REVIEW ARTICLE

Ocular barriers and ocular drug delivery: Bridging the gap using nanomicelles as drug carriers

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Abstract

Micelles came into existence in 1913 by G.S. Hartley by describing the self-assembling of the surface-active agents above certain concentrations called critical micelle concentration. Incorporating a nanotechnology approach in micelle formation results in the development of nanomicelles. Many novel drug delivery systems were been discovered for delivering the drug to the ocular cavity. However, they were not promising enough to give good bioavailability to the ocular tissues. It is mainly because of two major complex reasons First, where the tear fluid which is produced continuously by lachrymal glands dilutes the effectiveness of the preparation thus the preparation could not give its optimum effect. Second, the presence of goblet cells in the conjunctival coating of the eye. Delivery of the drugs through the posterior chamber of the eye is much more tedious because of the existence of the blood–retinal barrier, or the BRB which resembles a more complex blood–brain barrier. The utilization of micelles favors the topical delivery on the ocular surface because the presence of surfactants helps in solubilizing the drug in different barriers of the eye and thus intensifies the retention time of medication in the ocular cavity. The nanomicelles offer many benefits for transporting the medication to the ocular cavity without affecting the normal physiology of the eye. In this review article, efforts have been made to cover all the aspects of nanomicelles in ophthalmic drug delivery.

Key words: Critical micelle concentration, ocular barriers, ocular targeting, polymeric nanomicelles

INTRODUCTION

The eye is an exceptionally unique complex organ in any organism because of its anatomical beauty and structural morphology. Because the eye is protected by five primary barriers and a variety of physiological circumstances, administering drugs to the posterior/rare segment of the eye is a tough and complex task.[1] Topical administration offers patient compliance but the drug habitation time in the ocular cavity is for a very short time. The presence of efflux transporters also takes part in the movement of drugs out of the cell developing resistance. In the demand to accelerate the penetration of medicament through the anatomical barriers and increase the residence time, many novel formulations were developed. Any serious vision problems if not treated effectively cause ailments such as glaucoma, diabetic retinopathy, vitreoretinopathy, age-related macular degeneration, or AMD may lead to blindness.[2] Several systemic drugs given could not target and penetrate the eye effectively because of the manifestation of the blood–retinal barrier (BRB) and even the presence of multidrug-resistant protein (MRP) (P-glycoprotein) in it. Injections can be given in a vitreous cavity in a quantity of 20–100 µL of solution or suspension using a 27-gauge needle. However, it does not offer patient compliance, it may be painful or it may cause harm to the eye at times, and needs a well-trained person to inject the drug into the eye. Several novel formulations could be administered to target posterior eye diseases such as liposomes,

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nanoparticles, solid lipid nanoparticles, nanoemulsion-based gels, PEGylated nanoparticles, nanomicelles, niosomes, dendrimers, and lyotropic liquid crystal. Nanomicelles offer good entrapment efficiency, low levels of toxicity, improved blood circulation time, biocompatibility and deliver the medication at the site of interest and the release could be sustained using polymers which form polymeric nanomicelles. This review is discussed based on the barriers of ocular drug delivery, micelle preparation, types of micelles, evaluation parameters, applications of nanomicelles drug delivery for ocular systems, and patents on nanomicelles for drug delivery in ocular systems.

ANATOMICAL AND PHYSIOLOGICAL BARRIERS TO OCULAR DRUG DELIVERY

The eye can be split symmetrically into two segments. The front portion of the eye is known as the anterior portion of the eye which includes the iris, tear film, cornea, conjunctiva (sclera), ciliary muscles, lens, and aqueous humor.[3] The rare or back portion of the eye is known as the posterior portion of the eye which includes the sclera, macula, choroid, retina, optic nerve, and vitreous body. Both the anterior and the posterior parts of the eye are susceptible to various diseases which can cause visual threats. The topical method of drug delivery is considered a non-invasive technique that is dispensed into the cul-de-sac of the conjunctiva. The administered drugs offer poor bioavailability on the ocular surface because of various anatomical and physiological barriers that drain out the drug without making it available for absorption in the eye surface.

The anatomical barriers include:
- Tear film barrier
- Corneal barrier
- Conjunctival barrier
- Blood-aqueous barrier
- BRB.

The physiological barriers include:
- Nasolacrimal drainage
- Lacrimation rate
- Blinking.

The presence of efflux pumps such as P-glycoprotein which is a MRP also decreases the availability of the medication in the optic system.

ANATOMICAL BARRIERS

Tear Film Barrier

Tear film acts as a barrier and decreases the residence time of medication in the eye cavity. The tear film is composed of an outer lipid membrane produced by meibomian glands; in the middle aqueous membrane is present which is produced by the lacrimal gland, inner mucin membrane is produced by the goblet cells. Under physiological conditions, from the lacrimal gland, the tear flow is 1.2 mL/min. The tear film is regenerated every 5 min as a result of reflex stimulation. Lacrimation increases to 300 mL/min when the eye is irritated by reflex stimulation. These factors make the drug to be easily washed away or diluted from the eye cavity and reduce the retention time (RT) in the eye cavity. The mucin produced by the goblet cells is hydrophobic in nature and guards the eye against cell remains and extraneous particulate matter.

Corneal Barrier

The human cornea is avascular. The corneal barrier consists of 5 main layers which vary depending on the polarity. They are arranged in the order of epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium layer. The corneal epithelium is a very thick membrane composed of closely packed cells with tight junctions and prevents the entry of microorganisms and drugs. Epithelium and endothelium are lipophilic whereas the stoma is highly hydrophilic. Corneal epithelium presents as an obstacle for most of the hydrophilic medication which is 0.1-mm thick as depicted in Figure 1. The drugs are given topically penetrate the epithelium by the transcellular route mostly. If the drug is <350 Da molecular weight, the drugs can permeate through the corneal epithelium by the transcellular route. Drug absorption through the paracellular route is very difficult because the cornea is a tight junction tissue even more so when compared with the intestine, lung, and nasal mucosa.[4] The stoma is cellular, aqueous dispersed with glycosaminoglycans and collagen fibrils. It restricts the penetration of highly lipophilic and high-molecular-weight drugs. The ciliary epithelium is accountable for the making of aqueous humor. It is a clear, transparent fluid and provides nutrition to the cornea. The anterior cavity gets filled with aqueous humor flowing from the posterior chamber across the pupil. The drugs can penetrate the cornea by passive diffusion, facilitated diffusion, and active transport depending on the transporters present on the surface of the cornea. The sclera is the outer layer of the eye with irregular collagen fibers and prevents the entry of foreign substances which may be drugs or microbes to the posterior ocular tissues. Drugs with high molecular weight and high lipophilicity cannot permeate through this. The choroid which is in the middle part of the eye eliminates the drugs which are administered topically before they reach the Bruch's membrane. The accumulation of cell debris on the surface of Bruch's membrane prevents drug and nutrient exchange. The drugs with Log *P*-values of 2–3 generally show good penetration into the corneal barrier. Drugs must have a proper hydrophilic and lipophilic balance to penetrate the cornea.

Conjunctival Barrier

The conjunctiva is slender, fine, vascularized and includes 80% of the ocular surface. The conjunctiva acts as a passive

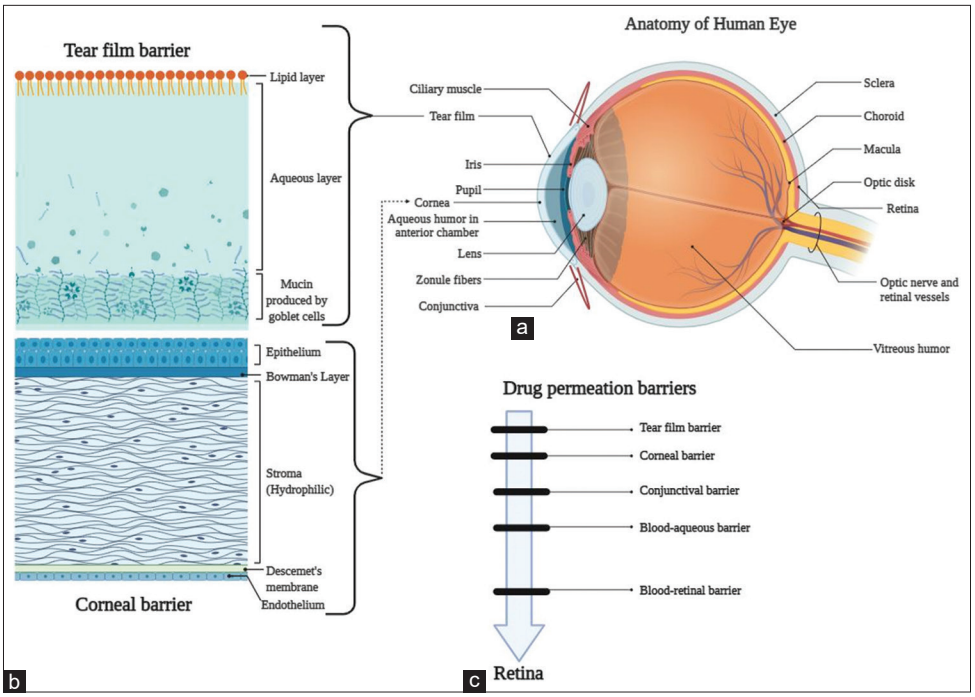

Figure 1: (a) Depicting the anatomy of the eye (b) Cross-section of tear film barrier and corneal barrier (c) Flow diagram showing the anterior to posterior segment barriers

physical barrier mainly by secreting mucus from the goblet cells. It consists of a heterogeneous tissue that mainly maintains the tear film constancy by the mucus secreted from the goblet cells.[5] Then, further studies performed proved that additional features of conjunctiva were found to be the management of electrolyte and fluid stability imparting a unique environment for delivering the drug to the anterior and posterior portion of the eye when used topically.

Blood-aqueous Barrier

The blood-aqueous wall blocks harmful or foreign substance's entry into the eye and maintains homeostasis of the eye. The blood-aqueous wall and BRB or BRB together constitute the blood-ocular barriers. The blood-aqueous wall is the anterior barrier of the ocular surface and comprises endothelial cells in the conjunctiva blood vessels in the iris and the non-tinted layer of epithelium in the ciliary body.[6] The blood-aqueous barrier alters itself during various pathological conditions such as inflammation, cataract surgery, trauma, and stress due to a rise in intraocular pressure. The inflamed cells may increase the vascular permeability but they disrupt the integrity of the blood-aqueous barrier. This disruption allows the infectious vehicle, inflammatory cytokines, and leukocytes approach to the uveal tract (middle layer of the wall of the eye), the stroma of the iris, and extend into the aqueous humor of the front chamber and continues throughout the ocular surface cavity. Due to its high selectivity, the contents in the aqueous humor are plasma protein free.[7] Blood-aqueous barrier, which is one of two blood ocular barriers along with the BRB, is a tight junction that is created between iris blood vessels which are made up of non-fenestrated endothelial cells and epithelial cells are present adjacent to the inner ciliary epithelium. Large molecular weight drugs or molecules or proteins are not able to penetrate the iris.[8] The blood vessels in the ciliary body are fenestrated which make a way for the passage of plasma proteins and molecules into stroma which is the main step in the production of aqueous humor. This barrier is located in the epithelium which forms a tight junction complex and covers every gap junction. Tight junctions restrict the large molecules which generally diffuse paracellularly. They prevent the backflow of aqueous humor.

BRB

BRBs displayed in the posterior section of the eye restrict the entry of drugs of any nature from systemic circulation in the blood into the posterior part of the eye. It is made up of mainly two segments: (a) The exterior segment developed by the retinal pigment epithelium or RPE and (b) the interior segment, which contains cells in the endothelial layer of retinal blood vessels. The binary segments are linked to each other using tight junctions which act as an obstacle to the penetration of hydrophilic and hydrophobic medication from the choroid hooked onto the retina and reaching the vitreous chamber. The BRB resembles similar to the blood–brain barrier. Several transporters were present on the surface of retinal pigment epithelium which takes part in active transport. Transporters mainly present in the retinal pigment epithelium have been identified as amino acid transporters, monocarboxylate transporters, folate and Vitamin C transporters, glucose transporters, organic anion transporters polypeptide, oligopeptide transporters, and organic anion transporters (OATs).

The efflux transporters are[9] P-glycoprotein, MRP-1, MRP-4, MRP-5, and the breast cancer resistance protein. Drugs mostly interact with organic anion transporter polypeptide and organic cation transporter in the BRB. Some drugs that transport using OATs include antibiotics such as penicillin and tetracycline and antivirals such as acyclovir and zidovudine. The substrates of organic cation transporters are antiglaucoma drugs, carbachol, brimonidine, timolol, etc., and organic anion transporter polypeptide substrates are antibiotics such as penicillin, erythromycin, and steroidal anti-inflammatory agents such as dexamethasone and prednisolone.[10] Transporters play a significant part in drug delivery to the posterior/rare segment of the eye which is very difficult to be reached. If the drug concentration at the BRB is low, the transporters across the eye cannot be saturated. Thus, the function of the transporter is reduced.

METHODOLOGY

Nanomicelles

Nanomicelles are vehicles used for drug delivery. They can assemble with themselves in an aqueous environment to form colloidal dispersions in nano size. Nanomicelles have a hydrophilic (water-loving) outer membrane with a hydrophobic (water-hating) inner core, and they can dissolve hydrophobic drugs very effectively and generate clear/transparent aqueous solutions. Nanomicelles self-assemble above a concentration of the surfactant denoted as critical micelle concentration (CMC).[11] A driving force makes self-assembly and maintains molecular assembly by hydrophobic interaction of core, for micelles. Micelles solubilize in the aqueous phase because the core-forming material is water soluble. These nanocarrier micelles are used to improve the water solubility of hydrophobic medicinal compounds since the core is hydrophobic. Nanomicelle's size ranges from 10 to 1000 nm. They are of different shapes such as spherical and cylindrical. The shape of nanomicelles depends on the branching of the polymer and its molecular weight, later they grow by the self-assembly of amphiphilic polymers. Polymers that contain both hydrophilic and hydrophobic parts in their structure are known as amphiphilic polymers. To solubilize hydrophobic pharmaceuticals, the drug delivery system self-assembles. The deepest core of nanomicelles, which comprises a hydrophobic core with hydrophilic tails on the outer/exterior surface, is compressed/encapsulated with hydrophobic medicines. Hydrophobic interactions exist amid the core and coating membrane.[12] Thus, the hydrophobic drug is encapsulated effectively. For maintaining rigidity, good stability, and better entrapment and avoiding leakage Van der Waal's forces, London forces, and hydrogen bonding which are molecular forces take part in the micelle preparation. Nanomicelles have the highest and maximum drug entrapment effectiveness and drug loading adeptness of hydrophobic medicines when compared to most nanosized colloidal drug delivery systems such as nanoparticles, liposomes, dendrimers, solid lipid nanoparticles, cubosomes, and niosomes.[13] Because nanomicelles may form transparent structures, they are ideal for ocular medicine administration of hydrophobic medications.[14] On the retina and choroid, micellar formulations containing polysorbate 80,[15] D-alpha-tocopheryl PEG,[16] octoxynol-40, and hydrogenated castor oil showed improved drug retention.

Types of Nanomicelles

Nanomicelles are broadly into 3 types

- Polymeric Nanomicelle
- Surfactant Nanomicelle
- Polyion Complex Nanomicelle.

Polymeric nanomicelles

Polymeric micelle is composed of triblock copolymers which consist of amphiphilic monomer units which in combination get converted into polymer units. They have both hydrophilic and hydrophobic properties.[17] In some formulations, two hydrophilic blocks may be used which are blocked by hydrophobic blocks. Polymeric micelles have excellent kinetic and thermodynamic constancy in solution. The polymers employed for the manufacturing of nanomicelles must be ecological and biodegradable by having control over the length of hydrophilic and hydrophobic blocks different hydrophilic-lipophilic balances and molecular weights are synthesized. The molar ratios of different block copolymers by altering the physicochemical and biological properties may be influenced. The micelle size is influenced by the relative proportion of hydrophilic and hydrophobic chains and the molecular weight of the block copolymer and its aggregations.[17] Due to its nano-size, increased solubility of drug, and chemical stability, it is a perfectly suitable nanocarrier for optic drug delivery. With these advantages, the API and gene delivery is done through the parenteral route, oral route, nasal route, ocular route, and topical or transdermal route.

Surfactant nanomicelle

Surfactants are called amphiphiles which have a hydrophilic head (water-loving) and two hydrophobic tails.[18] The head of the surfactant may be anionic, cationic zwitterionic, or non-ionic. Mostly non-ionic surfactants are generally used in ophthalmic drug delivery for the reason that they cause less irritation to the eye. The hydrophobic tail comprises long-chain hydrocarbons which may be substituted with halogen or oxygen or hydrocarbon chains. As the concentration of surfactants in the solution outdoes the (CMC micelles) is formed. Intermolecular forces such as Vander Waal interactions, hydrophobic, hydrogen bonding, and electrostatic interactions are constantly in equilibrium, which is critical for nanomicelle formation.[19] The shape of nanomicelle depending on the aggregation of surfactant

monomers may form a spherical, cylindrical, and disc shape. If there is a change in surfactant chemical structure and formulation conditions such as concentration of surfactant, pH of the formulation, temperature of the process, and ionic strength between the layers of core and coating also influence the shape and size of nanomicelle.

The most commonly used surfactants are:

- Sodium dodecyl sulfate is an anionic surfactant
- Dodecyltrimethylammonium bromide which is a cationic surfactant
- Dioctanoyl-phosphatidyl choline which is a zwitterionic surfactant
- Vitamin E TPGS (d-alpha tocopheryl polyethylene glycol [PEG] 1000 succinate)
- Octoxynol-40 which is a non-ionic surfactant.

Poly-ionic nanomicelle

Poly-ion complex (PIC) nanomicelles have been extensively used for the distribution of gene molecules and antigen delivery.[20] PIC nanomicelles are explored for the distribution of ionic drugs and hydrophilic drug moieties. Electrostatic interactions between the ions and the copolymer produce these nanomicelles. The neutral segment and ionic segment[21] are merged with oppositely charged ionic species in most cases. Hydrophilicity is a property of the block copolymer. The block copolymer used is usually PEG which is neutral in charge, and the ionic segment of the polymer is neutralized by counter-charges to form a hydrophobic core.

Preparation of Nanomicelles

- Direct dissolution method
- Solvent evaporation method
- Dialysis method
- Emulsion method
- Drug-encapsulating method by agitation.

Direct dissolution approach

In this technique,[22] the drug is directly dispersed in a block polymer in which both are soluble which is usually an aqueous solvent. On some changes such as a change in temperature and the addition of copolymer above the CMC, they self-associate to form a micelle. This process of micelle formation is employed for poloxamers which are hydrophobic. If the copolymer has high molecular weight or if the hydrophobic block is lengthy, then this method of preparation of nanomicelles is ineffective.[15] The drug loading time into the nanomicelles directly depends on the stirring time. If the stirring time increases, then drug loading also increases and if the stirring time decreases, then drug loading also decreases.

Solvent evaporation approach

This technique is also famous for solvent casting.[23] In this method, a volatile organic solvent is selected in which the drug and polymer are dissolved. Using a rotary vacuum evaporator, the solvent is evaporated and upon reconstitution, with water, the micelles in nano size can be obtained.

Dialysis method

In this method, the micelles are manufactured by solubilizing the drug and polymer in a solvent (diluent) that is miscible with water.[24] The solvent must be in such a way that the hydrophilic and hydrophobic portions of the polymer must be solubilized. Then the solubilized solution is dialyzed against water. As the water which is in higher concentration enters into the bag, the solution tends to form micelles. Since the dialysis bag is semipermeable, it does not allow the formed micelles to escape out of the dialysis bag.

Emulsion method

In this technique, water-immiscible solvents such as chloroform, tetrahydrofuran, acetone, or a blend of such solvents may be utilized to solubilize the drug and polymer.[25] After solubilizing the solution is mixed into the water gradually with brisk stirring, an emulsion is produced where the continuous phase is occupied with water and the dispersed phase is occupied with an organic solvent. On evaporating or lyophilizing the solvent, the liquid phase is removed. It can be reconstituted into micelles by adding the aqueous phase.

Drug encapsulation by agitation

It is a patented method for the preparation of nanomicelles.[26] The drug and polymer are dispersed in an organic solvent and upon removal of the solvent by solvent evaporation solvent is removed.[27] After the removal of organic solvent, aqueous solvents such as water are added. The temperature of the solution must not be above 30°. This method is used to maximize the entrapment effectiveness of the hydrophobic drugs into the micelles and these micelles can undergo a membrane filtration process as a part of sterilization.[28]

CHARACTERIZATION OF MICELLES

Morphology

To predict the *in vivo* conditions in the body, the permeability and solubility the effect of particle size and shape generally need to be determined.[29] Polymeric micelles can benefit from aiming the drugs to specifically cancer sites by improved penetration and retention effect (EPR effect). The EPR effect occurs only when the drug molecules are certain in size which is largely affected by the molecular weight of the copolymer, hydrophilic, or hydrophobic ratio of the polymer.[30] Transmission Electron Microscopy (TEM), Dynamic Light Scattering or Photon Correlation Spectroscopy, and Atomic Force Microscopy may all be used to regulate particle size and form. Cryo-TEM is the most preferred equipment for

measuring the particle size of the polymeric micelles because the structure of the micelles is retained as same.

Polydispersity Index of Micelle

The size dispersity of micelles can be known with the help of the polydispersity index. It is also called PDI.[31] For the preparation of the micelle to be the best formulation, micelle must be monodispersed and so it will form a translucent blue color. If micelles are unstable, aggregates of micelles are formed then white color is formed. For a monodisperse, the polydispersity index is very low, and for a polydispersion, the polydispersity index is high. A list of various patents of nanomicelles of the desired sizes is incorporated in Table 1.

Zeta Potential

Nanomicelles are colloidal drug carriers. The stability of the colloidal particles generally depends on the zeta potential of the micelle formulation. The zeta potential is often altered when it binds with cellular membrane proteins.[3] The absolute value of zeta potential must be 20–50 mV. The stability of the micelle formulations is influenced by the charge of the micelles.[32] The attractive and repulsive forces between the intermolecular particles generally depend on the zeta potential which influences the stability of the colloidal nanomicelle formulation.[33] More strong repulsive force is seen in between the surface charge of two particles with higher zeta potential and higher stability is observed.

Table 1: Patents of polymeric nanomicelles

Patent description	Patent number	Inventors	Year	Patent status	References
Polymeric micellar clusters using amphiphilic polymer	WO2008017839 A1	Igeoma F. Uchegbu Andreas G. Schatzlein Xueliang Hou	2008	Active	[38]
Block copolymer has two blocks where the first block contains temperature-sensitive monomer and the second block contains pH-sensitive hydrophobic monomer	WO2008004978 A1	Yi-Yan Yang Shao-Qiong Liu	2008	Withdrawn	[39]
Topical drug delivery systems for ophthalmic use by mixed nanomicelles	WO2010144194 A1	Ashim K. Mitra Poonam R. Velagaleti Ulrich M. Grau	2010	Active	[40]
Drug delivery system using hyaluronic acid-peptide micelle conjugate	US20120294945 A1	Sei Kwang Hahn Choun-Ki Joo	2012	Active	[41]
Polymeric micellar clusters and used in formulating drugs of particle size 20–500 nm	US8470371 B2	Ijeoma F. Uchegbu Andreas G. Schatzlein Xueliang Hou	2013	Active	[42]
Prolamine protein conjugated with PEG can be used for forming a micelle	US 8697098 B2	Omathanu P. Perumal Satheesh K. Podaralla Ranjith Kumar Averineni	2014	Active	[43]
Nanomicelles for hydrophobic drugs to the posterior segment of ocular drug delivery including with definite concentration of corticosteroids, vitamin E TPGS, octoxynol-40	US 9017725 B2	Ashim K. Mitra Poonam R. Velagaleti Ulrich M. Grau	2015	Active	[44]
Micelles which are peptide-based	WO2015041520 A1	Andreas Herrmann Jan Willem De Vries Martin Stephan SPITZER Sven Oliver SCHNICHELS	2015	Active	[45]
Aqueous topical nanomicelles which contain cyclosporins, fatty acid, polyalkoxylated alcohol	US8980839 B2	Ashim K. Mitra Sidney L. Weiss	2015	Active	[46]
Cyclosporine A loaded polymeric micelles particle size<20 nm	WO2021032073A1	Bo Liang Haizhou PENG Jieyu ZHU Xudong Yuan	2021	Active	[47]

Table 2: Ocular drug delivery using nanomicelles as carriers

Drug	Polymer/Surfactant	MOA	Target	Release profile (*In vivo*)	Indication	References
Curcumin	PVCL-PVA-PEG	Suppress oxidative stress	Anterior	Release for 72 h	Anti-oxidant, Anti-inflammatory	[48]
Dexamethasone	Pluronic F127, Chitosan	Inhibit phospholipase-A2	Anterior	Release for 10 h	Anti-inflammatory	[49]
Ketorolac	N-isopropyl acrylamide	Inhibit phospholipase-A2	Anterior	Release for 5 h	Post-operative inflammation	[50]
Metipranolol	Pluronic F127, Chitosan	Suppress aqueous outflow	Anterior	Release for 6 h	Glaucoma	[51]
alpha-tocopherl	Poly (propylene oxide)-Poly (ethylene oxide)	Suppress protein kinase-C	Posterior	Release for 24 h	Glaucoma, cataracts	[52]
Ethoxzolamide	(Tetronic) Poly (propylene oxide)-Poly (ethylene oxide)	Inhibit carbonic anhydrase	Anterior	Release for 1–5 days	Glaucoma	[53]
Tacrolimus	Amino-terminated poly (ethylene glycol-poly (D, L)-lactic acid) and HPMC	Supress immune system	Anterior	Released for 4 h	Anti-allograft rejection	[54]
Dexamethasone	Chitosan oligosaccharide-valylvaline-stearic acid	Inhibit phospholipase-A2	Posterior	Released for 5 h	Macular edema	[55]
Cyclosporine-A	D-α-Tocopherol polyethylene glycol succinate, Vit E-TPGS &Polyoxyl 40 hydrogenated castor oil	Calcineurin inhibitor	Anterior	Released for 0.5 h	Dry eye syndrome	[56]
Dexamethasone	Polycaprolactone-polyethylene glycol-polycaprolactone	Inhibit phospholipase-A2	Anterior	Released for 36 h	Uveitis	[57]
Lornoxicam	Poly (ethylene oxide)-poly (propylene oxide)	COX inhibitors	Anterior	Released for 6 h (*In-vitro*)	Post-cataract macular edema	[58]
Methazolamide	Methoxy-poly (ethylene glycol)-b-poly(ε-caprolactone)	Carbonic anhydrase inhibitor	Anterior	Released for 8 h	Glaucoma	[59]
Natamycin	Soluplus and Pluronic P103 mixed with cyclodextrins	Prevents ergosterol -dependent fusion	Anterior	-	Fungal keratitis	[60]
Nimodipine	Rebaudioside A and D -α-tocopheryl polyethylene glycol 1000 succinate	Calcium channel blocker	Anterior	Released for 6 h	Glaucoma	[61]
Myricetin	Polyoxyl 15 hydroxy stearate	Free radical scavengers	Anterior	-	Oxidative stresses	[62]
Dexamethasone	Polylactide-polycaprolactone -polyethylene glycol-polycaprolactone -polylactide	Inhibit phospholipase-A2	Posterior	-	Macular edema	[63]
Triamcinolone acetonide	Poly (ethylene glycol)-poly (e-caprolactone) and poly (ethylene glycol)-poly (lactic acid)	Phospholipase inhibitor	Posterior	Released for 72 h	Uveitis	[64]
Ciprofloxacin	Pluronic-Chitosan nanomicelle	Inhibit DNA gyrase or Topoisomerase IV	Anterior	Released for 840 min (*In-vitro*)	Bacterial infections	[65]
Progesterone	Pluronic F68 and Soluplus copolymers	Promote new myelin-forming and reduce myelin sheath loss	Posterior	-	Retinitis pigmentosa	[66]
Tacrolimus	PEG-hydrogenated castor oil-40 and octoxynol-40	Decrease inflammatory markers	Posterior	Release for 22 days	Age-related macular degeneration	[67]
Sunitinib	methoxy poly (ethylene glycol)-poly (caprolactone)	Inhibitor of tyrosine kinase	Posterior	Release for 168 h (*In-vitro*)	Age-related macular degeneration	[68]

Verification of CMC

The verification of CMC is an important characteristic feature to evaluate the prepared nanomicelle formulation, and it is because that the nanomicelle is formed only after the surfactant reaches the CMC. It is a chief cause that affects the constancy of a micelle formulation.[34] When the polymer exceeds, the CMC micelles are formed and upon dilution, the micelles are broken into fragments. The methods for determining CMC are done using surface tensiometer DSC,[35] chromatography, conductivity, osmometry, and light scattering methods.

In vitro Release of Drug

The majority of the polymeric nanomicelles are formed by physical entrapment or chemical conjugation. The release of drugs mainly depends on the physical or chemical conjugation.[36] The diffusion mechanism mainly occurs for a drug in the core entrapped physically by micelles. The drug release mechanism for chemical conjugation will be surface erosion or bulk degradation. Partition coefficient, core size, drug loading in the micelle, and presence of cross-linking agents are some other secondary parameters that influence drug release from the micelle.[37] Normally, the drug release from a micelle formulation dialysis method is mainly preferred. A phosphate buffer of pH 7.2 is selected as the media and sink condition must be maintained. The temperature of the buffer is maintained at 37°C. The *in vivo* studies performed for some therapeutics loaded into nanocarriers are tabulated in Table 2.

CONCLUSION

Prodrug approaches for transporter targeting and nanomicelle formulations are some of the best strategies to convalesce the ophthalmic bioavailability capable of being a targeting and sustained release formulation. Nanomicelles is a novel strategy for the growth and maturity of topical eye drops for rare/posterior optical diseases. This field of drug delivery needs more focus in which advanced investigation, research, and development are needed. Posterior optic diseases mainly affecting macula and diabetic retinopathy may lead to blindness in persons. At present, for treating these diseases, the routes of administration are intravitreal injections which may not offer patient compliance because they are painful and may cause retinal blood clots or damage ocular tissues and ocuserts which are drug-eluting implants. The nanomicelle strategy can be used to heal posterior optic diseases through topical application of the drug because it offers good entrapment efficiency, targeting, and good RT on the ocular surface. Although it has good entrapment efficiency, nanomicelle kind of medication delivery to rare parts of the ocular body is blocked through the blood-aqueous barrier. The therapeutic dose does not exactly attain the posterior/rare segment of the eye. If the drug concentration is less than the minimum effective concentration, then therapeutic response is not possible. Due to this reason, topical administration to the posterior part of the eye is much more difficult to achieve. Merely, few scholars have opened the eyes of topical drug delivery and moieties to the posterior part of the eye.[69] These researchers have tried transporting the drugs that pass from the sclera, choroid, and retina. The drug concentrations reaching the retina by intravitreal injections are much higher than a topical dose. Hence, the challenge for researchers is to develop a topical formulation that can reach the posterior part of the eye giving the exact bioavailability as that of an intravitreal injection.[70] The mechanism of nanomicellar drug formulation is not found using *in vivo* studies and needs more focus to be studied. Although there are some limitations, nanomicelles offer the best route of topical formulation for ophthalmic drug delivery. However, nanomicelles have increased drug assimilation through optical barriers and enhanced bioavailability in the ocular tissues.

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