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Review Article

# Key Therapies (Nano-Ophthalmology, Polymers, Lipids, Supramolecules and Stem Cells) for Anterior and Posterior Ocular Diseases: An Overview

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## Abstract

Recent advances in polymers, supramolecules, nanomaterials and stem cells fields have found tremendous growth in diagnosis and therapeutics of both anterior and posteriorocular disorders. Most of the research articles and reviews have focused on individual technologies.

The present review article has tried to compile some of the most recent advances accomplished for anterior and posterior ocular disorders using polymers, supramolecules, nanomaterials, lipids and stem cells. The author hopes to help researchers by providing with a few examples of latest research including recent stem cell and newly developed "Theranostics" field to realise safe and efficacious methods for the treatment of ocular disorders.

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## Introduction

### Part I: Eye Structure: Challenges & Opportunities

The eye anatomy, and ocular diseases and treatments has been studied for centuries and reported in multiple books and articles [1-4]. Anatomically, the eye globe is divided into Anterior Segment (AS) and Posterior Segment (PS), respectively occupying one-third and two-thirds of ocular tissues. The AS segment contains the cornea, conjunctiva, iris, ciliary body, tear film & aqueous humour and the PS segment encompasses the sclera, choroid, Bruch's membrane, retina & vitreous humour. The eye is kept firm by a clear fluid flowing continuously in and out of the anterior chamber, which helps to nourish nearby tissues with oxygen, sugars and other nutrients. The lens is a clear structure at the front of the eye and helps to focus light, or an image on the retina which is a thin layer of neural tissue located back of the eye. An Iris controls the pupil to control the light intake from surrounding. The layer between the retina and the blood vessels underneath (the choroid) is called "The Retinal Pigment Epithelium (RPE)" which helps to transport oxygen, sugar and other nutrients up to the retina and remove waste products such as cellular debris from the tips of the photoreceptors towards the choroid during the renewal process. At the retina, light is converted into electrical impulses by the light-sensing cells or photoreceptors. Photoreceptor cells exhibit either rod or cone morphology. Rods are concentrated along the outer perimeter of the retina to assist to see images in the peripheral vision and also in dark and dimly lit environments. Around 90-120 million rods and 4-5 million cone cells are present in the retina. Rods are more sensitive than cones for light and dark changes, shape and movement but are not colour-sensitive. Cones are concentrated in the "macula" - centre of the retina and help to visualise fine details including colours. Then visual centres in the brain interpret the information received from the retina and enable human to visualise the surroundings. The cornea cannot change its curvature but the curvature of the lens can change through the process called "accommodation" (Figure 1). Parallel rays from distant objects are generally converging onto the retina. If an object is moved closer to the eye, and if the lens does not change its curvature, then the sharp image will remain behind the retina and the brain visualise a blurry image (Figure 1a). If the lens changes it curvature (become thicker), light rays will converged on the retina, and the brain will visualise image clearly (Figure 1b). Also the anatomical components of the eye are provided in Table 1.

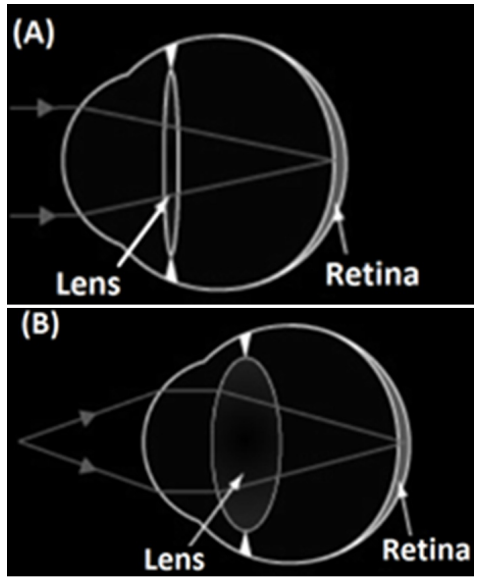


**Figure 1:** Accomodation (A) Thin curvature leading blurring image and (B) Thick curvature leading clear image.

| Component | Characteristics |
|---|---|
| Anterior chamber | The fluid filled space between the iris and the inner surface of the cornea |
| Angle of the anterior chamber (iridocorneal angle) | The width of iridocorneal angle affects the drainage rate of aqueous humour from the anterior chamber into the trabecular meshwork. A narrow or closed angle reduces the drainage of aqueous humour. |
| Aqueous humour | A transparent fluid that fills the anterior chamber of the eye. Its production is constant therefore drainage is the key determinant of intraocular pressure. |
| Choroid | A vascular layer between the sclera and retina that provides oxygen and nutrition to the retina |
| Ciliary body | The circumferential tissue, anterior to the retina, composed of ciliary muscle and ciliary processes that change the shape of the lens while adjusting the focus (accommodation process) and also produce aqueous humour. |
| Conjunctiva | A thin, and clear vascular epithelial layer and sub-epithelial tissue that covers the sclera and inside of the eyelids. Inflammation, conjunctivitis, causes vascular dilatation and can produce significant oedema of this tissue, chemosis. |
| Cornea | The transparent and convex layer of the eye present in front of the iris, pupil and anterior chamber. It is a mechanical barrier with its curvature helps most of the focusing power of the eye. |
| Iris | A thin, opaque (coloured), circular structure that controls the size of the pupil upon the exposure of light and control the amount of light that reaches the retina. |
| Lens | A biconvex structure behind the iris that helps to refract light to accurately focus on the retina. |
| Limbus | The border between the sclera and the cornea. |
| Sclera | The opaque protective outer layer of the eye (the "white of the eye") that covers everything (except the cornea). |

**Table 1:** Anatomical components of the eye.

# Part II: Types of Ocular diseases

Ocular diseases and drug delivery in ASs [5,6] are widely studied and assumed to be easily curable as compare to posterior ocular diseases. Ocular diseases in PSs [7,8] such as age-related macular degeneration (AMD), cytomegalovirus retinitis, diabetic retinopathy (DR), posterior uveitis and retinitis pigmentosa are difficult to treat and may lead to blindness. The repeated intravitreal injections for PSs may result in ocular complications [9,10]. The PS treatment needs a suitable drug delivery system that can provide the effective dose at the affected site with minimum systemic and local side effects.

## Epidemiology Studies

### Blindness and low vision

Cataract and under-corrected refractive errors are causing blindness in Asian countries [11]. AMD is a leading cause of blindness in Caucasians, and cataract and glaucoma are causing blindness in black people in Western countries [10]. Glaucoma is the principal cause of both unilateral and bilateral blindness in Singapore and Mongolia [12,13], AMD and myopic degeneration are causing blindness in Taiwan [14]. However, after refraction, more than 70% of subjects have improved their vision by at least one line and more than 30% by three lines [15,16].

### Age related cataract

A cataract is prevalence in 35% in 40+ years Chinese in Singapore [17]. High prevalence of pterygium [18] and cortical [19] cataracts in Singaporeans can be due to ultraviolet radiation exposure. Other risk factors identified for Asian cataract are: female sex, lower socio-economic status, diabetes mellitus, cigarette smoking and lower body mass index [20-25].

### Myopia and other refractive errors

The myopia is prevalence in 40+ years Singaporean Chinese adults which is nearly twice the rates in similarly aged Caucasians in Western countries [26,27]. Also, the higher prevalence of myopia is found in children and young adults in Singapore, Taiwan and Hong Kong [28-30] as compared to children in Western countries [31]. In comparison, the rates of myopia experienced by adult populations of other Asian countries such as India [32,33], Beijing [34], Taiwan [35], Bangladesh [36], and Mongolia [37] are comparable with Western Caucasians adult populations.

### Glaucoma

The prevalence of Primary Open Angle Glaucoma (POAG) is four times higher in black population (4-5%) as compared to Caucasians population (1.1%) in Western countries [37]. Half of the world's 70 million glaucoma patients reside in Asia [38] including 10 million in China [39]. However, the glaucoma is in the range of 2.1% -5.0% in rest of the Asian population [40-49]. POAG is more prevalent than Primary Angle Closure Glaucoma (PACG) in China. Additionally, the overall prevalence of PACG in Chinese population in Singapore and Mongolia is higher compared to Western population [50,51], possibly due to differences in anterior chamber and angle anatomy [52,53].

### Age related macular degeneration

Both early and late AMD are more prevalent in Caucasians than black people [54]. An early AMD is diagnosed clinically in 2.7% and late AMD in 0.6% of around 5000 Indian participants (40+ years) [55]. AMD is less prevalence in Japanese population than Caucasians due to the high antioxidant Japanese diet [56]. Hypertension is found to be a significant risk factor of AMD in men but not in women [57] whereas cigarette smoking is the only significant risk factor found for five year incident AMD [58].

Above studies provide understanding about the widespread issues of anterior and posterior ocular diseases and show an urgent need of better treatment regimes. The present review provide an overview of the latest progresses and trends in ocular drug delivery systems for treating anterior and posterior ocular disorders.

# Part III Key Therapies

## Possible routes of administration

Several ocular drug delivery methodologies are developed based on the target site (anterior or posterior). In general, topical and sub-conjunctival drug delivery routes are used for the anterior eye segment whereas intravitreal injections, periocular routes (e.g. retrobulbar, peribulbar, sub-tenon and sub-conjunctival routes) and implants are used for the posterior eye segment [59,60]. Topical routes are generally patient compliant routes as compared to injections and implants which are invasive, not comfortable and pose the risk of retinal detachment (RD) and cataracts [61,62].

## Challenges of Ocular Drug Delivery

Targeted ocular drug delivery needs to overcome a few challenges due to complex eye structure, tear dynamics, tissue and ocular-blood barriers. The eye has four potential target sites: (i) the pre-ocular structures in the front of the eye (e.g. conjunctiva, eyelids); (ii) the cornea; (iii) the anterior and posterior chamber and associated tissues; and (iv) posterior eye segment (e.g. retina, vitreous cavity) [63].

## Factors affecting drug delivery to anterior segment of eye

The drug delivery to the ASs involves pre-ocular, corneal and anterior/posterior regions. The tear dynamics creates a lively environment for anterior eye structures. The solution drainage rate constant from the pre-corneal area is found to be 1.45 $min^{-1}$. The rate of drug loss from the eye surface can be 500 -700 times greater than the rate of drug absorption into the anterior chamber due to which only less than 5% of the applied dose reaches the intraocular tissues [64,65]. The rate of aqueous humour turnover is around 1.0% - 1.5% of the anterior chamber volume per minute which equates to total turnover of 1.5 - 2 h. The drug can be delivered to the anterior chamber via either trans-corneal permeation from tears or blood-aqueous barrier from the systemic circulation. The drugs distribution volume in anterior chamber is in the range of 150-3000 microL and the drug clearance rates are in range of 1-30 microL/min [64]. Cornea is the major route of anterior drug absorption. There are three corneal layers: epithelium, stroma & endothelium and all of them play a distinct role in trans-corneal drug permeability [66]. The corneal epithelium is the major limiting barrier in trans-corneal drug absorption and the drug permeation across corneal epithelium is determined by passive diffusion, facilitated diffusion or active transport. However, passive permeation of drugs through cornea is dependent on the hydrophobicity of the drug molecule. The passive permeation of lipophilic drugs occurs via the transcellular pathway, whereas that of hydrophilic drugs occurs via the tight junctions regulated paracellular pathway. Overall, drug permeation across the corneal epithelium is $10^{-7}$ - $10^{-5}$ cm/s. The hydrophilic stroma exhibits a barrier to lipophilic substances which move along the transcellular route through the epithelium. Finally, the corneal endothelium monolayer helps the drug permeation and participates only marginally in the corneal barrier function. Clinically used drugs are generally small molecular weight molecules and lipophilic in nature. Therefore, the trans-corneal route of drug absorption is currently in demand despite that the trans-corneal rate constants are relatively low ($1\text{-}5 \times 10^{-3}$ $min^{-1}$) [67-70].

The surface area of the human conjunctiva is approximately 17-fold larger than the human corneal surface area. The conjunctival epithelium is comprised of 2-3 cell layers with tight junctions and acts as the barrier to the passive permeation of hydrophilic molecules found at the apical surface of these cells. However, human conjunctiva is between 2-30 fold more permeable to drugs than the cornea [71]. The conjunctival epithelium has 2 times larger paracellular pores and 16 times higher paracellular pore density than the cornea. The total paracellular space in the conjunctiva was estimated to be 230 times greater than that in the cornea [72].

Recently, the absorption of hydrophilic drugs and large drugs molecules through the conjunctival-scleral pathway is becoming an area of interest for the intraocular delivery of new biotech-drugs such as proteins, peptides and nucleic acid based therapeutics [68] to the retina and vitreous[10]. Permeability of hydrophilic drugs through the sclera is comparable to that of the corneal stroma hence hydrophilic drugs may diffuse through the scleral matrix pores more easily than lipophilic drugs. Also, the permeability of drug molecules across the sclera are inversely proportional to the molecular radius as well as lipophilicity of drug molecules [70]. The charge on the drug molecule can also influence its permeability across the sclera as positively charged drug molecules can exhibit poor permeability due to their binding to the negatively charged scleral matrix [71,73].

## Factors affecting drug delivery to posterior of eye

The blood-ocular barriers hinder the effective drug delivery to the PS from the systemic blood circulation. Additionally, the blood-aqueous barrier is located in the AS of the eye which limits the permeation of drugs from the blood into the aqueous humour. Furthermore, the blood-retinal barrier (BRB) restricts the drugs delivery from blood into the retina which is an inward movement following periocular or systemic drug administration and an outward movement after intravitreal drug administration [70,74]. Moreover, retinal layered structures restrict the drug permeation from the vitreous humour across the retina [75]. Due to all these challenges, the most common method for the posterior drug delivery is the use of ocular injections. Although intravitreal injection provides sufficient amount of the drug in the PS of the eye, it also brings in the highest risk of ocular complications. However, the risk is lower with periocular (e.g. sub-tenon) drug administration. Due to the invasive nature of the injection, it is important to optimise drug formulations to control the appropriate therapeutic drug concentration over prolonged periods and minimize the number of injections to improve patient's compliance [76-79].

## Nanomaterials based ophthalmic drug delivery (Nano-ophthalmology)

Recently, a new field of "nano-ophthalmology" has been developed to utilise the applications of nanomedicine to ocular diagnosis and treatment and enhance the efficacy of eye therapy and transform clinical ophthalmology [80,81]. Zou *et al.* [82] have summarised the use of nanoparticles (NPs) in ocular disease treatment (Figure 2). Ocular drug delivery nanosystems can be prepared as aqueous-based ophthalmic colloidal dispersions and used in eye drops or eye injections. Solutions, ointments and suspensions are accounted for more than 90% of all current ophthalmic formulations in USA. However, only 5% of drugs administrated by eye drops are bio available. The incorporation of drugs into specially designed nanocarriers can lead to the improved biopharmaceutical properties such as prolonged retention at the site of application. These systems can be used to develop simple and inexpensive sterile production with the possibility of sterile filtration due to its small particle size (usually less than 100 nm) and help to enhance ocular bioavailability [83-87]. However, nanosystems are difficult to commercialise due to the manufacturing cost, production scale up issues, regulatory issues and patient compliance (e.g: vision interference and discomfort). Some of nanocarriers developed to bypass and/or transport the drugs to the anterior and posterior segments of the eye are NPs [64,83,88,89], nanosuspensions [90,91], solid lipid nanoparticles (SLN) [92], nanostructured lipid carriers [93], liposomes [94], niosomes [95], cubosomes [96], microemulsions [97,98], dendrimers [99] and polymeric micelles [99-104]. Some of the important nanosystems are as follows.

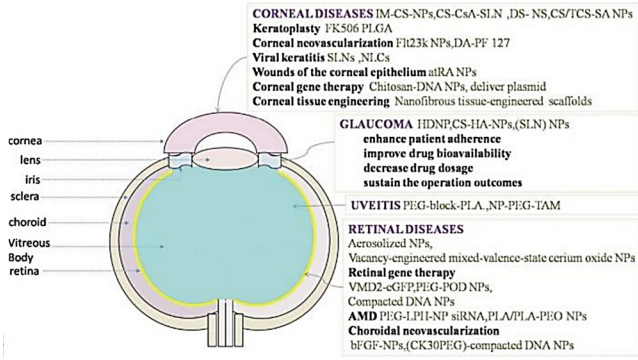


**Figure 2:** Use of nanoparticles of ocular disease treatments. Source: Reference 84. Copyright International Journal of Ophthalmology Press, 2016.

## Polymer NPs based ophthalmic drug delivery

Mahaling and Katti [105] have demonstrated that surface properties of nanoparticles (including polymeric) and penetration enhancers can be used to improve bioavailability in eye tissues. Wood *et al.* [106] demonstrated mucoadhesion property of Polyacryl-cyanoacrylate (PACA) NPs by adhering them to the corneal and conjunctival surfaces. PACA has the ability to entangle in the mucin matrix and form a noncovalent or ionic bond with the mucin layer of the conjunctiva. Polyalkyl-cyanoacrylate loaded with Betaxolol [107] and amikacin sulfate [108] has showed good result. PACA based NPs and nanocapsules have been shown to improve and prolong the corneal penetration of hydrophilic and lipophilic drugs. However PACA-NPs can cause disruption to the corneal epithelium cell membrane [109] so it will be difficult to commercialise these particle based drug delivery. Poly-€-caprolactone (PECL) nanocapsules have used for ocular drug delivery [110,111]. PACA-NPs have exhibited properties of biodegradation and bio adhesion. Marchal-Heussler *et al.* [111] have compared NPs prepared by using PACA, PECL, and polylactic-co-glycolic acid with betaxolol as model drug and found that the PECL NPs yielded the highest pharmacological effect due to the agglomeration of these NPs in the conjunctival sac. Nanocapsules for the topical ocular delivery of cyclosporin A (CyA) comprising an oily core of propylene glycol diester of fractionated vegetable (Coconut oil) fatty acids C8 and C10 (trade name: Miglyol 840) and a PECL coating increased the corneal levels of the drug by 5 times as compared to the oily solution of the drug when administered to the cul-de-sac of fully awake New Zealand white rabbits [112]. PECL nanocapsules also demonstrated increasing the ocular availability of hydrophobic drugs such as metipranolol [110] and betaxolol [111] while suppressing their systemic absorption. Moreover, PECL nanocapsules are specifically assimilated by the corneal epithelium cells without damaging the cell membrane [112] therefore PECL nanocapsules can be used to deliver hydrophobic drugs.

Eudragit® (RS100, RS, and RL100, RL), a class of acrylate polymers developed by Evonik can help to prolong the drug release and improve ocular availability of the drug [113]. Their nanoparticle suspensions are used for the ophthalmic release of nonsteroidal anti-inflammatory drugs such as ibuprofen, flurbiprofen and found to be devoid of any irritant effect on cornea, iris, and conjunctiva [114,115]. Polybutylcyanoacrylate (PBCA) NP delivery system for pilocarpine nitrate is compared with its solution for pharmacokinetic and pharmaco-dynamic aspects with respect to the glaucoma treatment [116]. Authors [116] found that PBCA, NPs help the prolongation of pharmaco-dynamic effects such as miosis and an elevated intra-ocular pressure (IOP) reduction at the lower drug concentrations as compared to the standard solution. Diepold *et al.* [60] used PBCA NPs loaded with pilocarpine to study the aqueous humour drug levels and the IOP lowering effects using three models (the water-loading model, the alpha-chymotrypsin model, and the betamethasone model) in rabbits and found that PBCA NPs enhance the miotic response by 33% with an increase in miotic time from 180 minutes to 240 minutes as compared to the control solution. Acyclovir-loaded PEG-coated polyethyl-2- cyanoacrylate (PECA) nanospheres prepared using the emulsion polymerization technique has showed an increase in drug levels in the aqueous humour compared to the free drug suspension in the rabbits [117]. Agnihotri and Vavia [118] have prepared nanoparticle suspensions (NS) from biodegradable polymers such as poly (lactide-co-glycolide) and poly (lactide-co-glycolide-leucine) and loaded with diclofenac sodium and found that these NS are devoid of any irritant effect on cornea, iris and conjunctiva until 24 hours after the application.

The cornea and conjunctiva have a negative charge and cationic polymeric NPs such as chitosan (CS) NPs may interact intimately with these extra ocular structures that will help to increase the concentration and residence time of the associated drug [119]. CS has exhibited acceptable biocompatibility and biodegradability [120,121]. Moreover, CS-coated nanocapsules are found to be more efficient at enhancing the intraocular penetration of some specific drugs [122,123]. CS NPs can be prepared under mild conditions and encapsulate macromolecular bioactive compounds and can be used for drugs, proteins, genes or hydrophobic molecules that are poorly transported across epithelia. The potential of CS NPs for ocular drug delivery and their interactions with ocular mucosa in vivo and also toxicity in conjunctival cell cultures are well-studied and found that CS NPs are able to interact and adhere to the ocular mucosa for extended periods of time. Therefore, CS NPs can be used for the control release of drugs to the ocular surface [124]. Moreover, CS NPs can penetrate conjunctival epithelial cells and found to be well tolerated by the ocular surface tissues of rabbits and suited for a drug delivery system for the ocular mucosa [125]. Furthermore, a recent study on the effect of acyclovir loaded CS NPs in rabbits eye demonstrated that CS NPs facilitated absorption of acyclovir compared to marketed products [126].

Agban *et al.* have developed NP cross-linked collagen shields for sustained delivery of pilocarpine hydrochloride to treat glaucoma [127].

# Nanowafers

To achieve the therapeutic efficacy of ophthalmic drugs and improve patient compliance, the controlled drug delivery system is needed to achieve a long drug residence time on the ocular surface, desired drug bioavailability and desired local tolerability of the drug. It becomes tedious to administer a drug for 4-8 times a day for a week to treat a chronic disease. Therefore a novel sustainable drug delivery system is required to deliver the therapeutically effective concentrations of the drug for a longer duration of time (from a day to a week). To address this unmet need, Yuan *et al.* have recently developed a novel nanowafer system [128]. The nanowafer fabrication and ocular drug delivery concept is explained in Figure 3. Figure 3 depicts the concept where the polymer nanowafer loaded with a drug (doxycycline) is implanted on the cornea (Figure 3a) and the drug

molecule diffused into the cornea (Figure 3b). Figure 3c depicts the Atomic Force Microscopy (AFM) image of a nanowafer comprised of an array of 500nm diameter nano-reservoirs. Figure 3d depicts the fluorescence micrograph of a nanowafer filled with doxycycline. A typical circular nanowafer is depicted in Figure 3e. Four different polymers, Poly (Vinyl Alcohol) (PVA), polyvinylpyrrolidone (PVP), (Hydroxypropyl) Methyl Cellulose (HPMC), and Carboxymethyl Cellulose (CMC) are used in nanowafer fabrication [129,130] because these polymers exhibit water solubility, biocompatibility, mucoadhesive, transparency, and film-forming properties and the ability to readily adhere to a wet mucosal surface and conform to the curvature of the eye [131]. A systematic screening of a series of polymers and confirmed that PVA is the best non-immunostimulatory polymer that can be used in the fabrication of ocular drug delivery nanowafers, and worked well with the drug axitinib synergistically [128]. Figure 4 represents an example of wound healing from ocular burn injury using the Axitinib nanowafer treatment with time (using the corneal fluorescein staining method) [128]. The effect of nanowafers containing 5 µg of axitinib (Axi-5-NW) on the corneal wound healing process is studied by corneal fluorescein staining and found that the corneal wound healing is unaffected by the Axi-5-NW treatment, and a normal healing pattern is observed. The rate of epithelial closure of the corneal surface is almost the same in both Axi-5-NW and axitinib eye drop (Axi-eye drop) treated groups, and complete corneal surface recovery is observed by the ninth day. However, the ocular burn (OB) controls and PVA nanowafer (PVA-NW) treated groups demonstrated a slightly slower recovery, and complete healing is observed by the 11$^{th}$ day (Figure 4). These results confirmed that axitinib is nontoxic and has not affected the epithelial recovery of the OB-induced corneas, unlike other antiproliferative agents such as mitomycin C and 5-fluorouracil (which are prone to retarding the corneal epithelial recovery) [132].

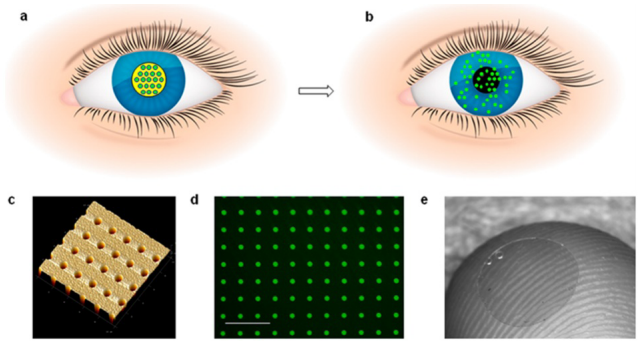


**Figure 3:** Ocular drug delivery by nanowafer. **(a)** Schematic of the nanowafer instilled on the cornea. **(b)** Diffusion of drug molecules into the corneal tissue. **(c)** AFM image of a nanowafer demonstrating an array of 500 nm diameter nano-reservoirs. **(d)** Fluorescence micrograph of a nanowafer filled with doxycycline (scale bar 5 µm). **(e)** Nanowafer on a fingertip. Source: Ref 124. Copyright © 2015 American Chemical Society.

## Lipid based ophthalmic drug delivery

Lipids can naturally form nano-films and nano-structures, micelles, reverse micelles, and liposomes. Lipid NPs such as SLNs and lipoplex (liposome-polycation-DNA complex) are used to deliver drugs and genes to ocular tissues [133]. SLNs are spherical in shape with an average diameter between 10 nm-1000 nm and can encapsulate lipophilic molecules in the solid lipid core matrix. The lipid core of SLNs is stabilized by surfactants and the lipid component may be comprised of a triglyceride, diglyceride, monoglyceride, fatty acid, steroid, or wax

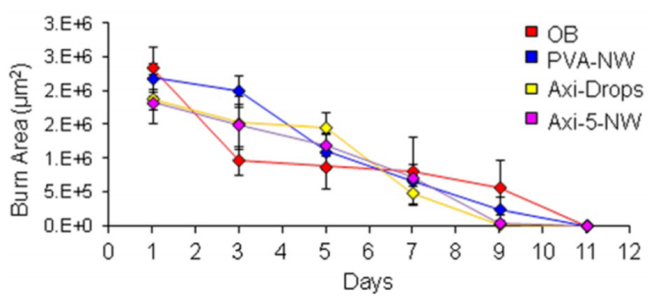


**Figure 4:** Axitinib nanowafer treatment to improve the corneal wound healing after ocular burn injury. Plot demonstrating corneal surface healing as a measure fluorescence intensity. n = 3 animals. All error bars represent standard deviation from the mean. (OB is ocular burn model, PVA-NW is PVA nanowafer, Axi-Drops and Axitinib eye drops and Axi-5-NW is 5microgram Axitinib based PVA nanowafer) Source: Ref 124. Copyright © 2015 American Chemical Society.

[133]. Cationic liposomes and an anionic protamine-DNA complex can electrostatically assembled to form the liposome protamine/DNA lipoplex (LPD) [134]. The LPD NPs contain a highly condensed DNA core surrounded by lipid bilayers. SLNs are used to deliver drugs to the cornea whereas LPD NPs are used for drug delivery to the retina. SLNs and nanostructured lipid carriers (NLCs) have been used to improve the ocular delivery of acyclovir into excised corneal tissue [135]. Methazolamide (MTA), an anti-glaucoma drug exhibits side effects upon systemic administration while providing insufficient ocular therapeutic concentrations [136]. SLNs containing MTA have been shown to have higher therapeutic efficacy at low doses with more prolonged effects than those of the drug solution itself [136]. Lipid NPs have also used for the ocular delivery of anti-inflammatory drugs [137]. SLNs do not show bio-toxicity but enhance the corneal absorption of drugs and improve the ocular bioavailability of both hydrophilic and lipophilic drugs [138]. Cyclosporine is commonly prescribed for chronic dry eye, caused by inflammation, and cyclosporine A-loaded SLNs provide improved drug efficacy to rabbit eyes [139,140]. Moreover, liquid lipid has also been incorporated into lipid NPs to enhance ocular drug delivery and resultant particles are tested on human corneal epithelial cell lines and rabbit corneas [141]. These NPs have found to improve the ocular retention and penetration of therapeutics [141]. Surface-modified SLNs improve the ocular bioavailability of drugs to bioengineered human corneas [142]. SLNs have also been used for retinal gene therapy and intracellular trafficking in RPE cells [143].

## Polymers for Drug Release for Ocular Treatment

### Polymer based therapeutic contact lenses

A contact lens is a prescription medical device manufactured from high-grade plastic polymers to aid the vision and deliver medication to the eyes [144,145]. The contact lens rests on the cornea and helps to provide clear vision by bending light rays to focus images on the retina. Some of the physicochemical properties of polymer used for contact lenses are: transparency, flexibility, low density, toughness, inert or safe to chemicals used in polymer synthesis on the eye surface, ease of bulk manufacturing, easy to mould, appropriate refractive index for bending light rays, hydrophilic ('water-loving') nature, oxygen permeation through to the eye surface, and finished lenses that are easy to insert, remove, clean and store.

Soaking of lenses in the drug solution is the simplest way to incorporate a drug into soft contact lenses (SCLs). This method is used to study the in vivo delivery of pilocarpine [146], antibiotics [145] timolol [147], and dexamethasone [148] from poly (2-hydroxyethyl methacrylate) (pHEMA) hydrogels based SCLs. Also, the commercially available SCLs based on silicon-containing hydrogels or PVA hydrogel are examined for the delivery of ophthalmic drugs [149-152]. In most of these cases, a higher drug bioavailability is delivered via contact lenses compared to eye drops. At least 20% of timolol from pHEMA contact lens delivered to the cornea which is larger than the fractional uptake recorded using eye drops [147]. However, the soaking method presents a few limitations because the drug uptake in SCLs is dependent on several factors such as the water content and lens thickness, the molecular weight of the drug, the solubility of the drugs in the gel matrix. These factors may limit the loading capacity in some cases of SCLs. Nakada and Sugiyama has developed a contact lens with a hollow cavity by bonding together two separate pieces of lens material to improve drug loading [153]. This sandwiched lens has exhibited more drug loading capacity. However, oxygen and carbon dioxide permeabilities of the resultant sandwiched lens are found to be smaller than regular SCLs. This is because of the presence of two separates sheets of lens material which may induce corneal edema. The other limitation of the soaking method is that the burst release of the drug from soaked contact lenses with the entire drug diffusing in a few hours. The corticosteroid prednisolone, the glaucoma drug pilocarpine, and the antibiotic ciprofloxacin are found to be released from hydrophilic SCLs within 1-3 hours [146,154,155]. Also the *in vitro* experiments have demonstrated that the complete release of ketotifen fumarate from drug-soaked alphafilcon A (pHEMA) SCLs in 5 hours [149]. Additionally, the ketotifen fumarate release from silicone hydrogel contact lenses is observed to be less than 4hours (reaching the release plateaus from 1-4 hours) with a significant burst release of ketotifen fumarate at 10-15 min [150]. Therefore, a slow and extended drug release is a challenge for soaked contact lenses.

Recently, Van Beek and Andrea Weeks *et al.* have reported the use of Hyaluronic Acid (HA) containing silicone hydrogels, and poly (2-HEMA) gels with HA immobilized as a wetting agent [156,157]. HA is well-known an ophthalmic comfort enhancing agent [157-160] and has demonstrated water retentive properties and viscoelasticity for the tear fluid stability in dry eyes. Therefore, HA is used for the relief of dry eye symptoms [161-165]. Based on these results, Maulvia *et al.* [166] have fabricated the contact lenses by entrapping HA in pHEMA hydrogel sheet which provided the extended and steady HA release over 15 days for the first time. As seen from Figure 5,the HA-encapsulated lenses exhibited an initial burst release ($C_{max}$ = 613.12 ± 128.59 µg/ml, $t_{max}$ =30 min), followed by a steady and an extended HA release for 15 days in tear fluid. These lenses delivered an average constant concentration of 290.12 ± 88.15 µg/ml HA in tear fluid. Authors demonstrated the controlled and sustained release of HA from the printed contact lenses maintained a stable HA concentration in the tear fluid despite the tear drainage and tear-film turnover rate. Prolonged retention in the precorneal area has helped to reduce the dosing frequency of HA. In eye drop-treated group, the HA concentration was exponentially decreased from $C_{max}$ = 804.06 ± 123 µg/ml and reach below 100 µg/ml after 3 hours of the treatment. Therefore, upon instillation of HA eye drop, most of the instilled amount is quickly eliminated from the precorneal area due to tear drainage via nasolacrimal duct. HA in tear film, as defined by the area under the curve (AUC) and mean residence time (MRT) values, was significantly greater for the contact lenses (AUC = 79,878 ± 9959 µg × hr/ml and MRT = 127.69 ± 28.06 h) as compared to commercial eye drops (AUC = 604.52 ± 290 µg × hr/ml and MRT = 0.74 ± 0.32 h) [167]. Therefore, the use of HA-based contact lenses helps to reduce the precorneal elimination of HA as compared to the eye drops, requiring much smaller amount of HA to achieve the desired therapeutic levels in comparison with 0.1% HA eye drop. Extended release of drugs from contact lenses also studied using silicone hydrogel contact lenses [167-169] and used for the glaucoma treatment [170].

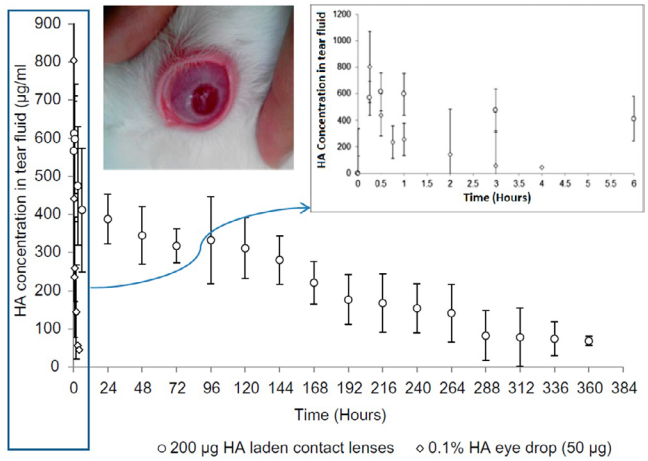


**Figure 5:** HA tear fluid concentration-time profiles after application of hydrated HA-laden contact lenses (DL-200 batch) and instillation of HA eye drop. The doses were 200 µg for lenses, and single eye drop instilled i.e. 50 µg for 0.1% HA eye drop. Each point represents the mean ± S.D. (n = 6) [166].

## Artificial Tears

Artificial tears, the most commonly used therapy for the dry eye group of ocular surface disorders have used hydrogels of high-molecular weight hydrophilic polymers [171]. These polymers provide viscosity; improve oncotic pressure, and demulcent action [172]. Palus *et al.* [172] also proposed that the efficacy of hydrogels in treating dry eye may be related to their ability to activate the epidermal growth factor receptors (which are critical for spontaneous corneal epithelial wound healing), therefore hydrogels are inexpensive, safe agents to promote healing of wounds in the cornea and possibly in other tissues. Also hydrogels such as methyl cellulose and CMC can be used to enhance healing of wounds in the cornea [173-175]. Aqueous solutions of polymers, PVA, PVP, HPMC, and CMC, are currently in clinical use as artificial tears, and therefore nanowafers (as mentioned above) fabricated with these polymers can function both as a drug delivery system and also as a lubricant [176,177]. Table 2 provide commercially available artificial tears that used polymers.

| Commercial Product Name | Polymer |
|---|---|
| Blink® Gel Tears | polyethylene glycol 400 |
| Systane® Gel Drops | polyethylene glycol 400 |
| GenTeal® Mild, Ultra Tears®, Tearisol®, Lacril®, Isopto®, Alkaline Natural Balance Tears, Rohto® Hydra | HPMC |
| Thera Tears®, Refresh Tears®, Refresh Plus®, Refresh Celluvisc®, Just Tears, Refresh Optive® Advanced | CMC |
| Tears Naturale® Free | dextran + HPMC |
| Hypotears® | dextran + PVA |

**Table 2:** Polymers used in commercially available artificial tears.

## Solid ophthalmic devices or insert

Various polymers based solid ophthalmic devices or insert are described as follows:

i) **Bioadhesive ophthalmic drug inserts**: Adhesive rods containing gentamicin have showed good tolerance, decreased expulsion, increased residence time and controlled drug release. Commonly used polymers in inserts are: hydroxypropyl methyl cellulose, ethyl cellulose, poly (acrylic acid), cellulose acetate phthalate [178].

ii) **Collagen shields**: Collagen corneal shields allowed an increase in tobramycin penetration into the AS compared with hydrophilic soft contact lenses. Polymers used are cross-linked porcine sclera collagen [179,180].

iii) **Dry drops freeze-dried device**: These preservative-free polymer HMPC based devices hydrates in the tear film [181].

iv) **Episcleral implants**: These silicone based devices (e.g. LX201 episcleral implant, Lux Biosciences Inc., Jersey City, NJ, USA) are capable of delivering drugs (e.g. cyclosporine) to the ocular surface up to one year. Implants are generally flat on the bottom in contact with the episcleral, and rounded on the top which is in contact with the anterior surface and continuously delivered drugs to the lacrimal gland [182].

v) **Gelfoam**: This is an absorbable gelatin sponge present in the form of a matrix system. *In-vivo* results showed that the gelfoam device is more effective than conventional pilocarpine based eye drops and gel in prolonging the duration of pilocarpine activity. Cetyl ester wax in chloroform is used in the Gelfoam [183].

vi) **Lacrisert**: The Rod-shaped water-soluble cul-de-sac insert (1.27 mm diameter, 3.5 mm long) are developed to treat moderate to severe dry eye syndrome. Hydroxypropyl cellulose is used in Lacrisert [184,185].

vii) **Minidisc or ocular therapeutic system**: A monolithic matrix-type device which is comprised of a contoured disc with a convex front and a concave back surface which is in contact with the eyeball. This system may help to solve the patient compliance issues of comfort and dosing frequency [186].

viii) **Ocusert**: An insoluble device with a matrix and reservoir comprised of ethylene-vinyl acetate copolymer, and pilocarpine in alginate, and provides controlled release of pilocarpine [187].

ix) **Mucoadhesive Ophthalmic inserts**: A rod-shaped mucoadhesive ophthalmic insert place in the upper/lower conjunctival fornix. These inserts are used for chemotherapy of ocular bacterial infections, such as trachoma. Polymers used in these inserts are: silicone elastomer, sodium chloride, poly (acrylic) acid, polymethacrylic acid [188].

x) **PVA flag device**: A PVA flag is attached to a handle which upon the application get detached from the handle and dissolved and releases the drug. Advantage is that the greater drug bioavailability at the low drug concentration can be achieved by this device. As much lower drug concentrations are needed with this device, the likelihood of systemic adverse reactions is very low [189].

xi) **Punctal plugs**: Silicone, collagen, acrylic polymers are used in plugs that plugs into the puncta and used to prolong the retention time and increase absorption of drugs after instillation of eye drops while treating dry eye. Punctal plugs for latanoprost and bimatoprost are developed by QLT Inc. (Vancouver, BC, Canada) and Vistakon Pharmaceuticals, LLC (Jacksonville, FL, USA), respectively. Both these plugs have shown no dose-response for intraocular pressure reduction [190,191].

xii) **Soluble ocular inserts**: These devices made from an N-vinyl pyrrolidone and ethyl acrylate based small oval wafer that softens in the inferior cul de sac (10-15 s) and fits well with the shape of the eye [186].

xiii) **Sub-conjunctival implants**: A sub-conjunctival insert comprising a tube with a latanoprost-core, currently tested under a Phase I clinical trial by Pfizer, Inc., NY, USA. One end of the tube is capped with impermeable silicone and the other end with a permeable polymer. Poly (D, L-lactide-co-glycolide) and PVA are used in these implants [192].

## Supramolecules based treatment

Supramolecules have been used to solubilised water insoluble drugs, increase drug's bioavailability, reduce the side effects of drugs and sustainable drug delivery to the target, and provide photostability. Additionally, cyclodextrins based supramolecular systems have exhibited excellent biocompatibility, low toxicity and low immunogenicity [193] and unique inclusion capability along with powerful functionalization capacity. Supramolecular cyclodextrin [194] is used to develop eye drops which are one of simplest and earliest developed delivery systems dominating the market. One of the commercially successful eye drops, Voltaren Ophtha eye drops developed by Novartis (Basel, Switzerland) contained diclofenac sodium as an active to treat inflammatory conditions. This eye-drop solution contains a supramolecule, hydroxypropyl-γ-cyclodextrin, which helps with corneal permeation of diclofenac sodium [195]. Zhang *et al.* [196] has recently developed micellar supramolecular hydrogel of a low-molecular-weight methoxy poly (ethylene glycol) (Mn = 2000 Da) block polymer and α-cyclodextrin (α-CD) through the host-guest inclusion method for the topical ocular drug delivery. This supramoleucular hydrogels has exhibited thixotropic properties, relatively low cytotoxicity toward L-929 and HCEC cells, and non-irritancy toward the rabbit eye. Additionally, the *in vitro* release studies showed that the α-CD concentration strongly influenced the release rate of diclofenac from this supramolecular hydrogel. Furthermore, it could significantly extend the retention time on the corneal surface in rabbits and greatly improve ocular drug bioavailability as compare to a plain micellar formulation. Chen *et al.* [197] have combined layer-by-layer (LbL) method with cyclodextrin to create a new type of supramolecular system for the ocular drug delivery. A supramolecular LbL system of polycarboxymethyl l-β-cyclodextrin (poly (CM-β-CD))/poly-L-lysine (PLL) multilayer film is developed since β-CD showed good drug delivery property [197]. The properties such as the contact angle and transparency are controlled by controlling the deposition of poly (CM-β-CD)/PLL multilayer. Ofloxacin and puerarin are loaded into multilayer during the self-assembly procedure and found that the concentration of loaded drug into poly (CM-β-CD) solution is larger than that of incorporating drugs into PLL solution. The sustainable drug release is achieved due to multi layers and the drug release properties can be controlled using drug loading method and pH of released medium.

## Stem cells based treatments

**Retinal Degeneration:** Many preliminary clinical trials have been conducted for retinal degeneration diseases like AMD, glaucoma, optic neuropathies, and retinal vascular complication using stem cells. The stem-cell-based therapy can correct defective function of retina photoreceptors [198,199], ganglion cells, RPE [200,201], and optic nerve [202,203].

**RPE and AMD:** AMD has the highest cases of blindness in the elderly population globally [204-206]. Wet AMD manifests as neovascularization which is managed with monthly inoculation of anti angiogenic drugs such as Lucentis® [207]. However, the monthly injection into the eye can cause discomfort and inconvenience to the patient and cost [208]. Schwartz *et al.* [209,210] have conducted clinical trials by injecting 50,000 to 200,000 hESC derived retinal pigment epithelial cells in worst affecting area of patients suffering from dry AMD (NCT01344993) and Stargardt's macular dystrophy (NCT01345006) [211]. These trials are resulted in an increase in the area size and sub-retinal pigmentation of patches of transplanted cells over a period of 3-15 months in 72% of the treated patients with dry AMD and Stargardt's macular dystrophy [209]. Generally, the patch of cells is transplanted at the boundary of atrophic lesion on the eye of dry AMD patients, which become larger and more pigmented within 6 months of transplant. Whereas, patches of pigmented cells are found around the boundary of baseline atrophy in retinal pigment epithelium layer which appeared more prominent after 12 months of transplantation in the Stargardt's macular dystrophy patient. The superior half of the atrophic lesion is totally filled-in by the transplanted retinal pigment epithelial cells after six months of the transplant. The filled area became larger in size along with more pigmented sites after 15 months of the transplant [209]. The vision-related quality of life is also enhanced in both patients of atrophic AMD and Stargardt's macular dystrophy due to the transplant of cells. No side effects including the abnormal tissue formation at either the local or ectopic site of injections or immune rejections even four months after injection are found with patients [209]. The retinal pigmented epithelium cells which are differentiated from human iPSCs reprogrammed from patient cells are transplanted into AMD patients [211-215]. The tissue where cells are transplanted has found to be intact without being attacked by the immune system [216].

**Glaucoma:** Despite prediction of worldwide increase in glaucoma incidences from 60.5 million in 2010 to 79.6 million by 2020 mostly due to ageing and raised intraocular pressure there is not much progress using stem cells so far except some of preclinical models have proven that ciliary neurotrophic factor could augment the survival and renewability of retinal ganglion cells [217,218].

**Optic Nerve Disease:** The bone marrow derived autologous cells may reduce the degeneration of the optic nerve and lead to improvement in visual function and decreased intracranial hypertension [219]. Despite some early progress with stem cells, there is a lot of investigation is needed from safety and efficacy point of view.

Applications of stem cells for ocular diseases have not reached full potentials so far. This field is still in its primary stages. Many technical and regulatory hurdles need to be addressed before realising applications of stem cells for the ocular treatments.

## Theranostics of ocular diseases

Theranostics is a new field where a single agent is used for both diagnostics and therapeutics purposes and reduces the need for two separate systems or materials. Theranostics systems can save the treatment time and cost, and reduce systemic toxicity and improve patient compliance. This field is still in its primary phase and not many research articles are published so far. Huang *et al.* [220] have designed and fabricated a hybrid hydrogel-based contact lens which comprises quaternized chitosan (HTCC), silver NPs, and graphene oxide (GO) with a combination of antibacterial and antifungal functions. This theranostic hydrogel is cross-linked through electrostatic interactions between GO and HTCC and exhibits strong mechanical properties. An antifungal drug, voriconazole, is loaded onto GO. Go retains the drug and promotes its sustained release from the theranostic hydrogel-based contact lenses. The contact lenses also exhibited good antimicrobial functions due to antibacterial property of glycidyltrimethylammonium chloride and silver NPs. These theranostic contact lenses loaded with Voriconazole have exhibited excellent antifungal efficacy *in vitro*. Therefore, theranostic hydrogel contact lenses-based drug delivery system can be further developed as promising therapeutic device for a rapid and effective treatment of fungal keratitis. This field is most likely to grow further in next 20+ years and find useful for rapid detection and treatment of ocular diseases.

# Conclusions

This review focused on the different types of ocular diseases (anterior and posterior) and their treatments using advanced technologies such as polymers, nano-ophthalmology, lipids, stem cells and theranostics. Despite the complex anatomy, researchers have overcome many barriers to achieve delivery of both hydrophilic and hydrophobic drugs to both anterior and posterior segments of the eye. Despite therapeutic advances, there is still a scope for further development to overcome technological barriers, improve bioavailability of drugs, particularly to the posterior ocular segment and biosafety to improve regulatory and patient compliances. Stem cell therapeutics is still an emerging field and should help to develop potential therapies in the future. Lastly, the theranostics is an emerging field which will find lot of applications in the ophthalmology.

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