Chapter 10
Other Advances in Ocular Drug Delivery

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Abstract Ocular drug delivery has many challenges due to the physiology of the eye and the many natural barriers that most drugs need to encounter to permeate the intended tissues. Although traditional eye drops are invasive and convenient, they are inefficient for several ocular diseases due to their low ocular bioavailability and difficulty in delivering a drug to the posterior segment of the eye. Procedures such as implants or frequent intravitreal injections are invasive and challenging; however, this challenges present unique opportunities for innovative drug delivery approaches. New approaches to ocular drug delivery are aimed at: overcoming the disadvantages of existing therapies, overcoming short ocular contact time, increasing low bioavailability drugs to permeate tissues better, limiting dosing frequency, and reducing the invasiveness of some methodologies. This chapter discusses other significant advances in ophthalmic drug delivery such as gene therapy, iontophoresis, sonophoresis, and use of microneedle, hydrogels, and punctual plug delivery systems. A method for restoring light sensing in using retinal prosthetics, optogenetics, and chemical photoswitches are also discussed.

Keywords Advances in ocular delivery · Iontophoresis · Microneedles · Gene therapy

Introduction

Gene therapy is aimed to deliver intracellular genetic material to block a dysfunctional gene or to deliver a gene for a therapeutic purpose (Kompella et al. 2013). Gene therapy was first tried and showed the promising result to treat serious disease Leber Congenital Amaurosis (LCA), an autosomal recessive disease due to a mutation in at least 15 genes that cause blindness in newborn and children.

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R.T. Addo (ed.), *Ocular Drug Delivery: Advances, Challenges and Applications*,
DOI 10.1007/978-3-319-47691-9_10

The promising result in clinical trials for LCA have prompted the study of other diseases using gene therapy such as glaucoma, age-related macular degeneration (AMD), retinitis pigmentosa, choroideremia, and others (Solinis et al. 2015).

Hydrogels are cross-linked chemically and physically three-dimensional structures that can control drug release in response to a stimulus. The gels are mostly liquid at room temperature and solid at body temperature. When implanted in the subconjunctival space, it can also sustain the release of drugs delivered to the posterior segment.

The hollow microneedle is an experimental device using injection for intrascleral and suprachoroidal spaces delivery of drugs. In animals, the insertion site was no longer visible 1 h after the injection and the eye appears indistinguishable from a naïve eye. In the clinical setting, microneedle injection of drugs into the suprachoroidal space (SCS) can be used as outpatient surgery procedure to treat diseases such as AMD, diabetic retinopathy and other eye disorders, similar to intravitreal injection, but less invasive (Patel et al. 2011, 2012).

Animal models used for studying ocular drug delivery are usually rabbits, dogs or monkeys because of their close structural and content proximity to human eyes. Animals usually have lower vitreous volumes than humans, but higher vitreous gel contents such as in rhesus monkeys about 60 % and in rabbits almost 100 % of gel, respectively. The anterior chamber and lens are comparatively larger in rabbits, but the vitreous volume is larger in the monkeys. In humans, the vitreous volume is about 4–5 ml with about 40–80 % of gel depending on the age. The monkey model usually provides the best predictive value, while other mammalian models may be selected on the basis of ethical concerns and cost. However, mathematical modeling and simulation should be used to predict human physiological response using data collected from several different animal species. Rats or rodents are not optimal models for scaling exposure or response relationships to humans. Summary of recent ocular delivery in development is listed by Chen (2015).

Gene Therapy

Currently, there are 33 clinical trials reported to have been approved, in progress, or have been completed in the database of Gene Therapy Clinical Trials Worldwide. Viral vector using Adeno-Associated Viruses (AAVs) were used in 22 of the 33 trials. Gene silencing using short interfering riboxy nucleic acid (RNA) (siRNA) was used in 5 of the trials, confirming that gene replacement therapy has a promising clinical approach in the treatment of ocular disease. To treat ocular diseases with gene therapy, there are three parameters that need to be considered for successful results: (a) the administration route, (b) the delivery system, and (c) the use of specific promoter elements (Gaudana et al. 2012).

Administration Routes

The administration route of gene therapy can be through: topical instillation, periocular route, intracameral injection, intravitreal injection, subretinal injection, or suprachoroidal injection. Each administration route shows advantages and disadvantages. The selection of route should be based on the targeted cells and the characteristics of the vector (Solinis et al. 2015). The scheme of different routes of administration is shown in Fig. 10.1.

The topical route is the easiest non-invasive method of gene delivery; however, penetration to the cornea and conjunctival epithelial to reach the posterior segment is limited to the size of the gene that can be delivered; therefore, gene therapy of topical route is usually limited for the treatment of an anterior segment of the eye.

The periocular route includes the administration of drugs to peribulbar, retrobulbar, posterior juxta scleral, sub-tenon, and subconjunctival injection. Subconjunctival injection is the most studied of gene delivery. The drug can penetrate to the anterior and posterior segment, but also can cause systemic absorption and adverse effects. Large particle and nucleic acid drugs are retained for a long time in this part.

Intracameral injection has been used to control intraocular pressure (IOP) with success in the equine model due to the gene injected into the corneal endothelial

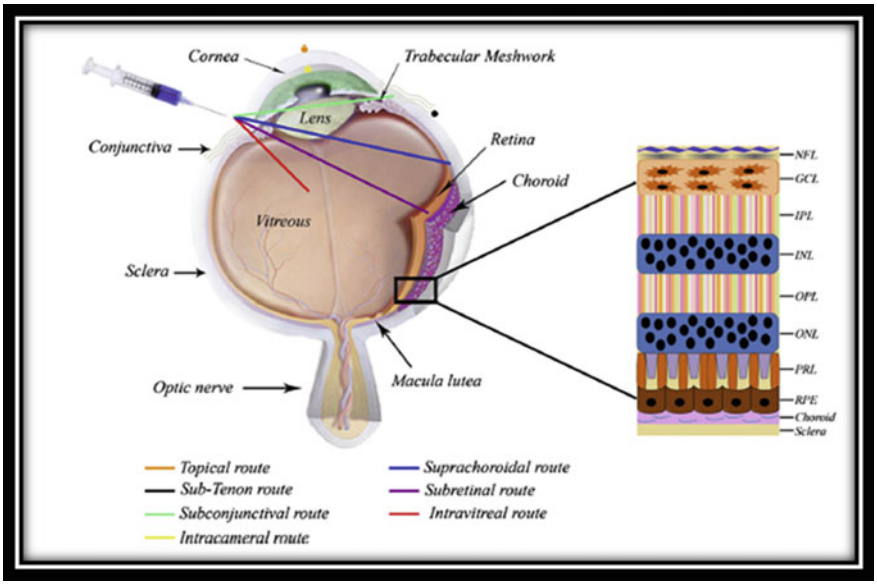

Fig. 10.1 Scheme of different ocular administration routes. *NFL* nerve fiber layer; *GCL* ganglion cell layers; *IPL* inner plexiform layer; *INL* inner nuclear layer; *OPL* outer plexiform layer; *ONL* outer nuclear layer; *PRL* photo receptor layer; *RPE* retinal pigment epithelia with permission from Solinis et al. (2015)

cells and trabecular meshwork produced stable protein expression (Shen et al. 2015; Gaudana et al. 2010).

Several works using intravitreal or subretinal injections showed a promising result for treatment of retinal degenerations of ganglion cells and photoreceptors; however, this is an invasive method that can cause ocular damage such as lesions in retinal pigment epithelial (RPE), hemorrhages, retinal tears, and retinal detachment.

Suprachoroidal, below the sclera and above choroid, administration of gene therapy using non-viral plasmid deoxynucleic acid (DNA) and electrical application have been successfully done in rat eyes without interfering with optical pathway (Kompella et al. 2010; Gaudana et al. 2012).

Delivery System

The ideal vectors to deliver gene should be: (a) they can take the gene efficiently into the target tissue, (b) vectors should carry large amount of genes to induce ocular improvement and also to stay long time in the eye compartment, (c) the vector should be well tolerated and not causing adverse effects such as inflammation, or activating immune response or toxic to the eye. Vectors commonly being researched are categorized into: (1) viral vectors and (2) non-viral vectors (Manning et al. 2002)

Viral vectors continue to be the gene delivery of choice to treat ocular diseases. These vectors include: (a) adenovirus vectors (AVs), (b) adeno-associated viral vectors (AAVs), (c) lentiviral vectors (LVs), and (d) retrovirus vector (RVs). Adenovirus is double stranded DNA vectors that are able to effectively transfect dividing and non-dividing cell without integrating their nucleic acid into the host genomes, thus avoiding the risk of mutagenesis but still large enough genes can be incorporated. However, AVs can induce an immune response and the duration of gene expression is relatively short. In a laboratory study, AVs are useful to carry interleukin (IL) 10 and nerve growth factor gene to improve allograft survival in corneal transplants rats. AVs have been designed to carry genes involved in retinitis pigmentosa, macular degeneration, diabetic neuropathies, and to reprogram fibroblasts to retinal ganglion-like cells in rats (Mohan et al. 2012; Solinis et al. 2015).

Adeno-associated viruses are non-pathogenic single strand DNA vectors that are able to transduce slow or non-dividing cells and to provide long-term gene transcription and expression for up to 6 years. AAVs may be recombined with capsid protein to increase efficacy and specificity, leading to the discovery of recombinant AAVs by some laboratory. The first number in the recombinant vectors denotes the serotype, while the second number corresponds to capsid (AAV n1/n2). For example, AAV2/8 was shown to effectively treat X-linked retinoschisis in mice model by slowing degeneration of the retina and repairing a retinal structure. As recombinants, AAV2/5, AAV2/8, AAV2/9 and AAV2/6 have been shown to be more effective than the original AAVs. Some researchers had a patent application for use in deficient herpes simplex virus-1 (HSV) that can incorporate growth factors, neurotrophins, cytokines, and drugs. In an attempt to deliver nucleic acid

which encodes pigment epithelium-derived factor (PEDF), recombinant AAVs has been successfully done in animal (Mohan et al. 2012; Surace and Auricchio 2008).

Lentiviruses are single-stranded RNA vector, are the most suitable vector due to their high and stable expression, ability to integrate cells, self-inactivating, and do not cause severe adverse effects. LVs have been studied on corneal endothelial cells of mice, sheep, and human to transduce genes related to retinal dystrophies, angiostatic proteins endostatin, and angiostatin to treat AMD, macular degeneration, and diabetic retinopathy, and other neovascular diseases (Staout and Appukuttan 2006).

Retrovirus vector carries RNA viruses but can cause oncogenicity. The use of retroviruses for gene therapy has been drastically reduced due to the development of T-cell leukemia in 4 and death of one patient enrolled in the clinical trials for X-linked recessive trials (Mohan et al. 2012).

Non-viral vectors contain cationic compound that binds electrostatically the genetic material and forms stable complex. The non-viral vector can be lipid based or polymer based vectors. Cationic lipids are positively charged amphiphilic molecules that form complexes with negatively charged nucleic acids. Modification of the composition and chemical structures of the lipids such as incorporating protamine sulfate, polyethylene glycol (PEG), or arginine-glycine-aspartate peptides, dextran, chitosan, hyaluronic acid and others are intended to increase nucleic acid protection from degradation by enzymes, to improve cell internalization, or to decrease the trafficking inside the cells, so gene delivery system is more effective. Many novel biodegradable polymers such as poly ethylene imine (PEI), polyesters, chitosan, hyaluronic acid, albumin, poly-L-Lysine (PLL), poly (glycolic) acid (PGA) dendrimers are among polymer based vector that have been studied in improving gene delivery system (Gaudana et al. 2012; Han et al. 2012; Tamboli et al. 2011; Solinis et al. 2015).

Short interfering nucleic acid (siNA) can modulate the gene expression and are designed as anti-angiogenic targeting genes responsible for angiogenesis such as vascular endothelial growth factor (VEGF) type 1, 2, 3 or connective tissue growth factor that cause glaucoma or macular degeneration. Several recent patents in gene therapies include: (a) application of lentiviral vectors to transduce mitotically active and inactive cells, (b) use of recombinant AAV to deliver anti-angiogenic factor, (c) use of mammalian gene CACNA1F encoding for mutated retinal calcium channel that causes congenital stationary night blindness, and (d) use of novel electroporation device to deliver DNA to specific site of the eye (Gaudana et al. 2012; Vargeese et al. 2005).

Promoter Elements

Promoters play an important role by engineering vector to specific tissue targeting and by enabling vector to turn on and off gene expression, and by responding to specific environmental signals. Several tissue-specific promoters for corneal and

retinal cells such as keratin 12 (epithelial specific), keratocan (keratocyte specific), cone and rod homeobox, rhodopsin, rod opsin have been tested successfully in the laboratories.

Gene therapy has been tested in several ocular diseases such as LCA, X-linked retinoschisis (XLRS), Stargardt disease, choroideremia, retinitis pigmentosa, AMD, a disease of the cornea, and glaucoma. Glaucoma affects about 3 % of people over 40 years worldwide by causing an increase in intraocular pressure (IOP) and if not treated on time can cause blindness. Gene therapy offered improvement in lowering IOP by inhibiting beta 2 adrenergic receptor via the use of siRNA and SYL040012 (a double strand oligonucleotides) as shown in clinical trials in 24 healthy volunteers (Solinis et al. 2015).

XLRS is retinal degenerative disease due to the mutation in gene encoding retinoschisis. This progressive disease can cause severe loss. Gene therapy with non-viral vectors and retinoschisis 1 (RS1) plasmid in an animal model showed promising results in slowing the progression of the disease (Solinis et al. 2015).

Stargardt disease is inherited juvenile macular degeneration that usually occurs in younger than 20 years old. The gene encodes for this disease is due to mutation of ABCA4. After the gene therapy, significant correction and functional structure are observed. There is a clinical trial that is currently underway using gene therapy (Solinis et al. 2015).

Choroideremia is an X-linked chorioretinal dystrophy that affects male. Mutation in CHM gene is associated with this disease. Successful gene therapy using AAV. REP1 in male patients showed improvement in the visual function and slowing down of the degeneration rate (Solinis et al. 2015).

Retinitis pigmentosa is the most common retinal degeneration responsible for the loss of vision of 1 in 4000 people worldwide. Defects in 60 genes include the mutation in inherited autosomal dominants, autosomal recessive, X-linked, or rhodopsin gene (RHO) have been identified. Suppression of mutant genes was successfully obtained using siRNA with AAV delivery (Solinis et al. 2015).

LCA is an autosomal recessive disease that causes marked impairment of visual acuity at birth. There is no successful treatment for LCA. Gene therapy has been conducted successfully in 4 clinical trials using lentiviral vector and AAVs to treat LCA (Solinis et al. 2015) (Fig. 10.2).

Iontophoresis

Iontophoresis is a non-invasive technique in which low electric current is applied to enhance ionized drug penetration into tissue. Iontophoresis increases drug penetration primarily through two mechanisms: electromigration (orderly movement of ions in the presence of an electrical current) and electro-osmosis (a convective solvent flow in the anode to cathode direction that occurs under a physiological condition when the epithelium is negatively charged). Neutral non-ionized molecules are more effectively delivered when anodal iontophoresis was used

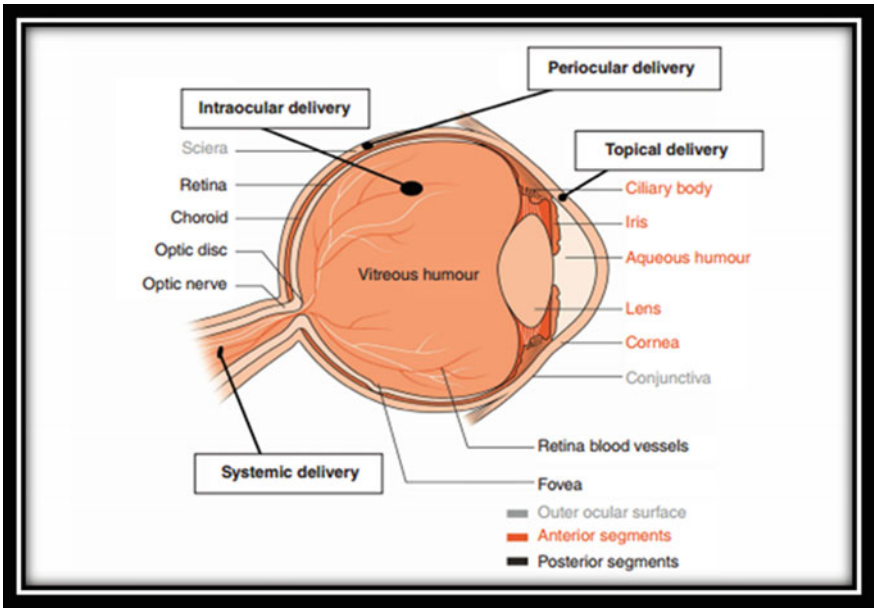

Fig. 10.2 Intraocular drug delivery bypasses anatomic and dynamic barriers of the posterior segment. The placement of a therapeutic substance directly into the vitreous (intravitreal injection) or the space between the retina and RPE (subretinal injection) though invasive, can achieve the highest intraocular bioavailability by bypassing several anatomical and dynamic barriers of the posterior segment. With permission from Shen et al. (2015)

(Kompella et al. 2010). This showed the importance of electro-osmosis on the transport of uncharged drugs. The negatively charged molecules are more effectively delivered when cathodal iontophoresis was used showing electromigration contributes to the corneal penetration of macromolecules (Horwath-Winter et al. 2005).

The drug is applied using an electrode carrying the same charge as the drug. An electrode with the opposite charge is placed elsewhere in the body to complete the circuit. Ionized drug substance through the anode (for a positively charged drug) or the cathode (for a negatively charged drug), or neutral molecules is delivered based on electro-osmosis or solute-associated fluid transport which under the action of the electrical current will penetrate into tissue (Vaka et al. 2008).

Iontophoresis may be an attractive option for patients who are not responsive to eye drop therapy. Iontophoresis technology is used to direct drugs to the target sites, due to ease of use, safe and limited systemic adverse effects. Several preclinical trials have been done successfully to deliver antibiotics such as ciprofloxacin or gentamicin (treatment of pseudomonas keratitis), antifungals, or non-steroidal anti-inflammatory drugs (NSAIDs) or steroids (dexamethasone or methylprednisolone to treat inflammation), antisense oligonucleotides (treatment of angiogenesis), carboplatin (treatment of retinoblastoma), and methotrexate (treatment of intraocular lymphoma) to anterior or posterior segments using trans-corneal or

transscleral iontophoresis. In general, transscleral iontophoresis is more effective for drug delivery to the posterior segment, while trans-corneal is more effective for anterior segment. The increase in the electrical current density and the duration of application enhance the drug penetration. In general currents for up to 3 mA for 20 min or 1.5 mA for up to 40 min are well tolerated without causing adverse effects or obvious blurred vision or pain (Souza et al. 2013).

Recently, iontophoresis method has been used to deliver nanoparticles. Positively charged nanoparticles showed better penetration into the inner tissue than negatively charged nanoparticles. Positive charged interact better with negatively charge cornea and conjunctiva mucosa (Souza et al. 2013).

The Visulex Company use transscleral iontophoresis with the shape of a lens to deliver a drug to posterior segment using 2 compartments: drug ion to be delivered and a counter ion to precipitate the drug. When the current is applied, the counter ion such as calcium and the drug ions penetrate the sclera, they then precipitate and form a depot. This system decreases the need for frequent application. Besides calcium, other ions such as Sn^{+2}, Fe^{+2}, Fe^{+3}, Mn^{+2}, Zn^{+2}, NH^{+4}, organic anion, chelating agents have also been tried in an attempt to decrease the clearance of the drugs from the desired site, so sustained delivery of drug can be achieved.

The Eyegate II Company makes ocular iontophoresis deliver dexamethasone phosphate to decrease sign and symptoms of inflammation in the anterior and posterior segments. The EyeGate II system design for trans-corneal drug delivery consists of an ocular applicator, syringe, adaptor for transferring the drug product from reservoirs to the applicator and generator to provide consistent current to the electrode as shown in Fig. 10.3. Figure 10.4 shows the change in the eye of rabbit after reverse iontophoresis (RI) (Sun et al. 2015).

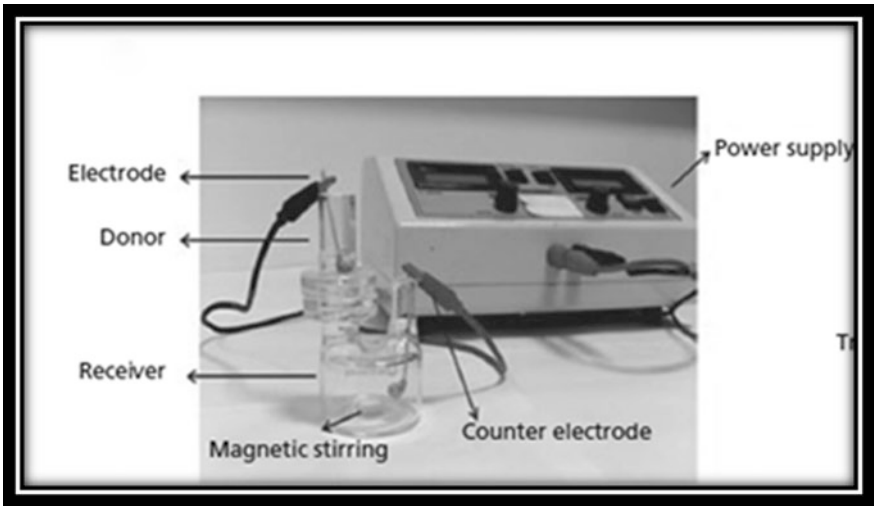

Fig. 10.3 Iontophoresis with electrode, generator, and syringe, with permission from Souza et al. (2013)

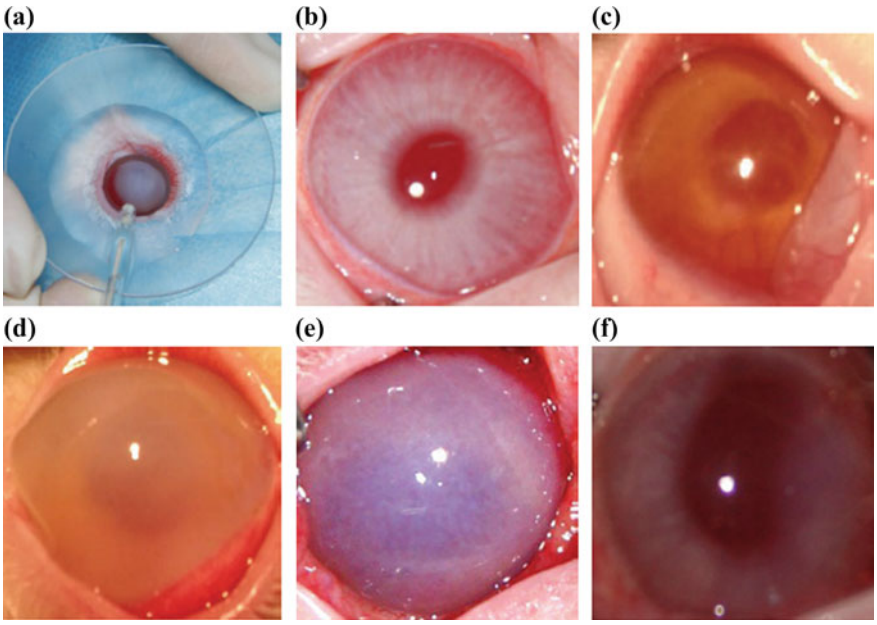

Fig. 10.4 Anterior segment of the eye. **a** Reverse iontophoresis (RI) cathode electrode and the eyecup. The cup is placed on the eye cornea, and Ag/AgCl electrode is inserted into the eyecup to provide the cathode current. **b** The normal rabbit eye with a smooth and transparent cornea, and a transparent anterior segment in the control group. **c** Immediate image after anterior segment iron foreign body model. The anterior segment was brown, and oozing around the pupil was observed. **d** 24 h after anterior iron foreign, there were conjunctival hyperemia, corneal edema, large bullous keratopathy and rust colored pigmentations and anterior segment was brown. **e** Six days with 0 mQA current RI. **f** Six days after 0.4 mA current RI. With permission from Sun et al. 2015 Open access from CCAL

Sonophoresis

Sonophoresis use ultrasound at low frequency (20–100 kHz), medium frequency (400–800 kHz) or high frequency (7000–16000 kHz). Low-frequency ultrasound was more efficient in increasing penetration of hydrophilic ocular drugs. High ultrasound was used to enhance the intrascleral delivery of peptide drugs by enhancing the permeation with no damage to retinal tissue even when using high-frequency ultrasounds (Souza et al. 2013) (Fig. 10.5).

Microneedles

The microneedle is invented to inject a drug into a certain area of the posterior segment of the eye such as suprachoroidal space (SCS). AMD with or without diabetic neuropathy (DN) can cause blindness. Currently, drugs used to treat this

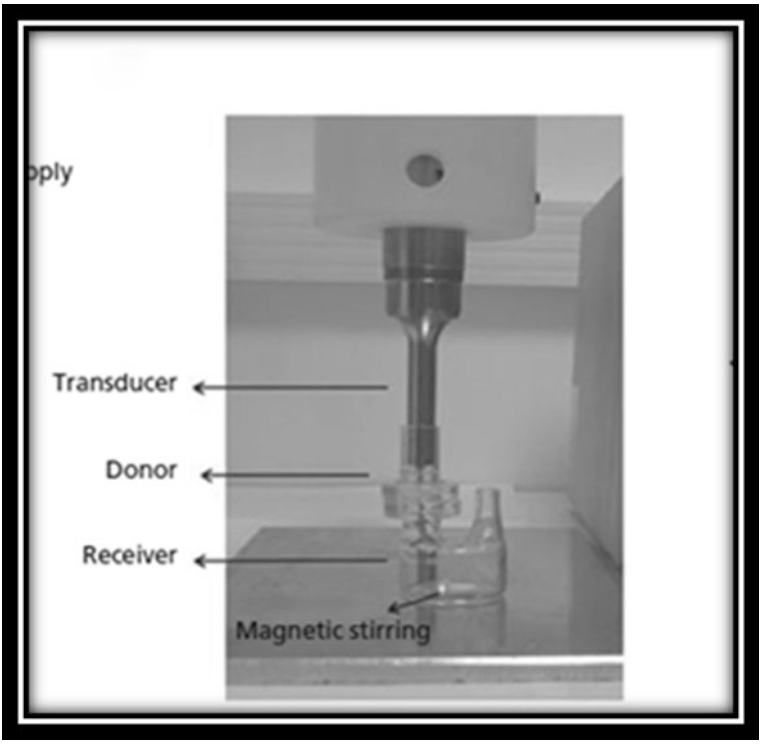

Fig. 10.5 Sonophoresis with an electrode, generator, and syringe. Picture with permission from Souza et al. (2013)

disease are delivered to choroid or retina using a intravitreal method by injecting a liquid formulation into the vitreous or by placing extended release implants in the vitreous (Kim et al. 2007; Lee et al. 2010). This method doesn't provide an effective drug concentration in the intended area of the choroid and retina (Patel et al. 2012).

To target a drug to treat AMD or DN more specifically closer to the choroid and retina, the SCS which is a space located between sclera and choroid can provide higher drug levels in the target tissue. For this reason, the SCS provide a promising site for administration of a drug to treat other disease related posterior segment also. In the past, to access the SCS site, either the surgical procedure or use of a long cannula or hypodermic needles is needed, but this technique is cumbersome. To improve this cumbersome techniques, injection into the SCS using a hollow glass microneedle was invented (Patel et al. 2011, 2012). Figure 10.6 showed the comparison of a microneedle for SCS injection to a 30-gauge hypodermic needle.

Targeting SCS provide accurate dosing and decrease exposure of drugs to non-targeted tissues. In the study using rabbit cadaver, Patel et al. demonstrated that clearance of molecules and particles injected into the SCS occurs at different rates.

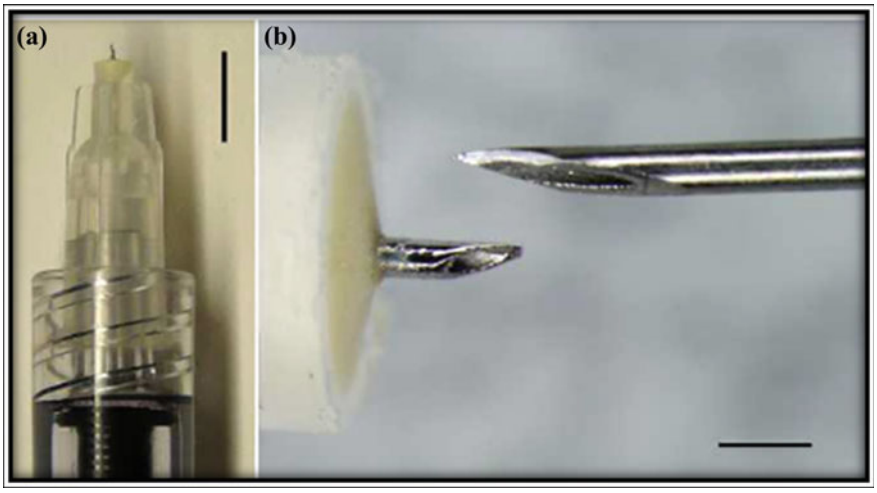

Fig. 10.6 Microneedle for SCS injection. Low magnification view of a microneedle at the end of a syringe (**a**) and high magnification comparison of a microneedle (*left*) to the tip of a 30 gauge hypodermic needle (*right*). *Scale bar* 5 mm (**a**) and 500 μm (**b**). With permission from Patel et al. (2012)

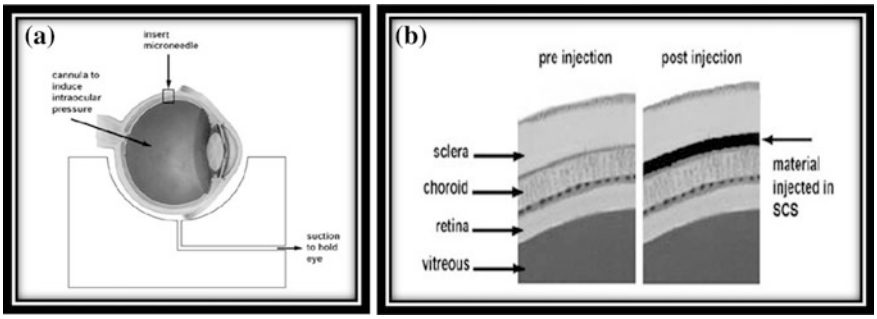

Fig. 10.7 **a** Schematic diagram of the experimental setup used to study suprachoroidal injection in which rabbit eye was placed on a custom-made mold with a channel through which suction was applied to hold the eye in the place. A cannula inserted through the optic nerve of the eye allowed application of intraocular pressure. The microneedle was inserted into the sclera using the custom made insertion device. (**b**) A magnified view of the boxed area in (**a**) shows an idealized schematic of the anatomy of the periocular tissues near the insertion site before and after the proposed suprachoroidal. With permission from Patel et al. (2011)

Figure 10.7 showed the schematic diagram for the microneedle injection. Figure 10.8 Showed rabbit eye tissue after microneedle injection.

Small soluble molecules or macromolecules exhibited a short period of time while nano or microparticles remain in the SCS for months with no sign of clearance. Suprachoroidal injection of drug loaded particles enabled the drug to be

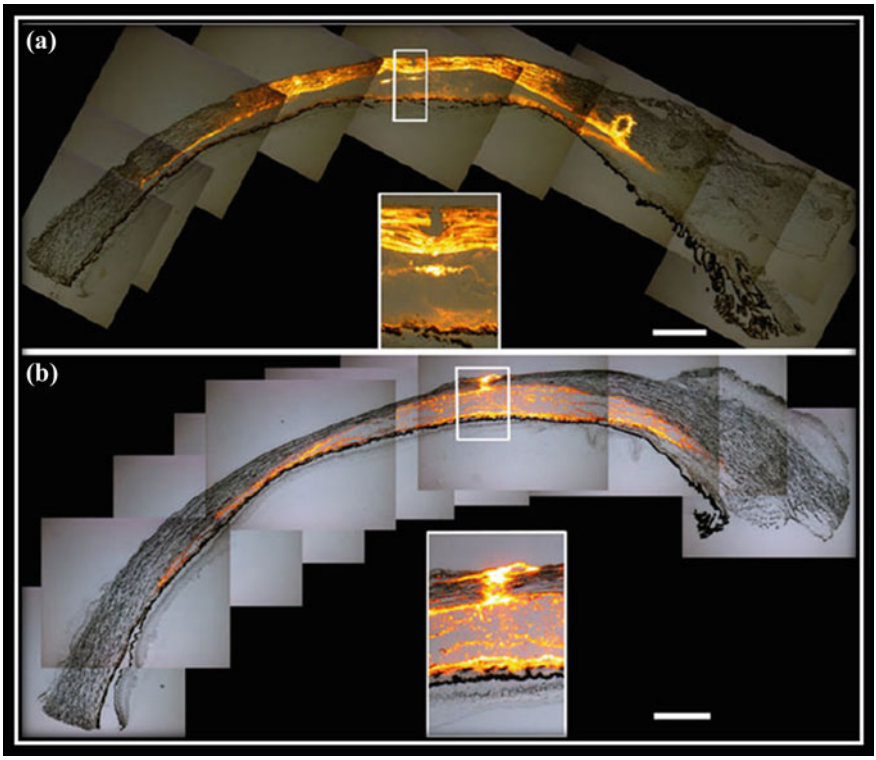

Fig. 10.8 Each of particle size on particle distribution in the eye. Collaged fluorescence microscopy images of tissue cryosections show the delivery of **a** (*top*) 20 nm particles and **b** (*below*) 1000 nm particles into the suprachoroidal space of pig eyes ex vivo. These images show that 20 nm particles spread into the suprachoroidal space and within the sclera. However, the 10,000 nm particles are primarily in the suprachoroidal space. The insertion sites are magnified in the *insets*. *Scale bar* 500 μm. With permission from Patel et al. (2011)

delivered to chorioretinal tissue for as short as half day or as long as several months based on particle degradation kinetics on how the drug is formulated. The use of microneedle causes less trauma to the eye because the needle tract is much shorter and narrower than other approaches and can provide a straightforward way to access the SCS.

Hydrogels

Hydrogels are hydrophilic system composed of polymers which form a three-dimensional (3D) network that water infiltrates and enable the drug to diffuse in and out of the gel. Hydrogels can be used as drug reservoirs and are more

resistant to removal from the eye through blinking because of their viscoelastic properties (Eljarrat-Binstock et al. 2008). A hydrogel is liquid at pH 6 and at room temperature, but undergo gelation at pH 7.4, the natural pH of the tear film. The hydrogel can deliver approximately 95 % of the drug and the drug can stay more than 8 h. in the eye. Different polymers can be blended to improve the hydrogel characteristics. Poloxamers, a thermo-sensitive in situ forming gel has weak mechanical strength; however, by blended poloxamers with polyacrylic acid, alginate, and chitosan, this combination of gel stayed at longer time on the eye surface. Sodium alginate is another polymer that is converted into the gel in the presence of calcium which is present in the lachrymal fluid. Sodium alginate with hydroxyl propyl methyl cellulose (HPMC) was formulated with moxifloxacin to improve sustained release of the drug from less than 4 h (in regular solution form) to more than 10 h in hydrogel form (Yang et al. 2012).

A blend of chitosan with other thermosensitive polymers such as poly-N-Isopropyl acrylamide showed increase permeability of drug such as timolol maleate for the treatment of glaucoma (Kompella et al. 2013). Commercial products known to treat glaucoma such as Timoptic-XE® is based on ion-activated gel that uses gellan gum as the ion-sensitive agent (made by Merck), while Zirgan (Bausch & Lomb) contains polyacrylic acid and ganciclovir as the active compound to treat herpetic keratitis (Yang et al. 2012).

A hydrogel can also be used for replacing nylon suture. Corneal wounds from surgical procedures (transplants, incisions for cataract removal, intraocular lens implantation), ulcer infections and traumatic injuries (laceration, perforation) are usually repaired using nylon suture. Multiple sutures are often needed to realign the edge of damaged tissue in effort to restore the structural integrity of the cornea. However, nylon suture has several disadvantages such as: trauma to corneal tissue, increase in corneal scarring, loose or broken suture, irregular astigmatism, and suturing requires technical skill that can vary widely from surgeon to surgeon. Therefore, an adhesive like hydrogel to replace or supplement sutures in the repair of corneal wound is a preferable technique. Hydrogel network can be formed using: (a) photocrosslinking, in which upon exposure to visible light, the acylated-modified dendritic macromolecules crosslinks to form a hydrogel or (b) nucleophile-electrophile reaction in which the crosslinking can occur at 37 °C under neutral aqueous solutions and chemoselective reaction (Grinstaff 2007). Figure 10.9 shows the hydrogel network. Figure 10.10 shows application of photo-crosslink hydrogel to the laceration followed by irradiation that sealed the wound in rabbit eye. Figure 10.11 shows comparison of the change between suture and hydrogel.

Punctual Plug Drug Delivery System (PPDS)

Punctual plugs (Fig. 10.12) have been used for more than 20 years for symptomatic relief of dry eye syndrome and glaucoma. Punctual plugs used for drug delivery can be made from polymers in a variety of shapes and sizes. The punctual plugs are

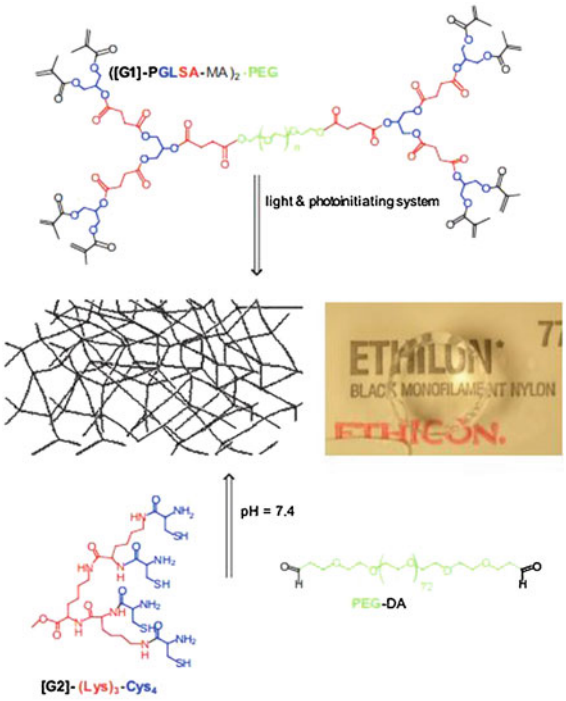

Fig. 10.9 (*Top*) Schematic of photocrosslinking reaction. (*Bottom*) Nucleophile-electrophile reaction. Picture with permission from Grinstaff (2007)

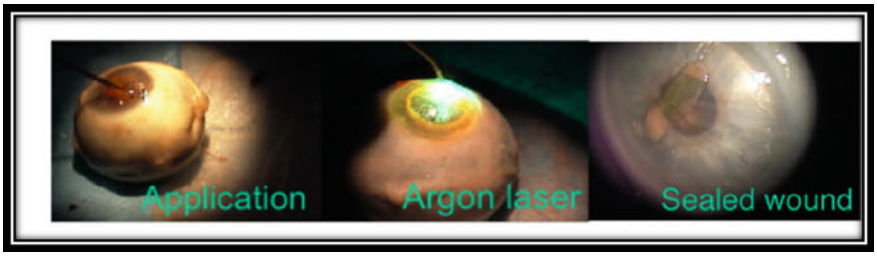

Fig. 10.10 Photographs of the closure procedure for a 4.1 mm full corneal laceration (*left*). Placement of the adhesive solution to the wound (*middle*). Photocrosslinking of the solution to form the adhesive hydrogel seal the corneal laceration (*right*). Picture with permission from Grinstaff (2007)

composed of: (a) cylindrical body containing the drug compound, (b) an optional outer shell made up of material impermeable to the drug and the tear fluid, (c) an optional cap material containing pores, and (d) an optional unit to retain the punctual plug over long period. The bottom end is tapered and narrower to allow

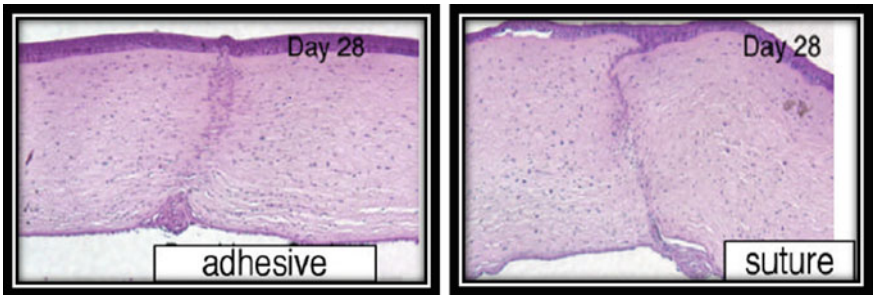

Fig. 10.11 Stains of the repair chicken cornea after treatment with hydrogel dendrimer adhesive and after suture. Picture with permission from Grinstaff (2007)

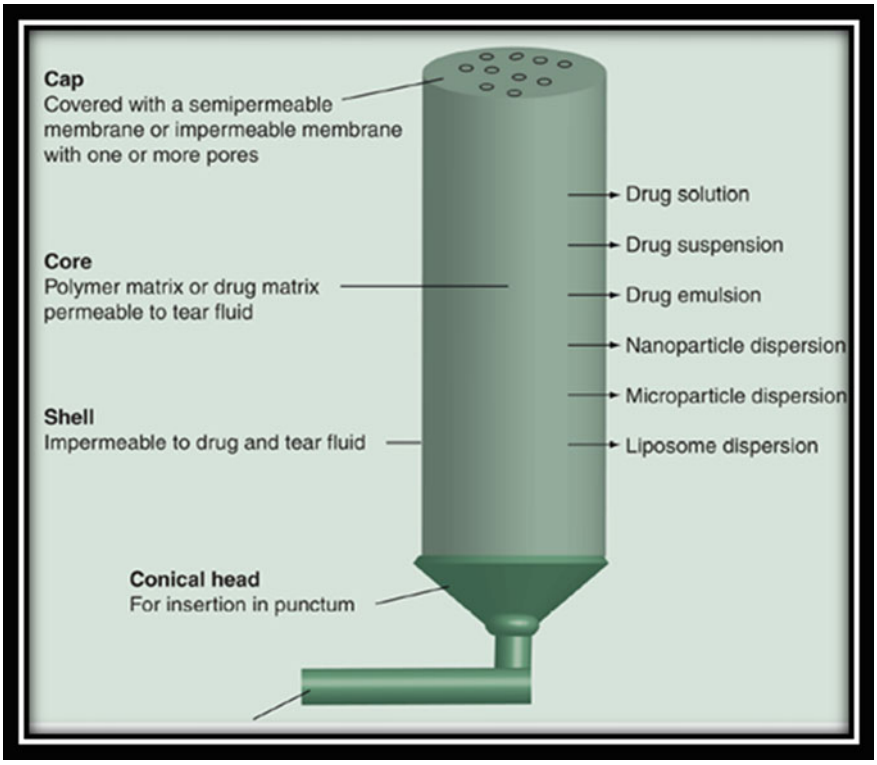

Fig. 10.12 Punctual plug delivery system with various components and drug-loading methods. The scheme captures a variety of technologies that are under development and is not intended to represent any technology completely. With permission from Kompella et al. (2010)

easy insertion into the punctum the head portion is exposed to tear film. The drug is released from a punctual plug by diffusion from the polymeric core to the tear fluid. The drug can be loaded into the central polymeric core as solution, suspension, microemulsions, nanoparticles, microparticles or liposomes with or without an additional polymer matrix (Kompella et al. 2010).

PPDS can be made from silicone, Teflon, hydroxyl ethyl methacrylate (HEM), polycaprolactone (PCL) or polydioxanone. The drug can stay for up to 180 days, after which the plug can be removed. Latanoprost-PPDS has been shown to decrease IOP in glaucoma patients with some adverse effects such as eye itchiness, eye irritation, increased lacrimation and ocular discomfort (Kompella et al. 2010).

Retinal Prosthetics, Optogenetics, Chemical Photoswitches

Retinal degeneration is inherited disorders that are directly or indirectly due to the death of rod photoreceptor cells. Many of these orders are called retinitis pigmentosa (RP), a name that reflects the common disease phenotype of exposed pigmentation from invading retinal pigmented epithelium (RPE) cells. There are over 200 sources of gene defects that cause retina to degenerate, but eventually many RP patients suffer total visual loss (no light perception, NLP) or are reduced to impair bare light perception (BLP) (Nirenberg and Pandarinath 2012).

There are strategies for restoring light-driven signaling with clinical potential: retinal prosthetics, optogenetics, or chemical photoswitches. Argus II retinal prosthetic technology use a stimulation arrayed with 60 platinum electrodes surgically positioned over the inner surface of retina (the epiretinal configuration), coupled to an embedded scleral electronics package via transscleral ribbon cable and driven by a head-mounted camera. This system permits significant recovery of positional, motion, and structural percepts in many patients (Zrenner 2013) (Fig. 10.13).

Optogenetics uses viral delivery of type 1 opsin genes to restore light responses in the survival neurons. Genes for various type 1 opsins are packed with promoter or enhancer elements into AAV viral gene that delivers by subretinal or intravitreal injection as non-replicating, long expression gene in animal neurons. By hijacking existing trafficking mechanisms, the translated proteins are successfully delivered to the cell membrane thus making the residual retinal cells become photosensitive again. Optogenetics could provide the ultimate in high-resolution vision due to the long persistent gene expression in animal models; however, optogenetics remains challenging to be implemented in human eyes with large volumes, complexity of the disease, and physical barriers for the viral penetration (Busskamp et al. 2012; Marc et al. 2014).

Chemical switchers use small molecules such as acrylamide-azobenzene-quaternary ammonium (AAQ) or better with diethylamino-azobenzene quaternary ammonium (DENAQ) that modulates neuronal electrical activity. Chemical photo switches act rapidly after a single intravitreal injection with no sign of toxicity. Targeting high-density ganglion cells with chemical photoswitches may rapidly

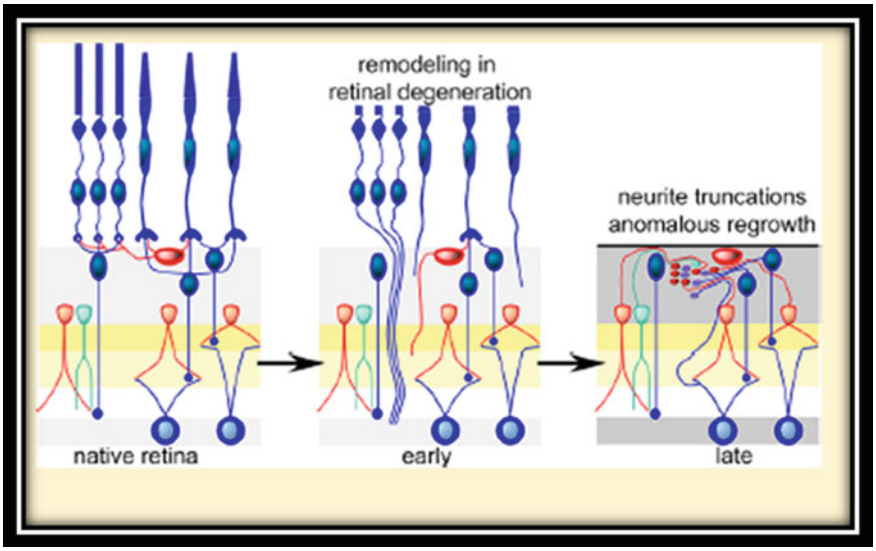

Fig. 10.13 Cellular composition of the retina and the phases or remodeling associated with retinal degeneration. With permission from Marc et al. (2014)

generate a high-resolution vision, and develop photo switches with longer physiological half-lives or delivery strategies providing long-term depots (Marc et al. 2014; Toschitsky et al. 2014).

Summary

Gene therapy has advanced since its introduction almost 20 years ago. Currently, there are over 100,000 articles in gene-based therapy for the treatment of many diseases in some clinical trials and laboratory animals. Although ocular gene therapy is still in its early stages of development, the potential of gene-based intervention for treatment of blindness, corneal diseases, abnormal wound healing, are progressing. Ocular drug delivery using iontophoresis improved electrical current density and application time which increase bioavailability of macromolecular drugs or drugs formulated as nanoparticles to the anterior and posterior segments of the eye. Transscleral iontophoresis is more suitable for posterior segment whereas application through the cornea is more effective for the anterior. Sonophoresis used ultrasound intensity and frequency improved drug permeability to corneal and scleral. Punctual plug using latanoprost to treat ocular hypertension and open angle glaucoma are in phase 2 clinical trials.

Some of the new drug delivery systems in the developmental stage are listed in Table 10.1

Table 10.1 Summary of drug delivery technologies in development (Chen 2015)

Technology	Description	Company	Phase	Indication
Punctual plug	Drug loaded polymeric, biodegradable, reside in puncta to release drug over time, non-invasive, focus on anterior diseases	Mati Therapeutics Ocular Therapeutix	2 3	Glaucoma Post-operation inflammation, pain, allergic conjunctivitis
Implants				
Polymerics	Biodegradable, implanted in subconjunctival or invitreal to release drug over time, invasive, focus on posterior diseases	pSivida, Allergan	2 2 1 3	Posterior uveitis, glaucoma, atrophy, retinitis pigmentosa, macula-off retinal detachment
Refillable	Refillable, non-degradable, subconjunctival to release drug over time, initial invasive, refillable less invasive, focus on posterior diseases	Genentech Replenish	1 1	Wet AMD, DME
Encapsulated cells	Reservoir, invasive, non-biodegradable, focus on posterior diseases	Neurotech Pharmaceuticals	2, 2, 1	Retinitis pigmentosa, macular telangiectasia type 2, atrophy, wet AMD, glaucoma, neuropathy, optic nerve stroke
Topical inserts	Soft elastomers, non-degradable, rest under eyelids over sclera to release drug over time, non-invasive, focus on anterior segment	ForSight Vision5, Amorphex Therapeutics	2, Preclinical	Glaucoma
Contact lens	Drug containing soft contact lens, non-degradable, contact lenses with drug reservoir that drug release over time, non-invasive, focus on anterior segment	Various research groups	Preclinical	Glaucoma
Iontophoresis	Wearable electrical device to drive drug into ocular tissue, non-invasive, focus on anterior and posterior diseases	EyeGate Pharma	3	Anterior uveitis, dry eye, cataract surgery

(continued)

Table 10.1 (continued)

Technology	Description	Company	Phase	Indication
Gene therapy	Viral vector-based delivery, injected to deliver genetic material, invasive, focus on posterior diseases	Spark Therapeutics, Avalance Biotechnologies, Genzyme, Oxford BioMedica	1, 2 2 1 1	Choroideremia, Wet AMD, LCA, Stargardt disease, Usher syndrome
Particulate systems	Polymeric/liposomal drug crystal, biodegradable, topical or injectable, focus on anterior and posterior diseases	Kala Pharmaceuticals	3 2	Ocular inflammation, post cataract surgery, dry eye

Abbreviation LCA Leber congenital amaurosis; *DME* Diabetic macular edema; *AMD* Age-related macular degeneration

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