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Eye Posterior Segment Drug Delivery and Nanomicelles as a Drug Delivery System for Age-Related Macular Degeneration

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Abstract: Scientists are still looking for a way to deliver a drug to a specific part of the eye. Static barriers (the different layers of the cornea, sclera, and retina, such as the blood-aqueous and blood-retinal barriers), dynamic barriers (blood flow in the choroids and conjunctiva, lymphatic clearance, and dilution of the drug in tears), and efflux pumps make it hard to deliver a drug alone or in a dosage form, especially to the back of the eye. So, looking into new drugs and finding the best ways to get them to people is important. Nanotechnology has used different nanocarriers to find ways to deliver drugs to the eye that interact with the ocular mucosa, keep drugs in the eye longer, and make the eye more permeable. Although nanotechnology-based drug delivery systems have applications in several diseases, we focus this review on recent developments of Nanomicelles, as a nanocarrier can deliver drugs to the back part of the eye, notably in the treatment of Age-Related Macular Degeneration.

Keywords: nanomicelles; drug delivery system; posterior segment; age-related macular degeneration; nanocarrier.

1. Introduction

The eye is a crucial organ that allows us to see by absorbing light, transforming it into electrical impulses in the retina, and sending those impulses via the optic nerve to the brain [1]. The eyeball's shape is that of a spheroid (Figure 1). Anterior and posterior poles are the central points of the eyeball's greatest anterior and posterior convexities, respectively. The anterior and posterior segments make up the eyeball. The cornea, the iris, and two aqueous humor-filled compartments are part of the anterior segment, together with the crystalline lens and the components anterior to them. The retina, choroid, vitreous humor, and optic disc are all parts of the eye located beyond the lens and are considered part of the posterior segment [2].

Managing eye illnesses that affect the posterior portion of the eye is becoming more complex and demanding, and innovative approaches to drug administration are being demanded in this challenging area. Although the intravitreal method is now the most common, it has been linked to adverse effects such as retinal detachment, endophthalmitis, and elevated intraocular pressure. To get around this, scientists have created various controlled drug delivery

systems [3,4]. The Nanoparticle Drug Delivery System stands out as the most practical option. We have settled on Nanomicelles as the medication delivery technology for this project via extensive reference and debate [5].

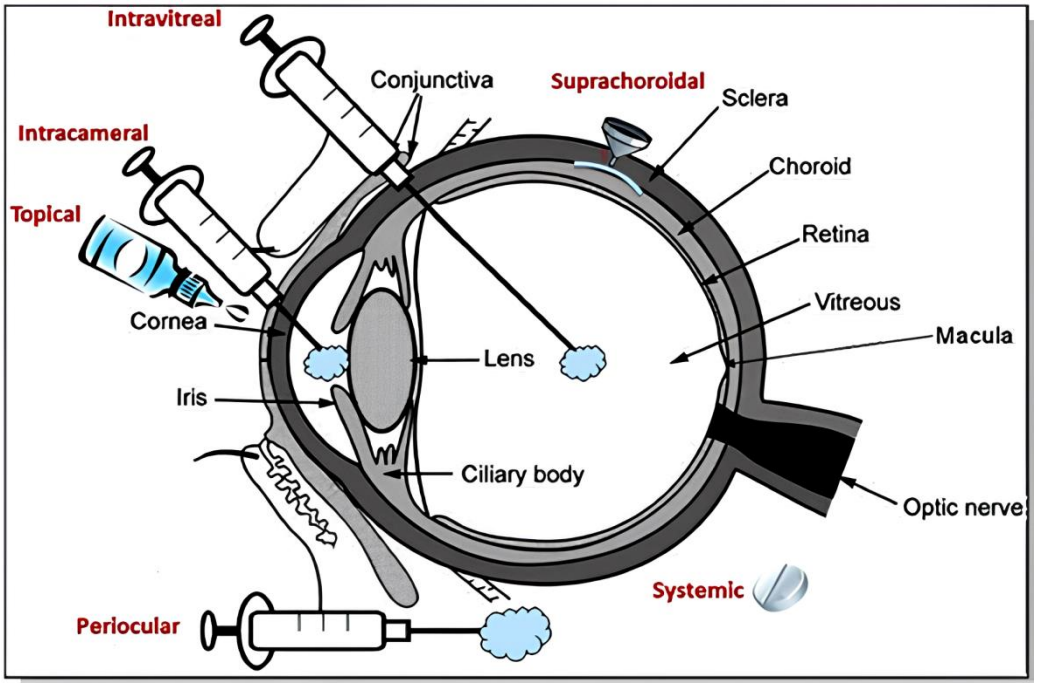

Figure 1. General anatomy of the eyeball. Reproduced with permission from *Patel et al*. 2013 [22].

1.1. Posterior segment drug delivery.

The retina, choroid, vitreous fluid, and optic nerve are all parts of the eye's posterior segment. Diseases of the posterior segment of the eye (PSEDs) are the most common cause of vision impairment and blindness in humans. As a result of a striking increase in incidence with age, choroid and retinal illnesses now affect millions of people worldwide and continue to rise each year steadily. Both conditions may be very challenging to manage but in different ways. Much work has been put into getting drugs into the eye, but they have yet to be delivered successfully [6]. Figure 2 illustrates the front and posterior portions of the eye schematically..

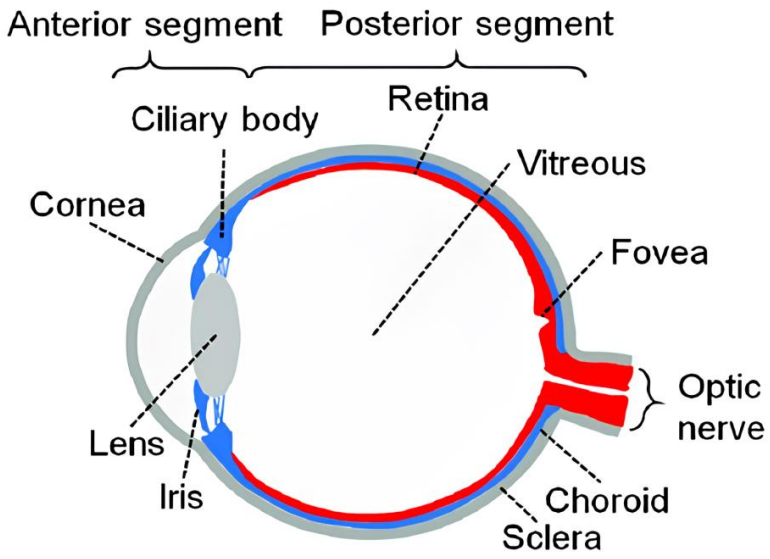

Figure 2. Route of administration to the eye. Reproduced with permission from Koutsoviti *et al*. 2021 [7].

Although topical and systemic delivery of injectable medicine has been reported with little success, intravitreal injection remains the preferred treatment method in clinical practice for these illnesses. Therefore, other routes of administration, such as suprachoroidal, subretinal, and periocular, have been devised for disorders of the posterior region. Each method involves injecting the medicine or system near the treatment location. The drug injected may not reach therapeutic levels at the site of action because of the many obstacles it must traverse on its way there. We can improve current treatment modalities by developing and deploying novel drug delivery systems and circumvent this constraint [7].

As a result of the medicine's limited efficacy and bioavailability, drug distribution to the rear of the eye requires strict dose intervals [8–10]. It's also important to remember that the intravitreal and periocular methods are intrusive and sometimes associated with pain and a lack of patient cooperation. When administered intraocularly, a medicine with a longer release time improves the patient's quality of life and decreases the therapy's financial burden by eliminating the need for as many injections.

As a result of the eye's unique architecture and physiology, drug distribution to the retina has proven to be a persistent challenge for the pharmaceutical industry. There have been few developments in keeping medicines at their active location. The ocular barrier plays a significant role in influencing drug pharmacokinetics and pharmacological impact. This is why it is essential to understand pharmacokinetics when developing an efficient pharmaceutical delivery system [11].

1.2. Routes of drug delivery to the posterior segment of the eye.

When treating illnesses of the anterior segment, topical instillation is the most popular and widely recommended non-invasive mode of administration. Ninety percent of ophthalmic formulations on the market are administered using more traditional means, such as eye drops. Its success includes small droplet size and high patient compliance [12]. However, topical drop delivery has little effect on ocular bioavailability. Several anatomical and physiological variables, including tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers, make deeper ocular medication penetration difficult. [13]. Therefore, less than 5% of the dosage administered topically is absorbed into the deeper ocular tissues [13]. Because of these obstacles, it is often impossible to accurately assess how much of a therapeutic medicine reached the tissues of the posterior portion of the eye after topical eye drop administration. Injections into the vitreous humor, the periocular space, or the bloodstream are only a few common medication delivery routes to the posterior segment's tissues. However, the blood-retinal barriers and relatively low attention volume compared to the rest of the body render systemic delivery a nonviable option. When treating illnesses of the back of the eye, intravitreal injection is the most frequent and recommended method of medication delivery. Nevertheless, the repeated eye punctures necessary for intravitreal injections pose a risk of endophthalmitis, hemorrhage, retinal detachment, and poor patient tolerance [14]. Transscleral drug delivery is another method for delivering medication to the tissues of the posterior region of the eye. Drug penetration is accomplished through ocular static and dynamic barriers, even though transscleral administration is straightforward, less intrusive, and patient-compliant. Both stationary and moving obstacles in the eye prevent effective transscleral medication delivery. Blood flow through the conjunctiva and episclera and lymphatic flow in the sclera and choroid are examples of dynamic barriers [15]. Static barriers include the sclera, choroid, and retinal pigment epithelium (RPE). A variety of

conventional and novel drug delivery systems, including suspensions, emulsions, aqueous gels, ointments, nanomicelles, liposomes, nanoparticles, dendrimers, implants, nanosuspensions, contact lenses, in-situ thermosensitive gels, and microneedles, have been developed to circumvent these ocular drug delivery barriers and improve ocular bioavailability.

1.3. Age-related macular degeneration.

One of the primary causes of blindness worldwide is age-related macular degeneration (ARMD). Senile macular degeneration is another name for this condition [16], and it may appear in either the 'dry' or atrophic form or the 'wet' or exudative form. Nearly 90% of people with ARMD are diagnosed with the atrophic type, far less severe than the exudative variant. Exudative diseases bring on nearly all cases of blindness in this population, which tend to be the most severe. The elderly, the white, and the female population are disproportionately affected by macular degeneration.

Thinner macular tissues, amorphous deposits, and macula coloring may accompany the atrophic type. When a choroidal neovascular membrane forms, it leads to exudative macular degeneration. Due to their fragility, these young blood vessels leak blood and fluid, harming the tissue around them. Risk factors include heredity, age, diet, smoking, hypertension, and sun exposure.

The drusen and pigment loss in the retina and pigment epithelium are ophthalmoscopic hallmarks of the dry form (Figure 3A). The metabolic products of the visual receptors and the Retinal Pigment epithelium (RPE) are deposited as mucopolysaccharides and lipids on Bruch's membrane, creating the tiny, yellowish deposits known as drusen. In exudative ARMD, aberrant blood vessels, fluid, and hemorrhage cause the neurosensory retina or pigment epithelium to rise [17] (Figure 3B and 3C).

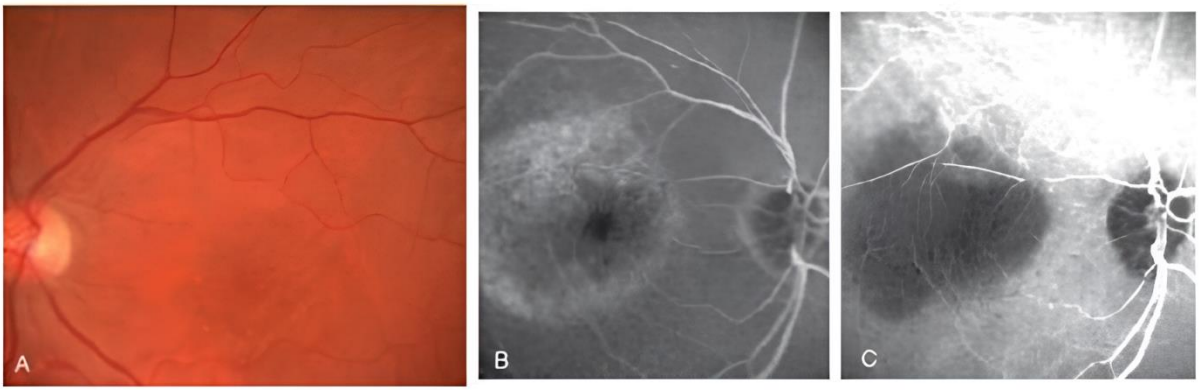

Figure 3. (**A**) Dry-type of ARMD, showing an absent foveal reflex and yellowish-white drusen below the macula. (**B**) Wet-type of ARMD seen on fluorescein angiography. (**C**) Indocyanine green angiography. Reprinted with permission from Sasaki *et al*. 2022 [17].

The root of ARMD is still a mystery. Antioxidant vitamins and zinc supplementation may slow or prevent the development of the disorder. Exudative macular degeneration is when blood and other fluids leak out of the retina, and laser photocoagulation may stop the bleeding. While this won't fix what's already wrong with your eyesight, it might help keep things from worsening. Effective and safe intravitreal medicines have replaced transpupillary thermotherapy, laser-based photodynamic therapy, and submacular and macular translocation surgery. Intravitreal medicines such as bevacizumab (Avastin), ranibizumab (Lucentis), pegaptanib sodium (Macugen), and aflibercept are used to treat exudative AMD (Eylea). All

of these treatments stop VEGF from doing its job (VEGF). Large drusen with hyperpigmentation increases the likelihood of establishing a choroidal neovascular membrane in the second eye.

1.4. The treatment employed for ARMD.

Patient education is the most important part of managing ARMD since early identification is key to effective therapy. ARMD may be treated in various ways, with the best method depending on the patient's specific diagnosis, stage of the disease, and availability of other treatment options. Laser-based treatments were the primary method of therapy throughout the 1980s and 1990s. A focused argon laser photocoagulation destroys the neovascular complex with high confluent burns to prevent CNV expansion or leakage [18]. However, recurrence was prevalent. Foveal leakage treated with photodynamic treatment (PDT) and a photosensitive dye (verteporfin) reduced vision loss to mild to moderate degrees in patients with mostly classic lesions [19]. Both of these approaches were intended to improve the visual output. Still, none of them did so. Using vascular endothelial growth factor (VEGF) inhibitors as a monotherapy, in conjunction with other medicines and nanotechnology, has resulted in significant improvements in patient care. Several studies (Table 1) have indicated that nanocarrier Drug Delivery Systems (DDS) may be effective in treating ARMD [20].

Table 1. Nanocarriers to Deliver Anti-Age-Related Macular Degeneration Agents.

Model Organism	Drug-Treated	Carriers	Results
Sprague-Dawley rats	Nintedanib	Nanoparticle	Stably retain encapsulated molecules in the vitreous; released cargo in response to UV exposure up to 30 weeks post-injection; light-triggered release of nintedanib 10 weeks post-injection suppresses CNV in vivo.
C57BL/6J mice and Cynololgus macaque monkeys	RGD-targeted	PLGA nanoparticle	Improved with nearly 40% restoration of visual loss induced by CNV.
Balb/c mice and Sprague-Dawley rats	LPD-mediated gene delivery	Lipid-based nanoparticle	Cell-specific promoters enable lipid-based nanoparticles to deliver genes to specific retinal cells in vivo.
An alkali-burn corneal neovascularization model in the mouse	Silicon	Nanoparticles	SiNPs-RGD features efficacious antiangiogenic ability; SiNPs-RGD can label antiangiogenic blood vessels and has neovascularization suppression.

2. Nanotechnology-Based Ocular Drug Delivery

Ophthalmic formulations based on nanotechnology are among the most promising anterior and posterior segment medication delivery methods. Bioavailability, minimal irritation, sufficient, and ocular tissue compatibility may all be guaranteed by carefully designing nanotechnology-based systems with the right particle size. Successful nanocarriers for ocular drug administration include liposomes, nanoparticles, nanosuspensions, nanomicelles, and dendrimers (Figure 4) [21,22].

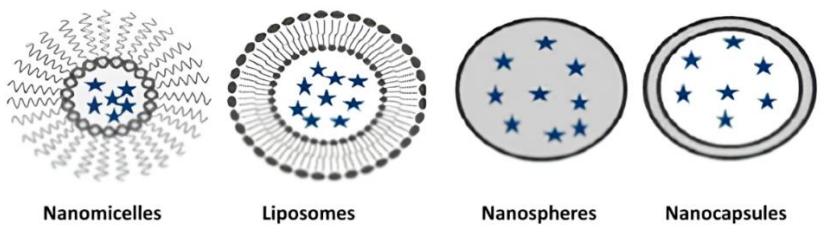

Figure 4. Nanocarriers for ocular drug delivery. Reprinted with permission from Patel *et al*. 2013 [22]

2.1. Nanomicelles.

Clear aqueous solutions of medicinal drugs are often formulated using nanomicelles as the carrier system. Amphiphilic chemicals are used to construct these Nanomicelles. Additionally, they are polymeric or surfactant-based. There is a great deal of focus on developing technologies based on nanomicellar creation for ocular medication delivery. One possible explanation is that they are easier to make, take up less space, and generate less static electricity than conventional corona generators since they are made of hydrophilic nanomicellar material. Better treatment outcomes may be anticipated due to micellar formation's potential to boost the bioavailability of therapeutic medicines in ocular tissues. So far, several studies have looked at the potential of Nanomicelles for use in ocular drug delivery [23].

Nanomicelles' hydrophilic outer surface increases medication solubility, whereas the lipophilic center encapsulates hydrophobic drugs in the micelle core. Due to their amphiphilic character, nanomicelles can enter the lipophilic corneal epithelial and endothelial cells. In addition to resolving drug-solubility issues, facilitating drug penetration, and raising the bioavailability of a medication, it may also permeate a hydrophilic matrix. In addition, ocular cells readily absorb nanomicelles due to their diminutive size [24]. The research on the tissue distribution of cyclosporine A in the rabbit eye showed that cyclosporine-loaded nanomicelles were created. Local instillation resulted in a significant concentration of CsA in the anterior eye tissue. Still, a greater level of CsA was discovered in the retina, indicating that the Nanomicelles may be able to transport the medication to the back of the eye [25].

Amphiphilic compounds have both hydrophobic and hydrophilic groups. When placed in a solvent of the correct kind and concentration, these molecules self-assemble and align to create nanomicelles, which may be either normal or reverse orientation. The hydrophilic side of the molecule faces the polar solvent, whereas the hydrophobic side faces away from it. This arrangement maximizes interaction with water by directing the hydrophobic components to congregate in the center (within the flakes) and the hydrophilic components to attach to the outside [26]. Normal nanomicelles are defined as aggregates that are already grouped. On the other hand, when amphiphilic molecules are placed in a hydrophobic solvent system, the hydrophobic portion of the molecule is pushed to the outside. In contrast, the hydrophilic portion is trapped within, forming micelles. It is possible to encapsulate, solubilize, and administer hydrophobic medicines using regular nanomicelles. Encapsulation using reverse nano micelles is a promising option for delivering hydrophilic medicines. Because of their potential to decrease medication degradation, lessen adverse effects, and increase drug bioavailability, nano micelles provide an excellent drug delivery method [27]. Nanomicelles are a promising drug delivery system for topical use in the eye because of their small size, ability to generate aqueous clear/clear drug formulations, encapsulation and solubilization of hydrophobic drugs, and their low or non-irritating effect on the ocular epithelium. To create nanomicelles, surfactants or polymer systems might be used.

3. Types of micelles

3.1. Regular micelles.

Consistent micelles are self-assembled structures of amphiphilic copolymers in water. They have a hydrophobic core surrounded by a hydrophilic shell that allows them to function

in an aquatic environment. Poly(ethylene oxide)–poly(propylene oxide), poly(ethylene glycol)–polylactic acid (PEG–PLGA), etc.

3.2. Reverse micelle.

Reverse micelles are amphiphilic copolymers that form stable, self-assembled structures in an organic solvent. They feature a hydrophobic outer layer and a hydrophilic interior and are manufactured in an organic medium. Micelles of PCLP2VP in oleic acid and micelles of phosphorene in chloroform are two such examples.

3.3. Unimolecular micelles.

Self-assembly of a single molecule into a micelle is made possible by the presence of both hydrophobic and hydrophilic areas inside a single molecule of an unimolecular micelle. These are produced in water from amphipathic molecules like Core (Laur) PEG micelles. They can retain stability due to drastic variations in pH, ionic strength, high dilution, temperature, and so on [28] because of their distinctive single-molecule structures (Figure 5).

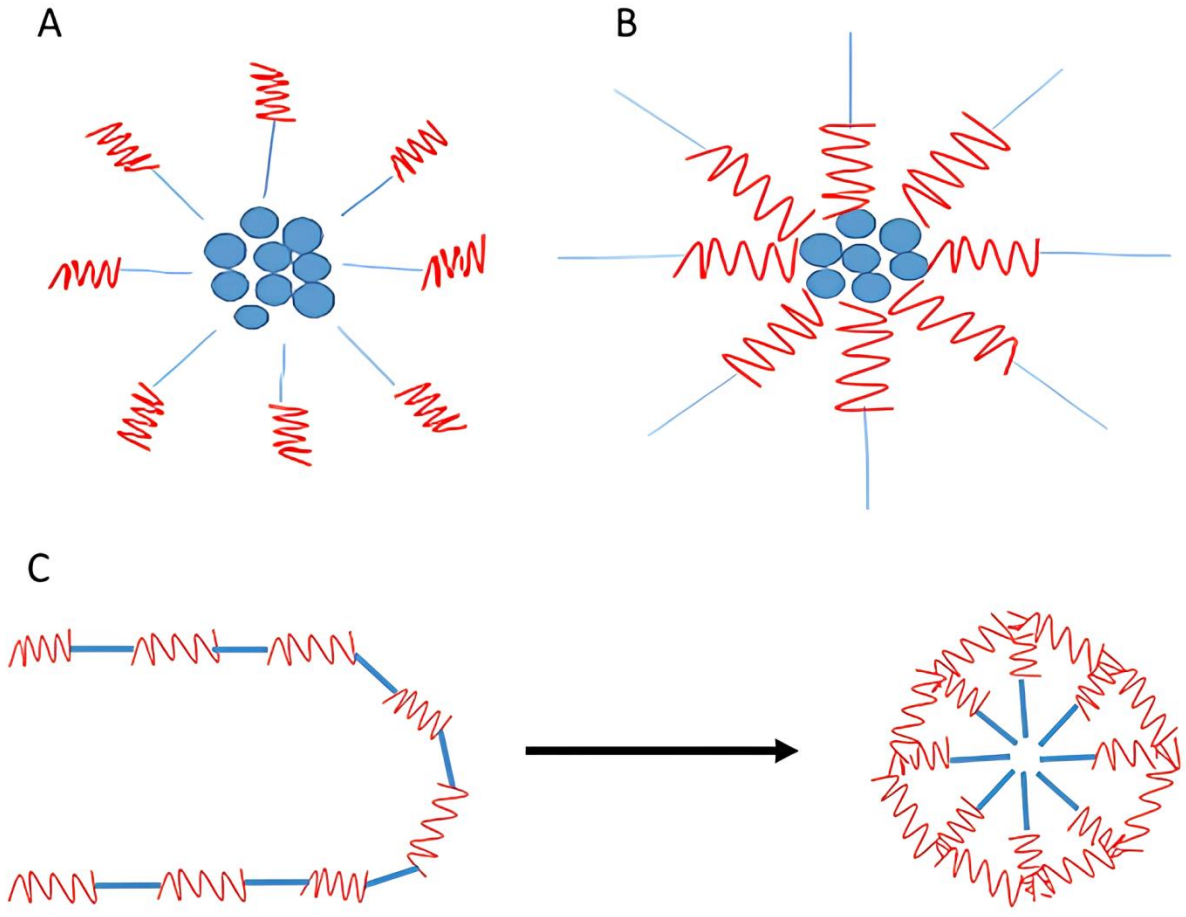

Figure 5. (**a**) Regular micelle (**b**) reverse micelle (**c**) unimolecular micelle The red line denotes hydrophilic, the blue line denotes hydrophobic, and the blue balls denote dug, respectively. Reprinted with permission from Bose *et al*., 2021 [28].

3.4. Polymeric micelles.

Amphiphilic polymers, like those used to create polymeric nanomicelles, have both hydrophobic and hydrophilic subunits. Micelles are formed when polymers self-assemble in aqueous liquids, with the hydrophobic segments forming the core and the hydrophilic segments

forming the corona. Polymeric micelles are excellent vehicles for drug delivery due to their inherent and customizable characteristics. Characteristics of polymeric micelles include a low Critical Micelle Concentration (CMC) and increased thermodynamic and kinetic stability in solution [29]. The recognized benefits and uses of polymeric micelles for drug administration are related to micellar association, shape, size, and stability, all of which may be characterized by their respective features. Advantages and uses include solubilizing poorly soluble compounds, protecting encapsulated chemicals from degradation and metabolism, and reducing the size of the encapsulated substances [30].

Nanomicelles preparation requires polymers that are both biocompatible and biodegradable. Common core-forming polymers. The high solubility of polyethylene glycol (PEG) in water makes it a popular hydrophilic polymer. Poly(propylene oxide), poly(L-amino acid), and poly(ester) are the three kinds of block copolymers that have been investigated the most due to the hydrophobic blocks they include [31]. Recent studies using formulation methods, including polymeric micelles to some of the pharmaceutical industry's most complex compounds, are summarised for each of the three-block copolymers. Attenuating toxicities, improving transport to targeted biological locations, and increasing the therapeutic efficiency of active pharmaceutical components are all possible thanks to polymeric micelles utilized in drug delivery [32].

3.5. PIC nanomicelles.

PICNMs are generated when a polyion copolymer binds to an ionic species with an opposite charge via electrostatic interactions. The monomers that makeup polyion copolymers may be either neutral or ionic. The hydrophobic core is formed from the block copolymer's ionic segment, which is neutralized by oppositely charged species, and PEG, the block copolymer's neutral segment. Block copolymer has limited polydispersity and is water soluble. Block copolymers typically consist of an ionic segment and a hydrophobic core, with the neutral section typically being PEG [33]. The use of poly-ion complex (PIC) nanomicelles as a nanocarrier system for transporting genes and antigen oligonucleotides has been extensively studied. Ionic hydrophilic medicines have been studied extensively for distribution using PIC nanomicelles.

3.6. Surfactant nanomicelles.

All surfactants are amphiphilic molecules, meaning they have both a hydrophobic tail and a hydrophilic head. Hydrophobic tails consist of long-chain hydrocarbons, whereas hydrophilic heads might be anionic, cationic, neutral, nonionic, or dipolar/zwitterionic. The surfactant molecules assemble into a supramolecular assembly, or colloidal dispersion, with a 5 to 100 nm diameter. The size of micelles may be modulated by adjusting the head group and alkyl chain lengths [34].

Surfactant in an aqueous solution initially collects at the air-liquid interfaces and then rotates so that its head faces the solvent. Inducing surfactant self-assembly into micelles requires adding more surfactant. Furthermore, the van der Waals bond recognition forms the hydrophobic core. Critical micellar concentration refers to the surfactant concentration at which micelles begin to form spontaneously (CMC). When micelles are created, the aqueous solution's head group and water molecules form a hydrogen bond crosslink. Cationic dodecyltrimethylammonium bromide (DTAB), anionic sodium dodecyl sulfate, nonionic

octoxynol-40, and zwitterionic dioctanoyl phosphatidylcholine are the most frequently employed surfactants for the manufacture of surfactant nanomicelles [35].

4. Conclusions

Managing eye illnesses that affect the posterior portion of the eye is becoming more difficult, and innovative approaches to drug administration are being demanded in this difficult area. Although the intravitreal method is now the most common, it has been linked to adverse effects such as retinal detachment, endophthalmitis, and elevated intraocular pressure. To get around this, scientists have created various controlled drug delivery systems. Most useful are the medication delivery methods based on nanotechnology. The field of nanotechnology has come a long way and is still evolving. There are advantages and disadvantages to each kind of medication delivery system—intravitreal, periocular, subretinal, and systemic. Along these lines, delivery techniques based on nanotechnology provide encouraging alternatives to the troublesome intravitreal injection. Our literature review suggests that nanomicelles provide significant benefits for drug administration to the posterior segment, including increased drug solubility and bioavailability, better drug penetration, a bigger absorption area, and fewer injections. Soon, improved ophthalmic medicines will be offered to patients thanks to multidisciplinary efforts across scientific disciplines. However, the poor scalability of nanoformulations has been reported to hinder the clinical translation of new products. There have been relatively interesting studies on using nanotechnology to cure ARMD, which should motivate future researchers. We believe the number of effective biological drug delivery systems being developed and brought to market will grow in the coming years.

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Conflicts of Interest

The authors declare no conflict of interest.

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