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BARRIERS IN OCULAR DRUG DELIVERY-A REVIEW

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Ocular Drug Delivery

The eye is considered to be very sensitive organ. The perfect vision and ocular functionalities of eyes are generally performed by the visual cells and transparent tissues due to tight cellular membrane and barriers which control the fluid and solvent.[1] The delivery and targeting of ocular therapeutics is generally hindered by some barriers. The tear flow and blinking reflex help in maintaining a good environment and remove foreign material from the eye.

The hindrance by barriers and tear flow lead to drainage of drug from the eye when instilled into it. This leads to poor bioavailability of drug, thus reducing the desired therapeutic effect of the drug.[2] But one of the advantage of ocular route is that drug enter to the systemic circulation by eliminating hepatic first pass metabolism[3].

Mechanism of Topical ocular drug absorption

The administration of drug into the eye cul-de-sac generally involve corneal and/or non corneal route where lachrymal fluid is responsible for carrying away the medication. The main absorption route for the ophthalmic therapeutics is corneal route. However corneal absorption is considered as the rate limiting step due to the presence of corneal epithelium[1, 4]Penetration across the conjunctiva and sclera into the intraocular tissue is the second pathway, but the presence of local capillary beds make this pathway less productive because drug get removed from the target site and reaches the general circulation. Despite of this drawback, certain drugs such as timolol maleate, gentamycin and prostaglandins $PGF_2\alpha$ that shows poor corneal permeability, reaches the intraocular section through the diffusion across the conjunctiva and sclera.[5-8] Thus, physiological characteristics of compound and biological membrane and barrier of target tissue are responsible for the absorption mechanism [9, 10]

Barrierin Ocular Drug Delivery

Drug faces several membranous barriers that are located in the cornea, conjunctiva, iris-ciliary body and retina, in which the epithelial and/or endothelial cells are sealed by the tightjunctional constituents after passing the tear film and lachrymal fluid to reach the desired.

1. Tear Film

The amount and composition of the tear film is responsible for a healthy ocular surface, which is tightly controlled by regulation of the orbital glands and ocular surface epithelial secretion. The tear film contains various factors such as nutrients, electrolytes, proteins, lipids and mucin[11]. The tear film is buffered aqueous fluid, having pH 7.2-7.5.

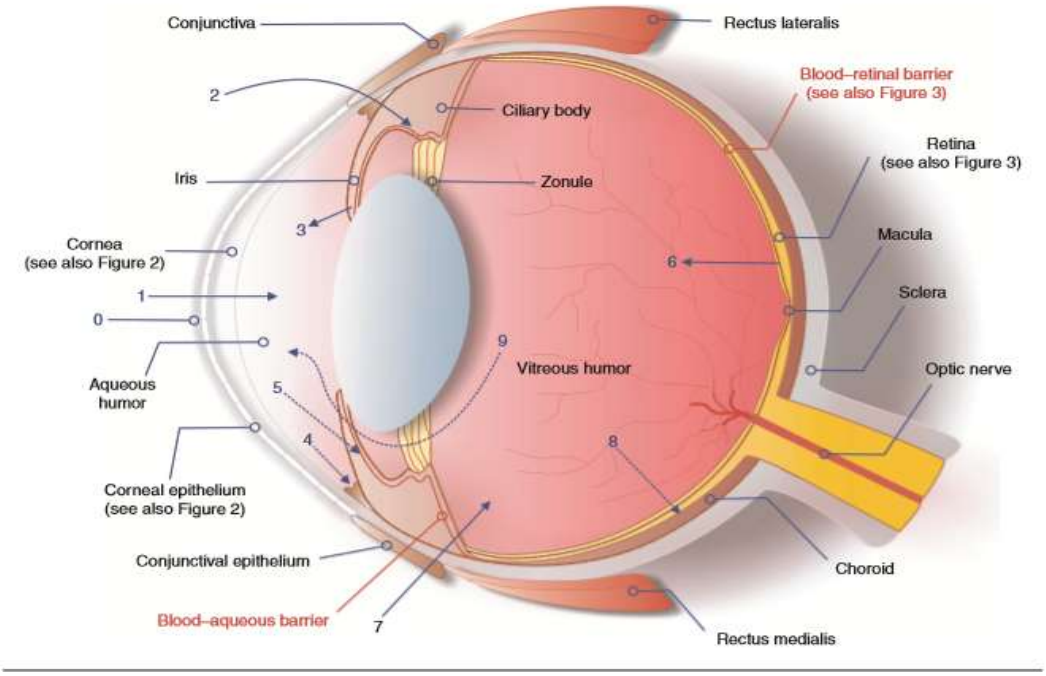

Figure 1: Schematic illustrations of eye and its biological barriers.

Foremost physiologic impediment against instilled drug is provided by tear film (0). The main route for drug transport to the anterior chamber is cornea (1). Macromolecules and hydrophilic drugs are transported through conjunctival and scleral route (2). Small compound penetrate from the iris blood vessels into the anterior chamber after systemic administration (3). Either aqueous humor (4) or venous blood flow (5) is responsible for transporting of drug away from anterior chamber. The main barriers for systemically administered drugs are retinal pigment epithelium and retinal capillary

endothelium (6). Intraviteral injection directly reaches to the vitreous (7). Blood-retinal barrier (8) and/or diffusion into anterior chamber (9) help in removing drug from vitreous [12].

2. Corneal Route: epithelial and endothelial barrier

The cornea is a avascular tissue that consists of various layers; corneal epithelium, basement membrane, Brownam's layer, stroma, Descemet's membrane and endothelium [13]. The traverse of ocular drug (in particular hydrophilic drug) is selectively controlled by the corneal epithelium barrier, whereas trans-corneal permeation is least controlled by stroma and endothelium [9, 14]. The stroma consists of organised matrix of hydrated collagen and proteoglycans with interspersed cells (keratocytes) [11]. This biostructure act as a barrier to highly lipohilic drug[12]

Corneal transparency was maintained by the cells of corneal endothelium through their transport, synthetic and secretory function. The plasma membrane transporters present at polarised cell form a cellular barrier between the stroma and aqueous humor which maintain the anterior chamber by selective carrier receptor medicated transport function [13, 15, 16]. The selective gates are provided by these membranes for hydrophilic drugs and macromolecules, and also control their traverse to the anterior segment [17].

Thus, the topically applied drug diffuses into the aqueous humor and to the anterior uvea after crossing the corneal impediment, but certain pharmaceuticals fail to reach the retina and vitreous at sufficient therapeutic concentration [18].

3. Non-corneal route: Conjunctiva and Sclera

Non corneal route is considered as a competing and parallel route of absorption, as compared to corneal route, it is a minor absorption route and contributes significantly for few compounds only[12].

The conjunctiva is a thin and transparent membrane lining inside of the eyelid and covering the anterior surface of sclera, extending to the edge of cornea .The conjunctiva consist of three different layer of mucous membrane;(i) an outer epithelium : act as a permeability barrier; (ii) substantiaproperia, consist of nerves, blood and lymphatic vessels; and (iii) submucosa, which provide a loose attachment to underlying sclera [12].

The rich vaculature nature of conjunctiva along with existence of goblet cells and transdifferentiation potential help in non corneal drug delivery [19]. Further, the tight junctionalbarrier of the conjunctival epithelium helps in permeation of hydrophilic substances and delivery of macromolecules.[20-22]Drug administered while crossing the conjunctiva is carried away by the systemic circulation, while the reaming drug reach to the posterior part by penetrating across the sclera[23-25]

Cationic amino acid transporter (ATB^{O}), nucleoside transporter (CNT2) and peptide transporter (PepT1) are certain transport present at the conjunctival epithelium for transporting of the drug [26-28]. In general, ophthalmic drugs can be absorbed from conjunctiva and delivered to eye via sclera. However conjunctival or scleral pathway is affected by the drainage loss through blood vessels of the conjunctiva. Therefore peptides and oligonucleotides are delivered through non corneal route[29].

4. Iris, Ciliary body and Aqueous Humor flow

Vascular uveal coat of eye consist of iris, ciliary body and choroid, where iris anterior is immersed in aqueous humor. The aqueous humor is derived from plasma within the capillary network of the ciliary by the mechanism of diffusion, ultrafiltration and active transport. Water soluble substances of larger size or higher charge are transported to the cellular membrane through expenditure of energy i.e., by active transportation[1].

5. Vitreous body and fluid flow

Clear and avascular connective tissue of vitreous (a gel like substance) is present in space between retina and lens. The delivery of drug into the posterior segment is generally administered through intraviteral route. The pathophysiological state and molecular weight of the administered drug is responsible for diffusivity potential of the vitreous[1, 30].

6. Blood -aqueous Barrier (BAB)

This barrier controls the traverse of solute between posterior and anterior chamber.BAB help the small and lipophilic drug to enter in uveal blood circulation for rapid elimination, whereas large and more hydrophilic drugs are eliminated through turnover of aqueous humor.

Locally used ophthalmic therapies fail to provide effective pharmacological effect in posterior segment because of continues drainage of aqueous humor[1].

7. Retina

A thin film that covers the entire inner wall of eye is Retina. It consist of neural cells as well as glial cells.

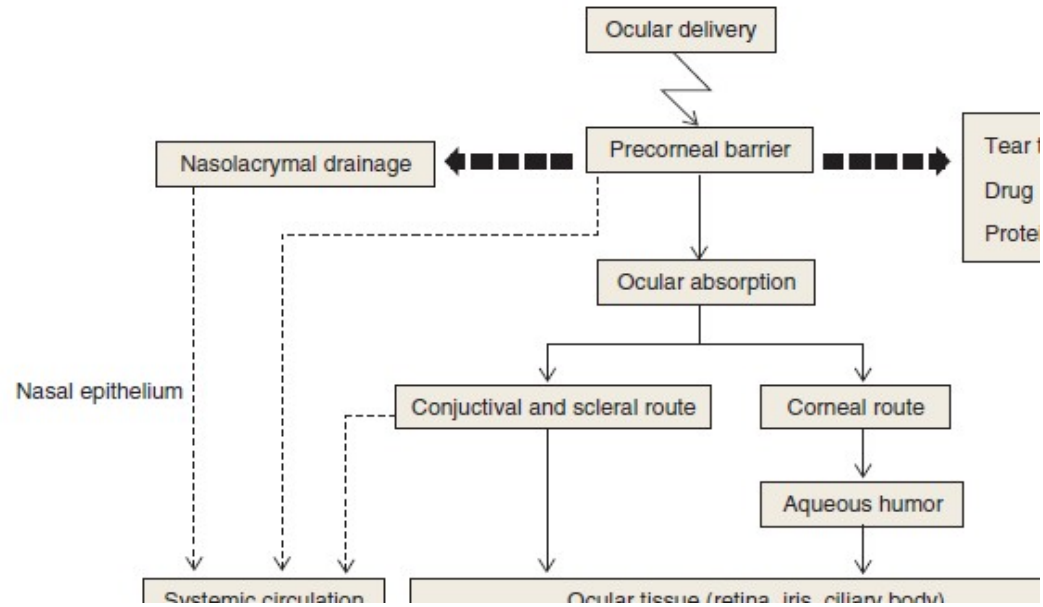

Figure 2: Schematic model depicting the drug movement and barriers in ocular delivery [31]

8.Blood-Retinal Barrier (BRB)

BRB consist of two type of cells, retinal capillary endothelial (RCE) and RPE cells which forms inner and outer BRB respectively. Traverse of nutrient and compound is controlled by specialized transport processes and robust barrier restrictiveness of RPE. Retina is selectively protected from blood circulating molecules through inner BRB. Lipophillic substances can easily permeate through RCE cells while BRB is responsible for poor permeation of small hydrophilic compound and proteins[13, 32].

Ocular drug delivery requires small dose of drug because restrictive function of BRB allow small amount of drug to reach posterior segment of eye and if large amount of drug is administered it gets disseminated in the entire body and cause adverse reaction[33].

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