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Review Article

OCULAR DELIVERY OF POLYMERIC MICELLAR SYSTEMS: A SHIFT TO FUTURE

Sagar Narala *

Department of Chemistry, St. Peter's Institute of Pharmaceutical Sciences, Hanamkonda, Warangal, TG, India – 506001

ABSTRACT

Exquisite elimination mechanisms and various physiological / metabolic barriers in the ocular milieu is the major hurdle for effective intraocular penetration of topically applied drugs/drug candidates, which render poor ocular bioavailability. Technological advancements in the niche of polymeric micellar systems over the past few decades did fulfil the unmet needs and gaps in ocular drug delivery. Promising results obtained exploiting these platforms from preclinical efficacy studies made their way into clinical trials. These systems comprise of amphiphilic molecules capable of self-assembly in aqueous media to form organized supramolecular structures. The advantages of these structural frameworks include mucoadhesivity, superior stability, tailored release profile, biocompatibility, ease of surface functionalization, scale-up feasibility and enhanced drug loading. The present review summarizes various underpinning factors controlling rationale design of micellar systems and recent advances of these micelles as effective ocular drug carriers emphasizing their performance in preclinical studies.

Keywords Ocular delivery; Polymeric micelles; Nano micelles; Ocular bioavailability; Posterior ophthalmic delivery; Ocular topical formulations.

INTRODUCTION

Diseases such as glaucoma, age related macular degeneration, choroidal neovascularization, retinoblastoma, vitritis and endophthalmitis affect posterior segment ocular tissues namely retina and vitreous humor. These sight threatening posterior ocular complications pose urgency for the intervention/treatment, which may cause blindness, if left untreated. Over the recent decades, there has been significant development seen in the field of ocular drug delivery. In spite of these advancements, ocular delivery through the topical application still remains a significant challenge, due to the immanent and exclusive barriers in eye. Literature reports indicate that only 1-10% of topical dose will be available for absorption into the ocular tissues and a negligible amount will be delivered into posterior inner ocular tissues (Gothwal, *et al.,* 2016). Delivering the therapeutic agents through the oral or systemic routes of administration needs to evade the blood ocular barriers namely aqueous and retinal barriers, requiring higher doses and thus resulting systemic toxicity. Injection of drugs into the vitreous humor appears to be most widely used method for delivering drug to the ocular posterior segment. Nonetheless, this method of administration is too invasive and suffers from various drawbacks such as endophthalmitis, retinal detachment, cataract and increased intraocular pressure (Adelli, *et al.,* 2017; Ananthula, *et al.,* 2015 and (Adelli, *et al.,* 2015). Other routes of administration along the periocular route including sub-conjunctival, sub-tenons and retrobulbar have gained success in ocular delivery, being minimally invasive. In comparison to all the ocular routes of administration mentioned above, topical application is the safest, easiest and patient compliant route. Reports suggest that topical drugs can penetrate through the scleral pathway, if corneal absorption route is blocked (Ahmed, *et al.,* 1985 and Cunha-Vaz, 1979). Scleral surface (17 cm^2) is significantly larger when compared to corneal surface (1 cm^2) providing considerably larger avenue for drug disposition with better permeability characteristics, to allow penetration and diffusion of drug molecules (Geroski, *et al.,* 2000; Prausnitz, *et al.,* 1998 and Ananthula, *et al.,* 2014). Administration of drug into subconjunctival space, which is the region between the conjunctiva and the sclera, is reported for trans-scleral delivery of therapeutic agents into the back-of-the eye. Tansmembrane transport of drugs across the scleral tissue could be quite higher due to close proximity of injected subconjunctival-drugs with the sclera/underlying posterior ocular

tissues. Conjunctival absorption leads to systemic drainage but subconjunctival injection obviates the barrier with respect to permeability and drainage (Duvvuri, *et al.,* 2003; Saha, *et al.,* 1996 and Adelli, *et al.,* 2015). Drug delivery systems for the treatment of ocular complications may vary from conventional topical solutions to advanced formulation platforms depending upon the etiology, state and complexity of ophthalmic disease (Hsu, 2007 and Adelli, *et al.,* 2014). Despite of the limitations with respect to corneal tight junctions/various ocular barriers that restrict the transport of drugs across ocular mucosa, delivery of therapeutic agents through novel ophthalmic drug delivery systems needs to needs to be addressed with novel strategic approaches (Del Amo, *et al.,* 2008; Kaur, *et al.,* 2002 and Ananthula, *et al.,* 2014). The design and development of novel topical delivery systems such as polymeric in situ gels, micellar complexes, colloidal systems, cyclodextrins and other advanced platforms has been shown to be effective in the treatment of ocular complications (Bourlais, *et al.,* 1998 and Lee, *et al.,* 2001). Polymeric micellar frameworks have gained lot of attention among the researchers from past few decades. This review summarizes recent concepts and advances in the niche of polymeric micelles aimed for ocular delivery.

MICELLAR SYSTEMS

Polymeric micellar systems have shown growing evidence as a potential nanocarrier in providing therapeutic concentrations of drugs in both anterior and posterior segments of the eye following topical application. The polymers used for the fabrication of micelles range from di-block, tri-block, penta-block, graft and ionic, where poly (ethylene glycol) constitutes the primary hydrophilic segment (Gothwal, *et al.,* 2016 and Ananthula, *et al.,* 2016). Polymer-drug conjugates, drug-encapsulated carriers, polyion complex micelles constitute multitude of facets as polymeric micelle structures. There are various methods of preparation include direct dissolution method, dialysis method, oil-in-water emulsion method, solvent/co-solvent evaporation method, freeze drying methods. These systems are 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 1-100nm (Pepiæ, *et al.,* 2012 and Balguri, *et al.,* 2015). Drug release from polymeric micelles depends upon various factors such as localization of drug in micelles, physico-chemical properties, design/preparation method, ultrastructure of micelle-drug complex. Drug release from polymer-drug conjugates

could occur either due to dissociation of micelles followed by drug cleavage from polymeric unimer or drug cleavage inside micelle structure followed by diffusion out of the carrier. Drug release from polyion complex micelles is triggered via ion exchange in physiological media whereas drug release from drug-loaded micellar carriers is usually preceded by diffusion (Li, *et al.,* 2000 and Nishiyama, *et al.,* 2003). Dexamethasone (DEX) was encapsulated into micelle systems prepared using nonionic surfactant Pluronic® F127 and cationic polysaccharide (CH) by Hafner and coworkers (Pepić, *et al.,* 2010). The micelles exhibited hydrodynamic radius and zeta potential ranging between 25.4 and 28.9 nm and 9.3 and 17.6 mV respectively. CH did not exert significant influence on loading capacity of DEX, and was found between 0.48% and 0.56%. Micellar systems showed prolonged release and CH in micellar system significantly improved DEX release rate and transmembrane transport across caco-2 cell monolayers. Also, the formulation was safe and well tolerated in the rabbits. There was 1.7 and 2.4-folds increase in bioavailability with micellar and CH-micellar systems in comparison to a standard DEX suspension (Pepić, *et al.,* 2010). Copolymers of *N*-isopropylacrylamide (NIPAAM), vinyl pyrrolidone (VP) and acrylic acid (AA) cross-linked with *N, N*'-methylene *bis*-acrylamide (MBA) were used for delivery of ketorolac. Studies demonstrated that formulation did not exert damage to cornea and ocular bioavailability was increased by two-fold compared to suspension at an equivalent dose (Gupta, *et al.,* 2000 and Balguri, *et al.,* 2017). Copolymers of polyhydroxyethyl-aspartamide (PHEA), with side chains containing polyethylene glycol (PEG) and/or hexadecylamine (C16) (PHEA-PEG, PHEA-PEG-C(16) and PHEA-C(16) respectively), for ocular delivery was described by Giammona *et al.,* 2007. DEX loaded polymeric micelles were prepared by Civiale *et al.,* 2009. *In vitro* permeability studies across corneal/conjunctival cell lines indicated higher drug permeation with PHEA-C(16) or PHEA-PEG-C(16) micelles in comparison to solution/suspension formulation. *In vivo* studies performed in rabbits with PHEA-PEG-C16 micelles provided higher bioavailability of DEX relative to suspension formulation. Ying et al developed the submicron sized lipid emulsion for intraocular delivery using eye drops (Ying, *et al.,* 2013). In the study coumairn-6 was used as a model drug with fluorescent 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 charge inducer and the functional polymers chitosan (CS) and poloxamer

407. Surface-modified lipid emulsions serve as potential formulation for delivery of hydrophobic drugs to the ocular posterior segment (Balguri, *et al.,* 2016 and Jang, *et al.,* 2006). Polyion complex micelle system was reported which incorporates a dendritic phtalocyanine photosensitizer, tested in rats for its efficacy in photodynamic therapy of choroidal neovascularization. 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 choroidal neovascularizated lesions, but these aspects require further development (Usui, *et al.,* 2005; Ideta, 2005 and Sugisaki, 2008). Photodynamic therapy (PDT) with dendrimer porphyrin (DP) loaded polyion complex (PIC) micelles developed by Usui *et al.,* 2005. Following preparation, micelles were evaluated for selective accumulation in the pathologic corneal neovascularization area. Nanocarriers consisting of PIC micelles demonstrated sustained and controlled release, good stability, drug loading efficiency characteristics (Kazuhito Yamada, 2005). In accordance to the patent US 20060039979A1, Kuwano *et al.,* 2002, studied the ocular disposition of betamethasone in posterior segment of the eye using gel formulations. In the study, the ophthalmic gel (50 µL) was administered through subconjunctival 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 *in vivo* study were Betamethasone (BMS) suspension (control), BMS ion sensitive suspension, BMS thermosensitive 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 thermosensitive suspension would be able to deliver the BMS into retinal-choroid tissue at the 7^{th} day with peak concentration of 10.05 µg/g (Cheng, 2004 and Kuwano, 2002). Cheng *et al.,* 2004, attempted to deliver the antiviral drugs to posterior segment of the eye namely ganciclovir and cidofovir in the form of crystalline lipid prodrug hexadecyloxypropyl-phospho-ganciclovir (HDP-P-GCV) and hexadecyloxypropyl-cyclic cidofovir (HDP-cCDV). In this study these lipid prodrugs were administered into rabbit eyes and their vitreal kinetics were determined. Microfluidized 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 108.3± 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 microfluidized 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 (Velagaleti, 2010). Mitsuaki *et al.,* delivered cysclosporine A into ocular tissues using nonionic surfactant, oil and emulsion formulations. Nonionic surfactants such as tween 80, hydrogenated castor oil-60 (HCO-60®) and polyoxyl 40 stearate (MYS-40®) were selected. *In vivo* ocular tissue distribution and pharmacokinetic studies with 0.1% CsA formulation were conducted and single topical drop application of CsA containing MYS-40® aqueous formulation resulted in improved tissue drug accumulation. Higher drug concentrations were observed in all the ocular tissues relative to oil and emulsion based formulations (Earla, 2010). Aqueous mixed nanomicellar topical eye drops were disclosed in US patent number US2009/0092665 in attempt to deliver therapeutic agents into ocular tissues (Chiappetta, 2011). Polymeric surfactants with biocompatible, biodegradable and amphiphilic characteristics to encase the drug in the micelle core. Voclosporin, a calcineurin inhibitor was encapsulated into aqueous mixed nanomicellar formulation prepared using Vitamin E TPGS and Octoxynol. Drugs such as DEX and rapamycin were also encapsulated in mixed nanomicellar formulation. The developed formulations were transparent with hydrodynamic radius between 10-25 nm. Ocular Pharmacokinetic studies following once a day single drop instillation conducted in Albino New Zealand rabbits and pigmented Dutch Belted rabbits for 7 days to determine drug levels in anterior and posterior ocular tissues. C_{max} in both rabbit strains after single drop administration were 1.73 and 1.28 ng/mL respectively at a T_{max} of 1 hr. On the other hand, multiple dosing in New Zealand rabbits resulted in T_{max} of 0.5 hr. After 7 days, C_{max} was found to 1.16 ng/ml (Salama, AH 2015 and Alvarez-Rivera, F 2016). Lornoxicam was encapsulated into mixed polymeric micelles composed of linear and branched poly (ethylene oxide)-poly (propylene oxide). The binary systems included different combinations with varying composition of highly hydrophilic poloxamers, Synperonic1 PE/P84 and Synperonic1 PE/F127, as well as the hydrophobic poloxamine counterpart (Tetronic1 T701). Physical stability of efavirenz-loaded micelles was improved using mixtures of poloxamers

and poloxamines (Yingfang, 2016). Mixed nanomicellar systems demonstrated seven-fold increase in LX solubility and high encapsulation efficiency. In vitro release studies demonstrated zero-order kinetics for mixed micelles and no signs of irritation were observed in the rabbit's eye. There were no changes observed in morphological characteristics of corneal membrane indicated in histopathological studies following exposure to micellar formulation. Polymeric nonionic surfactants used in the study are safe compared to cationic, anionic, or amphoteric counterparts (Vaishya, 2014). Alpha lipoic acid (ALA) loaded soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol copolymer) based polymeric micelles were prepared by Rivera *et al.*, 2016. Solubility of ALA was enhanced by ten-fold and may increase exhibit drug precorneal residence when compared to commercial topical drops (Mondon, 2011). PEG relieved irritation and cytotoxicity in human corneal epithelial cells. Monomethyl poly (ethylene glycol)-poly (ε-caprolactone) was used for entrapping pimecrolimus by Fang *et al.* 2016. The polymeric micelles exhibited hydrodynamic radius approximately 37 nm and increased tear production on day 20 in mice when compared to formulated artificial tears. Histological studies minimal damage to corneal epithelia. Polymeric micelles significantly enhanced drug solubility by 2000 folds when compared to control formulation (Aliabadi, 2005). Di-block polymers based on methoxy poly (ethylene glycol) and poly(ε-caprolactone) (mPEG-PCL) were used to prepare polymeric micelles by Ravi et al. The micelles exhibited particle size of nearly 29 nm. The topical application of polymeric micelles enhanced the scleral concentrations by 2.5-folds in comparison to DEX suspension (Li, 2015). Polymeric micelles of amphiphilic copolymers based on methoxy-poly (ethylene glycol) (MPEG) and hexyl-substituted poly(lactides) (hexPLA). CMC of MPEG–hexPLA micelles decreased with an increase in hexyl groups, which increased stability (Duan, 2015). Cyclosporine A aqueous solubility was enhanced by 500-fold when encapsulated into MPEG–hexPLA micelles. Twice the amount of CsA compared to MPEG–polycaprolactone (MPEG5000 g/mol–PCL13,000 g/mol) micelles at concentrations of 10 mg/ml was achieved by Aliabadi *et al.*, 2005. Triblock copolymer, poly (ethylene glycol)-poly(ε-caprolactone)-g-polyethyleneimine (PEG-PCL-g-PEI) based polymeric micelles were formulated by Liu *et al*. Cationic micelles enhanced corneal permeation significantly, which may be increased mucoadhesion and precorneal residence. Localization of drug in the corneal stroma indicated the potential of polymeric micelles in

overcoming epithelial barrier. PEGylation improved the solubility of drugs increasing penetration and stability of the formulation. Thermosensitive nanogel of muscone was prepared by the reverse micelle/positive micelle (RM-PM) method using poloxamer 407. The formulation prepared with 20-30% w/v poloxamer did not exhibit ocular irritation or toxicity. The formulation exhibited a narrow particle size distribution ranging from 55-90 nm with superior drug loading characteristics. The transcornela penetration was enhanced by 3.35 folds fromm muscone nanogel in comparison to muscone topical eye drops.

CONCLUSION

The solubility profile and therapeutic efficacy of hydrophobic drugs was enhanced by polymeric micelles as per published reports discussed in the review. Favorable properties of micellar systems such as better encapsulation efficiency, protection against chemical degradation, higher pre-corneal residence, small size can efficiently improve the permeation characteristics of entrapped drugs across the corneal membrane, delivering therapeutic concentrations into both segments of the eye. To further improve the current platform based on polymeric micelles, in-situ gelling systems can be used for cross-linking to significantly enhance stability and pre-ocular residence characteristics, thereby prolonging therapeutic effect in ocular tissues. Furthermore, numerous studies report the success of polymeric micellar systems in delivering macromolecules/large entities. *In situ* polymeric micellar systems, which respond to external stimuli such as pH, temperature, enzymes, light and ultra sound have shown promise in ocular delivery. Approaches illustrating the potential of polymeric constructs as novel delivery platforms for efficient treatment of ocular diseases may come in the near future.

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Correspondence Author:

Sagar Narala, M. Pharm

Assistant Professor, Department of Chemistry.

St. Peter's Institute of Pharmaceutical Sciences,

Hanamkonda, Warangal, TG, INDIA – 506001

Email: sagarnarala123@gmail.com

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