Recent Advances in Colloidal Systems and Gels for Posterior Ophthalmic Delivery

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Abstract

Drug delivery to the posterior segment of the eye is a difficult task owing to complexity and intricacy barriers of ocular milieu. Nonetheless, there is increasing need to overcome these barriers for the treatment of ophthalmic ailments. Delivery of drugs through ophthalmic route is compromised by multiple physiological processes including static and dynamic barriers. At present the intravitreal route is widely used to deliver therapeutic entities to the back-of-the eye. Various delivery systems such as colloidal systems and gels are in the progress of development and may improve drug delivery drastically in the years to come. In this review, the barriers of the posterior eye drug delivery and the recent advances in topical non-invasive formulations were discussed.

Abbreviations: BAB: Blood-Aqueous; BRB: Blood-Retinal Barriers; PAAm: Poly acryl amide; BSA: Bovine Serum Albumin

Keywords: Ophthalmic Delivery; Colloidal Systems; Nanoparticles; Liposomes; In situ gels

Introduction

Drug delivery to the posterior segments of the eye is highly challenging task. However, the limitations are needed to be overcome for the treatment of the sight threatening posterior ocular diseases. Drug delivery to posterior segments of the eye through topical route still remains challenge with only 1% or less of a topical dose delivered into the anterior segment [1]. Ahmed and Patton reported that topical tomfool and insulin can penetrate the sclera to enter intraocular tissues after topical application in rabbits, if the corneal route of absorption is blocked [2]. Oral or systemic administration of therapeutic entities is not effective because of blood-aqueous (BAB) and blood-retinal barriers (BRB) [3]. Intravenous administration is effective to maintain the drug concentrations in the posterior tissues relatively at high doses but pose adverse effects and systemic toxicity. Currently, intravitreal injection (i.e., direct injection of a drug into the vitreous body) is reported to be the most promising and unique method of delivering a drug to ocular posterior segments. However, this method of administration is too invasive technique and may lead to retinal detachment, cataract, endophthalmitis and increased intraocular pressure [4, 5].

Topical solutions

The most common method for treating ocular disorders is topical administration, due to its convenience and safety [6] topically instilled dose leaves the pre-corneal area within 5 min of instillation in humans and typically, less than 3% of the instilled dose reaches the aqueous humor [7,8]. Hence viscosifying agents, such as polyvinyl alcohol, hydroxypropyl cellulose and hyaluronic acid, are commonly added for improving pre-corneal residence time and thus bioavailability [9]. In one study Hollo et al attempted to deliver betaxolol hydrochloride into ocular tissues of patients with glaucoma following 1 month topical administration in humans, mean betaxolol concentrations (excluding the aphakic patient) were 71.4±41.8 ng/g in the retina, 31.2±14.8 ng/g in the optic nerve head, and 1290±1170ng/g in the choroid. Mean concentrations in the iris and ciliary body were 73,200±89,600 and 4,250±3,020 ng/g, respectively [10]. Kadam et.al studied the ocular pharmacokinetics of dorzolamide and brinzolamide following single and multiple topical dosing in pigmented rabbits. Prior to 1 hour dosing Cmax achieved was ~ 2 to 5-fold higher for dorzolamide than that of brinzolamide in all of the ocular...
tissues. After multiple dosing, dorzolamide levels in the aqueous humor, sclera, retina, vitreous humor, and optic nerve were higher than those of brinzolamide. Upon multiple dosing, accumulation of drugs was observed in all of the tissues except the conjunctiva, where the drug levels were lower than those with single dosing [11]. Haakon et al. attempted to study topical and systemic absorption of dexamethasone via eye drops. The drug levels achieved following topical administration was reported to be 170 ± 76 ng/g in aqueous humor and 33 ± 7 ng/g in retinal tissues. Further studies concluded that 60% of drug was delivered to retina through topical route and 40% via systemic circulation [12].

**Ophthalmic insitu gels**

The design and development of In-situ ophthalmic gel systems has attracted researcher’s interest over the past few years [13]. In-situ polymeric systems appears promising in terms of ease and low frequency of administration besides patient compliance and comfort; these polymers undergo sol-gel phase transition, once administered into ocular milieu [14]. The reversible phase transitions are due to change in specific physicochemical parameters (pH, temperature, and ionic strength) in the ocular environment, cul-de-sac in the case of eye [15]. In situ gel formation relies and triggers upon the external physiological stimuli induced (e.g., temperature and pH), physical changes in biomaterials (e.g., diffusion of solvent and swelling), and chemical reactions (e.g., enzymatic, chemical, and photosensitive polymerization). Thermo sensitive polymers such as pluronic or poloxamers (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) Triblock copolymers), polymer networks of and polyacrylamide (PAAm) (e.g. N-isopropyl acrylamide), poly(acrylamide-co-butyl methacrylate) are temperature-induced polymers which are liquid at room temperature (20°C-25°C) and undergo thermo reversible gelatin in the cul-de-sac (34°C-37°C), due to an increase in temperature [16,17]. Xyloglucan (Tamarind seed polysaccharide) developed from tamarind seeds is naturally occurring polymer which undergoes thermo reversible gelatin at even lower concentrations (1.5%w/v) than pluronics (20-30%w/v) [18] Miyazaki et al. attempted to deliver pilocarpine hydrochloride through in situ gels for ocular delivery using xyloglucan (1.5% w/w) as the natural polymer [19] Polymers such as poly acrylic acid (PAA) (Carbopol, carboromer) or its derivatives, mixtures of poly (methacrylic acid) (PMA) and poly(ethylene glycol) (PEG), undergo sol-gel phase transition with pH induced stimuli [20,21]. Certain polysaccharides of natural origin include carrageenan, gellan gum (Gelrite), pectin, and sodium alginate undergo phase transition in the presence of monovalent and divalent cations such as k+, Ca2+, Mg2+, and Na+ [41-43]. Kang derwent et al. developed thermo responsive hydrogels of poly (N-isopropylacrylamide) (PNIPAAm), cross-linked with poly (ethylene glycol) diacrylate (PEG-DA). Proteins were then encapsulated into the hydrogels, including bovine serum albumin (BSA), immunoglobulin G (IgG), and, finally, bevacizumab and ranibizumab. Cross-linked PNIPAAm fluoro is thioceyanate (FITC) labelled hydrogels exhibited a fast and reversible phase change with temperature in the eye after intravitreal injection via 30G needle. The rate of protein release was examined as a function of cross-link density. Release profiles of the proteins showed that there was an initial burst of release within 48 hours, and then a steady state was reached, which was sustained for approximately 3 weeks in the vitreous cavity. Hydrogels with less cross-linking demonstrated faster release kinetics into the posterior segment of the eye [22]. Wang evaluated the biocompatibility and biodegradability of RGD peptide hydrogels in the posterior segments of rabbit eye. RGD peptide hydrogels was injected into the vitreous cavity and supraocular space, and disappeared from the injection site progressively. The lifetime of the hydrogels was 25.7±2.65 days and 14.3±3.3 days in the vitreous cavity and supraocular space, respectively [23].

**Colloidal formulations**

The colloidal dosage forms include formulations such as liposomes, Nano particulate and micro particulate systems. Advantages of colloidal dosage forms include sustained and controlled release of the drug at the targeted site, reduced frequency of administration, ability to overcome blood–ocular barriers, and reduced eflux rate. Colloidal formulations serve as viable alternative to the conventional dosage forms in terms of localization of drug, bioavailability and other pharmacokinetic properties.

**Micro particulate systems**

Micro particulate systems are the colloidal drug carriers usually in size range of 1µm. These are monolithic spheres dispersed in polymeric matrix at molecular level. Microspheres are mainly prepared by solvent evaporation method, spray drying/emulsification techniques [24]. Mortimer et al formulated the microspheres of 5-fluorouracil (5-FU) with biodegradable polymers of lactic acid (PLA) or copolymers of poly(lactic -co-glycolic acid) (PLGA). Poly (lactic acid) microspheres released 70-85% of total 5-FU over 7 days. The intravitreal kinetics of the microspheres was studied in ten rabbits in vivo. A suspension of microspheres was injected into the vitreous cavity of five normal eyes and five vitrectomized eyes. Following 48 ± 5.2 days after injection, the microspheres disappeared from the vitreous cavity in the five normal eyes. Clearance from the vitreous cavity was accelerated in the five rabbits that underwent vascotomy (14 ± 2.4 days; P < 0.001). This study suggests that microspheres as potential drug delivery systems to back of the eye [25]. Carrasquilo et al reported the controlled release drug delivery system for the long term inhibition of VEGF and its mediators. Poly (lactic-co-glycolic) acid (PLGA) microspheres loaded with anti-VEGF RNA aptamer (EYE 001), placed on the orbital surface of sclera and the release kinetics are investigated. PLGA microspheres are effective and able to sustain the drug release to posterior segments of eye with average rate of 2µg/day over a period of 20 days [26]. Gomes dos Santos et al designed PLGA microspheres for the sustained release of the nanosized anti-TGFβ2 (transforming growth factor β2) phosphorothioate antisense oligonucleotide complexes [27]. Loftsson et al formulated water-soluble dexamethasone/γ-cyclodextrin (yCD) microparticles in a low-viscosity aqueous eye drop suspension. The aqueous suspension formulation was tested in rabbits(in vivo) and compared with an aqueous dexamethasone
Two hours after single application of the dexamethasone/γCD eye drops to rabbits the concentration in vitreous was found to be 29 ± 16 ng/g, 86% of which reached vitreous via the topical route and in retina the concentration was 57 ± 22 ng/g (49% via topical route). For the RMβCD the values were 22.6 ± 9 and 66 ± 49 ng/g–1 (73 and 14% via topical route), respectively. These steroid levels are comparable with the dexamethasone concentration achieved 1 month after intravitreal injection. The aqueous dexamethasone/γCD eye drop formulation was chemically stable during 7 months storage and well tolerated with no visible short-term side effects [28].

### Nano particulate systems

Nano particles are colloidal systems with in size range of sub-microns. Preparation of nanoparticles is carried out by methods such as Nano-precipitation, Nano Encapsulation, supercritical fluid technology, solvent evaporation, emulsification/solvent diffusion. Bourges et al showed that an intravitreal injection of Poly lactose (PLA) nanoparticles resulted in trans-retinal movement, with a preferential localization in the retinal pigment epithelium (RPE). The presence of the nanoparticles within the RPE cells for 4 months after a single injection shows that a continuous and septic delivery of drugs can be achieved. Histology demonstrated anatomic integrity with no signs of toxicity(29-31).Zhang et al reported that Intravitreal injection of dexamethasone (DEX)-loaded poly (lactic acid-co-glycolic acid) Nano particles sustained DEX concentrations for a long time in the posterior chambers thus can be used for the treatments of posterior segment diseases [32]. Nano particles prepared by using siatyl-Lewis X conjugated liposome as a site-directed delivery system containing dexamethasone showed selective targeting to the autoimmune uveo-retinitis [33]. Koirala et al reported that Sub retinal injections of rhodamine labeled nanoparticles using an RPE-specific reporter vector (VMD2-eGFP) can efficiently deliver genes to the retinal pigmental epithelium and thus can be employed in the retinal gene therapy [34]. Albumin nanoparticles are an interesting delivery system for intravitreal drug administration that has shown controlled drug release and degradation to safe products. In vivo rat studies demonstrated their localization in the vitreous cavity and ciliary body for at least two weeks after a single intravitreal injection [35].

### Micellar systems

Micellar systems are the colloidal formulation which is formed due to self-assembly of amphiphilic block copolymers at or above critical Micellar concentration (CMC).Polymeric micelles tends to form in size range between 100nm. Ying et al developed the submicron sized lipid emulsion for intraocular delivery using eye drops. In the study coumarin-6 was used as a model drug with fluorescein marker, and fluorescence was observed in the retina after administration of the lipid emulsion. The fluorescence intensity in the retina increased by surface modification using a positive charges inducer and the functional polymers chatoyant (CS) and poloxamers 407. Surface-modified lipid emulsions serve as potential formulation for delivery of hydrophobic drugs to the ocular posterior segment [36].

Polygon complex micelle system was reported which incorporates a dendrite phthalocyanine photosensitize, tested in rats for its efficacy in photodynamic therapy of choroid revascularization. The Micellar system exhibited absorption at 650 nm, which is advantageous for the treatment of deep lesions. The formulation may prolong the retention in the blood circulation and achieve a selective accumulation in the choroid neo vascularized lesions, but these aspects require further development [37]. In accordance to the patent US 2006039979A1, Kuwano et al studied the ocular disposition of betamethasone in posterior segment of the eye using gel formulations. In the study the ophthalmic gel (50uL) was administered through sub conjunctival route by 27G needle to form depot of the drug and the effective concentration was maintained and delivered into the posterior tissues. The formulations administered in the invivo study were Betamethasone (BMS) suspension (control), BMS ion sensitive suspension, BMS thermo sensitive suspension, BMS methyl cellulose suspension. Posterior retinal-choroid tissues were analyzed after 2 days and 7 days to determine drug concentration from the respective formulations. Moreover, Results indicated that BMS thermo sensitive suspension was able to deliver the BMS into retinal-choroid tissue at the 7th day with peak concentration of 10.05 µg/g [38]. Cheng et al attempted to deliver the antiviral drugs to posterior segment of the eye namely ganciclovir and cidofovir in the form of crystalline lipid prod rug hexadecyloxypropyl-phosph-ganciclovir (HDP-P-GCV) and hexadecyloxypropyl-cyclic cidofovir (HDP-cCDV). In this study these lipid prod rugs were administered into rabbit eyes and their virtual kinetics were determined. Micro fluidized particles of HDP-P-GCV showed an increased drug release rate compared with the large-particle drug formulation, with area under concentration-time curve (AUC) of 219.8 ±114.1 (n=3) versus 108 ± 47.2 (n=3) for unmodified HDP-P-GCV during the 12-week period after a 2.8 µmol intravitreal injection. There was a 103% increase of the drug released from the micro fluidized formulation of HDP-P-GCV versus the unmodified formulation. Following 100 µg eye injections, vitreous HDP-cCDV levels were at 0.05 µmol at week 5, which declined to 0.002 µmol at week 8. The concentration at week 8 (0.002 µmol) remained above the IC50 for cytomegalovirus (0.0003 µmol). The pretreatment study demonstrated an antiviral effect that lasted 100 days after a single intravitreal injection [39].

### Liposomes as colloidal systems

Liposomes are the colloidal drug delivery carriers used since 1965. Liposomes are microscopic vesicular systems made up of aqueous core compartments enclosed by phospholipid bilayers of natural or synthetic origin. The lipid layers are comprised mainly of phospholipids. Phospholipids are amphiphilic, with characteristic structure comprising hydrophilic head and a lipophilic tail. In the lipid bilayer, the polar hydrophilic groups are oriented outwards, exterior and the fatty acid tails being non-polar are located in the membrane’s interior. Liposomes are structurally categorized on the basis of lipid bilayers such as small unilamellar vesicles (SUVs) or multilamellar vesicles (MLVs). A single lipid bilayer enclosing an aqueous compartment is referred to as unilamellar lipid vesicle; according to their size they are known as small uni-lamellar vesicles (SUV) or large unilamellar vesicles (LUV). Multilamellar
vesicles (MLV) are to be referred when vesicular system is composed of various phospholipid bilayers. Lipophilic and hydrophilic molecules can be encapsulated by the liposomal formulations. Hydrophilic drugs could be entrapped in the aqueous core compartment, while hydrophobic drugs will get trapped into the lipid bilayers. Loading capacity of charged drug molecules can be further prominently improved by using cationic or anionic lipids for the preparation of liposomes formulations. Numerous methods have been proposed for liposomal formulations. solvent evaporation method, reverse phase evaporation method and detergent dialysis method are commonly employed methods for liposomal formulation preparation [40]. The lipids and lipophilic components are dissolved in an organic solvent and the solvent is evaporated under vacuum by rotary evaporator. Residual film of the lipid will be formed on walls of the container. An aqueous solution generally comprising electrolytes and water soluble components of the product is added to the film. Continuous agitation produces large MLV. SUV can be prepared by ultra-sonication or sequential filtration through filters with decreasing pore size [41]. Liposomal formulations can be administered as topical solutions, subconjunctival injections, intravitreal injections and through systemic route depending on the desired effective drug concentrations to be maintained in the ophthalmic tissues. Takashima et al attempted to deliver the nucleic acids (siRNA and pDNA) to posterior segment of the eye for treatment of ophthalmic diseases such as age-related macular degeneration (AMD) using noninvasive ophthalmic liposomes. Detergent removal method was employed for preparation of liposomes. These liposome demonstrated high pDNA encapsulation efficiency with good cellular uptake ability in human retinal pigment epithelial cells (ARPE-19 cells). Author reported that further more modification of ligand which binds to specific receptor on the RPE cells to the liposomes could improve gene delivery efficacy to the posterior segment of eye by non-invasive ocular instillation [42]. Hironaka et al formulated submicron-sized liposomes (ssLips) for the delivery to the posterior segment of the eye. The ssLip based on l-alpha-distearoyl phosphatidylcholine (DSPC ssLip) showed higher fluorescence emission in the retina than that based on egg phosphatidylcholine (EPC ssLip). Magnitude of fluorescence in the retina was closely related to both liposome rigidity and particle size. ssLip delivered via the non-corneal pathway after administration was confirmed by eye imaging. The liposomes tested in ocular cells showed little cytotoxicity. These results suggest that ssLip can be used to deliver drugs to the posterior segment of the eye [43]. Manuel Diaz et al delivered ganciclovir (GCV) intravitreally for the treatment of retinitis by cytomegalovirus (CMV) in AIDS patients. In the study intravitreal application of liposomally-entrapped GCV kinetics were compared with the intravitreal injection of free GCV and the results suggest that of liposomally-encapsulated GCV showed no retinal toxicity, and therapeutic levels were detected up to 14 days after injection. Author concluded that intravitreal injection of liposomally-encapsulated GCV increases the time period required for reinition’s in the treatment of CMV retinitis [44]. Zeng et al formulated amikacin encapsulated liposomes for the delivery to vitreous body to treat bacterial endophthalmitis. The liposome-encapsulated amikacin was prepared by reverse-phase evaporation method and intravitreal kinetics of the liposomes was compared with amikacin in PBS by fluorescence polarization immunoassay. Results suggest that the liposome-encapsulated amikacin prolonged half-life of the drug in vitreous and pharmacokinetic analysis suggested that in endophthalmitis, especially in severe cases, the liposomes may be preferable to conventional preparation [45]. In one study Abraham et al delivered bevacizumab loaded liposomes in to vitreous humor of the eye to treat ocular complications. Bevacizumab was encapsulated into liposomes via the dehydration-rehydration method. The free drug concentration in vitreous humor was determined by enzyme-linked immunosorbent assay. Mean concentration of free bevacizumab in the eyes that received liposomal bevacizumab compared with the eyes injected with soluble bevacizumab was 1 and 5 times higher at days 28 and 42, respectively. The results suggest that liposomal formulations can employed to prolong the residence time of bevacizumab in the vitreous body [46]. Fishman et al studied the effect of liposomal encapsulation on the pharmacokinetics of gentamicin, after injection in rabbits. Intravitreal injection of 100 mg liposome-encapsulated gentamicin or 100 mg gentamicin in 0.1 mL of phosphate-buffered saline was administered to each rabbit. The peak free drug concentration in the vitreous was significantly greater for liposome-encapsulated gentamicin than for gentamicin at 24, 72, 120, and 192 hours respectively. The areas under the drug concentration-time curve for the total drug and for the free drug in the case of liposome-encapsulated gentamicin were twofold and 1.5-fold higher, respectively, than those for gentamicin [47]. Carmen et al developed liposomal formulation of foscarnet for the treatment of Cytomegalovirus retinitis. Foscarnet inhibits replication of herpes viruses, including CMV. Liposomes were prepared by reverse-phase evaporation method and pharmacokinetic parameters in vitreous humor were evaluated. Results suggested that liposomal formulation achieves stable and durable therapeutic levels in retina for 72 hours reaching the vitreous humor with adequate levels to accomplish the aims of intravitreal therapy [48]. Coco et al determined the pharmacokinetics governing the distribution and elimination of intravitreal injected vancomycin in normal and infected rabbit eyes. The half-lives were 69 hours in normal vitreous and 14.53 hours in infected vitreous. Therapeutic drug levels were present in the vitreous 84 hours post-injection in all eyes; they were detected from 2 to 48 hours in normal vitreous but at lower levels in the infected ones [49]. Zhang et al utilized cytochrome-C (Cyt-C) loaded cationic liposomes for the treatment of selenite-induced cataract in rats. These liposomes were fabricated by thin layer evaporation technique. Cyst-C loaded freeze-dried liposomes were stable for one year at 4°C. Furthermore, these liposomes exhibited remarkable efficacy (28%) decreases in lens opacity) by minimizing the cataract formation [50]. In one study Kawakami attempted to deliver O-palmitoyl prod rug of tilisolol-encapsulated liposome to improve the retention time of tilisolol in the preconeral area and vitreous body. The liposomes were administered topically, as well as intravitreally to the rabbit eye. Following topical administration, very low retention of O-palmitoyl tilisolol in the tear fluid was observed even when it was applied as liposomal formulation. The researchers significantly increased the retention property of liposomes by adding 2% of carmellose sodium which acted as a reservoir for
liposomes. In case of intravitreal administration, o-palmitoyl
tilisolol-encapsulated liposomes achieved higher drug
concentration in the vitreous body compared to free tilisolol
[51] in a study tacrolimus encapsulated liposomes were
formulated and subsequently evaluated for efficacy and safety
following intravitreal injection in rats. The vesicles were
prepared by reverse phase evaporation technique. Significant
changes in the retinal function were not observed in the
liposome-treated rats. His too-pathological examination
revealed reduced inflammatory response in comparison to free
drug. Liposomes were able to maintain the vitreous concentration
more than 50ng/ml for 2 weeks after single administration.
Investigators concluded that tacrolimus-loaded liposomes were
more effective in the treatment of uveoretinitis [52]. Gupta et al.
tried to deliver fluniconazole-encapsulated liposomes to
vitreous body of rabbit eyes. Entrapment of fluniconazole into
liposomal cavity significantly reduced clearance of free
fluniconazole after intravitreal injection with higher fluniconazole
concentration in the vitreous. The liposomes showed longer
half-life (23.40h) in comparison to free fluniconazole (3.08h)
[53,54].

Conclusion

It’s evident that drug delivery to the posterior segments of
eye presents significant confrontations. Topical administration
of drugs is not yet promising and needs to be addressed.
Multidisciplinary integration of delivery technologies to
optimize drug bioavailability is needed. Advancements in fields
of biomedical engineering, nanotechnology and non-invasive
drug delivery techniques could explore new avenues for drug
delivery to the ocular posterior segment in the near future.

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