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KEYNOTE (GREEN)

Block copolymer micelles as ocular drug delivery systems

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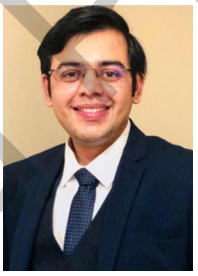
Block copolymer micelles, formed by the self-assembly of amphiphilic polymers, address formulation challenges, such as poor drug solubility and permeability. These micelles offer advantages including a smaller size, easier preparation, sterilization, and superior solubilization, compared with other nanocarriers. Preclinical studies have shown promising results, advancing them toward clinical trials. Their mucoadhesive properties enhance and prolong contact with the ocular surface, and their small size allows deeper penetration through tissues such as the cornea. Additionally, copolymeric micelles improve the solubility and stability of hydrophobic drugs, sustain drug release, and allow for surface modifications to enhance biocompatibility. Despite these benefits, long-term stability remains a challenge. In this review, we highlight their preclinical performance, structural frameworks, preparation techniques, physicochemical properties, current developments, and prospects as ocular drug delivery systems.

Keywords: ocular drug delivery; block copolymer micelles; ocular barriers; characterization; anterior segment; posterior segment



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Introduction

Ocular diseases, such as age-related macular degeneration (AMD), cataracts, corneal injury, diabetic retinopathy (DR), glaucoma, and refractive errors, can cause vision impairment or be vision threatening. Other ocular disorders, particularly those affecting the front of the eye, such as conjunctivitis, pinguecula, dry eye, blepharitis, pterygium, chelation, hordeolum, and subconjunctival hemorrhage, do not cause visual impairment.[(p1),(p2),(p3)] A prevalent approach in the clinical management of anterior segment disorders typically revolves around administering the required medication through topical formulations, ideally as eye drops or suspensions.[(p3)] For instance, eye conditions affecting the front part of the eye often respond well to treatment with eye drops. Recent research has focused on innovative drug delivery methods, including implants, patches, nanosuspension, microneedles, hydrogels, and contact lenses, tailored for ocular applications.[(p4),(p5),(p6),(p7),(p8)] This is in contrast to the more invasive treatment strategies typically used to treat posterior segment diseases, such as periocular or intravitreal injections, and long-acting implants.[(p9),(p10),(p11)]

The presence of biological barriers within the ocular environment hinders the efficacy of numerous drugs and often necessitates frequent high-dose treatments that can result in adverse effects.[(p12)] This presents a notable obstacle to developing ocular drug delivery systems that are both safe and efficient.[(p13)] Nonetheless, recent studies have shown that polymer nanomicelles have distinctive traits, such as mucosal adhesion and small size, which can improve drug bioavailability, promote enhanced penetration into the cornea and absorption within the eye, decrease ocular irritation, and mitigate adverse reactions to medications.[(p14)] Copolymeric micelles have been particularly successful in nanocarrier systems and are easily produced through self-assembly. Their chemical, physical, and surface properties can be modified by altering the structure of the copolymer or modifying the surface.[(p15)] Copolymeric micelles have made significant progress in clinical and preclinical trials, with several treatments reaching various developmental stages. For instance, rapamycin nanomicelle eye drops have been authorized for immune rejection inhibition, whereas terbinafine hydrochloride nanomicelles are now used to combat fungal infections in the eye. Moreover, Cequa®, an ophthalmic solution containing 0.09% cyclosporine, has gained approval for dry eye treatment. Nonetheless, despite these advances, the number of efficacious formulations brought to the market and integrated into clinical settings remains low.[(p16),(p17),(p18)]

An amphiphilic block copolymer comprises multiple unique monomer units (two or more) arranged in a sequence, resulting in discernible interfaces between various blocks. The structural distinction between block copolymers endows them with unique physical and chemical properties. Block polymer nanomicelles have a decreased likelihood of being identified as foreign substances, and their hydrophilic shells facilitate evasion of detection by the endothelial network, which minimizes the exclusion of micelles from the bloodstream.[(p19)] Focusing on attaining both thermodynamic and kinetic stability is essential for the development of polymer nanomicelles. The equilibrium between hydrophilicity and hydrophobicity within amphiphilic block copolymers has a pivotal role in determining the critical micelle concentration, and enhancing stability involves fine-tuning this balance. Hydrogels made from amphiphilic block polymers offer a convenient solution by obviating the necessity for surface treatment, while simultaneously delivering the dual advantages of hydration and deterring surface deposition. Nanoparticle (NP) stability can be effectively modulated through chemical alterations. For instance, augmenting the benzyl group proportion within a polyethylene glycol-b-benzyl-protected polyaspartic acid amphiphilic block copolymer resulted in a ten-fold decrease in the critical micelle concentration, thereby significantly bolstering the copolymer stability. Amphiphilic block copolymers can form micelles and NPs, which have garnered considerable attention for drug delivery. Furthermore, they can be utilized to eliminate organic pollutants from water through the formation of micelles or the preparation of films.[(p20),(p21),(p22)]

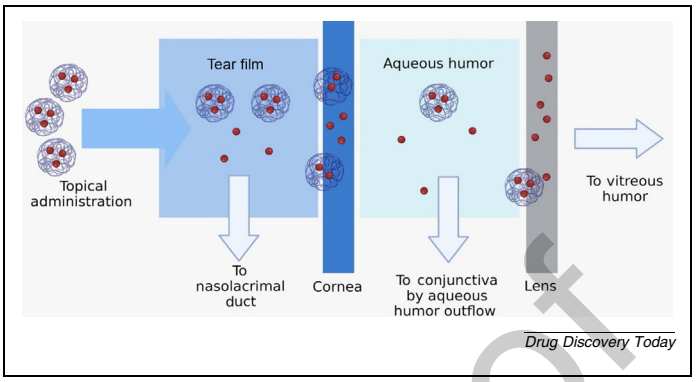

FIGURE 1

Ocular pathways of drugs after their release from micelles. These drugs can enter the tear film and pass through the cornea or conjunctiva into the aqueous humor, where they spread to the lens and vitreous humor. In certain instances, some drugs can reach the nasolacrimal duct and be systemically absorbed.

Once a drug is released from the copolymeric micelles, the fate of the micelles in the eye is an important consideration. Tear and tear clearance, aqueous humor (AH) clearance, vitreous humor (VH) clearance, and ocular blood flow can all affect the fate of micelles in the eye. Tear flow and clearance can remove micelles from the eye (Figure 1), whereas ocular blood flow can also affect micelle distribution and clearance. The properties of a drug, such as its size, charge, lipophilicity, solubility in eye fluid, and metabolic stability, can affect the behavior of micelles.[(p23)] For example, inulin-based micelles functionalized with permeation enhancers can enhanced the penetration and permeation of dexamethasone (DEX) through bovine cornea.[(p24)] Although copolymeric micelles are promising for ocular drug delivery, further research is needed to optimize the system and address the challenges associated with this approach.[(p14),(p25),(p26)]

Block copolymer micelles offer several benefits for ocular drug delivery, including efficiently encapsulating hydrophobic drugs, improved stability, sustained release, and straightforward preparation methods.[(p14),(p27)] However, there are also some drawbacks, such as the potential toxicity of certain synthetic polymers and the need for careful design to achieve optimal drug release kinetics. Compared with other nanocarrier systems, block

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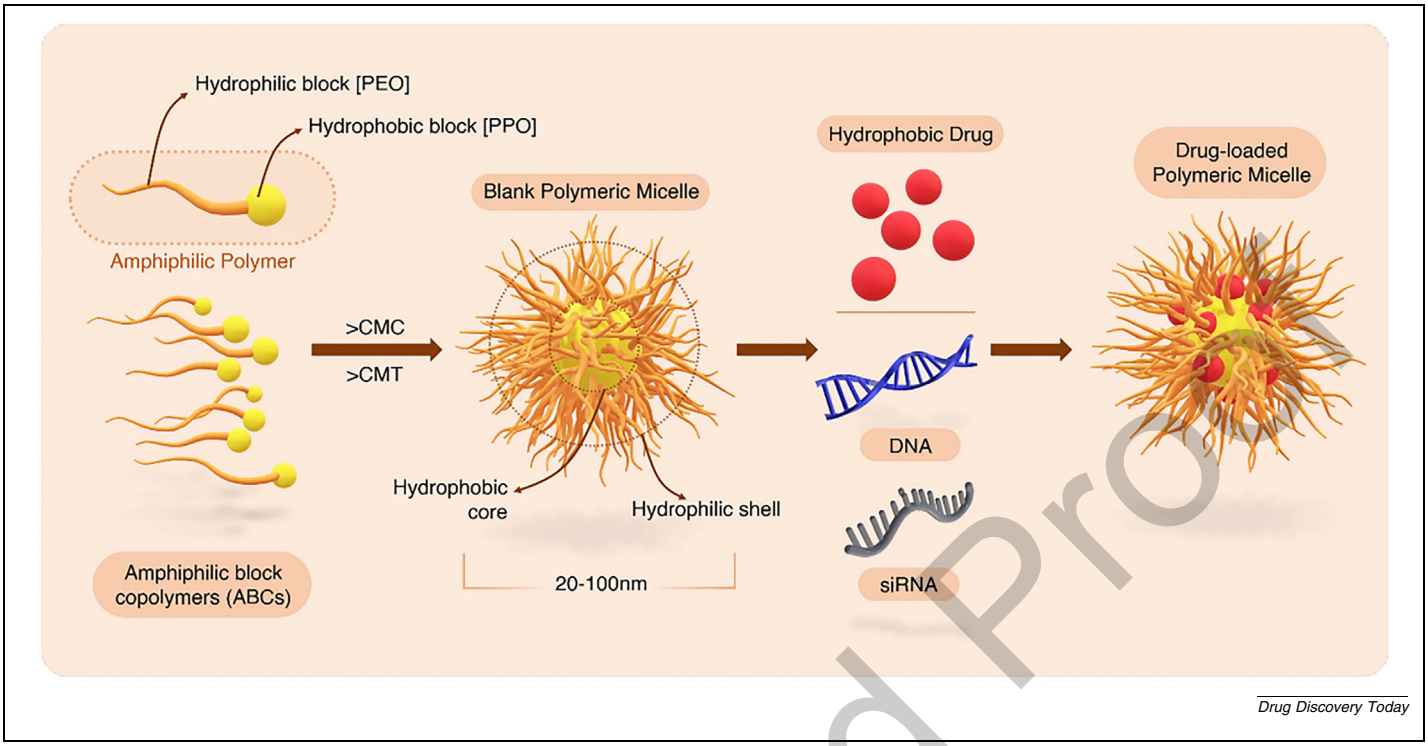

FIGURE 2

Drug-loaded copolymeric micelle formation using block copolymers. The hydrophobic blocks, comprising polyethylene oxide (PEO), form the micelle core, whereas the hydrophilic blocks, comprising polypropylene oxide (PPO), create the shell. The core encapsulates hydrophobic drugs of sizes ranging from 20 to 100 nm, and can also carry DNA or small interfering RNA (siRNA) for drug delivery purposes. Reproduced from (p171).

copolymer micelles have some unique advantages. While liposomes have been widely studied for ocular drug delivery because of their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs, they can have limited stability and rapid drug release compared with block copolymer micelles.(p28) Polymeric NPs, such as those based on PLGA, offer good biocompatibility and sustained release, but they may have lower drug loading capacity compared with block copolymer micelles.(p29),(p30) Dendrimers provide precise control over size and surface functionality, but they can be more complex and costly to synthesize.(p31) Niosomes/cubosomes can enhance drug permeation and bioavailability, but can have lower drug-loading capacity, as well as sterilization issues.(p32),(p33) Nanoemulsions offer enhanced drug permeation and bioavailability,(p34) but might have lower long-term stability compared with block copolymer micelles.(p35),(p36)

In this review, we provide an overview of the performance of block copolymeric micelles in preclinical trials of ocular drug delivery, and summarize their structural frameworks, preparation techniques, physicochemical properties, patented inventions, current developments, and prospects as effective carriers for ocular drug delivery.

Block copolymer micelle formation

Copolymeric micelles are nanoscale drug delivery systems characterized by a core–shell structure. These systems are formed through the self-assembly of amphiphilic block copolymers in aqueous solutions. Amphiphilic molecules have both hydrophobic and hydrophilic regions, allowing them to exist separately in dilute aqueous solutions and act as surfactants, reducing the surface tension at the air–water interface. As the concentration of the solution increases owing to the addition of more amphiphilic molecules, so too does the degree of adsorption at the interface; upon reaching the critical micelle concentration (CMC), the polymeric units aggregate to form micelles. CMC is the minimum amount of polymer required to create the micelle. Above CMC and XXX (CMT), amphiphilic block copolymers self-assemble to create an inner hydrophobic core and an outer hydrophilic shell. Copolymeric micelles can be used to convey drugs, including doxorubicin, paclitaxel, docetaxel, DNA, small interfering (si)RNA, or any near-infrared (NIR) dye, to a specific target. Loading these substances into micelles enables effective delivery (Figure 2).(p37)

Copolymeric micelles are essential for enhancing topical ocular drug delivery by forming multiblock polymers that improve drug solubility, stability, and bioavailability. These micelles have emerged as promising drug delivery platforms for the management of various ocular diseases affecting different segments of the eye.(p14) Given their amphiphilic nature, these polymers form micelles in aqueous media, enabling the solubilization of poorly water-soluble drugs.(p38) The formation of micelles allows for the encapsulation of drugs within the hydrophobic core of the micelle, protecting them from degradation and enhancing their delivery to the target site within the eye.

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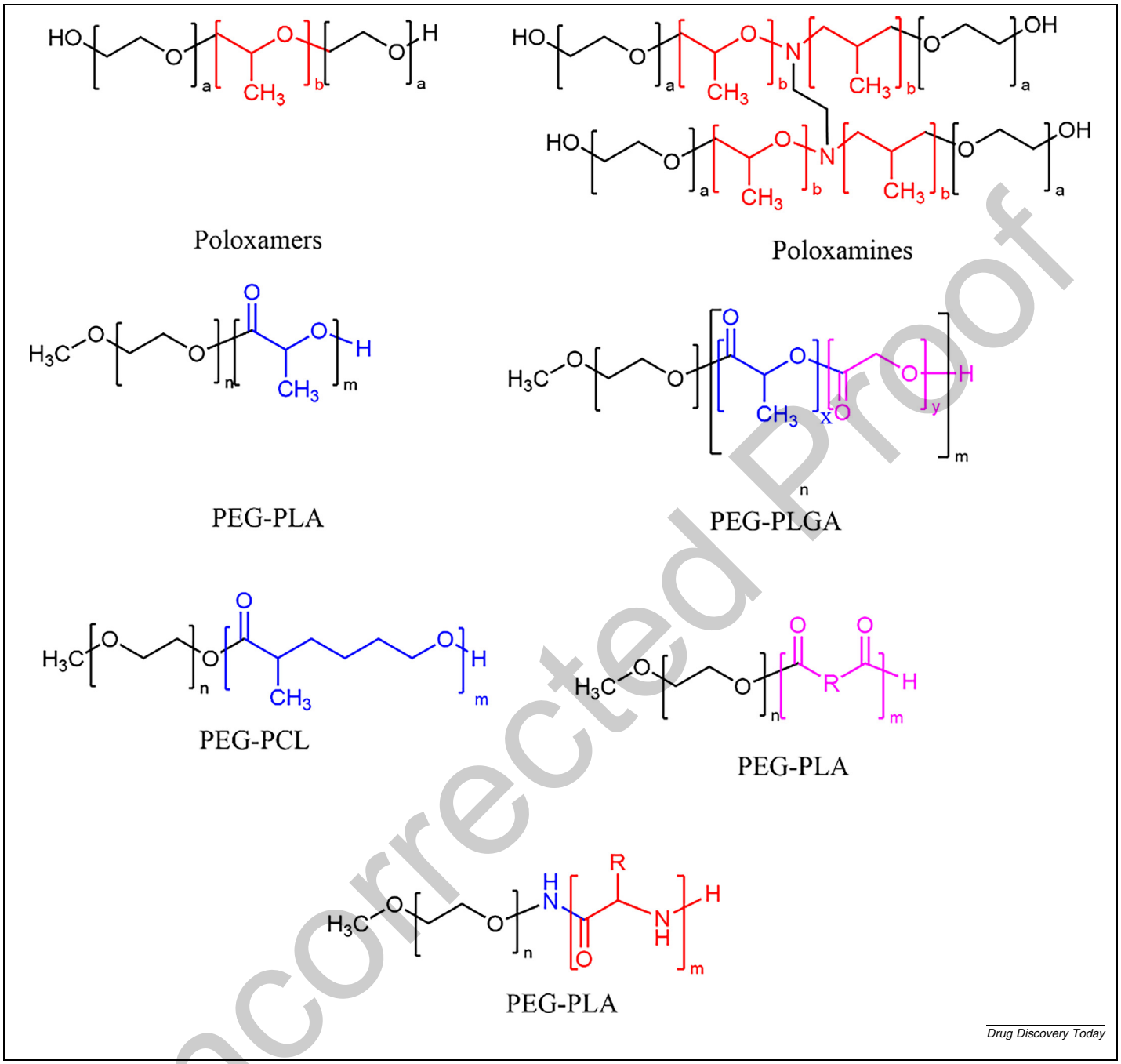

FIGURE 3

Chemical structures of amphiphilic block copolymers commonly utilized for the preparation of copolymeric micelles. These polymers comprised poly (ethylene glycol) (PEG)–polylactide (PLA), PEG–poly(ε–caprolactone) (PCL), PEG–poly(lactide-co-glycolide) (PLGA), PEG–poly(D,L-lactide) (PDLLA), and PEG–polyglutamic acid (PGA). PEG serves as the hydrophilic block, whereas PLA, PCL, PLGA, PDLLA, and PGA constitute the hydrophobic blocks. Specific combinations and block lengths can be adjusted to regulate micelle properties. Amphiphilic macromolecules have been extensively utilized in drug delivery applications.

Hydrophilic polymers in block copolymer micelles

Given that the hydrophilic shell has 'antifouling' properties, hydrophilic blocks in copolymeric micelles have a crucial role in biological interactions by shielding the loaded drug and preventing inadvertent cargo loss during systemic circulation. These interactions can be minimized by designing copolymeric micelles. Failure to do so leads to the removal of the polymeric micelle system from the circulation by the reticuloendothelial system (RES).[(p39),(p40)]

Hydrophilic polymers are essential components of multiblock copolymers for topical drug delivery to the eye, because they enhance drug solubility, bioavailability, and controlled release. Multiblock copolymers that include hydrophilic elements, such as poly(ethylene glycol) (PEG), have been developed as potential drug carriers for ophthalmic applications. These copolymers offer advantages, such as improved biocompatibility, controlled drug release, and enhanced drug delivery efficiency within the eye.[(p41)] Moreover, the incorporation of hydrophilic groups, such

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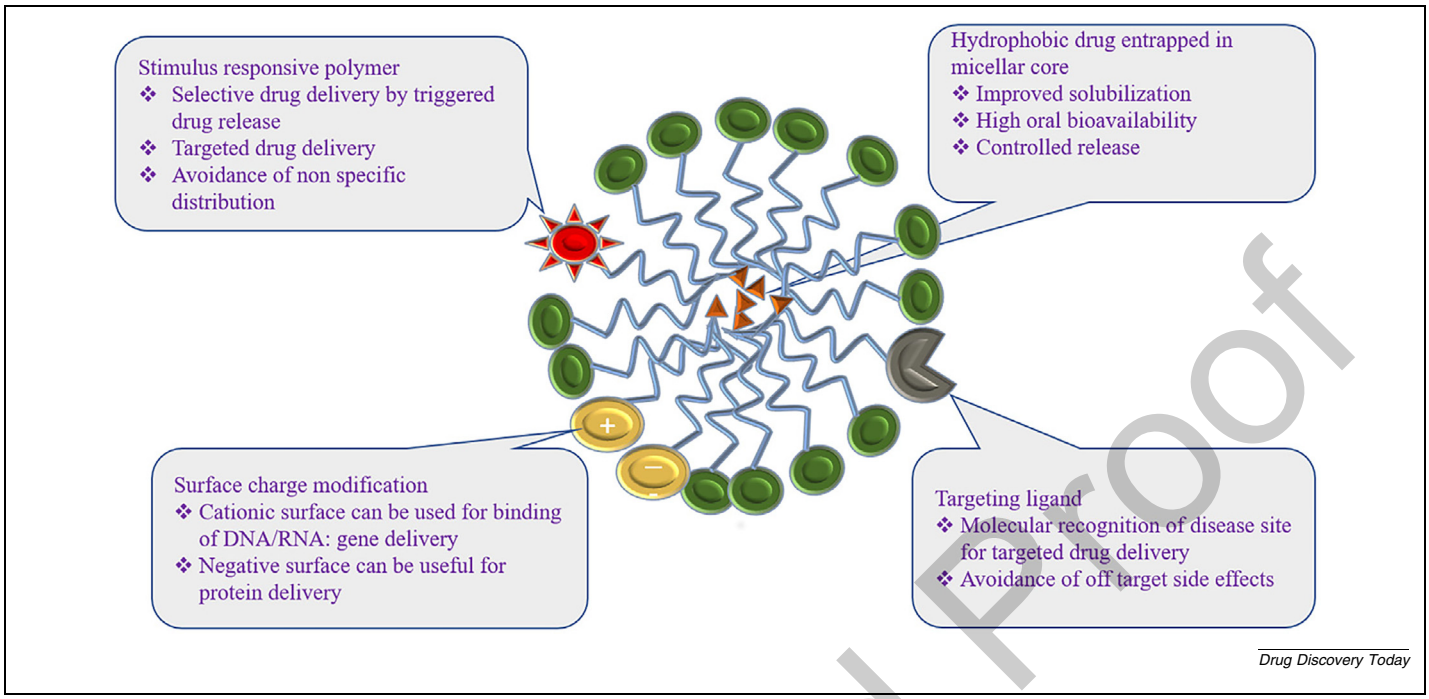

FIGURE 4

Stimulus-responsive copolymeric micelles for targeted drug delivery. The surface of micelles can be modified with targeting ligands for site-specific delivery and to avoid off-target effects. Additionally, micelles can respond to stimuli, such as pH, temperature, or light, to trigger drug release. Cationic surface charges can be used for DNA/RNA binding and gene delivery, whereas negative surfaces are useful for protein delivery. Adapted from (p172).

as phosphorylcholine, into multiblock copolymers induces structural transitions in the micelles, enhancing their drug delivery capabilities and allowing the design of drug carriers with tailored properties for efficient drug delivery to the eye.(p42) In healthy individuals, immune complexes are removed by the RES, which comprises phagocytic cells in the systemic circulation that reside in the tissues. Many hydrophilic blocks with antifouling properties have been used as hydrophilic shells in copolymeric micelles to overcome the drug delivery barrier posed by RES,(p43),(p44) and the effects of properties, such as their molecular weight and surface density on their ability to evade RES, have been widely studied. In copolymeric micelles, these properties have a crucial role in the systemic circulation time, stability, and biodistribution *in vivo*.(p45),(p46)

Hydrophobic polymers in block copolymer micelles

The hydrophobic segments of block copolymers have a significant role in the solubilization and encapsulation of hydrophobic drugs in the polymeric micelle core. In block copolymer micelles, the core of the hydrophobic part aims to solubilize poorly soluble drugs and adjust their release from the copolymeric micelles.(p47),(p48),(p49) The process involves trapping a drug within a hydrophobic core, where it remains stable during circulation throughout the body and is gradually released into the surrounding environment. The interactions between the drug and the hydrophobic core are well understood, and are crucial in determining the solubility of the drug in copolymeric micelles. Other types of interaction, such as hydrogen bonding and π–π interactions, also have an important role in strengthening the molecular bond between the hydrophobic block and the drug within the micelle core.(p47),(p48) Manufacturers have synthesised and examined various hydrophobic polymers as core-forming blocks in copolymeric micelles. These core-forming blocks are commonly used to encapsulate hydrophobic drugs (Figure 3). Polyethers and polyesters are the most frequently used core-forming polymers in copolymeric micelles.(p52)

Hydrophobic polymers are essential components of multiblock copolymers used for topical drug delivery to the eye. They also enhance drug encapsulation, controlled release, and bioavailability. Incorporating hydrophobic polymers into multiblock copolymers can facilitate selective permeation across mucus membranes when applied topically, minimizing the diffusion of therapeutics away from the target region and enabling slow release.(p53) The hydrophobic nature of polymers can lead to desirable properties, such as increased cellular uptake and efficient drug delivery, making them valuable components in multiblock copolymers.(p54) Additionally, hydrophobic polymers can be used to stabilize water-insoluble drugs in aqueous environments without complex encapsulation techniques, thereby providing a straightforward approach for topical ocular drug delivery.(p55)

Stimuli-responsive copolymeric micelles

Stimuli-responsive copolymeric micelles are 'smart' nanocarriers that respond to various biological and external stimuli (Figure 4), making them promising candidates for drug delivery and imaging. Biological stimuli include acidic pH, altered redox potential, and upregulated enzymes, whereas external stimuli include magnetic field, light, temperature, and ultrasound. These stimuli can trigger the release of drugs from the micelles, allowing targeted

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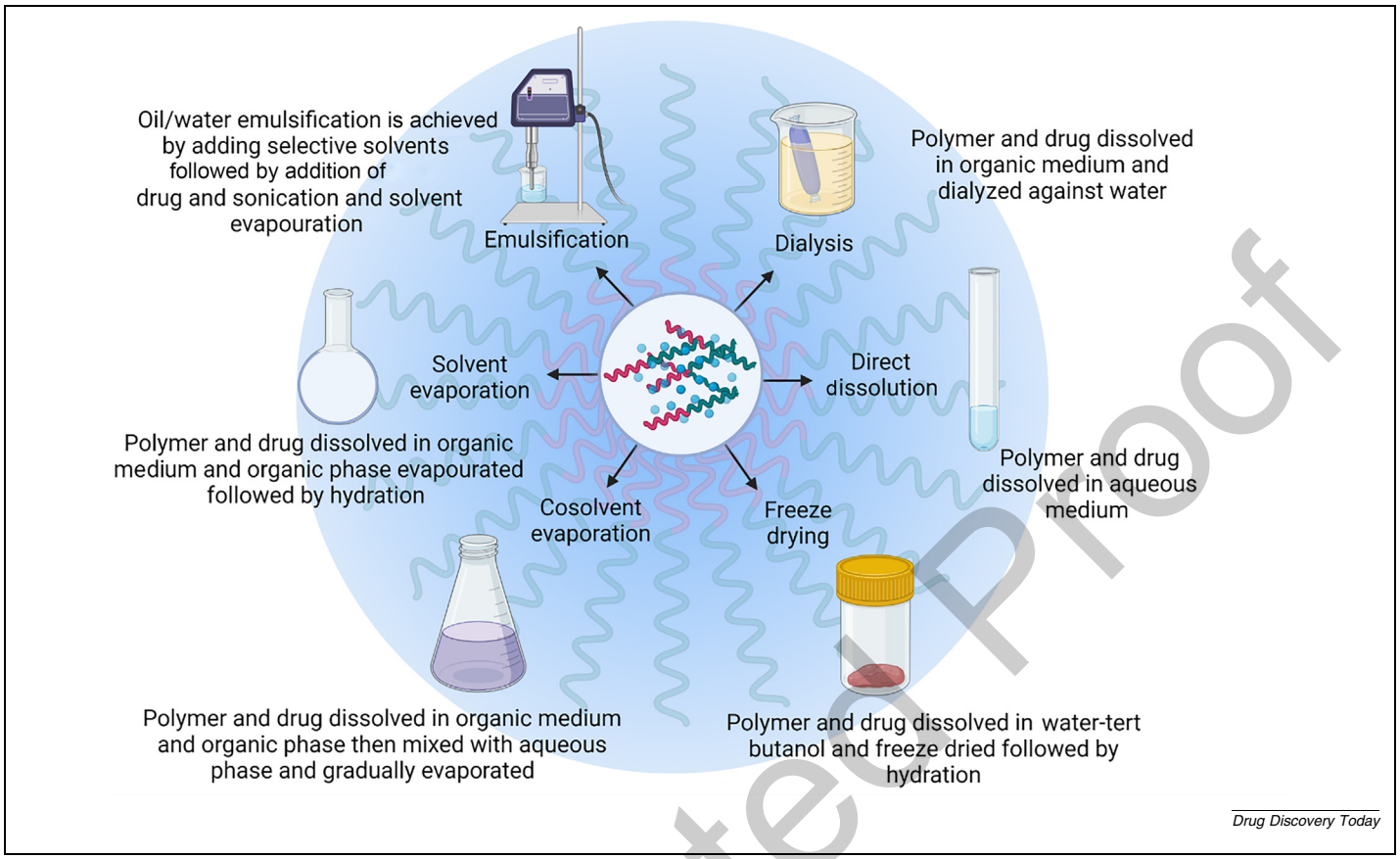

FIGURE 5

Four methods for preparing drug-loaded block copolymer micelles. The choice of method depends on factors such as drug/polymer solubility, desired drug loading and release, and scalability.

and controlled drug delivery.[p56],[p57] In ocular drug delivery, stimuli-responsive polymers in copolymeric micelles are gaining attention for their ability to respond to specific triggers, such as changes in pH, temperature, light, enzymes, or ions, offering advantages such as enhanced drug stability, targeted and controlled drug release, improved bioavailability, and reduced side effects.[p58] Despite their potential, research and development in this field continue to focus on optimizing the design and properties of these delivery systems, with challenges such as stability, scalability, and the need for thorough biocompatibility studies, remaining areas of active investigation.[p59],[p60] The application of stimuli-sensitive polymers in copolymeric micelles for ocular drug delivery holds immense promise for revolutionizing the treatment of various ocular diseases. Advancements in this area are expected to lead to the development of improved ocular drug delivery techniques.

Block copolymer micelle fabrication and characterization

Fabrication methods

Copolymeric micelles can be prepared using various techniques that are mainly influenced by the physicochemical characteristics of the block copolymer.[p61] An appropriate method is selected based on the solubility of a block copolymer of micelles in an aqueous solution. Copolymeric micelles are prepared using the following methods: (i) direct dissolution; (ii) precipitation/evaporation; (iii) oil-in-water emulsion; (iv) thin-film hydration; (v) ultrasonication; (vi) dialysis; and (vii) freeze-drying (Figure 5). The selection of a method depends on the characteristics of both the polymer and the drug, as reviewed elsewhere.[p17] Fabrication strategies for block polymer nanomicelles are discussed in detail by Kapse *et al.*[p62]

For block copolymer micelle preparation, either direct dissolution or dialysis is used. In the direct dissolution approach, the copolymer is introduced into water or similar aqueous solutions. Conversely, the dialysis method initially involves dissolving the copolymer in an organic solvent, such as dimethylacetamide or dimethylformamide, which is miscible with water, followed by gradual blending with water at a controlled rate. Finally, the organic solvent is removed from the formulation by evaporation.

The solubility of a polymer in water or an aqueous environment determines which method can be used. Copolymers with limited solubility in water are typically subjected to dissolution. However, dialysis is preferred for those with high water solubility. For copolymers with different segments (amphiphilic molecules) and solubilities, solubility is determined by the length of the blocks.[p63]

Characterization of block copolymer micelles

Characterization of copolymeric micelles is a fundamental step that provides information about their morphology, size, polydispersity index, zeta potential, and aggregation, which are key

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parameters for nanomedicine formulation development. Various crucial characterization parameters of the micelles are discussed in detail below.

The CMC reflects the propensity of molecular building units, that is, block polymer units, to aggregate or disassociate in solution. The assembly of nanomedicines starts at this concentration to form stable and organized nanostructures owing to the noncovalent interactions of the building unit. For the micelles to remain stable and prevent conversion back to the monomeric state, dynamic equilibrium must be maintained between the micelles and monomers in the solution. CMC can be measured using a variety of techniques, including surface tension, light scattering, comma electric conductivity, osmotic pressure, surface plasmon resonance, and fluorometric methods.[p64]

Micellar morphology, size, and size distribution can be determined using atomic force microscopy (AFM), cryogenic transmission electron microscopy (cryo-TEM), and dynamic light scattering (DLS). Notably, cryo-TEM is more beneficial compared with TEM for studying micellar morphology because the original micellar structure is preserved.[p65] Cryo-TEM was used to assess the dimensions of copolymeric micelles, revealing sizes up to 45 nm.[p66] DLS, TEM, and AFM were used to analyze the morphology of cabazitaxel-loaded mPEG-PCL copolymeric micelles. The particle size determined through DLS analysis was 28.77 nm, surpassing measurements obtained through TEM and AFM techniques, which indicated a spherical size of 20 nm.[p67]

A crucial parameter affecting nanomicelle size is the molecular weight (MW) of the block polymer. The MW of the polymers can be determined using gel permeation chromatography (GPC) and mass spectrometry. Understanding drug loading and target specificity necessitates comprehension of the size and morphology of micelles, as well as the MW of the polymers used in their fabrication.[p68],[p69]

In recent years, increasing interest has been directed toward the self-assembly of multiblock copolymers into multicomponent micelles owing to their ability to segregate incompatible subdomains, broadening their application in therapeutics.[p70],[p71] Forecasting the intricate configurations of the core and shell, as well as evaluating the structural integrity of the complex micellar arrangements arising from the self-assembly of multiblock copolymers into multi-compartment micelles, are distinctive challenges.[p72] Computer-based dissipative particle dynamics (DPD) has emerged as an efficient technique for determining the intricate architecture of multicomponent micelles. This offers a straightforward approach for predicting both the internal organization of micelles and the dispersion patterns of the drugs within them.[p73]

The physical and kinetic stability of nanomicelle systems can be assessed using zeta potential, Förster resonance energy transfer (FRET), resonance energy transfer (RET), and electronic energy transfer (EET).[p74] FRET facilitates the understanding of micellar assembly, structural stability, and drug–micelle associations.[p75] By contrast, AFM, using single-molecule force spectroscopy (SMFS), is an additional approach used to assess microscale forces arising from covalent bonds, host–target recognition, interactions, intercalating forces, and hydrogen bonding.[p76] Yu *et al.* used this technique to investigate the degradation behavior of a triblock copolymer comprising poly (acrylic acid), polyfluorene, and poly(acrylic acid) (PAA-PF-PAA) under the influence of ethanol and water.[p77]

Drug release from copolymeric micelles can occur through either diffusion from intact micelles or the disassembly of micelles (Figure 6). However, to ensure controlled drug release during administration, micelles must have robust thermodynamic and kinetic stability.[p78],[p79],[p80] To prevent rapid disaggregation of the system or stabilize the drug encapsulated in the micellar core, a variety of physicochemical techniques,

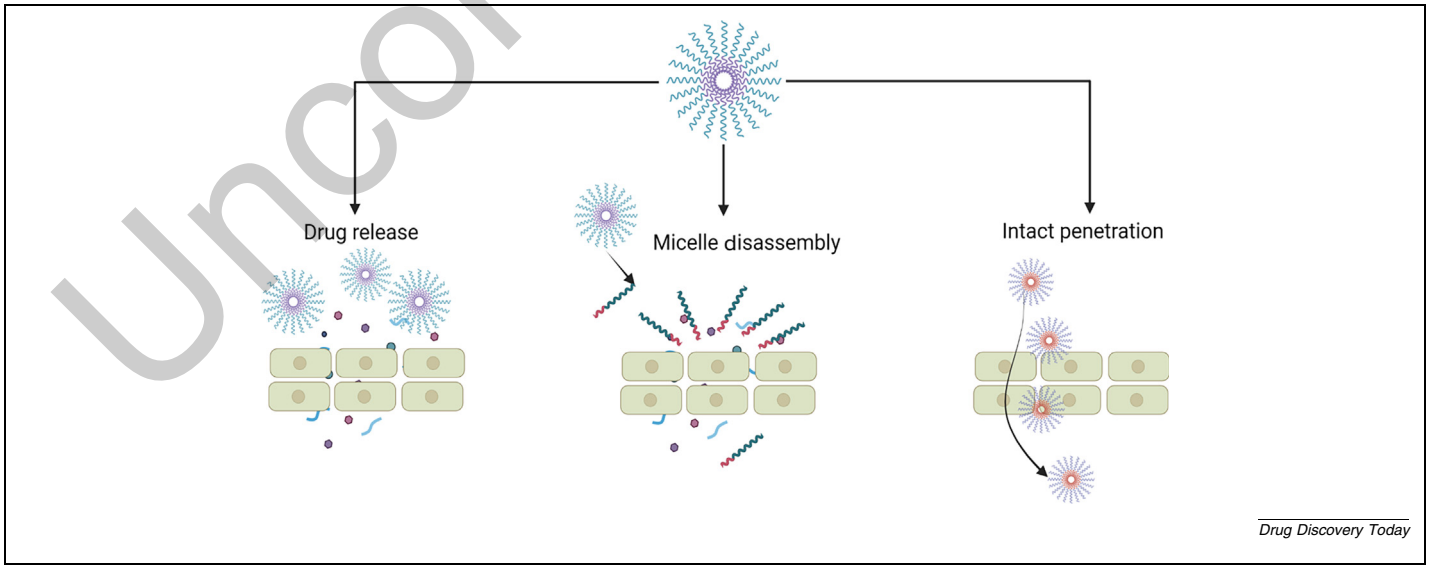

FIGURE 6

Key processes in drug delivery using block copolymer micelles. The first is the release from the micelle of the encapsulated drug molecules into the target tissue, followed by disassembly of the micelles into individual polymer chains. Finally, the copolymeric micelles penetrate cells through endocytosis or direct permeation across the cell membrane. Micelle interactions between cells and tissues have been studied by Ghezzi *et al.*[p17]

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including physical and chemical strategies, have recently been proposed.[p51] The interactions established between nanomicelles and cells and/or tissues can be studied using various techniques, such as X-ray scattering, Förster resonance energy transfer, and cryo-TEM. X-ray diffraction (XRD), used to determine the atomic and molecular structures of solid crystals,[p81],[p82] is one of the models used to study the interaction of nanomicelles with mucous membranes and the effect of enzymes on nanoparticles. XRD studies can reveal the mucoadhesiveness and penetration properties of nanomedicines.[p83] Cryo-TEM is widely used to visualize NP uptake by cells and tissues. The intracellular distribution of NPs can also be determined using TEM.[p84] FRET is a position-dependent phenomenon in which nonradiative energy is transferred from a donor fluorophore to an acceptor fluorophore. This energy transfer is contingent on the distance between them. Consequently, varicella infections involving both donor and acceptor fluorophores can be investigated by FRET.[p85]

Cellular uptake of polymeric nanomicelles is a complex process that depends on various factors, such as the physicochemical characteristics of the nanomicelles, encapsulated drug, and cell type. Although it is challenging to generalize the mechanisms by which copolymeric micelles are taken up, energy-dependent endocytosis is the primary cellular pathway by which these materials are internalized by cells. Endocytosis is a process in which cells incorporate extracellular materials by forming vesicles from their plasma membranes. Different mechanisms and regulatory pathways characterize various types of endocytosis, including clathrin mediated, caveolae mediated, and macropinocytosis. The preservation of the structural integrity of a drug-loaded nanocarrier after internalization is also pivotal because it can influence the uptake kinetics and toxicity of the system, in both experimental cell cultures and living organisms.[p86]

The design of targeting micelles involves four strategies for endogenous targeting (Figure 7): (i) attaching specific moieties to micelles enables precise drug delivery through covalent or noncovalent interactions with the targeted tissues; (ii) stimuli-responsive micelles release the drug payload upon exposure to endogenous stimuli, such as changes in pH, metabolic patterns, and reactive oxygen species (ROS) levels in the targeted tissue microenvironment; (iii) different ligand groups can be conjugated onto micelles to recognize and bind with high affinity to overexpressed receptors on the targeting sites, facilitating the enhanced accumulation of micelles within targeted tissues; and (iv) surface modification of micelles allows them to blend into cells and evade detection by the immune system, thus improving targeting and therapeutic effects. These strategies rely primarily on precise targeting based on endogenous chemical groups, such as diol groups, environmental cues, such as pH changes, or specific ligands, such as αVβ3 integrins, on the targeted sites.[p87],[p88]

A range of experimental techniques are usually used to uncover particular uptake mechanisms, including fluorescence microscopy, flow cytometry, and confocal microscopy.[p86] Research on the cellular uptake and intracellular trafficking of copolymeric micelles has been extensive in the development of efficient nanodrug delivery systems.[p89],[p90] Moreover, investigations have delved into the contribution of cellular internalization to reversing multidrug resistance through the utilization of copolymeric micelles.[p91] A comparative analysis investigated the cellular uptake and intracellular behavior of a collection of cyclic peptide-polymer nanotubes exhibiting diverse self-assembly properties.[p58] Copolymeric micelles with enhanced cellular uptake and combination therapy capabilities have also been developed through dual-drug delivery-based charge conversion.[p92]

Pharmaceutical applications of block copolymer micelles

Recent developments have highlighted the potential of copolymeric micelles in the field of drug delivery, drawing attention to their core–shell structure, stability over extended periods, and capacity to encapsulate hydrophobic pharmaceuticals. These characteristics equip copolymeric micelles with the capability for targeted drug delivery, thereby enhancing tissue retention and facilitating cellular uptake.[p93],[p94] The increasing popularity of block copolymeric micelles can be attributed to not only advances in fundamental understanding, but also the diverse practical applications that span various scientific fields.[p95] The use of block copolymer nanomicelles has benefited a range of areas, including nanomedicine, therapeutic and diagnostic formulations, and functionalized nanomaterial fabrication.

Various smart nanomicellar systems for ocular drug delivery have been developed, including pH-responsive, temperature-responsive, and electrically responsive systems. pH-responsive nanomicelles have garnered attention because of their ability to actively target therapeutic sites by responding to changes in pH induced by infections or other factors, triggering drug release.[p96],[p97],[p98] Two synthetic strategies involve the protonation/deprotonation of acid-sensitive bonds or acid-labile linkers between the micelle and the drug.[p97] Temperature-responsive systems, such as those based on Pluronics, can undergo gelation and release drugs in response to temperature changes.[p99],[p100],[p101],[p102],[p103]. Electrically responsive conducting polymers, such as polypyrrole, can modulate drug release rates upon electrical stimulation owing to changes in polymer properties.[p97] These stimulus-responsive nanomicellar systems offer potential for precisely controlled and targeted ocular drug delivery, and some have entered clinical trials (Table 1).[p104],[p105],[p106],[p107],[p108],[p109],[p110],[p111],[p112],[p113],[p114],[p115],[p116]

Applications in ocular drug delivery

Table 2 details studies involving the use of copolymeric micelles to bypass the barriers to the anterior segment of the eye for anterior segment ocular drug delivery.[p117],[p118],[p119],[p120],[p121],[p122],[p123],[p124],[p125],[p126],[p127],[p128],[p129],[p130] In open-angle glaucoma, the increased stiffness of endothelial cells within Schlemm's canal is a contributing factor to the increase in intraocular pressure above normal levels (10–22 mmHg), which underpins the pathology of glaucoma. Stack *et al*. developed PEG-bI-poly(propylene sulfide) copolymers encapsulated with the toxin latrunculin A to overcome the limitations of existing treatments to treat endothelial cell stiffness, such as rho kinase inhibitors, which often have off-target effects. The micelles were

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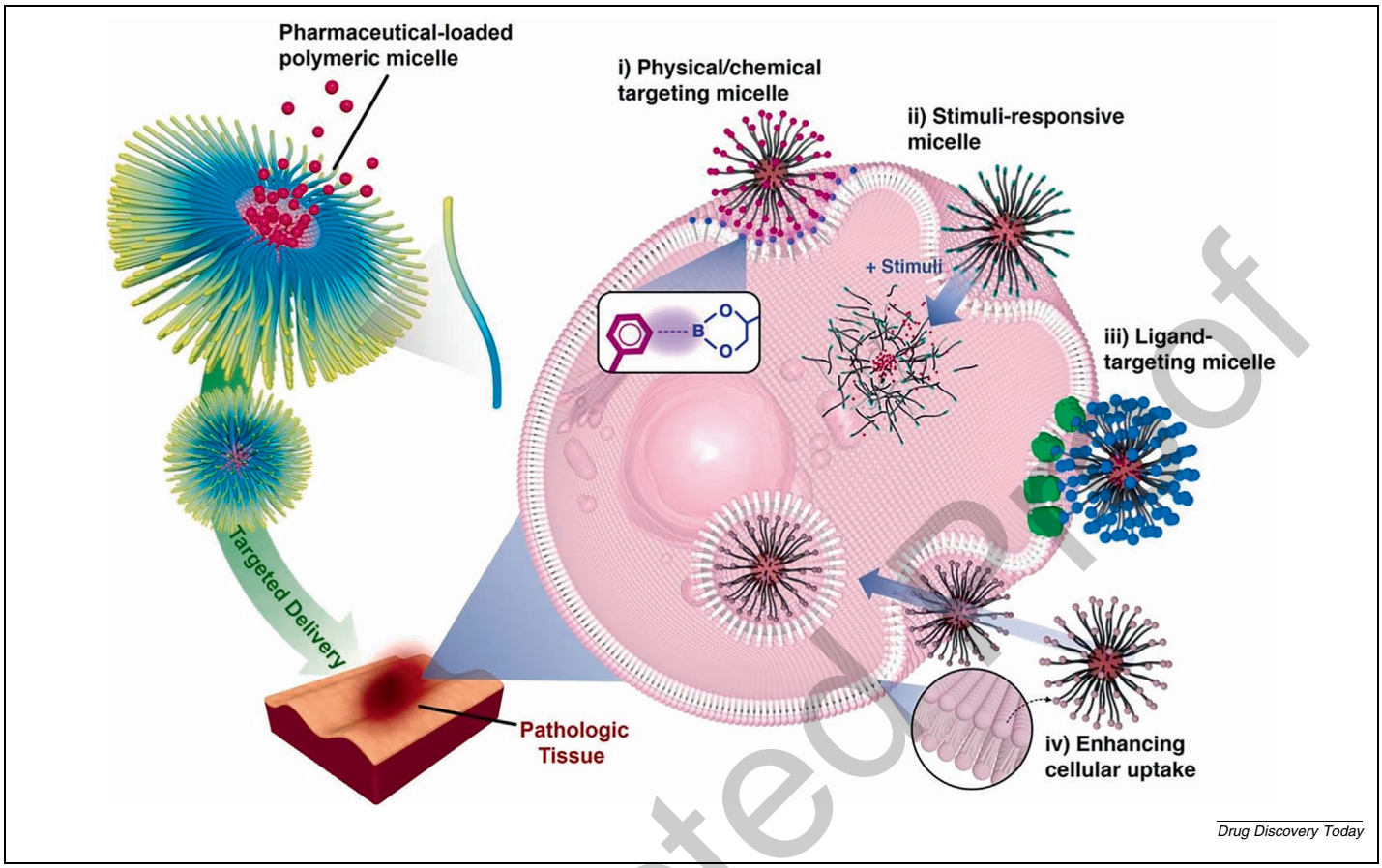

FIGURE 7

Polymeric micelle systems designed to enhance targeted therapeutic delivery. These systems include: (i) physical/chemical targeting micelles, which utilize conjugates that bind to specific target tissues through noncovalent interactions or covalent bonds; (ii) stimuli-responsive micelles, which incorporate moieties that trigger drug release upon exposure to specific stimuli, such as pH, temperature, or enzymes at the target site; (iii) ligand-targeting micelles, which display ligands conjugated to the surface that recognize and bind overexpressed target receptors with high affinity, facilitating accumulation within targeted tissues; and (iv) micelles designed to enhance cellular uptake, which have surface modifications that help them mimic cell membranes, avoid immune clearance, and promote effective internalization. These advanced micellar designs interact with pathological tissues to achieve improved targeted drug delivery compared with conventional drug-loaded copolymeric micelles. Reproduced from (p88).

fabricated via the solvent evaporation method, achieving an encapsulation efficiency of 62% without affecting the activity of latrunculin A, and were retained for 3 weeks without any *in vitro* cytotoxicity. AFM confirmed the significant reduction in endothelial cell stiffness, signified by rounding of the cell morphology, following treatment with 0.5 μM drug-loaded block copolymer micelles. Furthermore, the formulation of this toxin as a stable micelle formulation reduces any potential off-target effects, while delivering an efficacious treatment for endothelial stiffness reduction. Additionally, while the hydrophobic nature of the poly(propylene sulfide) component drives the self-assembly mechanism, the hydrophilic PEG domain enables chemical/surface modification to decrease nonspecific cell interactions and allow targeted delivery.(p131)

Lin *et al.* developed positively charged block copolymer micelles that were surface-modified with hexapeptides to induce a positive charge, which in turn enhanced the interaction between the micelles and the anterior ocular surface. This modification strategy successfully increased the retention and permeability of tacrolimus-loaded micelles, both *ex vivo* and *in vivo*. Tacrolimus is a hydrophobic immunosuppressant that has been used for the treatment of keratoconjunctivitis sicca. This study provides an example of how micelles can be used to promote the permeability of hydrophobic drugs, leading to an improved diffusion profile. While the commercial drug formulation, which acted as the control, showed improved permeability compared with the tacrolimus suspension formulation, permeability was still significantly lower in all three micelle formulations investigated in this study. Three block copolymer micelle formulations were investigated, with formulation NC-1 (PEP-PEG-PBG) showing the highest corneal permeation and most favorable therapeutic effects in terms of the suppression of the proinflammatory cytokines IL-17 and IL-1β, indicating the ability of these micelles to provide more favorable treatment outcomes compared with traditional suspension formulations.(p123)

Block copolymer formulation strategies can also be used along with other approaches to further enhance drug delivery, such as the incorporation of supramolecular hydrogel systems. The unique characteristic of supramolecular hydrogel systems is their ability to undergo a sol–gel transition in response to external

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TABLE 1

Examples of products based on copolymeric micelles approved for clinical trials[(p104)]

Product code name	Active pharmaceutical ingredient	Polymer	Development stage	Clinicaltrial.gov ID	Refs
Genexol® PM	Paclitaxel	mPEG-b-PDLLA	Approved in South Korea, Philippines, India, and Vietnam	NCT00876486 NCT02064829	(p105) (p106)
Papilock mini®	Cyclosporin A		Approved in Japan for treatment of vernal keratoconjunctivitis sicca		(p107)
TJ Cyporin®	Cyclosporin A		Approved in South Korea		(p107)
Modusik-a ofteno®	Cyclosporin A		Approved in Latin America		(p107)
3-A Ofteno®	Diclofenac sodium				(p108)
Cequa®	Cyclosporin A		Approved by FDA		(p109)
Nanoxel®	Docetaxel	mPEG-b-PDLLA	Approved in South Korea	NCT01336582, NCT02639858	(p110)
NK105	Paclitaxel	mPEG-b-modified P (Asp)	Phase III (completed)	NCT01644890	(p111), (p112), (p113)
NC-6004	Cisplatin	PEG-b-P(Glu) coordination complex	Phase III (completed)	NCT02043288	(p113)
SP1049C	Doxorubicin	Pluronic® L61 and F127	Phase II (completed)	N/A	(p114), (p115)
NK012	7-Ethyl-10-hydroxycamptothecin	PEG-b-P(Glu) covalent drug-copolymer conjugate	Phase II (completed)	NCT00951054, NCT00951613	N/A
CPC6346 (CriPec))	Docetaxel	PEG-b-P (HPMAm-Lacn(HPMAm-Lacn) covalent drug–copolymer conjugate	Phase II (recruiting)	NCT02442531, NCT03742713	N/A
NK 911	Doxorubicin	PEG-b-P(Asp) covalent drug–copolymer conjugate	Phase I (completed)	N/A	(p116)
NC-4016	Exaliplatin	PEG-b-P(Glu) coordination complex	Phase I (completed)	NCT03168035	N/A

stimuli, such as light. Furthermore, their thixotropic nature means that the hydrogel retained on the ocular surface will change into a solution under physical shear introduced by continuous blinking, thus leading to sustained drug delivery.

Zhang *et al*. produced PEG-PCL block polymer/α-cyclodextrin (CD) supramolecular thixotropic hydrogels using the host–guest inclusion method, specifically through the interaction of the PEG chain with CD. The micelles were then loaded with the hydrophobic nonsteroidal anti-inflammatory drug diclofenac, the release of which was influenced by α-CD concentration. The hydrogel formulation demonstrated an extended retention time compared with the control micellar formulation in an *ex vivo* rabbit model in the absence of irritability, as confirmed by the Draize test. Moreover, the micelles demonstrated low levels of cytotoxicity, with viability remaining above 85% after 24 h in both the L-929 and HCEC cell lines. Similarly, improved bioavailability was observed *in vivo* (C_{max} 2.66 ± 1.18 μg/ml) compared with the micellar formulation (C_{max} 1.12 ± 0.24 μg/ml, $P < 0.05$), as well as distribution, as confirmed through the delivery of Nile Red compared with simple micelle formulations. This hydrogel approach allowed the sustained release of diclofenac for 216 h, compared with 12 h for control micelles, which were not formulated within the hydrogel platform.[(p132)]

Safwat *et al*. used the cosolvent evaporation method to fabricate PEG-b-PCL and PEG-b-PLA block copolymer micelles, which were subsequently loaded with hydrophobic triamcinolone acetonide for the treatment of anterior segment inflammation. Given their higher loading capabilities, which were dependent on the polymer type, PLA micelles were selected for further *in vivo* and drug release studies.

Following its formulation into block copolymer micelles, there was a tenfold improvement in the aqueous solubility of triamcinolone acetonide. Sustained release of the drug was achieved *in vivo* (45 ± 3.2% release by Day 7) compared with the hydrogel formulation (42.8 ± 1.6% release by Day 7). The anti-inflammatory effects of these block copolymer micelles were tested using an *in vivo* rabbit model of carrageenan-induced anterior segment inflammation. On Day 14, the block copolymer micelle group demonstrated a decrease in inflammatory activity, as confirmed by histological imaging, which confirmed a normal structure. The hydrogel group alone led to minor improvements in corneal architecture, whereas the nontreatment group showed impaired corneal architecture, such as disorganization of the collagen arrangement.[(p133)]

Micelles have also been used to deliver antibiotics to the anterior eye segment. Zhang *et al*. delivered ciprofloxacin to the cornea via encapsulation into nanomicelles fabricated from amphiphilic glycopolymers. Functionalization of glycopolymers to include moieties of boron dipyrromethan and boronic acid was shown to improve internalization into bacterial cells, enabling the resolution of bacterial keratitis in a rat model through a reduction in proinflammatory cytokines. Micelles also showed tailored release in the presence of *Staphylococcus aureus*-induced keratitis (75.5% in 48 h) versus conditions without bac-

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TABLE 2

Nanosystems based on copolymeric micelles intended to bypass barriers to reach the anterior segment of the eye

Nanosystem	Active compound	Size (nm)	Zeta potential (mV)	Targeted disease	Key observations	Refs
mPEG (5kD)-PCL (2 kDa) copolymeric micelles	Curcumin-loaded copolymeric micelles	29.1	N/A			(p117)
MPEG-hexPLA copolymeric micelles	Cyclosporine A physically entrapped in polymeric micelle		N/A	Prevent cornea graft rejection after keratoplasty	CsA-loaded micelles bypassed corneal limitations to provide therapeutic CsA concentration in ocular tissues	(p118)
F68 copolymeric micelles	Plasmid (pCMV–bcl-xL–eGFP) encoding functional antiapoptotic gene (*bcl-xL*) physically entrapped into micelles by complex formation	47.6 nm	−1.3 mV	Stromal keratocyte apoptosis triggered by epithelial injury	After epithelial debridement, eye drops of pCMV-bcl-xL-eGFP-loaded micelles decreased corneal apoptosis	(p119)
	Plasmids (pCMV-Lac Z, pK12-Lac Z and pKera3.2-Lac Z) containing the Lac Z gene physically entrapped into micelles by complex formation	187 nm	−12 mV	β-galactosidase promoter	By using cornea-specific promoters derived from keratin 12 and keratocan genes, targeted gene expression within corneal epithelium and stroma was achieved Delivery of genes facilitated through non-invasive eye drops formulated with copolymeric micelles, administered to both mice and rabbits Transfection mechanism of plasmid-copolymeric micelles formulation might involve paracellular transport, which is contingent upon endocytosis mechanisms and particle size	(p120)
Polyoxyl 40 stearate copolymeric micelles	CsA physically entrapped into micelles at concentration of 0.1% (w/v)	200 nm	N/A	Treatment of immune-mediated ophthalmic diseases	Enhanced *trans*-corneal permeation of CsA as well as its distribution into various eye tissues, including cornea, conjunctiva, and lacrimal gland	(p121)
Copolymeric micelles of copolymer of N-isopropylacrylamide (NIPAAM), vinyl pyrrolidone (VP) and acrylic acid (AA) crosslinked with MBA	tromethamine salt (KT) physically entrapped into micelles; entrapment efficiency: 80%	35 nm	N/A	Anti-inflammatory activity	Corneal absorption of KT from micelles significantly greater compared with aqueous drug suspension Displayed significantly stronger anti-inflammatory effects over a longer time	(p122)
Micelles based on amphiphilic PEG-polyglutamic acid benzyl ester block copolymer	Tacrolimus (FK506) with loading of 4.5% at 80/920 ratio (w/w)	270 nm	+14 mV	Dry eye syndrome (DES)	FK506 contained within positively charged nanomicelles exhibited prolonged retention on eye surface and enhanced permeability across cornea compared with FK506 in negatively charged nanomicelles and commercially available FK506 formulation	(p123)
Triblock copolymer PEG-poly (ε-caprolactone)-g-polyethyleneimine (PEG-PCL-g-PEI)	Cyclosporine A: drug-loading efficiency and drug-loading content of 75.37% and 3.47%, respectively	27.74 nm	+12 mV	DES	*In vivo* and *in vitro* outcomes obtained using FDA-labeled micelles demonstrated significant prolongation of retention time and enhanced penetration of drugs into cornea when loaded into micelles	(p124)

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TABLE 2 (*CONTINUED*)

Nanosystem	Active compound	Size (nm)	Zeta potential (mV)	Targeted disease	Key observations	Refs
PVCL-PVA-PEG micelles	Myricetin (Myr)	–	−2.58 mV	Ocular anti-inflammatory	Myr contained within micelles exhibited no significant cytotoxicity, but considerable ocular tolerance *in vivo* Solubility and stability of Myr significantly improved, making micelles suitable for use as Myr eye drops Boosted cellular uptake *in vitro* and permeation across the cornea *in vivo* Augmented antioxidant potential *in vitro* and anti-inflammatory efficacy *in vivo* of Myr	(p125)
F127/chitosan copolymeric micelles	DEX physically entrapped in micelles by direct dissolution method, with drug-loading ratio 0.48–0.56%	25.4–28.9 nm	+9.3–+17.6 mV	Anti-inflammatory	2.4 improvement in bioavailability using fourfold lower dosage for a single instillation of DEX-loaded micelles relative to marked DEX eye drops	(p126)
Octoxynol-40	Cyclosporine A in aqueous micellar solution	20–80 nm	N/A	DES	FDA approved in 2018 as ophthalmic micellar solution for treatment of DES	(p127)
Sympatens AS-200 G/ Sympatens ACS-200 G/ Solutol HS 15	Cyclosporine A in aqueous micellar solution	10–12 nm	N/A	DES	Drug intake levels improved compared with CsA nanoemulsion in Phase III and free CsA *in situ* porcine model in olive oil (3- and 3.5-fold higher)	(p128)
PEG-DSPE	Rapamycin in aqueous micellar solution	11 nm	N/A	DES	Lymphocytic infiltration Activity of cathepsin S in tear and lacrimal gland lysates decreased compared with conventional eye drops	(p129)
PVCL-PVA-PEG	Curcumin	N/A	N/A	Oxidative stress	After intranasal administration, ocular effects on trigeminal ganglion enhanced corneal epithelial wound healing and corneal sensation recovery	(p130)

teria (57.8% in 48 h).[(p134)] The simplistic and patient-friendly topical application strategy of these platforms highlights their potential to assist in the clinical treatment of frequent ocular diseases, such as keratitis. Such advantages have already been observed for topical eye drops; however, their formulation into micelles has been shown to improve corneal retention and extend release profiles, which would help reduce dosing frequency and potentially improve patient acceptability and compliance.

Furthermore, in addition to their primary application in drug delivery, ocular micelles have the potential to be used as a secondary therapeutic approach, such as in the prevention of allograft rejection. Recently, Zhang *et al.* prepared polyvinyl caprolactam–polyvinyl acetate–PEG (PVCL-PVA-PEG) nanomicelles loaded with rapamycin through thin-film hydration as an approach to prevent corneal allograft rejection. The micelles successfully downregulated genes associated with cytokine interactions and T cell receptor pathways, which are characteristic of corneal allograft rejection. This might be a result of the improved permeability of hydrophobic rapamycin through the nanomicelle formulation approach, with a 50-fold improvement compared with the control group (rapamycin solution). Furthermore, micelles demonstrated long-term stability over ~3 months at both room temperature and refrigerated temperature conditions because of their low CMC values. Almost complete encapsulation of the drug was achieved (99.25 ± 0.55%), which was loaded at an optimal 18:1 ratio of polymer to rapamycin, and the nanomicelles demonstrated a uniform size distribution (PDI = 0.076 ± 0.016) with an average size of 64.42 ± 1.18 nm. Although the optimized formulation demonstrated good biocompatibility, as confirmed through a modified Draize test, further confirmation under *in vivo* conditions is required.[(p135)]

Despite the application of conventional topical drug delivery systems, such as eyedrops, proving unsuitable for the treatment of posterior eye diseases, block copolymer micelles have been used to successfully target and treat such diseases. Topically

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TABLE 3

Examples of nanosystems based on block copolymer micelles

Nanosystem	Active compound	Size (nm)	Zeta potential (mV)	Targeted disease	Key observations	Refs
Chitosan/Luterol F68/F127	Diclofenac sodium	18.7 nm ± 0.31 nm/25 nm ± 0.25 nm	–6.45 ± 0.18–37.00 ± 0.25	Anterior segment (e.g., conjunctivitis, eye irritation, etc.)	Studied factors leading to aggregation using quality by design High chitosan concentration (X%) led to higher self-aggregation of F68 particles compared with F127, because of disruption of crystal structure by chitosan Optimized formulation within chitosan/Lutrol F127 micelle design space	(p138)
Poly (ethylene glycol) stearate (Myrj™)-*block*-poly(ε-caprolactone) (Myrj-*b*-PCL)	Cyclosporine A	<200 nm	−1.6 ± 1.7 to −6.8 ± 2.1	DES/uveitis	Range of PCL MW used Zeta potential decreased for PCL_{44} and PCL_{131} after drug loading, but PCL_{88} increased Myrj S100-*b*-PCL produced optimized micelles concerning PDI, size (<200 nm), etc. Encapsulation improved cyclosporin A solubility significantly (23 μg/mL to >540 μg/ml) Comparable transcorneal permeation to Retasis®, with minimal irritation	(p139)
PEG-PCL-TMC	–	30 nm	–2.7 (p22) to –4.9 (p44)	Posterior segment (retina/optic nerve)	Micelles demonstrated shorted half-lives in vitreous (4–9 days) versus polymersomes (11–33 days) Polymersomes remain accumulated at optic nerve on Day 111 Convection had lesser role in micelle distribution because of their smaller size versus polymersomes	(p140)
PEG-*block*-poly(ε-caprolactone) (PEG-*b*-PCL) and poly (ethylene glycol)-*block*-poly(lactic acid) (PEG-*b*-PLA)	Triamcinolone acetonide	59.44 ± 0.15 to 64.26 ± 0.55 nm for PEG-*b*-PCL and from 136.10 ± 1.57 to 176.80 ± 2.25 nm for PEG-*b*-PLA micelles	Not provided	Uveitis	Up to tenfold increase in solubility observed for PEG-*b*-PLA PEG-*b*-PLA suspended in chitosan hydrogels showed enhanced anti-inflammatory effects versus control groups in *ex vivo* rabbit model, with ~40% of initial drug loading released within 1 week	(p133)
PLA–PCL–PEG–PCL–PLA	DEX	65 nm	Not provided	Anterior segment inflammatory diseases	Release profile followed Weibull's distribution model over 24 h, with no cytotoxicity observed Burst release (approx. 35%) in 2 h Significantly higher corneal permeability (0.44×10^{-6} cm/s) versus eye drop formulation (0.17×10^{-6} cm/s) in an *ex vivo* bovine eye model	(p141)
P123 and F68, and 2% w/v of Labrasol	Voriconazole	21.8 nm	–9.0 mV	Ocular fungal mycosis	Produced an optimized block copolymer formulation using 3-factor D-optimal design: "Pluronics to drug weight ratio of 22.89: 1, 1:1 wt ratio of Pluronic® P123 and F68, and 2% w/v of Labrasol" Better inhibition versus voriconazole suspension	(p142)

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TABLE 3 (*CONTINUED*)

Nanosystem	Active compound	Size (nm)	Zeta potential (mV)	Targeted disease	Key observations	Refs
Not provided	Posaconazole	11.63 ± 2.947–13.64 ± 5.013 nm	–1.31 ± 5.96 to –3.85 ± 6.92 mV	Ocular fungal infections	Good safety and stable for 3 months Showed good efficacy against *Candida albicans*, safely. 35 vs 27 mm zone of inhibition. Improved corneal (5.56 ± 0.01 μg/cm^2–75.10 ± 1.04 μg/cm^2) permeability of Posaconazole micelles versus oral suspension 0.30 ± 0.01 μg/cm^2	(p143)
PCL120-g-P(NVCL507-co-NVP128) (Cop A)/[PCL120-g-P (NVCL1253-co-NVP139) (Cop B)	Dorzolamide and indomethacin	39.4 ± 0.1/47.2 ± 0.2 (no drug loading)	–3.3/–3.5 (no drug loading)	Glaucoma	Drug encapsulation led to increased micelle size All IMC released within ∼3h, while dorzolamide release was maintained for over 24 h Both micelles were stable ∼1 month at 4 °C Reduced IOP after 15 days post administration in *in vivo* rabbit model compared with DEX because of enhanced mucoadhesive properties and sustained release provided by micelles	(p144)
PVCL-PVA-PEG (SoluPlus)	Everolimus	65.55 nm	–15.4 mV	Posterior uveitis	Low CMC of 7.2 μg/ml, providing 3 months of stability Released 39.9 ± 1.8% of load within 24 h, versus 51.8 ± 1.5% of control group (everolimus suspension) Significant improvement in permeation by micelles (67.14 ± 2.4%) versus everolimus suspension (34.06 ± 2.4%) in *ex vivo* goat cornea model, without any ocular toxicity Rhodamine B-loaded nanomicelles provided deeper penetration of cornea tissue (48.3 μm) versus dye solution (24.2 μm)	(p145)
F127	Voriconazole	84.45 ± 1.39 nm	–20.3 ± 0.29 mV	Ocular fungal diseases	Demonstrated high encapsulation efficiency (95.33 ± 0.06%), with a low CMC of 1.28 × 10^{-4} mg/ml Significant improvement in antifungal activity (31.5 ± 1.12 mm) versus voriconazole solution (15.5 ± 0.50 mm) against *Candida albicans* Demonstrated approximately twofold increase in cellular uptake versus solution of same fluorescent marker (Coumarin-6), and with lower cytotoxicity	(p146)
Chitosan-poly(lactide)/poloxamer	Moxifloxacin	127 ± 2	36.0 ± 2.4	Bacterial keratitis	Demonstrated high cellular uptake Showed high therapeutic effects in *Pseudomonas aeruginosa* and *Staphylococcus aureus* bacterial keratitis	(p147)

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TABLE 3 (*CONTINUED*)

Nanosystem	Active compound	Size (nm)	Zeta potential (mV)	Targeted disease	Key observations	Refs
PCL-PVA-PEG (Solulus)	Natamycin	19.91 ± 0.31 nm	–18.27 ± 1.38 mV	Fungal keratitis	Natamycin-loaded nanomicelles demonstrated higher corneal permeation compared with eye drops through enhancement of mean residence time Sustained release achieved over 24 h Stable at 4 °C for 6 months Formulation into nanomicelles enhanced stability and efficacy of low-dose natamycin	(p148)
mPEG-PCL	Brinzolamide and timolol	37.34 ± 4.62 nm	–	Glaucoma	Co-administration of brinzolamide and timolol though micelle-loaded contact lenses enhanced bioavailability tenfold versus eye drops Contact lenses showed acceptable transmittance and ionic permeability Sustained release of brinzolamide and timolol achieved over 84 and 72 h, respectively *In vivo* studies demonstrated IOP-lowering effect of micelle-loaded contact lenses	(p149)
d-α-Tocopheryl polyethylene glycol succinate	Butenafine	13.12 ± 0.24 nm	–0.56 ± 0.44 mV	Fungal keratitis	High encapsulation efficiency of butenafine (96.34 ± 1.65%) Demonstrated superior *in vivo* permeability in cornea compared with suspension control group and similar efficacy Well tolerated in *in vivo* rabbit eyes	(p150)
N,O-carboxymethyl chitosan	Latanoprost	94.07 ± 2.48 nm	–16.03 ± 0.66 mV	Glaucoma	Demonstrated sustained release over 24 h versus ∼1h for latanoprost eye drop formulation HET-CAM and *in vivo* Draize assays demonstrated biocompatibility and cellular tolerability of micelles *In vivo* residence time of micelles greatly enhanced compared with solution control group	
Pluronic F68® (PF68) and Soluplus®	Posaconazole	66.30 ± 2.10 nm	−51.1 ± 2.4 mV	Fungal treatment	Demonstrated sustained release, with only 80% of payload delivered after 24 h Biocompatibility demonstrated using *in vitro* hemolysis studies	(p151)
Rubusoside with Poloxamer 407	CBD	103 ± 2.66 nm	–	–	Demonstrated 6 months stability at 4 °C Antioxidant properties of CBD not compromised by encapsulation process	(p152)

applied drugs follow the corneal or conjunctival–scleral route to reach the target site of the posterior segment.

Li *et al*. used the Michael polymerization/addition reaction to fabricate spherical MPEG-b-PAE copolymer micelles (84.5 mm diameter), which were then loaded with the hydrophobic isoflavone genistein and modified with hyaluronic acid. Topical administration of these block copolymers was used to treat posterior eye diseases that involve angiogenesis. The micelles showed a sustained drug release profile (10% release versus 20% for micelles versus solutions in 1 h, respectively) and good penetration of the cornea in an *ex vivo* rabbit model, with a favorable safety profile without any toxicity at concentrations up to 500 μg/ml. Importantly, angiogenesis was inhibited in human umbilical vein endothelial cells following micelle administration, demonstrating an efficacious sustained-release drug delivery strategy for the treatment of neovascular disease. This therapeutic approach negates the use of intravitreal injection and its associated adverse effects, such as potential infection and poor patient compliance.(p136)

Nanomicelle platforms have also demonstrated the possibility of including biomolecules as cargoes. For example, topical ocular delivery of aflibercept *via* PEG-PPG-PCL micelles has been

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demonstrated to provide synergistic advantages in reducing angiogenesis in the treatment of retinal diseases. Despite a somewhat lower encapsulation efficiency (47.3%) than typically observed for small molecules, it was concluded that sufficient concentrations of aflibercept were present at the target site to enable therapeutic effects in choroidal neovascularization murine models *in vivo*. Such studies highlight the potential of mitigating the limitations associated with highly invasive delivery strategies, such as intravitreal injections, through the less invasive topical administration of drug-loaded nanomicelles. However, further research is needed on the *in vivo* therapeutic profiles of more species that closely resemble human ocular physiology.[p137]

As described earlier, research on block copolymer micelles has explored various applications in ocular drug delivery, targeting anterior segment conditions such as dry eye disease and posterior segment ailments such as diabetic retinopathy. Given their advantages in providing sustained drug delivery to the eye, these platforms have received growing attention, particularly in recent years and at the beginning of this decade. Table 3 summarizes developments in this area since 2020.[p133],[p138],[p139],[p140],[p141],[p142],[p143],[p144],[p145],[p146],[p147],[p148],[p149],[p150],[p151],[p152]

Prospects

Over the last four decades, block copolymer micelles have shown promise as vehicles for the administration of a wide variety of pharmaceuticals, each with unique properties.[p153],[p154] The high structural stability of these copolymeric micelles, resulting from the interactions between the polymeric chains of the hydrophobic blocks in their core, allows them to maintain encapsulated pharmaceuticals and remain stable during metabolism in the body.[p37] Furthermore, a variety of flexible hydrophilic polymers, such as PEG, can be used as shell-forming segments. The formation of hydrophilic polymers leads to the assembly of dense palisades of tethered chains, resulting in effective steric stabilization.[p155] This allows for the adjustment of the chemical and physical characteristics of the treatment, which leads to an increase in drug solubility within the treatment environment, better control over the rate of therapeutic release, and improved drug retention, particularly within the eye. Additionally, the straightforward methods of scaling up and low production costs make it feasible to transform block copolymer micelles into genuine drug delivery systems for use in the clinic.[p156]

According to the US Center for Drug Evaluation and Research (CDER),[p157] which reviews applications for novel drugs, there has been a significant rise in the number of drug product submissions utilizing nanomaterials over the past two decades. Polymeric nanomicelles are a relatively recent development in terms of both medication formulation and regulatory considerations. In 2013, a guideline, *Joint MHLW/EMA reflection paper on the development of block-copolymer micelle medicinal products* was released.[p158] Ther are 11 features that are crucial for defining the quality of the final polymeric micelle product, as outlined in this review: micelle size, morphology, zeta potential, aggregation number, critical micelle concentration, drug loading, physical state of the active substance, viscosity, *in vitro* stability, *in vitro* release, and *in vitro* degradation. However, characterization can also be a double-edged sword. On the one hand, completing these characterization steps might result in the production of a reliable product, but on the other hand, it will require an enormous amount of time and work before a polymeric micelle can be registered with regulatory bodies for clinical trials.

From the perspective of ocular drug delivery, the most significant obstacle that polymeric nanomicelles must overcome is the combination of the physiological and biophysical barriers of the eye.[p159] This combination of barriers results in a reduction in delivery efficiency to the anterior segment and, ultimately, to the posterior segment. For instance, in the anterior segment, copolymeric micelles that are mainly administered topically are lost because of blinking, nasolacrimal drainage, and systemic absorption via the conjunctiva.[p160] In addition, for nanomicelles to target the posterior segment, they must pass through scleral–conjunctival routes. These pathways contain additional multiple-layer barriers, which further reduce delivery efficiency.[p161]

To overcome these challenges, the ideal design of copolymer micelle formulations for ocular drug delivery is as follows: (i) mucoadhesive: by adding mucoadhesive qualities, micelles can stick to the ocular surface for longer, resulting in extended drug release and improved therapeutic effects. To accomplish this, chitosan or hyaluronic acid can be added to the formulation[p162]; (ii) high drug loading: a high capacity to load drugs and maintain a controlled and sustained release profile is essential for micelles that target the posterior portion of the eye. This guarantees the maintenance of therapeutic levels of the medicine for a prolonged duration, minimizing the need for frequent administration and enhancing patient compliance[p163]; (iii) small, uniform particle size: the micelles should have a small and consistent particle size, often within the 10–200 nm range. Smaller particles have a greater ability to penetrate ocular barriers, resulting in improved medication bioavailability and micelle stability. Additionally, they contribute to prolonging the duration of contact with the ocular surface[p164]; (iv) proper surface charge: It is preferable to have a surface charge that is neutral or slightly negative to minimize discomfort and prevent quick removal from the surface of the eye. Nevertheless, a marginally positive charge can augment the ability to adhere to the negatively charged mucus layer of the eye, thereby enhancing retention[p165]; (v) stability: the micelle formulation must exhibit stability in the aqueous environment of the eye, demonstrate resistance to dilution, and preserve its structural integrity to guarantee continuous drug release. Moreover, the copolymers must have a suitable equilibrium between the hydrophilic and lipophilic segments to guarantee sufficient solubilization of both hydrophobic and hydrophilic drugs[p166]; and (vi) safe and scalable: to prevent negative reactions in sensitive ocular tissues, it is important to select copolymers that are both biocompatible and nontoxic. The formulation procedure should be capable of undergoing sterilization without causing degradation of the drug or micelles. Additionally, it should be easily adjustable for large-scale production, while ensuring uniformity in dimensions, drug capacity, and release properties.

The performance of copolymeric micelles in ocular drug delivery is influenced by their hydrophilic and hydrophobic compo-

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nents. The selection of polymers and their molecular weights can be adjusted to optimize drug release, corneal permeability, pharmacokinetics (PK), and distribution within ocular tissues, ultimately enhancing the therapeutic effectiveness of drug-loaded micelles.[p167]

When a manufacturing process is scaled up, complete control over each technical parameter is necessary. This must be carried out in such a way that there are only minute variances between batches of the same nanoproduct. The scaling up of micelles presents challenges because of potential alterations in particle attributes that distinguish them from their bulk counterparts, such as stability, mean particle size, and morphology. Controlling these features is crucial to guarantee that each industrial batch has physicochemical, PK, and biopharmaceutical characteristics identical to those of the laboratory-scale batch. There are also economic issues that need to be taken into account, specifically the amount of investment that is necessary to support the commercial manufacturing of innovative micelle candidates and the development of CMCs. When it comes to manufacturing equipment, instruments, and/or facilities, the need for customization might be prohibitive for some companies. Additionally, these companies might require well-thought-out investment staging plans that match clinical development milestones.

Combined with the enormous workload associated with the characterization techniques and manufacturing, and despite the numerous polymeric nanomicelles reported here, <10% have been successfully converted to clinical use. According to Clinicaltrials.gov, as of May 2024, there were 59 ongoing and completed clinical trials investigating the safety and efficacy of micelles. In addition to manufacturing obstacles, legislation regarding clinical trials and good manufacturing practices (GMP) for nanotherapeutics require further investigation to address the insufficient knowledge about micellar PK/pharmacodynamic (PD) characteristics, clearance rate, and *in vivo* degradation profiles of the materials and micelles. Presently, the IVIVC profiles predominantly center on the lethal dosage (LD_{50}), inhibitory concentration (IC_{50}), and maximum tolerated dose (MTD).[p19] However, to obtain a thorough understanding of toxicity, it is essential to incorporate acute and subacute models. Given these criteria, micelles might require distinct registration obligations. Furthermore, regulatory frameworks that control manufacturing operations, process control, quality evaluation, pharmaceutical quality, product standards, and stability need to be strengthened and made more explicit.

Currently, more drug formulators are attempting to find solutions for these problems. For example, there have been more than 300 entries of nanomicelles for ocular delivery studies in Google Scholar since January 2022, highlighting the promise of these polymeric constructions as innovative ocular delivery platforms.

Despite the numerous advantages and promising preclinical results of polymeric micelles for ocular drug delivery, the number of efficacious formulations that have reached the market and been integrated into clinical settings remains limited. Several factors contribute to this challenge. First, the complex anatomy and physiology of the eye present significant barriers to drug delivery, requiring careful optimization of micelle properties to overcome these obstacles.[p168] Second, the lack of standardized characterization methods and quality control criteria for polymeric micelles can hinder their translation from bench to bedside.[p169] Third, the scaling up of micelle production from the laboratory to industrial scale can be challenging, because it requires precise control over various technical parameters to ensure batch-to-batch consistency and reproducibility. Moreover, the regulatory framework for nanomedicines, including polymeric micelles, is still evolving, and there is a need for clearer guidelines on the manufacturing processes, quality assessment, and stability testing of these products.[p170] Finally, the high costs associated with the development and clinical testing of novel micelle formulations, coupled with the uncertainty of market success, might deter pharmaceutical companies from investing in this technology. Addressing these challenges through collaborative efforts between academia, industry, and regulatory agencies is crucial for realizing the full potential of polymeric micelles in ocular drug delivery and bringing more effective and patient-friendly formulations to the market.

Concluding remarks

Overcoming the formidable barrier properties of the eye poses a significant challenge for ocular drug delivery researchers in the pursuit of maintaining consistent therapeutic drug levels in target tissues through the conventional topical ocular drug delivery route. Addressing the obstacles linked to these pathways requires the development of specialized drug delivery systems tailored to transport medications to precise ocular tissues. Over the past few decades, extensive research has been conducted on nanotechnology-based formulations. To overcome these drawbacks, various types of nanocarrier have been developed to increase ocular bioavailability. One strategy involves the development of polymeric nanomicelles.

Copolymeric micelles have considerable potential as ocular drug delivery systems for diverse applications. Their appeal lies in their ability to spontaneously form core–shell nanostructures in aqueous environments, along with their biocompatibility, physiological stability, nontoxic nature, ease of manufacture, and adaptability for functionalization. Numerous strategies have been explored to prolong circulation time and enhance the bioavailability of micellar drug delivery vehicles within the eye, such as PEGylation and chemical and physical stabilization techniques (e.g., cross-linking and stacking). Another appealing feature of long-circulating micelles is tissue-specific targeting, which can be accomplished passively (through the EPR effect) or actively (with targeting moieties), enabling selective drug delivery to cells that overexpress their receptors.

Given the distinctive properties of micelles, nanosized micellar carriers to carry drugs have drawn much interest as a noninvasive topical administration technique because they can deliver therapeutic drug levels into the desired ocular regions. By overcoming the current challenges in their clinical translation, as discussed in this review, nanosized micellar carriers could soon be commercially available and used as an efficient alternative to

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current invasive drug delivery methods, such as intravitreal and periocular injections, to treat anterior and posterior eye diseases.

Uncited reference

(p50).

CRediT authorship contribution statement

Ahmad A. Assiri: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation, Conceptualization. **Katie Glover:** Writing – review & editing, Writing – original draft, Data curation. **Deepakkumar Mishra:** Writing – review & editing, Writing – original draft. **David Waite:** Writing – original draft. **Lalitkumar K. Vora:** Writing – review & editing, Supervision, Resources. **Raghu Raj Singh Thakur:** Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Conceptualization.

Data availability

No data was used for the research described in the article.

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