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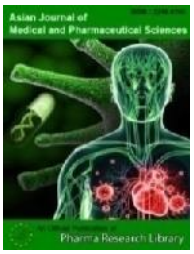

Posterior Eye Therapeutics

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A B S T R A C T

The treatment of eye diseases of the posterior segment of the eye, such as age-related macular degeneration, cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis and retinitis pigmentosa, requires novel drug delivery systems that can improve the efficacious delivery of therapeutic drug concentrations. The development of new biodegradable and nonbiodegradable sustained-release systems for injection or transplantation into the vitreous as well as drug-loaded nanoparticles, microspheres and liposomes. The drug delivery systems utilize topical, systemic, subconjunctival, intravitreal, transscleral and iontophoretic routes of administration. The systemic application of drugs is another method of access to the posterior segment. The drugs are administered orally or intravenously, enabling distribution throughout the body via the blood-stream. From the blood, the drugs can easily enter the choroidal extravascular space as the choroid has an extensive vascular network and leaky walls. The development of new alternative administration routes to the posterior segment of the eye, including intravitreal and periocular pathways can helpful for reducing the eye diseases.

Keywords: Eye diseases, drug delivery system, intravitreal and periocular pathways.

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C O N T E N T S

1. Introduction

Drug delivery, in its simplest, most common form, is comprised of fast-acting chemical compounds that are dispensed either topically or systemically. Depending on the method of application, the drugs are distributed locally, regionally or systemically, and may lead to various undesired side effects, such as drug accumulation and toxicity. While the topical and systemic forms of drug delivery are useful in certain disease processes, they pose many limitations to the treatment of diseases of the posterior eye, including age-related macular degeneration (AMD), diabetic macular edema (DME), endophthalmitis and retinitis pigmentosa.

Topical drug application

Topical application to the anterior eye has been proven successful in the treatment of diseases owing to easy access to the target site. However, the adoption of mechanisms in ensuring topical drug penetration to the posterior eye presents numerous challenges. While being the least invasive method of drug application, topically applied drugs are hindered by many components of the anterior eye,

including the corneal epithelium, corneal endothelium, conjunctiva and sclera[1-4]. In addition, the longer diffusion distance to the posterior eye and the acellular nature of the vitreous negatively impact the pharmacokinetics and distribution of the topical drugs. Simple physiologic processes such as tear production, blinking, drug metabolism and drug binding also impact topical applications, hindering the access of topical drugs to the target locations. All of these factors and limitations lead to increased dosing and a higher frequency of drug application in order to attain therapeutic concentrations, making the use of topical drugs relatively inefficient for patients and leading to decreased patient compliance.

Systemic drug delivery

The systemic application of drugs is another method of access to the posterior segment. The drugs are administered orally or intravenously, enabling distribution throughout the body via the blood-stream. From the blood, the drugs can easily enter the choroidal extravascular space as the choroid has an extensive vascular network and leaky walls. However, the entry of the drug into the posterior segment is often limited by the outer and inner blood–retinal barriers that are made up of retinal pigment epithelium (RPE) and endothelial cells of the retinal blood vessels, respectively. The RPE contains several efflux pumps including P-glycoprotein and multidrug resistance-associated protein, which reduce the permeability of various endogenous compounds into the vitreous. The systemic application of drugs not only increases the quantity of a drug necessary to achieve therapeutic concentrations, but it also increases the risk of adverse effects due to the accumulation of a drug in other tissues throughout the body[5-9].

Intravitreal injection

Intravitreal injection is one means of drug delivery that is becoming more popular in the clinical setting. Anti-VEGF drugs, such as pegaptanib, ranibizumab and bevacizumab are new intravitreal treatments for AMD and macular edema; intravitreal injection is currently the most acceptable and effective method to treat vitreoretinal disease. This method allows a direct application of the drug into the posterior eye, thus eliminating the barriers common with topical and systemic administration.

Diffusion

A relatively newer method of drug delivery is transscleral delivery, a less invasive method in which the drug permeates through ocular tissues to reach the neuroretina. Transscleral delivery includes such avenues as subconjunctival, retrobulbar, peribulbar, sub-Tenon's and intrascleral delivery.

Transscleral iontophoresis

Another transscleral method involves an electrodynamic process of drug delivery termed iontophoresis. In this technique, charged molecules are delivered across the sclera and into the posterior chamber of the eye via a direct electric current. In most cases, an iontophoretic probe is placed over the pars plana, enabling a bypass of the lens–iris barrier. This arrangement permits the precise delivery of high quantities of drugs through changes in the intensity of the applied current, yielding improved control of constant, uniform drug delivery. Animal and human studies have shown that iontophoresis eliminates many of the unwanted side effects of intravitreal injections and may improve the efficacy of periocular injections by decreasing the risk of retinal detachment, endophthalmitis, globe perforation and ptosis[10-14].

Novel drug delivery: microparticles & nanoparticles

Many sustained intraocular drug delivery methods have been developed as alternatives to implantation. Ocular drug delivery systems using particulates have been developed, which provide sustained release with high target specificity in the form of microspheres and microcapsules with diameters of 1–1000 µm, as well as nanospheres and nanocapsules with diameters of less than 1 µm. Drugs can be incorporated into biodegradable polymers to form either a matrix system or a reservoir system. In a matrix system, the drugs and polymer are combined and the drug is released through diffusion from the polymer matrix with simultaneous polymer degradation. This system is used for micro-and nanospheres. The reservoir-type system involves encapsulating drugs within polymeric shells and is the system used for biodegradable micro- and nanocapsules. Some of the commonly used synthetic biodegradable polymers are the aliphatic polyesters such as PLA, PGA, PLGA and poly (caprolactone).

Ultrasound-mediated microbubble drug delivery

Ultrasound-mediated microbubble drug delivery stems from the field of ultrasonic contrast imaging. Commercially available microbubble contrast agents are gas-filled bubbles (1–8-µm diameter) made with a shell coating that is stabilized with phospholipids, surfactant, denatured serum albumin or synthetic polymer. The posterior segment of the eye comprises the back two-thirds of the eye, including the vitreous humor, the retina, the choroid and the optic nerve. Posterior Segment Eye Diseases (PSEDs) are then defined as the disorders that affect these tissues with the common main outcome of varying degrees of visual impartment and blindness. The most prevalent diseases are glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy. Nowadays, millions of people are suffering from retinal and choroid diseases and the number is increasing every year, as the incidence significantly increases with age. Both disorders are characterized by their severity and difficulty of treating. Despite numerous efforts, effective intraocular drug delivery remains unresolved and therefore, it is highly desirable to improve the current treatments of diseases affecting the vitreous cavity.

Routes of Drug Delivery to the Posterior Segment of the Eye

Intravitreal Administration

Intravitreal injection is the mainstream route of administration to treat diseases affecting the posterior segment of the eye. The drug is placed directly into the vitreous humor, though it is a highly targeted drug route. It has the inconvenience of being an invasive route. However, intravitreal drug administration is always selected to deliver to the posterior ocular segment due to the possibility of overcoming systemic exposure and obtaining high drug levels into the vitreous chamber.

Vitreous and Posterior Compartment Barriers to Drug Delivery

Vitreous

The vitreous body shows a transparent jelly-like structure mostly composed of types II, IX, and V/XI collagen fibers, whose spaces are filled with glycosaminoglycans, mainly hyaluronic acid. This structure acts as both a static and dynamic barrier. The static barrier is the vitreous structure by itself, although it is not a very restrictive barrier in terms of molecular mobility.

Posterior Compartment Barriers to Drug Delivery

The inner limiting membrane is a mechanical and electrostatic barrier located between the vitreous and the retina composed of collagen, laminin, and fibronectin. Its composition and thickness (~4 µm) may be variable along its structure, showing a 10 nm pore size. Both drug charge and size can play an important role in the passage of molecules through this membrane, being the charge the most critical factor. Thus, positively charged nanoparticles seem to present more difficulty than neutral and negatively charged ones because of the negative charge of the membrane. The neural retina is the innermost layer of the eye and consists of a multi-layered structure which is responsible for transmitting the light to the brain by means of photoreceptors, neurons, and glial cells[15].

Blood–Retinal Barrier (BRB)

The BRB is composed of two types of cells: The retinal capillary endothelial cells (which make up the inner BRB) and the retinal pigment epithelial cells (RPE) (which form the outer BRB) [5]. Both are considered an important impediment to retinal drug delivery as it restricts the drug transport between neural retina and circulating blood. In the RPE, drug permeability is determined by physicochemical factors (e.g., molecular weight, lipophilicity, protein binding), as well as drug concentration gradient and their affinity with the existing transporters at that level, which can increase or decrease drug transfer through RPE.

The BRB limits the drug diffusion from the vitreous humor to inner parts of the retina. It is composed of the inner BRB, which contacts with the vitreous humor and it is formed by capillary endothelial cells connected by tight junctions, and the outer BRB, also called the RPE, which exhibits a high amount of melanin, being surrounded by choroidal capillaries. Paracellular transport through retinal capillaries is limited by the tight junctions (about 2 nm), although certain larger-size molecules can transcellularly permeate by passive diffusion and/or active transport (e.g., ganciclovir or dexamethasone). Nevertheless, both processes are also restricted due to the absence of fenestrations and the lack of transport vesicles in the endothelial cells. The choroid is a highly vascularized barrier that lies between the RPE and the sclera. This layer supplies oxygen and nutrients to the retina. It has a 200 µm thickness and it is divided into five layers: The Bruch's membrane, the choriocapillaris layer, two vascular layers, and the suprachoroidal layer. The Brunch´s membrane presents a 2–4 µm thickness, whose structure is composed of collagen and elastin fibers. The choriocapillaris layer is formed by highly fenestrated capillaries with a 6–12 nm pore size, allowing the passage of large molecules. The suprachoroid is located between the sclera and the choroid and it is composed of collagen fibers, melanocytes, and fibroblasts. In terms of drug delivery, it must be taken into consideration that choroid shows two different behaviors: (1) It acts as a static barrier due to suprachoroid structure and (2) it provides a dynamic barrier as a consequence of a high choriocapillaris-layer blood flow. Both actions prevent the passage of hydrophilic compounds while positively charged lipophilic drugs can stabilize bindings with the tissue, leading to slow-release depots. The molecular size of the drug also determines the diffusivity into the posterior segment[16].

Topical Administration

Ophthalmic topical administration by eye drops is commonly used for the treatment of anterior-segment diseases. Most of the topically applied drugs are intended for the treatment of diseases that affect different layers of the cornea, the conjunctiva, iris, or the ciliary body. However, topical administration for the treatment of posterior ocular diseases is considered an ineffective pharmacological strategy since therapeutic drug concentrations are not reached in the posterior segment of the eye due to low drug penetration.

Ocular Barriers for the Entry of Drugs: Precorneal Factors

After topical eye-drops administration, the first tissue barrier that drug molecules must overcome to access the target is the tear drainage of the excess volume through the nasolacrimal duct. In normal conditions, this drainage occurs at 1.45 $\mu L \cdot min^{-1}$ and it results in a drug loss into systemic circulation, especially related to hydrophilic molecules. In fact, the loss of eye drop solution occurs until the tear volume returns to a normal range (7–9 µL).

Corneal and Anterior Compartment Barriers

Cornea

The cornea is the transparent portion surrounding the sixth anterior part of the eyeball with a 0.5 mm thickness and a 12 mm diameter. Tear film and aqueous humor provide nourishment and oxygen as it lacks blood vessels. The stratified, squamous and non-keratinized epithelium is the most critical barrier to penetration with a 10^{-7}–10^{-5} cm^{-1} drug permeability rate because of the fact that tight junctions impair the permeation of low lipophilic molecules. Drug absorption depends on their physicochemical characteristics. In consequence, only hydrophilic molecules can diffuse through the stroma due to the hydrophilic nature of the hydrated collagen. Only small molecules with a log D value between 2 and 3 can penetrate through all the layers.

Posterior Juxtascleral Route

The posterior juxtascleral injection, recently developed by Alcon Laboratories, is an alternative administration route based on the therapeutic agent deposition directly in the closest area to the macula, without puncturing the eyeball. It allows achieving higher drug concentrations in the target site due to the fact that the scleral thickness decreases near the equatorial region, an aspect that promotes a greater drug penetration towards the posterior segment of the eye[17].

Suprachoroidal Route

Suprachoroidal injection was introduced as a potential drug administration route to the posterior segment of the eye although it is not clinically used at present. Drug is injected into the suprachoroidal space below the sclera inner surface using microneedles (micron-dimensions needles that can infuse fluid into tissue with excellent spatial targeting), up to 50 µl maximum volume. Formulation is distributed throughout the suprachoroidal space as a consequence of the pressure exerted by the injection process itself.

Drug Delivery Systems

Currently, there are no pharmaceutical forms commercialized to be administered by suprachoroidal injections. Nevertheless, this type of administration was widely studied by using fluorescein and fluorescently tagged dextrans (40 and 250 kDa), bevacizumab and polymeric particles (20 nm to 10 µm in diameter). Sulforhodamine B microneedle injection was also studied as well as nanoparticle and microparticle suspensions into the suprachoroidal space.

Subretinal Route

Drug subretinal route has emerged as an alternative administration route to intravitreal administration due to its side effects and lower adherence to treatment by patients derived from the latter. Thus, subretinal administration involves drug inoculation into the subretinal space, an ocular space located between RPE cells and photoreceptors[18-22].

2. Conclusion

The eye is one of the most inaccessible organs in terms of obtaining therapeutic drug concentrations, especially in the treatment of posterior segment ocular pathologies. The conventional administration pathways, such as topical or systemic routes, usually show important limitations, either by low ocular penetration or by the appearance of side effects linked to the posology, among others. The new drug delivery systems are needed to prolong the administration intervals for posterior segment ocular pathologies, even though the development of novel DDS is particularly complicated due to several aspects must be considered, such as pharmacokinetics, immunogenicity, biodegradation, tolerability and toxicity, among others. The biodegradable and non-biodegradable implants, microparticles, nanoparticles, microneedles, and microelectromechanical systems are the most innovative ones.

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