Biomedicine & Pharmacotherapy 107 (2018) 1564–1582

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

A review on recent drug delivery systems for posterior segment of eye

Kritika Nayak, Manju Misra*

Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Opposite AirForce station, Palaj Basan Road, Village Palaj (Gandhinagar), Gujarat, 382355, India

ARTICLE INFO

Keywords:
Trans-scleral
Drug delivery system
Nano-formulations
Posterior segment of eye

ABSTRACT

Eye is the unique sense organ with complex and sophisticated anatomy and physiology. Being most instrumental for vision, it is secured by varied protective barriers; ranging from static (membranous) to dynamic (vascular) barrier. Although these barriers are very efficient to protect eye from exogenous substances and external stress, it is caught by various irreversible vision impairing ailments like cataract, conjunctivitis, glaucoma, uveitis, diabetic retinopathy (DR), diabetic macular edema (DME), age related macular degeneration (AMD), cytomegalovirus (CMV) retinitis, retinitis pigmentosa (RP), retinal vein occlusion (RVO), endophthalmitis affecting both anterior and posterior segment of eye. The treatment needed to reach the site of action is restricted by its characteristic barriers. The protective mechanism turns into hurdles when it comes to drug delivery especially in case of posterior segment of eye. Most common and preferable routes for ocular drug delivery are topical and systemic routes owing to their compliance and non-invasive nature, however they turned inefficient in delivering drugs to posterior segment. Currently, other local routes like intraocular and periocular (subconjunctival, subtenon, posterior juxtascleral, retrobulbar, peribulbar) are being explored and are showing positive outcomes in terms of symptomatic relief for a certain time period. But as these are invasive techniques, they also have some hidden long-term drawbacks on other side. Various advancements have been achieved till date in delivery of drug to posterior segment of eye, however despite these advancements; there is need of non-invasive or preferably less invasive technique considering prolonged treatments for such ailments. At times, dependency on invasive techniques may cause problems like patient incompliance, inflammation, contact cataract, retinal detachment, endophthalmitis etc. Here, in this review, barriers in ocular delivery, routes and recent advances in drug delivery to eye including patented commercial formulations with emphasis on posterior segment will be discussed.

1. Introduction

Eye is one of the most sophisticated sense organs of human body which is responsible for vision. Being unique in purpose, it has distinctive features like its specified anatomy and physiology. Human eyeball present in pair are located in the eye socket and are held by the six muscles in place which help in their movement. The anterior posterior diameter of eye ball is about 24 mm with approximate total volume of 6.5–7 ml. Eye can be anatomically divided into anterior and posterior segment; accommodating one third and two third of ocular architecture respectively. Anterior segment consists of tear, cornea, conjunctiva, anterior and posterior chamber, iris, ciliary body, lens, and aqueous humor while posterior segment encompasses sclera, choroid, retina, Bruch's membrane, vitreous humor, optic nerve, and retinal blood vessels. Each and every element has its own distinct construction and functionality coordination which enables vision formation. Fig. 1 illustrates the complex anatomy of eye. Instrumentality of eye is maintained by coactions of several and variedly related bio-microphenomena counting from mechanical incidents (muscular movement of eyeball, lachrymal secretion, reflection of pupil), receptiveness of brain (cortical and subcortical region) to hormonal equilibrium (melatonin production etc.). Alterations/violations of this setup trigger emergence of myriad ailments which, if remain un-noticed/untreated, may evolve into serious consequences like temporary or complete visual impairment or blindness [1].

The internal and external stresses affecting normal ocular health include change in ocular secretion dynamics (lower-or over-secretion of lachrymal or aqueous humor), aging, ultraviolet exposure, pollution, injury, harmful chemicals, lifestyle changes etc. The diseases affecting anterior segment counts cataract, glaucoma, pterygium, conjunctivitis, etc. while those attacking posterior segment are vitreoretinal diseases like RP, RVO, DME, DR, AMD, CMV retinitis, choroidal

* Corresponding author.
E-mail address: manju@niperahm.ac.in (M. Misra).

https://doi.org/10.1016/j.biopha.2018.08.138
Received 1 February 2018; Received in revised form 24 August 2018; Accepted 25 August 2018

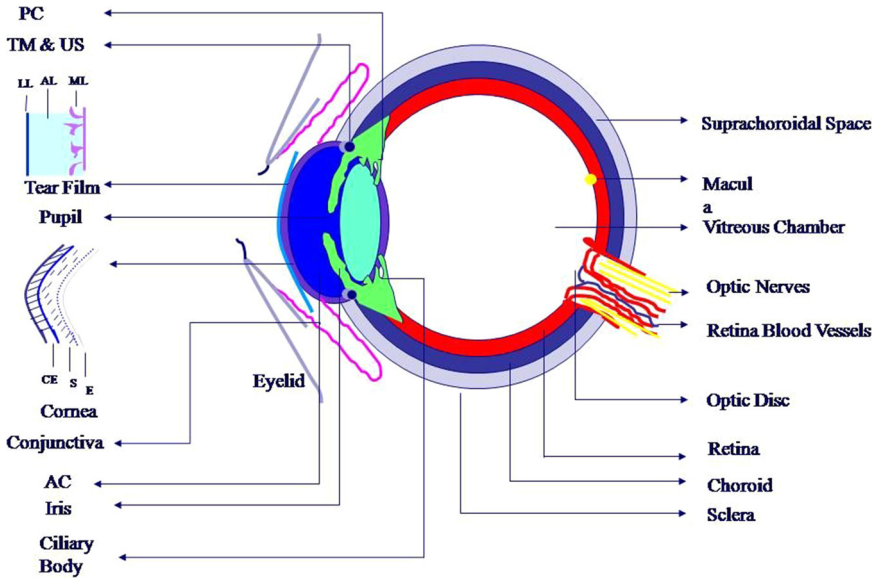

Fig. 1. Eye anatomy. AC = Anterior Chamber, AL = Aqueous Layer, CE = Corneal Epithelium, E = Endothelium, LL = lipid Layer, ML = Mucin Layer, PC = Posterior Chamber, S = Stroma, TM = Trabecular Meshwork, US = UveoScleral Elimination.

neovascularization (CNV) etc. Chronic ocular diseases striking majority of population (mostly aged population) are related to posterior segment [2]. Continuously growing aged population inflames the risks of these diseases. Although the investigation of etiology/pathophysiology of these diseases is going on, a little is known. Symptomatically, elevation in intraocular pressure (IOP), vascular endothelial growth factor (VEGF), or insulin receptor substrate-1 etc. in posterior segment is suspected to be prime cause. Usually, corticosteroids, anti-VEGF drugs, insulin etc. are utilized for relief, but these are not targeted therapy [3].

The conventional routes of administration (systemic and topical) and dosage forms (eye drops) are found inefficient in delivering drugs to posterior segment owing to different ocular barriers and limitations of routes. Being chronic in nature, it is prerequisite that the drug should be available to the targeted site/site of action in sufficient amount and for sufficient time period. Extremes in terms of drug concentration and drug release rate are always harmful. The various ocular barriers namely, lachrymal outflow, differential lipophilicity of different ocular layers, counter-flow of aqueous humor, permeability via corneal epithelium, retinal pigmental epithelium (RPE) and other membranes, diffusion within vitreous chamber, eliminatory secretions etc. which are meant to safeguard the eye turn into obstacles when it comes into drug delivery with conventional routes. There is need of advancement in drug discovery and delivery to target the origin of diseases rather than symptoms and overcome the ocular barriers [4–6]. Herein, various ocular barriers, limitations of routes of administration and the newer approaches to tackle these will be illustrated.

2. Barriers

2.1. Tear

It is the outermost precorneal thin film; consisting of three layers (lipid, aqueous and mucin layer; from exterior to interior) with total thickness of approximately 3 µm. Outermost lipidic layer composing free fatty acids, triglycerides, phospholipids, cholesterol, wax etc. is secreted by meibomian, Zeiss and Moll glands and helps to seal the natural tear to protect from evaporation [7]. Middle aqueous layer; also the thickest one is maintained by the main and accessory lachrymal glands constituting about 90% of total tear film volume while the innermost thinnest (0.02-0.05 µm) layer; mucin layer is embodied by the continuous secretion from the stratified squamous epithelial cells of cornea and conjunctiva, and goblet cells of conjunctiva. The middle layer moistens and lubricates the ocular surface, washes away the foreign particles and helps to protect against infection (consists of antibacterial lysozyme, betalysin). The mucin layer helps aqueous layer to be adhered to ocular surface and provides nourishment to cornea as well [8]. Accurate composition of tear is still unknown but MUC5AC is found to be the only secreted gel forming mucin identified till date. Major eliminatory route for tear is via nasolacrymal drainage system. Excess tear gets collected into the sac then, through the ducts poured into nasal path. Tear film is the most prominent barrier for topically administered dosage form to attain therapeutic concentration due to tear dilution by continuous tear turnover (approximately 1 µl/min), high clearance, and protein binding of drug [9]. Usually size of one eye drop is 20–50 µl while cul-de-sac can hold only 7–10 µl volume which leads to spillage and/or nasolacrymal drainage. Reflex actions further enhance this phenomenon. The lachrymal fluid is of approximately 310-350mOsm/kg osmolality in normal conditions which is maintained by the monovalent and divalent inorganic ions present in it such as Na^+, K^+, Cl^-, HCO_3^-, and proteins. The mean pH is about 7.4 which are influenced by diurnal pattern of pH changes (generally shifting from acidic to alkaline during day). Its buffer capacity depends upon bicarbonate ions, mucin and protein. It is basically of non-newtonian nature with viscosity of about 3mPas and surface tension of about 44 mN/m. To be retained or permeate through ocular surface, drug or dosage form first have to pass through the tear film which require it to be isotonic, nonirritant, nontoxic, of normal pH and with proper spreadability over entire film [10].

2.2. Cornea

Cornea is transparent, avascular part of human eye playing vital role in vision formation. It is basically made up of 5 layers: epithelium, Bowman membrane, stroma, Descemet's layer, and endothelium. Epithelium; consisting of surface cells, wing cells and 5–6 layers of columnar stratified cells with tight junction, hemidesmosome and desmosomes project barrier for most hydrophilic drugs meanwhile microvilli on surface provide more surface area for drug absorption. These tight junctions create high paracellular resistance of 12–16kΩcm disallowing hydrophilic drugs to pass through intercellularly. Its permeability majorly depends on distribution coefficient of drug; increase in distribution coefficient increases corneal permeability. Molecular