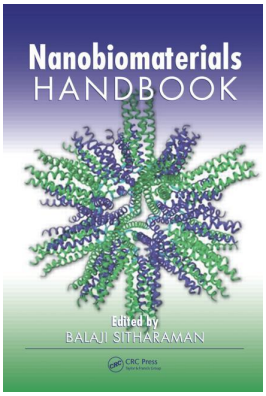

Nanobiomaterials Handbook

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Nanobiomaterials for Ocular Applications

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Nanobiomaterials for Ocular Applications

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15.1 Introduction

The development of suitable biomaterials for replacement of different parts of the eye is challenging due to the stringent criteria that need to be fulfilled by such materials in order to maintain vision and prevent foreign body sensation on implantation. Various nanostructured materials and nanoparticles have been developed in recent years, which have the potential to improve ocular

residence times, cellular interactions, and drug delivery in the eye. This chapter describes some of these advances and is organized into two main areas, namely, nanobiomaterials for ocular drug delivery and nanobiomaterials for ocular implants.

15.2 Nanobiomaterials for Ocular Drug Delivery

15.2.1 Anatomical Considerations for Ocular Drug Delivery

The delivery of drugs to the posterior segment of the eye after topical administration is very less. This is because drugs have to cross many anatomical barriers, and the sources of removal at each step are multiple. The drug is first distributed in the tear fluid and then passes through the cornea to the anterior chamber. To reach the retina and adjacent structures, it has to cross through the vitreous cavity.

The precorneal tear film (PTF) is the first barrier encountered by the topically administered drug. It is secreted by lacrimal glands and covers the cornea and conjunctiva in the form of a thin film. Spontaneous blinking of eyelids, volume of tear fluid, and its drainage dynamics influence the ocular bioavailability and residence time of drugs in the PTF. Reflex blinking ensures the uniform spread of the tear film and prevents the cornea from drying. It also helps in the spread of the drug in the PTF and causes its removal through nasolacrimal drainage. In humans, blinking occurs approximately at the rate of 15 times per minute. A mucin layer covers the anterior surface of the conjunctiva and cornea and is secreted by the goblet cells of the conjunctiva. Ocular mucoadhesives interact with this layer to prolong the residence time of drugs.

The cornea may act as a pathway, a barrier, or a reservoir for topically applied drugs. Since the lipid content of the epithelium and the endothelium are much higher than that of the stroma, the transfer of drugs through the cornea is largely determined by phase solubility. The epithelium and endothelium are highly permeable to the substances that are fat soluble whereas the stroma is permeable to substances that are water soluble.

Further routes to the posterior chamber have several anatomical barriers. Lipophilic drugs can partition into the lens from aqueous humor and then diffuse around the cortex to the vitreous body. When the drug molecule reaches the anterior surface of the vitreous, it can further progress to the fundus by diffusion through the vitreous gel or by convection when it is liquefied. The several topical barriers prevent adequate drug levels in the posterior chamber and the presence of the blood retinal barrier prevents systemic drugs from reaching adequate levels in the retinal tissues.

15.2.2 Need for Drug Delivery Systems

The need for novel drug delivery agents exists in ophthalmology due to the poor residence time and pulse kinetics of the conventional formulations like eyedrops. Materials in the form of solid reservoirs, liposomes, nanoparticles, and gels can be used for sustained release of drugs in the eye. This is particularly important for conditions of the posterior segment of the eye as only 1%–2% of the conventional eyedrops actually reach this site.

15.2.3 Materials Used in Conventional Ocular Formulations

To overcome the disadvantages of eyedrops, various ophthalmic drug delivery systems such as hydrogels, and shields have been developed. Polymeric gels used for ophthalmic drug delivery may be either preformed gels or in situ gelling systems. Hydrogels are used in the eye to increase the ocular residence time of the drugs due to their increased viscosity and in some cases the mucoadhesive property. Hyaluronic acid is an example of a biological polymer that has mucoadhesive properties and hence can be used for increasing the ocular residence time of drugs. Since it is a component of aqueous and vitreous humor, its ocular tolerance and safety are not a concern. In a study by Kyyronen et al. (1992), the in vivo release of methylprednisolone in hyaluronic acid gels was 9–12 times lower than the control suspension. The burst release of the control was not observed when using the gel, which showed a slow

sustained release of drug over several hours. Synthetic mucoadhesive polymers include water-soluble polymers that are linear chains and water-insoluble polymers that are swellable networks joined by cross-linking agents. The polyanionic polyacrylic acid is one example of a synthetic mucoadhesive drug delivery agent (Le Bourlais et al., 1998). Mucoadhesion occurs due to interactions between the polymer chains and mucin molecules present in the ocular mucus layer.

One disadvantage of these gels is that they interfere with eyelid motion and lead to ocular discomfort and blurring of vision due to their highly viscous nature. Though the lacrimation and blinking mechanisms help in improving the ocular tolerance to the eye, in situ forming gels, which can be instilled in solution form, are preferred. In situ acting gelling systems, as described earlier, are viscous liquids that on exposure to physiological conditions will shift to a gel phase. The poloxamers are polyols with thermal gelling properties whose solution viscosity increases when temperature is raised from its critical temperature of 16°C to the ocular temperature of 33°C–34°C. Cellulose acetophthalate is a solution at pH 4.4, which undergoes coagulation when the pH is raised by tear fluid to 7.4 (Ding, 1998). Gellan gum, an anionic extracellular polysaccharide secreted by *Pseudomonas elodea*, can be administered as an aqueous solution that forms clear gels in the presence of mono or divalent cations present in the tear fluid.

Shields or inserts act as solid reservoirs of drugs over prolonged durations but have low patient tolerance. Ocusert is an insoluble ophthalmic insert that consists of a central reservoir of drug enclosed between two semipermeable membranes that allow the drug to diffuse at a predetermined rate over several days (usually a week). However, after prolonged wear over 12 h, these inserts swell and get partially fragmented. Collagen shields are soluble ophthalmic inserts that are fabricated from porcine scleral tissue, which has a collagen composition similar to that of human cornea. The collagen shields are hydrated before being placed on the eye. On hydration with tear fluids, they form clear thin films of around 0.1 mm in thickness, which conform to the corneal surface and dissolves slowly over a predetermined period usually a couple of days to cause prolonged release of the drug.

15.2.4 Role of Nanoparticles in Ocular Drug Delivery

Nanoparticles have many advantages as potential carriers for drugs in the eyes. These include their ability to penetrate through several anatomical barriers in the eye. Hence, the nanoparticles can reach the posterior parts of the eyes even when applied to the anterior surface. Further, nanoparticles can be made of mucoadhesive polymers, which allow them to stick to the surface of the sclera and increase the ocular residence time of the drugs, withstanding washout by the tear fluid. This allows the drugs to be delivered in more patient compliant schedules. The nanoparticles also act as depots of the drug maintaining a sustained release of the drugs over several hours. The small sizes of the nanoparticles allow them to be directly internalized by endocytosis by corneal endothelial cells. Figure 15.1 depicts the different types of nanoparticles commonly used in ocular drug delivery.

15.3 Liposomes and Solid Lipid Nanoparticles

Liposomes are microscopic vesicles that consist of membrane like lipid bilayers, which surround aqueous compartments. They are biocompatible and biodegradable and can be used for delivery of both hydrophilic and hydrophobic drugs. Liposomes with positive surface charge are relevant for the eye as they provide more stable adsorption to the corneal surface, which is coated with negatively charged mucin (Durrani et al., 1992). However, stearylamine is avoided as it causes irritation to the eye (Taniguchi et al., 1988). Positively charged unilamellar liposomes increased the flux of penicillin G across isolated rabbit corneas more than fourfold. Solid lipid nanoparticles have also been developed as nanocarriers for ocular drug delivery. Cavalli et al. (2002) have developed solid lipid nanoparticles <100 nm in size loaded with tobramycin, which achieved higher bioavailability in the rabbit aqueous humor than the free drug. Attama et al. (2008) have shown increased oentration of diclofenac-loaded solid lipid nanoparticles through human corneal constructs.

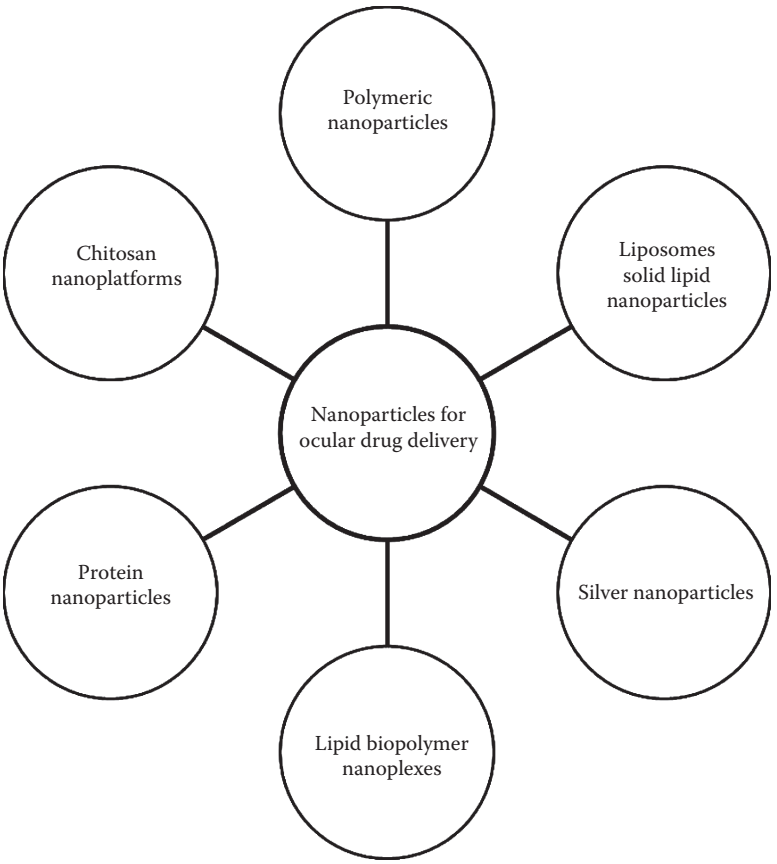

FIGURE 15.1 Overview of nanoparticles used in ocular drug delivery.

15.4 Niosomes

Niosomes are bilayered nonionic surfactant vesicles that encapsulate hydrophilic and hydrophobic drugs and are chemically more stable than liposomes. Niosomes have been found to increase the ocular bioavailability of cyclopentolate (Sahoo et al., 2008).

15.5 Polymeric Nanoparticles

Nanoparticles are colloidal particles of sizes 10 nm to less than 1 μm in diameter and are in the form of either nanocapsules or nanospheres. The small sizes allow increased penetration through the ocular membranes and less of a foreign body sensation on topical administration. Slow sustained release of drugs is obtained by the use of nanoparticulate carriers. Materials like polyalkyl cyanoacrylate, poly-ε-caprolactone, polylactic-*co*-glycolic acid, gelatin, and albumin have been used for the preparation of the nanoparticles. All these are widely studied biodegradable polymers offering good ocular tolerance (Zimmer and Kreuter, 1995). Gupta et al. (in press) developed polylactide-*co*-glycolide nanoparticles loaded with sparfloxacin, which showed higher ocular residence time than the conventional formulation. Recently, Das et al. (in press) synthesized amphotericin B–loaded Eudragit nanoparticles, which were found to be nontoxic to the eyes and can be used for ocular drug delivery. Pignatello et al. (2002) have developed Eudragit nanosuspensions loaded with ibuprofen for ocular delivery of nonsteroidal anti-inflammatory agents. Gupta et al. (2000) have developed polymeric micelles of copolymers

N-isopropylacrylamide, vinyl pyrrolidone, and acrylic acid loaded with ketorolac and found a sustained ocular anti-inflammatory effect as compared to the free drug. Yenice et al. (2008) found that hyaluronic acid coated polycaprolactone nanoparticles delivered several folds higher cyclosporine A levels in the cornea as compared to the free drugs.

15.6 Biopolymeric Nanoparticles

Campos et al. (2001) have developed chitosan nanoparticles loaded with cyclosporine A by ionic gelation. The nanoparticles were 290 nm in diameter and following topical administration in rabbits, achieved therapeutic concentrations in cornea and conjunctiva over 48 h higher than those achieved by the free drug solutions. Yuan et al. (2006) also studied cyclosporine A–loaded nanoparticles using cholesterol modified chitosan self-aggregated nanoparticles <230 nm in diameter, which showed increased retention in precorneal areas and may have the potential for treatment of extraocular conditions like keratoconjunctivitis sicca, which is limited by the lacrimal washout and poor ocular residence of conventional eyedrops.

15.7 Protein Nanoparticles

Merodio et al. (2002) have developed ganciclovir-loaded albumin nnaoparticles by coacervation technique. Intravitreal injection of these nanoparticles were well tolerated and 2 weeks after the injection, a significant amount of the nanoparticles were found in the vitreous humor, in a thin layer overlying the retina and close to the blood aqueous barrier. Such nanoparticles have the potential to treat cytomegalovirus infections that affect the endothelial cells of ocular blood vessels, optic nerve, and the retina. Das et al. (2005) have also developed aspirin-loaded albumin nanoparticles for ocular dug delivery. Similarly, gelatin nanoparticles have also been developed as platforms for ocular delivery using model drugs pilocarpine hydrochloride and hydrocortisone (Vandervoort and Ludwig, 2004). Jain and Banerjee (2008) have compared albumin, gelatin, chitosan, and solid lipid nanoparticles as carriers for ciprofloxacin hydrochloride in the eye. Solid lipid nanoparticles and chitosan nanoparticles were found to have favorable properties of high encapsulation, stability, and sustained release suitable for carriers in ocular drug delivery.

15.8 Combination Nanosystems

Newer delivery systems are being developed that combine the advantages of two or more of the above systems. Polylactide-*co*-glycolide nanoparticles can be suspended in a mucoadhesive polymeric solution or an in situ gelling solution to obtain colloidal particles trapped within a gel (Dillen et al., 2004).

Diebold et al. (2007) developed a novel nanoplatfom that combines the advantages of hydrophilic and hydrophobic carriers. Liposome chitosan nanocomplexes were developed that allow efficient coencapsulation of different types of drugs. Liposome chitosan nanocomplexes were found to have high cellular uptake within conjunctival epithelial cells and were well tolerated in rabbit eyes. The penetration and distribution of the nanostructures could be modulated depending on the compositions and charges.

15.9 Nanoparticles for Ocular Gene Delivery

Efficient delivery of genes to the retina can be promising in the treatment of several retinal diseases like retinitis pigmentosa and proliferative vitreoretinopathy. Viral gene carriers have risks of infection. Intravitreal injection of nonviral nanoparticles are a safe and promising strategy for gene delivery in retinal diseases. The nanoparticles need to be optimized to reduce their binding to the glycosaminoglycans in the vitreous to increase their internalization within the target retinal cells and their escape from the endosome (Sanders et al., 2007; Cai et al., 2008). Ultrapure oligomeric chitosan DNA complexes have been

shown to be effective for transfection in corneal cells (Klausner et al., 2010). Chitosan oligomers that are fully deacetylated and have a low molecular weight <9.5 kDa are preferred to higher weight chitosans for ocular gene delivery as they overcome the viscosity-enhancing properties of higher weight chitosans and are more easily dissociated from DNA, allowing more efficient release from the nanoparticles.

15.10 Nanoparticles for Ocular Delivery of Nucleic Acids

Antisense oligonucleotides are complementary to a RNA sequence to which they bind and prevent the translation of a specific protein. Some targets for gene inhibition in the eye include vascular endothelial growth factor (VEGF), transforming growth factor B, fibroblast growth factor, herpes simplex virus, and cytomegalovirus. Oligosense nucleotides are hydrophilic, negatively charged, and require nanocarriers for delivery in the posterior segment of the eye. The nanoparticles are required to allow intracellular delivery and sustained residence time intraocularly, preventing the need for multiple intravitreal injections (Fattal and Bochot, 2006). For example, lipoaminoacids like lipid lysine dendrimers have been found to deliver a phosphodiester oligosense nucleotide, which inhibits VEGF in human retinal cell lines (Wimmer et al., 2002). A 40%–60% reduction in VEGF expression was observed within 24 h.

15.11 Functional Nanoparticles for Ocular Diseases

Diabetes causes severe vascular complications in the eyes including diabetic retinopathy. Advanced glycation products cause increased endothelial permeability of the blood retinal barrier. Sheikpranbabu et al. (2010) have found that silver nanoparticles (without any drugs) acted as potent antipermeability agents and blocked the biological effects of advanced glycation products by targeting the Src signaling pathway and tight junction proteins.

15.12 Nanobiomaterials for Ocular Implants

Nanoparticles are incorporated in many implants. Nanostructured implants allow various improvements over conventional ocular implants with regard to their cellular interactions, physical properties, and ability to be multifunctional. Table 15.1 summarizes some of the recent nanostructured ocular implant strategies.

15.13 Contact Lenses

Contact lenses are a means of vision correction by the use of a lens in intimate contact with the cornea. Contact lenses are used to correct refractive errors of the eyes as an alternative to spectacles. They have the advantages of an increased field of vision and the ability to correct irregularities of the corneal surface and the corresponding astigmatism. Further, they are preferred in cases of

TABLE 15.1 Types of Nanostructured Ocular Implants

Implant	Nanostructure Strategies
Soft contact lenses	Molecular imprinting
	Cyclodextrin linked
	Microemulsion droplets
Intraocular lens	Inorganic nanoparticle incorporated within polymeric matrix
Ocular inserts	Nanoparticle in polymeric membranes
Corneal adhesives	Dendrimers
Vitreous substitutes	Nanoparticles in gels

severe ametropia and in cases where the powers of refraction are widely different in each eye. Recent advances also allow the use of drug-loaded contact lenses for sustained topical release of the drugs. Cosmetic uses of tinted contact lenses are also common.

15.13.1 Anatomical Considerations for Contact Lenses

The anatomical considerations for development of a contact lens are that the lens is to be implanted on the anterior most surface of the eye, overlying the cornea. The cornea is an avascular structure that obtains oxygen from the atmosphere and the tear film for adequate nutrition and for maintenance of its structure. The cornea consists of an outer epithelium, an internal stroma containing keratocytes and an internal endothelial layer. The stroma comprises over 90% of the total thickness of the cornea and is composed mainly of parallel arrays of collagen fibers. This regular arrangement allows the maintenance of corneal transparency under normal fluid conditions. The Bowman's layer, consisting of randomly arranged collagen fibers and proteoglycans, separates the stroma from the corneal epithelium that resides on the outer surface of the eye. The endothelial layer is only single cell thick and is separated from the stroma by the Descemet's membrane. The endothelial cells play an important role in the maintenance of transparency in the corneal stroma both by actively pumping water out via a sodium–potassium adenosine triphosphatase and a coupled bicarbonate pump and by serving as a tight barrier to fluid entry (Geroshi et al., 1995). The ophthalmic compatibility of a contact lens on the eye requires that the lens maintain a stable, continuous tear film for clear vision, sustain normal hydration, and be permeable to oxygen in order to maintain corneal metabolism. Further, the material should be nonirritating and must have excellent surface characteristics.

15.14 Current Materials for Contact Lenses

Historically, though the earliest reference to the concept of contact lenses dates back to Leonardo da Vinci, the first clinical application was that of a glass corneoscleral lens in the 1880s. The first polymeric contact lens was devised of polymethymethacrylate (PMMA) in the 1940s. Today, contact lenses are classified into hard and soft lenses based on the modulus of elasticity of the materials. The PMMA lens is now classified as a hard contact lens. It has good optical properties and high durability but is less well tolerated. The low oxygen permeability limits the long-term wear of these lenses. To avoid corneal anoxia, these lenses need to be small in diameter and need to be designed to float on a precorneal tear film such that tear film exchange during blinking and movement of the lens allows oxygenation of the cornea. Soft contact lenses are either hydrogels or are silicone-based elastomers and are more comfortable to the user. A third category of lenses includes the rigid gas permeable lenses that have superior oxygen permeability while maintaining the mechanical properties similar to hard lenses. This category may be considered as an improved version of the original hard contact lenses.

The first soft contact lens material was polyhydroxyethyl methacrylate (PHEMA), which contained 38% water, had excellent wettability and improved wearer comfort. Since then, several modifications have been made to develop soft contact lenses with superior oxygen permeability. The oxygen permeability of these hydrogels can be increased by increasing the water content or by decreasing the thickness of the lenses. Very thin lenses lead to difficulties in handling. Increasing the water content of the lenses is achieved by copolymerizing HEMA with hydrophilic monomers such as methacrylic acid and vinyl pyrrolidone. Hydrogels with high water content (>70%) have the advantage of improved oxygen permeability but have low tear resistance and an increased tendency to adsorb proteins from the tear fluid leading to spoilation. Actifresh 400, from Hydron, is an example of a conventional hydrogel soft contact lens composed mainly of MMA/NVP having 73% water content and an oxygen permeability of 36 Barrers (Lloyd et al., 2001).

Soft contact lenses based on the silicone elastomer, polydimethysiloxane (PDMS), also can be used as extended wear contact lenses. The material has excellent optical properties and high oxygen permeability (Dk upto 600 Barrers). The main disadvantage of this material is its low surface energy leading to poor tear fluid wetting and an increased tendency to bind lipids from the tear fluid. This can be

overcome by surface modification techniques and by the grafting hydrophilic polymers to its surface. The combination of the high oxygen permeability of PDMS with the excellent wettability and patient tolerance of conventional hydrogels can be achieved by the development of silicone-based hydrogels. Silsoft is a PDMS-based contact lens from Bausch & Lomb that has a water content of 0.2% and an oxygen permeability of 340 Barrers. There is a distinct difference in the relation of water content to oxygen permeability in the two types of soft contact lenses. In case of conventional hydrogels, the oxygen permeability increases with the increasing water content. However, in case of silicone hydrogels, the increase in water content is achieved by increasing the portion of the conventional hydrogel monomer to the silicone monomer and this reduces the oxygen permeability of the material (Lloyd et al., 2001).

Daily wear, rigid, gas-permeable lenses have been developed by copolymerization of methyl methacrylate with methacrylate functionalized siloxanes like methacryloxypropyltris (trimethyl siloxy silane) (TRIS). The various properties of these lenses are modulated by the TRIS-to-cross-linker ratio. The disadvantages of decreased wettability with the use of high concentrations of TRIS are overcome by the addition of methacrylic acid. Quantum II lens made of silicone acrylate is a product of Bausch & Lomb and has an oxygen permeability of around 100 Barrers with no water content. Further improvements in rigid gas-permeable lenses have been developed by the use of fluoromethacrylates. The low surface energies of such lenses cause reduced spoliation but have the disadvantage of poor wettability. Some of these lenses are suitable for 7 day extended wear.

15.15 Advances in Contact Lenses due to Nanotechnology

The use of a contact lens for localized sustained delivery of drugs has been achieved successfully recently (Hiratani et al., 2005). Therapeutic soft contact lenses fabricated by the molecular imprinting method have been found to have a drug loading capacity two- to threefold greater than that of the contact lenses made by conventional methods (Hiratani and Alvarez-Lorenzo, 2002). Furthermore, the adsorption affinities for the drug used as template were 9- to 20-fold higher in the case of the imprinted contact lenses (Hiratani and Alvarez-Lorenzo, 2004). Thus, adsorption sites capable of capturing the target drug can be effectively encoded into the polymer network by molecular imprinting and, in consequence, can improve the specific drug loading capacity of the contact lenses. Such imprinted soft contact lenses are able to provide greater and more sustained drug concentrations in tear fluid with lower doses than conventional eyedrops.

Similarly, Santos et al. (2009) developed soft contact lenses functionalized with pendant cyclodextrins for controlled drug delivery over 2 weeks in the lacrimal fluid. Ophthalmic solutions containing cyclodextrins undergo instantaneous decomplexation of drugs when diluted in ocular fluids preventing sustained release. On the contrary, if the cycodextrins are attached to a polymeric network, dilution effects are minimized and controlled release of the drug can be achieved. Such networks have potential as drug-loaded soft contact lenses.

The development of glucose-sensing contact lenses has been envisaged. These will aid in the determination and monitoring of tear fluid glucose levels, which in turn track blood glucose with an approximate 30 min lag time. These disposable colorless contact lenses can be worn by diabetics and changes in the color of their lenses can give an indication of glucose levels in tear fluid and blood (Badugu et al., 2005).

Further, synthetic corneal onlays or implantable contact lenses are also being developed either as part of partial thickness epikeratopathy or as the optical portions of full-thickness keratoprostheses.

15.16 Corneal Adhesives and Nanoparticulate Inserts

Corneal wounds are presently repaired using nylon sutures. Sutures have many disadvantages like additional trauma due to multiple sites of suturing, uneven healing leading to astigmatism, sites of infection, and removal if nonbiodegradable. Dendrimers are highly branched polymers having three structural parts, namely, the central core, the intermediate branching layers, and the peripheral groups.

Dendrimer-based adhesives can offer a minimally invasive technique for efficient corneal wound healing. Dendrimers have been recently explored as adhesives for corneal wound healing posttraumatic injury or postsurgical procedures (Grinstaff, 2007). Photocross-linking or peptide ligation strategies have been used to couple individual dendrimers to form an adhesive.

Jain et al. (2010) have developed nanoparticulate polymeric membranes as biodegradable drug-loaded inserts for ocular drug delivery. The nanoparticles act as depots for the sustained release of drugs and the polymeric matrix acts as an insert and allows the ease of regional application of the nanoparticles on the eye. These inserts were found to sustain drug release over 5 days in simulated ocular conditions and allowed increased penetration of drug into posterior segment of the explanted goat eyeballs. The nanoparticulate inserts are biodegradable and act as platform technologies for delivering both hydrophilic and hydrophobic drugs in the eye. The inserts are mucoadhesive and prevent washout of the drugs by the tear fluid.

15.17 Intraocular Lenses

An intraocular lens is a synthetic lens that is placed within the eye to replace the dysfunctional crystalline human lens after its removal. The commonest condition that requires the use of intraocular lenses is cataract. In cataract, there is opacification of the normally transparent crystalline lens leading to loss of vision. On removal of the cataractous lens, the intraocular lens is placed within the eye as a substitute.

15.18 Anatomical Considerations for Intraocular Lenses

The human ocular lens is situated just behind the iris and the pupil and is attached to the ciliary body via the suspensory ligament. It is transparent and biconvex with an outer capsule consisting of type IV collagen. Inner to the anterior capsule is a single layer of lens epithelial cells. These epithelial cells give rise to the nondividing enucleate lens fiber cells that along with the interstitial material form the main part of the internal lens substance. The high refractive index of the lens is due to the specialized proteins called crystallins secreted by the lens cells.

A special feature of the human lens is its ability to change its shape and hence focal lengths to allow images of both near and far objects to form sharply on the retina. This is achieved by accommodation. During this process, the contraction and relaxation of the ciliary muscles and suspensory ligament control the shape of the lens. During the viewing of distant objects, the lens is flattened by the pull of the suspensory ligaments on the lens margin. By contrast, for viewing near objects, there is contraction of the ciliary muscle causing relaxation of the suspensory ligament and leading to thickening of the lens. These factors must be kept in mind while designing intraocular lenses.

15.18.1 Current Strategies for Intraocular Lenses

In 1950, Harold Ridley first implanted a polymethylmethacrylate (PMMA) intraocular lens (IOL) following removal of a cataractous crystalline lens. The initial procedure entailed total cataractous lens extraction or intracapsular cataract extraction and fixation of an IOL in the anterior chamber, which was supported by the iris. In due course of time, it was realized that several complications are reduced if the posterior capsule of the lens is not removed. Based on these considerations, the procedure was modified to leave the lens capsule in place. This change caused the procedure to be redesignated as extracapsular cataract extraction. Though several other polymeric materials have been developed, PMMA remains one of the standard materials for intraocular lenses even today.

The types of intraocular lenses are based on their position of replacement within the eye as well as the mechanical properties of the lens. According to position, intraocular lenses are classified as anterior chamber IOLs, which are positioned in front of the iris but behind the cornea, and iris clip lenses, which straddle the pupil and posterior chamber IOLs, which are placed behind the iris within or on

the lens capsular bag. Based on the mechanical properties of intraocular lenses, they are either rigid or foldable. This classification has implications on the manner of handling of the IOLs. Previously, the lenses were almost always made of rigid material, and an incision of approximately 6 mm (roughly equal to the diameter of the lens) was required to insert the lens into the capsule. Smaller incisions are clinically advantageous, with less patient discomfort and faster recovery from surgery but perhaps more importantly, they reduce astigmatism. These advantages have fostered the development of foldable IOLs. Foldable intraocular lenses can be inserted through smaller incisions of less than 3.5 mm size. These new lenses can be folded into a "taco" shape, to be inserted through a small tube into the eye. After the folded IOL has been pushed completely through a delivery tube introduced into the eye, the IOLs "memory" causes it to spring back, regaining its original shape.

Intraocular lenses consist of two parts an optic and haptics. The optic is the central part of the lens responsible for the refraction through the lens. The haptics are projections from the optic that allow the attachment of the lens within the eye. Though PMMA has the advantages of excellent optical properties and low weight, its low surface energy leads to complications like corneal endothelial damage and post-operative adhesion of inflammatory cells to its surface. This has led to the development of lenses with soft high energy surfaces using *N*-vinyl pyrrolidone and hydroxyethylmethacrylate.

Foldable lenses are made from silicone elastomers, PHEMA hydrogels, and acrylic polymers. A special requirement of these lenses is that they must be easy to insert and should unfold slowly in a controlled manner without any creases. In this respect the acrylic lenses unfold more slowly than the silicone lenses (Kohnen, 1996; Lloyd et al., 2001). Examples of foldable intraocular lenses are Alcon HydroSof made of HEMA having a water content of 38% and a refractive index of 1.44 and Chiron C10UB made of PDMS having <1% water content and a refractive index of 1.41.

Current IOLs have different chemical properties and shapes. The shape of the lens optics differs in an effort to design lenses that require smaller incision sizes and reduce the incidence of posterior capsule opacification. Prolate IOLs have also been developed that are steeper centrally and flatter peripherally to offset the age-induced spherical aberration (Lazzaro, 2005).

Phosphorylcholine-based polymeric coated intraocular lenses have been developed in an effort to reduce protein adsorption, cellular adhesion, and inflammatory changes (Lloyd et al., 1997). Also, heparin covalently bound to PMMA surfaces have been associated with improved compatibility due to lower activation of complement and decreased outgrowth of fibroblasts and macrophages, activation of granulocytes, and adhesion of platelets (Lamson et al., 1989).

15.18.2 Advances in Intraocular Lenses due to Nanotechnology

Nanoparticles have been impregnated within intraocular lenses to produce haptics having high fracture toughness. Further, in the optical portion incorporation of nanosized inorganic fillers of high refractive index can lead to the increase in the global refractive index and the development of thinner intraocular lenses requiring smaller incisions for surgical procedures.

The need for improving standard intraocular lenses to provide accommodation is recognized. Recently, a two-piece lens system has been developed in which the distance between the two lenses is controlled by the pressure exerted by the ciliary muscle on a U-shaped flange connecting the periphery of the two lenses. Relaxation of the ciliary muscle causes the lens to flatten and the focal length of the lens can be dynamically altered (Smith, 1989; Lloyd et al., 2001). Injectable intraocular lenses that consist of viscoelastics have also been developed in which the viscoelastic gel dimensions and refractive properties are modified as the ciliary muscle contracts and relaxes leading to stretching or bulging of the capsular bag.

Alcon Laboratories has developed AcrySof Natural IOL, which mimics the UV and blue-light attenuating properties of human crystalline lens (Ernest, 2004). This IOL contains a covalently bound chromophore that absorbs light in the 400–500 nm range, adding this light protection to that already provided in the UV range.

15.19 Vitreous Substitutes

The vitreous humor is a transparent gel that occupies the posterior two-thirds of the eye. It is damaged in various vitreo-retinal pathologies and requires replacement by a suitable substitute to aid in vision and to support the retina preventing its detachment.

15.20 Anatomical Considerations for Vitreous Substitutes

The vitreous is a gelatinous mass located posterior to the lens and consists mainly of hyaluronic acid and collagen. The vitreous can be considered as a fiber-reinforced biocomposite with the amounts of the nonaqueous components reduced to a minimum compatible with maintaining mechanical stability (Bishop, 2000). The water component of vitreous accounts for 99% of its composition. This ensures that a minimal amount of solid matter comes in the light path.

Both vitreal and retinal pathologies together comprise the posterior segment disorders that require vitreous substitutes. These conditions are interrelated as retinal tears can lead to vitreous displacement and vitreous scarring can cause retinal detachment. When the vitreous gel shrinks due to disease- or age-related changes, it pulls on the retina and leads to a tear, the vitreous then seeps in between the different layers of the retina, and causes their separation and detachment from the eyeball, leading to blindness. Common conditions requiring vitreous replacements are traumatic injuries to the eye, diabetic retinopathy, and age-related macular degeneration. Vitreous substitutes are required to act as short-term tamponade agents providing retinal support during surgical procedures of the posterior segment of the eye, as well as a long-term tamponade to support the retina in cases of retinal detachment and cases of degeneration of vitreous humor.

15.20.1 Current Strategies for Vitreous Replacements

Air was first used as early as 1911 as a vitreous replacement but the major problem with air, in addition to tissue reactions, was the rapid absorption from the vitreous cavity by diffusion across the retina and hence a reduction in the tamponade effect.

Perfluorocarbon gases like perfluoroethane and perfluoropropane expand on intravitreal injection due to diffusion of other gases from the blood stream. Perfluoropropane expands to four times its original volume by the fourth day of injection and is resorbed at a slower rate than air. They are useful in short-term procedures like pneumatic retinopexy. They have disadvantages of requiring postoperative positioning of the patient and causing increases in the intraocular pressure. They are not suited for long-term replacement.

Silicone oil and its derivatives are the commonly used vitreous substitutes for long-term tamponade. The silicone oils in current use are polydimethylsiloxanes with various chain lengths and molecular weights. The viscosity of the oils varies linearly with the chain lengths and molecular weight. The high interfacial surface energy of silicone oil at the tamponade/aqueous/retina interface ensures the closure of the retinal breaks and reduces subretinal leakage. However, the hydrophobic nature of silicone oil leads to a poor contact with the retina and aqueous fluids, which inhibits the total filling of the vitreous cavity, which is required for effective closure of retinal breaks. Also, the persistence of silicone oil leads to life-threatening complications of cataract, glaucoma, and keratopathy, which necessitate its removal after 2–3 months (Nakamura et al., 1991; Ohira et al., 1991).

Perfluorocarbon liquids have also been tried as vitreous substitutes but cannot be used for more than a week due to the irreversible damage caused to the inferior retina. Further, their low interfacial surface tensions make them poor tamponade agents.

Semisynthetic polymers like hyaluronic acid, collagen, their mixtures, and hydroxypropylmethylcellulose have been evaluated as possible vitreous substitutes. Hyaluronic acid and collagen have the advantages of biocompatibility and hydrophilic nature but do not form suitable gels even in several fold

higher concentrations than those present in the vitreous. Perhaps cross-linked structures may help in improving the performance of these materials (Nakagawa et al., 1997).

Polyvinylpyrrolidinone (PVP) was the first synthetic polymer to be used experimentally as a vitreous substitute in rabbits in 1954. It was used as an aqueous solution and had a short residence time. However, hydrogels of PVP may be used as vitreous substitutes. They undergo biodegradation within 4 weeks and hence can be used only for short-term purposes. Cross-linked polyvinyl alcohol is a promising candidate as a vitreous substitute. It forms a transparent hydrogel and has superior tamponade properties (Colthurst et al., 2000; Soman and Banerjee, 2003).

15.20.2 Recent Advances in Vitreous Substitutes

The possibility of using smart materials that undergo in situ gelation as vitreous substitutes is promising. The material requires to undergo a sol–gel transition due to physiological triggers like ocular temperature, ionic contents in ocular fluids, or changes in pH. Such a material would be easily injected and would form a gel with low syneresis within the posterior chamber of the eye. Such in situ gelling systems have been developed for drug delivery systems and can be combined to serve both as a vitreous substitutes as well as drug delivery agents. Cross-linked polyacrylic acid derivatives have been used for in situ gel formation triggered by pH changes. Methycellulose is an example of a temperature-triggered in situ gelling system whereas alginates can form gels in the presence of cations. However, to function as a vitreous replacement, the agent will need to be nondegradable or very slowly degradable with a prolonged intravitreal residence time.

A vitreous body prosthetic device, though not a vitreous substitute strictly, can act as a functional replacement of the vitreous temporarily. Such a device comprises a thin-walled inflatable balloon made of silicone rubber. The balloon is provided with means for stabilizing and fixing the balloon within the eye. The balloon has an inflow tube made of silicone rubber and is in fluid-tight communication with the interior of the balloon. The other end of the inflow tube is connected to a bulb through which fluid can be introduced into and removed from the tube. Thus the degree of inflation of the balloon can be controlled in order to force the thin-walled balloon against the retinal surface, leading to short-term functional support of the retina (Joseph, 1990).

15.21 Miscellaneous Applications

Orbital implants are used to replace the eyeball for cosmetic reasons after enucleation of the eye. Hydroxyapatite or porous polyethylene implants are used for this purpose.

Intracorneal lenses are implanted within the central stroma of the cornea and augment the normal corneal function. PMMA intracorneal lenses have good optical properties but disrupt nutrient transport across the cornea. Hydrogel and polysulfone intracorneal lenses have also been developed.

Keratoprostheses are penetrating total replacements of the cornea. Lee et al. (1996) identified a variety of criteria that must be met by an ideal keratoprosthesis. These are as follows: (1) the device should be tightly retained in the cornea to prevent extrusion, (2) it should be easily and completely colonized by corneal epithelial cells on the external surface, and (3) it should suppress downgrowth of such cells into the implant bed. Custom-made prostheses of polytetrafluoroethylene having 50 μm pores have shown a refractive index similar to the natural cornea, good collagen synthesis and have been clinically successful (Legeais et al., 1994).

Glaucoma filtration devices are useful in the drainage of fluid in glaucoma. Galucoma is a condition in which raised intraocular pressure causes progressive optic nerve damage and visual field loss. The devices consist of silicone tubes and plates of silicone, polypropylene, and silicone–PMMA combinations (Lim et al., 1998).

Scleral buckles are materials that are used to indent the sclera bringing the choroid in contact with the retina and thus being useful in retinal support in cases of retinal detachment. The simplest absorbable

scleral buckles consist of autogenous tendons and fascia lata from the patient. Another resorbable material commonly used as a scleral buckle is pigskin gelatin, which is resorbed over 3–6 months (Schepens and Acosta, 1991). Nonabsorbable buckles are made of silicone or hydrogels. An advantage of the use of silicones is the formation of a tough fibrous capsule around the implant, which both strengthens the sclera and allows easy removal of the implant in the future if required.

15.22 Clinical Implications and Future Prospects

The ocular toxicity of nanoparticles needs to be clearly evaluated. In a recent study, Prow et al. (2008) evaluated the ocular toxicity and transfection potential of chitosan and synthetic polymeric and magnetic nanoparticles in retinal cells. Intravitreal injection of chitosan nanoparticles were found to show an inflammatory reaction. Subretinal magnetic nanoparticles did not show any inflammation or toxic changes over 7 days and had a high transfection potential. The study indicates that different types of nanoparticles have varying cellular interactions in the eyes and ocular toxicity needs to be evaluated over long-term periods. Many biopolymeric and lipid nanoparticles have been found to be nontoxic when applied in the eye.

Lipimix, a drug-free phospholipid emulsion, has been commercialized to replace the lipid layer of the acrimal fluid after refractive surgeries. Clinical trials of Piloplex (pilocarpine-loaded nanospheres made of polymethylmethacrylate acrylic acid copolymer) showed a reduction in intraocular pressure levels but commercialization was not undertaken due to nonbiodegradability, local toxicity, and difficulty in large-scale manufacture of sterile preparations (Araújo et al., 2009). Pegylated RNA aptamers directed at vascular endothelial growth factor have been approved for the treatment of neovascularization in acute macular degeneration (Santos et al., 2006). The use of nonviral nanoparticle delivery strategies can improve transfection and reduce the risk of repeated intravitreal injections.

Nanobiomaterials can provide many promising strategies for diagnostic and therapeutic improvements in ocular drug delivery and in ocular implants. The nanoparticles can especially be useful to overcome the ocular penetration barriers and to prevent washout by the lacrimal fluid. The importance of such nanoparticles is particularly for posterior segment ocular diseases like retinopathies, acute macular degeneration, and other retinal diseases due to the negligible reach of current modalities of therapy in such conditions. The concepts of nanoparticle-impregnated implants like inserts, corneal bandages, and contact lenses can open up new therapeutic avenues for combined biomaterial applications and drug delivery. Further preclinical and clinical trials are warranted to allow the clinical benefits of nanotechnology to be reaped in ophthalmic practice.

References

Araújo, J., Gonzalez, E., Egea, M. A., Garcia, M. L., and Souto, E. B. (2009) Nanomedicines for ocular NSAIDs: Safety on drug delivery. *Nanomedicine* **5**, 394–401.

Attama, A. A., Reichl, S., and Muller-Goymann, C. C. (2008) Diclofenac sodium delivery to the eye: In vitro evaluation of novel solid lipid nanoparticle formulation using human cornea construct. *Int. J. Pharm*. **355**, 307–313.

Badugu, R., Lakowicz, J. R., and Geddes, C. D. (2005) A glucose-sensing contact lens: From bench top to patient. *Curr. Opin. Biotech*. **16(1)**, 100–107.

Benjamin, W. J. (1996) Down sizing of Dk and Dk/l: The difficulty in using hPa instead of mm Hg. *Int. Contact Lens Clin*. **23**, 188–189.

Bishop, P. (2000) Structural macromolecules and supramolecular organization of the vitreous gel. *Prog. Ret. Eye Res*. **19**, 323–344.

Brennan, N. A. (1988) New technology in contact lens materials. *Trans. Br. Contact Lens Assoc. Ann. Clin. Conf*. **11**, 23–28.

Bruinsma, G. M., van der Mei, H. C., and Busscher, H. J. (2001) Bacterial adhesion to surface hydrophilic and hydrophobic contact lenses. *Biomaterials* **22**, 3217–3224.

Cai, X., Conley, S., and Naash, M. (2008) Nanoparticle applications in ocular gene therapy. *Vision Res*. **48**, 319–324.

Calvo, P., Thomas, C., Alonso, M. J., Vila-Jato, J., and Robinson, J. R. (1994) Study of the mechanism of interaction of poly(ε-caprolactone) nanocapsules with the cornea by confocal laser scanning microscopy. *Int. J. Pharm*. **103**, 283–291.

Campos, A. M. D., Sanchez, A., Alonso, M. J. (2001) Chitosan nanoparticles: A new vehicle for the improvement of the delivery of drugs to the ocular surface. Application to cyclosporin A. *Int. J. Pharm*. **224**, 159–168.

Cavalli, R., Gasco, M. R., Chetoni, P., Burgalassi, S., and Saettone, M. F. (2002) Solid lipid nanoparticles as ocular delivery system for tobramycin. *Int. J. Pharm*. **238**, 241–245.

Colthurst, M., Williams, R., Hiscott, P., and Grierson, I. (2000) Biomaterials used in the posterior segment of the eye. *Biomaterials* **21**, 649–665.

Das, S., Banerjee, R., and Bellare, J. (2005) Aspirin loaded albumin nanoparticles by coacervation: Implications in drug delivery. *Trends Biomater. Artif. Organs* **18(2)**, 203–212.

Das, S., Suresh, P. K., and Desmukh, R. Design of Eudragit RL 100 nanoparticles by nanoprecipitation method for ocular drug delivery. *Nanomedicine.* In press.

Davson, H. (1990) *Physiology of the Eye: The Aqueous Humor and Intraocular Pressure*. London: Macmillan Press, pp. 3–65.

Diebold, Y., Jarrin, M., Saez, V., Carvalho, E. L. S., Orea, M., Calonge, M., Seijo, M., and Alonso, M. J. (2007) Ocular drug delivery by liposome–chitosan nanoparticle complexes (LCS-NP). *Biomaterials* **28**, 1553–1564.

Dillen, K., Weyenberg, W., Vandervoort, J., and Ludwig, A. (2004) The influence of the use of viscosifying agents as dispersion media on the drug release properties from PLGA nanoparticles. *Eur. J. Pharm. Biopharm*. **58**, 539–549.

Ding, S. (1998) Recent developments in ophthalmic drug delivery. *PSTT* **1**, 328–336.

Dufrene, Y. F., Boonaert, C. J. P., and Rouxhet, P. G. (1996) Adhesion of *Azospirillum brasilense*: Role of proteins at the cell–support interface. *Colloids Surf. B* **7**, 113–128.

Durrani, A. M., Davies, N. M., Thomas, M., and Kellaway, I. W. (1992) Pilocarpine bioavailability from a muco-adhesive liposomal ophthalmic drug delivery system. *Int. J. Pharm*. **88**, 409–415.

Ernest, P. H. (2004) Light-transmission-spectrum comparison of foldable intraocular lenses. *J. Cataract Refract. Surg*. **30**, 1755–1758.

Fatt, I. (1996) New physiological paradigms to assess the effect of lens oxygen transmissibility on corneal health. *Contact Lens Assoc. Ophthalmol. J*. **22**, 25–29.

Fattal, E. and Bochot, A. (2006) Ocular delivery of nucleic acids: Antisense oligonucleotides, aptamers and siRNA. *Adv. Drug Deliv. Rev*. **58**, 1203–1223.

Geroshi, D. H., Matsuda, M., and Yee, R. W. (1995) Pump function of the human corneal endothelium. *Ophthalmology* **92**, 1.

Grinstaff, M. W. (2007) Designing hydrogel adhesives for corneal wound repair. *Biomaterials* **28**, 5205–5214.

Gupta, H., Aqil, M., Khar, R. K., Ali, A., Bhatnagar, A., and Mittal, G. Sparfloxacin loaded PLGA nanoparticles for sustained ocular drug delivery. *Nanomedicine*. In press.

Gupta, A. K., Madan, S., Majumdar, D. K., and Maitra, A. (2000) Ketorolac entrapped in polymeric micelles: Preparation, characterisation and ocular anti-inflammatory studies. *Int. J. Pharm*. **209**, 1–14.

Hiratani, H. and Alvarez-Lorenzo, C. (2002) Timolol uptake and release by imprinted soft contact lenses made of N, N-diethylacrylamide and methacrylic acid. *J. Control. Release* **83**, 223–230.

Hiratani, H. and Alvarez-Lorenzo, C. (2004) The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. *Biomaterials* **25**, 1105–1113.

Hiratani, H., Fujiwara, A., Tamiya, Y., Mizutani, Y., and Alvarez-Lorenzo, C. (2005) Ocular release of timolol from molecularly imprinted soft contact lenses. *Biomaterials* **26**, 1293–1298.

Holden, B. A. and Mertz, G. W. (1984) Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. *Invest. Ophthalmol. Vis. Sci*. **25**, 1161–1167.

Jain, D. and Banerjee, R. (2008) Comparison of ciprofloxacin hydrochloride loaded protein, lipid and chitosan nanoparticles for drug delivery. *J. Biomed. Mater. Res. B* **86(1)**, 105–112.

Jain, D., Carvalho, E., and Banerjee, R. (2010) Biodegradable hybrid polymeric membranes for ocular drug delivery. *Acta Biomaterialia* **6(4)**, 1370–1379.

Joseph, N. (1990) Vitreous body prosthetic device. U.S. Patent No. 4902492.

Ketelson, H. A., Meadows, D. L., and Stone, R. P. (2005) Dynamic wettability properties of a soft contact lens hydrogel. *Colloids Surf. B* **40**, 1–9.

Klausner, E. A., Zhang, Z., Chapman, R. L., Multack, R. F., and Volin, M. V. (2010) Ultrapure chitosan oligomers as carriers for corneal gene transfer. *Biomaterials* **31**, 1814–1820.

Kohnen, T. (1996) The variety of foldable intraocular lens materials. *J. Cataract Refract. Surg*. **22**, 1255–1257.

Kyyronen, K., Hume, L., Benedetti, L., Urtti, A., Topp, E., and Stella, V. (1992) Methylprednisolone esters of hyaluronic acid: In ophthalmic drug delivery: In vitro and in vivo release studies. *Int. J. Pharm*. **80**, 161–169.

Lamson, R., Selbn, G., Bjiirklund, H., and Fagerholm, P. (1989) Intraocular PMMA lenses modified with surface-immobilized heparin: Evaluation of biocompatibility in vitro and in vivo. *Biomaterials* **10**, 511–516.

Lazzaro, D. R. (2005) What's new in ophthalmic surgery. *J. Am. Coll. Surg*. **200**, 96–102.

Le Bourlais, C., Acar, L., Zia, H., Sado, P. A., Needham, T., and Leverge, R. (1998) Ophthalmic drug delivery systems recent advances. *Progr. Retinal Eye Res*. **17**, 33–58.

Lee, S. D., Hsiue, G. H., Kao, C. Y., and Chang, P. C. T. (1996) Artificial cornea: Surface modification of silicone rubber membrane by graft polymerization of pHEMA via glow discharge. *Biomaterials* **17**, 587–595.

Legeais, J. M., Renard, G., Parel, J. M., Serdarevic, O., Mei Mui, M., and Pouliquen, Y. (1994) Expanded fluorocarbon for keratoprosthesis cellular ingrowth and transparency. *Exp. Eye Res*. **58**, 41–52.

Lim, K. S., Allan, B. D. S., Lloyd, A. W., Muir, A., and Khaw, P. T. (1998) Glaucoma filtration implants: Past, present and future. *Br. J. Ophthalmol*. **82**, 1083–1089.

Lindstrom, R. L. and Doddi, N. (1986) Ultraviolet light absorption in intraocular lenses. *J. Cataract Refract. Surg*. **12**, 285–289.

Lloyd, A. W., Bowers, R. W. J., Dropcova, S., Denyer, S. P., Faragher, R. G. A., Gard, P. R., Hall et al. (1997) In vitro evaluation of novel biomimetic intraocular lens materials. *Invest. Ophthalmol. Vis. Sci*. **38**, 884.

Lloyd, A. W., Faragher, R. G. A., and Denyer, S. P. (2001) Ocular biomaterials and implants. *Biomaterials* **22**, 769–785.

Lundberg, F., Gouda, I., Larm, O., Galin, M. A., and Ljungh, A. (1998) A new model to assess staphylococcal adhesion to intraocular lenses under in vitro flow conditions. *Biomaterials* **19**, 1727–1733.

Mainster, M. A. (1986) The spectra, classification, and rationale of ultraviolet-protective intraocular lenses. *Am. J. Ophthalmol*. **102**, 727–732.

Merodio, M., Irache, J. M., Valamanesh, F., and Mirshahi, M. (2002) Ocular disposition and tolerance of ganciclovir-loaded albumin nanoparticles after intravitreal injection in rats. *Biomaterials* **23**, 1587–1594.

Nakagawa, M., Tanaka, M., and Miyata, T. (1997) Evaluation of collagen gel and hyaluronic acid as vitreous substitutes. *Ophthalmic Res*. **29**, 409–420.

Nakamura, K., Refojo, M., Crabtree, D., Pastor, J., and Leong, F. (1991) Ocular toxicity of low molecular-weight components of silicone and fluorosilicone oils. *Invest. Ophthalmol. Vis. Sci*. **32**, 3007–3020.

Ohira, A., Wilson, C., de Juan Jr., E., Murata, Y., Soji, T., and Oshima, K. (1991) Experimental retinal tolerance to emulsified silicone oil. *Retina* **11**, 259–265.

Pignatello, R., Bucolo, C., Ferrara, P., Maltese, A., Puleo, A., and Puglisi, G. (2002) Eudragit RS100® nanosuspensions for the ophthalmic controlled delivery of ibuprofen. *Eur. J. Pharm. Sci*. **16**, 53–61.

Prow, T. W., Bhutto, I., Kim, S. Y., Grebe, R., Merges, C., McLeod, D. S., Uno et al. (2008) Ocular nanoparticle toxicity and transfection of the retina and retinal pigment epithelium. *Nanomedicine* **4**, 340–349.

Sahoo, S. K., Dilnawaz, F., and Krishnakumar, S. (2008) Nanotechnology in opcular drug delivery. *Drug Discov. Today* **13**, 144–150.

Saika, S. (2004) Relationship between posterior capsule opacification and intraocular lens biocompatibility. *Progr. Retinal Eye Res*. **23**, 283–305.

Sanders, N. N., Peeters, L., Lentacker, I., Demeester, J., and De Smedt, S. C. (2007) Wanted and unwanted properties of surface PEGylated nucleic acid nanoparticles in ocular gene transfer. *J. Control. Release* **122**, 226–235.

Santos, J. F. R., Alvarez-Lorenzo, C., Silva, M., Balsa, L., Couceiro, J., Torres-Labandeira, J. J., and Concheiro, A. (2009) Soft contact lenses functionalized with pendant cyclodextrins for controlled drug delivery. *Biomaterials* **30**, 1348–1355.

Santos, A. L. G. D., Bochot, A., Doyle, A., Tsapis, N., Siepmann, J., Siepmann, F., Schmaler, J., Besnard, M., Behar-Cohen, F., and Fattal, E. (2006) Sustained release of nanosized complexes of polyethylenimine and anti-TGF-beta2 oligonucleotide improves the outcome of glaucoma surgery. *J. Control. Release* **112**, 369–381.

Schepens, C. L. and Acosta, F. (1991) Scleral implants: An historical perspective. *Surv. Ophthalmol*. **35**, 447–453.

Schneider, R. P. and Marshall, K. C. (1994) Retention of the Gram-negative marine bacterium SW8 on surfaces effects of microbial physiology, substratum nature and conditioning films. *Colloids Surf. B* **2**, 387–396.

Sheikpranbabu, S., Kalishwaralal, K., Lee, K., Vaidyanathan, R., Eom, S. H., and Gurunathan, S. (2010) The inhibition of advanced glycation end-products-induced retinal vascular permeability by silver nanoparticles. *Biomaterials* **31**, 2260–2271.

Smith, S. G. (1989) Accommodating intraocular lens and method of implanting and using same. U.S. Patent 50782.

Soman, N. and Banerjee, R. (2003) Artificial vitreous replacements. *Biomed. Mater. Eng*. **13**, 59–74.

Sparrow, J. R., Miller, A. S., and Zhou, J. (2004) Blue light-absorbing intraocular lens and retinal pigment epithelium protection in vitro. *J. Cataract Refract. Surg*. **30**, 873–878.

Stenevi, U., Gwin, T., Harfstrand, A., and Apple, D. (1993) Demonstration of hyaluronic acid binding to corneal endothelial cells in human eye-bank eyes. *Eur. J. Implant Refract. Surg*. **5**, 228–232.

Taniguchi, K., Yamamoto, Y., ltakura, K., Miichi, H., and Hayashi, S. (1988) Assessment of ocular irritability of liposome preparation. *J. Pharmacobiodyn*. **11**, 607–611.

Tighe, B. J. and Ng, C. O. (1979) The mechanical properties of contact lens materials. *Ophthal. Optician* **19**, 394–402.

Tranoudis, I. and Efron, N. (2004a) Tensile properties of soft contact lens materials. *Contact Lens Ant. Eye* **27**, 177–191.

Tranoudis, I. and Efron, N. (2004b) Water properties of soft contact lens materials. *Contact Lens Ant. Eye* **27**, 193–208.

Vandervoort, J. and Ludwig, A. (2004). Preparation and evaluation of drug-loaded gelatin nanoparticles for topical ophthalmic use. *Eur. J. Pharm. Biopharm*. **57**, 251–261.

Wimmer, N., Marano, R. J., Kearns, P. S., Rakoczy, E. P., and Toth, I. (2002) Syntheses of polycationic dendrimers on lipophilic peptide core for complexation and transport of oligonucleotides. *Bioorg. Med. Chem. Lett*. **12**, 2635–2637.

Yenice, I., Mocan, M. C., Palaska, E., Bochot, A., Bilensoy, E., Vural, I., Irkeç, M., and Hincal, A. A. (2008) Hyaluronic acid coated poly-3-caprolactone nanospheres deliver high concentrations of cyclosporine A into the cornea. *Exp. Eye Res*. **87**, 162–167.

Yuan, X., Li, H., and Yuan, Y. (2006) Preparation of cholesterol-modified chitosan self-aggregated nanoparticles for delivery of drugs to ocular surface. *Carbohydr. Polym*. **65**, 337–345.

Zimmer, A. and Kreuter, J. (1995) Microspheres and nanoparticles used in ocular delivery systems. *Adv. Drug Deliv. Rev*. **16**, 61–73.