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# Engineering Ophthalmic Nanoemulsion Platforms: Design Principles and Translational Applications in Ocular Drug Delivery

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**Abstract** Due to physiological constraints that negatively affect the efficiency of conventional ocular preparations, such as fast tear turnover, poor corneal penetration, as well as short in-precornereal resident times, ocular drug delivery has long been a technical challenge. Nanoemulsion strategies based on engineering principles have been identified as a promising solution to overcome these challenges for improved solubilization, ocular bioavailability, as well as drug preparation stability. An eye preparation nanoemulsion consists of water, an oil phase, surfactants, as well as a cosurfactant, forming a kinetically stable colloidal system characterized by a mean particle diameter measuring less than 200 nm.

The design principles and translation properties of ocular nanoemulsion systems are discussed in this review. Formulation components and the manufacturing methods, along with the stability problems and recent advances, are discussed. The suitability of the systems to both high-energy production methods (such as spontaneous emulsification, ultrasonication, and high-pressure homogenization) and the stability of the ocular nanoemulsions and recent advances on novel methods such as stimuli-sensitive, mucoadhesive, or positive nanoemulsions will be discussed.

Despite these advantages, however, some challenges such as stability for a extended period, complexity, and cost of production still exist. In conclusion, customized ocular nanoemulsion delivery systems are quite viable and flexible research strategies for successful ocular drug delivery.

**Keywords** Ophthalmic nanoemulsions; Ocular drug delivery; Formulation engineering; Nanotechnology; Controlled drug release

## 1. Introduction

Due to the unique anatomy and protective barriers of the eye, efficient ocular drug delivery has remained one of the greatest hurdles in pharmaceutical and biomedical technologies[1]. Poor ocular bioavailability and frequent administration arise from the low drug retention, fast precorneal clearance, and limited corneal permeability characteristics of the

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conventional ophthalmic dosage forms such as eye drops and solutions[2]. These disadvantages have often affected patient compliance and the efficacy of the therapy in various chronic ocular disorders[3].

To overcome such problems, novel drug delivery systems based on nanotechnology have garnered significant interest. The nanoemulsion-based delivery platform is one of the most promising technical solutions for the delivery of ocular medications[4]. Nanoemulsions are submicron-sized suspension systems that enhance surface area and solubilize poorly water-soluble drugs for improved interactions with the eye tissues[5]. Nanoemulsions are optically clear, with easy sterilisation and flexibility in formulation processes. Therefore, nanoemulsion-based delivery systems have numerous benefits for use in ocular medication delivery[6].

From a technical point of view, nanoemulsions for the eyes allow for very precise control of the features of the composition concerning size distribution of the droplets, charge, viscosity, and release characteristics[7]. All of these factors contribute to an extended precorneal residence time and an augmented penetration through the barrier in the eye. Moreover, the ability to be produced on a large scale simplifies the transition to industrial production[8].

The present paper is designed to provide a technological review of the ophthalmic nanoemulsion platform, focusing on the main principles of formulation design, preparation procedures, stability issues, and new trends in ocular drug administration. The essay discusses recent progress and remaining challenges, with a focus on tailored nanoemulsions as next-generation colloid systems for the successful and patient-friendly treatment of ocular disorders[9].

## 2. Challenges in Conventional Ocular Drug Delivery

The conventional routes of ophthalmic delivery of medication in the form of aqueous eye drops, suspensions, ointments, and gels are still the most popular dosage forms for the treatment of eye disorders. Unfortunately, the above dosage forms of medication have some physiological and technical limitations. The eye is one of the most challenging biobarriers for the delivery of medication, with a lot of protection and dynamic clearance mechanisms[10].

### 2.1 Limited Ocular Bioavailability

However, a drawback in the conventional formulation is the low bioavailability. This value is found to be less than 5% of the injected dose. This is due to the fast turnover in tear fluids, blinking, and nasolacrimal

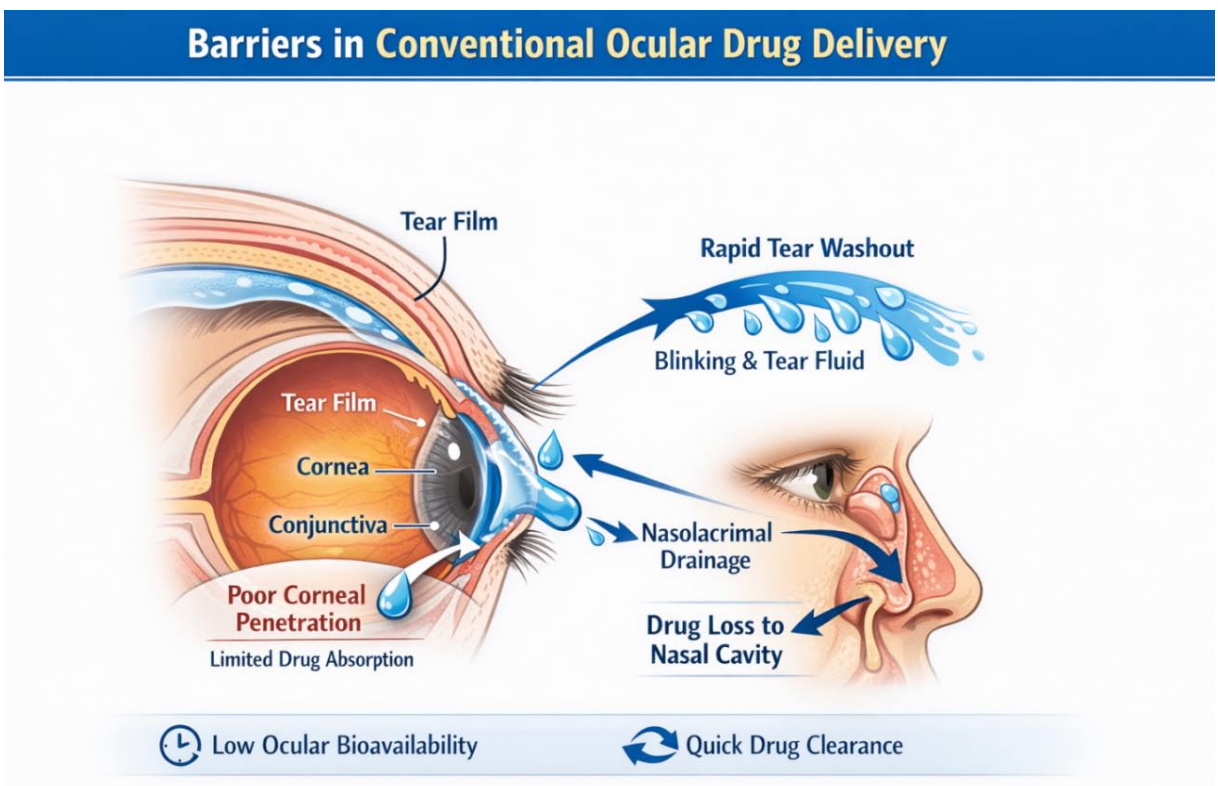


**Figure 1:** Barriers in Conventional Ocular Drug Delivery

drainage, leading to the overall removal of the drug from the surface. Thus, achieving and sustaining the therapeutic concentration in the tissues is difficult[11].

### 2.2 Anatomical and Physiological Barriers

The cornea is the main barrier for the penetration of drugs, which is both lipophilic as well as hydrophilic in nature. Although the stromal layer of the cornea impedes the diffusion of lipophilic drugs, the corneal epithelium impedes the diffusion of hydrophilic drugs. In addition, the conjunctival epithelium, as well as the blood-aqueous barrier and the blood-retinal barrier, impede the entry of drugs into the deeper tissues of the eye[12].

### 2.3 Short Precorneal Residence Time

Conventional eye drops remain on the ocular surface for a short duration of 2-3 minutes because of tear dilution and drainage. This is a limiting factor for decreasing drug-tissue interaction and increasing the frequency of administration. Ointment or gel formulation may improve persistence in the tear film, but may cause vision discomfort and is a source of dissatisfaction to patients[13].

### 2.4 Frequent Dosing and Poor Patient Compliance

Low bioavailability coupled with rapid loss of drugs requires a high frequency of dosages, especially in conditions such as glaucoma and dry eye syndrome. Frequent injection also affects compliance, in addition to the possibility of irritation and systemic uptake through the nasolacrimal duct[14].

### 2.5 Stability and Irritation Concerns

Chemical decomposition, microbiological contamination, and toxicity triggered by preservatives are universal weaknesses of conventional aqueous preparations. Preservatives such as benzalkonium chloride may cause irritation to the eyes and may impair the epithelium for an extended period; this has underscored the use of safe and stable forms for administration[15].

### 2.6 Need for Advanced Drug Delivery Platforms

The limits of existing ophthalmic formulations highlight the need for innovative, technology-driven drug delivery methods that can improve medication retention, penetration, and stability while preserving ocular comfort. Nanoemulsion-based platforms have emerged as a possible alternative for resolving these issues by controlling droplet size, improving solubility, and extending ocular residency[16].

## 3. Nanoemulsions as Ocular Drug Delivery Platforms

Nanoemulsions have gained considerable attention as better formulation platforms for drug delivery due to their ability to enhance the solubility, stability, and bioavailability of medicinal drugs. For ophthalmic use, nanoemulsions represent a reliable technical solution to overcome the limitations of current ocular drug delivery platforms[17].

### 3.1 Definition and Key Characteristics

Nanoemulsions: Nanoemulsions are kinetically stable dispersion systems that contain two immiscible components, mostly oil and water. The size of the particles in the nanoemulsion varies from 20 nm to 200 nm. This leads to optical transparency with a large interfacial area. Nanoemulsions include oil-in-water emulsions (W/O), water-in-oil emulsions (W/O), and bi-component systems based on the structure[18].

Oil-in-water nanoemulsions can be recommended for use in treating eye conditions due to their compatibility with the tear fluid, ease of use, and lack of effects on vision. Nanoemulsions can easily interact

**Table 1:** Comparison of Conventional Ophthalmic Formulations and Nanoemulsion-Based Systems

| Parameter | Conventional Eye Drops | Ophthalmic Nanoemulsions |
|---|---|---|
| Drug solubility | Limited, especially for lipophilic drugs | High solubilization of hydrophobic drugs |
| Particle size | Large (>1 µm) | Nanoscale (<200 nm) |
| Precorneal residence time | Short due to tear washout | Prolonged due to nanosize and formulation design |
| Ocular bioavailability | Low (≤5%) | Significantly enhanced |
| Dosing frequency | Frequent administration | Reduced dosing frequency |
| Drug protection | Minimal | Protects drug from degradation |
| Patient compliance | Moderate | Improved |

Comparative evaluation of conventional ophthalmic formulations and nanoemulsion-based ocular drug delivery systems.

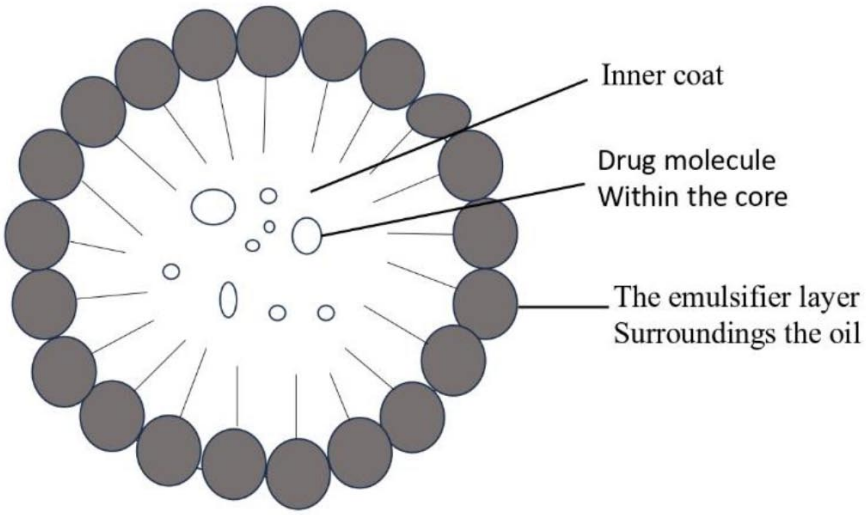


**Figure 2:** Structural Design of an Ophthalmic Nanoemulsion Platform

with tissues due to their small size[19].

### 3.2 Rationale for Ophthalmic Application

Using nanoemulsions in ophthalmic drug delivery is rational based upon their capacity to easily circumvent formulation barriers such as low solubility, rapid clearance, and poor corneal penetration difficulties, particularly for hydrophobic drugs, without compromising formulation clarity and comfort. Nanoemulsions can solubilise these types of drugs in the oil component while retaining formulation clarity[20].

In terms of engineering principles, the very small size of the droplet will result in minimal gravitational separation. In addition, the use of surfactants will reduce the interfacial tension, hence increasing the wetting properties of the eye surface and the absorption of the drug[21].

### 3.3 Mechanisms of Drug Delivery Enhancement

Nanoemulsion-based ophthalmic solutions improve medication delivery through numerous mechanisms[22].

- Lipophilic drugs are successfully integrated into the oil phase; hence, solubility is enhanced[7].
- Surfactants and co-surfactants help promote corneal permeability through temporary modification of epithelial barriers[18].
- Nanoscale droplets and viscosities offer improved tear retention properties[7].
- Controlled drug release: The diffusion process from the oil phase helps in releasing drugs in a controlled manner[8].

### 3.4 Translational Relevance

Nanoemulsions offer a balance between research and applications because of the flexibility of formulation, simplicity of sterilisation methods, and compatibility with manufacturing processes. Translational efficacy has been proven through the effectiveness of some nanoemulsion-based ophthalmic drugs that are currently available to the public[23].

## 4. Formulation Design and Components of Ophthalmic Nanoemulsions

The effective performance of an ophthalmic

**Table 2:** Formulation Components Used in Ophthalmic Nanoemulsion Platforms and Their Functional Roles

| Component | Examples | Functional Role |
|---|---|---|
| Oil phase | Castor oil, medium-chain triglycerides | Solubilization of lipophilic drugs |
| Surfactants | Polysorbate 80, lecithin | Reduce interfacial tension |
| Co-surfactants | PEG 400, propylene glycol | Improve emulsion stability |
| Aqueous phase | Purified water, buffer | Continuous phase |
| Mucoadhesive polymers | Chitosan, hyaluronic acid | Increase ocular residence time |
| Charge modifiers | Stearylamine | Enhance corneal interaction |

Common formulation components employed in ophthalmic nanoemulsion systems and their technological functions.

nanoemulsion requires rational formulation design and careful excipient selection to ensure ocular safety, physicochemical stability, and therapeutic efficacy. Each component within the nanoemulsion serves a particular purpose in terms of drug release, stability, droplet size, and comfort for the patient[24].

Common formulation components employed in ophthalmic nanoemulsion systems and their technological functions.

### 4.1 Oil Phase

In the case of lipophilic drugs, the reservoir effect mainly resides in the oil phase and significantly influences the release behaviour, permeability, and solubility. Oils incorporated into ophthalmic nanoemulsions should be chemically stable, biocompatible, and non-irritating[25].

Medium-chain triglycerides, castor oil, soybean oil, and mineral oil are commonly used oils. These oils facilitate the passage of pharmaceuticals through the lipoid-rich corneal epithelium and enhance the solubilization of poorly water-soluble drugs. Droplet size, viscosity, and long-term stability are directly affected by the type and amount of oil added[26].

### 4.2 Aqueous Phase

In the case of oil-in-water nanoemulsions, the aqueous component is the continuous phase and ensures tear fluid compatibility. To resist degradation caused by pH changes, it is a combination of buffering components and filtered water[27].

To maintain the pH in a range of 6.5 to 7.5, buffers like the phosphate or borate systems are often used. For achieving isotonicity and diminishing irritation to the eyes, agents like sodium chloride or glycerol/ mannitol may be added[28].

### 4.3 Surfactants

Surfactants are critical for the stabilisation of nanoscale droplets as well as for reducing interfacial tension within the oil and aqueous phases. The use of non-ionic surfactants is preferred when designing eye droplets due to their high tolerance to the eyes and lack of toxicity[29].

Lecithin, poloxamers, and polysorbates ( Tween 20 and Tween 80 ) are popular surfactants. The character and the stability of the emulsion mostly rely on the hydrophilic-lipophilic balance value of the surfactant; in the case of oil-in-water emulsions, the HLB value would be between 8 and 16[30].

### 4.4 Co-surfactants

Co-surfactants enhance the flexibility of the interfacial film and promote smaller droplet formation. Propylene glycol, polyethene glycol, and ethanol are popular cosurfactants[19].

Co-surfactants increase droplet uniformity and emulsification efficiency, but their concentration needs to be carefully adjusted to prevent irritation or formulation instability[31].

### 4.5 Stabilisers and Viscosity Modifiers

To enhance stability and the residence time of the preparation in the precorneal space, stabilisers and substances increasing the viscosity of the preparation may be employed. The polymers used include xanthan gum, Carbopol, and hydroxypropyl methylcellulose.

Chelating agents like EDTA can stabilise by binding trace metal ions and by increasing the efficacy of preservatives[32].

### 4.6 Preservatives and Antioxidants

When required, antioxidants and preservatives might be added to prevent the chemical damage of oxidation as well as microbial contamination. Tocopherol components or Ascorbic acid protect sensitive components from oxidation, and preservatives should be used at the lowest concentration feasible to prevent damage to the eyes[33].

## 5. Preparation Techniques for Ophthalmic Nanoemulsion Platforms

The preparation technique plays a significant role in ophthalmic nanoemulsion droplet size, stability, clarity, and scalability. The best method is decided by the formulation's composition, the energy needs, how accessible the equipment is, and its compatibility with ophthalmic medications[34].

### 5.1 Classification of Preparation Methods

The ways of preparation of nanoemulsions may be broadly classified as:

- High-energy methods that reduce the size of the resulting droplets through the use of mechanical forces[7]
- Low-energy processes, which rely on the physicochemical properties of the formulation constituents[7].

Both of these techniques are also employed in the formulation of ocular nano-emulsions.

### 5.2 High-Energy Methods

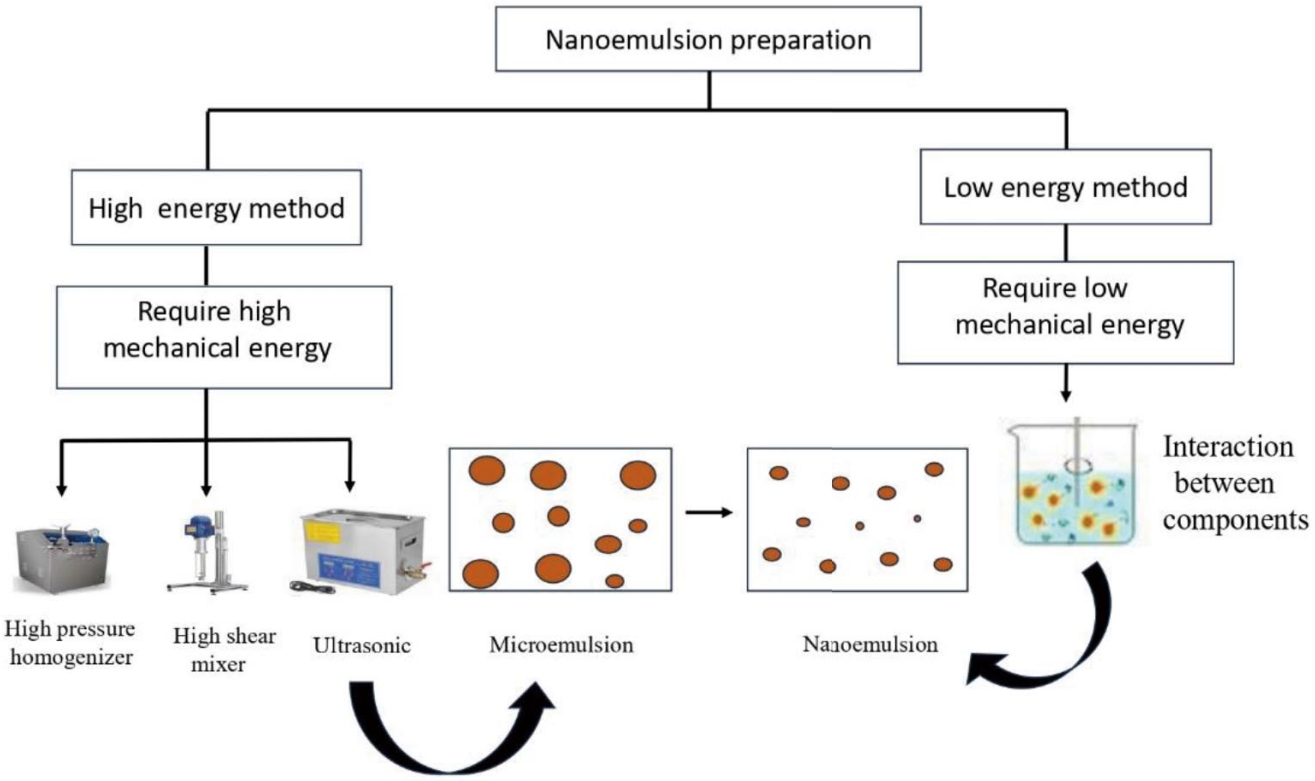


**Figure 3:** Preparation Techniques and Advanced Nanoemulsion Strategies

#### *5.2.1 High-Pressure Homogenization*

In high-pressure homogenization, the coarse emulsion is pushed at high pressure through a very small valve, which generates considerable shear force and turbulence that break the emulsion droplets into nanosized particles. High kinetic stability with a dispersion of droplets is achieved through this process[35].

It can be produced on a large scale; however, it might have limited applications in the case of thermolabile drugs owing to the requirement of heavy power inputs and homogenization cycles[7].

#### *5.2.2 Ultrasonication*

Higher frequency sound waves help in the production of cavitation during ultrasonication, thereby disrupting and reducing the size of the droplets. It is an easy and effective technique for preparation on a lab scale[7].

Even though ultrasonication is a fast emulsification technique, the limited scalability of the method and the localised production of heat can both be considered drawbacks[36].

#### *5.2.3 Microfluidization*

High-pressure interaction chambers are employed in microfluidization in order to produce highly homogeneous nanoemulsions by colliding fluid streams. A great control over size and dispersity can be achieved by this process[36].

In addition to this, its widespread industrial applications may be hindered by the cost of the equipment and energy required[37].

### 5.3 Low-Energy Methods

#### *5.3.1 Spontaneous Emulsification*

When the oil part with the surfactant and co-surfactant is mixed with the water part while gently stirred, the process of spontaneous emulsification occurs. The creation of nanosized droplets happens without the use of external mechanical energy.

Even if precise formulation composition adjustment is important, this method works best for heat-sensitive drugs and requires relatively simple equipment[38].

#### *5.3.2 Phase Inversion Techniques*

Phase inversion techniques produce nanoemulsions at low interfacial tension by changing the affinity of surfactants via modifications in temperature or composition. While these techniques present energy-efficient preparation, their process parameters need to be controlled with great care[39].

### 5.4 Selection Criteria for Ophthalmic Use

Ophthalmic nanoemulsions would require preparation

methods that yield droplets with consistent size, low contamination, and ease of sterilisation. These two methods involve a compromise on the level of scalability, efficiency, and safety to the eyes. Spontaneous emulsification and high-pressure homogenization methods fall into this category[40].

## 6. Stability Considerations and Evaluation Parameters

Because it impacts shelf life, safety, and therapeutic efficacy directly, stability is one of the most important quality aspects of the ophthalmic nanoemulsion systems. Nanoemulsions, though considered as kinetically stable systems, are thermodynamically unstable; an improperly designed nanoemulsion may degrade either chemically or physically after some time[41].

### 6.1 Physical Stability

Droplet size, size distribution, and interfacial properties are the key factors that control the physical stability of nanoemulsions. The reduced droplet dimensions show less trend toward coalescence or creaming, or gravitational separation. A restricted size dispersion ensures optical clarity and consistent performance[4], [7].

The most significant physical instability processes are flocculation, coalescence, creaming, and Ostwald ripening. These may produce phase separation and reduce formulation effectiveness. Such instability can be minimised by judicious choice of the oil phase, surfactant concentration, and viscosity modifiers[42].

### 6.2 Droplet Size and Polydispersity Index

Analysis of droplet size is of primary importance for estimating the efficiency of nano-emulsion systems. For ophthalmic nano-emulsions, generally homogeneous dispersion with a small particle size of < 200 nm and a polydispersity index of < 0.3 is desired. Larger particles may lead to stability-related problems or discomfort in the eye[43].

### 6.3 Zeta Potential

Through electrostatic repulsion, the importance of zeta potential in preventing aggregation by representing the charge on nanoemulsion particles can't be overemphasised; higher absolute levels of zeta potential improve physico-stability. Electrostatic interaction with the negatively charged conjunctival epithelium could help cationic nanoemulsions in enhancing precorneal retention in ophthalmic formulations[44].

### 6.4 Chemical Stability

The prevention of deterioration of medicine and excipients due to hydrolysis, oxidation, or photodegradation is defined as chemical stability. The common ways through which chemical stability can be maintained include the use of antioxidants, pH control, or protection from ultraviolet rays[44].

### 6.5 Microbial Stability

Ophthalmic nanoemulsions are prone to microbial contamination due to their aqueous composition. This mandates the need for sterilised preparation methods, preservatives, or preservative-free single-use systems to ensure microbiological safety[45].

### 6.6 Stability Evaluation Techniques

A number of analytical techniques, like droplet size analysis, zeta potential, centrifuge analysis, freeze-thaw cycle test, and accelerated stability studies at defined temperature and humidity conditions, are employed to estimate the stability of the ophthalmic nanoemulsions. These studies help predict the stability of the formulation[8].

## 7. Recent Technological Advances and Translational Applications

The creation of ophthalmic nanoemulsion vehicles has been made easier by the recent developments in formulation engineering and nanotechnology. Except preserving formulation safety, scaleability, and ease of use, modern formulation designs aim for enhanced ocular retention, penetration, and drug release[4].

### 7.1 Cationic Nanoemulsion Systems

Cationic nanoemulsions containing positively charged surfactants or polymers that interact electrostatically with the negatively charged ocular surface are being used. The interaction increases the duration of stay on the pre-corneal surface and the absorption of medication. These systems prove useful in the prolonged medication exposure that is associated with chronic diseases like glaucoma[18].

### 7.2 Mucoadhesive Nanoemulsions

In order to improve adhesion to ocular mucosa, mucoadhesive nanoemulsions rely on chitosan, hyaluronic acid, or carbopol. With this approach,

treatment efficacy is enhanced, and tear-mediated loss of medication is reduced. Mucoadhesive systems further cause less patient discomfort and administer fewer doses[46].

### 7.3 Stimuli-Responsive Nanoemulsion Platforms

Stimuli-responsive nanoemulsions aim to respond to physiological stimuli such as pH changes, temperatures, and enzymatic activity. The intelligent technology has shown improved eye therapy due to site-specific and controlled drug delivery systems. An example of stimuli-responsive nanoemulsion is thermosensitive gels that transform from a liquid to a gel after making contact with tear fluid[47].

### 7.4 Hybrid and Multifunctional Nanoemulsions

To further improve stability, dual drug loading, or targeted delivery, hybrid nanoemulsion systems combine nanoemulsions with other nanocarriers such as liposomes or polymeric nanoparticles. These versatile delivery platforms represent an innovative solution in the treatment of complex eye disorders[22].

### 7.5 Translational and Commercial Relevance

Several nanoemulsion-based ocular formulations have already shown practical usefulness by translating successfully from laboratory to clinical use. Biocompatible excipients available for its preparation and scalable production methods have made the path of commercialisation and regulatory acceptability easier[48].

## 8. Advantages and Limitations of Ophthalmic Nanoemulsion Platforms

Ophthalmic nanoemulsion platforms offer a number of technical and therapeutic advantages over traditional ocular formulations. On the other hand, various development and commercialisation issues regarding formulation complexity and stability need to be considered[8].

### 8.1 Advantages

Nanoemulsions increase the solubility of poorly soluble drugs by incorporating them into the oil phase, thereby easily delivering lipophilic drugs effectively. With a nanoscale droplet size, the surface area created is enormous, thereby improving the bioavailability of the drug by enhancing absorption[17].

Additionally, nanoemulsions have another important advantage in that their residence time in the precorneal area is longer, allowing them to remain in contact with the conjunctival/corneal surface and resist tear flow in the precorneal area. This increases patient compliance and ensures that drug release is controlled and that the frequency of dosing can be reduced[3].

In a formulation-based viewpoint, nanoemulsions are compatible with other excipients, are optically clear, and are easily sterilised. The adaptability of nanoemulsions opens a range of variability in terms of surface charge, viscosity, and release characteristics to adapt to the specific demands of therapy.

Additionally, nanoemulsion technology can also improve shelf life by protecting sensitive drugs from chemical degradation[4].

### 8.2 Limitations

Although nanoemulsions have great benefits, they actually exist as unstable systems that could potentially undergo Ostwald ripening, separation, or coalescence. It requires specific considerations for the components and storage conditions to stabilise the system[40].

Preparation methods of high energy might require specialised equipment and a higher production cost. If not properly optimised, excessive use of either the surfactant or the cosurfactant might pose the potential risk of eye irritation[11].

In addition, a great deal of stability, safety, and quality testing is required for approval and mass production of the nanoemulsion-based formulation, which may increase the time and expenses of the development process[22].

## 9. Future Perspectives and Research Directions

The pressing need for non-invasive, patient-friendly, and more efficacious eye drugs has fueled a continued effort towards developing nano-emulsion platforms for ocular drugs as innovative drug delivery systems. The future would likely focus on improving clinical translation, targeted efficacy, and robust formulation in upcoming research studies[3].

One area with potential is the preparation of intelligent or stimuli-responsive nanoemulsions capable of releasing drugs upon recognition of physiological stimuli such as pH, temperature changes, or enzymatic reactions. This can lead to more accurate drug delivery by reducing drug loss or adverse reactions[28].

Hybrid/multifunctional delivery systems, where nanoemulsion is coupled with another nanocarrier

such as polymeric nanoparticles or lipids, are also an emerging area. For cases involving complex eye conditions, these technologies may help achieve sequential release, multiple drug delivery, and enhanced therapeutic outcomes[49].

It is expected that advances in manufacturing technologies, including continuous processing solutions, as well as low-energy emulsification, could drive production cost savings and scalability for these injectable products. Another area where safety, regulatory acceptability, and biocompatibility improvements are welcome is in biodegradable excipients[50].

Prediction of formulation behaviour, as well as the acceleration of development timelines, may also benefit from the availability of computational modelling and artificial intelligence-based optimisation tools. A cross-disciplinary research effort may be required to maximise the potential of nanoemulsion platforms in the clinical arena[51].

## 10. Conclusion

The ocular delivery of medications has improved greatly with the development of ophthalmic nanoemulsion platforms. This is because ophthalmic formulations had limitations in medication solubilization and bioavailability that can be countered by a nanoemulsion formulation[8].

The various major concepts of design, formulation components, methods of preparation, stability aspects, as well as recent technological advancements applicable in ocular nanoemulsion systems have been underscored in the current work. These systems are also favoured for translational and commercial endeavours because of their versatility, scalability, and suitability for industrial-scale preparations[7], [8].

Though there are still concerns regarding long-term stability, formulation difficulties, and production costs associated with nanoemulsions, these limitations are currently being overcome by continuous advancements. Ophthalmic nanoemulsion platforms are expected to play an important role in the development of the next generation of eye drugs, offering better efficacy, safety, and compliance[52]

### Author Contribution Statement

All authors contributed to the conception, literature review, writing, editing, and final approval of the manuscript.

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### Conflict of Interest

The authors declared there is no conflict of interest.

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