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Review: Recent Perspectives in Ocular Drug Delivery

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Abstract

The delivery of drugs to the eye has been a major challenge for pharmacologists due to the unique anatomy and physiology of the eye. Static barriers (various layers of the cornea, sclera, and retina, including aqueous and blood-retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and drip pumps. especially in the rear segment. The identification of impulse transporters on different ocular tissues and the design of a transporter-targeted parenteral drug delivery have gained momentum in recent years. In parallel, colloidal dosage forms such as nanoparticles, nanocells, liposomes, and micro emulsions have been extensively studied to overcome various static and dynamic barriers. Novel drug delivery strategies such as bioadhesive gels and fibrin glues have been developed to maintain drug levels at the target site. The development of non-invasive continuous drug delivery systems and research into the feasibility of local use for post-drug delivery could greatly improve drug delivery in the years to come. Recent developments in the field of ophthalmic drug delivery promise significant improvements in overcoming the challenges of various diseases of the anterior and posterior segments of the eye. A better understanding of the nature of ocular diseases, barriers, and factors affecting in vivo performance would significantly advance the development of new delivery systems. The current momentum in the invention of new drug delivery systems promises greatly improved therapies for the treatment of vision disorders.

Keywords: Eye; Ocular drug delivery system; Novel drugs; Mechanism; Topical; Administration; Technology

Introduction

The delivery of drugs to the eye remains one of the most challenging tasks for pharmaceutical scientists. The unique structure of the eye limits the penetration of drug molecules to the required site of action. Drug delivery to the eye can be roughly divided into anterior and posterior segments. Traditional systems such as eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision-threatening eye diseases [1]. However, over 90% of the ophthalmic preparations available on the market are in the form of eye drops. These preparations are primarily aimed at diseases of the anterior segment of the eye [2] Most topical drugs are cleared from the eye by various mechanisms (lacrimation, tear dilution, and tear turnover), resulting in poor drug bioavailability in the eye. In addition, the human cornea, which consists of epithelium, stroma and endothelium, also restricts the entry of drug molecules into the eye [3]. Because of these factors, less than 5% of the administered drug reaches the eye. Alternative approaches such as incorporating penetration enhancers/cyclodextrinsand increasing the viscosity of the solutions did not provide significant improvements. Recently, several drug efflux pumps have been identified and significant increases in drug absorption in the eye have been achieved after inhibition or avoidance. However, long-term use of such inhibitors can cause side effects [4]. Treating posterior segment disease remains a Herculean task for formulation scientists. The tight junctions of the blood-retinal barrier (BRB) limit the penetration of systemically administered drugs into the retina [5]. In the treatment of diseases of the posterior segment of the eye, high drug concentrations in the vitreous body are required. This is only possible with local administration (intravitreal injections/implants and periocular injections). Compared to intravitreal injections, periorbital injections are associated with relatively high patient compliance [6]. Dramatic changes have been observed in the field of ocular drug delivery over the past decade. Knowledge of the different membrane transporters/receptors present in the eye has opened up new possibilities. Particularly polar drug molecules that do not penetrate the eye's barrier can be conveniently delivered via transporter/receptor-directed drug delivery systems [7]. This review article briefly discusses the pathology of various eye diseases and their current therapies. We also highlighted the role of multiple ocular transporters and recent developments (Figure 1) in drug delivery strategies, including gene therapy. We briefly talked about ocular delivery systems, gene therapy, and newer developments like microneedling and iontophoresis.

Routes of ocular drug delivery

There are several possible routes of drug delivery into the ocular tissue (Figure 2). The choice of route of administration depends mainly on the target tissue. Traditionally, topical ocular and subconjunctival delivery is used for anterior targets and intravitreal delivery for posterior targets. The design of the dosage form can have a significant impact on the resulting drug concentrations and the duration of the drug effect.

- **Topical administration**

Typical topical administration of ophthalmic drugs is via eye drops, but these have only a short contact time with the ocular surface. Appropriate formulation design (e.g. gels, gel preparations, ointments, inserts) can extend contact and thus the duration of action. With brief contact of the drug with the corneal surface, it partitions into the epithelium and, in the case of lipophilic compounds, remains in the epithelium and is slowly released into the corneal stroma and further into the anterior chamber. After administration of eye drops, the

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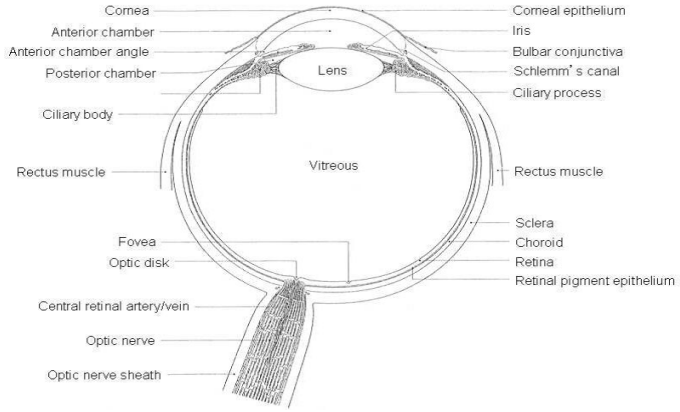

Figure 1: Schematic of the eye-ball structure.

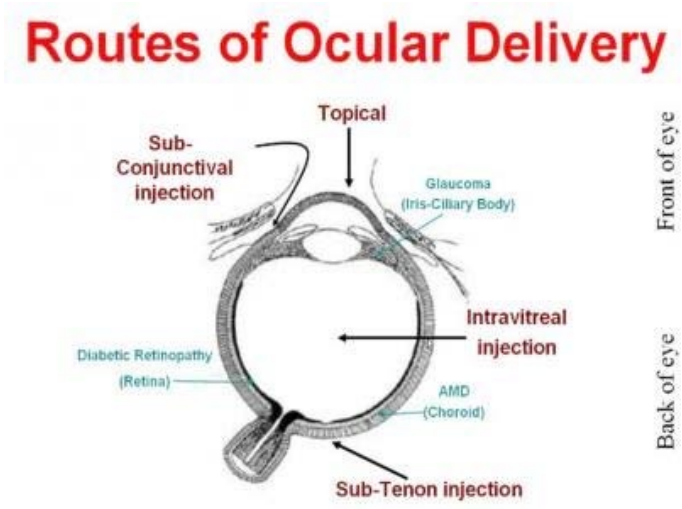

Figure 2: Routes of ocular drug delivery.

maximum concentration in the anterior chamber of the eye is reached after 20-30 minutes, but this concentration is usually two orders of magnitude below the concentration of lipophilic compounds that are instilled by the eye itself. The drug easily travels from the aqueous humor to the iris and ciliary body, where it can bind melanin. The melanin-bound drug can form a reservoir that is gradually released into surrounding cells, prolonging the effect of the drug. Diffusion into the lens is much slower than diffusion into the uvea [6]. Unlike the porous uvea, the lens is a dense, protein-rich structure in which drug degradation occurs slowly.Removal of the drug from the aqueous humor occurs by two main mechanisms: rotation of the aqueous humor in the angle of the ventricle and Sclemm's duct and outflow of venous blood through the anterior part of the uvea. The first mechanism has a flow rate of approximately 3 µl/min and this convective flow is drug independent. Instead, elimination through the vascular bloodstream depends on the drug's ability to penetrate the endothelial walls of the vessels. For this reason, the anterior chamber clearance is faster for lipophilic drugs than for hydrophilic drugs. The clearance of lipophilic drugs can be about 20-30 µL/min. In such cases, excretion of the drug occurs largely through the bloodstream across the vascular membrane of the eye. The half-life of drugs in the anterior chamber is usually short, about an hour. Volumes of distribution are difficult to determine due to slow drug equilibration in ocular tissue. In rabbits, estimates range from aqueous humor volume (250 µl) to 2 ml. In the latter case, the slow intravitreal distribution of the drug is included in the volume of distribution. This distribution is slow because the lens prevents the drug from penetrating the vitreous. Another limiting factor is the outflow of aqueous humor from the posterior chamber into the anterior chamber. Some topically administered drugs can be absorbed through the bulbar conjunctiva into the sclera and further into the uvea and posterior segment of the eye. This is an inefficient process, but one that can be improved with dosage forms that continuously deliver the drug to the conjunctival surface. The role of this extracorneal absorption pathway depends on the properties of the drug. In general, more hydrophilic and larger molecules can be absorbed in this way. They have particularly poor corneal penetration and therefore the relative proportion of non-corneal births is higher. Conjunctival and posterior administration would be desirable, but unfortunately penetration is clinically insignificant.

- **Subconjunctival administration**

Traditionally, subconjunctival injections have been used to deliver drugs at elevated concentrations into the uvea. Currently, this mode of drug delivery has gained new momentum for several reasons. Advances in materials science and pharmaceutical formulations have created exciting new opportunities for the development of controlled-release formulations to deliver drugs to the posterior segment and direct the healing process after surgery (e.g. glaucoma surgery). Second, the development of new therapies for macular degeneration (antibodies, oligonucleotides) must target the retina and choroid. After subconjunctival injection, the drug must pass through the sclera, which is more permeable than the cornea. Interestingly, the permeability of the sclera does not depend on the lipophilicity of the drug. In this it differs significantly from the cornea and conjunctiva. Even more interesting is the surprisingly high permeability of the sclera for large molecules of the same protein size. It therefore seems possible to deliver drugs through the sclera to the choroid. However, delivery to the retina is more complicated because in this case the drug has to pass through the choroid and the RPE. The role of blood flow is kinetically well characterized, but based on existing information there is good reason to believe that drugs can be significantly eliminated in choroidal blood flow. Pitkanen have recently shown that RPE is a stronger barrier than the sclera for the penetration ofhydrophilic compounds. For small lipophilic drugs they have similar permeabilities. A more complete understanding of the kinetics in the sclera, choroid, and RPE should aid in the design of drugs with optimal activity in selected posterior target tissues. The combination of kinetic knowledge and selective cellular molecules offers very interesting possibilities.

- **Intravitreal administration**

Direct intravitreal administration of the drug has the distinct advantage of easier access to the vitreous body and retina. However, it should be noted that vitreous delivery to the choroid is more complicated due to the obstruction of the RPE barrier. Small molecules can diffuse rapidly in the vitreous, but the mobility of large molecules, especially positively charged ones, is limited. Likewise, the mobility of nanoparticles is strongly dependent on the structure. In addition to diffusion, convection also plays a role. Convection is caused by eye movements. After intravitreal injection, the drug is eliminated via two main routes: anterior and posterior. All unions can use the road directly. It involves diffusion of drug through the vitreous into the posterior chamber, followed by removal by aqueous turnover and blood flow across the vascular membrane. Posterior elimination is achieved by penetrating the posterior barrier of the eye of blood. This requires adequate passive permeability (i.e. small particle size, lipophilicity) or active transport across these barriers. For these reasons, the high

molecular weight and water solubility tend to increase the half-life of glass. The drugs can also be administered intravitreally in the form of controlled-release preparations (liposomes, microspheres, implants) to prolong the effect of the drug.

Mechanism of drug release

The mechanism of controlled drug release into the eye is as follows:

A. Diffusion,

B. Osmosis,

C. Bio-erosion.

- **Diffusion**

In the diffusion mechanism, the drug is released continuously across the membrane into the tear fluid at a controlled rate. When the insert consists of a non-erodible solid with pores and dispersed active substance. Drug release can occur by diffusion through the pores. The controlled release can be further controlled by the gradual dissolution of the dispersed solid drug in this matrix by inward diffusion of aqueous solutions. In a dissolvable device, true dissolution occurs primarily through swelling of the polymer. In devices with controlled swelling, the drug is evenly dispersed throughout the glassy polymer. Because glassy polymers are essentially impermeable to drugs, there is no diffusion through the dry matrix. After inserting the insert into the eye, water from the tear fluid begins to penetrate into the matrix, then swells and, as a result, the polymer chain relaxes and the drug diffuses. The dissolution of the matrix after the swelling process depends on the polymer structure: linear amorphous polymers dissolve much faster than cross linked or semi-crystalline polymers. The release of these devices follows Fick's general "square root of time" kinetics; however, in some cases it is known as Case II or zero-order transport.

- **Osmosis**

In the osmotic mechanism, the housing includes a transverse flexible waterproof membrane dividing the interior of the housing into a first chamber and a second chamber; the first compartment is defined by a semi-permeable membrane and a flexible waterproof membrane, and the second compartment is defined by an impermeable material and a flexible membrane. A drug delivery port is provided in the impermeable wall of the liner. The first compartment contains the solute, which cannot pass through the semipermeable membrane, and the second compartment provides a drug reservoir, again in the form of a liquid or gel. When the insert is placed in the aqueous environment of the eye, the water diffuses into the first compartment and stretches the flexible membrane to expand the first compartment and contract the second compartment, forcing the drug through the drug delivery port.

- **Bioerosion**

In the mechanism of bioerosion, the configuration of the insert body is formed by a matrix of bioerodible material in which the drug is dispersed. The contact of the insert with the tear fluid causes a controlled and prolonged release of the drug through bioerosion of the matrix. The drug can be evenly dispersed throughout the matrix, but it is believed that more controlled release is achieved if the drug is concentrated superficially in the matrix. In truly erosive electronic devices, the drug release rate is controlled by a chemical or enzymatic hydrolytic reaction that dissolves the polymer, or breaks it down into smaller water-soluble molecules. These polymers can undergo volumetric or surface hydrolysis according to Heller's definition. Surface hydrolyzable erosion pads can exhibit zero-order release kinetics; provided the devices maintain constant surface geometry and the drug is poorly soluble in water.

Novel ocular drug delivery systems

- **Nanotechnology based ocular drug delivery**

Over the past few decades, many approaches have been used to treat eye diseases. Nanotechnology-based ophthalmic formulations are one of the current approaches for drug delivery to the anterior and posterior segments of the eye. Nanotechnology based systems with appropriate particle sizes can be designed to ensure low irritation, adequate bioavailability and compatibility with ocular tissues. Several nanocarriers such as nanoparticles, nanosuspensions, liposomes and nanomicelles have been developed for drug delivery to the eye. Some of them have shown promise in improving ocular bioavailability.

- **Nanomicelles**

Nanomicelles are the most commonly used carrier systems to formulate therapeutic agents in clear aqueous solutions. In general, these nanocells are made up of amphiphilic molecules. These particles can be surface-active or polymeric. Recently, Cholkar performed a detailed review of ocular barriers and the use of nanomicelle technology in drug delivery to the eye. There is currently a great deal of interest in developingtechnology based on a nanocell preparation for drug delivery to the eye. The reasons can be attributed to their high drug encapsulation capacity, ease of manufacture, small size, and crown-producing hydrophilic nanocellular aqueous solution. In addition, the micellar formulation can increase the bioavailability of therapeutic drugs in the ocular tissue, indicating better therapeutic outcomes. To date, several concept studies have been conducted to investigate the suitability of nanocells for drug delivery to the eye.

- **Nanoparticles**

Nanoparticles are colloidal carriers with sizes from 10 to 1000 nm. For ocular administration, nanoparticles are typically composed of lipids, proteins, natural or synthetic polymers such as albumin, sodium alginate, chitosan, poly(lactide-coglycolide) (PLGA), polylactic acid (PLA) and polycaprolactone. The active substance-containing nanoparticles can be nanocapsules or nanospheres. In nanocapsules, the drug is encased in a polymer shell, while in nanospheres; The drug is uniformly distributed within the polymer matrix of. In recent decades, nanoparticles have drawn attention to drug delivery to the eye, and several investigators have attempted to develop drug-containing nanoparticles for delivery to anterior and posterior ocular tissues. Nanoparticles represent a promising candidate for ocular drug delivery due to their small size, which results in low irritation and sustained release properties, avoiding frequent dosing.

- **Liposomes**

Liposomes are lipid vesicles with one or more phospholipid bilayers surrounding an aqueous core. The size of liposomes generally ranges from 0.08 to 10.00 μm, and based on the size and phospholipid bilayers, liposomes can be divided into small unilamellar vesicles (10-100 nm), large unilamellar vesicles (100-300 nm) and multilamellar vesicles (having more than one bilayer). In ophthalmic applications, liposomes are ideal delivery systems because of their excellent biocompatibility, cell membrane-like structure, and ability to encapsulate hydrophilic and hydrophobic drugs.In several scientific studies, liposomes have shown good delivery efficiency to the anterior and posterior segments of the eye. In a recent study of the administration of latanoprost in tissues of the anterior segment, Natarajan have developed a liposomal preparation. A single subconjunctival injection of latanoprost/ liposome into a rabbit eye resulted in sustained IOP reduction for

50 days, with IOP reduction comparable to daily administration of eye drops. Regarding drug delivery to the anterior ocular segment, efforts are mainly aimed at improving precorneal residence time by incorporating positively charged lipids or mucoadhesive polymers into liposomes. Positively charged liposomes, i. H. cationic liposomes, showed better delivery efficiency to the eye than negatively charged and neutral liposomes due to binding to the negatively charged corneal surfaces. Didecyldimethylammonium bromide, stearylamine and N-[1-(2,3-dioleoyloxy)propyl]- N,N,N-trimethylammonium chloride are commonly used in the preparation of cationic liposomes.

- **Implants**

Intraocular implants are specifically designed to provide controlled local release of drugs over an extended period of time. These devices make it possible to avoid multiple intraocular injections and related complications. To deliver the drug to the back tissues of the eye, the implants are typically placed in the vitreous by making a small incision in the flat part behind the lens and in front of the retina. Although implantation is an invasive procedure, these devices are gaining interest due to their associated benefits, such as barrier. Several implantable devices have been developed to deliver drugs to the eye, particularly in the treatment of chronic vitreoretinal disorders. Ocular implants are available as biodegradable and non-biodegradable drug delivery devices. Non-biodegradable implants allow long-term release due to near-zero release kinetics. Polymers such as polyvinyl alcohol (PVA), ethylene vinyl acetate (EVA) and polysulfone hollow fiber (PCF) are used to make non-biodegradable implants. Examples of commercially available nonbiodegradable implants are Vitrasert® and Retisert®.

Recent inventions for ocular drug-delivery technologies

- **Anterior segment ocular drug-delivery technologies**
- **Punctum plugs**

Punctum Plugs are biocompatible devices that are placed in the tear ducts to block the flow of tears. Also called occlusions or tear plugs, they are 2-5 mm in size. Puncture suppositories are non-invasive and can provide controlled drug delivery to the anterior segment of the eye. The construction of such spectacle inserts is possible from non-biodegradable and biodegradable materials. The non-biodegradable Punctum Pug Delivery Systems (PPDS) are made of silicone, polycaprolact and-hydroxyethyl methacrylate, which is said to provide controlled drug release for up to 180 days. After this time, the insert will be removed. Recently, a heat-sensitive hydrophobic acrylic polymer PPDS (Smart Plug, Medennium Inc.) has been developed for dry eye treatment. The heat-sensitive PPDS transforms from a rigid solid to a soft, gel-like structure when inserted into the eye (http://www.eyeconsultant.info/pdfs/smartplug.pdf). Ocular Therapeutix (Bedford, MA) developed the Travoprost Point Plug Insert (OTX-TP) to deliver travoprost to the ocular tissue for 90 days. Phase III clinical trials are on going to evaluate the safety and efficacy of OTX-TP in reducing intraocular pressure (IOP) and ocular hypertension (NCT02914509). Ocular Therapeutix also recently completed a Phase III clinical trial to evaluate the safety and efficacy of OTX-DP (Dexamethasone Plug-Insert) in the treatment of chronic allergic conjunctivitis and inflammation following cataract surgery compared to placebo spot capsules investigate (NCT02988882, NCT02736175)

- **Cul-de-sac Implants**

The ocular cul-de-sac is a pocket-like depression where the bulbar and palpebral conjunctiva meets on the upper or lower eyelid. Ophthalmic devices such as Lacrisert (Bausch & Lomb) and Ocusert (Akorn) are examples of dead end implants designed to deliver drugs to the anterior segment of the eye. These devices are safer and less invasive than conjunctival and epidural implants. Lacrisert (Bausch & Lomb) is a bottom neck hydroxypropyl cellulose plant. Theimplant is suitable for patients with moderate to severe dry eye syndrome. Lacrisert reduced corneal sensitivity, recurrent corneal erosions and keratitis exposure. It is also effective in treating conjunctival hyperemia. Lacrisert releases cellulose and helps maintain the integrity of the tear film. The implant acts as a lubricant and helps protect the surface of the eye. However, Lacrisert can cause discomfort. Causes foreign body sensation, eye irritation, hypersensitivity, constipation and blurred vision. Ocusert is a drug-eluting implant that releases pilocarpine over a 7-day period to treat glaucoma. However, the pilocarpine in the pad has caused unwanted side effects such as irritated eyebrows and constricted pupils. This led to Ocusert's withdrawal from the market. Another dead-end implant is DSP-Visulex (Aciont Inc., Salt Lake City, UT), which has completed a Phase II clinical trial in the treatment of anterior uveitis (NCT02309385). DSP-Visulex contains dexamethasone and is inserted into the bulbar conjunctiva.

- **Posterior segment ocular drug-delivery technologies**

Novel drug delivery systems such as implants are now being used by physicians to increase drug delivery for the treatment of posterior eye conditions such as DR, AMD, DME, retinal vein occlusion (CRVO) and posterior uveitis. Intravitreal implants are injected or surgically implanted into the vitreous of the eye. Vitreous implants can prolong the effect of the drug to several months and reduce the need for frequent intravitreal injections of drugs. Such frequent administration can cause retinal detachmentand retinal hemorrhages and can be painful for patients. These disadvantages of intravitreal injections can be minimized by using intravitreal implants. the following Section discusses the various intravitreal ocular implants currently available in the clinic and in clinical trials.

- **The durasert technology system**

Durasert's "pSivida Corp., Watertown, MA" technology system delivers medication at various preset times depending on the implant design. Drug release ranges from days to years. Durasert consists of a drug core surrounded by polymer layers. Drug release is a function of the permeability of the polymer layer. Vitrasert (Bausch & Lomb) is the first intravitreal delivery system containing an antiviral drug (ganciclovir) for the treatment of CMV retinitis. It uses the Durasert technology system and releases the active drug through a small hole in the insert over a period of 6-8 months. Retisert releases fluocinolone acetonide into the vitreous fromto 3 years.

NOVADUR drug-delivery technology

NOVADUR system "Allergan Inc." consists of therapeutics in a PLGA polymer matrix. PLGA is biodegradable and biocompatible polymer that breaks down into lactic and glycolic acids on contact with the vitreous body. Ozurdex (Allergan) is a US-approved controlled-release intravitreal dexamethasone implant. stFDA for the treatment of DME, RVO and posterior uveitis. Ozurdex contains 0.7 mg dexamethasone in a PLGA matrix that releases the drug for up to 90 days Mayer recently evaluated the effect of intravitreal bevacizumab followed by Ozurdex and Ozurdex alone in the treatment of CRVO and macular edema. The research team concluded that there is no difference between the above CRVO treatment strategies. However, when occluding branch retinal veins, Ozurdex monotherapy achieved better functional results. At the moment

- **Encapsulated cell technology**

Renexus (NT-501) is an encapsulated cell (ECT) technology for human RPE ocular implants transfected with a plasmid encoding ciliary neurotrophic factor. Renexus (NT-501) is in Phase III trials in dry AMD, glaucoma and retinitis pigmentosa (NCT03316300). The implant consists of a tubular hollow capsule made of a polymer matrix that can be loaded with genetically modified cells. Various biocompatible polymers such as collagen and hyaluronic acid hydrogel are used to manufacture the ECT matrix. The implant capsule is semi-permeable, which allows proteins to diffuse across the membrane but inhibits entry of immune cells. Genetically modified matrix cells take up nutrients from the surrounding tissue after implantation. Encapsulated cell technology is implanted in the pars plana and attached to the sclera. ECT may have advantages over other corticosteroid implants because it can secrete biologically active molecules for a longer period of time, reducing the need for implant replacement. Conturi demonstrated an engineered RPE capable of secreting a soluble VEGF receptor to inhibit VEGF activity in choroidal neovascularization and retinal neovascularization. This proof-of-concept study demonstrated that the human RPE cell line remained viable for up to 50 days with consistent secretion of the soluble VEGF-1 receptor. Although the researchers found slight inhibition of VEGF in an in vivo model, this delivery technology shows promise for the use of ECT in the treatment of diseases such as wet AMD, DR and MDG. ECT can be considered as a versatile platform that can be used to secrete targeted therapeutic biotechnology drugs such as antibodies, antibody fragments, growth factors, cytokines and prostaglandins for posterior eye diseases.Wang et al. developed an injectable alginate-collagen complex (ACC) gel matrix for ECT containing human retinal pigment epithelial cells and glial-derived neurotrophic factor (GDNF) secreted by HEK293 cells. HEK293 cells secreting GDNF were transfected with lipofectamine repressor DNA (TetR) and procaspase-8 transcript DNA.

- **Ideal characterstics of ocular drug delivery system**

1. Good corneal penetration.

2. Maximize drug absorption into the eye by increasing contact time with corneal tissue.

3. Easy instillation for the patient.

4. Decreased administration frequency.

5. Patient Compliance.Less toxicity and side effects.

6. Minimize prefrontal drug leakage.

7. Non-irritating and convenient form (viscous solution should not cause lacrimation or reflex blinking).

8. Should not cause visual disturbances.

9. Relatively not bold.

10. Rheological properties and suitable concentrations of the viscous system.

Conclusions

Effective treatment of ocular diseases is a major challenge for scientists in this field, mainly due to the nature of the diseases and the presence of ocular barriers, particularly in the posterior segments of the eyeball. Ideally, therapy should maintain effective drug levels over a long period of time after a single application. Topical and intravitreal drug delivery cannot be considered safe, effective, or patient-friendly. Periorbital drug delivery has the potential to overcome many of these limitations and can provide consistent drug levels even in ocular pathologies affecting both segments. The targeted delivery of transporters can be a promising strategy for many drug molecules. Colloidal carriers can significantly improve the current treatment and appear as an alternative after their periocular administration. In recent years, researchers have focused on developing strategies using a multidisciplinary approach, including microneedling, iontophoresis, and MRI. Continuous innovation in gene delivery appears to be very exciting for many diseases. The design of these innovative techniques has given their intellectual property protection an unprecedented boost. Going forward, the focus will be on achieving sustainable non-invasive drug delivery for eye diseases in both segments. A clear understanding of the complexity associated with tissues under normal and pathological conditions, physiological barriers, and multicompartment pharmacokinetics would greatly accelerate future developments in this field.

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