RESEARCH PAPER

Nanomicellar Systems in Ocular Drug Delivery: Overcoming Anatomical Barriers for Enhanced Intraocular Bioavailability

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ABSTRACT

Ocular drug delivery is constrained by intricate anatomical and physiological barriers, including rapid nasolacrimal drainage, corneal tight junctions, and the blood-retinal barrier. These defence mechanisms typically restrict the intraocular bioavailability of conventional topicals to less than 5%. To circumvent these limitations, nanomicelles have emerged as a sophisticated delivery platform. These self-assembled amphiphilic structures (5–100 nm) utilize a hydrophobic core to solubilize BCS Class II/IV drugs, while a hydrophilic shell ensures stability within the tear film. Nanomicelles offer superior stability due to low critical micelle concentrations and can be engineered for mucoadhesion to prolong precorneal residence. Formulated via thin-film hydration or direct dissolution, these carriers particularly polyion complex micelles facilitate the targeted delivery of agents against VEGF and inflammatory cytokines (HIF-1α) in vitro retinal disorders. By optimizing polymer composition and zeta potential, researchers can achieve high encapsulation efficiency and sustained release profiles, effectively reducing dosing frequency and local toxicity. Despite hurdles regarding large-scale manufacturing and drug-loading capacity, the clinical success of FDA-approved formulations like cyclosporine underscores their transformative potential. Future advancements are directed toward the development of stimuli-responsive and ligand-targeted nanocarrier systems, frequently combined with in situ gelling platforms, to enhance drug retention and facilitate effective delivery from the anterior segment to posterior ocular tissues, thereby overcoming current therapeutic limitations.

Keywords: Nanomicelles, Neovascularisation, VEGF inhibition, Corneal penetration, Ocular drug delivery

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INTRODUCTION

One of the biggest problems for pharmacists and eye specialists is the targeted drug delivery of medications into the intraocular tissues. Classic topical ophthalmic formulations like eye drops, suspensions, and ointments have sufficient capacity to increase intraocular tissue bioavailability without increasing drug toxicity. All restrictions related to ocular delivery-like structure of the eye; its physiological and anatomical barriers are incredibly complicated. Nanotechnology has entered as a new era that can overcome these obstacles by scientific advancements .

Neovascularization is the development of new blood vessels. This process is of three types: angiogenesis (creation of a new capillary network from an existing one), arteriogenesis (creation of arteries), and vasculogenesis (creation of new capillaries). The creations of vessels' development increased the flow of fluids and occasionally blood into the retina .

Nanotechnology involves creating materials 1-100 nm in size. The application of nanotechnology within the biomedical field has helped the advancement of advanced drug delivery systems, mentioned as nanosystems. which act as nanocarriers. Conventional treatments have some problems, such as low solubility, slow metabolism, frequent dosing, and targeting difficulties. Nanocarriers solve these problems by overcoming them. Nanocarriers are divided in to mainly three types: polymeric, non-polymeric, lipid-based (Dinesh *et al.,*2018). The polymeric nanocarrier is further subdivided into dendrimers, nanogels, nanomicelles, and polymeric nanoparticles. However, the non-polymeric nanocarrier was divided into mesoporous silica and gold nanoparticles. The lipid-based nanocarriers includes vesicles emulsion system etc. (Jain *et al.,*2019).

Nanomicelles are amphiphilic colloidal particles with a size range between 5 and 100 nm formed by the joining of amphiphilic molecules at a specific temperature and concentration. They are used as drug carrier for various pharmaceutical products due to their ability to carry lipophilic drugs in the centre and outer hydrophilic part. Micelle formation occurs when the hydrophilic groups form hydrogen bonds with one another, pushing the hydrophobic group away. As a result, the system's free energy is reduced. Amphiphilic block copolymers create polymeric micelles (Marija *et al.,*2017) which exhibit greater stability, significant drug accumulation at the target and a decreased critical micelle concentration (CMC). The small and homogeneous size of micelles, similar to viruses and lipoproteins, is crucial in controlling their biodistribution under the enhanced penetration and retention (EPR) effect.

Nanomicellar drug delivery systems significantly enhance the penetration of therapeutic agents into deeper tissues due to their nanoscale size and improved physicochemical properties. Conventional micelles are self-assembled structures in which amphiphilic molecules organize with a hydrophobic inner core and a hydrophilic outer shell when dispersed in a polar solvent environment. The solubility and bioavailability of poorly water-soluble drugs can be markedly improved by incorporating them into nanomicellar carriers (Letchford *et al.,* 2017). In reverse micelle systems, the hydrophilic groups orient toward the internal region while the hydrophobic segments remain exposed outward. This type of structural arrangement typically occurs in nonpolar solvent conditions. Hydrophilic biomolecules and drugs, including proteins such as lysozyme (Cabral *et al.,* 2018), dyes like trypan blue and fluorescent compounds such as fluorescein (Trivedi *et al.,* 2017), can be effectively encapsulated and transported through reverse nanomicellar systems. The treatment of severe infections, chronic disorders, and cancer, which represent major healthcare challenges today, requires controlled and sustained drug delivery strategies. Sustained drug release from nanomicelles can be achieved through various approaches, including prodrug formation, layer-by-layer micellar assembly on solid supports, reverse micelle structuring, and drug–polymer conjugated micelle development. Due to their extremely small size, micelles provide superior advantages for targeted drug delivery compared with larger carrier systems (Blanco *et al.,* 2019). The aggregation of amphiphilic molecules improves structural stability, facilitates sterilization processes, and enhances the solubility of poorly water-soluble therapeutic compounds. Micelles possess a hydrophilic corona that enables active targeting through ligand conjugation (Torchilin *et al.,* 2018) and a hydrophobic core stabilized by van der Waals interactions that accommodates lipophilic drugs (Zhang *et al.,* 2020). Furthermore, the hydrophilic outer layer prolongs systemic circulation by reducing recognition and clearance by the reticuloendothelial system (RES) (Li *et al.,* 2021).

STRUCTURE OF EYE AND OCULAR BARRIER ASSOCIATES WITH DRUG DELIVERY

The eye is a highly specialized sensory organ with complex anatomical layers that significantly influence ocular drug delivery. The outer protective layer, the sclera, is a dense fibrous tissue composed mainly of collagen fibres and proteoglycans that maintain the structural integrity of the eye and regulate intraocular pressure. Although it serves as a protective barrier, the sclera is relatively permeable to hydrophilic molecules, allowing limited diffusion of certain drugs (Gorantla *et al.,* 2020). As shown in Figure 1, the cornea is the primary route for topical drug absorption. It is transparent, avascular, and composed of three layers epithelium, stroma, and endothelium. The epithelium contains tight junctions that restrict hydrophilic drug penetration, whereas the stromal layer, due to its high-water content, limits the movement of lipophilic compounds, creating a selective permeability barrier. The conjunctiva, a thin membrane covering the anterior eye and inner eyelids, contributes to tear film stability by secreting mucus and electrolytes. However, its rich blood and lymphatic supply can lead to systemic drug absorption, reducing ocular bioavailability (Huang *et al.,* 2018). Internally, the iris regulates pupil size, while ciliary muscles control accommodation and aqueous humor secretion. Aqueous humor maintains intraocular pressure and provides nutrients to ocular tissues (Wu *et al.,* 2019). The vitreous humor supports retinal structure, while the retina and underlying choroid play critical roles in vision and nutrient supply. Protective structures such as eyelids and the lacrimal system produce tears that drain through the nasolacrimal duct, shortening the residence time of topically administered drugs (Joseph *et al.,* 2017; Weng *et al.,* 2016).

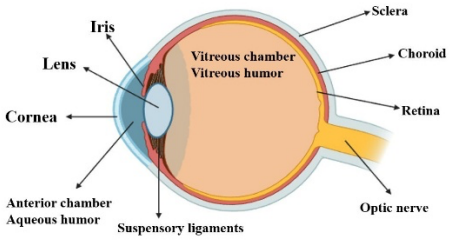

Figure 1:- Structure of eye

Several physiological barriers further limit the effectiveness of ocular drug administration. Precorneal barriers such as tear turnover, reflex blinking, and lacrimal fluid secretion rapidly remove applied drugs from the ocular surface. The lacrimal fluid turnover rate is approximately 1 µL/min, and when the instilled volume exceeds the conjunctival sac capacity of around 7–9 µL, the excess fluid drains through the nasolacrimal duct, leading to significant drug loss (Huang *et al.,* 2018). The nasolacrimal drainage system, which consists of canaliculi, the lacrimal sac, and the nasolacrimal duct, is responsible for eliminating nearly 95% of the topically administered ophthalmic solution. Because these tissues are highly vascularized, part of the drug may be absorbed systemically through the nasal mucosa, reducing ocular therapeutic efficiency (Joseph *et al.,* 2017). Another important barrier involves efflux transport proteins located in ocular tissues such as the corneal epithelium, conjunctival epithelium, ciliary body, and retinal endothelial cells. Transporters such as P-glycoprotein (P-gp), multidrug resistance protein (MRP), and breast cancer resistance protein (BCRP) actively pump drug molecules out of cells, reducing intracellular drug accumulation and limiting drug penetration into ocular tissues (Subrizi *et al.,* 2019). The corneal epithelial layer also serves as a primary barrier to drug diffusion due to tight junctions between epithelial cells that restrict paracellular transport. However, disruption of these junctions or the chelation of calcium ions using agents such as EDTA may temporarily enhance drug permeability. In addition to surface barriers, the eye contains specialized blood–ocular barriers that regulate drug movement between systemic circulation and ocular tissues. These include the blood–aqueous barrier (BAB) and the blood–retinal barrier (BRB). The BAB consists of tight junctions present in the ciliary epithelium and iris vasculature that restrict drug entry into the aqueous humor. The BRB, formed by retinal capillary endothelial cells and retinal pigment epithelial cells, protects the neural retina and maintains retinal homeostasis by restricting the diffusion of substances from the bloodstream (Kritika *et al.,* 2021; Rudeen *et al.,* 2020). Drug penetration across these barriers depends on factors such as molecular size, lipophilicity, and particle characteristics. Experimental studies have shown that retinal capillaries can restrict the passage of nanoparticles larger than approximately 20 nm, while only very small molecules can pass through tight junctions between epithelial cells. Therefore, these anatomical, physiological, and biochemical barriers significantly reduce ocular drug bioavailability and must be carefully considered when designing effective ophthalmic drug delivery systems.

PATHOPHYSIOLOGY

The development of hypoxia and ischemia from DR happens very gradually, in contrast to CRVO, where the usual NVG happens three months after the commencement of ischemic RVO (commonly referred to as "100-day glaucoma").The two main causes of vascular problems in diabetes are ischemia-reperfusion and persistent hyperglycemia. Numerous neovascular-related factors are formed as a result of retinal hypoxia and ischemia, according to studies (Senthil *et al.,*2021), This results in an imbalance between activities that promote and inhibit angiogenesis. The levels of angiopoietin-2 and the angiogenesis factor VEGF are normally balanced. The stimulation, movement, and proliferation of immune, pericyte, and endothelial cells, as well as an imbalanced overexpression of VEGF, result from this imbalance when hypoxia and ischemia are present. The fundus, iris, and frontal chamber angle can create neo vasculature and neovascular layers by promoting angiogenesis. Because the anterior chamber angle is blocked and stretched, and iris trabecular meshwork adhesion is forced, the imbalance ultimately increases intraocular pressure and vision impairment. VEGFs, insulin-like growth factor (IGF), hepatocyte growth factor (HGF), hypoxia-inducible factor 1-alpha (HIF1a), tumor necrosis factor (TNF), and inflammatory cytokines (e.g., IL-1β, IL-6, IL-8, etc.),Angiogenesis-related factors that contribute to the pathophysiology include thrombospondin, changing growth factor-beta (TGF-β), pigment epithelium-derived factor (PEDF), somatostatin, and others (Senthil *et al.,*2021).

Angiogenesis and Vascular Endothelial Growth Factor

Researchers found that the most common factor for NVG is NEGF and angiogenesis (Sun *et al.,*2016). VEGF produce by non-pigmented ciliary epithelium and several retinal cells (Pericytes, ganglion cells, Muller cells, and retinal pigment epithelium). Little amount of VEGF is essential for proper growth of retina and blood flow in eye. But overproduction of VGEF causes serious pathological condition for NVG. Patients with diabetes-related NVG have elevated VEGF levels in their aqueous humor, particularly in eyes following ocular operations, which may facilitate VEGF diffusion into the anterior chamber (Jeganathan *et al.,*2016). This suggests that VEGF plays a crucial role in the pathophysiology of NVG. Additionally, experimental data shown that iris neovascularization and NVG may be produced in monkeys by injecting them with human recombinant factor VEGF.

VEGF is divided into five subtypes, each of which can attach to particular subtype receptors and promote angiogenesis in particular tissues. The isoform VEGF is responsible neovascularization, VEGF-A, promotes the survival of endothelial cells by preventing capillary degeneration and cell death. PDR patients had significantly higher levels of VEGF-A in their vitreous. Conditions of hyperglycemia and hypoxia trigger downstream pathways, which in turn trigger an inflammatory cataract and increase VEGF expression (Tang *et al.,*2020). VEGF-A release may also be stimulated by cells that generate HIF-1a. It binds to VEGF receptors on endothelial cells, circulated VEGF-A which triggers the tyrosine kinase pathway and tissue angiogenesis.

Hyperglycaemia and Metabolic Alteration

Long-term hyperglycemia with elevated intraocular pressure (IOP) has been clearly linked to diabetes, according to studies on large populations in Singapore and Japan that controlled for central corneal thickness (Yang *et al.,*2018 Hanyuda *et al.,*2020). Shows that diabetes might increase the chance of having high IOP. The blood-retina barrier (BRB) is broken down by hyperglycaemia because it causes the loss of pericytes, endothelial cell apoptosis, swelling of the basal membrane, and disruption of cell attachment (Feldman-Billard *et al.,*2018). The passage of angiogenesis and inflammatory substances is significantly increased by these morphological alterations in tissue structure, which activate other biological processes. Additionally, hyperglycaemia may alter how glucose is metabolized. The metabolic pathway includes the accumulation of advanced products of glycation, oxidative stress, the polyol pathway and protein kinase C (PKC) activation (Whitehead *et al.,*2018). Aldose reductase uses the polyol pathway to convert glucose to sorbitol. Cell osmotic damage and pressure fluctuations are caused by the build-up of impermeable sorbital. The change of the basement membrane and vascular permeability is further accelerated by PKC activation. Furthermore, the production of advanced by-products of glycation modifies extracellular matrix proteins, resulting in both cell death and cumulative damage to retinal arteries.

Immune Response and Inflammation

Inflammation is another big factor responsible for NVG, according to collected data (Sun *et al.,*2020), the precise molecular mechanism is yet unknown. Chronic low-grade inflammation is responsible for VEGF production and vascular anomalies, which are the main cause of capillary blockage and hypoxia. Ischemia, hyperglycaemia, and oxidative stress are some of the factors that affect the inflammatory process. Increased levels of neurotrophins and inflammatory cytokines, including TNF-α, IL-6, IL-8, and IL-1β, have been seen in the vitreous of people with DR (Boss *et al.,*2017). Moreover, NVG patients' aqueous humor contained significantly higher levels of VEGF-A, IL-8, and EPO than the control groups, even after taking PRP and anti-VEGF medication (Jiang *et al.,*2020). TNF-α, IL-6, IFN-r, MCP-1, and VEGF are released when Muller cells, microglia, astrocytes, and T cells become activated in an inflammatory environment, which damages the endothelium and impairs BRB and causes neurodegeneration (Tang *et al.,*2020). Moreover, the NVG process is associated with neutrophils, white blood cell counts, the neutrophil/lymphocyte ratio (NLR), and the lymphocyte/monocyte ratio (LMR). Additionally, NLR is much increased in NVG after RVO or DR compared to healthy people (Zhang *et al.,*2017), which may be an indicator for NVG.

Anti-inflammatory medications, including NSAIDs and intravitreal triamcinolone acetonide, have been demonstrated to decrease VEGF expression and vascular permeability, halt retinal cell death, lower leukostasis, and eventually enhance retinal function and visual acuity. Even though the pathogenesis of NVG in uveitis-affected eyes is still unknown, studies have indicated that anti-inflammatory medication may be the first line of treatment for anterior uveitis-associated NVG (Sora *et al.,*2018). Targeting microglia to change the retinal microenvironment might potentially provide an anti-inflammatory therapy option in the future (Wang *et al.,*2022).

NANOMICELLES

Nanomicelles are nanosized, self-assembled colloidal carriers formed from amphiphilic molecules that contain both hydrophilic and hydrophobic segments. In aqueous environments, these molecules spontaneously organize so that the hydrophobic portions form an inner core while the hydrophilic segments remain on the outer surface, stabilizing the structure in biological fluids.in figure 2 the structure of nanomicelles id shown. This core–shell arrangement enables nanomicelles to encapsulate poorly water-soluble drugs within the hydrophobic core and significantly enhance their apparent solubility and bioavailability (Li *et al.,* 2022). Typically ranging from 10–100 nm in size, nanomicelles possess a very small particle diameter that facilitates efficient drug transport and improved penetration across biological membranes. Because of these characteristics, nanomicelles are considered promising carriers for targeted drug delivery applications. In ocular drug delivery, they offer clear advantages over conventional ophthalmic formulations such as eye drops and ointments, which often show poor drug absorption due to physiological barriers like the corneal epithelium and tear film. The nanoscale size and adaptable surface properties of nanomicelles allow better interaction with ocular tissues and enhance corneal permeation, enabling drugs to reach deeper ocular regions and improving therapeutic effectiveness (Akhter *et al.,* 2022). Additionally, nanomicelles can provide controlled and sustained drug release, maintain therapeutic drug levels and improve patient compliance (Luhar *et al.,* 2024).

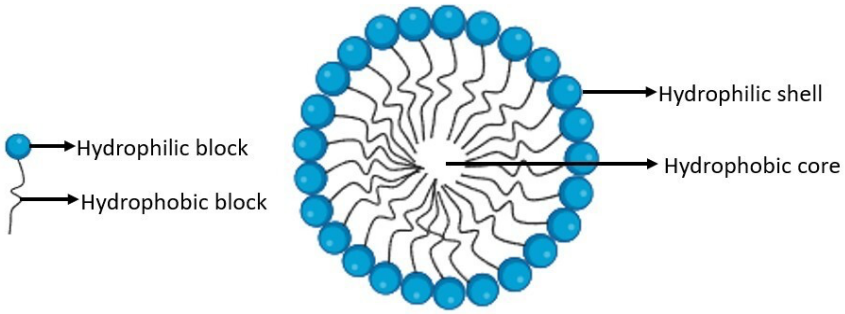

Figure 2:- Structure of nanomicelles

Nanomicelles possess several important properties that make them effective drug delivery carriers. Those are high structural stability, which results from the self-assembly of amphiphilic polymer chains and their extremely low critical micelle concentration (CMC) values (10^{-6}–10^{-7} M), allowing nanomicelles to maintain their integrity even after significant dilution compared with conventional surfactant micelles (Cabral & Kataoka, 2019). Their ability to solubilize lipophilic drugs, where the hydrophobic core encapsulates poorly water-soluble molecules while the hydrophilic shell stabilizes the system in aqueous environments and forms clear drug solutions (Kotta *et al.,* 2022). Nanomicelles also exhibit distinct physicochemical characteristics due to their amphiphilic block copolymer composition, commonly forming diblock (AB) or triblock (ABA/ABC) structures that enhance drug loading efficiency and stability through hydrophobic, electrostatic, hydrogen-bonding, or metal–ligand interactions (Ghezzi *et al.,* 2021, Talebian *et al.,* 2022). Furthermore, some nanomicellar systems are pH-responsive, where ionization of polymer groups destabilizes the micelle at specific pH conditions and triggers-controlled drug release for targeted delivery (Zhang *et al.,* 2019). Nanomicelles also exhibit mucoadhesive properties that prolong residence time on mucosal surfaces, enhance local drug concentration, and improve absorption and therapeutic efficiency (Singh S *et al.,* 2020, García-Díaz *et al.,* 2021).

Nanomicelles used in ocular drug delivery are mainly classified into surfactant nanomicelles, polymeric nanomicelles, and poly ionic complex (PIC) nanomicelles, each differing in composition, stability, and drug–carrier interactions. Surfactant nanomicelles are formed from amphiphilic molecules that contain hydrophilic heads and hydrophobic tails and self-assemble in aqueous environments when the concentration exceeds the critical micelle concentration (CMC). However, these micelles usually possess relatively higher CMC values and may become unstable upon dilution, which can affect their stability in biological fluids (Vaishya *et al.,* 2014). Common surfactants used for nanomicellar formulations include vitamin-E TPGS, octoxynol-40, sodium dodecyl sulfate, and dodecyltrimethylammonium bromide Mandal *et al.,* 2017 prepared antiviral drug-loaded nanomicelles using hydrogenated castor oil-40 and octoxynol-40, which significantly improved drug solubility, corneal permeation, and sustained drug release (Mandal *et al.,* 2017). Polymeric nanomicelles are formed from amphiphilic block copolymers that self-assemble in aqueous media to create a hydrophobic drug-loading core surrounded by a hydrophilic corona. These micelles generally have lower CMC values and greater thermodynamic and kinetic stability than surfactant micelles. Different polymers used in the formation of nanomicelles are summarized in Table 1, while Figure 3 shows the chemical structures of these polymers used in nanomicelles preparation. Varela-Garcia *et al.,* 2018 developed polymeric micelles using Soluplus and Solutol to enhance ocular delivery of acyclovir, improving drug solubility and providing sustained release (Varela-Garcia *et al.,* 2018). Li *et al.,* 2020 prepared PEG-PCL polymeric micelles that improved drug solubility, stability, and corneal permeation (Li *et al.,* 2020). The poly ionic complex micelles are formed through electrostatic interactions between oppositely charged polymers or drugs and are particularly useful for delivering charged biomolecules such as DNA and oligonucleotides (Vaishya *et al.,* 2014).

Table 1: -List of micellar formulation studied for Ocular Drug Delivery

S. No.	Polymer / Surfactant	Size	Therapeutic Agent	Reference
1	Pluronic F127 (surfactant micelle)	~20–30 nm	Pilocarpine	(Vaishya *et al.,*2014)
2	Tetronic (Poloxamine) T1107, T908, T1307	30–40 nm (multimodal distribution)	Ethoxzolamide	(Vaishya *et al.,*2014)
3	MPEG-hexPLA (methoxy-PEG–hexyl-lactic acid) micelles	~54 nm	Cyclosporin A	(Vaishya *et al.,*2014)
4	mPEG-PDLLA block copolymer micelles	~50–150 nm (depends on ratio)	Pirenzepine hydrochloride	(Vaishya *et al.,*2014)

5	Pluronic F127 + Chitosan	~25–29 nm	Dexamethasone	(Vaishya *et al.,*2014)
6	VitE-TPGS + RH-40 (non-ionic surfactants)	9.7–10.1 nm	Cyclosporine-A (CyA)	(Terreni *et al.,*2021)
7	mPEG-PCL micellar nanoparticles (NanoCA)	(size not specified)	Carbonic anhydrase inhibitor (CA)	(Binkhathlan *et al.,*2023)
8	Smart biocompatible graft copolymer micelles	(size not specified)	Dorzolamide (glaucoma treatment)	(Ozturk *et al.,*2022)
9	Dextran-based micelles	10–100 nm	Doxorubicin, Paclitaxel, etc. (cancer drugs)	(Ozturk *et al.,*2022)
10	Thermosensitive nanomicelles (in situ gelling)	(not specified)	Various, enhanced retention & release	(Bairagi *et al.,*2025)
11	Stimuli-responsive PEG-PNIPAM micelles (CG-MD)	Varies; molecular simulation	Doxorubicin (DOX)	(Jamirad *et al.,*2025)
12	Polymeric micelles (general review)	(commonly 10–100 nm)	Poorly soluble drugs (general)	(Mandal *et al.,*2017)
13	Nanomicelles (surfactant/amphiphilic polymer)	(not specified)	Various ocular drugs	(Paganini *et al.,*2024)
14	Polymeric micelles for enhancing bioavailability	(not specified)	Hydrophobic ocular drugs	(Meltem *et al.,*2019)
15	Polymer-lipid nanocarriers (polymersomes)	(not specified)	Various ocular applications	(Haijie *et al.,*2023)

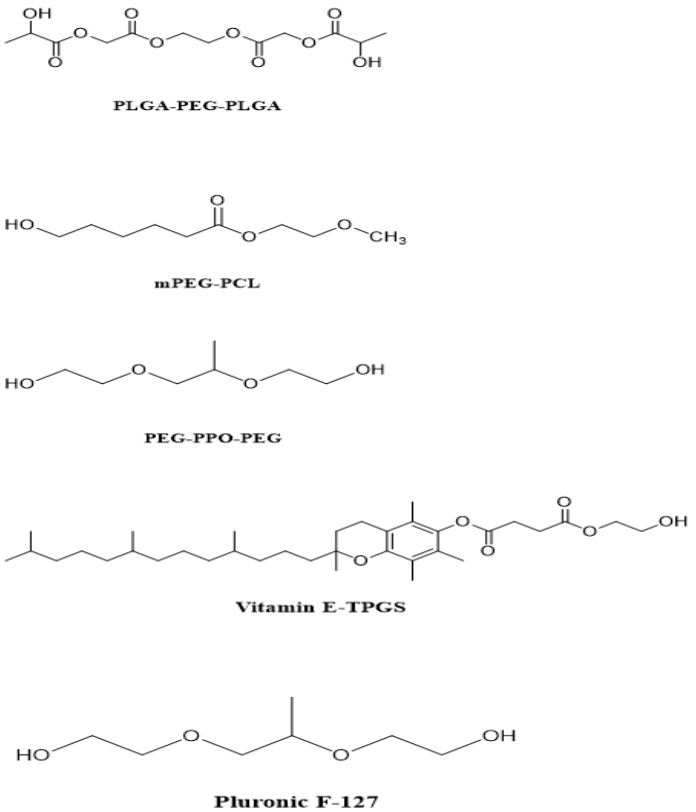

Figure 3: - Chemical structure of polymers used in micelles preparation

Nanomicelles are commonly prepared using biocompatible and biodegradable polymers such as polyethylene glycol (PEG) and amphiphilic block copolymers. These materials enhance drug stability, protect the encapsulated drug from premature degradation, and minimize the risk of ocular irritation or toxicity (Bose *et al.,* 2023). Additionally, their structural flexibility allows the incorporation of targeting ligands on the micellar surface, which can facilitate active targeting of specific ocular tissues and further improve drug delivery efficiency (Chetna *et al.,* 2024). Despite these advantages, certain challenges remain in the development of nanomicelle-based ocular drug delivery systems. Dilution by tear fluid and interactions with ocular components may destabilize micelles and lead to premature drug release. Moreover, large-scale manufacturing, long-term stability, and regulatory approval still require further standardization and clinical validation to ensure consistent safety and efficacy (Yun-Long *et al.,* 2021; Li S *et al.,* 2023). Nevertheless, continuous research and technological advancements are expected to further optimize nanomicellar formulations and expand their potential as efficient carriers for ocular drug delivery.

PREPARATION OF NANOMICELLES

Surface-active agents such as synthetic block copolymers and surfactants are employed in the formation of nanomicelles. Amphiphilic monomers can be classified into three categories: ionic, non-ionic, and zwitterionic. Ionic surfactants may possess either anionic or cationic charges, exemplified by sodium dodecyl sulfate and dodecyl trimethyl ammonium bromide, respectively. Neutral non-ionic surfactants include compounds such as n-dodecyl tetra(ethylene oxide). Zwitterionic surfactants, such as decanoylphosphatidylcholine, contain both positive and negative charges. Amphiphilic block copolymers, including polyester and biocompatible, biodegradable polyoxins, can be derived from polypeptide derivatives. Various polymer block architectures exist, including branched structures, linear diblocks, triblocks, and pentablocks, classified as A-B, A-B-A, or A-A-B-A-A types. Examples of block copolymers include poly(lactic acid)-poly(ethylene glycol) (PEG)-poly(L-lysine) (PLL), polyethylene oxide, poly(D,L-lactic acid), polypropylene oxide, poly(glycolic acid), poly(aspartic acid), poly(glutamic acid), poly(L-lysine), and poly(histidine). In most copolymer configurations, PEG serves as the hydrophilic segment due to its advantageous properties, including enhanced water solubility, reduced toxicity, biological compatibility that mitigates reticuloendothelial system recognition, and steric stabilization.

Solvent Evaporation Method The solvent evaporation method, also termed the thin film hydration method, is a broadly adopted technique for fabricating polymeric nanomicelles with notably high drug incorporation efficiency, particularly effective for amphiphilic copolymers exhibiting low water solubility and low hydrophilic–lipophilic balance (HLB) values. In this approach, a hydrophobic drug and an amphiphilic copolymer (e.g., Pluronic, Soluplus, PEG-PLA) are co-dissolved in a volatile organic solvent or solvent mixture commonly acetone, chloroform, methanol, or ethanol to generate a homogeneous solution that is subsequently subjected to solvent removal under reduced pressure to form a thin polymeric film on the vessel surface, which upon hydration in water or aqueous buffer self-assembles into micelles via the amphiphilic copolymer's spontaneous organization. The step-by-step process is mentioned in Figure 4. Mechanistically, micellization is driven by the segregation of hydrophobic polymer segments that encapsulate the drug within the micellar core, while hydrophilic blocks from the corona interfacing with the aqueous phase; operationally, this self-assembly is triggered after the thin film is rehydrated, typically under controlled agitation and temperature, to ensure complete dispersion and uniform micelle formation (Parra *et al.,*2021, Pignatello *et al.,*2022).

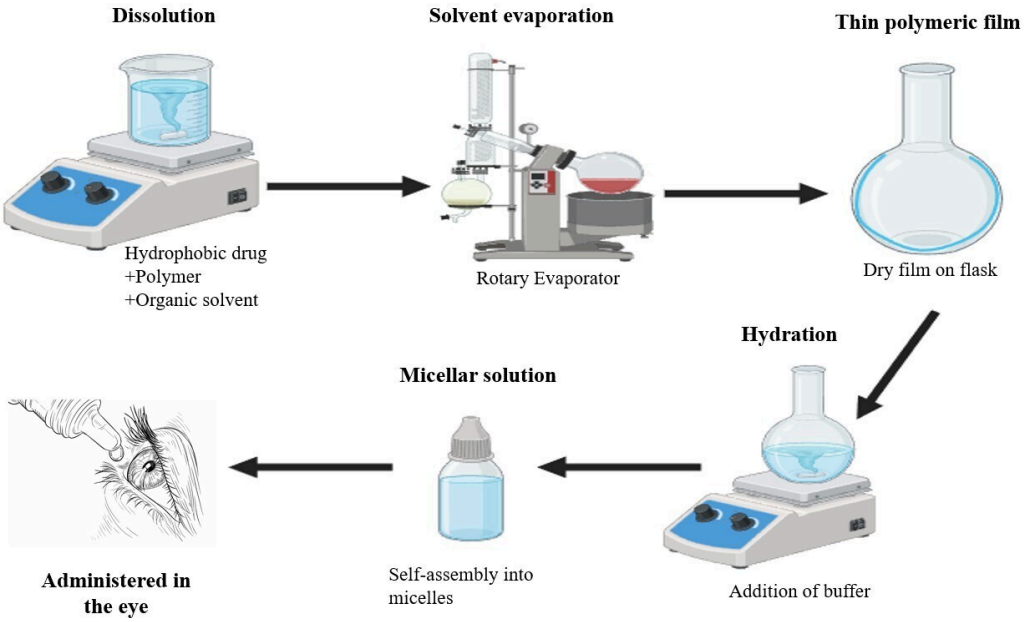

Figure 4: - Schematic representation of solvent evaporation method

Several scientists have utilized this technique in their formulations. Aliabadi and Lavasanifar *et al.,*2006 prepared polymeric micelles using the solvent evaporation approach with methoxy poly(ethylene oxide)-block-poly(ε-caprolactone) (MePEO-b-PCL) as the amphiphilic polymer to encapsulate cyclosporine A. Their study showed that micelles formed efficiently with improved drug loading and enhanced solubility of hydrophobic drugs. In another investigation (Aliabadi & Lavasanifar *et al.,* 2006), Perumal *et al.,*2022 described the preparation of spherical micelles using poly (lactic-co-glycolic acid) (PLGA) along with polyvinyl alcohol (PVA) through a solvent evaporation process, producing nanosized particles of about 158 nm, demonstrating good stability and suitability for drug delivery (Perumal et at., 2022). Similarly, Cho *et al.,*.2025 investigated polymeric micelles prepared by solvent evaporation using block copolymers such as p(HPMAm)-b-p(HPMAm-Bz), and reported that careful selection of organic solvent and mixing conditions significantly influenced micelle size and dispersion properties (Cho *et al.,* 2025). These studies demonstrate that the solvent evaporation method is a reliable technique for producing polymeric nanomicelles with controlled size, high drug encapsulation efficiency, and improved solubility of hydrophobic therapeutic agents.

Direct dissolution method

The direct dissolution method is best suited for amphiphilic block copolymers with good water solubility and low critical micelle concentration (CMC), as micelles form when the polymer concentration exceeds the CMC under gentle stirring in water or buffer. Micellization is typically carried out by dissolving the polymer in water or buffer under gentle continuous stirring at room temperature to 40–50 °C, ensuring the final concentration is above the CMC (Negut *et al.,*2023). The drug can be added directly if it dissolves in water at the working temperature, or pre-wetted and added slowly to the polymer solution with mild heating (30–50 °C) and/or brief sonication to facilitate partitioning into the micellar core. Stirring is maintained for 30–120 min depending on drug solubility and target loading, and mild bath sonication (5–10 min cycles) may be applied to improve homogenization without degrading the drug (Mandal *et al.,*2017, Vinchurkar *et al.,*2021). For enhanced loading, a thin drug film can be prepared by evaporating a volatile solvent containing only the drug, followed by hydration with a warm polymer solution, which helps capture the drug into micelles. Figure 5 gives the graphical representation of the process of nanomicelles formation. This approach is particularly useful for low-loading drugs and should be performed at ≤50 °C to avoid degradation, balancing the benefits of temperature-induced CMC reduction against stability concerns.

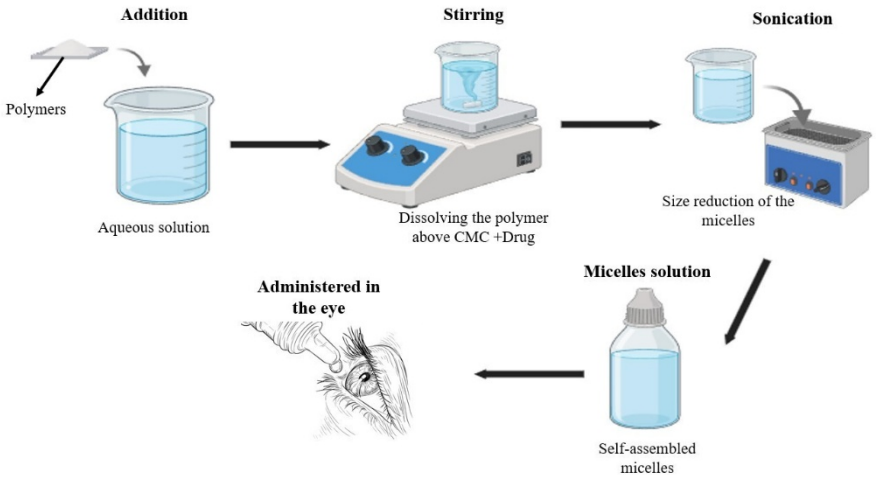

Figure 5: - Schematic representation of direct dissolution method

Hwang *et al.,* 2020 reported that amphiphilic block copolymers such as poly (ethylene glycol)-block-poly (lactic acid) (PEG-PLA) can be dissolved in water with hydrophobic drugs to form stable polymeric micelles, improving the solubility of poorly water-soluble compounds and enhancing drug delivery efficiency (Hwang *et al.,* 2020). Similarly, Ghezzi *et al.,* 2021 explained that direct dissolution involves dissolving the amphiphilic polymer in an aqueous medium above the critical micelle concentration, where the molecules self-assemble into nanosized micelles capable of encapsulating hydrophobic drugs and improving their bioavailability (Ghezzi *et al.,* 2021). Another study by Kotta *et al.,* 2022 described the preparation of polymeric micelles using water-soluble copolymers such as PEG-b-poly(L-lysine) or PEG-b-poly (aspartic acid). In their method, the copolymer and drug were dissolved separately in aqueous solvents and then mixed under mechanical stirring followed by sonication, resulting in the formation of stable polyion complex micelles that can encapsulate biomolecules such as nucleic acids or therapeutic drugs (Kotta *et al.,* 2022). Furthermore, Gutiérrez-Saucedo *et al.,* 2023 developed nanomicelles using Pluronic block copolymers (PEO-PPO-PEO) prepared by direct dissolution, which produced nanosized micelles capable of solubilizing drugs such as doxorubicin and docetaxel and providing sustained drug release over time (Gutiérrez-Saucedo *et al.,* 2023). These recent studies demonstrate that the direct dissolution method is an efficient and straightforward strategy for producing polymeric nanomicelles. The use of amphiphilic polymers such as PEG-PLA, PEG-poly(amino acid) copolymers, and Pluronic block copolymers leads to spontaneous micelle formation with sizes generally in the nanometre range, improved solubility of hydrophobic drugs, and enhanced stability for drug delivery applications.

Dialysis method

The dialysis method is a commonly technique for the preparation of polymeric nanomicelles, particularly suitable for amphiphilic block copolymers and drugs that are sensitive to harsh preparation conditions. In this method, both the hydrophobic drug and the amphiphilic polymer are initially dissolved in a water-miscible organic solvent such as dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetone, or ethanol to form a homogeneous solution. This organic solution is then transferred into a dialysis bag or membrane with a defined molecular weight cut-off and immersed in a large volume of distilled water or aqueous buffer. Gradual diffusion of the organic solvent through the semi-permeable dialysis membrane into the external aqueous phase leads to a progressive change in solvent polarity. As the solvent is slowly replaced by water, the amphiphilic copolymers undergo spontaneous self-assembly into nanomicelles. During this process, the hydrophobic segments of the copolymer aggregate to form the micellar core that encapsulates the poorly water-soluble drug, while the hydrophilic polymer chains extend outward to create a stabilizing corona in the aqueous environment (Perumal *et al.,* 2022). The slow and controlled removal of the organic solvent is a key factor in this method, as it promotes uniform micelle formation and prevents sudden precipitation of the polymer or drug. Parameters such as dialysis time, membrane pore size, polymer concentration, and solvent type play significant roles in determining the final micelle size, stability, and drug loading efficiency.

Study shown by, Xu *et al.,* 2017 prepared polymeric micelles composed of methoxy poly (ethylene glycol)-poly (lactic acid) (mPEG-PLA) using dialysis to load the hydrophobic drug curcumin. The resulting nanomicelles exhibited uniform particle size, high encapsulation efficiency, and enhanced aqueous dispersibility of the drug (Xu *et al.,* 2017). Similarly, Liu *et al.,* 2021 utilized the dialysis technique to fabricate polymeric micelles based on poly (ethylene glycol)-block-poly (aspartic acid) for anticancer drug delivery. Their findings showed that gradual solvent exchange during dialysis enabled the formation of well-defined micellar structures with improved stability and controlled drug release properties (Liu *et al.,* 2021). Studies demonstrate that the dialysis method is an effective and widely used technique for producing polymeric nanomicelles with controlled particle size, high drug

loading capacity, and improved stability for targeted drug delivery.

Emulsion solvent evaporation method

The emulsion solvent evaporation method is a widely used technique for the preparation of polymeric nanomicelles and nanoparticles, particularly suitable for encapsulating poorly water-soluble or hydrophobic drugs. In this method, the hydrophobic drug and amphiphilic polymer are first dissolved in a water-immiscible organic solvent, such as dichloromethane, chloroform, or ethyl acetate, to form the organic phase. This organic solution is then emulsified into an aqueous phase containing stabilizers or surfactants (commonly polyvinyl alcohol or similar emulsifiers) using mechanical stirring, ultrasonication, or high-shear homogenization. The process forms an oil-in-water (O/W) emulsion, where small droplets of the organic phase are dispersed within the aqueous phase. Subsequently, the organic solvent is gradually removed by evaporation under reduced pressure or continuous stirring, which leads to polymer precipitation and the formation of nanomicelles or nanoparticles containing the encapsulated drug (Cho *et al.,* 2025). The evaporation of the solvent causes the amphiphilic polymer chains to self-assemble, forming a hydrophobic core that traps the drug molecules while the hydrophilic segments extend outward into the aqueous environment to stabilize the micellar structure. Parameters such as the type of solvent, polymer concentration, emulsification speed, and surfactant concentration play a critical role in determining the final micelle size, morphology, and encapsulation efficiency. This technique is particularly advantageous because it allows efficient loading of hydrophobic drugs and produces particles with controlled size and good stability. Ortac *et al.,* 2024 reported the formation of polymeric micelles through an oil-in-water emulsion system in which the polymer and drug were dissolved in an organic solvent to form the internal phase. After emulsification in water and subsequent solvent evaporation, stable nanostructures with hydrophobic cores were obtained, demonstrating the efficiency of this method for loading hydrophobic therapeutic compounds (Ortac *et al.,* 2024).

Sonication method

Polymeric nanomicelles and other nanoscale drug delivery devices are frequently prepared using the sonication approach. This method utilizes ultrasonic energy to facilitate the dispersion of amphiphilic polymers and drugs in an aqueous medium, promoting the formation of stable micellar structures. In this technique, the hydrophobic drug and amphiphilic block copolymer are first dissolved either in a small quantity of organic solvent or directly dispersed in an aqueous medium depending on the solubility of the components. The mixture is then subjected to ultrasonic irradiation using a probe sonicator or bath sonicator, which produces high-energy acoustic waves. These waves generate microscopic cavitation bubbles in the solution that collapse rapidly, producing localized high temperature and pressure. This process enhances the mixing of components and breaks down large aggregates into nanoscale particles. As a result, the amphiphilic copolymers spontaneously self-assemble into nanomicelles, where the hydrophobic segments form the inner core that encapsulates the drug molecules, while the hydrophilic chains extend outward into the surrounding aqueous environment to stabilize the structure. The sonication process helps reduce particle size, improve dispersion, and increase the uniformity of micelle formation. Important parameters influencing micelle formation in this method include sonication time, ultrasonic power, polymer concentration, temperature, and solvent composition, all of which can affect the final particle size and drug encapsulation efficiency. Zhang *et al.,* 2021 developed polymeric micelles using methoxy poly (ethylene glycol)-block-poly (lactic acid) (mPEG-PLA) for the delivery of hydrophobic anticancer drugs. In their study, the drug and polymer were dissolved in an organic solvent and then dispersed in water followed by probe sonication. The ultrasonic treatment facilitated the formation of stable nanosized micelles with improved drug loading efficiency and enhanced aqueous solubility of the encapsulated drug (Zhang *et al.,* 2021).

In another study, Hwang *et al.,* 2020 prepared polymeric nanomicelles composed of poly(ethylene glycol)-poly(ε-caprolactone) (PEG-PCL) using the sonication technique for controlled drug delivery. The authors reported that sonication significantly reduced particle size and produced micelles with narrow size distribution and improved colloidal stability. The resulting nanomicelles exhibited efficient encapsulation of hydrophobic drugs and demonstrated sustained drug release behaviour (Hwang *et al.,* 2020). Similarly, Xi *et al.,* 2022 reported the preparation of polymeric micelles based on poly(ethylene glycol)-poly(aspartic acid) copolymers using an ultrasonic-assisted self-assembly method. Their results showed that the application of ultrasonic energy promoted rapid micelle formation and improved dispersion of the polymeric system in aqueous media. The prepared nanomicelles displayed uniform particle size and enhanced stability, making them suitable for drug delivery applications (Xi *et al.,* 2022). Based on these findings, the sonication approach is a simple and effective way to formulate polymeric nanomicelles for the creation of nanoscale drug delivery systems for hydrophobic medicinal drugs.

APPLICATIONS OF NANOMICELLES AND NANOMICELLES UNDER CLINICAL TRIALS

Nanomicelles are versatile nanoscale drug delivery systems formed by the self-assembly of amphiphilic molecules into a hydrophobic core and hydrophilic shell. Because of their small size, high stability, and ability to encapsulate poorly soluble compounds, they are widely explored for improving drug solubility, targeting efficiency, and controlled drug release. In recent years, advances in polymer chemistry and nanotechnology have expanded their biomedical applications, particularly in cancer therapy, ocular delivery, and stimuli-responsive drug systems. Several nanomicellar formulations have also progressed to clinical trials,

highlighting their translational potential in modern nanomedicine (Mariana *et al.,* 2024).

Solubilization of Poorly Water-Soluble Drugs

A major application of nanomicelles is improving the solubility and bioavailability of hydrophobic drugs classified under class II and IV of the Biopharmaceutics Classification System. Their hydrophobic core can encapsulate lipophilic drugs, while the hydrophilic corona stabilizes the formulation in aqueous environments. This property significantly enhances the dissolution and therapeutic effectiveness of poorly soluble drugs. Some studies demonstrate that polymeric micelles can increase the solubility and pharmacokinetic performance of hydrophobic drugs such as paclitaxel and curcumin. Mariana *et al.,* 2024 developed Soluplus-based nanomicelles containing efavirenz and curcumin, which increased the apparent aqueous solubility of efavirenz by more than 1000-fold and improved its oral bioavailability (Mariana *et al.,* 2024). Similarly, Hwang *et al.,* 2020 reported that polymeric micelles significantly enhance the pharmacokinetic profile of poorly soluble anticancer drugs by protecting them from degradation and enabling higher drug loading. These studies highlight the potential of nanomicelles as efficient solubilizing carriers for hydrophobic therapeutic agents (Hwang *et al.,* 2020).

Targeted Nanomicelle Drug Delivery

Nanomicelles can also be engineered for targeted drug delivery by attaching specific ligands such as peptides, antibodies, or aptamers on their surface. These ligands interact with receptors overexpressed on diseased cells, enabling selective drug accumulation at the target site while minimizing systemic toxicity. Cai *et al.,* 2020 developed paclitaxel-loaded polymeric micelles functionalized with tumor-targeting peptides to enhance selective uptake in breast cancer cells. The targeted micelles demonstrated significantly higher cellular internalization and improved anticancer efficacy compared with non-targeted micelles (Cai *et al.,* 2020). Similarly, Zheng *et al.,* 2024 reported that ligand-conjugated micelles using antibodies and folate groups can selectively bind to tumor receptors, thereby increasing therapeutic efficiency and reducing adverse effects. These targeted nanomicelle systems are particularly promising for cancer chemotherapy and precision medicine (Zheng *et al.,* 2024).

Stimuli-Responsive Nanomicelles

Stimuli-responsive nanomicelles are designed to release drugs in response to internal or external triggers such as pH, temperature, light, or ultrasound. These smart systems improve site-specific drug release and minimize damage to healthy tissues.

pH-Sensitive Nanomicelles:

Tumour tissues typically exhibit a slightly acidic microenvironment (pH 6.5–7.2) compared with normal physiological pH (7.4). pH-responsive nanomicelles utilize acid-labile linkers that remain stable in normal tissues but release drugs under acidic tumor conditions. For example, PEG-based pH-sensitive micelles loaded with doxorubicin have shown selective drug release in tumor cells and enhanced anticancer activity in experimental models.

Temperature-Sensitive and Light-Responsive Nanomicelles:

Thermosensitive polymers such as poly(N-isopropylacrylamide) undergo structural changes at specific temperatures, triggering drug release at the target site. Studies have shown that temperature-responsive micelles can deliver anticancer drugs more effectively during hyperthermia-based cancer therapy. Light-triggered nanomicelles release drugs upon irradiation with ultraviolet or near-infrared light. These systems allow spatial and temporal control of drug release, making them useful in photodynamic therapy.

Ultrasound-Responsive Nanomicelles:

Ultrasound can disrupt micellar structures and enhance drug penetration into tissues. Rajabi *et al.,* 2025 demonstrated that ultrasound-activated micelles significantly increased the release and cellular uptake of doxorubicin, improving therapeutic efficiency in tumor models. Stimuli-responsive micelles therefore represent an advanced strategy for controlled and targeted drug delivery (Rajabi *et al.,* 2025).

Multifunctional Nanomicelles for Theragnostic

Another emerging application is the development of multifunctional nanomicelles that combine therapeutic and diagnostic capabilities. These systems can simultaneously deliver drugs and imaging agents, enabling real-time monitoring of treatment. Jin *et al.,* 2019 developed folic-acid-modified polymeric nanomicelles encapsulating doxorubicin and superparamagnetic iron oxide nanoparticles for magnetic resonance imaging (MRI). The system allowed targeted drug delivery to tumour cells while enabling visualization of micelle accumulation in cancer tissues. Such multifunctional nanomicelles improve both diagnostic accuracy and therapeutic efficacy, representing an important advancement in theragnostic nanomedicine (Jin *et al.,* 2019).

Applications in Oral and Ocular Drug Delivery

Nanomicelles are also widely studied for improving drug absorption across biological barriers such as the gastrointestinal tract and ocular tissues. Polymeric micelles can protect drugs from enzymatic degradation and enhance permeability through epithelial barriers, thereby improving oral bioavailability. In ocular drug delivery, micellar formulations increase drug retention and penetration into deeper eye tissues, making them promising carriers for treating retinal and corneal diseases (Hanan *et al.,*2025).

Several nanomicelles-based drug formulations have progressed to clinical evaluation, particularly in cancer therapy. Polymeric micelle formulations such as paclitaxel-loaded systems have demonstrated improved pharmacokinetics and reduced toxicity compared with conventional formulations. The increasing number of

clinical trials highlights the growing translational potential of nanomicellar drug delivery systems. A summary of selected nanomicellar formulations currently undergoing clinical evaluation or approved for therapeutic use is presented in Table 2, which illustrates their drug type, target disease, and clinical development status.

Table 2:- Examples of micelles under clinical trails

S. No.	Drug (brand) Nanomicelle/Platform	Trial phase / status	Indication	Block copolymer / surfactant system (as disclosed)	Reference
1	Cyclosporine 0.09% (CEQUA/OTX-101) — nanomicelles	Phase 2/3 RCT (completed); FDA-approved 2018; ongoing Phase 4 onset studies (2025)	Dry eye disease (DED)	Mixed micelles of Vitamin E TPGS + Solutol/Kolliphor HS-15 (non-ionic amphiphiles)	Li *et al.,* 2023
2	Cyclosporine 0.05% (MNP-CyA) — micellar nanoparticles (mixed nanomicelles)	Randomized clinical study (2023)	Dry eye disease	Not disclosed (reported as mixed nanomicelles)	Rathi *et al.,* 2023
3	Voclosporin Ophthalmic Solution (VOS) — nanomicelles	Phase 2 RCTs completed; program discontinued for DED (still a human nanomicelle dataset)	Dry eye disease	Not disclosed (company states "nanomicellar formulation")	(Alam *et al.,*2020)
4	Cyclosporine 0.09% (CEQUA/OTX-101) — nanomicelles	Phase 3 confirmatory / real-world studies	Dry eye disease	TPGS + Solutol HS-15 mixed micelles	(Li *et al.,* 2023)
5	Cyclosporine 0.09% (CEQUA/OTX-101) — nanomicelles	U.S. approval (2018); ongoing post-approval studies	Dry eye disease	TPGS + HS-15	(Li *et al.,* 2023)
6	Latanoprost 0.005% (XELPROS) — Swollen Micelle Microemulsion (SMM)	Pivotal RCTs; FDA-approved (2018)	Glaucoma / Ocular Hypertension	SMM micellar microemulsion; specific surfactants proprietary/undisclosed	(Shen *et al.,*2022)
7	Latanoprost 0.005% (XELPROS) — SMM	Open-label extension data (2022)	Glaucoma / OHT	SMM (as above)	(Shen *et al.,*2022)
8	Cyclosporine 0.09% (CEQUA/OTX-101) — nanomicelles	Additional Phase 4 / real-world analyses (2024–2025)	Dry eye disease	TPGS + HS-15	(Li *et al.,* 2023)
9	Cyclosporine 0.09% (CEQUA/OTX-101) — nanomicelles	U.S. label-supported clinical studies	Dry eye disease	TPGS + HS-15	(Li *et al.,* 2023)
10	Latanoprost 0.005% (XELPROS) — SMM	Pivotal RCTs summarized in prescribing info	Glaucoma / OHT	SMM micellar microemulsion (proprietary)	(Li *et al.,* 2023)

Future prospective

Nanomicelles have shown significant potential as advanced drug delivery systems due to their ability to improve drug solubility, enhance targeted delivery, and enable controlled drug release. Despite these promising applications, ongoing research continues to address challenges related to stability, large-scale production, and clinical translation. Therefore, future developments in nanomicelles technology are expected to further expand their therapeutic potential in modern nanomedicine.

New Developments in Nanomicelles Architecture

The goal of developments in nanomicelles design is to improve the specificity and efficiency of medication delivery. Stimuli-responsive nanomicelles, which can release medications in response to environmental factors like pH, temperature, or light, are being investigated by researchers. For example, light-responsive nanomicelles have been created to provide precise spatiotemporal control over medication delivery by enabling regulated drug release

upon exposure to particular wavelengths. Targeting ligand integration on nanomicelles surfaces is also being researched in an effort to improve treatment effects by facilitating receptor-mediated absorption by ocular tissues (Rodrigues *et al.,*2020).

Personalized Medicine's Potential

Nanomicelles provide considerable promise for personalized treatment in the field of eye diseases. Due to its versatility, a range of medicinal substances, including peptides, nucleic acids, and small molecules, may be encapsulated to satisfy the requirements of particular patients. It is feasible to attain patient-specific medication release patterns and targeting capabilities by altering the composition and surface properties of nanomicelles. This flexibility is especially helpful for treating complicated eye disorders, where customized treatment can result in increased effectiveness and fewer adverse effects (Li *et al.,* 2023).

Combining Gene Delivery with Integration

One new area of ocular therapies is the use of nanomicelles in gene delivery systems. To transfer genetic elements like siRNA, mRNA, or plasmid DNA to the intended ocular tissues, nanomicelles can act as carriers. By making gene silencing or replacement treatments possible, this strategy presents the possibility of treating hereditary eye problems. Nanomicelles' biocompatibility and protective environment improve genetic materials' stability and cellular absorption, creating new therapies for eye disorders such as retinal illnesses (Tawfik *et al.,*2022).

Combination Treatments

One strategy to enhance eye treatment involves combining nanomicelles with other therapies. For example, pairing nanomicelles with in situ gelling systems boosts bioavailability by prolonging ocular surface residence. Co-delivering multiple medications in one nanomicelles system can reduce side effects and dosage needs. Such combination treatments are under investigation for complex disorders like diabetic retinopathy and age-related macular degeneration (Terreni *et al.,*2021).

CONCLUSION

By avoiding the eye's complex physiological and anatomical hurdles, nanomicelles offer a possible breakthrough in ocular medication delivery. Eye drops and ointments are examples of traditional ophthalmic formulations that have difficulties with limited bioavailability, quick elimination, and insufficient penetration into deeper ocular tissues. The use of nanotechnology more especially, nanomicelles provides a focused and effective method of medicine administration. Amphiphilic compounds create nanomicelles, which improve the solubility of hydrophobic medications for improved absorption and extended retention in ocular tissues. Their mucoadhesive qualities, pH sensitivity, and stable structure enhance medication absorption and reduce systemic adverse effects. Nanomicelles offer regulated medication release in contrast to traditional techniques, which lessens the need for frequent administration and increases patient compliance.

Nanomicelles have drawbacks despite their benefits, such as physiological obstacles, possible toxicity, stability issues, and scalability in production. Drug delivery to the posterior portion of the eye is still a challenge, despite their well-established capacity to enter the anterior section. To improve targeting and retention in retinal tissues, future studies should concentrate on improving nanomicelles compositions. Due to the ongoing development of standardized criteria for ocular therapeutics based on nanomedicine, regulatory approval and clinical translation also pose substantial hurdles. However, these problems should be resolved by further developments in formulation techniques, bioengineering, and polymer science, which should result in safer and more efficient ocular drug delivery systems. Nanomicelles have the potential to completely transform ocular pharmacotherapy by providing accurate, long-lasting, and effective medication administration with fewer side effects. Their use in the treatment of different eye illnesses will be further optimized by ongoing research and innovation.

ABBREVIATIONS

NVG- Neovascular Glaucoma
CMC- Critical Micelle Concentration
BCS- Biopharmaceutics Classification System
VEGF- Vascular Endothelial Growth Factor
HIF-1α - Hypoxia-Inducible Factor 1-Alpha
PDI- Polydispersity Index
DED- Dry Eye Disease
FGF- Fibroblast Growth Factor
EPR-Enhanced Permeation Retention
RES- Reticular Endothelial System
MDR- Multidrug Resistance Mutation
MRP- Multidrug Resistance Protein
BCRP- Breast Cancer Resistance Protein
EDTA- Ethylenediaminetetraacetic Acid
BRB- Blood–Retinal Barrier
BAB- Blood–Aqueous Barrier
RPE- Retinal Pigment Epithelium
ILM- Inner Limiting Membrane
CRVO- Central Retinal Vein Occlusion
RVO- Retinal Vein Occlusion
HGF- Hepatocyte Growth Factor
TNF- Tumor Necrosis Factor
IGF- Insulin-Like Growth Factor
IL- Interleukin
TGF- Thrombospondin, Changing Growth Factor
PEDF - Pigment Epithelium-Derived Factor
PDR- Proliferative Diabetic Retinopathy
PKC- Protein Kinase C
MCP- Monocyte Chemoattractant Protein
DR –Diabetic Retinopathy
HLB- Hydrophilic-Lipophilic Balance
ODD- Ocular Drug Delivery

MPEG-HexPLA - Methoxy-PEG–Hexyl-Lactic Acid
TPGS- D-A-Tocopheryl Polyethylene Glycol Succinate)
mPEG- Methyl Polyethylene Glycol
DTAB-Dodecyl Trimethylammonium Bromide
SDS- Sodium Dodecyl Sulfate
Cya- Cyclosporine-A
PPO- Poly(Propylene Oxide)
PCL- Poly(E-Caprolactone)
DEX- Dexamethasone
PEG- Poly(Ethylene Glycol).

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