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OPHTHALMIC NANOEMULSIONS: INVESTIGATING COMPOSITION, TECHNOLOGICALPROCESSES, AND QUALITY MANAGEMENT

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ABSTRACT

Nanoemulsions designed for ocular drug delivery present significant potential in pharmaceutical applications, attributed to their transparency at increased droplet volume fractions, enhanced bioavailability rates, and extended shelf life. These formulations are components of multiphase colloidal dispersions, characterized by a heterogeneous system that includes fine oil-in-water or water-in-oil dispersions, along with surfactants and co-surfactants, containing droplets within a size range of 20–600 nm, exhibiting a narrow size distribution. This review outlines the preparation, characteristics, evaluation, and application of nanoemulsions as a means for drug delivery in ocular treatments. It provides a comprehensive summary of the development of ophthalmic nanoemulsions that facilitate sustained release and prolonged therapeutic effects. The review discusses various methods, including both high-energy and low-energy techniques, in detail. Lastly, it briefly addresses the techniques for characterization, in-vivo evaluation, and applications.

1. INTRODUCTION

1.1Importance: Ophthalmic therapy primarily relies on the topical application of aqueous solutions containing active pharmaceutical ingredients (APIs), which are quickly removed after instillation by the nasolacrimal drainage system. The brief residence time of

conventional ocular formulations, such as eye drops, restricts drug penetration into the deeper layers of the eye to less than 5% of the administered dose, while other studies suggest that the actual absorbed ocular dose is even below one percent of the amount injected. This phenomenon occurs due to the rapid elimination of the drug caused by blinking and tearing, which is exacerbated by the use of nonphysiological concentrations of substances applied to the eye (e.g., in the form of eye drops or suspensions).

Additionally, factors such as the binding of drugs to tear fluid proteins, drug metabolism facilitated by enzymes in the tear fluid, and poor corneal permeability contribute to the low bioavailability of drugs following their topical application to the eye. Despite these challenges, a considerable number of commercial ophthalmic preparations are available solely in the form of droplets and suspensions.[1,2,3] The growing interest in the further development of topically applied ocular formulations stems from their convenient, noninvasive method of drug delivery, high patient minimal manufacturing costs and compliance. In addition to the formulation of traditional topical drug dosage forms for ophthalmic conditions (i.e., solutions, emulsions, suspensions, gels, and ointments), there is a rising interest in creating novel, advanced ocular carriers, such as implants, dendrimers, liposomes, nanomicelles, nanoemulsions, nanosuspensions, or in situ thermosensitive gels. Although commercially available nanocarriers remain scarce, formulations based on nanotechnology are currently viewed as the most promising systems for enhancing the delivery of APIs to the eye.[1,4,5,6]

1.2 Limitations of Conventional Ophthalmic Formulations: The eye is a remarkable organ, both anatomically and physiologically, containing a diverse array of structures that serve

independent physiological functions. This complexity introduces particular challenges for ocular drug delivery strategies. One notable challenge is absorption; similar to traditional eye drops, the ocular bioavailability after topical administration is low, typically between 3% and 4%, due to the eye's impermeable properties and its small surface area. Additional challenges include the poor solubility of drugs, as lipophilic medications cannot be incorporated into conventional aqueous eye drops. As a result, they must be formulated as suspensions. In terms of patient compliance, frequent applications of eye drops are often required to achieve the desired therapeutic drug levels. The demand for high tolerability or comfort further restricts formulation possibilities. In terms of excipient selection, there are a limited number of agents recognized in ophthalmology. Ultimately, delivering conventional eye drops to the posterior segment of the eye is not feasible.[7,8,9]

1.3 Advantages of Nanoemulsion Systems in Ophthalmic Delivery: Nanoemulsions improve the bioavailability of drugs, are non-irritating, non-toxic, and exhibit physical stability. They enhance drug absorption owing to their large surface area and small droplet size. Additionally, nanoemulsions can be developed in various formulations, solubilize lipophilic drugs, necessitate a reduced amount of energy, and facilitate taste masking.[7]

2. Fundamentals of Nanoemulsions

2.1 Definition and Characteristics of Nanoemulsions: Nanoemulsions can be described as a clear and stable emulsion of oil and water. They are primarily made up of the internal, dispersed, and external phases, or the dispersion medium. The surfactant and cosurfactant molecules are instrumental in the formation of nanoemulsions due to their ability to decrease interfacial tension and generate small particle sizes, which contribute to the stability of the preparations through repulsive electrostatic interactions and steric hindrance. Typically, surfactants are molecules that possess a bipolar structure consisting of both hydrophilic and hydrophobic segments. Nanoemulsions act as colloidal carriers for drug molecules, with droplet sizes typically ranging from 500-1000 nm, ideally from 100 nm to 500 nm. As a drug delivery system, they enhance therapeutic efficacy while minimizing adverse effects and toxic reactions associated with the administered drug.

Nanoemulsions can be differentiated from microemulsions based on their droplet size and physical stability characteristics. Microemulsions are isotropic and transparent systems that contain spherical droplets of either the water or oil phase (with diameters ranging from 10-100 nm) dispersed in an external oil or water phase, respectively. Microemulsions are

thermodynamically more stable than nanoemulsions, as the preparation of nanoemulsions necessitates the application of thermal and/or mechanical energy (i.e., mixing and heating), resulting in phase separation after a certain period following the preparation of nanoemulsions. This condition represents one of the most significant differences between microemulsions and nanoemulsions in terms of stability. The preparation of nanoemulsions can be divided into two main categories: high-energy methods, such as high-pressure homogenization and ultrasonication, and low-energy methods, such as phase inversion.[7]

2.2 Types of films surrounding dispersed globules in nanoemulsions

Monomolecular film: In the field of nanoemulsions, the existence of a monomolecular layer is one of the primary determinants of the emulsion's stability over time. When molecules of surfactants, which are substances with both hydrophilic (loving water) and lipophilic (loving oil) ends, align themselves at the interface between the water and oil phases, this film is created. By forming a single, well-organized layer of molecules or ions at the contact, these surfactants help to lower interfacial tension. Combining two different kinds of emulsifying agents is a creative tactic utilized in many formulations to enhance this effect even more. While a lipophilic emulsifier enters the oil phase, a hydrophilic emulsifier is supplied to the water phase.

Multimolecular film: Multimolecular films employ a somewhat different strategy than monomolecular films, which depend on individual surfactant molecules. Each scattered droplet is surrounded by a bigger molecule, usually a hydrated lyophilic colloids such as gum acacia, casein, or gelatin. These colloids accumulate into larger, more cushion-like layers as opposed to a single, compact layer. They increase the viscosity of the continuous (external) phase, which helps to promote stability even if they don't directly lessen surface tension.Droplets move more slowly in this thicker, more viscous liquid, which reduces the likelihood of collisions and mergers.

Solid particulate film: Using solid particle coatings is a third method of stabilizing emulsions. This technique uses small solid particles that sit at the oil-water interface, such as colloidal silica, metal oxides, or finely divided clays, in place of molecules or colloids. Although these particles have the proper surface characteristics to adhere firmly to the interface, they are insoluble in either phase. Once in position, they surround each droplet with a hard, armor-like shell. The droplets cannot physically come into contact with one another and merge (a process called coalescence) because of their structure.[10,11] Because of the

scientist who originally described it, this technique is frequently referred to as Pickering stabilization. It is especially prized for creating extremely stable emulsions without the use of artificial surfactants, which makes it appealing for "clean label" or environmentally friendly formulations in food, cosmetics, and even medications. Even under difficult circumstances like heat or shaking, the emulsion can stay stable for extended periods of time because the solid particles are securely attached at the interface.[7,12]

2.3 Mechanism of Drug Delivery through Ocular Barriers

Among the various categories of NEs, o/w NEs have proven to be an attractive option for ocular drug delivery, thanks to their specific characteristics. One of the more desirable characteristics of o/w NEs is (i) the continuous phase of water, which facilitates easy dilution with physiological eye fluids (the tears), (ii) the capacity of this type of NEs to encapsulate lipophilic medications in the oily phase, and (iii) the extended retention period guarantees the drug's deep penetration into ocular barriers by decreasing the contact angle between the droplets of the formulation and the cornea, this improved retention duration is accomplished, which increases the spreading coefficient and, consequently, the wettability and retention time of the administered NEs. The contact angle between the administered drops and the cornea is said to be decreased by surfactants, which are utilized in the formulation of ocular delivery systems.

NEs are extensively studied as a cost-effective formulation and a non-invasive method due to their ability to enhance drug bioavailability. Moreover, ophthalmic NEs offer several advantages: (i) prolonged pre-corneal retention time, (ii) high penetration ability, (iii) improved ocular bioavailability, (iv) enhanced drainage of drops through the cornea and reproducible quantities of the drug in the eye compared to gels or ointments, (v) the lipid interface present in NEs contributes to increasing the retention of ocular formulations in the conjunctival sac for an extended period, and (vi) by utilizing cationic NEs, it is possible to enhance the drug residence time through electrostatic interactions with the anionic surface of corneal mucin, enhancing the bioavailability of drugs in the eye. The interaction between cationic NEs and the mucin surface increases the residence time of NEs at the pre-corneal site; however, it is unlikely that the particles will penetrate the cornea due to the binding that occurs. In this context, it is to be expected that the drug delivery will take place through passive diffusion over time. The application of cationic surfactants in conjunction with anionic surfactants results in a synergistic effect, as demonstrated by the low critical micelle

concentration, improved surface activity, and increased tensioactivity. However, mixtures of cationic and anionic surfactants are likely to precipitate.

The eye is made up of three layers: a lipid layer, an aqueous layer, and a mucin layer. Each layer has a specific role; the lipid layer is tasked with preventing water evaporation and ensuring the lubrication of the eye and the surface tension of tears, the aqueous layer is homogeneously spread across the entire eye surface, and the mucin layer can modify the lipophilicity of the corneal epithelium. The interaction of nanoemulsions (NEs) with these layers ensures a longer retention time and promotes the spreading of the drop on the eye surface, thereby increasing the bioavailability of the drug encapsulated. The use of surfactants in the formulation of NEs enhances the wettability of the tear film and boosts the interaction of NEs with the mucin layer.[13]

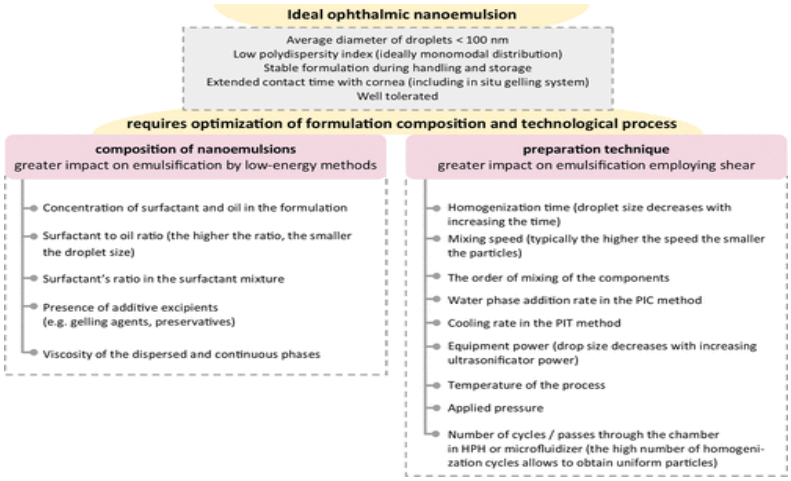


Figure 1. Optimization of the scientific procedures and composition needed to create the ideal ocular nanoemulsion.

2.4 Critical Parameters Affecting Stability and Performance: Flocculation is defined as theprocess in which small globules aggregate to form larger floccules. Creaming refers to thesettling or rising of floccules, resulting in a concentrated layer. The emulsion can be reconstituted upon agitation. Cracking denotes the permanent instability of a nanoemulsion, where the internal phase separates into a layer. In this instance, the emulsion cannot be reconstituted upon agitation, and the addition of surfactants may be beneficial. Miscellaneous instability signifies the instability of a nanoemulsion due to extreme temperature and light conditions. In this case, it is advisable to store the emulsion in a tightly sealed, colored container. Changes in the volume ratio of phases or the addition of electrolytes can cause

phase inversion, which changes the type of emulsion from water/oil to oil/water and vice versa.[7]

3. Composition of Ophthalmic Nanoemulsions

Ophthalmic oil-in-water nanoemulsions are typically regarded as dispersions of oil droplets within a water-based environment. As such, these formulations require careful selection of the aqueous medium composition and the oily phase components (i.e., the use of non-toxic, non-irritating, and pharmaceutically authorized oils) (Figure 1).

Figure 1. Optimization of the scientific procedures and composition needed to create the ideal ocular nanoemulsion. In a manner similar to ophthalmic drops, the necessity for isotonicity in ocular nanoemulsions requires meticulous attention to the desired pH, a specific buffering capacity, the incorporation of preservatives (antimicrobial agents), viscosity modifiers, and antioxidants. Moreover, to achieve nanosized uniform droplets of oils, a comprehensive optimization of both the composition and the concentration of surfactants and cosurfactants in the formulation is essential. The complexity inherent in ophthalmic nanoemulsion compositions demands extensive knowledge and experience in pharmaceutical formulations to develop stable products of pharmaceutical quality. In this section, we outline the detailed characteristics of the most commonly used components in ophthalmic nanoemulsions, which include oils, emulsifiers, surfactants, and cosurfactants, as well as additives that are employed to alter their pharmaceutical properties.

Ingredients for Ocular Nanoemulsion Formulation

TableNo. 1: Ingredients for Ocular Nanoemulsion Formulation.

Components	Examples
Phase of oil/lipid	Linseed oil, mineral oil, peanut oil, soybean oil, castor oil, coconut oil, corn oil, evening primrose oil, and olive oil DOTAP, Estasan, ethyl oleate, Eutanol G, Epikuron 200, isopropyl myristate, Capmul MCM, Capryol 90, Dermol M5, Labrasol, phospholipon 90H, oleic acid, lipoid S75, lipoid E80, lipoid S100, MCT, miglyol 812, triacetin, transcutol, and vitamin E
emulsifier/surfactant	derivatives of castor oil, phospholipids, polysorbates, stearylamine, natural lecithins derived from plants or animals, Span 20, Span 40, Span 80, Brij 35, Kolliphor RH60, Miranol C2M conc NP, Poloxamer 188, Poloxamer 407, Soluphor P, Tyloxapol, vitamin E-TPGS, Tween 20, Tween 40, and Tween 80
cosurfactant	Ethanol, glycerin, PEG 300, PEG 400, propylene glycol, polyene glycol, poloxamers, Miranol C2M conc NP, Soluphor P, triacetin, Transcutol P, Kolliphor EL, Kolliphor RH40
tonicity modifiers	xylitol, propylene glycol, sorbitol, mannitol, glycerol, and dextrose
additives	Propylene glycol, 1,3-butylene glycol, DOPE, DOTAP, lower alcohols (such as

Components	Examples
	ethanol), sugars such glucose, sucrose, fructose, maltose, cetylpyridinium chloride, benzalkonium chloride, and benzethonium poly(ethylenimine), poly(L-lysine), stearylamine, oleylamine, cetrimide, chloride, and cetalkonium chloride
antioxidant	Tocopherol and ascorbic acid

3.1 Oil Phase**:** Ophthalmic nanoemulsions are formulated with 5 to 20 wt % of oil or lipid as the scattered stage. A crucial factor in the creation of nanoemulsions is the choice of lipid phase., as the active pharmaceutical ingredient (API) is dissolved in an oil prior to its dispersion in an aqueous phase. The choice of oil phase for nanoemulsion formulation is frequently influenced by the solubility of the API in different oils. Moreover, the oil incorporated in the formulation must be well tolerated and compatible with the other excipients present in the nanoemulsion. The following compounds are commonly used to create ophthalmic nanoemulsions Long-chain unsaturated fatty acids, medium-chain triglycerides, glycerides, vegetable oils, and polyalcoholic esters of medium-chain fatty acids. The vegetable oils that are applied topically to the eye, such as Babchi seed oil, olive oil, peanut oil, soybean oil, castor oil, and jojoba oil. Miglyol 812, Captex 355, 200 or 8000, Witepsol, and Labrafac are examples of medium-chain triglycerides along with long-chain unsaturated fatty acids (oleic and octanoic acids), are also utilized as the inner phase of nanoemulsions. Among the polyalcoholic medium-chain and long-chain fatty acid esters, the following are employed: ethyl oleate, isopropyl myristate, and isopropyl palmitate. Additionally, triacetin and vitamin E are mentioned as ingredients in the nanoemulsion applied to the eye, and these two compounds can also act as humectants and antioxidants in ocular formulations. [1]

The formulation and maximum permissible concentrations of FDA-approved excipients utilized in the production of NEs are determined by the intended application and route of administration. The process of formulating NEs requires the use of components that are recognized as safe, which encompasses oils, surfactants, emulsifying agents, polymers, viscosity and density modifiers, as well as ripening inhibitors . The chemical stability of NEs can be improved through various methods, such as the incorporation of antioxidants or complexing agents, modifying the properties of the interfacial film specifically its strength, flexibility, charge, thickness, and chemical inertness and shielding them from different environmental stressors, including pH, oxygen, and temperature. Generally, NEs consist of 5 to 20% dispersed phase in an O/W emulsion, although the lipid concentration may reach

nearly 70%. Due to diminished optical and mechanical properties, lipid-based interfacial films are often thick, brittle, and translucent. Currently, the oil phase primarily comprises long-chain, medium-chain, and short-chain triglycerides, ethyl oleate, oleic acid, and vitamin E (tocopherol), either individually or in combination . A range of artificial lipids, such as Caproyl 90, triacetin, isopropyl myristate, oleic acid, palm oil esters, Labrafil M1944CS, Maisine 35-1, Miglyol 812, isopropyl palmitate, Captex 200, Captex 355, and Captex 8000, are commonly employed in the production of NEs . The selection of oil necessitates a balance between its drug solubilization capability and its ability to form a microemulsion. In the development of NEs using natural oils, an HLB value exceeding 10 typically yields O/W NEs, whereas a value below 10 generally results in W/O NEs .[14]

3.1.1 Types of Oils[1]

Table 2. Selected Properties of Lipids Used in the Formulation of Ocular Nanoemulsions

oil phase component	surface tension at 20 °C [mN/m]	dynamic viscosity at 20 °C [mPa·s]	density at 20 °C [g/cm^3]	refractive index [nD] at 20 °C
castor oil	39.0	950–1100	0.955–0.968	1.477–1.479
corn oil	31.6 at 23 °C	31 at 40 °C	0.915–0.918	1.474–1.476
coconut oil	33.4	39 at 30 °C	0.917	1.448–1.450 at 40 °C
soybean oil	25	50.09 at 25 °C	0.916–0.922 at 25 °C	1.470–1.478
evening primrose oil	-	-	0.926 at 25 °C	1.479
linseed oil	-	-	0.928–0.933	1.479–1.481
liquid paraffin	35 at 25 °C	110–230	0.827–0.89	1.476–1.480
olive oil	31.9 at 23 °C	80	0.914	1.467–1.471
peanut oil	31.3 at 23 °C	68–77	0.912–0.920	1.460–1.472
oleic acid	32.79	26 at 25 °C	0.895	1.458 at 26 °C
isopropyl myristate	29.7	5–7 at 25 °C	0.850 at 25 °C	1.434
glyceryl triacetate	36.5	17.4 at 25 °C	1.160 at 25 °C	1.429
Miglyol 812	25–33	-	0.93–0.96	1.449–1.451
transcutol	31.8 at 25 °C	3.85 at 25 °C	0.999 at 25 °C	1.427
alpha tocopherol	-	-	0.947–0.951	1.503–1.507
ethyl oleate	32.3 at 25 °C	3.9 at 25 °C	0.870 at 25 °C	1.451
Eutanol G	-	58–64	0.835–0.845	1.453–1.455

[a]TDS - Technical Data Sheet.

3.1.2 Role in Drug Solubilization and Bioavailability: Drug Solubilization (Making the Medicine "Fit" to Travel) Most eye drops are just watery solutions. But if the medicine (the drug) is like grease or butter (hydrophobic/lipophilic), it just clumps up and won't dissolve in the water. The oil's job is to solve this:The Perfect Solvent: The oil acts like the drug's best friend it loves the greasy medicine and easily dissolves it. You're now putting the drug into an oily droplet instead of trying to force it into the water.High Loading Capacity: Since the drug is so happy in the oil, you can pack a lot more of it into each tiny droplet. The oil is a much better container for the medicine than water is. Boosting Bioavailability (Sneaking Past the Eye's Guard) The eye is designed to protect itself; it has a protective, lipid-rich outer layer (the cornea) that acts like a wall, and tears quickly wash away anything that lands on the

surface. Getting medicine through that wall and having it stick around is what we call improving bioavailability.

The "Grease Loves Grease" Trick: The oil droplet, carrying the medicine, is also greasy. When it touches the lipid-rich surface of the cornea, the barrier doesn't see a foreign invader it sees something familiar (a lipid). This helps the tiny oil droplet gently melt or sneak its way into the corneal layer, pulling the drug along with it.

The Sticky Effect: The oily nature of the nanoemulsion helps it hang out on the surface of the eye for a longer time, like a drop that's harder to wash away. This longer contact time means the drug has more minutes to cross the barrier before it's washed away by tears, giving you a much stronger and more effective dose.[15]

3.2 Surfactants and Co-surfactants: The significant components of nanoemulsions that influence their physical stability are surfactants and cosurfactants, which facilitate the successful emulsification of oil into the continuous phase. The surfactant must be soluble in the continuous phase of the nanoemulsion, ensure a very low interfacial tension, and prevent the coalescence of oil droplets during the homogenization process. The HLB values of a few chosen surfactants employed in ocular nanoemulsions are shown in the table. To produce a 20 wt % o/w nanoemulsion, a surfactant concentration of 5−10 wt % is essential. In preparations intended for application to the eyeball, low-toxicity nonionic emulsifiers are predominantly used. This group comprises the following: hydrogenated castor oil derivatives (Kolliphor EL, Kolliphor RH40, Kolliphor RH60), polysorbates (Tween), sorbitan esters (Span), poloxamers (Pluronic F68, Pluronic L-62TM, Pluronic F127), polyoxyethylene fatty acid esters (Emulphor), Tyloxapol, Solutol HS 15, Vitamin E-TPGS, and polyethylene glycol succinate.[1]

Table 3. HLB Value of Commonly Used Surfactants in Ocular Nanoemulsion.

surfactant	HLB value
Brij 35	16.9
Span 20 (sorbitan monolaurate)	8.6
Span 40 (sorbitan monopalmitate)	6.7
Span 80 (sorbitan monooleate)	4.3
Tween 20 (PEG-20 sorbitan monolaurate)	16.7
Tween 40 (PEG-20 sorbitan monopalmitate)	15.6
Tween 80 (PEG-20 sorbitan monooleate)	15.0
Kolliphor RH60 (Polyoxyl 60 hydrogenated castor oil)	15−17
Poloxamer 188 (Pluronic F68)	29.0
Poloxamer 407 (Pluronic F127)	22.0
Tyloxapol	13.0
Soluphor P	12−14

Surfactants attach at the interface between the dispersion medium and droplets, forming a flexible monomolecular film. This action leads to a reduction in γ and surface free energy, thereby lowering the likelihood of droplet coalescence and ensuring the stability of NEs. The addition of a cosurfactant or auxiliary emulsifying agents, such as medium- or short-chain alcohols and polyols, can serve as thickening agents and aid in stabilizing the emulsion. These additives decrease γ and enhance fluidity at the interface in NEs. By improving the mobility of hydrocarbon tails, miscibility is increased, which enhances oil diffusion in this region. The preparation of NEs is significantly affected by the selection and concentration of an appropriate surfactant, which facilitates rapid adsorption and stabilization of the formed nanoscale droplets, achieving pressures ranging from 10 to 100 atm. Because it may swiftly rebuild if broken or disturbed, the surfactant's contribution to the interfacial film's flexibility is also essential. Finally, the dispersed phase must remain highly insoluble in the dispersion medium to prevent Ostwald ripening. The cosurfactant assists in maintaining the flexibility of the emulsifier film, enabling it to smoothly deform around each droplet by minimizing interactions between polar head groups and hydrocarbon chains. Short to medium-chain alcohols are frequently employed as effective cosurfactants.[16]

3.3 Aqueous Phase and pH Adjusters: The formulation of the water phase may also play a role in determining droplet size and the stability of the nanoemulsion. When formulating nanoemulsions, it is important to evaluate the pH value and the presence of electrolytes and ions, as these elements may affect the size of the dispersed phase and the stability of the formulation.47,48 The water phase that is predominantly used in ophthalmic preparations is pharmacopoeial water for injections or buffered saline solution.[1]

3.4 Drug Molecule Considerations: Lipophilicity and Solubility: This represents the most vital consideration in the selection of a drug for a nanoemulsion. Lipophilic (Poorly Water-Soluble) Drugs: Nanoemulsions are optimally designed for drugs that exhibit high lipophilicity (high Log P value) yet have poor solubility in water. The oily phase within the nanoemulsion functions as a large-capacity reservoir for dissolving the drug, thereby significantly augmenting the overall drug load and therapeutic amount that can be delivered to the eye.[17] Small Molecules: The corneal route of absorption is particularly suited for small molecules (typically those with a molecular weight below extbf{500} Da). Nanoemulsions facilitate the delivery of these small lipophilic drugs by presenting them in a highly permeable oily droplet. Larger Molecules: While the cornea is preferential to small

molecules, the conjunctival/scleral route allows for greater permeability to larger, hydrophilic molecules (for instance, peptides or small proteins). NEs can still be applied for larger drugs by integrating penetration enhancers into the formulation or by designing the ext{NE} to be absorbed via the conjunctiva. Corneal Permeation: The cornea features both lipophilic (epithelium, endothelium) and hydrophilic (stroma) layers. Generally, drugs are absorbed most effectively when they are in their unionized (lipophilic) form. Formulation pH: It is necessary for the NE to be formulated to a comfortable {pH} (around 7.4, similar to tear fluid). Consequently, the drug's pKa must be evaluated to enhance the unionized fraction at the physiological pH of the eye. Nanoemulsions present a significant advantage by allowing the drug to be dissolved in the oil phase, thus avoiding the strict solubility restrictions imposed by the {pH} of the aqueous environment.[18]

3.5 Stabilizers and Preservatives: The selection of stabilizers and preservatives in ophthalmic formulations is essential because of the eye's sensitivity. Continuous efforts are being made to utilize highly effective but less irritating ingredients. Certain nanoemulsions can be developed as preservative-free single-dose units, thereby removing the necessity for these agents, particularly in the treatment of chronic conditions.[1]

3.6 Stabilizers

Table 4. Stabilizers used in Opthalmic Nanoemulsions

Component	Role	Examples in Ophthalmic Nanoemulsions
Surfactants	Form a stable film around the dispersed phase (oil or water) droplets, reducing interfacial tension and providing steric or electrostatic repulsion to prevent coalescence and phase separation.	**Non-ionic:** Polysorbates (e.g., Tween 80), Poloxamers (e.g., Pluronic F68), Polyoxyethylene hydrogenated castor oils (e.g., Cremophor RH40). **Cationic:** Cetalkonium Chloride (CKC) - often used to impart a positive charge for enhanced corneal residence time.
Co-surfactants	Work synergistically with surfactants to further reduce interfacial tension and increase the fluidity of the interfacial film, which helps in droplet size reduction and stability.	Short- to medium-chain alcohols (e.g., ethanol, isopropanol), Propylene glycol, Polyethylene glycols (PEGs).
Other Stabilizers	May be added to modify viscosity and increase physical stability.	**Viscosity Enhancers:** Carboxymethylcellulose (CMC), Hydroxypropyl methylcellulose (HPMC), Carbomers.

Table 5. Preservatives Used in Opthalmic Nanoemulsions

Component	Role	Examples in Ophthalmic Nanoemulsions
Preservatives	Provide antimicrobial activity to maintain the sterility of the product throughout its shelf life and period of use.	**Quaternary Ammonium Compounds: Benzalkonium Chloride (BAK)** (widely used, but known to cause ocular surface irritation with long-term use). **Oxychloro-complexes:** Stabilized Oxychloro Complex (e.g., Purite), which breaks down upon contact with the tear film into inactive components (water, oxygen, and sodium chloride). **Alcohols/Others:** Chlorobutanol.

Preservatives

3.7 Other Auxiliary Substances: The formulation of ophthalmic products requires the addition of various excipients that enable their application to the eyeball, including preservatives, buffers, osmotic pressure agents, viscosity modifiers, humectants, or gelling agents. The preservatives commonly used in ocular nanoemulsions include benzalkonium chloride (0.01−0.1% w/v), cetrimide (0.01−0.1% w/v), chlorocresol, parabens, and alcohols (such as chlorobutanol and phenoxy-2-ethanol). If buffering is deemed necessary, citrate, phosphate, or borate buffers are typically employed. The osmotic pressure of ophthalmic nanoemulsions is adjusted by incorporating mannitol (0.15−0.3% w/v), glycerol (2.5−5% w/v), sorbitol, propylene glycol, and dextrose. [1,19,20]

4. Formulation Strategies and Design

4.1 Formulation Challenges in Ophthalmic Nanoemulsions

The eye is a distinct organ both anatomically and physiologically, and it consists of a diverse array of structures that have independent physiological roles. This complexity inherent in the eye poses particular challenges for ocular drug delivery strategies.One of the primary challenges is absorption; akin to traditional eye drops, the ocular bioavailability after topical application is low, at approximately 3% to 4%, due to the eye's impermeable properties and its small surface area. Other challenges include insufficient drug solubility. Lipophilic drugs cannot be included in standard aqueous eye drops. Thus, they must be formulated as suspensions. With respect to patient compliance, frequent instillations of eye drops are generally necessary to achieve the desired therapeutic level of the drug. High requirements for tolerability or comfort limit the formulation choices. In terms of excipient selection, there are few agents recognized in ophthalmology. Finally, the administration of conventional eye drops to the posterior segment of the eye is not possible.[7]

5. Technology and Manufacturing Processes

Based on the energy consumption during the technological process, nanoemulsion formulation techniques can be categorized into low-energy and high-energy methods. Low-energy techniques encompass spontaneous emulsification, solvent evaporation, the phase inversion temperature (PIT) method, and the solvent displacement method. In contrast, high-energy methods consist of high-energy mixing (high-energy stirring), high-pressure homogenization (HPH), microfluidization, membrane emulsification, ultrasonication, and jet homogenization.

5.1 Spontaneous Emulsification or Self-Emulsifying Methods: The spontaneous emulsification technique is the most frequently cited method for the formulation of ophthalmic nanoemulsions. This technique involves the gradual addition of the water phase to a mixture of oil combined with chosen surfactants and cosurfactants at room temperature while stirring gently. The preparation of nanoemulsions using the spontaneous emulsification technique unfolds in three distinct stages: first, two phases are established, one being a uniform lipid phase that includes oil and a lipophilic surfactant in a water-miscible solvent, and the second phase is composed of water and a hydrophilic surfactant. The second stage sees the immediate formation of an oil-in-water emulsion as the lipid phase is added to the water phase with continuous magnetic stirring, and lastly, in the third stage, evaporation at lower pressure eliminates the water-miscible solvent.

High-Energy Methods

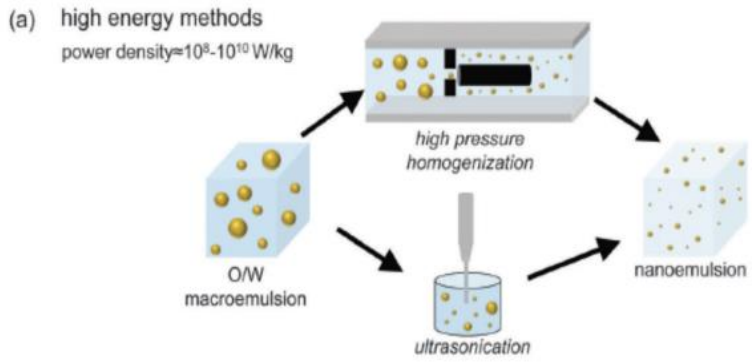


Figure 2. High-Energy Methods used for manufacturing of ophthalmic nanoemulsions.

High-energy techniques facilitate the regulation of the size of dispersed phase particles through various technological processes, including homogenization conditions (such as time and temperature), as well as the characteristics and composition of the initial mixture. To formulate nanoemulsions, several distinct methods have been utilized, including high-pressure homogenization, microfluidization, and ultrasonication. The substantial energy input necessary for these techniques may lead to a localized rise in temperature within the formulation, rendering them unsuitable for the homogenization of thermolabile compounds like retinoids and macromolecules (such nucleic acids, proteins, or enzymes). Moreover, the significant energy consumption and the need for specialized equipment contribute to the increased production costs associated with nanoemulsions.

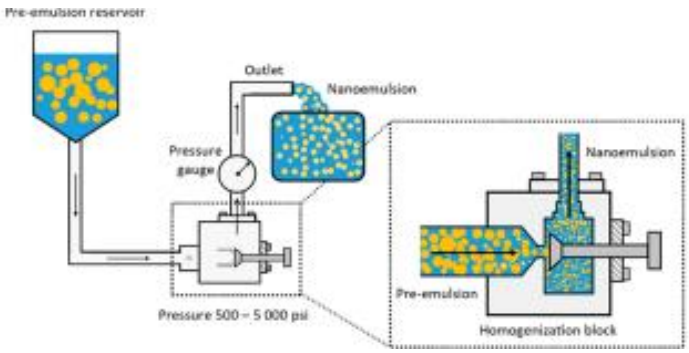
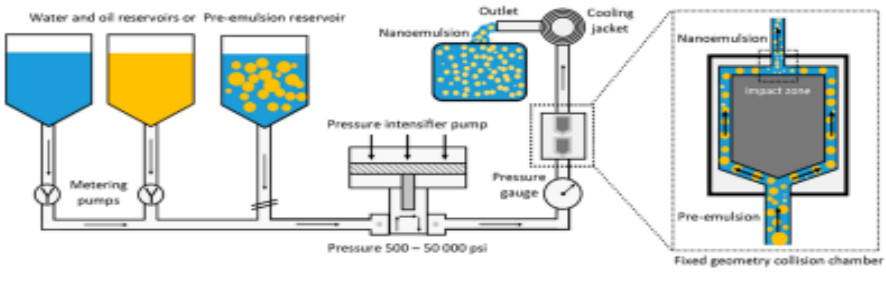


Figure 3. High-Pressure Homogenization Method.

5.1.1 High-Pressure Homogenization: The typical protocol for the formulation of o/w nanoemulsions utilizing high-energy methods initiates with the homogenization of a combination of oil, surfactant, and water via a high-shear mixer to create a macroemulsion (pre-emulsion). In the following step, the macroemulsion is subjected to homogenization with a high-pressure homogenizer, which utilizes hydraulic shear, intense turbulence, and cavitation. In a high-pressure homogenizer, the two immiscible liquids, along with emulsifiers, are forced through a piston gap that is a few microns in height under high pressure (between 500 and 5000 psi or 35 to 445 bar), resulting in a uniform nanoemulsion with a particle diameter of the dispersed phase of around 100 nm. The mixture is generally processed several times through the homogenizer, and the ultimate droplet size is contingent upon the number of homogenization cycles and the formulation's composition. The key advantages of high-pressure homogenization in the industrial manufacturing of nanoemulsions are its high efficiency, scalability, and the repeatability of the process. The significant limitations associated with this method are the adverse coalescence process, which can be alleviated by the addition of an excess of surfactants, and the relatively low oil phase content that permits the formulation of oil in water nanoemulsions, which shouldn't be more than 20% of the mixture.



FigNo. 4: The microfluidization method.

5.1.2 Microfluidization: The microfluidization method serves as a technique for the preparation of nanoemulsions, relying on the interaction of two immiscible phases introduced from opposite microchannels, which collide in the impact zone of a high-pressure positive displacement pump under pressures ranging from 500 to 20,000 psi (approximately 35 to 1380 bar) and can reach up to 50,000 psi The reduction of droplet size in the microfluidizer is achieved through a combination of cavitation, severe turbulence, impact, attrition, impingement, and hydraulic shear. The droplet size of the dispersed phase produced by this method is contingent upon the pressure applied, the number of passes through the device's chamber, and the formulation's composition. Since microfluidization eliminates the need for pre-emulsification, it is also acknowledged as a direct emulsification method. Instead, the dispersed phase is injected directly into the continuous phase through the microchannels, providing an advantage over the high-pressure homogenization method. From a mechanical perspective, a microfluidizer acts as a static mixer with no moving parts, allowing for the production of small droplets of the dispersed phase with a narrow size distribution. Furthermore, microfluidization is suitable for both laboratory and industrial-scal formulations.

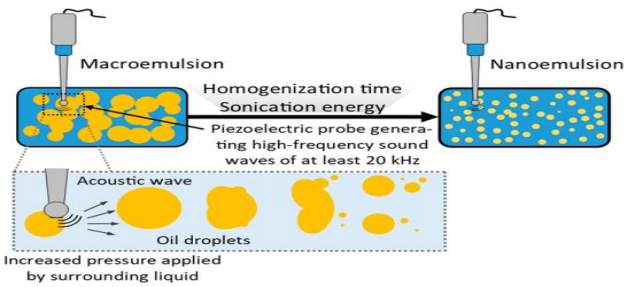


Figure 5. Ultrasonication Method.

5.1.3 Ultrasonication: In the context of ultrasonic emulsification, the energy needed to disintegrate the droplets of the inner A sonicator probe (sonotrode) that produces high-frequency sound waves of at least 20 kHz delivers the emulsion's phase. Sonotrodes incorporate a piezoelectric quartz crystal that can expand and contract in the solution depending on the alternating voltage applied. As the ultrasonic probe's tip makes contact with the liquid, it generates mechanical vibrations that induce cavitation (i.e., the creation and collapse of voids in the liquid triggered by a local reduction in pressure to or below the vapor pressure of the liquid). The forces of expansion generated by the sound wave during the expansion phase instigate the disruption of the liquid structure. Cavitation causes shear strains, shock waves, turbulence, and microjets (acoustic jets) to occur in the fluid medium.

5.2 Low-Energy Methods

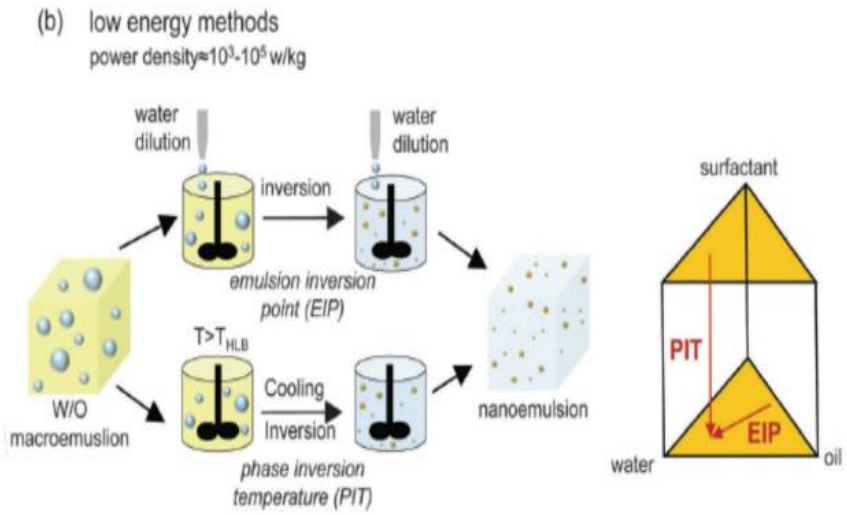


Figure 6. Low Energy Methods Used for Manufacturing.

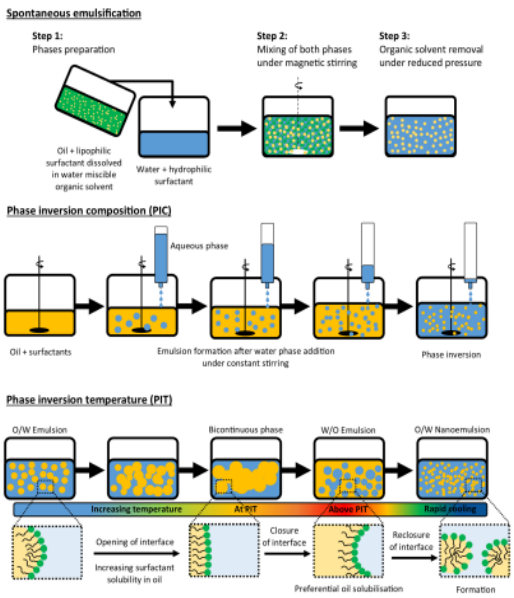


Figure 7. (a) Spontaneous Emulsification (b) Phase Inverse of Opthalmic Nanoemulsions Composition (c) Phase Inversion Temperature.

5.2.1 Spontaneous Emulsification: Spontaneous Emulsification or Self-Emulsifying Methods: The method of spontaneous emulsification is the most frequently cited technique for the preparation of ophthalmic nanoemulsions. In this method, the water phase is added incrementally to the mixture of oil combined with chosen surfactants and cosurfactants at room temperature while stirring gently. The process of preparing nanoemulsions using the spontaneous emulsification method unfolds in three stages: first, two phases are created, which include a homogeneous lipid phase made of oil and a lipophilic surfactant in a water-

miscible solvent, and a second phase consisting of water and a hydrophilic surfactant. In the second stage, an oil-in-water emulsion is formed instantaneously as the lipid phase is introduced into the water phase with continuous magnetic stirring. Finally, in the third stage, the water-miscible solvent is removed through evaporation under reduced pressure. As a result, nanodroplets of oil are dispersed in an aqueous solution of water and hydrophilic surfactant. The formulation of nanoemulsions using the self-emulsification method takes advantage of the chemical energy released during the dilution of the inner phase with a continuous phase, generally at a constant temperature without any phase changes during emulsification. The formation of nanoemulsions via the spontaneous emulsification method is a two-step process. Initially, a bicontinuous microemulsion is formed at the interface between the organic and aqueous phases, which then disorganizes, leading to the spontaneous generation of fine oil droplets. The bicontinuous microemulsion can only be formed within a specific range of surfactant-oil-water ratios, which depend on the components of the nanoemulsion. The use of mild stirring may enhance the breakdown of the bicontinuous phase due to improved mixing of surfactant, oil, and water molecules.

5.2.2 Emulsification and Solvent Evaporation Methodology: Ophthalmic nanoemulsions can also be created using the spontaneous emulsification methodology, which follows the evaporation of a water-miscible organic solvent that contains the oil phase. In this process, a blend of solvent and oil at room temperature is introduced into the aqueous phase where a surfactant is present. After mixing, the organic solvent quickly diffuses into the water, leading to the dispersion of the oil in the form of nanosized droplets. At the conclusion of the process, the solvent is evaporated from the emulsion under reduced pressure. The subsequent step involves adding the organic phase to the aqueous phase with moderate agitation to form a nanoemulsion, followed by the removal of the organic phase and part of the water phase under reduced pressure at a temperature below 35 °C. This method can produce a homogeneous nanoemulsion with droplets averaging around 200 nm in diameter.

5.2.3 Phase Inversion Technique. The low-energy methods also include the phase inversion technique, where the inner phase is dispersed within the continuous phase due to changes in the formulation composition (phase inversion composition method, PIC) or temperature (PIT). The phase inversion point can be defined as the moment when the surface tension between the water and oil phases of the emulsion (approximately 10 μN/m) allows for the spontaneous formation of nanosized droplets without any energy input. In the phase inversion

methods, one can distinguish between transient or irreversible inversion of the system. Transient phase inversion can be triggered by changes in temperature or electrolyte concentration, which in turn affects the HLB of the formulation. Irreversible phase inversion occurs simultaneously at a constant temperature and is triggered by a change in the emulsion's composition. Transient inversion takes advantage of the differences in solubility of emulsifiers in water or oil at various temperatures, which induces the conversion of a water-in-oil (w/o) emulsion to an oil-in-water (o/w) emulsion, or the opposite. In the first phase of this process, a macroemulsion is heated to a temperature that corresponds to the phase inversion point of the formulation, followed by a rapid cooling of the mixture to 25 °C in the second phase. The rise in temperature results in the opening of the surface film at the interface between the two phases, leading to their inversion, which is then quickly followed by a decrease in temperature that re-establishes the interfacial structure of the droplets. The dispersed nanoemulsion droplets remain stable over an extended period due to their surfactant coating. Generally, the effective mutual solubility of water, oil, drug substances, and surfactants facilitates the phase transition in this method. However, the primary limitation of this method is its restricted applicability to thermolabile substances.

5.3 The instability of nanoemulsions: Flocculation can be described as the process where small globules aggregate to form larger floccules.Creaming is defined as the settling or rising of floccules, which creates a concentrated layer. The emulsion can be reconstituted through agitation. Cracking represents a permanent instability in a nanoemulsion, where the internal phase separates into a layer. In this case, the emulsion cannot be reconstituted upon agitation, and the addition of surfactants may be beneficial. Other techniques for preparing nanoemulsions, including bubble bursting, evaporative ripening, and microfluidization, are also employed31658 DHAHIR et al. Nanoemulsions as Ophthalmic Drug Delivery. Miscellaneous instability indicates the instability of a nanoemulsion due to extreme temperature and light exposure. In this scenario, it is recommended to store the emulsion in a tightly sealed, colored container. Phase inversion occurs as a result of variations in the volume ratio of phases or the addition of electrolytes, leading to a change in the emulsion type from water/oil to oil/water, and vice versa.[1]

5.4 Regulatory and GMP Guidelines for Ophthalmic Products: The European Pharmacopeia does not feature any specific chapters dedicated to the manufacture of ophthalmic preparations; however, the monograph on eye preparations includes a concise section on

production (01/2008:1163). In contrast, the United States Pharmacopeia provides guidance through USP general chapter Ophthalmic Ointments <771>. This chapter covers several parameters and characteristics related to the preparation of ophthalmics, such as added substances, containers, metal particles, and leakage .Looking ahead, performance tests (dissolution and drug release) for ophthalmic preparations will be incorporated into a new general chapter titled Ophthalmic Preparations Performance Tests <1771>, which is expected to be published in 2015. Additionally, there are numerous guidelines available regarding aseptic filling, which is the conventional method for preparing ophthalmic dosage forms. Aseptic processing is heavily regulated, and there is extensive guidance available in the US Code of Federal Regulations (CFR 21, including CFR 21 Sub-part C (211.42)), FDA documents, and the EU GMP "Rules and Guidance for Pharmaceutical Manufacturers and Distributors". However, regulatory guidance is limited to the essential principles anticipated in pharmaceutical manufacturing. Certain elements are subject to interpretation or are part of current Good Manufacturing Practice (cGMP). For aseptic filling, the main sources of guidance are:

• FDA Guidance for Industry 2004 on Drug Products Produced by Aseptic Processing
• USP 1116 Microbiological Control and Monitoring of Aseptic Processing Environments
• ISO 13408 Aseptic Processing of Healthcare Products
• ISO 14698-1.Cleanrooms and associated controlled environments–Biocontamination Control': Part 1: 'General principles and methods
• ISPE Baseline Guide to Sterile Manufacturing Facilities.[21]

6. Description and Assessment

6.1 Physicochemical Evaluation

6.1.1 Visual Examination and Transmittance Testing: The visual evaluation of nanoemulsions is executed under diffused daylight on both white and black backgrounds, which aids in assessing the clarity of the formulations being tested. The clarity of the formulation is determined by the size of the dispersed phase droplets in relation to the wavelength of light ($380\ nm < \lambda < 780\ nm$); a formulation may be clear if the droplet diameter is <50 nm, or it may be cloudy if the droplet size is between $50\ nm < d < 200\ nm$. The extent of light scattering in nanoemulsions is influenced by the quantity of the dispersed phase, the size of the droplets, and the refractive index of the dispersed particles. Two types of measuring

devices are utilized to evaluate the optical properties of nanoemulsions: UV−vis spectrophotometers and colorimeters.

6.1.2 Particle Size Distribution of Nanoemulsions. The size of the dispersed particles, which ranges from 1−500 nm, considerably boosts the stability of the emulsion after preparation and enhances the contact area of the API with the surface of the eyeball. Consequently, this may lead to improved absorption of the drug upon application. Additionally, the reduction in the dispersed phase droplet size in nanoemulsions increases the penetration of the drug substance into the deeper layers of the eye, including the aqueous humor. The droplet size and polydispersity of the nanoemulsions are measured at room temperature through dynamic light scattering (DLS), photon correlation spectrometer (PCS), or microscopic methods.

6.1.3 Other Evalaution Test

- Zeta potential: The measurement of charge repulsion between oil nanodroplets is known as the zeta potential. One of the most important factors affecting the stability of distributed systems is this variable. A steady nanoemulsion is facilitated by a strong zeta potential. The electrical potential variations between the stationary layer of fluid close to the dispersed oil nanodroplets and the dispersion medium affect its value. The optimal range for zeta potential is +20 mV to +40 mV.
- Refractive index: The refractive index can be measured with an Abbes refractometer. This index is important for assessing any potential vision impairment or discomfort after administering an eye drop. The refractive index for tear fluid is between 1.340 and 1.360. Eye drops should maintain refractive index values not exceeding 1.476. Percentage transmittance The percentage transmittance can be quantified using a spectrophotometer at a specific wavelength, with distilled water as the blank. A nanoemulsion is considered transparent if its percentage transmittance is greater than 99%.
- pH: A pH meter can be used to measure the pH, and nanoemulsions should have a pH of 7.2±0.2 for maximum comfort. Depending on the amount of time the solution is in contact with the eye surface, its composition, the volume instilled, and its buffering ability, a pH difference between the implanted solution and the tear pH might cause discomfort and irritation. However, because the tear pH can adjust to physiological levels, a nanoemulsion with a changeable pH can be tolerated in many cases where the preparation is unbuffered or only weakly buffered; the acceptable pH range for preparations is between 3.5 and 8.5.

- Surface tension: The tear film is compromised when the surface tension of eye drops is considerably lower than that of the lachrymal fluid (40-50 mN/m). [1,22,23]

6.1.4 Rheological measurement: The impact of an ophthalmic preparation on the normal behavior of tears should be kept to a minimum; a less viscous preparation results in limited blinking pain and enhanced tolerance,the viscosity of eye drops shouldn't be more than 20 mPa s, even if a more viscous preparation can increase the drug's residence time and ocular bioavailability.

- Osmolality: Lacrimal fluid osmolality is typically between 280-293 mOsm/kg. However, when the eye is open, the osmolality can range from 231-446 mOsm/kg due to evaporation. If the osmolality of a solution is below 100 or above 640 mOsm/kg, it will irritate the eye. However, the osmolality is restored within 1-2 minutes following the instillation of a non-isotonic solution.
- Ocular irritation study: These studies should verify that the corneal integrity and structure are preserved.
- Dilution test: This procedure confirms that the stability of an ophthalmic nanoemulsion remains unaffected after dilution; it involves the addition of the aqueous phase to the nanoemulsion withoutexperiencing any complications.
- Cytotoxicity test: This assessment evaluates the effects of a formulation on a particular culture of mammalian cells. [7]

6.2 Stability Studies

Nanoemulsions are inherently thermodynamically unstable and can experience flocculation, coalescence, Ostwald maturation, and phase inversion during storage, potentially leading to phase separation. Consequently, the final formulation of the nanoemulsion must maintain both physical and chemical stability under ambient conditions throughout production, storage, transport, and application. Changes in the characteristics of nanoemulsions, caused by the alteration of pH, ionic strength, temperature, and mechanical forces, may result in their destabilization and variations in particle size distribution and morphology, which, in turn, can affect how chemicals are released from the dispersed phase. Techniques for evaluating stability can either rely on tracking emulsion systems over a predetermined period of time (emulsion aging method) or enable a quick assessment of the formulation's durability (accelerated stability testing methods). The long-term stability analysis of nanoemulsions

allows for real-time stability assessment as it does not employ conditions that hasten the decomposition of the system. The formulations are maintained at different specific temperatures for three to six months as part of the long-term stability analysis. During this time, the nanoemulsion's characteristics namely, its viscosity, pH, refractive index, average droplet size, and drug substance content are assessed at various points in time. Stable formulations are identified by the absence of phase separation, a clear appearance, and only minimal variations in physicochemical parameters. Accelerated stability evaluations, such as the centrifugal method and thermal tests, are also employed to determine the stability of nanoemulsions. These techniques can be used to expedite the development of robust formulations during preformulation studies within a stringent time frame.[22,23]

6.3 In-vivo Evaluation: In Vivo Studies. A high concentration of ingredients in a nanoemulsion may cause irritation to the ophthalmic tissues due to the selection of an unsuitable emulsifier or oil. This irritation can manifest as excessive tearing, conjunctival hyperemia, corneal swelling, or cloudiness. In vivo tissue examination involves the inspection of eye structures (i.e., cornea, conjunctiva, and iris) after the administration of the formulation being tested. Despite the anatomical and physiological differences across species, such as blinking frequency and eye surface permeability, albino rabbits (e.g., New Zealand rabbits) are frequently used to evaluate the safety of ocular drug substances. This is because their large corneal surface and conjunctival areas allow for easy monitoring of any changes that occur in the eye following the application of the formulation being assessed. Additionally, the iris of rabbits is free of pigment, which facilitates the observation of blood capillaries. The Draize test or its modified equivalents, such as the Low Volume Eye Test (LVET test), can be used to assess the safety profile of a nanoemulsion formulation following administration.

- Eye Irritation Tests: Low Volume Eye Test (LVET Test) and Draize Eye Test. The Draize eye irritation test is traditionally conducted to assess the irritation potential of pharmaceutical and cosmetic formulations in the eyes of rabbits. In this test, 0.1 mL of the formulation being evaluated is introduced into the conjunctival sac or applied directly to the cornea of the rabbit. Typically, the left eye is treated as a control. A realistic dosage of ocular formulations administered in a single administration is represented by the 0.01 mL of the formulation injected to the eye in the modified Draize test (also known as the LVET test). The assessment of changes in the eye is usually performed at 1, 24, 48, and

72 hours after the application of the formulation, and if necessary, at 7 and 21 days later. The state of the eyeball is evaluated through direct observation, utilizing either a magnifying glass or a slit lamp. The changes that occur are categorized using the modified Friedenwald and Draize scale.The changes noted include hemolysis, redness, and inflammation. A total eye irritation index score exceeding 2 in each category signifies a strong irritant effect. [1,24,25]

- API Biodistribution into the Eye Compartments: To evaluate the biodistribution of a drug substance across various compartments of the eyeball and into the bloodstream, At predetermined intervals, Akhter et al. applied single drops of cyclosporin A nanoemulsions to the albino rabbits' eyeballs. Then, using the ultraperformance liquid chromatography method (UPLC), the authors determined the concentration of the API in the biological samples (aqueous fluid, conjunctiva, cornea of the eyeball, and blood from the marginal ear vein) in order to examine the distribution of the material in the aqueous fluid and the eye structures.[26,27,28]

7. Quality Control and Regulatory Aspects

Quality control assessments for ophthalmic formulations are grounded in pharmacopoeial standards and further elaborated by the internal product specifications deemed crucial for ensuring product quality as defined by the manufacturer. These assessments encompass the evaluation of pH, tonicity, viscosity, clarity, ocular compatibility, sterility, among other factors. The parameters must be routinely tested not only as part of batch evaluations but also throughout the process (as intermediate stability data) and at the conclusion of the stability program.

Additionally, regulatory agencies often have supplementary expectations regarding product specifications. Consequently, it is vital to collaborate closely with regulatory bodies during the formulation of innovative drug delivery systems that must adhere to regulatory requirements and guidelines. Identifying critical quality attributes (CQAs) that are directly linked to product quality, efficacy, and toxicity is essential, as these attributes should underpin the quality control measures for the product. CQAs for ophthalmic nanoemulsions may encompass factors related not only to the technological process, such as particle size and size distribution, but also the purity and stability of the active pharmaceutical ingredient (API) and key excipients post-processing and during storage, in addition to sterility and preservative

effectiveness for multidose products. Moreover, industrial quality control entails testing the final product, which is the nanoemulsion in its container. This necessitates additional tests to evaluate the integrity of the packaging, withdrawal content, interactions between the nanoemulsion components (API and excipients) and the packaging material, as well as the assessment of weight changes during storage.[1]

8. Current Marketed Ophthalmic Nanoemulsions[29,30]

Table 6. Current Marketed Opthalmic Nanoemulsions.

Ophthalmic Nanoemulsion Product	Active Ingredient / Type	Indication
Restasis	Cyclosporine A	Dry eye disease
Ikervis	Cyclosporine A	Keratitis
Durezol	Difluprednate	Postoperative ocular inflammation
Xelpros	Latanoprost	Open-angle glaucoma
Cyclokat	Cyclosporine A	Dry eye disease
Systane Complete	(Lubricant)	Relieve dryness of the eye
Cationorm	Medical device	Dry eye disease
Verkazia	Cyclosporine	Vernal keratoconjunctivitis

9. Prospects and Difficulties for the Future

Future Prospects

The future role of ophthalmic nanoemulsions primarily involves addressing the poor bioavailability linked to traditional eye drops, which frequently lose more than 90% of the medication due to physiological barriers.

- Enhanced Bioavailability and Efficacy: The droplets' nanoscale, which is typically between 20 and 200 nm, increases their surface area and improves their interaction with the corneal and conjunctival epithelia, which improves medication absorption and, consequently, increases their effectiveness.
- Targeting the Posterior Segment: Future investigations are focused on employing nanoemulsions, often by altering their surface characteristics (for instance, cationic nanoemulsions), to bypass the blood-retinal barrier for non-invasive delivery to the retina and vitreous humor, addressing serious conditions such as age-related macular degeneration (AMD) and diabetic retinopathy.
- Reduced Dosing Frequency: Their capacity to function as a drug reservoir and extend the drug's residence time on the ocular surface facilitates sustained release, which can diminish the necessity for frequent daily applications, significantly enhancing patient adherence.

Current Challenges

In spite of the potential, numerous substantial technical and regulatory challenges must be resolved for ophthalmic nanoemulsions. Ensuring long-term physical stability continues to pose a significant challenge...

- Toxicity and Excipient Concerns: Surfactant Toxicity: Nanoemulsions necessitate a relatively high concentration of surfactants and co-surfactants to maintain droplet stability. It is crucial to ensure that these excipients are non-irritating, non-toxic, and compatible with the sensitive ocular surface.
- Ocular Irritation: The final formulation must possess suitable viscosity, pH, and tonicity to prevent irritation, reflex tearing, and rapid clearance following instillation, as these factors can undermine the advantages of the nano-carrier.
- Regulatory Framework: The regulatory pathway for innovative nanotechnology-based drug delivery systems is still developing and remains complex. An inadequate or incomplete regulatory framework can prolong development time and increase costs, thereby obstructing clinical translation.[1,31,32]

10. CONCLUSION

Due to the advancement of nanoformulations, which are favored over the systemic route, there has been a notable enhancement in the treatment of ocular diseases. The preparation of nanoemulsions necessitates the application of heating and/or mixing, while phase separation may take place post-preparation. Consequently, nanoemulsions exhibit lower thermodynamic stability compared to microemulsions. The translucent nature of nanoemulsions is attributed to their droplet size, which is less than 100 nm. This diminutive droplet size results in nanoemulsions being classified as thermodynamically unstable dispersions. A substantial concentration of surfactants is essential, leading to the formulation's sticky consistency. After storage, a yellowish hue and rancid smell may develop due to the presence of phospholipids, which are typically employed to stabilize nanoemulsions. Nanoemulsions can be readily produced through systems that may or may not depend on energy. In contrast to conventional ocular solutions and suspensions, which possess significant bioavailability and necessitate frequent dosing, nanoemulsions hold great promise in improving bioavailability and decreasing the frequency of drug administration.

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