Recent Advances In Drug Delivery To The Posterior Segment Of The Eye

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Abstract

Vitreoretinal diseases, including age-related macular degeneration (AMD), cytomegalovirus retinitis, diabetic retinopathy, posterior uveitis and retinitis pigmentosa, which are considered the main causes of blindness all over the world, are refractory to both topical and systemic pharmacological approaches because of the unique anatomy of the eye which represent a several barriers that resist the passage of required drug.

Since blindness and visual impairment become a nightmare to those patients, the treatment of such diseases has the interest of the pharmaceutical scientist in order to develop novel drug delivery systems that can overcome these barriers and reach the target tissue in an efficacious concentration without causing any patient discomfort or alteration in protective physiological mechanisms

Ocular drug delivery has been a challenging task for pharmaceutical researchers in order to treat various ocular diseases especially that affecting posterior segment.

Key Words:

Ocular Anatomy and physiology, Conventional routes of drug delivery to the posterior segment, Intravitreal injection, Trans-scleral diffusion, Trans-scleral Iontophoresis, Super-selective intra-arterial chemotherapy.

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This essay is dedicated to the soul of my great father Also dedicated to my great beloved mother and to my brother and sister.

And a special dedication to such a cooperative kind husbend and to my beloved small family.

Doaa M. Kareem Akl

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List of Abbreviations

ABLC: Amphotericin B lipid complexes.

ACE: Angiotensin-converting enzyme.

AIDS: Acquired immune deficiency syndrome.

AMD: Age related macular degeneration.

ASC: Alanine–serine–cystein.

BM: Bruch's membrane.

BRB: Blood-retinal barrier.

BRVO: Branch retinal vein occlusion.

BSA: Bovine Serum Albumin.

CRD: Chemoreduction.

CNV: Choroidal neovascularization.

CNTF: Ciliary neurotrophic.

CNV: Choroidal neovascularization.

CMV: Cytomegalovirus.

CRVO: Central retinal vein occlusion.

CsA: Cyclosporine A.

DDS: Drug delivery systems.

DME: Diabetic macular edema.

DMPC: Dimyristoylphosphatidylcholine.

DR: Diabetic retinopathy.

EBRT: External beam radiotherapy.

ECT: Encapsulated cell technology.

EIU: Endotoxin-induced uveitis .

Egg yolk PG: egg yolk phosphatidylglycerol.

ERG: electroretinogram.

EVA: Ethylene vinyl acetate.

FA: Fluocinolone acetonide.

FAD: Flavin adenine dinucleotide.

FITC: Fluorescein isothiocyanate.

FMN: Flavin mononucleotide.

FN: Fibronectin.

FR: Folate receptors.

GLUT1: Glucose transporter.

HAART: Highly active antiretroviral therapy.

IA: Intra-arterial.

ICA: Internal carotid artery.

IgG: Immuno- globulin G.

ILM: Internal limiting membrane.

IOP: Intra-ocular pressure.

ISCEV: International Society for Clinical Electrophysiology of Vision.

L-AmB: Liposoma-encapsulated amphotericin B.

LAT: Large neutral amino-acid transport.

LCST: Lower critical solution temperature.

MEMS: Micro Electro-Mechanical System.

MMA: Middle Meningeal Artery.

OA: Ophthalmic artery.

OCT: Optical Coherence Tomography.

PCFT: Proton-coupled folate transporter.

PEG: Polyethylene glycol.

PEG-DA: Poly ethylene glycol diacrylate.

PepT1: Peptide transporter.

PGA: Polyglycolic acid.

PGLC: Poly glycolide-co-lactide-co-caprolactone copolymer.

PLA: Poly lactic acid.

PLC: Poly e-caprolactone.

PLGA: Poly lactide-co-glycolide.

PMMA: Poly methylmetacrylate.

PNIPAAm: Poly N-isopropylacrylamide.

POE: Poly ortho esters.

PVA: Polyvinyl alcohol.

PVR: Proliferative vitreoretinopathy.

RFC: Reduced folate carrier.

RFT: Riboflavin transporters.

RPE: Retinal pigment epithelium

SIRC: Seruminstitut rabbit corneal.

SGLT1: Sodium-dependent -glucose transporter.

SLO: Scanning laser ophthalmoscope.

SMVT: Sodium-dependent multivitamin transporter.

SOAI: Selective ophthalmic artery infusion.

STRIDE: Sustained Triamcinolone Release for Inhibition of Diabetic Macular Edema.

SVCT: Sodium-dependent vitamin C transporters.

TA: Triamcinolone acetonide.

TEM: Triethylene melamine.

t-PA : Tissue plasminogen activator.

TSP : Tamarind seed polysaccharide.

VEGF: Vascular endothelial growth factor.

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Introduction

The unique structure of the eye restricts the entry of drug molecules at the required site of action. Conventional systems like eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision threatening ocular diseases.[1]

Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs. Moreover, human cornea comprising of epithelium, substantia propria and endothelium also restricts the ocular entry of drug molecules.[2]

Treatment of 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 overcome the many barriers for efficacious delivery of therapeutic drug concentrations.[3]

There was an urgent need to develop ocular drug delivery systems which provide controlled release for the treatment of chronic diseases, and increase patient's and doctor's convenience to reduce the dosing frequency and invasive treatment.[4]

There are different routes of drug administration to the posterior segment of the eye with recent advances in the research and development of drug delivery devices.[3]

Topical drug application; Topical eye drops are far superior to all other routes of administration with respect to safety, comfort, affordability and ease of use. However topical medications are least effective in delivering therapeutic concentrations of the drug to the retina.[5]

Systemic drug delivery; The systemic application of drugs is another method of access to the posterior segment. From the blood, the drugs can easily enter the choroidal extravascular space. However, the entry of the drug into the posterior segment is often limited by the outer and inner blood–retinal barriers. It also increases the risk of adverse effects due to the accumulation of a drug in other tissues throughout the body.[3]

Intravitreal injection; Intravitreal injection was introduced in 1945.[6,7] It 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 with topical and systemic administration. As a result, a much higher dose of drug can reach the target site and yield a more efficacious treatment of posterior eye diseases. However, multiple injections may be necessary as a result of the limited half-life of many compounds in the vitreous, potentially causing trauma and increasing the risk of cataract, retinal detachment, hemorrhage and endophthalmitis.[8]

Transscleral diffusion; 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, and sub-Tenon's delivery.[9]

Transscleral Iontophoresis; Another transscleral method of drug delivery in which charged molecules are delivered across the sclera and into the posterior segment of the eye via a direct electric current.[9]

Many types of controlled-release drug delivery systems have been developed, including nanoparticles, microcapsules, liposomes and implants.[10]

Intraocular implants; are designed to provide drug release into the posterior segment for longer periods of time (months or even years) compared to particles or solutions. These implants are usually placed at the level of the parsplana during a surgical procedure.[11]

Compared to intravitreal injections, drugs released from implants deliver more consistent levels of the drug, avoids side effects associated with frequent intravitreal injections, minimize peak concentrations and result in smaller quantities of drug being required for treatment.[5,12] Implants can be either nonbiodegradable or biodegradable.[13]

Ocular drug delivery system using particulates 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.[14,15]

Liposomes, Phospholipid bilayer encapsulated drug delivery system. Liposomes with encapsulated drug can bind to a cell membrane and facilitate drug transfer across the membrane. They are less stable than particles made of polymer. Both hydrophilic and hydrophobic drugs can be encapsulated into liposomes.[13]

Thermoresponsive gels; A study examined the use of thermoresponsive gels for the delivery of anti-VEGF for the regulation of angiogenesis.[16]

Hydrogels have been proposed as an alternative method of delivering anti-VEGF drugs to the posterior eye. Anti-VEGF therapies may not be effective in eyes after vitrectomy owing to a shortened half-life time in the vitreous cavity. Hydrogels may prolong the drug residence in the vitreous even after vitrectomy.[17]

Ultrasound-mediated microbubble drug delivery, Ultrasound has long been used for diagnostic imaging, but there has been a focus on its therapeutic applications such as drug delivery.[18]

A sustained, controlled-release delivery system for the posterior segment comprised of biodegradable, polymeric nano- and microbubbles that use ultrasound to selectively trigger the release of drugs or genes encapsulated within an oily core.

The delivery system has been mathematically modeled to determine the frequency required for drug release given the size and material properties of the microbubble shell.[19,20]

Micro-Electromechanical Intraocular Drug Delivery Device; A microelectromechanical systems (MEMS) drug delivery device is investigated for the treatment of chronic and refractory ocular diseases. It can be re-filled with the drug solution, giving long-term drug therapy.[21,22]

Transporter Targeted Drug delivery to the retina; this method of drug delivery targets nutrient transporters on ocular barriers utilizing a prodrug approach. Nutrient transporters are transmembrane proteins involved in the transportation of essential nutrients and xenobiotics across biological membranes, thereby regulating the supply of essential ingredients into the cell.[13]

Super selective intra arterial chemotherapy; It is used in retinoblastoma to deliver a high concentration of the drug to eliminate the need for enucleation and systemic chemotherapy in children.[13]