

Chapter 5

Topical Versus Systemic Ocular Drug Delivery

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Abstract The eye is a very complex sensory organ consists of numerous structures function to coordinate sight properly. Several diseases related to eye include: (a) common inflammation and allergic reactions due to bacterial, viral, fungal or chemicals such as cytomegalovirus (CMV) retinitis and allergic rhinitis; (b) inflammatory and autoimmune disease such as scleritis and uveitis; (c) ocular neovascularization such as age-related macular degeneration (AMD), diabetic retinopathy (DR); and (d) retinal vein occlusion that can cause blindness if untreated or treated improperly. For years, ophthalmic formulations have been one of the most important, widely developed and challenging as pharmaceutical companies try to develop innovative drugs. Due to the complicated anatomical structure and a small absorptive surface of the eye, it is difficult to reach the eye compartment properly. Ophthalmologists still face challenges in treating different diseases of the anterior and posterior segments. Systemic, intraocular, and other methods of drug delivery are explained below with major emphasis on topical deliveries.

Keywords Topical delivery · Systemic delivery · Diseases of the eye · Intraocular delivery

Introduction

Systemic, extraocular (topical and subconjunctival), and intraocular (intrastromal, intracameral, subretinal, intravitreal), are the three main routes of delivering ophthalmic drugs. Each has its own advantages and disadvantages. Topical drug delivery is the most common route accounting for about 90 % of available formulations used for the treatment of conjunctivitis, uveitis, keratitis, scleritis, and others. The anatomical structure of the eye causes difficulty in delivering effective

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drug concentration to the intended site and the ability of the drugs to stay longer to be effective. Some of these problems are: small absorptive surface of the eye, low transparency of the cornea, lipophilicity or hydrophilicity moieties of different epitheliums of the eye, low capacity of conjunctival sac that can only hold 30 μL of drugs, weak bonding of the drug with proteins contained in tear fluid, blinking which cause loss of the drugs, the presence of efflux transporter such as P-glycoprotein (P-gp) that efflux drugs out of the eye, and the presence of several barriers such as blood-aqueous barrier (BAB) and blood-retinal barrier (BRB) that prevent optimal drug delivery to the intended area of the eye (Gaudana et al. 2009; Jarvinen and Jarvinen 1996; Rajasekaran et al. 2010). Chapter 4 discussed in detail barriers facing drugs delivery to anterior or posterior segments of the eye.

Giving oral drugs using sustained-release (SR) formulation can be an advantage for patients' compliances in the treatment of lifelong disease such as glaucoma, AMD, but systemic undesirable adverse effects should also be expected (Morrison and Khutoryanskiy 2014; Martin 2012).

Intraocular delivery is a technique used to deposit drug to the eye directly using injection to the cornea (intrastromal), anterior segment (intracameral), or vitreous cavity in the center of the eye (intravitreal). These methods are effective in getting the ophthalmic drugs into the posterior segment of the eye such as for AMD treatment, but they are invasive procedures require sterile techniques with increased risks of retinal detachment, hemorrhage, endophthalmitis, and ocular hypertension (Bell et al. 2004; Jiang et al. 2009; Patel et al. 2011).

Systemic Delivery

Oral and parenteral injections are the two most common methods of delivery that can achieve systemic dosing. Oral delivery of large molecule drug is a non-invasive method to deliver a drug, but it has a limited penetration into the targeting eye tissue. The drug is also easily degraded in the gastrointestinal tract and become inactive after going through the first-pass metabolism in the liver; therefore, the amount of active drug that reaches the eye and its bioavailability is very minimal (less than 2 %). Small molecule drugs such as analgesics, antibiotics, and antiviral ophthalmics reach the intended site at low concentration (Kim et al. 2014). Formulating drug into SR such as for the treatment of glaucoma allow continuous and effective concentration of the drug at the intended site, but the systemic undesirable side effects are also greater and need to be considered.

Several systemic deliveries for the treatment of CMV retinitis, uveitis, and scleritis have been employed. CMV is an opportunistic virus that can infect ocular tissue such as the retina. This disease affects up to 25 % of patients with acquired immune deficiency syndrome (AIDS). Ganciclovir is the first line treatment that was initially given to the patient intravenously. Due to unwanted systemic side effects such as neutropenia, the systemic delivery has been replaced by intravitreal delivery (Yasin et al. 2014; Gaudana et al. 2010).

Uveitis is inflammation of the uvea that can cause blindness. It is divided into 4 types: (1) inflammation of the iris also called anterior uveitis, (2) inflammation of ciliary body also called intermediate uveitis, (3) inflammation of the choroid also called posterior uveitis, and (4) inflammation of all the part also called panuveitis. The current treatment is to suppress the inflammation by using topical or systemic immune suppressive such as methotrexate, cyclosporine A (CsA), cyclophosphamide, and biologics such as adalimumab or infliximab. Most of these drugs are given systemically. The drugs are less efficacious and have less specific effect at the intended site of the eye. It also causes systemic undesirable side effects which if severe enough prompt patients to discontinue taking the drug, thus causing a relapse of the disease (Yasin et al. 2014).

Scleritis is a serious inflammatory disease that can be due to infection, autoimmune or idiopathic. It can cause severe ocular pain, headache, periorbital pain, congestion of blood vessels and edema of the sclera, and occasionally blindness. Steroids are given systemically or topically have been used to treat this inflammation, but the systemic side effects cause steroids as non—preferable agents. Oral CsA 2–3.5 mg/kg/day have been used successfully in several case reports to treat uveitis and scleritis with minimal or no side effects. The ideal value of CsA ranges from 50 to 150 ng/ml to avoid systemic side effects and yet still achieving disease remission (Cholkar et al. 2015).

The choroid is the most common ocular site for breast or lung cancer to metastasis, due to its abundant vascular supply. Treatment option for choroidal metastases includes whole eye radiotherapy, systemic chemotherapy, immunotherapy, or hormone therapy. A large portion of choroidal metastases also expresses estrogen or progesterone receptors, making therapy with oral or parenteral injections as an effective option. For example, tamoxifen or aromatase inhibitors which are used to treat breast or lung cancer, also benefit to prevent cancer metastasis to choroid (Arepalli et al. 2015).

Following oral or parenteral injections, the BAB, BRB, and efflux transporter are obstacles that drugs encounter to enter the eye. Large size molecules are rarely used to deliver the drug to the eye due to poor absorption across many ocular barriers while increasing the dose of the drug can increase the severity of systemic side effects with the bioavailability of the drug is still very low. Targeting drugs to the posterior segment of the eye can be achieved by intravenous, but the drug penetration is limited due to BRB. After systemic administration, drugs can penetrate through any leaky vessels in the choroid and diffuse into the posterior segment. Numerous fenestrae are present in the endothelium of the choriocapillaris resulting in very little resistance for the transport of systemic solutes into the choroid. However, the presence of efflux transporters such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP) found in the cell membrane of RPE can limit drug permeability from choroid to retina and vitreous chamber (Kompella et al. 2013).

Several attempts to improve drug delivery systematically using drug transporters have been done successfully in several animal models and ophthalmic cell lines. Cellular transporters play an important role in the disposition of drugs at the site of therapeutic action. An efflux transporter such as P-gp and MRP can limit the amount of drug reaching the target ocular tissue, thus limiting their efficacy, while an uptake or influx transporters present in ocular such as amino acid and peptide transporters are known as ASCT1A, peptide/histidine transporters (PHT1 and PHT2) can elevate the level of drugs in the target ocular tissue. Using influx transporter-targeted prodrugs, oral and systemically administered drugs can be distributed more efficiently. These molecules can interact with topical drugs by altering their local pharmacokinetics, safety, and efficacy. In the same way, topically administered drugs can affect the ocular distribution of orally or parenterally administered drugs by inhibiting the efflux transporters in the blood-ocular barriers, in which the oral/systemic drugs behaves as a substrate of transporters (Chemuturi and Yanez 2013). Further investigations are needed to modify the action of efflux and influx transporters system in the eye, so systemic ocular delivery, which usually have higher compliance and non-invasive route, can deliver drugs to the eye compartment with the highest bioavailability and lowest systemic side effects.

For systemic delivery to be successful, a relatively high drug concentration needs to be circulating in the blood plasma in order to achieve a therapeutically effective dose within the eye. Avoiding ocular barriers, altering influx systems, changing the formulations of oral or parenteral formulations are important innovations to make a systemic delivery to the eye efficient, with less systemic side effects, and minimal metabolism and clearance by the liver and kidney.

Topical Delivery

Topical delivery is the most accepted route accounting for approximately 90 % of aqueous ophthalmic formulations. Advantages of topical delivery are their relative simplicity to formulate, minimal storage of the drug, and ease of drug instillation thus increasing patients' compliances. Disadvantages include limited drug concentration at the eye if formulated as lipophilic drugs, significant loss at precorneal, the different barriers in the eye that cause low bioavailability at the intended site. There are several topical deliveries commercially available or in the research such as: (1) liquid forms (eye drops, ophthalmic solutions, micro or nanoemulsions); (2) semisolid forms (in situ gel, ointment); (3) solid forms (soft contact lenses, different inserts, mini tablets); and (4) other forms of delivery (sprays, iontophoresis, filter strips).

Liquid Ophthalmic Forms

Eye Drops

Eye drops are available as water and lipid solutions or suspensions. These forms are sterile, isotonic, with the pH equal to tear fluid (pH 7.4), and they may contain preservatives for multi-use packages. If the pH of the drugs is outside the range of 4–8, the drug can cause eye irritation and decrease in their bioavailability. The eye drops are easy to instill, but only a very small amount of the drugs are being absorbed into the target tissues. Therefore, it is important to apply large doses of drugs frequently to achieve the therapeutic doses, but large doses can cause more local and systemic side effects. (Baranowski et al. 2014; Gaudana et al. 2009; Jarvinen and Jarvinen 1996; Rajasekaran et al. 2010).

Ophthalmic Solutions

Ophthalmic solutions are sterile aqueous solution used to cleanse and rinse eye. It may contain excipients to regulate osmotic pressure, the pH, and viscosity of the products. The advantages are non—invasive, low systemic absorption, avoidance of first pass metabolism, ease of application with a small dose. Disadvantages include rapid drainage, rapid drug removal due to reflex blinking, and rapid degradation by enzymes such as esterases and amidases. Drugs should possess active molecules with a balance of hydrophilicity and hydrophobicity to generate longer time when in contact with cornea and conjunctiva. (Baranowski et al. 2014; Gaudana et al. 2009; Jarvinen and Jarvinen 1996; Rajasekaran et al. 2010).

Microemulsions and Nanoemulsions

Emulsions are fine dispersion of droplets of two immiscible liquids. Nanoemulsions have a particle size in the range of submicron or nanometer range. It comprises of one or more amphiphilic lipids or surfactants. Surfactants are molecule with bipolar structure with hydrophilic and hydrophobic part. Because of their globule sizes, nanoemulsions are thermodynamically unstable dispersions that require high concentration of surfactants to stabilize the formulation which can cause a sticky feeling when the drug is applied to the eye. To make more stable formulations, non-ionic polymers, oxyethylenated or non-oxyethylated sorbitol fatty esters can be used to modify the viscosity of lipid-in-water nanoemulsions without compromising the drug's transparency and bioavailability. The water soluble, non-ionic or neutral polymers of ethylene oxide, vinyl caprolactam, or polyvinyl methyl ether result in nanoemulsion that was stable, transparent with oil globules of less than 100 nm (Lallemand et al. 2012; Hofland et al. 2004; Velagaleti et al. 2010).

The first nanoemulsion approved by the FDA is Restasis[®] that deliver 0.05 % CsA used for the treatment of dry eye. This drug exhibits satisfactory physico-chemical properties, sustained release, higher therapeutic efficacy, and fast onset of action as compared to the solution from Trusopt[®]. Cyclokat[®] is another novel nanoemulsion of CsA using Novasorb[®], a technology in which cationic nanoemulsion interact well with anionic eye surface, thus improving the bioavailability of this drug to treat dry eye (Chaurasia and Lim 2015; Chauhan and Gulsen 2012; Ako-Adounvo 2014).

Prostaglandins (PGs) are oxygenated cyclic fatty acids that have been used to treat glaucoma. Available PG analogs on the market are bimatoprost, latanoprost, travoprost, and others. However, several of these drugs may have poor water solubility and chemically unstable in aqueous solution. Nanoemulsion formulation made of an oil phase containing PG dispersed in an aqueous phase that is stabilized by a combination of two or more non-ionic surfactants result in a chemically and physically stable emulsion and non-toxic drug such as Catioprost[®], a nanoemulsion formulation of latanoprost (Velagaleti et al. 2010).

Semisolid Ophthalmic Forms

In Situ Gels

Also called “Sol-to-Gel” system are viscous liquids that can change from solution to gel by changing pH, temperature and electrolytes, therefore causing slowing drainage from the eye surface and increase the ophthalmic drug bioavailability. Polymers such as anionic gellan gum, poloxamer, cellulose acetate phthalate (CAP) are added to increase the viscosity of the ophthalmic drug gel system when it comes into contact with cation (Rathore and Nema 2009; Gaudana et al. 2009). Combine poloxamer and chitosan allow site-specific drug delivery with gel strength and mucoadhesive properties. Several drugs used in situ gel system that has been approved by the FDA include: pilocarpine, timolol (Timoptic-XE[®]), tobramycin (Tobradex-ST[®]), ciprofloxacin, fluconazole, and ganciclovir useful for the treatment of glaucoma, bacterial, fungal or virus infections, respectively. Excipients such as carbopol gels, cellulose derivatives, dextran, gelatin glycerin, polyethylene glycol (PG), and poloxamer 407, and polysorbate 80, polyvinylpyrrolidone are added due to their viscosity enhancing or bioadhesive properties that can significantly improve the ocular retention time (Ako-Adounvo 2014; Velagaleti et al. 2010; Rathore and Nema 2009).

Eye Ointment

Ointments use semisolid or solid hydrocarbon base compound with melting point close to human body temperature. After applying the ointment to the eye, it slowly

becomes small drops and stays longer time in conjunctival sac increasing its bioavailability. Although these formulations are well tolerated and safe, they can cause blur vision and irritation to the eye. It should be applied at night time (Baranowski et al. 2014).

Solid Ophthalmic Forms

Soft Contact Lenses Coated with Drug

Soft contact lenses have been used to prevent drug loss, to reduce systemic side effects, and to improve efficacy. The contact lenses served as a matrix for the drug nanoparticles which range from 50 to 200 nm with the lens being clear and not to hinder the vision. Polymers that are widely used with the lenses are cross-linked poly 2-hydroxy ethyl methacrylate and ethylene glycol dimethyl acrylate (HEMA). The drug was released from the lens by diffusion from the particles of the lenses matrix. The lens increased the drug retention time and drug permeability across the cornea, provided sustained drug release and minimizes the systemic absorption *via* nasolacrimal sac (Gong et al. 2009; Lallemand et al. 2012). Drugs such as ciprofloxacin, timolol, dexamethasone, and CsA have been added to these polymer coated lenses successfully, and they stay in the eye for longer period of time than conventional eye drops (Baranowski et al. 2014).

Ocular Inserts

Ocular inserts are solid or semisolid dosage form of drug designed to reside within the ocular cul-de-sac, intended to attach to conjunctiva or directly into the cornea. The insert acts as controlled release reservoir added with polymeric materials such as hydroxyl propyl methyl cellulose (HPMC), hydroxyl ethyl cellulose (HEC), chitosan, or polyvinyl the pyrrolidone (PVP-K-90) and gelatin. The insert causes feeling of foreign body in the eye. Failure of inserting the insert properly into the eye make these forms less desirable. The first ocular insert Ocuser[®] was the first successful ocular insert to deliver pilocarpine for the treatment of ocular hypertension (Gaudana et al. 2009). Advantages of using ocular insert include: increase bioavailability, precise dosing, controlled release of drugs, avoidance of pulsating drug delivery, minimal systemic absorption, reduced frequency of administration, better sclera or conjunctiva route to the internal target, better shelf life with no need of preservatives (Morrison and Khutoryanskiy 2014). Disadvantages of these formulations include: physical and psychological obstacles of placing solid objects in the eye, vision can interfere due to movement of the inserts, potential accidental loss of the insert, and difficulty to remove the inserts (Baranowski et al. 2014; Aburahna and Mahmoud 2011).

SODIs (Soluble Ophthalmic Drug Inserts)

SODIs are small oval wafers soluble eye inserts that upon application to the conjunctiva sac become moistened by tear fluid; they become soft and adhere to eye surface better. The drug is released in a pulsatile manner to ensure its prolonged effect. The small wafers are made from acrylamide, N-vinylpyrrolidone, and ethyl acrylate. Several drugs such as neomycin, kanamycin, atropine, pilocarpine, dexamethasone, sulfapyridine, and tetracaine had been successfully formulated using SODIs system (Baranowski et al. 2014).

Minidisc Ocular Therapeutic System (OTS)

Minidisc contact lens-sized 4–5 mm in diameter that contains α - ω -bis (4-methacryloxy)-butyl poly (dimethylsiloxane) and poly (hydroxyethyl methacrylate). It is a profiled, convex outside with concave from the inside that increases contact with the eye surface. The OTS can hold hydrophilic or hydrophobic drugs over extended time. The ophthalmic drugs that have been utilized using this system include sulfisoxazole and gentamicin which are able to stay in the sclera from 3–14 days (Nisha and Deepak 2012).

Artificial Tear Inserts

This insert is made with hydroxypropyl cellulose shaped as a long rod. The insert absorbs water from conjunctiva and cornea, forming a hydrophilic layer that stabilizes the tear film and moistens the cornea. Lacrisert[®] has been marketed for the treatment of dry eye syndrome (Nisha and Deepak 2012).

Collagen Shield

The older version of collagen shields was developed from the porcine sclera, but its use caused discomfort and vision problem. Recent dosage formulation is collasomes, a small piece of collagen (1 × 2 × 0.1 mm) suspended in 1 % methylcellulose. Collagen shield can carry antibiotics, anti-inflammatory, or other drugs (Tangri and Khurana 2011).

Mini Tablets

Mini tablets are biodegradable, solid drug applied to conjunctiva sac which after long contact with the cornea become gel due to a mucoadhesive polymer, the active ingredients would gradually be released. Mini tablets consist of polymers such as HPMC, HEC, carbopol, chitosan, starch and mannitol excipients and magnesium

stearate or sodium stearyl fumarate that has lubricating properties. Active ingredients incorporated into the mini tablets include timolol, piroxicam, ciprofloxacin, gentamicin, and acyclovir (Gaudana et al. 2009; Rajasekaran et al. 2010).

Other Ophthalmic Drug Forms

Sprays

Spray ophthalmic drugs include cycloplegics, mydriatics, and phenylephrine-tropicamide. The distance between the spray device and eye should be around 5–10 cm. The active ingredients in the spray drug should be around 1–4 % which has similar effect like eye drops at a concentration of 1 %. The advantage is the drug can be applied on closed eyelid (Gaudana et al. 2009).

Ocular Iontophoresis

The positively charged molecules are introduced to eye tissue from an anode and the negatively charged ion from the cathode. Iontophoresis enables fast, safe and painless delivery of high concentration of drug to the desired areas (Souza et al. 2013). Drugs delivered using this method include gentamicin, dexamethasone, ciprofloxacin, and ketoconazole.

To deliver drugs to posterior segment, a traditional iontophoretic method is not very effective due to short half-life water soluble compounds that require frequent administration of this drug which is costly and reduce patients' compliances. A Newer approach to this problem is to deliver the active agent and depot forming agent separately. After the depot forming agent was administered, it will make an ionic complex with the active agent and it releases the active drug slowly and in the sustained release into ocular tissues. The depot forming agent such as Ca^{2+} , Sn^{2+} , Fe^{2+} , Fe^{3+} , Mn^{2+} , Zn^{2+} , NH_4^+ , organic anion, chelating agent have been successfully used. This depot should have an opposite charge than the active drug (Gaudana et al. 2012).

Filter Paper Strips

The paper strips sized 5×15 mm is covered with 1 mg pigments such as sodium fluorescein. The strips are used as diagnostic tools for the cornea, conjunctiva, palpebral damage, or to check the presence of viral or bacterial eye infections (Tangri and Khurana 2011; Bernard et al. 2012).

Intraocular Delivery

Intraocular drug delivery technique is intended to deposit the drug in the eye directly at the site of action. The advantage of the intraocular delivery is: shorten the distance drugs need to diffuse therefore increasing local concentration, reducing drug delivery to other off-target sites to decrease undesirable side effects, and bypass ocular epithelial and other ocular barriers to increasing bioavailability. The disadvantages are invasive methods, repetitive injections can cause complication such as vitreous hemorrhage, retinal detachment, cataract, endophthalmitis, and inflammation (Gaudana et al. 2012; Jiang et al. 2009). Several methods of intraocular deliveries include: intrastromal, intracameral, suprachoroidal, subretinal and intravitreal.

Intrastromal Delivery

Intrastromal injection is used to deliver macromolecules ophthalmic drugs so the half-life of drugs is extended inside the stroma. Densely packed corneal stromal structure and proteoglycans in the corneal of stroma hinder the diffusion of macromolecule inside the stroma. Anti-vascular endothelium growth factor (VEGF) such as bevacizumab to treat corneal neovascular showed dramatic regression of corneal neovascularization, therefore, increasing visual acuity (Avisar et al. 2010; Storobinsky et al. 2009).

Intracameral Delivery

Intracameral injection is the method of injecting ophthalmic drugs to the anterior segment of the eye. The injection has been used to improve bioavailability to both the anterior and posterior segments of the eye, although this method can't deliver significant concentration to the posterior. Intracameral injection has been used as prophylactic delivery of antibiotic CsA after cataract surgery to prevent endophthalmitis or antifungals that cause deep corneal infections. However to combat the rapid turnover of fluid in the anterior segment, repeated intracameral injections are needed to maintain therapeutic concentrations of the drugs over time, which can cause increased risk of infections (Kim et al. 2014).

Suprachoroidal Delivery

Suprachoroidal are designed to place drugs in the suprachoroidal space (SCS). Normally, the SCS is collapsed due to the deformity of the chorioretinal and the

hydrostatic pressure in the eye, but with the positive pressure from the injection, space can be expanded and incorporate fluid. SCS delivery is expected to have a higher bioavailability of the drug, higher concentration of the drug in the choroid, and fewer sides. The SCS injection is best used for sustained release drugs because high blood flow in the chorio-capillaries can wash away small and macromolecules (Kim et al. 2014; Patel et al. 2011).

Subretinal Delivery

The subretinal space is the extracellular space that exists between the photoreceptors of the retina and RPE layer. The subretinal space is a loosely organized space several microns in thickness where macromolecules are specifically injected to the retina. Subretinal space injection has been used clinically, but long-term safety of this injection procedure has not been fully studied (Kim et al. 2014).

Intravitreal Delivery

Intravitreal injection is important to deliver ophthalmic drugs to posterior segment by injecting drugs to all layers of the ocular globe. But with frequent injections, this method is very invasive and can cause retinal damage risks such as retinal detachment, iritis, uveitis, endophthalmitis, intraocular hemorrhage, and cataract. To have their therapeutic effects, the drug molecules must diffuse through the vitreous, chorioretinal, multiple sub-layers of the retina and the RPE to reach the choroid. Drugs injected by this route are cleared either by anterior or posterior route. Several drugs that have been using this delivery include pegaptanib, anti-VEGF bevacizumab and ranibizumab, and aflibercept for treatment of neovascular macular degeneration (Kaur and Kakkar 2014; Kim et al. 2014; Avisar et al. 2010; Donovan 2004).

By formulating the drug into nanoparticles and using intravitreal delivery, it was shown that the drug retention can increase from 1 day to more than 15 days, thus decreasing intravitreal injection frequency (Kaur and Kakkar 2014; Kim et al. 2014; Avisar et al. 2010).

Ocular Implant Delivery

Ocular implants deliver sustained release drugs over several months to years. There are several types of implants: non-biodegradable implants, biodegradable implants, and stimuli-responsive implants. Non-biodegradable implants can trap active drugs by dispersion throughout polymer matrix storage inside a reservoir which is

surrounded by a release controlling non-biodegradable polymer membrane. Polyvinyl alcohol (PVA), ethylene vinyl acetate, and silicon are the most commonly used non-biodegradable ocular implants. FDA approved Vitracert[®] implant containing ganciclovir for the treatment of cytomegalovirus and Retisert[®] implant containing fluocinolone for the treatment of uveitis, respectively. These implants are sutured to the sclera and need to be inserted and surgically removed. They are effectively implanted in the eye for over 5–8 month for Vitracert[®] and up to 2.5 years for Retisert[®] (Yasin 2014; Molokhia et al. 2010).

Biodegradable polymeric implants are made of PLGA, polylactic acid (PLA) which is degradable in the body by water or enzyme to become CO₂ and water. Ozurdex[®] which contains dexamethasone is FDA's approved for the treatment of diabetic macular edema and is effectively implanted for up to six months in the eye (Yasin 2014; Molokhia et al. 2010).

Figure 5.1. shows classification of ocular implants, Fig. 5.2 shows the location of different implants. Figure 5.3 shows non-biodegradable implant and Fig. 5.4 shows biodegradable implant.

Nano Formulations Delivery

Nano-formulations (NF) use nanoparticles sizes range from 10 to 1000 nm, while microparticles range from 1 to 10 μ m. The advantages of nanoparticles or microparticles include: increased corneal penetration, improvement of

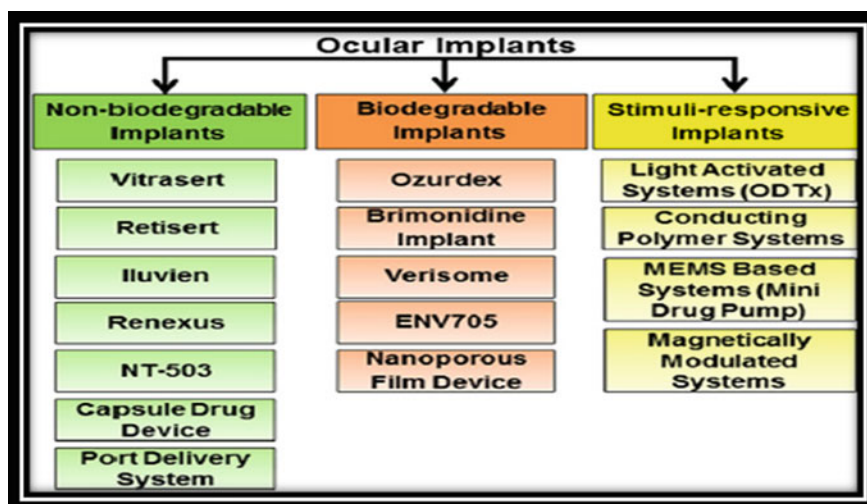


Fig. 5.1 Classification of ocular implant. With permission from Yasin et al. (2014)

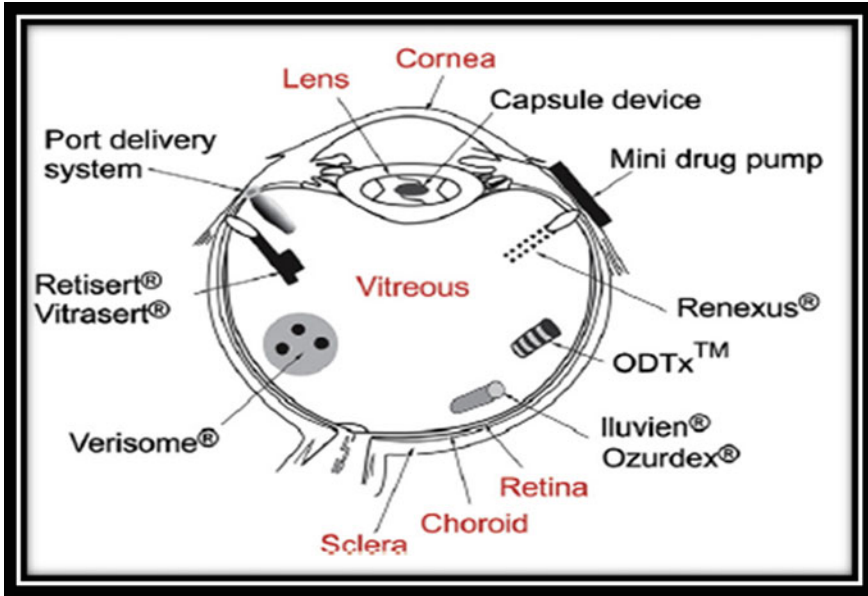


Fig. 5.2 Selected implants and their location in the eye. With permission from Yasin et al. (2014)

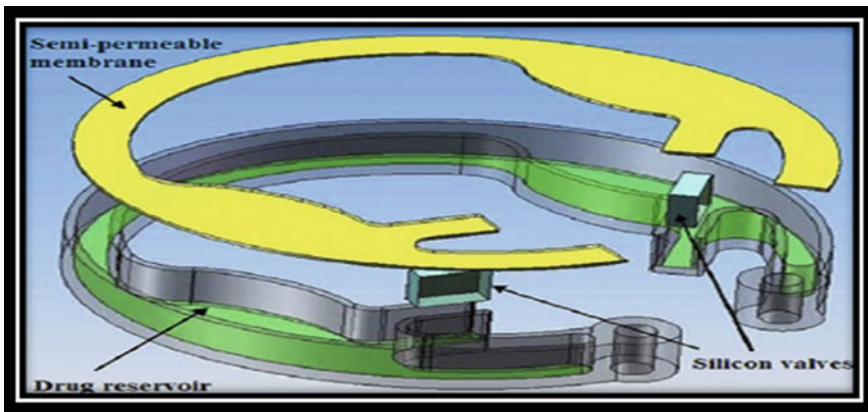


Fig. 5.3 Non-biodegradable implant. Capsule drug device showing the drug reservoir, semipermeable membrane and location of the silicon valves. With permission from Molokhia et al. (2010)

bioavailability of active ingredients. However, it has low capacity to deliver the active drug (Chaurasia et al. 2015).

Nanoparticles usually consist of: nanospheres, solid monolithic spheres built from dense polymer matrix where the active ingredient is scattered, and nanocapsules constituting reservoirs built from polymer membrane surrounding the drug in

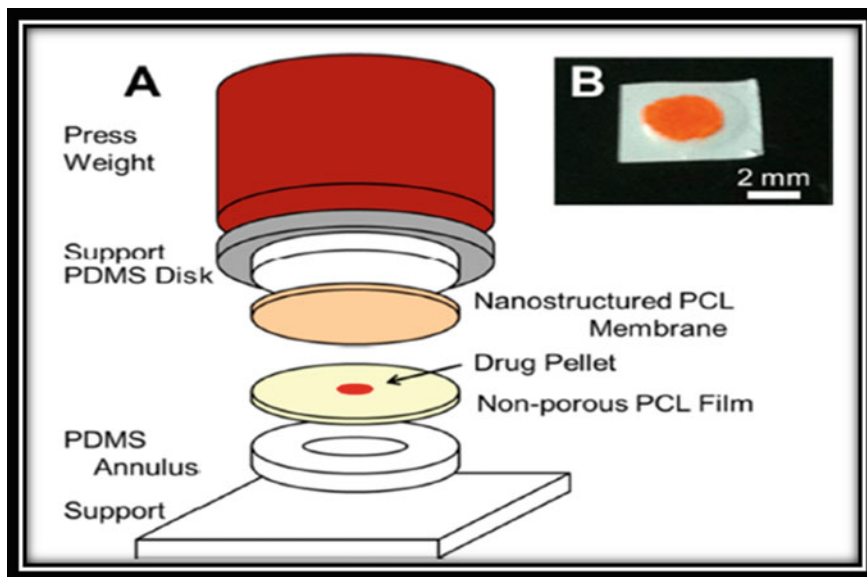


Fig. 5.4 Assembly of nanoporous thin film devices. **a** From the *bottom up*, devices consist of a flat polycaprolactone (PCL) film sandwiched between supporting structures using a press weight. The apparatus containing the constituent device layer is placed on a hot plate to fuse the PCL films. The annulus base support causes the device center to experience considerably less heating. **b** An example of prototypical device loaded with a model protein, fluorescein isothiocyanate labeled bovine serum albumin (FITC-BSA). Reprinted with permission from Bernards DA, Lance KD, Ciaccio NA and Desai TA, 2012. Copyright 2012 American Chemical Society

solid or liquid form. Active ingredients known to deliver by this system include sulfacetamide, levofloxacin, acyclovir, piroxicam, CsA, flurbiprofen, and pilocarpine (Gaudana 2009; Kompella et al. 2013).

Different types of nanoparticles (bioadhesive, sustained release, stealth, targeted and stimuli response) can be used for different routes of administrations as shown in Fig. 5.5.

There are many types of NFs such as: (a) Polymeric nanoparticles; (b) Polymeric nanogels and hydrogels; (c) Liposomes; (d) Nanomicelles; (e) Chitosan nanoparticles; (f) protein nanoparticles; (g) Calcium phosphate nanoparticles; and (h) Dendrimers. Figure 5.6 shows different types of NFs.

Polymeric Nanoparticles

Polymeric nanoparticles such as poly (DL-lactic-co-glycolic acid) (PLGA), poly-vinyl alcohol, poly (ethylene-co-vinyl acetate), polymethyl methacrylate have been

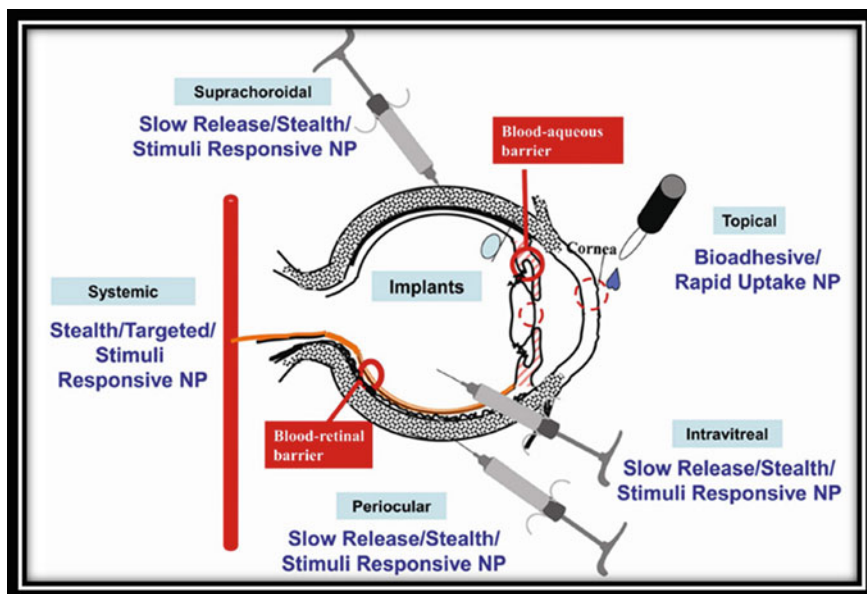


Fig. 5.5 Route of administration (topical, intravitreal, suprachoroidal, periocular and systemic) for delivering different types of nanoparticles (bioadhesive/rapid uptake, sustained release, stealth, targeted, and stimuli response) to the back of the eye. In addition, future applications of nanotechnology include nanofabricated devices, implants, films and particles. With permission from Kompella et al. (2013)

used to carry drugs such as dexamethasone implant (Ozurdex[®]). These carriers are biodegradable, biocompatible and have minimum side effects (Gong et al. 2009).

Polymeric Nanogels and Hydrogels

Nanogels are hydrogels of a nanoscale network of hydrophilic polymers. Nanogel is loaded with active drug and when the gels collapse, it forms compact nanoparticles. Nanogels can be used for controlled release of hydrophilic and hydrophobic drugs by varying the composition and conformation of polymers and the degree of crosslinking and external stimuli (Lo et al. 2009; Kompella et al. 2013).

Liposomes

Liposomes are vesicular system with diameters ranging from 50 nm to several microns. It contains one or more concentric lipid bilayers separated by aqueous

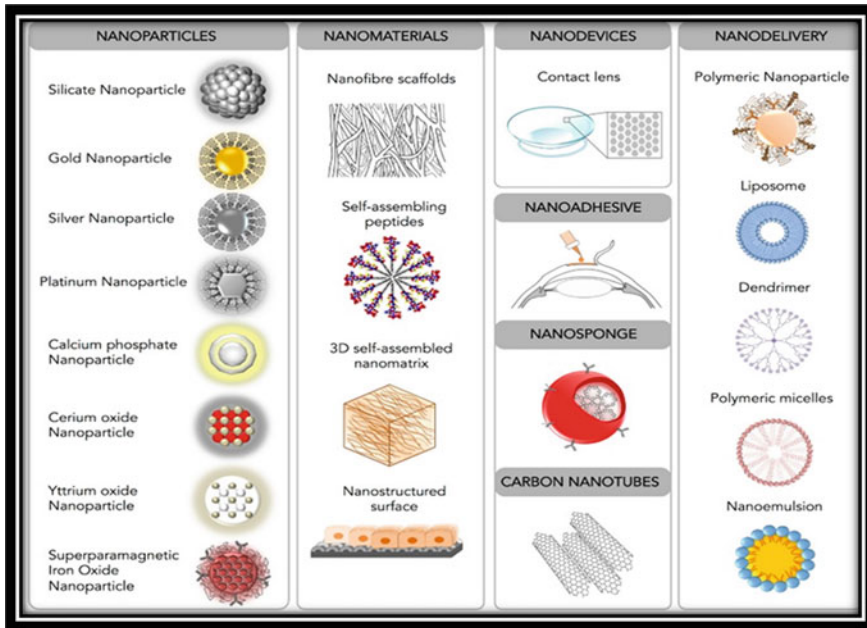


Fig. 5.6 Schematic diagram depicting nanomedicine technique available for the corneal disease. With permission from Chaurasia et al. (2015)

buffer compartment. There is three category of liposomes: (1) multilamellar vesicles (contain more than one lipid bilayer); (2) small unilamellar vesicles (size 10–100 nm), and (3) large unilamellar vesicles (0.1–10 μm).

Liposomes can encapsulate hydrophilic (in aqueous compartment) and hydrophobic (in lipid bilayers) drugs. The advantage of liposomes are biocompatibility, biodegradability, amphiphilic properties, protection from degradation by metabolic enzymes such as protease, esterase, present on the surface of conjunctiva, tear fluid, and corneal surface, low toxicity, have membrane that is flexible and can support deformation stress (Hofland et al. 2004; Tangri and Khurana 2011).

Liposomes are positively charged compounds that disintegrate completely upon contact with high affinity to the negatively charged corneal surface and conjunctival mucoglycoproteins causing slowing elimination of active ingredient from the eye. Liposomes have been successfully used for the treatment of keratitis, uveitis, endophthalmitis and proliferative vitreoretinopathy. Some active ingredients with liposomal form include acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin. For delivery to the anterior segment, several research endeavor is targeted to coating the exterior surface of liposomes with bioadhesive and penetration enhancing polymers for improving corneal or conjunctival adhesion and permeability (Rothore and Nema 2009; Tangri and Khurana 2011). For posterior segment delivery, research is focused on improving intravitreal drug half-life.

There are several patents with liposomal technology such as use amine derivative lipid component ($-\text{NH}_2$ group is separated from lipid polar head region by carbon-containing spacer-arm), neutral lipid (soybean oil based phospholipid), mucoadhesive agents, carbopol 934P, polyaxomers, carbomers, lectins, cationic lipid consisting stearylamine, cholesterol, dimethyl-dioctadecyl-ammonium bromide, DNA encapsulated liposomes prepared by dilauroyl-phosphatidylcholine (DLPC) or dioleoyl phosphatidylethanolamine (DOPE), and latanoprost-loaded egg-phosphatidylcholine (Jin et al. 2011; Lallemand et al. 2012).

Nanomicelles

Nanomicelles are self-assembling nano-sized (10–100 nm) colloidal dispersion with a hydrophobic core and hydrophilic shell. Nanomicelles solubilize hydrophobic drugs within their hydrophobic core. Some formulations that have been developed using nanomicelles include: rapamycin which had poor aqueous solubility and now has solubility of 1000 folds higher than its origin, or ketorolac for anti-inflammatory using polymeric micelles with copolymer of *N*-isopropyl acrylamide, vinyl pyrrolidone, and acrylic acid cross-link with *N*, *N*-methylene bisacrylamide; and voclosprin a calcineurin inhibitor for the treatment of dry eye use a mixed combination of two non-ionic surfactants, d- α -tocopheryl polyethylene glycol 1000 succinate (vitamin ETPGS) co-stabilized with octyl phenol ethoxylate. Many of these micelles result in the nanometer size range that creates aqueous homogeneous and clear solution that makes nanomicelles ideal ophthalmic drug delivery vehicle (Gong et al. 2009; Chauhan and Gulsen 2012).

Chitosan Nanoparticles

As polysaccharides derived from the natural compound chitin found in the exoskeleton of crustaceans, chitosan provides unique property as mucoadhesive that prolong time on the ocular surface. The hydroxyl groups in the polysaccharide structure of chitosan compete with water on the surface of eye tissue providing additional bio-adhesion. A hybrid of PLGA-chitosan nanoparticles loaded with plasmid delivered to retina after intravitreal injection has shown the drug stayed in the posterior segment longer than without chitosan nanoparticles (Kompella et al. 2013).

Protein Nanoparticles

Albumin, the primary protein of blood plasma, provides advantages over other nanoparticles. Human serum albumin increases drug solubility, decrease drug toxicity, protects drug against oxidation and increase drug half-life. In the eye, serum albumin can pass through BAB. It is the major component of aqueous humor that plays important role in rapidly dividing epithelial lens cells (Kompella et al. 2013).

Calcium Phosphate Nanoparticles

Calcium phosphate (CaP) nanoparticles are inorganic that are chemically stable and biocompatible, works by reducing drug binding to the pigment of the eye, therefore, increase its bioavailability. CaP nanoparticles are biodegradable, dissociates into calcium and phosphate ions. Ophthalmic formulations using 7-hydroxy-2-dipropyl-aminotetralin (7-OH-DPAT) and CaP nanoparticles was shown to decrease the intraocular pressure (IOP) in glaucoma patients compared to using the drug 7-OH-DPAT alone. CaP has delivered methazolamide, a carbonic anhydrase inhibitor for the treatment of glaucoma that has a better-sustained release than free drug without CaP. CaP has also been used as carrier tool for DNA transfection into corneal cells (Malik et al. 2012; Silva et al. 2012; Yavuz et al. 2013).

Dendrimers

Dendrimers are branched, spherical, monodisperse three-dimensional polymer structure of specific size, shape and molecular mass that are typically water soluble. Dendrimers can have neutral, negative, or positive functional group at the terminal. Because the presence of many functional groups on the surface such as $-NH_2$, $-COOH$, and $-OH$ of dendrimers, they can form electrostatic or covalence bonds with the drug. The structure mimic globular proteins, therefore, referred to as “artificial protein”. They are used as carriers with the active ingredients inside the polymer structure. Active ingredients used by these systems are: tropicamide, pilocarpine, carteolol, carboplatin, fluocinolone, brimonidine, and timolol (Yavuz et al. 2013).

There are many types of dendrimers such as: (a) poly-amidoamine (PAMAM) dendrimers that are considered ideal carrier for drug delivery due to their high aqueous solubility, large surface groups. Their size ranged from 1.1 to 12.4 nm. Another similar form of PAMAM called poly-amidoamine organosilicon (PAMAMOS) are silicon inverted unimolecular micelles dendrimers that contain exterior hydrophobic organosilicon and interior hydrophilic nucleophilic

polyamidoamine; (b) polypropyleneimine (PPI) dendrimers which are toxic due to poly-alkyl amines and usually not a useful dendrimers; (c) poly aryl ether dendrimers which are poor water soluble; and (d) biodegradable dendrimers such as polylysine, polydisulfide amine, polyether, or polyester provide promising candidates as antiviral, antibacterial, and vaccine for ophthalmic drugs. Several dendrimers have been used for treatment of: miosis, mydriasis, glaucoma, conjunctivitis, intraocular infections, retinoblastoma, ocular hypertension, retinal neuroinflammation, cataract incisions. Dendrimers delivery system have been useful to increase corneal residence time, to prolong reduction of IOP, to reduce toxicity, to enhance corneal transport, to increase antimicrobial activity, to increase half-life and bioavailability, to promote adhesion and proliferation of human corneal epithelial cells, to increase uptake of drugs, and to expedite wound healing (Malik et al. 2012; Silva et al. 2012).

Dendrimers have the ability to encapsulate drug molecules into their internal cavities to enhance drug solubility, permeability and retention time in the eye. Drug absorption is much better for cationic molecule; followed by uncharged and the least absorption is anionic molecules. Cationic dendrimers have increased permeability due to their interacting with lipid bilayers but it is also more toxic. In order to reduce toxicity, it is necessary to modify the surface with amine group that makes the dendrimer to be neutral or have anionic moieties (Malik et al. 2012; Silva et al. 2012; Yavuz et al. 2013).

Niosomes and Discosomes

Niosomes are chemically stable non-ionic surfactants Solulan C24, two-layered carriers used for hydrophilic or hydrophobic drug. These biodegradable, biocompatible, and non-immunogenic carriers extend the contact period between the drug and cornea for better drug bioavailability.

Discosomes are modified from the of niosomes with disc shape that fits better into conjunctival sac and do not enter the general circulation. Active ingredients known to use these systems are ganciclovir, timolol, cyclopentolate (Cholkar et al. 2013).

NFs can be administered using various routes such as intravenous, topical, periocular, intravitreal or suprachoroidal. The selection of route of administration depends on drug properties, disease state, target tissues/cell, and nano material properties such drug loading, encapsulation, efficiency, and safety. Various nanocarriers ranging from the more established systems like liposomes, polymeric nanoparticles, solid lipid nanoparticles, Nano micelles, to the most novel systems like Nanosuspensions, Nanoemulsions, nanocrystals, hydrogel, and dendrimers. NF with the whole antibody, Fab nanosphere has been shown to increase retention time following intravitreal administration from 1 day to 28 days (Cholkar et al. 2013).

However, several aspects need to be addressed to produce successful nano delivery such as minimizing toxic effects, low quantities of impurities, batch to batch reproducibility and safety in large-scale manufacturing should be established. Nanoparticles can aggregate and grow in size during storage and important approach to minimize aggregation in aqueous, biological media, and shelf, the tendency of nanoparticles to aggregate when administered in periocular space, the need to influence vitreous humor, aqueous humor, blood with nanoparticles properties.

Summary

Despite many achievements in the field of ophthalmic delivery, majority of active substance delivered to the eye are in the forms of topical such as eye drops, ophthalmic solutions. Intraocular delivery is intended to deposit the drug in the eye directly at the site of action, but these methods are invasive. Scientists are still looking for the “perfect” ophthalmic system that would possess desired properties such as controlled release, minimizing systemic effects, ease of use, and extended retention time at the site of application.

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