REVIEW PAPER

Revolutionizing Ocular Drug Delivery: Role And Challenges Of Nanoemulgel Technology

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ABSTRACT

Many ocular diseases are treated with conventional eye drops, but these suffer from poor drug retention and low bioavailability—typically under 5% of the instilled dose actually penetrates the eye's tissues. Nanoemulgel technology, which marries nano-scale emulsions with a gel matrix, has emerged as a promising strategy to address these limitations. By incorporating sub-100 nm, drugloaded droplets into a mucoadhesive hydrogel, nanoemulgels can prolong the formulation's residence time on the eye, sustain drug release, and enhance corneal drug penetration. This review provides a comprehensive examination of nanoemulgel formulation strategies for ocular drug delivery and explores their clinical applications. Key formulation factors are discussed, including methods for preparing nanoemulsions, choices of oils, surfactants and gelling agents, as well as characterization techniques. The paper also summarizes results from recent studies and clinical evaluations, which highlight improved therapeutic outcomes in conditions like glaucoma, dry eye disease, and ocular infections when nanoemulgels are used. The advantages of nanoemulgels— such as better patient compliance and higher efficacy—are weighed against the challenges they face, including formulation stability issues, sterility requirements, potential ocular irritation, and regulatory hurdles. Preclinical findings demonstrate that nanoemulgels can significantly enhance drug delivery to the eye, but further clinical trials and clear regulatory guidance are needed to translate this innovative platform into approved treatments. Overall, nanoemulgel technology shows great promise to transform ocular pharmacotherapy by bridging advances in nanomedicine with sustained-release gel systems.

Keywords: ocular drug delivery, nanoemulgel, nanoemulsion, sustained release, ophthalmic formulations

How to cite this article: Rana L, Garg G. Revolutionizing Ocular Drug Delivery: Role and Challenges of Nanoemulgel Technology. Int J Drug Deliv Technol. 2026;16(23s): 245-260. DOI: 10.25258/ijddt.16.23s.26.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Delivering drugs to the eye is notoriously challenging due to the eye's unique anatomy and protective barriers. Most ocular medications are administered as topical eye drops, which are convenient but highly inefficient—the majority of an applied dose is quickly drained through the nasolacrimal duct or lost due to tear turnover and blinking. As a result, typically under 5% of a drug actually penetrates the cornea and reaches intraocular tissues. This poor bioavailability often necessitates frequent eye drop instillation to maintain therapeutic levels, leading to fluctuations in drug concentration and an increased risk of systemic absorption. Conventional ocular formulations like simple solutions or suspensions therefore struggle to sustain therapeutic drug levels at the target site (especially for diseases of the posterior segment), and rapid precorneal clearance combined with tear dilution further limits efficacy. Moreover, repeated dosing is associated with side effects and patient non-compliance.

In pursuit of better ocular therapies, researchers have explored a variety of advanced drug delivery systems, including hydrogels, ocular inserts, microspheres, and nanocarriers. Nanoemulsions— submicron oil-in-water emulsions—have drawn particular interest as vehicles to solubilize hydrophobic drugs and enhance their corneal penetration. Several ophthalmic nanoemulsion products have even reached the market (for example, cyclosporine emulsions such as Restasis® and Ikervis® for dry eye, and the difluprednate emulsion Durezol® for inflammation). These products leverage nanotechnology to improve drug delivery; for instance, Restasis employs nanodroplets to increase the drug's residence time on the ocular surface, resulting in better therapeutic effect in dry eye disease. However, even nanoemulsion eye drops can still be cleared relatively quickly by blinking. This limitation has prompted the development of nanoemulgels, which are hybrid systems designed to combine the benefits of nanoemulsions and gels.

A nanoemulgel is essentially a nanoemulsion embedded within a semi-solid gel matrix. In these formulations, drug-loaded oil nanodroplets (typically <100 nm in diameter) are dispersed throughout a three-dimensional hydrogel network. The gel component increases the

viscosity of the formulation, helping it adheres to the eye's surface and resist nasolacrimal drainage. Meanwhile, the nano-sized droplets provide a large surface area and improved permeability for drug molecules across the corneal epithelium. By merging these two approaches, nanoemulgels aim to transform ocular drug delivery by achieving sustained drug release, enhanced drug absorption, and improved patient compliance.

Nanoemulgels are particularly advantageous for lipophilic drugs that are poorly soluble in water. In a nanoemulgel, the oil phase can dissolve such hydrophobic drugs, while the gel phase ensures the formulation remains in contact with the eye long enough for the drug to be absorbed. Additionally, the gel can act as a reservoir that gradually releases drug-loaded nanodroplets over time. Chronic ocular conditions like glaucoma, dry eye syndrome, and ocular infections could be treated more effectively with these sustained-release formulations. For example, glaucoma therapy often requires daily eye drops; a nanoemulgel delivering an intraocular pressure–lowering drug over several hours could reduce dosing frequency and provide steadier IOP control. Likewise, in dry eye disease, a cyclosporine nanoemulgel could increase corneal contact time and drug uptake, potentially enhancing efficacy compared to standard cyclosporine emulsion eye drops.

This paper presents a detailed review of nanoemulgel technology for ocular drug delivery. We discuss formulation strategies, including how nanoemulsions are prepared and incorporated into gels, and highlight key formulation parameters. The *Methodology* section describes the development and evaluation of ocular nanoemulgels, and the *Results* section compiles findings from recent studies demonstrating how nanoemulgels perform relative to conventional therapies. In the *Discussion*, we analyze the advantages of nanoemulgels and the challenges that need to be addressed for clinical translation—such as stability issues, safety considerations, and regulatory aspects. Finally, the *Conclusion* summarizes the potential of nanoemulgels in ocular therapy and future prospects. By examining both the benefits and remaining hurdles, this review aims to inform pharmaceutical scientists and clinicians about the state-of-the-art in ocular drug delivery and the path forward for this innovative approach.

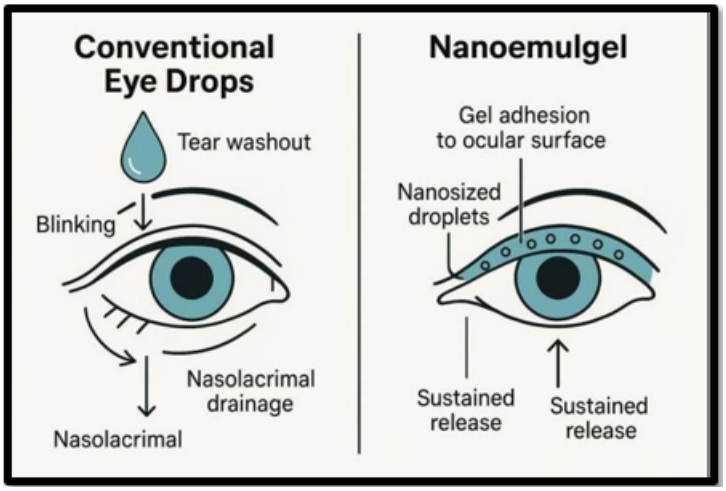

Figure 1: *Major precorneal and corneal barriers limiting conventional eye drops and how nanoemulgels improve residence time and penetration through increased viscosity, mucoadhesion, and nanoscale droplets.*

Methodology (Formulation and Characterization Strategies)

Developing an effective ocular nanoemulgel involves multiple formulation steps, beginning with the creation of a stable nanoemulsion and ending with the incorporation of that nanoemulsion into a gel base. Throughout this process, careful consideration is given to the selection of components (oils, surfactants, polymers, etc.) and process parameters to ensure the final product is safe, effective, and patient-friendly.

- **Nanoemulsion preparation:** Nanoemulsions for ocular use can be prepared by either high- energy or low-energy emulsification methods.
  - ***High-energy methods:*** These employ external mechanical forces to break down droplets to the nanometer scale. Common techniques include:

  High-pressure homogenization – The oil phase (containing the drug) and the aqueous phase (often with surfactants) are forced together at high pressure to produce fine droplets. Repeated cycles through a

high-pressure homogenizer can yield a uniform dispersion with droplet sizes often below 100 nm.

 Ultrasonication – High-frequency ultrasound is applied to an emulsion mixture, creating intense shear forces that disrupt and reduce droplet size. Ultrasonication is useful for laboratory-scale preparation of nanoemulsions, though careful control of sonication time and intensity is necessary to avoid degrading sensitive drug molecules.

 Microfluidics – In this approach, the liquid phases are pushed through microchannels or specialized microfluidic devices that promote controlled mixing and shearing, resulting in nano-scale emulsification. Microfluidic techniques can produce very uniform nanoemulsions and are advantageous for precise control over droplet size distribution (especially in small-scale formulations).

- ***Low-energy methods:*** These rely on the intrinsic physicochemical properties of the formulation components (such as surfactant self-assembly) rather than external high-shear forces. For example, in a spontaneous emulsification method, an organic phase (oil plus surfactant) is slowly added to an aqueous phase, leading to the spontaneous formation of nanodroplets as the solvents diffuse. Another low-energy approach is phase inversion (e.g., the Phase Inversion Composition method), where gradually changing the composition or temperature causes an emulsion to invert from water-in-oil to oil-in-water, yielding nano-sized droplets. Low-energy methods typically require careful formulation optimization (such as choosing appropriate surfactant/co-surfactant ratios) but have the advantage of being energyefficient and can often be performed at room temperature.

Once a nanoemulsion is prepared, it is characterized by key parameters such as droplet size, polydispersity index (PDI), and zeta potential. Dynamic light scattering (DLS) is commonly used to measure the average droplet size and PDI, which indicates the uniformity of the dispersion. For ocular use, droplet sizes below roughly 200 nm are usually desired to ensure the formulation remains transparent and non-irritating (indeed, many nanoemulsion formulations achieve mean droplet sizes in the 20–100 nm range). Zeta potential (the surface charge of the droplets) is measured to assess colloidal stability—a higher magnitude of charge (either positive or negative) helps repel droplets from one another and prevents coalescence. Additionally, techniques like transmission electron microscopy (TEM) can provide visual confirmation of droplet morphology and size at the nanoscale.

Incorporation into a gel base: The next step is to integrate the nanoemulsion with a gelling agent to form the final nanoemulgel. Broadly, two approaches can be taken (illustrated schematically in Figure 1):

1. *In situ emulsification:* The oil phase containing the drug (along with surfactants) is directly added to an aqueous phase that already contains a dissolved polymer (gelling agent). Emulsification is then carried out in this mixture, forming nanodroplets within the gel matrix itself.
2. *Post-emulsification mixing:* Alternatively, a nanoemulsion is first prepared separately, and this pre-formed nanoemulsion is then gently blended into a pre-made hydrogel base.

Both methods aim to achieve a homogeneous distribution of drug-loaded nanodroplets throughout the gel. Key excipients in the gel base include hydrophilic polymers such as carbomers (e.g., Carbopol®), cellulose derivatives (e.g., hydroxypropyl methylcellulose, HPMC), poloxamers (Pluronic® block copolymers), or natural polymers like hyaluronic acid, chitosan, and xanthan gum. These polymers impart viscoelastic properties to the formulation, enabling it to adhere to the ocular surface.

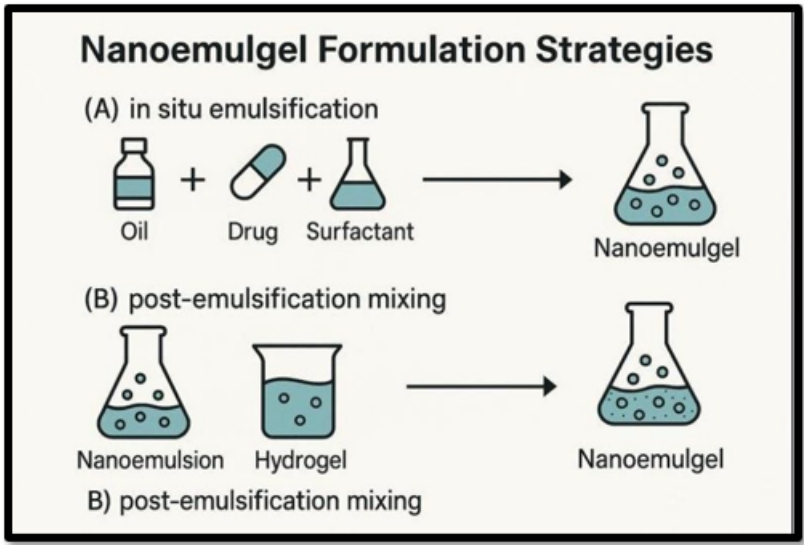

Figure 2: *Schematic illustration of two nanoemulgel preparation methods. (A) The oil phase (containing the drug and surfactants) is added directly to an aqueous phase that includes the gelling agent, and emulsification is performed in situ to form nanodroplets within the developing gel. (B) A nanoemulsion is prepared separately by emulsifying oil and water (with surfactants), and this nanoemulsion is then incorporated into a pre-formed hydrogel by gentle mixing. Both approaches yield a nanoemulgel in which nano-scale, drug-loaded oil droplets are uniformly dispersed in a semi-solid gel matrix.*

After formulation, the nanoemulgel must have a suitable viscosity: it should be fluid enough to be administered easily (for instance, as eye drops or a thin ribbon of gel), yet sufficiently viscous once on the eye to resist immediate tear washout. Many ocular nanoemulgels are designed as in situ gelling systems, meaning they are instilled as liquid drops that then undergo a phase transition into a gel upon contact with the eye. For example, a nanoemulgel formulated with gellan gum remains a liquid in the bottle but rapidly gels upon instillation because gellan gum cross-links in the presence of the calcium ions in tear fluid. Similarly, poloxamer-based formulations can be engineered to be liquid at room temperature but to gel when warmed to ocular surface temperature (~35°C). These approaches allow for easy administration (similar to conventional eye drops) while still achieving prolonged retention of a gel on the eye.

- **Physical appearance and pH:** The formulation should be uniform and ideally translucent, with no phase separation or precipitation of drug. The pH is typically adjusted to be close to physiological tear pH (~7.0–7.4) to minimize irritation. For example, a cyclosporine nanoemulgel was prepared at approximately pH 7.2 and made isotonic (~155 mOsm/kg) with tear fluid for comfort.
- **Rheological behavior:** The gel's flow properties (rheology) are optimized for ocular use. Most ocular gels are designed to be pseudoplastic (shear-thinning), meaning the gel becomes less viscous under shear stress (such as blinking or when being squeezed out of a dropper) and quickly recovers its viscosity when at rest. This ensures that the formulation spreads easily over the eye during blinking but remains adhesive on the ocular surface afterward. Rheological measurements (viscosity and viscoelasticity tests) are performed to confirm these properties.
- **Drug content and uniformity:** The nanoemulgel must contain the intended drug dose uniformly distributed throughout the gel. Assays of drug content are conducted to ensure the actual drug concentration is close to the theoretical value and that there are no significant concentration gradients within the product. Successful formulations typically achieve over 95% of the expected drug content, indicating minimal drug loss and uniform mixing.
- **In vitro drug release:** Drug release studies (for instance, using dialysis membranes or simulated tear fluid as a medium) are carried out to evaluate the release kinetics of the drug from the nanoemulgel. Nanoemulgels usually exhibit a sustained or controlled release profile, in contrast to the rapid release seen with simple eye drop solutions. For example, an in situ nanoemulgel of moxifloxacin was reported to release about 84% of its drug over a 12-hour period in vitro, whereas a conventional eye drop formulation would release the drug much more quickly under similar conditions.
- **Stability studies:** Stability testing under various conditions (e.g., room temperature and accelerated high-temperature/high-humidity conditions) is

performed to ensure the nanoemulgel remains stable over time. Important parameters include checking that the nanodroplets do not coalesce or grow significantly in size (maintaining a stable droplet size distribution) and that the gel base does not degrade or lose its viscosity. Many nanoemulgels have shown good stability over several months, maintaining consistent droplet size and drug potency throughout the testing period.

- **Sterility and preservative efficacy:** Ocular formulations intended for multi-dose use must be sterile. If the nanoemulgel is heat-tolerant, sterilization can be achieved by autoclaving (for example, one study autoclaved a timolol maleate nanoemulsion in situ gel at 121°C for 15 minutes without causing instability). If heat sterilization is not feasible due to temperature-sensitive ingredients, the formulation must be prepared using aseptic techniques. This might involve sterile-filtering the nanoemulsion (through 0.22 μm filters) before mixing it with a sterile gel base under sterile conditions. Multi-dose containers often require a preservative like benzalkonium chloride (BAK), but nanoemulgel formulations can sometimes be packaged in specialized multi-dose dispensers that avoid the need for preservatives, or they include only minimal concentrations of preservatives to prevent microbial growth while minimizing irritation.
- **Biocompatibility and irritation testing:** Before advancing to human trials, nanoemulgels are subjected to ocular safety testing. In vitro tests such as the Hen's Egg Test on the Chorioallantoic Membrane (HET-CAM) provide an initial screen for irritation potential. For instance, a levofloxacin nanoemulgel that used limonene as a permeation enhancer showed no signs of hemorrhage or coagulation in the HET-CAM assay, indicating good ocular compatibility. In vivo animal tests (such as the Draize eye test in rabbits) are also performed to confirm that the nanoemulgel does not cause unacceptable irritation (like redness, swelling, or excessive tearing) or damage to ocular tissues. Additionally, cytotoxicity assays on cultured corneal or conjunctival cells help ensure that the formulation (including its excipients, like surfactants) is non-toxic to ocular surface cells.
- **In vitro/ex vivo permeation studies:** Studies using setups like Franz diffusion cells with excised animal corneas or artificial membrane models are used to assess how well the drug penetrates ocular tissues from the nanoemulgel, compared to other formulations. These experiments often demonstrate that nanoemulgels enhance drug permeation due to their combination of nano-droplet delivery and prolonged contact time (mucoadhesion). For example, ex vivo tests have shown that a given drug in a nanoemulgel penetrated deeper and in greater amounts into corneal tissue than the same drug in a simple solution or nonnano gel.
- **Pharmacodynamic and efficacy studies:** Animal models of ocular diseases are utilized to evaluate the actual therapeutic efficacy of nanoemulgels. Key outcomes relevant to the specific condition are measured—such as reduction in intraocular pressure (for glaucoma treatments), increased tear production (for dry eye therapies), or improved infection clearance (for antimicrobial treatments). The results frequently show that nanoemulgels can achieve equal or superior therapeutic effects at lower or less frequent doses compared to conventional eye drops. For instance, in a rabbit glaucoma model, a single dose of a timolol nanoemulgel maintained a reduction in IOP for a much longer duration than a dose of a standard timolol eye drop, reflecting the extended release and retention capabilities of the nanoemulgel.

By following these formulation and evaluation steps, a robust ocular nanoemulgel can be developed and thoroughly tested. In the next section, we review how various nanoemulgel formulations have performed in practice, summarizing their pharmacological outcomes and comparing them with conventional ocular therapy where applicable.

Recent Studies

A number of recent studies have developed and tested nanoemulgels for ocular drug delivery, and the results have been largely positive. In general, ocular nanoemulgels exhibit significant improvements in drug retention and therapeutic efficacy compared to traditional eye drop formulations. Below, we highlight some key findings from these studies, including comparative performance metrics and specific case studies illustrating the capabilities of nanoemulgel systems.

Comparative formulation performance: Nanoemulgels fundamentally differ from simple aqueous eye drops in both their physical properties and drug delivery profiles. Table 1 highlights several important differences between a typical nanoemulgel and a conventional eye drop formulation on key parameters.

Table 1. Key Differences Between Nanoemulgels and Conventional Eye Drops

Parameter	Nanoemulgel	Conventional Eye Drops
Particle size of drug	Typically < 100 nm (nanoscale)	Generally > 1000 nm (micro-/macroscale)
Drug release profile	Prolonged (controlled release)	Rapid (immediate release)
Corneal permeability	High (improved penetration)	Low (limited penetration)
Ocular residence time	Extended (mucoadhesive retention)	Short (rapid clearance)
Patient compliance	Improved (less frequent dosing)	Lower (frequent dosing required)
Formulation stability	Enhanced (stable dispersion)	Limited (prone to phase separation)

These trends are supported by experimental data. For instance, in an in vitro release experiment, a nanoemulgel formulation of cyclosporine A for dry eye released its drug over more than 6 hours, whereas a comparable marketed cyclosporine eye drop (Restasis®) released about 90% of the drug in under 3 hours (Phadatare et al., 2024). This sustained release suggests that the nanoemulgel could maintain therapeutic drug levels on the ocular surface for a longer period, potentially reducing the dosing frequency needed for patients with chronic dry eye.

-Glaucoma (Bimatoprost In Situ Nanoemulgel): A notable example of a nanoemulgel for glaucoma therapy involves the prostaglandin analog bimatoprost. Glaucoma requires sustained reduction of intraocular pressure (IOP) to prevent optic nerve damage, but patient compliance with daily eye drops is often poor. Singh et al. (2025) developed an ionsensitive in situ nanoemulgel of bimatoprost using gellan gum as the gel-forming polymer that triggers gelation upon contact with tear fluid. The nanoemulsion component consisted of an algal oil (rich in omega-3 fatty acids) as the oil phase combined with surfactants (Tween 40 and lecithin), producing nanodroplets with an optimized mean size of about 39 nm and a positive zeta potential (~+34 mV). When this nanoemulsion was dispersed in the gellan gum solution, the final formulation remained a liquid that rapidly formed a clear gel in the presence of simulated tear fluid (due to gellan gum's calcium- induced gelation). The bimatoprost nanoemulgel exhibited excellent in vitro characteristics: nearly 100% of the expected drug content was present, the formulation was sterile and isotonic, and it demonstrated a sustained drug release profile indicative of diffusion-controlled release. In pharmacodynamic tests using animal models, the nanoemulgel significantly lowered IOP over an extended duration and, importantly, also mitigated side effects commonly associated with glaucoma eye drops. The inclusion of hyaluronic acid and omega-3 lipids in the formulation likely contributed to reducing dry eye symptoms and conjunctival hyperemia (redness), which are adverse effects often seen with long-term glaucoma therapy. This case illustrates how a thoughtfully designed nanoemulgel can improve treatment outcomes by providing prolonged IOP control while addressing tolerability issues

Table 2. Sustained Drug Release Performance of Nanoemulgels

Drug	Formulation Type	Release Duration	Key Observation	Reference
Cyclosporine A	Nanoemulgel	> 6 hours	Sustained release, prolonged ocular retention	Phadatare et al., 2024
Cyclosporine A	Marketed eye drop (Restasis®)	< 3 hours	Rapid drug release	Phadatare et al.,

				2024
Bimatoprost	In situ nanoemulgel	Extended	Diffusion-controlled sustained release	Singh et al., 2025
Levofloxacin	Nanoemulgel	Prolonged	Improved antimicrobial exposure	Mehanna et al., 2020

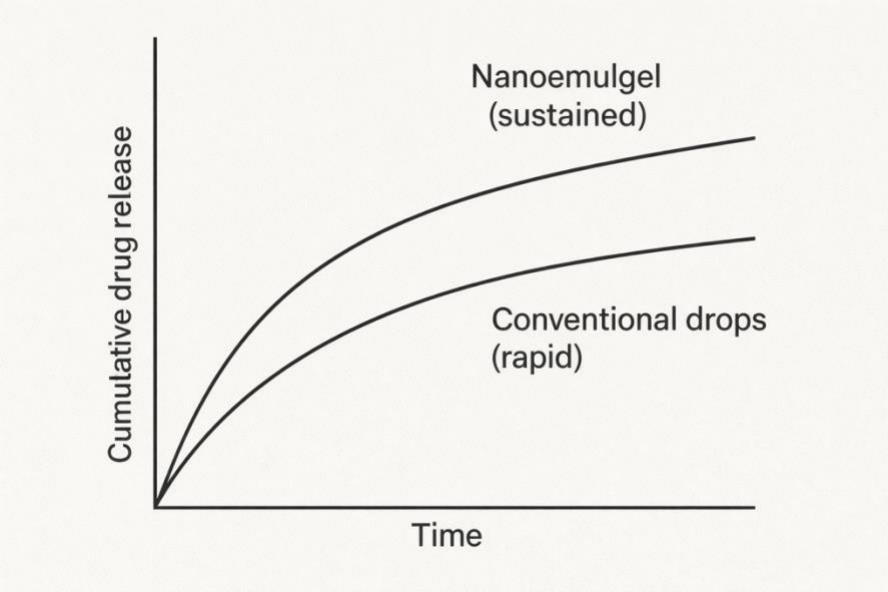

Figure 3 : *Illustrative comparison of drug release behavior: nanoemulgels exhibit prolonged release compared to rapid release from conventional eye drops, supporting reduced dosing frequency.*

– Dry Eye Disease (Cyclosporine Nanoemulgel): Chronic dry eye (keratoconjunctivitis sicca) is often treated with immunomodulatory eye drops like cyclosporine A (CsA), but conventional emulsions have limited residence time on the ocular surface. Phadatare et al. (2024) developed a lipid-based nanoemulgel formulation of cyclosporine to address this issue. In their formulation, a lipid nanoemulsion (stabilized by surfactants such as polysorbates and sorbitan esters) was incorporated into a gel, yielding a viscous "liquigel." The formulation was adjusted to physiological conditions (approximately pH 7.2 and 155 mOsm/kg) to ensure comfort upon instillation. The nanoemulgel achieved an average droplet (globule) size of around 190 nm with a narrow size distribution, as confirmed by cryo-SEM images that showed smooth, spherical nanodroplets. The drug was almost entirely loaded (~99.5% of the intended amount), indicating uniform drug distribution. In vitro release testing demonstrated a markedly prolonged release of CsA: the nanoemulgel released the drug over roughly 6 hours, following first-order kinetics ($R^2 \sim 0.98$). By contrast, a conventional cyclosporine eye drop released the majority of its drug within about 2–3 hours. This sustained release implies that the nanoemulgel could maintain therapeutic drug levels on the ocular surface for much longer, potentially enhancing efficacy in treating dry eye. Moreover, the extended release and mucoadhesive retention suggest that dosing might be reduced to perhaps twice daily, instead of the typical two to four times daily regimen required with standard drops. Such an improvement would significantly benefit patient comfort and compliance in this chronic condition. Similar favorable results with a cyclosporine nanoemulsion gel were reported by Suvarna et al. (2024), further supporting the potential of this platform for enhancing corneal drug delivery in dry eye disease.

Table 3. Case Studies of Nanoemulgel Applications in Ocular Diseases

Ocular Condition	**Drug**	**Key Formulation Feature**	**Therapeutic Outcome**
Glaucoma	Bimatoprost	Ion-sensitive in situ	Sustained IOP reduction,

		nanoemulgel (gellan gum)	reduced side effects
Dry eye disease	Cyclosporine A	Lipid nanoemulgel with mucoadhesive gel	Improved retention, reduced dosing frequency
Ocular infections	Levofloxacin	Limonene-based nanoemulgel	Enhanced antibacterial efficacy
Post-surgical inflammation	Diclofenac / Nepafenac	Nanoemulgel formulation	Prolonged anti-inflammatory action

Ocular Infection (Levofloxacin Nanoemulgel): Bacterial eye infections, especially those caused by resistant strains like *methicillin-resistant Staphylococcus aureus* (MRSA), may benefit from enhanced antibiotic delivery systems. Mehanna et al. (2020) formulated a levofloxacin- loaded nanoemulgel that incorporated a natural monoterpene, limonene, as a permeation enhancer to treat MRSA-associated ocular infections. In this formulation, limonene served as the oil phase of the nanoemulsion, which was then gelled into an in situ gelling system. The resulting nanoemulgel had a mean droplet size of around 119 nm. In microbiological assays, the limonene- based nanoemulgel significantly improved the antibacterial efficacy of levofloxacin against MRSA, effectively penetrating bacterial biofilms that can shield microbes from treatment. The enhanced performance is attributed to the dual role of limonene: it can disrupt bacterial cell membranes (increasing the antibiotic's access to the bacteria) and it improves drug permeation into ocular tissues, all while the gel prolongs contact time at the infection site. Importantly, ocular irritation tests (HET-CAM) revealed no signs of irritation from this formulation, supporting the ocular safety of using such permeation enhancers. This case underlines how nanoemulgels can be engineered with functional excipients (like essential oils) to tackle challenging infections, providing potent therapy without compromising ocular safety.

Table 4. Formulation Characteristics of Selected Ocular Nanoemulgels

Parameter	Observed Range	Significance
Droplet size	39–190 nm	Enhanced corneal penetration
Zeta potential	Up to +34 mV	Improved formulation stability
Drug loading	~99–100%	Uniform drug distribution
Gelation trigger	Ions / temperature	In situ gel formation
Release kinetics	First-order / diffusion-controlled	Sustained drug action

– Anti-Inflammatory and Posterior Segment Applications: Nanoemulgel formulations have also been explored for delivering anti-inflammatory drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), to the eye. For example, nanoemulgels of diclofenac and nepafenac have been formulated to prolong their analgesic and anti-inflammatory effects after ocular surgery or in conditions like uveitis (Chauhan et al., 2024). While specific outcomes depend on the formulation details, these NSAID nanoemulgels generally exhibit slower drug release and greater tissue penetration than standard eye drops, which may translate to improved pain control and faster recovery after ocular procedures.

Another intriguing application of nanoemulgels is in addressing posterior segment eye diseases. Topical therapy for conditions affecting the retina or vitreous (e.g., diabetic retinopathy or agerelated macular degeneration) is notoriously difficult because very little drug reaches the back of the eye via conventional drops. Researchers have attempted to bridge this gap by combining in situ gelling systems with nano-sized carriers to improve drug delivery to posterior tissues. For instance, a nanoemulgel containing the antioxidant flavonoid myricetin was investigated as a topical approach for diabetic retinopathy, aiming to increase drug bioavailability in the retina by prolonging precorneal retention and enabling deeper penetration of the nano-droplets (Chauhan et al., 2024). While achieving therapeutically significant drug levels in the posterior segment through topical application remains challenging, such strategies have shown incremental improvements.

In one report, a nanoemulgel delivered higher concentrations of drug to the retina than an equivalent conventional eye drop, though these concentrations were still far lower than those achieved by direct intraocular injection (Thrimawithana et al., 2017).

In Vivo Efficacy and Safety: Across various studies, ocular nanoemulgels have demonstrated significant in vivo benefits (Chauhan et al., 2024; Donthi et al., 2023). For glaucoma medications such as timolol or bimatoprost, nanoemulgels have consistently produced greater and longerlasting reductions in IOP in animal models compared to commercial eye drops. In some instances, a nanoemulgel allowed once-daily dosing to achieve the same effect that required twice-daily dosing of a conventional drop. Safety profiles have also been favorable: most studies report minimal to no ocular irritation from nanoemulgel treatments. Histological examinations of rabbit eyes after prolonged use of nanoemulgels have shown no significant toxic changes or damage to ocular tissues. Some nanoemulgel formulations include soothing, tear-mimicking components (such as hyaluronic acid or carboxymethylcellulose) to enhance tolerability. While mild side effects like temporary blurred vision or slight discomfort have occasionally been noted (often attributable to the higher viscosity of the gel), these effects are typically transient and mild, and are generally outweighed by the therapeutic gains.

Table 5. In Vivo Efficacy and Safety Outcomes of Ocular Nanoemulgels

Evaluation Parameter	**Observation**
Intraocular pressure reduction	Greater and longer-lasting than eye drops
Antimicrobial efficacy	Improved penetration and biofilm disruption
Ocular irritation	Minimal to none
Histopathology	No significant tissue damage
Visual disturbance	Mild and transient (if present)
Overall tolerability	High

Collectively, these results show that nanoemulgels can achieve their intended goal of sustained, enhanced ocular drug delivery. They outperform conventional eye drops in maintaining drug presence on the ocular surface and often in therapeutic outcomes (whether reducing IOP, healing the ocular surface, or clearing infections). The following section discusses the broader implications of these findings—namely, what makes nanoemulgels so beneficial, what challenges remain in their development and use, and how regulatory and clinical pathways are evolving for this promising technology.

DISCUSSION

The emergence of nanoemulgel technology marks a significant leap forward in ophthalmic drug delivery, combining the solubilization capabilities of nanoemulsions with the retention benefits of hydrogels. The benefits demonstrated by nanoemulgels in the results above align closely with the theoretical advantages anticipated for this hybrid system. However, there are also substantial challenges that must be addressed before nanoemulgels can fully realize their potential in routine clinical practice. In the following discussion, we first highlight the key advantages of ocular nanoemulgels and then critically examine the formulation, safety, and regulatory challenges that researchers and pharmaceutical developers need to overcome.

Advantages of Nanoemulgels in Ocular Therapy

- **Enhanced drug bioavailability:** By increasing the formulation's residence time on the eye and improving drug permeability, nanoemulgels can dramatically enhance ocular bioavailability. The tiny droplet size of the nanoemulsion component (often on the order of tens of nanometers) increases the contact area with the corneal epithelium and can exploit microchannels between epithelial cells, leading to higher drug penetration into ocular tissues. At the same time, the gel matrix prevents immediate washout, allowing more time for drug absorption. The net effect is that a greater fraction of the applied dose reaches the anterior chamber or target tissue compared to a conventional eye drop. As noted earlier, traditional drops may deliver less than 5% of the drug to intraocular tissues, whereas nanoemulgel systems have been shown in animal studies to improve this fraction severalfold.
- **Sustained release and reduced dosing frequency:** A core advantage of nanoemulgels is their ability to provide sustained drug release. Unlike the rapid bolus release from eye drops (which often necessitates dosing every few hours), nanoemulgels can be formulated to release drug gradually over 8–12 hours or more. This controlled release is achieved as the drug diffuses from the oil nanodroplets and the

gel matrix in a regulated manner (often following diffusion-controlled or near zero-order kinetics) (Alghazali et al., 2022). Maintaining therapeutic drug levels for extended periods translates to less frequent administration. Improved patient compliance is a direct result—patients do not need to instill medication as often, which is particularly beneficial for those who struggle with frequent dosing (such as elderly glaucoma patients or those with memory impairments).

- **Improved patient comfort:** Conventional ophthalmic gels or ointments (e.g., petrolatumbased formulations) can blur vision and cause discomfort, but nanoemulgels are generally designed to be lighter and more transparent. Because the oil droplets are nano- sized, they scatter less light, so many nanoemulgels appear only slightly turbid or almost clear, minimizing visual disturbances after application. Moreover, by using water-based hydrogels that are adjusted to ocular pH and tonicity, formulators can ensure good tolerability. Some nanoemulgel formulations include lubricating or tear-like components(such as hyaluronic acid or glycerin) that soothe the eye and alleviate dryness. In clinical evaluations, patients have often reported comfort levels similar to regular eye drops, especially when the nanoemulgel's viscosity is optimized so that it is not excessively thick.
- **Multifunctional excipient use:** The combined nanoemulsion–gel platform offers opportunities to include excipients that provide additional therapeutic or protective effects. For example, the bimatoprost nanoemulgel case included omega-3 fatty acids in the oil phase and hyaluronic acid in the gel phase—these not only helped formulate the nanoemulgel but also provided ancillary benefits for dry eye and inflammation. Similarly, in the levofloxacin nanoemulgel, limonene in the oil phase functioned as both a permeation enhancer and an antimicrobial agent. This multifunctionality can be leveraged to create more comprehensive treatments; for instance, one could formulate a single nanoemulgel that contains both an antibiotic and an anti-inflammatory agent for treating bacterial conjunctivitis, or combine two different glaucoma drugs (e.g., a beta-blocker and a carbonic anhydrase inhibitor) in one gel. Nanoemulgels are amenable to carrying multiple drugs either by co-dissolving them in the oil phase or by partitioning one drug in the oil droplets and another in the aqueous gel phase, though careful compatibility and stability studies are required in such cases.
- **Stability and shelf-life:** When properly formulated, nanoemulgels have shown good physical stability, which is a critical practical advantage. The gel structure can help stabilize the nanoemulsion by restricting droplet movement and coalescence. In stability studies, many nanoemulgels have remained stable for months, with negligible changes in droplet size distribution or drug potency. This performance often compares favorably to plain nanoemulsions, which can be more prone to issues like creaming or phase separation over time. Additionally, as semi-solid formulations, nanoemulgels may be less sensitive to certain environmental stresses (such as minor temperature fluctuations) than liquid eye drops—though extreme conditions can still pose a risk depending on the polymer properties. Overall, a stable shelf-life is important for commercial viability, and nanoemulgels have generally shown promise in this regard.
- **Broad applicability to ocular conditions:** Nanoemulgels are a versatile platform that can be tailored for a wide range of ocular diseases. For anterior segment conditions—such as glaucoma, dry eye, conjunctivitis, keratitis, or post-surgical inflammation—nanoemulgels are particularly well-suited because these conditions can be managed with topical therapies and benefit from extended drug contact time. For posterior segment conditions (affecting the retina or vitreous), topical treatment remains extremely challenging; however, using nano-sized carriers combined with permeability enhancers in a sustained-release gel offers a potential route to deliver at least a small fraction of drug to the back of the eye. This opens possibilities for non-invasive adjunct therapy for diseases like diabetic retinopathy or age-related macular degeneration. While serious posterior segment diseases typically still require intraocular injections or systemic therapy, nanoemulgels could serve as complementary treatments—addressing anterior segment complications of those diseases or providing baseline therapy with less invasive means.

In summary, the benefits of nanoemulgels revolve around more efficient drug delivery and a better patient experience. By overcoming key limitations of traditional eye drops (short contact time, rapid clearance, poor penetration) and by improving formulation stability and comfort, nanoemulgels indeed hold the potential to revolutionize ocular therapy. However, achieving these benefits in real-world clinical settings requires addressing several challenges, as discussed next.

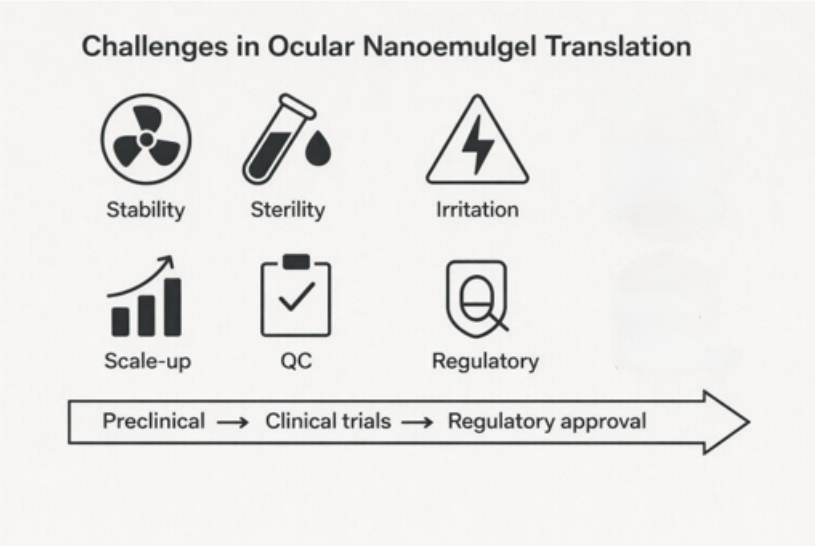

Figure 4: Key translational challenges for ocular nanoemulgels, including stability, sterility, tolerability, scale-up, quality control, and evolving regulatory expectations.

Challenges and Considerations in Nanoemulgel Development

- **Formulation complexity and optimization:** Developing a nanoemulgel involves tuning a large number of variables, which can make formulation development complex. The composition of the oil phase, the types and concentrations of surfactant and co-surfactant, the choice of polymer (gelling agent) and its concentration, as well as the specific preparation method all need to be optimized. Achieving the ideal balance to obtain the desired droplet size, stability, and gelling behavior can be challenging. For instance, the concentration of surfactant is critical: insufficient surfactant can result in an unstable emulsion, whereas an excessive amount can irritate ocular tissues. Similarly, the polymer concentration must be optimized to provide the desired viscosity without causing blurred vision. Formulators often employ Quality by Design (QbD) approaches and systematic experimental designs (such as factorial design studies) to methodically optimize nanoemulgel formulations. This complexity means development can be time-consuming and may require specialized equipment (e.g., high-pressure homogenizers, particle size analyzers) and expertise in both nanoformulation and polymer science.
- **Physical stability of the nanoemulsion:** Ensuring the long-term stability of the nanoemulsion component is a major consideration. Nanoemulsions are thermodynamically metastable and over time may undergo phenomena like droplet coalescence or Ostwald ripening (gradual growth of larger droplets at the expense of smaller ones). Incorporating the nanoemulsion into a gel can help mitigate these issues by physically hindering droplet movement, but careful selection of formulation components is still key. For example, adding a small amount of a co-surfactant (such as ethanol or propylene glycol) can sometimes reduce Ostwald ripening by better solubilizing any diffusing oil, but such additives must be non-irritating and not excessively volatile. Temperature fluctuations can also impact stability; a formulation that is stable at room temperature might experience droplet growth at higher temperatures or separate if frozen and thawed. Therefore, accelerated stability testing under various temperature conditions is essential to ensure the product remains stable throughout its shelf-life. If instabilities are observed (e.g., increasing droplet size or phase separation), reformulation or inclusion of stabilizers (like antioxidants in the oil phase or buffering agents in the aqueous phase) might be necessary.
- **Sterility and packaging:** All multi-dose ophthalmic products must be sterile, which poses manufacturing and packaging challenges for nanoemulgels. As mentioned earlier, if a nanoemulgel can tolerate heat, autoclaving is an effective sterilization method. However, many formulations contain heat-sensitive drugs or polymers that would be degraded by high temperatures, so those must be manufactured aseptically. Aseptic processing involves sterile filtration of the nanoemulsion (possible only if the formulation is sufficiently low in viscosity to pass through 0.22 μm filters), followed by combining it with a sterile gel base in a cleanroom environment. Packaging is another consideration: a very viscous

nanoemulgel might not dispense easily from a standard eye dropper bottle, so alternative packaging such as tubes or specially designed droppers may be required. The packaging must ensure that patients can administer the correct dose (a drop or a small ribbon of gel) without contaminating the remaining product. Innovative multi-dose packaging systems that are preservative-free (using one-way valve mechanisms) are being explored to allow nanoemulgels to be dispensed without the need for traditional preservatives. Overall, producing nanoemulgels at scale with consistent quality will require pharmaceutical manufacturers to adapt facilities and processes that can handle both sterile liquid and semisolid production, as well as packaging that maintains sterility over the product's use period.

- **Ocular irritation and safety:** The eye is very sensitive, and adding new excipients or using higher concentrations of excipients (such as surfactants in a nanoemulsion or polymers in a gel) raises concerns about irritation or toxicity. For example, surfactants like polysorbate 80 (Tween 80) or Cremophor EL are common in nanoemulsions and are generally considered safe, but at higher concentrations they can disrupt the tear film or irritate ocular tissues. Some gelling polymers, like carbopol (carbomer), can cause a transient burning sensation if the formulation's pH is not appropriately neutralized. Therefore, extensive safety testing is mandatory. Developers typically conduct Draize tests in animal models, carefully observing for any signs of conjunctival redness, corneal clouding, or irritation after repeated dosing. Encouragingly, many nanoemulgel formulations tested so far have shown ocular safety comparable to existing eye drops. In addition, for chronic-use products, longer-term toxicity studies may be required to ensure that daily use over months does not damage ocular tissues. Another aspect is the nanotoxicology concern—whether the presence of nano-sized particles in the eye could have unforeseen long-term effects. Current evidence suggests that inert oil nanodroplets made from biocompatible lipids are well-tolerated and eventually cleared through normal ocular pathways (e.g., tear drainage or the trabecular meshwork), but regulatory bodies will still expect comprehensive safety data addressing these concerns.
- **Regulatory and quality control hurdles:** Nanoemulgels, being complex multi- component systems, are likely to face stringent regulatory scrutiny. They can be seen as novel drug products that require thorough characterization and quality control. Regulatory agencies like the FDA and EMA will likely require detailed data on critical quality attributes such as droplet size distribution, rheological properties, in vitro release profiles, and stability data as part of the product dossier (Gawin-Mikołajewicz et al., 2021). Defining acceptable specifications for a nanoemulgel (for example, the allowable droplet size range, viscosity range, and release rate) is more complex than for a simple solution, and manufacturers will need to justify these parameters with supportive data. If a nanoemulgel uses any novel excipients, or existing excipients at concentrations higher than previously approved in ocular products, additional toxicological justification will be necessary. For instance, using a new polymer or a novel penetration enhancer in an eye formulation might require standalone safety studies. Another challenge is developing appropriate in vitro release testing methods for these products—regulators will expect the manufacturer to have a discriminating and reproducible release test (often involving specialized dissolution apparatus and membranes that simulate ocular conditions) to ensure batch-to-batch consistency in drug release. Moreover, since nanoemulgels combine aspects of both nano-drug delivery and gel formulations, regulatory guidelines are still evolving. Manufacturers are encouraged to adopt QbD principles and robust process controls; even minor changes in the manufacturing process could potentially affect a nanoemulgel's performance, so a thorough understanding of the formulation and process is needed to set reliable control strategies.
- **Patient acceptance:** Even if nanoemulgels are scientifically superior, patient acceptance of a new dosage form is not guaranteed. In situ gelling nanoemulgels that instill as drops are usually well accepted, since the experience is similar to a normal eye drop aside from a slight increase in viscosity after blinking. However, if a formulation is too viscous or causes prolonged blurred vision, patients may be reluctant to adopt it over familiar eye drops. It is important to optimize the user experience – for instance, ensuring that any blurring is minimal and short-lived. Patient education will also be key: explaining how to administer the nanoemulgel and what to expect can alleviate concerns. In some cases, dosing strategies can mitigate issues (for example, recommending that a more viscous gel be applied at bedtime to avoid daytime blurriness). Another factor is cost: advanced formulations like nanoemulgels could be more expensive to produce than simple generic eye drops, which might limit their uptake unless they clearly demonstrate superior outcomes. Health insurance coverage and cost-benefit perceptions will influence whether patients and providers embrace these new products.

- **Scale-up and commercial production:** Transitioning nanoemulgel production from the laboratory scale to industrial manufacturing presents several challenges. High-pressure homogenization and ultrasonication, commonly used in the lab to create nanoemulsions, may not scale directly to large batch production without adjustments. Industrial-scale homogenizers and continuous mixing equipment can be employed, but achieving the same nano-droplet size distribution consistently at large volume requires careful process design and validation. Similarly, uniformly mixing a nanoemulsion into a large batch of gel can be difficult; any uneven distribution could lead to variability in dosing. Quality control for nanoemulgels likely needs to be more extensive than for simpler products: each batch may require testing for particle size distribution (e.g., via dynamic light scattering or laser diffraction), viscosity, drug content uniformity, sterility, and perhaps in vitro release performance. The necessity for these multiple tests means production must be tightly controlled. Despite the added complexity, the pharmaceutical industry has relevant experience to draw on. For example, there are already FDA-approved ophthalmic nanoemulsion products (like Restasis®) and in situ gelling eye drops (like Timoptic-XE® for glaucoma, which uses gellan gum). These precedents suggest that, with appropriate expertise and investment, similar production and quality control frameworks can be established for nanoemulgels. In fact, the FDA has approved several nanotechnology-based ocular therapies in recent years, indicating that a regulatory pathway exists for nanoemulgels as long as comprehensive data on safety, efficacy, and quality can be provided. Ongoing collaborations among formulation scientists, clinicians, and regulatory experts are helping to refine guidelines for such nanomedicine products, ensuring they meet the necessary standards.

From a clinical perspective, the true test for nanoemulgels will come as more human clinical trials are conducted. To date, much of the evidence for nanoemulgels has come from laboratory and animal studies, with only a few early-stage clinical trials underway (for instance, preliminary trials of nanoemulsion-based gels for glaucoma and dry eye are starting to emerge). These trials will be crucial in determining how well the promising preclinical results translate to patient outcomes. They will also shed light on inter-patient factors: for example, variability in tear film composition or differences in patient perception of the gel may influence performance and acceptance in a realworld setting. It is heartening that many ophthalmic clinical trials are now including patient-centric measures—such as comfort, convenience, and quality of life—in addition to traditional efficacy endpoints. This means nanoemulgels will have the opportunity to demonstrate not just pharmacological superiority but also tangible benefits for patient well-being and daily life, which could be a key factor in their adoption.

In summary, nanoemulgels face a broad set of interdisciplinary challenges—scientific

(formulation design and stability), technical (manufacturing and quality control), safety-related (biocompatibility), and regulatory. Overcoming each of these will require sustained research and development efforts. However, none of these challenges is insurmountable. Steady advances in nanotechnology, polymer chemistry, and ocular pharmacology are providing new tools and strategies to address these hurdles. For example, more effective combinations of surfactants and stabilizers are yielding nanoemulsions with improved stability; innovative packaging solutions are mitigating the need for preservatives; and regulatory science is gradually adapting to accommodate complex nanomedicine products. As these issues are resolved one by one, nanoemulgels are poised to progress from experimental concepts to practical ophthalmic therapies.

CONCLUSION

Nanoemulgel technology represents a new frontier in ocular drug delivery, offering innovative solutions to longstanding challenges. By synergistically combining nanometer-scale emulsions with gel-based delivery systems, nanoemulgels create a platform capable of prolonged drug retention, controlled release, and enhanced ocular penetration. The research highlighted in this review demonstrates that nanoemulgels can significantly improve therapeutic outcomes across a range of eye conditions—from lowering intraocular pressure in glaucoma to enhancing drug efficacy in dry eye disease and ocular infections. These formulations exemplify how cutting-edge pharmaceutical science can transform ocular therapy, truly living up to the vision suggested by the title of this paper.

The successes of nanoemulgels are built on sophisticated formulation strategies, including advanced emulsification techniques and judicious polymer selection, that have been key to achieving the desired performance. Equally important have been the rigorous characterization and preclinical evaluation efforts, which have shown nanoemulgels to be generally safe and highly effective in experimental models. In numerous instances, nanoemulgels have outperformed conventional eye drops by sustaining therapeutic drug levels in the eye for longer durations and by reducing systemic exposure and side effects. They have also demonstrated the ability to enhance patient adherence by requiring less frequent

dosing and providing a more convenient treatment regimen.

Translating these promising results into clinical reality now hinges on carefully navigating the challenges discussed earlier. Factors such as manufacturing scale-up, long-term stability, sterility assurance, and regulatory approval processes will largely determine how quickly nanoemulgel therapies move from the laboratory bench to the patient's bedside. Regulatory agencies will demand comprehensive data packages, but the growing body of experience with nanopharmaceuticals and existing ocular drug products (like ophthalmic nanoemulsions and in situ gelling systems) provides a solid foundation to build upon. It is likely that the first approved ophthalmic nanoemulgels will be for anterior segment diseases such as glaucoma or dry eye, where the risk–benefit profile is favorable and clinical endpoints are well-defined. Success in these areas will pave the way for tackling more complex applications, potentially even some aspects of posterior segment delivery or combination therapies.

Ultimately, the adoption of nanoemulgels in clinical practice will depend on demonstrating clear advantages in patient outcomes. This means not only showing superior efficacy in clinical trials but also highlighting improvements in patients' day-to-day experience—such as less discomfort, fewer daily drops, and faster recovery times. The evidence to date is encouraging: nanoemulgels have the pharmacological attributes to provide these benefits, and preliminary studies suggest they can fulfill those expectations. As more peer-reviewed research and clinical trial data emerge, it is likely that confidence in this technology will grow among ophthalmologists and patients alike.

In conclusion, nanoemulgels represent a highly promising frontier in ophthalmic drug delivery. They encapsulate the principles of modern pharmaceutics—providing targeted, efficient, and patient-centric therapy. By addressing both the biological barriers of the eye and the practical challenges of patient adherence, nanoemulgels have the potential to substantially improve the management of many ocular diseases. The journey from a revolutionary concept to a standard- ofcare treatment is already underway. With continued research, development, and collaboration across scientific disciplines and regulatory frameworks, nanoemulgel-based ophthalmic treatments may soon become a reality in everyday clinical practice, ultimately revolutionizing ocular drug delivery for the benefit of millions of patients worldwide.

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