Conventional and Advanced Ocular Formulation and Delivery: A Mini Review

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Abstract: Objective: To review available ocular formulation and delivery for the treatment of eye diseases, and to discuss the advantages and disadvantages of the ophthalmic formulation and delivery due to the complexity anatomical of the eye.

Data Sources: A literature search through Pub Med (1984 – December 2016) was performed using the key words: ocular barrier, posterior segment, anterior segment, disease of the eye, peptide delivery, ocular delivery, ophthalmic.

Study Selection and Data Extraction: Articles in English identified from reviews, abstracts, and presentations on eye formulation and delivery were included.

Conclusion: Effective treatment of ocular diseases has been difficult challenges due to the nature of the disease, the presence of the ocular barriers, and the unique structure of the eye. Within the last 2 decades, challenges in drug delivery have been partially met through modification of the ophthalmic formulations using viscosity enhancing polymers, hydrogels; through formulation of novel drugs approach using prodrugs, gene therapy and peptide delivery; and through making the drug particles smaller using nano-formulations techniques which all are aimed to increase the drug’s retention time in the eye, to have the least side effects, and to be minimally invasive. However, there are many more challenges that need to be addressed including: the application from the research bench top using rabbit or cadaver into patients’ specific diseases, decreasing the toxicities of the formulations, and making the ophthalmic formulations and deliveries safe, well-tolerated and cost efficient.

Keywords: Ophthalmic, Ocular, Anterior segment, Posterior segment, Eye.

INTRODUCTION

The eye is a unique organ. Although it is a small portion of the body, it is a very intricate structure that make ophthalmic drugs delivery to be difficult. The eye is divided into two compartments: anterior and posterior. Because of the small size, limited absorptive surface, the presence of tear fluid, reflex blinking and the many barriers in the compartments of the eye, it is very difficult for ophthalmic drugs to reach intended sites effectively. Despite several ophthalmic formulations available on the market and many more research being done intensively to study the best way to treat ocular diseases, no single route ocular administration or formulation has gained wide acceptance.

This review discuss barriers to the eye, known diseases that affect eye, conventional and advance in drug delivery, non-invasive versus invasive, and several drugs formulations and delivery that are in the clinical trials.

PROBLEMS TO DELIVER DRUGS TO THE EYE

The eye is divided anterior segment (front) and posterior segment (back). The anterior segment occupies one-third of the eye and includes cornea, pupil, epithelium, endothelium, Bowman’s layer, Descemet’s membrane, stroma, crystalline lenses, conjunctiva, iris, ciliary body, trabecular meshwork, uveal meshwork, corneoscleral meshwork, juxtacanalicular meshwork, tear film, and fluid filled aqueous humor. The anterior is responsible to collect and to focus light [1-6].

The posterior occupies two-thirds of the eye and includes the sclera, choroid vessels, episclera, Bruch’s membrane, retinal pigmented epithelium (RPE), retina, macula, photoreceptor cells, neuronal cells, glial cells, optic nerve, and fluid filled vitreous humor. The posterior is responsible to detect incoming light [1-6]. Figure 1. Depicted the anatomy of the eye. So why is it difficult to deliver drugs to the eye? These are attributed to: the static (corneal epithelium, corneal stroma, and blood-aqueous barrier BAB) or the dynamic (tear drainage, conjunctival blood and lymph flow) barriers exist in different part of the eye, the presence of efflux pumps, and the size of the eye [7-10].

Several known barriers to anterior and posterior segments are: a) separation of retina from the vitreous...
through BRB (blood retinal barrier) that make drug difficult to penetrate effectively; b) inner membrane structure that control the exchange and entry of drug particles from the vitreous to the retina; c) barrier known as BAB (blood-aqueous barrier) that limits the transport of drugs from the blood to the inner part of the eye; d) layers of hydrophobic epithelium, hydrophilic stroma, hydrophobic endothelium, desmosomes and tight junction that resist passage of most ophthalmic drugs; and e) the presence of tear film that forms a muco-aqueous barrier which continuously wash away drugs from the anterior surface of the eye [7, 11].

Additionally, the presence of trans membrane efflux pump such as P-glycoprotein (P-gp), multi-drug resistance protein (MDRP) and breast cancer resistance protein (BCRP) found on the eye membrane make drug absorption to be minimal [7, 12]. Furthermore, other problems encountered include small absorptive surface of the eye, low transparency of the cornea, low capacity of conjunctival barriers that can only hold 30 µL of drugs, weak bonding between the drugs and proteins contained in tear fluid which cause loss of the drugs when blinking [8-10].

COMMON DISEASES OF THE EYE

Because the eye is such a delicate organ, any disturbances to the eye such as virus, bacteria, fungal, abrasive materials, or other allergens can cause inflammatory or infectious disease such as retinitis, uveitis, scleritis, blepharitis, conjunctivitis (pink eye), and eye allergies. Additionally, diseases such as diabetes when progressed can cause diabetic retinopathy (DR). There are more than 100 eye diseases identified, some require short topical treatment, some require surgical intervention.

Common diseases of anterior segment includes: open angle glaucoma (OAG), closure angle glaucoma (CAG), cataract and dry eyes. Although many topical formulations can deliver drugs to this segment, due to the barriers in this segment, only small amount of drugs can be delivered thus minimal drug concentration is achieved [13]. In general, less than 7% of the ophthalmic drug administered as eye drops can reach the aqueous humour part due to the corneal and conjunctival barriers or precorneal clearance by tear drainage [14-15]. Therefore, designing a new drug delivery system that can efficiently target the anterior segment of the eye by generating high drug levels and maintaining prolonged and effective concentration with no or minimal side effects are important features for a successful drug delivery.

Common diseases affecting posterior segment of the eye includes: age related macular degeneration (AMD), proliferative vitreo-retinopathy (PVR), uveitis, DR, diabetic macular edema, viral retinitis, posterior uveitis, choroid neovascularization (CNV), retinitis pigmentosa, cytomegalovirus (CMV) retinitis, and other ocular neovascular diseases [16-17]. Of the total

Figure 1: Anatomy of the eye. Available from http://www.mastereyeassociates.com/eye-anatomy [6].
debilitating diseases, 55% of the diseases affect the posterior segment, with only about 5% ophthalmic drugs available for posterior treatment. Many drugs need to be delivered via invasive intraocular (injection to the eye ball) method using different routes such as intrastromal, intracameral, suprachoroidal, subretinal, or intravitreal deliveries or via systemic method (intravenous). Frequent intraocular injections may cause complications such as retinal detachment or systemic toxicity [12, 18-22]. Although there have been intense efforts to develop new drug delivery system to the posterior segment, there are several factors that are still not well-understood. These problems are the need to: understand the diffusion rate in the vitreous humor, identify the kinetics between the posterior and anterior segments, and learn the relationship between the clearance of vitreous humor and penetration of the drugs across the sclera, choroid, and retina, and understand the role of blood lymphatic clearance [23-25]. Figure 2 depicted some intraocular administration [26], while Figure 3 illustrated different route of administration [27].

CONVENTIONAL OCULAR FORMULATIONS & DELIVERY

Systemic and topical ocular deliveries have been the conventional method to treat different diseases including: cytomegalo virus (CMV) related eye diseases such as retinitis (commonly encountered by patients with acquired immune deficiency syndrome, AIDS), uveitis (inflammation of the uvea that can cause blindness) and scleritis (inflammation due to infection, autoimmune or unknown) or dry eyes, glaucoma, and others [28-30].

To achieve systemic dose, oral and parenteral injections are the two methods use that can achieve the desired effects. When ophthalmic drugs are given as parenteral (intravenous, IV), the drug will encounter barriers such as BAB and BRB. Large size molecules are rarely given as IV due to the poor absorption of the drug and the severity of systemic side effects. Although advancements in nanotechnology has encouraged researchers in overcoming BRB or BAB to make the drug molecules to be smaller, the pharmacokinetic studies of several drugs such as micafungin, amphotericin B, marbofloxacin using IV administration had shown that the drugs also being distributed to other ocular tissues [31-32]. Due to the toxicity and delivery concerns, IV administration is not very common in treating ocular disorders [30]. Visudyne® (Verteporfin) which is used in photodynamic therapy to treat AMD is one of the very few IV ophthalmic formulation available [30].

Topical drug delivery is the most common route of about 90% ophthalmic formulations useful to treat conjunctivitis, uveitis, keratitis, scleratitis, and others. There are several advantages of topical products such as the simplicity of the formulation, storage of the drugs that are minimal, and increased in patients’

Figure 2: Scheme of different ocular administration routes. NFL=nerve fiber layer; GCL=ganglion cell layers; IPL=inner plexiform layer; INL=inner nuclear layer; OPL=outer plexiform layer; ONL=outer nuclear layer; PRL=Photo receptor layer; RPE=retinal pigment epithelia [26].
compliances due to easy drug instillation. There are, however, several disadvantages of topical formulation including significance loss of the drug at the precorneal area and different barriers of the eye structure that cause low bioavailability of the drugs at the intended site. There is less than 5% of the drugs that are administered can get absorbed; this are due to the washing off of the drugs through tear dilution, reflex blinking, or nasolacrimal drainage [8, 30, 33]. These losses of drugs are attributed to the static (corneal epithelium, corneal stroma, and BAB) or the dynamic (tear drainage, conjunctival blood and lymph flow) barriers [7]. To increase bioavailability of ophthalmic drugs and the contact time of the drugs to the cornea, several methods have been employed such as formulation of prodrugs, addition of viscosity enhancing polymers, use of cyclodextrins, nano formulations (NFs), and others.

Prodrugs are bio reversible derivatives of drug molecules and are designed to be therapeutically inactive until enzymatic and/or chemical bio reversion occurs [7]. Ester or amide linkages are usually added to the ophthalmic drugs to make them become prodrugs so they can withstand hydrolysis by the enzymes esterases or amidases. Drug can penetrate the cornea or conjunctiva and enters into the aqueous humor, iris or ciliary body [34-35]. Some prodrugs that have been marketed successfully include analogs of prostaglandin (PGF2α) such as latanoprost, travoprost, or timolol, or dipivefrine for treatment of glaucoma; ganciclovir, dexamethasone and flurbiprofen used as antiviral or anti-inflammatory [36-37].

Hydroxyl propyl methyl cellulose (HPMC), hyaluronic acid, polyvinyl alcohol (PVA), hydroxyl ethyl cellulose (HEC) and methylcellulose are polymers viscosity enhancing compound that are usually added to ophthalmic formulations to improve drug absorption across the precornea and cornea area and to increase drug retention at the intended site [7, 38].

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, ibuprofen and corticosteroids are commonly prescribed for anti-inflammation purposes, but their highly lipophilic molecules made them difficult to be formulated intoaqueous ophthalmic drops [7]. Cyclodextrins (CD) such as randomly methylated β-CD (RMβCD) and 2-hydroxypropyl-β CD (HP β CD) were shown to improve solubility and to increase ocular bioavailability of diclofenac and dexamethasone [39].

Several topical formulations have been commercially available for decades, however, research aimed to improve bioavailability and retention time of the drugs are continually extended. Common available formulations includes: liquid forms (eye drops, ophthalmic solutions, micro or nano emulsions); semisolid forms (in situ gel, ointment); and solid forms (soft contact lenses, ocular inserts, mini tablets).

Eye drops are formulated as sterile, isotonic with pH equal to the tear fluid (pH 7.4) with addition of
preservatives. Although eye drop is convenient, non-invasive, and can be self-administered which increase patients’ compliances, the amount of drug being absorb is less than 5%. Human tear volume is estimated to be 7 µl and the cul-de-sac can contain only around 30 µl of eye drops. In addition, tear film wash away the ophthalmic drop within just 15-30 seconds after instillation [30, 40]. Ophthalmic solutions are sterile aqueous that is used to cleanse and to rinse the eye. Although the solution is ease to use, rapid drug removal due to reflex blinking and rapid degradation by enzymes present in the eye make this ophthalmic solution a perfect candidate for better formulation to balance hydrophilicity and hydrophobicity properties of the drug [8, 10].

Restasis® (Allergan, Irvine, CA) was the first cyclosporine A (CsA) formulated as nano emulsion that is approved by the Food and Drug Administration (FDA) to treat dry eye. However, Restasis® induces a burning sensation and redness after topical instillation [41]. To improve Restasis® formulation, an attempt using Novasorb®, a technology in which cationic nano emulsion interact well with anionic eye surface, has been successfully improve the drug bioavailability and less side effects [42]. Another attempt is to make nano micellar formulation blend of polyoxethylene hydrogenated castor oil (HCO-40) and Octoxynol 40 (Oc-40) with CsA [28].

Ophthalmic semisolid forms that have gain popularity are in situ gel which is also called “sol-to-Gel” system. In situ ophthalmic gel that have 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 [11, 42-43].

Several ocular inserts have gained popularity in recent years. These formulation include artificial tear inserts (Lucrisert® for dry eye syndrome), minidisk ocular therapeutic system (OTS that can hold hydrophilic or hydrophobic drugs over time), soluble ophthalmic drugs inserts (SODIs, an oval wafers that upon apply to conjunctiva sac become moistened by tear fluid), minitab (biodegradable tablets that after long contact with conjunctiva sac become gel), soft contact lenses coated with drug, and ocular inserts (Ocusert® the first ocular insert delivering pilocarpine to treat ocular hypertension) [8, 10, 13, 43-44].

**ADVANCED IN OCULAR FORMULATIONS AND DELIVERY**

In recent years, use of different routes, better formulations, new ways and more effective ocular delivery have been the focus to deliver ophthalmic drug more efficiently with less side effects. There are several well-published papers on ophthalmic drugs using peptide, protein or recombinant proteins. Gene therapy, iontophoresis, sonophoresis, micro needles, and hydrogels are also in the horizon in the ophthalmic drug development.

Biotechnology plays important role in the development of many drugs including ophthalmic formulations. The numbers of protein or peptide-based oculares being developed, in the clinical trials or available on the markets have increased in the last decade. Table 1 list potential protein or recombinant protein-based ophthalmic drugs with their indications [45]. Proteins and peptides are vital constituent of the body. The chemical structure of proteins allows them to perform specific reactions in the body, to increase the efficacy of drug deliverance and to decrease their side effects [46-47]. Several disadvantages of delivering ocular protein formulation includes: short half-lives of the drug that make it necessary to administer repeatedly, instability of the protein structure that is easily denaturized by theenzymes, pH of the environment, and their short retention at the intended site of action [46-48]. Several strategies have been used to improve bioavailability of proteins and peptides-based ophthalmic drugs. These strategies include:use of penetration enhancers, addition of enzymatic inhibitors and protein encapsulate technique. Penetration enhancers such as chelators (citric acids, salicylates), surfactants (sodium lauryl sulfate, polyoxyethylene-9-lauryl ether), bile salts (sodium glycocholate), fatty acids (oleic acid, capric acid), and non-surfactants (unsaturated cyclic ureas) have been shown to improve bioavailability of peptide drugs, to reduce barrier function of eye mucosal membranes, and to protect proteins and peptides from proteolytic activity of enzymes present in the eye [49].

Several enzymatic or protease inhibitors such as bacitracin, metalloprotease inhibitors, aspartylprotease inhibitor, cysteine proteinase inhibitor, serine protease inhibitors, and amino peptidase inhibitors have been tested successfully in the ophthalmic products; however these inhibitors can cause undesirable side effects such as causing absorption of unwanted
proteins, biodegradation of normal nutritive proteins, and secretion of protease in the body as a result of feedback mechanism [47, 50].

Encapsulating therapeutic proteins such as using liposomes, double emulsions, polymeric nanoparticles, and solid lipid nanoparticles have been studied to increase longer half-life of the proteins, to protect protein integrity until the drug reaches the target site, to increase precorneal time, to incorporate hydrophilic and hydrophobic drugs [8, 27, 51].

Gene therapy is a method to deliver intracellular genetic material using different vectors including: 1) viral vectors such as Adeno-Associated Viruses (AAVs), adenovirus vectors (AVs), lentiviral vectors (LVs), retrovirus (RVs), 2) short interfering riboynucleic acid (siRNA), or 3) non-viral vectors such as lipid based, polymer based, or nano particles. Currently, there are 33 clinical trials using gene therapy [12]. Administration of gene therapy can be through topical instillation, periocular route, intracameral injection, intravitreal injection, subretinal injection, or suprachoroidal injection. The selection of route should be based upon the targeted cells and the characteristics of the vector [26]. Gene therapy have been tested in several ocular disease such as Leber

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapeutic Agents</th>
<th>MW</th>
<th>Potential Indications</th>
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<tr>
<td><strong>Neurotropic agents</strong></td>
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<td>Growth Factors</td>
<td>Nerve growth factor (NGF)</td>
<td>26 kDa</td>
<td>Glaucoma, wound healing, RGC</td>
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<td>Acid fibroblast growth factor (aFGF, FGF-1)</td>
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<td>Illumination</td>
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<td></td>
<td>Basic fibroblast growth factor (bFGF, FGF-1)</td>
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<td>Illumination</td>
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<td>Neurotropic factors</td>
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<td>23 kDa</td>
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<td></td>
<td>Glial cell line neurotrophic factor (GDNF)</td>
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<td></td>
<td>Adalimumab: anti TNF rhuMab</td>
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<td>Recombinant TNFR</td>
<td>Etanercept: TNFR-II/Fc fusion protein</td>
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<td>Uveitis</td>
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<td>Anti-VEGF antibodies</td>
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<td>150 kDa</td>
<td>CNV, RVO, CME, PDR</td>
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<td>Ranibizumab rhuMab VEGF Fab fragments</td>
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<td>Antibody</td>
<td>Anti-HER2 rhuMab</td>
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<td>Anti proliferative</td>
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<td>PIOL</td>
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<td><strong>Others</strong></td>
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<tr>
<td>Model protein</td>
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<td>PVR, PDR, endophthalmitis</td>
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**Abbreviation:** AMD=age related macular degeneration; CME=cystoid macular edema; CNV=choroidal neovascularization; HER2=human epidermal growth factor receptor 2; Mab=monoclonal antibodies; MW=molecular weight; NV=neovascularization; rhuMab=recombinant humanized monoclonal antibodies; TNF=tumor necrosis factor alpha; PIOL=primary intraocular lymphoma; PR=photoreceptors; PVR=proliferative vitreoretinopathy; PDR=proliferative diabetic retinopathy; RP=Retinitis pigmentosa; RGC=retinal ganglion cells; RVO=retinal vein occlusion; VEGF=vascular endothelial growth factor.
congenital amourosis (LCA, autosomal recessive in children and newborn that can cause blindness), X-linked retinoschisis (XLRS, retinal progressive disease that can cause severe loss), Stargardt disease (inherited juvenile macular degeneration in people younger than 20 years), choroideremia (X-linked chorioretinal dystrophy that effect mostly male), retinitis pigmentosa (retinal degeneration that cause loss of vision in people worldwide), AMD and glaucoma. Glaucoma affects about 3% people over 40 years worldwide by causing increase in intraocular pressure (IOP) and if not treated on time, this disease can cause blindness. Gene therapy offered improvement in lowering IOP by inhibiting beta 2 adrenergic receptor via use of siRNA and SYL040012 (a double strand oligonucleotides) as shown in clinical trials in 24 healthy volunteers [26].

Iontophoresis is a non-invasive technique aimed to increase drug penetration using low electric current through the use of electro migration (orderly movement of ions in the presence of an electrical current) and the use of electro-osmosis (a convective solvent flow from the anode to cathode direction that occurs under physiological condition). Neutral or non-ionized molecules are more effectively delivered when anodal iontophoresis is used [52-53]. The drug is applied using an electrode that carry the same charge as the drug, while an electrode with opposite charge is placed in the body to deliver the drug based on electro migration and electro-osmosis principles [54]. Trans-scleral is more effective to deliver drug to posterior segment, while trans-conneal to anterior segment [55]. Sonophoresis use similar method like iontophoresis except ultrasound are used to deliver the drug [55].

Microneedle techniques are invented to inject drug to posterior segment of the eye, in particular the suprachoroidal space (SCS, space between sclera and choroid) [56-58]. AMD which affect about 1.8 million and DNthat inflict 4.1 million people in the United States alone,can cause blindness if untreated early [59-60]. While intravitreal injection has been used to treat these diseases, this method doesn’t always provide effective drug concentration [58]. To inject the SCS area, either surgical procedure or use long needle are needed, but these procedure are invasive. A Hallow glass microneedle size of about 750 µm long, 33 gauge was used to deliver drug such as bevacizumab in nanoparticles or micro particles size to model rabbit eyes or human cadaver with some success and some problems [58, 61].

Hydrogels is another advancement in ocular research. This hydrophilic viscoelastic compound is liquid at pH 6 or at room temperature and become gel at pH7.4 the natural pH of the tear film, can deliver about 95% of drug and cause the drug to stay for more than 8 hours in the eye [62]. There are several commercial products using hydrogel system such as Timoptic-XE® useful to treat glaucoma (developed by Merck using ion-activated gel and beta blocker) and Zirgan® useful to treat herpetic keratitis (developed by Bausch & Lomb using hydrogel polycrylic acid and ganciclovir) [27, 62]. Alginate hydrogels use with pluripotent stem cells transplantation; polymer micelles combine with antibiotics and hydrogel use for contact lenses;and use of hydrogel as adhesive in repairing wounded eye after transplantation, incisions during cataract removal, or perforated eyes are a few examples of hydrogel technology now in hot topic research [63-65]. Several polymers or compounds can be added to improve the hydrogel characteristics such as polycrylic acid, alginate, chitosan, poly vinyl alcohol and others [66].

Intraocular drug delivery is intended to deposit the drug directly to the eye at the site of action using intrastromal, intracameral, suprachoroidal, subretinal, and intravitreal injections (see Figure 2). Several advantages of intraocular injection are: decrease side effects on other off-target sites, increase local drug concentration, and increase bioavailability of the drug by bypassing ocular barriers. The disadvantages are: invasive methods, causing complications of vitreous hemorrhage, retinal detachments, cataracts, endophthalmitis and inflammation [12, 18]. Attempts have been made to formulate the drugs as nanoparticles to increase drug retention, to decrease injection frequency or to use microneedle to decrease the invasiveness and side effects [18, 20, 22]. Table 2 listed some drug delivery technologies in different phases of FDA clinical trials [67].

Nano formulations use particles sizes in the range of 10 to 1000nm, as compared to micro particles (particles range from 1000 nm to 10,000 nM). Nanoparticles usually consisted nano spheres made of polymer matrix that can incorporated the active ingredients such as sulfacetamide, levoflaxacin, acyclovir, piroxicam, CsA, flurbiprofen, and pilocarpine and nanocapsules that act as the reservoir for the drug [8, 27]. There are many types of nanoparticles available such as silicate, gold, silver, platinum, calcium phosphate, cerium oxide, super magnetic iron
oxide. These nanoparticles can be delivered by making them into polymeric nanoparticles, liposome, dendrimer, polymeric micelles, or nano emulsion.

**CONCLUSIONS**

With more than 100 known ocular diseases, advanced in ocular therapy are needed. Majority of
ophthalmic drugs are topically delivered as eye drops, ophthalmic solution, ocular inserts, and others. Intraocular delivery is intended to deposit drug to treat diseases of the posterior segment, however this method is invasive. Protein or peptide ophthalmic drugs provide advantage due to their high potency and specificity. Currently there are several phase 2 or 3 protein or peptide formulation in the pipeline. Although ocular gene therapy is still in its early stages of development, currently there are more than 30 clinical trials with over 100,000 articles written on the promising and problems with this therapy. Advanced in ophthalmic drug formulation and delivery are promising and exiting.

DEVELOPMENT OF CONFLICTING INTERESTS

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REFERENCES


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https://doi.org/10.1016/j.biomaterials.2007.08.041

https://doi.org/10.1016/j.actbio.2016.11.016

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