, comprises three layers: an outer lipid layer, a middle aqueous layer, and an inner mucous layer [3]. The outer lipid layer prevents water evaporation but also hinders drug absorption into the cornea and sclera [4]. Meanwhile, the mucous layer in the tear film acts protectively, forming a hydrophilic barrier that efficiently removes debris and pathogens.

The lacrimal turnover rate is approximately 1~3 μL/min, causing drug loss from the ocular surface to be 500 to 700 times greater than the drug absorption rate into the anterior chamber. Irritant drugs, certain excipients, and pH deviations can trigger lacrimation, increasing tear production to about 300 mL per minute [5]. This rapid increase leads to immediate drainage through the nasolacrimal duct, causing over 85% of the administered drug dose to be lost before reaching the corneal surface. The retained drug may also undergo further dilution due to rapid tear turnover, reducing the concentration gradient and diffusion rate. This results in low bioavailability of intraocular

drugs within the aqueous humor, leading to poor drug bioavailability with topical delivery, typically ranging from 0.1% to 5% [6].

2.2. Cornea and Conjunctival Barrier

The cornea, the outermost transparent avascular layer of the eye, has essential refractive and barrier functions. It consists of three cell layers: the lipophilic epithelium, the hydrophilic stroma, and the lipophilic endothelium, along with two interfaces: The Bowman layer and Descemet's membrane. The corneal epithelium, comprising 5–7 lipid-rich cell layers with tight junctions and desmosomes, forms a robust barrier against drug penetration and microbial invasion [5][7]. The Bowman layer between the epithelium and stroma consists of acellular condensation of type I and type III collagen fibrils [8]. The Bowman layer allows drug and particle passage into the stroma, which makes up most of the cornea's volume. It consists of hydrated type I collagen, providing structural support, optical clarity, and ocular immunity, facilitating the permeation and diffusion of hydrophilic drugs. Descemet's membrane contains collagen type IV and VIII fibrils that provide support for the monolayer of corneal endothelial cells. Despite larger pore sizes in Descemet's membrane reducing its barrier function, it can still filter macromolecules and particles that are directly administered into the stroma, protecting the endothelium. The corneal endothelium is a monolayer of cells that maintains stromal dehydration and allows the transportation of water and solute to the anterior chamber through both active (sodium–potassium ATPase pumps) and passive (endothelial intercellular tight junctions) mechanisms [7][9].

In contrast to the cornea, drug absorption through the conjunctiva is hindered by conjunctival capillaries and the lymphatic system, leading to drug leakage into the bloodstream and reduced bioavailability. Tight junctions in the conjunctival epithelium also impede the passive movement of hydrophilic molecules. The sclera, primarily composed of collagen fibers and proteoglycans, has a permeability similar to the corneal stroma. Recent studies suggest that drug permeation through the sclera inversely correlates with molecular size [10]. Linear dextrans exhibit lower permeability than globular proteins, and positively charged molecules have limited permeability due to interactions with the negatively charged proteoglycan matrix [11].

2.3. Blood–Aqueous Barrier

The blood–aqueous barrier (BAB) is formed by tight junctions in the ciliary process's non-pigmented epithelium, endothelial cells in the iris vasculature, and the inner wall endothelium of Schlemm's canal. The tight junctions regulate paracellular transport, controlling the movement of ions and small substances between adjacent cells. The BAB is not completely impermeable; instead, it serves as a specialized gateway for controlled molecule movement [12].

3. Barriers of the Posterior Segment

3.1. Vitreal Barrier

The vitreous is a gel-like, transparent substance that fills the space between the lens and the retina. It mainly consists of water, collagen types II, IX, V/XI, hyaluronic acid, and other extracellular matrix components. Positively charged nanomaterials may interact with the negatively charged components of the vitreal network and thus block its diffusion ability, while negatively charged particles, based on the example of poly lactic-co-glycolic acid (PLGA) or human serum albumin, can distribute successfully across the vitreous humor [13]. The vitreous provides structural support to the eye, maintaining its shape against intraocular pressure. The vitreoretinal interface acts as a barrier, restricting substances from passing into the retinal layers [14]. This interface comprises three main components: (1) The cortical vitreous, a thin layer (100–300 µm) rich in collagen parallel to the inner limiting membrane (ILM). (2) The ILM, at the innermost boundary of the retina, is primarily composed of collagen type IV, laminin, and fibronectin, serving as a physical barrier. (3) Expanded Müller cell footplates, glial cells extending from the vitreous side to the outer nuclear layer of the retina.

3.2. Blood–Retinal Barrier

The blood–ocular barrier (BOB) system includes two key barriers: the BAB and the blood–retinal barrier (BRB). The BRB is highly selective, controlling the passage of ions, proteins, and water to and from the retina. It comprises two parts: the outer BRB (oBRB), which includes the choroid, Bruch's membrane (BM), and the retinal pigment epithelium (RPE), and the inner BRB (iBRB), formed by tight junctions among retinal capillary endothelial cells [15].

Starting from the outermost layer, the choroid includes the suprachoroid, large and medium blood vessel layers, and the choriocapillaris. The choriocapillaris play a role in nutrient supply and waste removal from the outer retinal layers. The Bruch's membrane (BM), positioned between the choriocapillaris basement membrane and the RPE basement membrane, comprises outer and inner collagenous layers separated by a central elastic layer. BM allows size-selective passive diffusion but can block larger molecules. The RPE is a single layer of pigment-containing cells located beneath the neural retina layer. Its tight junctions maintain the integrity of the oBRB. For the iBRB, the retina vasculature penetrates at three main plexuses: the nerve fiber layer, inner plexiform layer, and outer plexiform layer. The iBRB mainly consists of the neurovascular unit, similar in structure and function to the blood–brain barrier, providing a barrier from systemic circulation. Molecule permeation is restricted based on size, charge, and lipophilicity. Small hydrophilic compounds can pass through junctions, while lipophilic molecules use the transcellular route [16].

The iBRB and oBRB have specific systems that allow substances to enter (influx transporters) or leave (efflux pumps) the retina. Developing drugs that mimic the substances recognized by influx transporters can help deliver drugs better into the retina. Additionally, designing drugs that are unrecognizable to the efflux pumps, or using inhibitors for these pumps, can help retain drugs in the desired location [13].

3.3. Sclera and Bruch's–Choroid Complex Barrier

The choroid serves as a densely vascularized barrier situated between the retinal pigment epithelium (RPE) and the sclera. With a thickness of approximately 200 µm, it is structured into five distinct layers: Bruch's membrane, the choriocapillaris layer, two vascular layers, and the suprachoroidal layer [13][17]. The choroid acts as a barrier against hydrophilic compounds, while positively charged lipophilic drugs can bind with the tissue to create slow-release depots. Additionally, drugs' molecule sizes impact their ability to diffuse into the posterior eye segment. Bruch's membrane, approximately 2–4 µm thick, consists mainly of collagen and elastin fibers. The choriocapillaris layer comprises highly fenestrated capillaries with pores ranging from 6 to 12 nm, allowing the passage of larger molecules [18].

The sclera, the eye's outer opaque layer, is primarily made up of collagen fibers, proteoglycans, and glycoproteins, with an average thickness of 0.5–1 mm. Drug permeability through the sclera is influenced by factors such as molecular weight, size, charge, and lipophilicity. For instance, hydrophilic compounds like methazolamide can penetrate the sclera. The proteoglycan matrix in the sclera carries a negative charge under normal pH conditions, aiding the passage of negatively charged solutes through this barrier [19].

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