REVIEW PAPER

A review of novel nanoformulations for treatment of dry eye disease and ocular surface inflammation

Alireza Nouralishahi[1,2], Navid Fazlinejad[3], Mohamad Saeid Hoseinzade Firozabadi[4], Saman Mohammadzadehsaliani[5], Rand Otbah Farqad[6], Haider Radhi Saud[7], Hadis Kheradjoo[8*]

[1] Isfahan Eye Research Center, Isfahan University of Medical Sciences, Iran
[2] KIMS Hospital, Oman
[3] Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Rehabilitation Research Center, Department of Optometry, School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran
[5] Ophthalmology Department, Buraimi Hospital, Buraimi, Oman
[6] Department of Dentistry, Al-Noor University College, Nineveh, Iraq
[7] College of Health and Medical Technology, National University of Science and Technology, Dhi Qar, Iraq
[8] Laboratory Department, Buraimi Hospital, Buraimi, Oman

ABSTRACT

Dry eye disease (DED) is a multifactorial condition frequently encountered in ocular disorders. DED not only causes ocular discomfort but also leads to damage to the cornea and conjunctiva. The topical route of drug administration is commonly used for treating ophthalmic diseases; however, its major limitation is the low ocular drug bioavailability, which typically amounts to less than 5%. This limitation arises due to the multiple permeation barriers between the tear film and the inner layers of the cornea, which hinder the achievement of therapeutic drug concentrations in ocular tissues. Researchers have significantly advanced in developing practical and safe drug delivery systems to address these challenges. These innovations have improved the penetration of medications through ocular barriers, enabled targeted delivery to specific cells and tissues, and enhanced the retention time, solubility of hydrophobic drugs in aqueous solutions, and overall bioavailability. Encapsulating drugs within nanoparticles has protected against degradation, further improving therapeutic efficacy. This review aims to explore various nanoformulations (e.g., liposomes, niosomes, suspensions, and emulsions) designed to enhance the ocular bioavailability of topically administered medications. A comprehensive DED inflammation overview focuses on the disease's etiology, clinical manifestations, and therapeutic approaches. It is anticipated that the development of advanced medication delivery systems will lead to improved management of DED shortly. The advancements discussed here may pave the way for creating novel, highly effective, and essential ocular nanosystems.

Keywords: *Dry eye syndromes, Drug delivery systems, Pharmaceutical formulations, Nanotechnology*

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ABBREVIATION

DES: Dry eye syndrome; DED: Dry eye disease; KCS: Keratoconjunctivitis sicca; HCL: Hydrogen chloride; HPMC: *Hydroxy Propyl Methyl Cellulose*; PVA: *Polyvinyl alcohol;* TQ: Thymoquinone; *TFOS: Tear Film and Ocular Surface Society*; PRK: Photorefractive keratectomy; LASIK: Laser in situ keratomileusis; ROS: Reactive oxygen species; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; GSDMD*: Gasdermin-mediated inflammatory cell death*; BAC: Benzoalkonium chloride; MT: Melatonin; TAT: Trans-activator of transcription; SpA: Società per Azioni; Vitamin E TPGS, or simply TPGS: D-α-tocopheryl polyethylene glycol succinate; FDA: Food and Drug Administration; O/W: Oil-in-water; MBA: Mean breakup area; QoL: Quality of life; PG-HPG: Propylene glycol-hydroxypropyl guar; OSDI: ocular surface disease index; DMPC: 1,2-dimyristoyl-sn-glycero-3-phosphocholine; MGD: Meibomian gland dysfunction; CI: Conjunctival injection; CS: Corneal staining; LLT: Lipid layer thickness; CE: Cationic emulsion; SUVs: Small unilamellar vesicles; LUVs: Large unilamellar vesicles; MLVs: Multilamellar vesicles; TFH: Thin film hydration; EI: Ethanol injection; EV: Ethoniosomal vesicles; IOP: Intraocular pressure. LE: Loteprednol Etabonate; DoE: Design of Experiments.

* *Corresponding author:* Hadis Kheradjoo, Professor, Laboratory Department, Buraimi Hospital, Buraimi, Oman. E-Mail address: hadiskheradjoo12@gmail.com.

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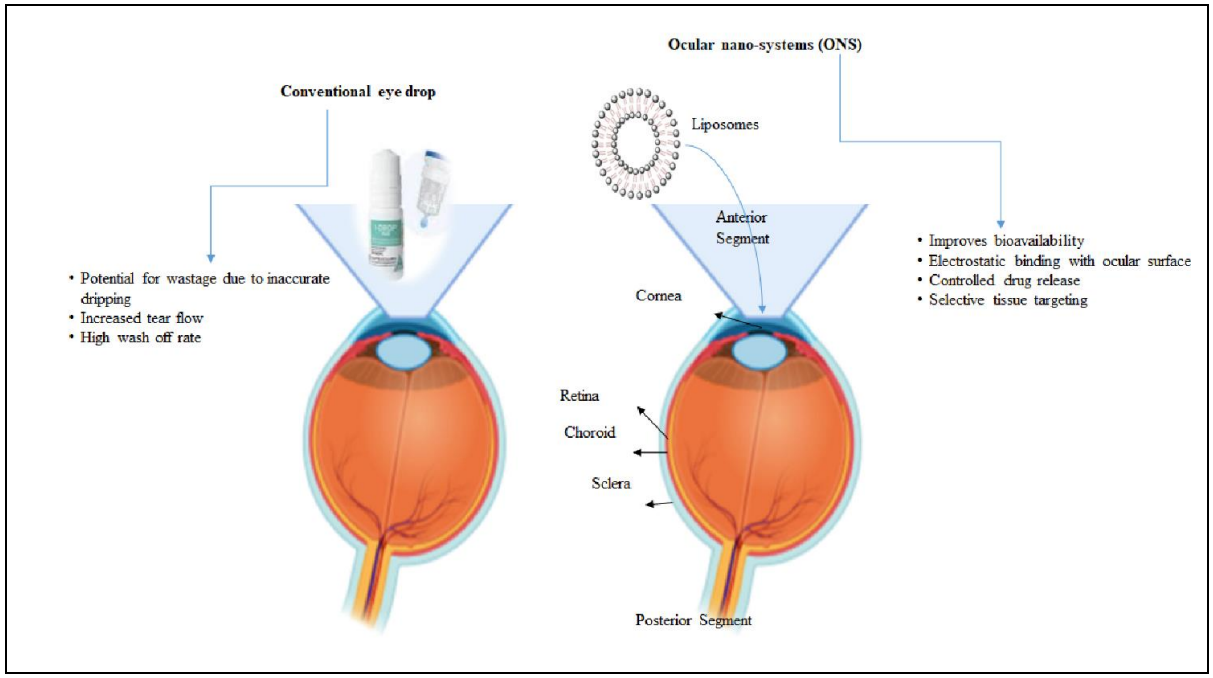
GRAPHICAL ABSTRACT



INTRODUCTION

Dry eye syndrome (DES), also referred to as keratoconjunctivitis sicca (KCS) or dry eye disease (DED), is a multifactorial ocular surface pathology that causes discomfort and visual disturbances [1]. With a prevalence ranging from 5% to 50%, DED is one of the most common ocular surface disorders, affecting millions of individuals worldwide [2, 3]. DED leads to a reduction in the size of epithelial cells, an increase in their thickness and density, and an enhancement in epithelial cell turnover [4]. Several risk factors have been identified, including advanced age, female gender, Sjögren syndrome, androgen insufficiency, thyroid disorders, menopause, smoking, and the use of certain medications such as antihistamines, antidepressants, anxiolytics, and oral contraceptives [5]. Moreover, the prevalence of DED has increased due to the prolonged use of contact lenses, environmental factors such as high pollution levels or low humidity, and excessive use of computers and smartphones [6]. Epidemiological studies report varying prevalence rates of DED, ranging from 21% to 30% in China, 12.5% to 21.6% in Japan and the Republic of Korea, and approximately 7% in Europe and North America. In some regions of Russia, the incidence ranges from 40% to 55% [7-11].

Inflammation of the ocular surface is closely linked to epithelial dysfunction [4]. Numerous therapies targeting inflammatory pathways have been investigated since their role in dry eye disease was recognized. Current treatments include tacrolimus, corticosteroids, cyclosporine A, autologous serum, and tetracycline derivatives. Additionally, many anti-inflammatory drugs are under development or undergoing clinical trials. These agents work by restoring the secretion of a healthy tear film and alleviating symptoms through the inhibition of inflammatory mediator expression on the ocular surface [12].

Approximately 90% of marketed ophthalmic formulations utilize topical drug delivery to the anterior eye segment, typically in the form of conventional dosage forms such as ointments (17.4%), suspensions (8.7%), and solutions (62.4%). However, due to the reduction in retention time caused by lacrimal secretions and the limited permeability across the corneal epithelium, topical administration (e.g., eye drops) results in poor ocular bioavailability (<5%). As a result, these barriers lead to a loss of approximately 95%, with the remaining drug encountering the corneal epithelial barrier [13].

Researchers have developed nanotechnology-based nanomedicines and novel nanosystems (e.g., liposome and niosome, suspensions, and emulsion) to enhance drug bioavailability in the eye [14-16].

In certain studies, eye drops of poorly soluble medications are often formulated as suspensions. For example, Reb ophthalmic solutions have successfully restored the microstructure responsible for tear stability, effectively treating mucin-induced ocular epithelium degradation and tear deficiency [17]. In addition, a study demonstrated that flurbiprofen axetil, a

nanoemulsion, exhibited significantly higher effectiveness than the free drug in solution in a rabbit model of endotoxin-induced uveitis [18]. Furthermore, Alotaibi et al. studied niosomes filled with mucoadhesive and biodegradable ocular inserts for the prolonged pilocarpine hydrochloride (HCl) release. They found that drug-free ocular inserts combining two polymers—hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA)—outperformed single polymer-based inserts (HPMC or PVA alone). The resulting niosomes exhibited excellent entrapment efficiency (49.7% ± 7.0) and an average particle size of 325.7 ± 3.5 nm [19]. Additionally, phospholipid-based liposomes are considered an excellent option for drug delivery due to their superior biocompatibility, stability, and adaptability [20]. For instance, liposomes have encapsulated the macromolecular protein lactoferrin and the antioxidant astaxanthin. In vivo pharmacodynamics studies have demonstrated that these liposomes offer positive therapeutic effects against DED [7]. Furthermore, Landucci et al. showed that liposomes provide slow and sustained drug release while reducing the toxicity of Thymoquinone (TQ) seen at higher doses [21]. In a separate study, Chen et al. employed the film hydration method to create cationic liposomes containing tacrolimus. Due to its anti-inflammatory properties and ability to support epithelial cell repair, the resulting formulation enhances the concentration of FK506 in the cornea, prolongs its retention on the ocular surface, and demonstrates positive therapeutic effects [22].

As highlighted in the preceding content, nanotechnology-based drug delivery systems hold significant promise in the development of novel treatments for DED [23]. This study underscores recent advancements and emphasizes the critical role of nanotechnology in creating innovative therapies. Ongoing research brings hope for more effective anti-inflammatory treatments with fewer side effects; however, ensuring these nanomaterials' safety and evaluating toxicity profiles remain paramount. Researchers in the pharmaceutical and academic sectors focused on DED therapeutics will find this information particularly relevant.

Dry eye syndrome

The Tear Film and Ocular Surface Society (TFOS) defines dry eye as a multifactorial condition associated with tear film instability and ocular surface inflammation, which is characterized by underlying ocular surface damage, high osmotic pressure, and inflammation of the ocular surface, ultimately leading to discomfort and visual disturbances [24]. In individuals with dry eyes, the reflex responsible for blinking and the secretion of supportive tear substances is impaired. Symptoms of dry eye include decreased tear film break-up time, photophobia, excessive tearing, a foreign body sensation in the eye, ocular burning, grittiness, dryness, excess debris in the tear film, increased conjunctival redness, refractive impairment, and ocular sensitivity. Keratitis is also a common manifestation. One or more of these symptoms may be present in affected individuals [26,25].

Numerous factors can potentially influence a patient's dry eye symptoms, including hormone levels in the blood, autoimmune conditions such as Sjögren's syndrome and systemic lupus erythematosus, and ocular surgeries like photorefractive keratectomy (PRK) or laser in situ keratomileusis (LASIK). In addition, various drugs, environmental factors, visual tasks (such as computer use), ocular fatigue, contact lens wear, mechanical factors like corneal sensitivity, partial lid closure, and surface irregularities (e.g., pterygium) can all play significant roles. Lid irregularities, such as ptosis, entropion, ectropion, and pinguecula, are also significant contributors. Furthermore, environments with low humidity, particularly those leading to dehydration, can exacerbate or trigger dry eye symptoms [4, 27, 28].

The delivery of nonsteroidal and anti-inflammatory drugs

Different strategies are employed in treating ocular diseases based on the patient's specific condition and the underlying cause of the disease. These strategies include the use of topical or systemic anti-inflammatory medications, such as corticosteroids [29, 30] and nonsteroidal anti-inflammatory drugs (NSAIDs) [30], immunosuppressive therapies with agents like methotrexate or cyclosporine (CsA) [31], and prescribing antiviral or antibacterial drugs when infectious causes are involved. Surgical interventions may sometimes be necessary to address more challenging instances. Early diagnosis of the condition and the timely implementation of appropriate management strategies are crucial to minimize unpredictable outcomes [32].

Applying topical steroidal formulations on the ocular surface, such as cyclosporine A, glucocorticoids, and corticosteroids, has demonstrated anti-inflammatory effects, relief from dry eye symptoms, and improvements in ocular surface pathology. However, topical eye drops are limited due to potentially severe side effects, including glaucoma and cataracts.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce pain, inflammation, and fever [33, 34].

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen, salsalate, diclofenac, meloxicam, nabumetone, and amfenac (AF), are frequently prescribed for treating inflammatory conditions by inhibiting COX-2. However, their undesirable side effects primarily result from the inhibition of COX-1. As a consequence, many NSAIDs are associated with an increased risk of severe allergic reactions, heart attacks, strokes, stomach ulcers, and bleeding, particularly when taken at high doses over extended periods. While selective COX-2 inhibitors, such as celecoxib and rofecoxib, are available to minimize side effects by explicitly targeting COX-2, both non-selective and selective COX-2 NSAIDs have limited efficacy in repairing ROS-induced damage at inflammatory sites [34].

As a result, these molecules have been identified as potential targets for nanotechnology-based drug delivery strategies [35]. Researchers have also explored nanosome-based drug delivery systems for NSAIDs as a promising approach to treating ophthalmological conditions. For example, liposomes and niosomes have been proposed for the topical delivery of NSAIDs. Chitosan-coated liposomes demonstrated a prosperous enhancement in precorneal retention of diclofenac compared to control groups that received the medication in solution or non-coated liposomes, followed by instillation in healthy rabbits. Similarly, sodium diclofenac and opioid naltrexone were encapsulated in niosomes. Some researchers employed the calcium acetate gradient method to encapsulate diclofenac in liposomes and achieved an impressive encapsulation efficiency of 97%. Animal studies showed that this treatment increased the retinal-choroidal drug concentration (up to 1.8 times higher) compared to conventional diclofenac eye medications [36].

Barriers related to ocular drug delivery

Mild dry eye patients may find relief with artificial tears alone for ocular drug delivery. However, moderate-to-severe cases often require the use of single or multiple drugs. In this context, researchers are focusing on enhancing drug delivery through well-designed systems that are tailored to specific drug properties and disease conditions [37-39].

Tear film hyperosmolarity triggers the excessive production of reactive oxygen species (ROS), damaging biomolecules (including DNA, proteins, and lipids) and leading to ocular surface inflammation. This inflammation exacerbates tear evaporation, perpetuating a “vicious cycle of inflammation” [40, 41]. Some researchers have studied animal models of dry eye and hypertonic conditions in human corneal epithelial cells. They found that ROS in the corneal epithelium increased the expression of NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) at both the gene and protein levels. This, in turn, led to the secretion of IL-1β, resulting in ocular surface inflammation. Notably, activation of the NLRP3 inflammasome triggered the proteolytic cleavage of gastrin-mediated inflammatory cell death (GSDMD), leading to pyroptotic cell death via activation of caspases (1, 4, 5, and 11) [42, 43]. Various stimuli, including ROS production, chloride ion efflux, and mitochondrial dysfunction, contribute to NLRP3 inflammasome activation and subsequent pyroptosis. A commonly used preservative in eye drops, benzalkonium chloride (BAC), induces ROS generation, DNA damage, and mitochondrial dysfunction, ultimately leading to the death of corneal epithelial cells [40, 44, 45]. On the other hand, eye drops frequently used to treat ocular diseases suffer from limited bioavailability, significantly reducing their effectiveness. As a result, there is a need for improved interventions to address ocular diseases more effectively.

The treatment of dry eye disease and ocular surface inflammation with novel nanoformulations

The development of dry eye involves a complex pathogenesis, including immune-inflammatory responses, apoptosis, and neurogenic inflammation, among other factors. The interaction of these elements amplifies their effects, contributing to the onset and progression of dry eye. Current studies suggest that a hyperosmotic tear film and immune-mediated inflammation of the lacrimal gland are key contributors to the continuous progression of dry eye [46]. Several cytokines, including IL-6, IL-17, IL-1β, tumor growth factor-γ (TGF-γ), and TNF-α, have been implicated in the disease's pathogenesis. Medications remain the primary approach to treatment, with ongoing ophthalmologic research focused on this area. Available topical treatments include autologous serum, cyclosporine A (CsA), artificial tears, tetracycline derivatives, and corticosteroids [47]. Artificial tears temporarily relieve mild dry eye symptoms and help improve the tear film but do not address the underlying inflammation. Dry eye treatment aims to reduce ocular surface inflammation (OSI), promote the development and healing of ocular surface epithelial cells, and

enhance lacrimal gland function. In this context, a novel therapeutic strategy involving nanotechnology to target ocular surface inflammation holds promise [47].

The term "nanotechnology" was first used in 1974 by Norio Taniguchi to describe the manipulation of submicron particles, while Richard Feynman introduced the concept of nanostructures in 1959 [48]. A magnitude of 10^{-9} is referred to as "nano." According to the British Standards Institution, nanotechnology involves designing, characterizing, manufacturing, and using systems, devices, and structures by manipulating their size and shape at the nanoscale. Nanoparticles are a broad class of materials that include particulate substances with at least one dimension smaller than 100 nm [49]. The surface-to-volume ratio increases as the particle size is reduced to the nanoscale. The main benefits of nanoparticles are as follows: (i) The particle size and surface characteristics can be tailored to meet the specific needs or convenience of the user. (ii) Nanoparticles facilitate the controlled release and improved bioavailability of medications. (iii) Using nanoparticles as a delivery base can enhance drug absorption. (iv) Nanoparticle-based targeting ligands enable precise site targeting with relative ease [50-53]. Appropriate nanoparticle-based formulations can be developed by effectively managing and understanding these processes [54-56]. For example, certain nanoformulations (liposomes, niosomes, suspensions, and emulsions) used for drug delivery have improved adhesion to the ocular surface, thereby minimizing drug washout caused by blinking. This enhancement allows the drug to pass through the ocular barrier more effectively and reach its target while extending its residence time on the ocular surface. Consequently, these systems improve the drug's bioavailability and therapeutic efficacy [57, 58]. Figure 1 illustrates the various nanoformulations used for drug delivery.

Since lipids are a key component of cell membranes, lipid-based formulations have been extensively studied to develop biocompatible nanocarriers. Liposomes, for example, are vesicular systems composed of one or more concentric phospholipid bilayers separated by an aqueous buffer. These structures allow for the encapsulation of hydrophilic drug molecules in the aqueous compartment and hydrophobic drug molecules within the lipid bilayer [59]. Like liposomes, niosomes are also formed from a lipid bilayer, enabling them to encapsulate hydrophobic and hydrophilic drugs [57, 60]. However, there are notable differences between liposomes and niosomes. Specifically, liposomes comprise double-chain phospholipids (which can be charged or neutral), while niosomes are made from uncharged single-chain surfactants and cholesterol [61].

Among various nanoformulations, nanoemulsions are noteworthy. These are two-phase mixtures composed of water, oil, and amphiphilic surfactants. Over time, nanoemulsions can serve as a reservoir for drug release by interacting with the lipid layer of the tear film, remaining in the conjunctival sac [57, 62]. Hydrophobic drugs can be safely and effectively delivered to the ocular surface using nanosuspensions, colloidal dispersions in which drug particles are reduced to the nanometer scale. However, as with nanoemulsions, improving the physical stability of these nanocarriers is crucial for their practical use [63, 64].

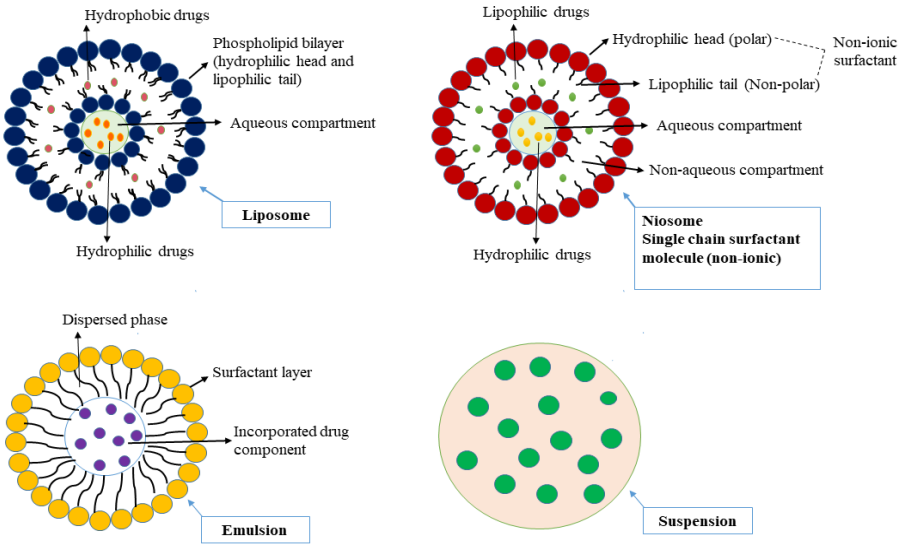


Fig 1. Different nanoformulations for ocular drug delivery.

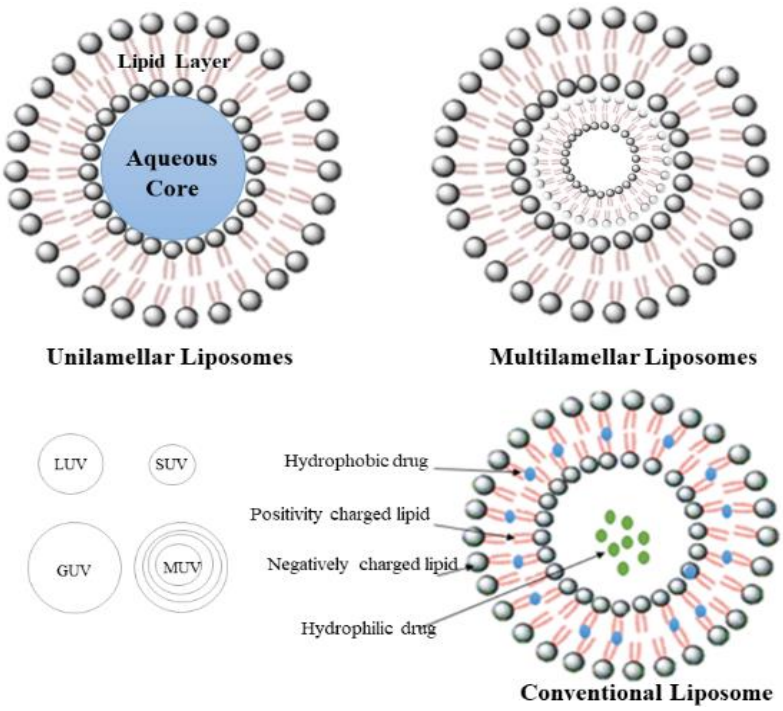


Fig 2. Schematic illustration of the various liposome types and their basic structures.

Nano-liposome drug delivery system in treating DED and ocular surface inflammation

Liposomes, as biocompatible and biodegradable nanovesicles, enhance the bioavailability of ophthalmic medications when applied topically. These lipid-based structures can be loaded with drugs and serve as carriers for drug delivery in treating conditions such as cancer and other diseases. The membranes of liposomes primarily consist of phospholipids, which are molecules that have a hydrophilic head and a hydrophobic tail. The hydrophilic head is attracted to water, while the hydrophobic tail, composed of a long hydrocarbon chain, repels water. In natural systems, phospholipids form stable bilayer membranes. Structurally, liposomes are classified into two main categories: unilamellar vesicles (ULVs) and multilamellar vesicles (MLVs). The former is further subdivided into small unilamellar vesicles (SUVs, approximately 20 nm to 200 nm), large unilamellar vesicles (LUVs, approximately 200 nm to 1 µm), and giant unilamellar vesicles (GUVs, greater than 1 µm) [65-68] (see Fig 2).

Soriano-Romaní et al. introduced an anti-inflammatory agent into an unpreserved, liposome-based formulation used as artificial tears. They evaluated the localization and uptake of the formulation by human corneal epithelial (HCE) cells in ex vivo pig corneas using a formulation of fluorescently tagged liposomes. After 60 minutes of exposure, the liposome formulation demonstrated no cytotoxicity to HCE cells and met all physicochemical requirements. The liposome-based formulation, designed to replenish tear film lipids, was also loaded with anti-inflammatory agents capable of targeting specific drug receptors within cells. These agents have the potential to reduce the production of inflammatory cytokines and could be effective in managing inflammatory conditions associated with ocular diseases [69].

In a study by Huang et al. [70], a liposome formulation containing one bromoheptadecafluorooctane and tetrandrine (PFOB@LIP-Tet) was developed for the anti-inflammatory treatment of dry eye disease (DED). Notably, this approach had minimal impact on intraocular pressure, offering an alternative therapeutic strategy for DED. The study found significant retention of PFOB@LIP-Tet on the ocular surface, particularly in the corneal epithelial cells of DED rabbits. Over seven days, rabbits treated with artificial tear substitutes (ATS), PFOB@LIP-ATS, Tet-ATS, and PFOB@LIP-Tet-ATS exhibited notable improvements in corneal staining scores. Notably, the synthesized PFOB@LIP-Tet demonstrated effective anti-inflammatory properties, as indicated by a significant downregulation of related cytokines. However, no statistical significance was found in intraocular pressure changes before and after PFOB@LIP-Tet treatment [70]. Liposomes, versatile carriers for drug delivery, have been explored with a variety of medications, including fluconazole (antifungal), ciprofloxacin (antibiotic), and acyclovir/ganciclovir (antiviral). In a study on

rabbits with C. albicans-induced keratomycosis, fluconazole-loaded liposomes achieved an 86.4% recovery rate in treated corneas, surpassing the fluconazole solution treatment. Coating ciprofloxacin-loaded liposomes with chitosan extended the drug's retention in ocular mucosa [71]. Liposomes have also shown efficacy in inhibiting P. aeruginosa growth for 24 hours after a single instillation, outperforming the marketed Ciloxan® formulation, with rapid symptom improvement observed using liposomal monotherapy [72]. Additionally, liposomes have enhanced the topical delivery of antiviral drugs, resulting in higher drug concentrations in healthy rabbit corneas and ocular tissues compared to free acyclovir [73]. Lactoferrin (LF) has shown promise as a therapeutic tool; however, its limited aqueous stability and rapid drainage through the nasolacrimal duct have hindered its efficacy. LF-loaded liposomes provide an innovative nanotechnological solution for treating DED. According to research by López, LF-loaded liposomes contained 53% of a high molecular weight protein, exhibited a monomodal distribution, had a positive surface charge, and had an average size of 90 nm. These nanocarriers improved biopharmaceutical behavior and demonstrated anti-inflammatory effectiveness without irritating the eyes [74]. Topical medications, including eye drops, commonly contain benzalkonium chloride (BAC) as a preservative. However, prolonged exposure to BAC can induce DED-like changes in ocular tissues, such as abnormalities in the corneal epithelium, loss of conjunctival goblet cells, tear film instability, and chronic ocular surface inflammation [40, 75]. In a recent study, melatonin (MT) was loaded into trans-activator of transcription (TAT)-modified liposomes to create MT liposomes (TAT-MT-LIPs). These liposomes successfully prevented corneal epithelial and conjunctival goblet cell death, reduced tissue inflammation, and alleviated clinical symptoms of BAC-induced DED (BAC-DED) by blocking mt-DNA oxidation, which in turn reduced NLRP3/Caspase-1/GSDMD transduction and subsequent corneal epithelial pyroptosis. Continuous exposure of the ocular surface to BAC triggers corneal epithelium pyroptosis, mediated by NLRP3, Caspase-1, and GSDMD. BAC-induced mt-DNA oxidation exacerbates this process. However, TAT-MT-LIPs effectively mitigate BAC-induced corneal epithelium pyroptosis and inflammation by preventing mt-DNA oxidation and disrupting subsequent signaling. This study highlights the role of NLRP3/Caspase-1/GSDMD in developing BAC-induced dry eye disease [40]. Innovative liposome-based drug delivery systems have emerged as effective therapies for DED (Source: ClinicalTrials.gov). For example, VisuEvo® liposomes, developed by Visufarma Società per Azioni (SpA) in Rome, Italy [76, 77] (VisuEvo®'s main ingredients are phospholipids, omega-3s, and vitamins D and A, etc.), and Optima Pharmazeutische in Hallbergmoos, Germany, developed the Tears Again® liposome spray. The primary ingredients of the Tears Again® liposome spray include sodium chloride, soy lecithin, palmitic acid, and vitamins A and E. This spray explicitly targets the three layers of the tear film, enabling sodium hyaluronate to substitute for the mucus layer while phospholipids repair the lipid layer. The solution is isotonic, effectively restoring the aqueous layer. The active components are absorbed transdermally upon application, while preservatives remain on the surface, preventing eye damage. Clinical trials have shown that the Tears Again® liposome spray reduces pain and stabilizes the tear film more effectively than saline spray and 0.1% sodium hyaluronate [37, 78].

Patents on liposomes for dry eye disease and ocular surface inflammation

Despite the potential for improved dry eye therapy with liposomes, formulating an efficient treatment presents several challenges. One of the key difficulties is ensuring the product's stability over an extended period. It is well known that liposomes can undergo lipid peroxidation/oxidation and hydrolysis processes even when stored for several months at refrigerator temperatures. In this context, a patent (US4818537A) describes a liposome-based compound that helps treat dry eye. This composition consists of an aqueous suspension of liposomes, with a lipid composition containing 15–30 moles of benzyldimethylstearylammonium chloride and approximately 70–85 moles of hydrogenated phosphatidylcholine (Table 1). Similarly, the invention described in US10835494B2 involves liposomes comprising lactoferrin and a component selected from hyaluronic acid or chitosan as active ingredients. The patent also covers compositions containing these liposomes and their use in preventing and/or treating ocular diseases, particularly those characterized by an inflammatory condition. Another patent, US5945121A, relates to liposome eye drops. In this formulation, taurine and inorganic salts, with a pH of 5.5-8.0, are encapsulated in the liposomes, and the osmolarity ranges from 250 to 450 mOsm. Additionally, a liposomal eye drop solution described in EP3673896A1 contains non-hydrogenated phospholipids, D-α-tocopheryl

polyethylene glycol succinate (Vitamin E TPGS), linseed oil, vitamin A palmitate, as well as vitamin B12 and pycnogenol in the aqueous phase. In this formulation, the presence of Vitamin E TPGS enhances the antioxidant effect in the lipophilic phase of the liposomes. At the same time, pycnogenol improves the antioxidant capacity in the external water phase. Furthermore, the internal presence of Vitamin E TPGS and the external presence of pycnogenol and Vitamin B12 provide a shield against UVA and UVB radiation.

Table 1. List of patents on liposome for dry eye treatment (Google Patents).

Title	Publication Year	Patent number	Country of invention	Inventor
Liposomial eye drops solution and uses thereof for the treatment of dry eye syndrome	2020	EP3673896A1	EPO	Rolf Lambert Giovanni Cavallo
Liposomes for the treatment of ocular diseases	2020	US10835494B2	U.S.	Ana laura lópez machado, Elena sánchez lópez, Maria luisa garcia lopez, Martina biancardi
Liposome eye drops	1999	US5945121A	U.S.	Muneyoshi Kato Tomohiro Ohtsuki Fuminobu Egami Kenji Tsunoda
Liposome composition for treating dry eye	1989	US4818537A	U.S.	Luke S. S. Guo

European Patent Office; EPO, United States; U.S.

Clinical trials on liposomes for dry eye disease and ocular surface inflammation

The Food and Drug Administration (FDA) has approved liposome-based nanocarriers for therapeutic use, which can encapsulate hydrophilic and hydrophobic drugs in their core and shell [79, 80]. For example, Optima Pharmazeutische (Hallbergmoos, Germany) developed the Tears Again® liposome spray, a novel liposome-based supplement that can repair the three layers of the tear film [81]. The phospholipids in the components restore the lipid layer, the isotonic solution replenishes the aqueous layer, and sodium hyaluronate is a substitute for the mucus layer. After application, the active components are absorbed through the skin, while the preservatives are prevented from entering the tear film by being blocked outside the skin, thus protecting the eyes [81, 82]. Additionally, Eye-logic liposomal eye spray by Naturalife in Ireland is already available on the market [83]. These recent nanosystems have facilitated targeted drug delivery, allowing for achieving desired drug concentrations without adverse effects on ocular tissues. Furthermore, fluorescent nanoliposomes have been developed as a noninvasive method for measuring the local osmolarity of the tear film, which can aid in understanding the pathophysiology of DED [82, 83]. Several liposome delivery techniques have led to the development of novel treatments that are either being studied in clinical settings or are ready for clinical use (See Table 2).

Table 2. List of current clinical trials for liposomal dry eye drug delivery products (Source: ClinicalTrials.gov).

Title	Identifier	Study Type ---------- Intervention / Treatment	Phase	Summary of the Invention
Comparison of the Clinical Effects of Two Tear Substitutes in Patients with Dry Eye Syndrome	NCT02992392	▪ Drug: Tears Naturale Forte & Liposic	Not Applicable	Tears Naturale Forte and Liposic, which transfer phospholipid liposomes to the tear film through the surface of the closed eyelid, have been created with the potential to treat evaporative dry eye. This study examines how applying Tears Naturale Forte and Liposic affects the stability and lipid content of the tear film in people with dry eyes.
Liposomal Sirolimus in DED	NCT04115800	▪ Drug: Liposomal Sirolimus	Early Phase 1	The safety and efficacy of applying a newly developed medication called liposomal sirolimus subconjunctivally to patients with moderate to severe DED. This clinical trial was

Title	Identifier	Study Type --- Intervention / Treatment	Phase	Summary of the Invention
				double-blind, randomized, and placebo-controlled.
Clinical Study to Evaluate the Efficacy of Ectoin® Containing Eye Spray for the Treatment of DED	NCT03519815	▪ Device: Liposomal eye spray Tears Again® ▪ Device: Ectoin® Eye Spray - Colloidal	Not Applicable	Objective and subjective assessment of the effectiveness and tolerability of "Ectoin® Eye Spray - Colloidal" without preservatives, as well as a comparison of the effectiveness and tolerability of Tears Again® and "Ectoin® Eye Spray - Colloidal" in patients with mild-to-moderate DED.
Crosslinked Hyaluronic Acid with Liposomes and Crocin in Dry Eye	NCT03617315	▪ Drug: Hylauronic Acid	Not Applicable	The trial participants received the artificial tears three times a day for six weeks, and they were clinically examined both before and 45 days after the artificial tear treatment. Despite repeating the first tests, he did not develop meibografía since the use of fake tears did not result in the creation of Meibomio glands.
Study to Assess the Safety and Patients' Satisfaction of Tears Again* in the Treatment of Dry Eye Symptoms	NCT00535054	▪ Drug: Tears Again	Not Applicable	Determining patient satisfaction and safety when utilizing Tears Again to treat dry eye symptoms was the aim of this study.

Nano-suspension drug delivery system in treating DED and ocular surface inflammation

Colloidal nanocarriers (nanosuspensions) consist of lipophilic or semi-lipophilic drugs suspended in a dispersion medium and stabilized by polymers or surfactants [84]. Nanosuspensions have been investigated as a potential therapeutic option for dry eye disease (DED) to enhance the transport of therapeutic agents to the ocular surface. Common nanosuspension creation techniques include precipitation, controlled flocculation, and direct dispersion. The drug particles in the suspension settle gradually to prevent interference with accurate dosing. Even after prolonged storage, these particles can be uniformly redistributed by shaking and do not clump together. Key benefits of nanosuspensions include improved drug solubility and bioavailability, extended residence time on the ocular surface, and prolonged drug release [85].

Patents on suspensions for dry eye disease and ocular surface inflammation

Ophthalmic formulations are available that, when applied to a subject's ocular surface, increase the tear film's break-up time and/or ocular protection index, thereby prolonging the integrity of the tear film (see Table 3). For instance, in patent WO2007087609A2, techniques and formulations for preventing and treating dry eye and extending the time it takes for the tear film to break up are provided. Additionally, patent CN114585357A describes a composition for treating dry eye that includes (E)-2-(7-trifluoromethyl chroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl) acetamide, or a pharmaceutically acceptable salt or solvate thereof. This composition contains a Vi/Vc region inhibitor formulated explicitly for dry eye treatment.

Table 3. List of patents on suspension for dry eye treatment (Google Patents).

Title	Publication Year	Patent number	Country of invention	Inventor
Aqueous ophthalmic suspension of crystalline rebamipide	2013	KR101271959B1	South Korea	Not Applicable
Formulations and methods for treating dry eye	2007	WO2007087609A2	WIPO (PCT)	George W. Ousler Matthew J. Chapin Mark B. Abelson
Medicine containing heterocyclic subunit acetamide derivative	2022	CN114585357A	China	Not Applicable

Furthermore, patent KR101271959B1 presents an ophthalmic preparation containing levamipid, which has a neutral to weakly acidic pH and is transparent to the extent that it causes no discomfort during use while not damaging the cornea in dry eye conditions. Aqueous suspensions of crystalline levamipids with improved transparency include aqueous solutions of levamipids or levamipid salts dissolved in a base such as sodium hydroxide or hydrochloric acid, containing one or more substances selected from surfactants and water-soluble polymers. These patents collectively highlight ongoing efforts to advance suspension formulations to effectively manage dry eye conditions.

Clinical trials on suspensions for dry eye disease and ocular surface inflammation

Hydrophobic medications commonly used to treat dry eye disease (DED) are frequently administered in suspension form. One example is the FDA-approved loteprednol etabonate suspension, Alrex® (Bausch & Lomb, Clearwater, FL, USA), which is primarily used as an anti-inflammatory drug. Clinical studies have demonstrated that either monotherapy with this medication or combined therapy with artificial tears can effectively treat DED [7]. Additionally, suspensions of mucin-stimulating medications like Reb and the immunosuppressant cyclosporine have been approved for the treatment of DED [86]. In a randomized multicenter phase III study, DED patients were administered 2% Reb suspension and 0.1% sodium hyaluronate. The results showed that the 2% Reb suspension was more effective in reducing ocular pain and foreign body sensation [87]. Reb suspension is a milky liquid that temporarily blurs the patient's vision, which can reduce visual quality despite its effectiveness in treating DED. According to an in vivo pharmacokinetics study, the concentrations of Reb in the cornea and conjunctiva were higher than those of the traditional solution. This suggested faster absorption rates and improved bioavailability [87, 88]. Urashima et al. investigated the pharmacological effects of OPC-12759 and its potential as a therapy for dry eye in a preclinical study. OPC-12759, a novel quinolinone derivative developed by Otsuka Pharmaceutical Company, Ltd. (Japan), significantly affected corneal epithelial cells and conjunctival PAS-positive cells. This compound improved ocular surface damage and increased mucin content on the ocular surface. It directly enhanced the secretion and membrane-spanning mucin in corneal epithelial cells. By expanding the mucin content on the ocular surface, OPC-12759 may offer therapeutic potential in treating dry eye disease [89]. In addition, Kala Pharmaceuticals (Arlington, MA, USA) developed the innovative loteprednol nanosuspension, Eysuvis® [7], utilizing the Amplify mucus-penetrating particle drug delivery technology. This technology lets loteprednol be delivered to the eye without breaking down in the tear film. Compared to the commercial product Lotemax® (0.38% loteprednol etabonate eye gel, Bausch & Lomb, Clearwater, FL, USA), a single application of Eysuvis® can increase the concentrations of loteprednol in the aqueous humor, cornea, and conjunctiva by up to three times. When used to treat dry eye disease (DED), Eysuvis® demonstrated high efficacy. Moreover, it was safe and well-tolerated for short-term use (two to four weeks) in a multicenter randomized clinical trial. However, its long-term in vivo safety has not yet been established [90, 91]. In general, nanosuspension-based therapies have the potential to overcome the limitations of traditional eye drops, offering a more effective and targeted approach to treating DED [23, 63] (see Table 4). Additional research is necessary to further improve nanosuspension formulations and assess their safety and effectiveness in clinical settings.

Table 4. List of current clinical trials for suspension dry eye drug delivery products (Source: ClinicalTrials.gov).

Title	Identifier	Study Type ---------- Intervention / Treatment	Phase	Summary of the Invention
Safety and Efficacy of KPI-121 in Subjects With Dry Eye Disease (STRIDE 1)	NCT02813265	▪ Drug: Vehicle of KPI-121 0.25% Ophthalmic Suspension ▪ Drug: KPI-121 0.25% Ophthalmic Suspension	III	The purpose of this Phase 3 multi-center, randomized, vehicle-controlled, double-masked, parallel-group trial was to compare the safety and effectiveness of KPI-121 0.25% ophthalmic suspension to vehicle in DED patients.
Late Phase 2 Study of OPC-12759 Ophthalmic Suspension	NCT00475319	▪ Drug: 1% OPC-12759 ophthalmic suspension ▪ Drug: placebo ▪ Drug: 2% OPC-12759 ophthalmic suspension	II	This research was out to assess the OPC-12759 suspension's dose-response in individuals with dry eyes.

Title	Identifier	Study Type ---------- Intervention / Treatment	Phase	Summary of the Invention
Study of Tisporin Eye Drops Group and Restasis Eye Drops Group After Treatment, Each Treatment Group Comparisons for Evaluation of Efficacy and Safety in Moderate to Severe DED (HL_TSPR_302)	NCT02229955	▪ Drug: Cyclosporine ophthalmic solution	III	Twelve weeks following treatment, the Restasis Eye Drops 0.05% (Cyclosporine ophthalmic suspension) group and Tisporin Eye Drops 0.05% (Cyclosporine ophthalmic solution) group were compared to assess the safety and effectiveness of each treatment group in Moderate to Severe DED.
Loteprednol Etabonate Opthalmic Suspension for the Treatment of Dry Eye	NCT00560638	▪ Drug: vehicle of loteprednol etabonate ▪ Drug: loteprednol etabonate ophthalmic suspension, 0.5% ▪ Drug: loteprednol etabonate ophthalmic suspension, 0.5%	II	According to randomization, subjects were told to dose bilaterally either TID or QID and were randomized to receive either loteprednol etabonate ophthalmic suspension, 0.5%, or a placebo (a vehicle of loteprednol etabonate ophthalmic suspension, 0.5%).
Comparing Treatment of Dry Eye With Intracanalicular Dexamethasone, Restasis, and/or Lotemax	NCT04555694	▪ Drug: Cyclosporine ▪ Drug: Dexamethasone Ophthalmic 0.4 Mg Ophthalmic Insert ▪ Drug: Loteprednol Etabonate	IV	This six-month study compares the use of Intracanalicular Dexamethasone in combination with Restasis (cyclosporine ophthalmic emulsion) to Restasis with Lotemax (loteprednol etabonate ophthalmic suspension 0.5%) and Restasis monotherapy.
Study Assessing Safety and Efficacy of DE-101 Ophthalmic Suspension in Dr y Eye Patients	NCT01118754	▪ Drug: DE-101 ophthalmic suspension ▪ Drug: DE-101 ophthalmic suspension ▪ Drug: DE-101 ophthalmic suspension vehicle	I	This study sought to determine if DE-101 ophthalmic fluid may safely and efficiently alleviate DED symptoms.
Confirmatory Study of OPC-12759 Ophthalmic Suspension	NCT00885079	▪ Drug: Hyalein Mini Ophthalmic solution ▪ Drug: OPC-12759 Ophthalmic suspension	II	This research sought to confirm the effectiveness of OPC-12759 ophthalmic fluid in dry eye patients when compared to active control.
Dose-response Study of OPC-12759 Ophthalmic Suspension	NCT00234078	▪ Drug: 0.5% OPC-12759 Drug: 2% OPC-12759 ▪ Drug: placebo ▪ Drug: 1% OPC-12759	II	This research was out to assess the OPC-12759 ophthalmic suspension's dose-response in individuals with dry eyes.
Safety and Efficacy Study of DE-110 Ophthalmic Suspension for the Treatment of DED	NCT01239069	▪ Drug: DE-110 ophthalmic suspension low dose Drug: DE-110 ophthalmic suspension high dose	II	Examining the efficacy and safety effectiveness of two DE-110 concentrations for the treatment of DED in comparison to a placebo.
Safety and Efficacy of Licaminlimab Ophthalmic Suspen sion for the Treatment of DED (RELIEF)	NCT05896670	▪ Drug: licaminlimab ▪ Other: vehicle of OCS-02	II	The purpose of this multicenter, randomized, double-masked, active-control, Phase 2b trial was to assess the safety and effectiveness of licaminlimab in treating DED symptoms.
Long Term Administration Study of OPC-12759 Ophthalmic Suspension	NCT00818324	▪ Drug: OPC-12759 Ophthalmic suspension	III	This research aimed to assess the safety and effectiveness of OPC-12759 ophthalmic suspension in individuals with dry eyes over a 52-week period.
Study of Cyclosporine Ophthalmic Soution Group and	NCT01768312	▪ Drug: Cyclosporine ophthalmic solution	III	Twelve Weeks Following Treatment for Moderate to Severe DED in a Multicenter, Randomized, Double-blind Phase Ⅲ Study of

Title	Identifier	Study Type ---------- Intervention / Treatment	Phase	Summary of the Invention
Cyclosporine Ophthalmic Suspens ion Group (Cyclosporine)				Cyclosporine Ophthalmic Solution Group and Cyclosporine Ophthalmic Suspension Group.
A Study Assessing the Safety and Efficacy of DE- 101 Ophthalmic Suspension in Dr y Eye Patients	NCT01468168	▪ Drug: DE-101 Ophthalmic Suspension Vehicle ▪ Drug: DE-101 Ophthalmic Suspension ▪ Drug: DE-101 Ophthalmic Suspension	II	To look into DE-101 effectiveness and safety in reducing the symptoms and indicators of dry eye condition.
Study to Assess the Safety and Efficacy of BOL-303242- X Ophthalmic Suspension in Dry E ye Syndrome	NCT01163643	▪ Drug: Placebo Comparator: Vehicle ▪ Drug: 2% BOL-303242-X ophthalmic suspension ▪ Drug: 0.3% BOL-303242-X ophthalmic suspension	II	Finding the BOL-303242-X ophthalmic suspension's concentration and daily dosage frequency for the treatment of dry eye syndrome throughout, a 12-week dosing period was the aim of this investigation.
The DEPOT Study (Dry Eye Prescription Options for Therapy)	NCT04911361	▪ Drug: Dexamethasone	IV	Comparing topical loteprednol suspension to DEXTENZA's safety and effectiveness when applied to the lower eyelid canaliculus for dry eye flares.
Safety and Efficacy Study of Rebamipide 2% Ophthalmic Suspension in Subjects With Dry Eye - Effects on Central Cornea	NCT01057147	▪ Drug: rebamipide 2% ophthalmic suspension ▪ Drug: placebo eye drops	II	This research set out to determine if 2% rebamipide was safer and more effective than a placebo at removing fluorescein staining from the central cornea in DED patients.
Safety, Efficacy, Tolerability and Pharmacokinetics of AGN- 223575 Ophthalmic Suspension i n Patients With DED	NCT02435914	▪ Drug: AGN-223575 vehicle ophthalmic solution ▪ Drug: AGN-223575 ophthalmic solution	II	In comparison to the AGN-223575 vehicle, this research assesses the systemic pharmacokinetics, safety, effectiveness, and tolerability of three distinct topical ophthalmic AGN-223575 solution dosages in DED patients.

Nano-emulsion drug delivery system in treating DED and ocular surface inflammation

Oils-in-water nanoemulsions comprise a dispersed oil phase in which surfactants stabilize in an aqueous medium. These formulations interact with the lipids in the tear film to provide sustained drug release and act as a reservoir for lipophilic medications [92, 93]. Surfactants play a crucial role in enhancing drug solubility and interacting with the corneal surface [94, 95]. However, two potential disadvantages of nanoemulsions include reduced ocular tolerance due to high surfactant concentrations and impaired vision if the particle size exceeds 100 nm [96].

Patents on emulsion for dry eye disease and ocular surface inflammation

Various patents related to emulsions for dry eye treatment have been reported (see Table 5). For example, patent US6656460B2 addresses the management of dry eye disease. The composition includes a non-soluble medicinal substance, such as cyclosporine, which is effective against eye diseases and delivered to the eye by the film. Similarly, cyclosporine can be administered using a microemulsion carrier, as described in patent US7732404. Sandimmune Neoral forms an oil-in-water emulsion in which the oily component is distributed as droplets in the water phase. At the same time, a novel cyclosporine formulation in this invention creates a solid nanodispersion at room temperature. Patent US9044388B2, reported in 2009, pertains to an emulsion composition designed to create an artificial tear film on the ocular surface. This film helps reduce fluid evaporation while providing mechanical lubrication to the ocular surface. The emulsion is characterized by using a surfactant mixture consisting of primary

and secondary surfactants, where the primary surfactant enables emulsion formation and the secondary surfactant facilitates the autoclaving process. Ideally, the emulsion forms a meta-stable state. A technique for preparing this emulsion is also included in the patent. When topically applied, the emulsion is electrostatically attracted to the anionic eye surface, forming the tear film described in patent TWI292325B. Patent US20210085603A1 relates to a composition for ophthalmic delivery of a therapeutic agent. This composition consists of an oil-in-water (o/w) microemulsion, with a fatty acid ester or fatty acid as the oil phase, an aqueous phase, a co-surfactant, and a surfactant. It also includes a suspension of therapeutic agent-loaded nanoparticles. Additionally, the patent covers a mechanism for treating or preventing eye disorders, an eye drop dispenser, and instructions for using the composition for these purposes. Ophthalmic oil-in-water emulsions comprise colloidal particles with an oily core encased in an interfacial membrane. These emulsions include tyloxapol, an oil (preferably at least 50% MCT), and immunosuppressive agents. Patent EP1809238 describes ophthalmic oil-in-water emulsions containing an immunosuppressive agent as an active ingredient in a specific oil and tyloxapol-containing vehicle. The emulsion is free of castor oil and is intended to treat eye conditions, particularly dry eye disease (DED).

Table 5. Summary of patents on emulsion for dry eye treatment (Google Patents).

Title	Publication (Year)	Patent number	Country of invention	Inventor
Composition for dry eye treatment and use of an emulsion in preparing the same	2008	TWI292325B	Taiwan	Benita Simon Lambert Gregory
Method and composition for dry eye treatment	2003	US6656460B2	U.S.	Simon Benita Gregory Lambert
Dry eye treatment	2015	US9044388B2	U.S.	Donald R. Korb Chris J. Brancewicz
Microemulsion for opthalmic drug delivery	2021	US20210085603A1	U.S.	Gautam behl Sangeeta kumari Niall o'reilly Orla o'donovan Peter mcloughlin Ddavid kent
Oil-in-water emulsion (medium chain triglycerides, Tyloxapol, Poloxamer, Vitamin E, Glycerin)	2008	EP1809238	EPO	Laurence fitzhenry Betty Philips Séverine Bague Laura Rabinovich-Guilatt Grégory LAMBERT
Pro-nanodispersion formulation prepared using solid fat; tricaprin or ethyl stearate, ethyl lactate, macrogolglycerol hydroxystearate, lecithin at room temperature	2010	US7732404	U.S.	Abraham J. Domb Avi Avramoff Victor Pevzner

European Patent Office; EPO, United States; U.S.

Table 6. List of current clinical trials for emulsion dry eye drug delivery products (Source: ClinicalTrials.gov).

Title	Identifier	Study Type ---------- Intervention / Treatment	Phase	Summary of the Invention
A Phase 4 Study Investigating the Efficacy of Retaine™ in Managing Signs and Symptoms Associated With Dry Eye Syndrome	NCT02139033	▪ Drug: Retaine™	IV	The effectiveness of Retaine™ ophthalmic emulsion in managing the symptoms and indicators of dry eye syndrome is assessed in this study.

Title	Identifier	Study Type --- Intervention / Treatment	Phase	Summary of the Invention
The Effects of Cyclosporin A in a Low Humidity Environment, on the Ocular Surface (CsA)	NCT02199964	▪ Drug: Endura, Refresh artificial tears ▪ Drug: Cyclosporin 0.05% emulsion	Not Applicable	This study tests the hypothesis that topical application of cyclosporin A emulsion, an FDA-approved immunomodulatory drug, reduces ocular surface illness and irritation brought on by a brief environmental stressor including low humidity.
Effect of Cequa™ in Subjects With DED	NCT04357795	▪ Drug: CequaTM (Cyclosporine 0.09%) ophthalmic solution	IV	Participants in this 12-week, single-arm, Phase 4 multicenter trial had DED, which is not well controlled with cyclosporine 0.05% ophthalmic emulsion.
Physician's Evaluation of Cyclosporine Ophthalmic Emulsion 0.05%	NCT00827255	▪ Drug: Cyclosporine Ophthalmic Emulsion 0.05%	Observational	Treatment variations, examining the patient characteristics, and effectiveness of a second trial of Cyclosporine Ophthalmic Emulsion 0.05% therapy in chronic dry eye patients.
Double-Masked Trial of NOVA22007 (Ciclosporin 0.1%) Versus Vehicle in Patients With Moderate to Severe Dry Eye Syndrome	NCT00814515	▪ Drug: NOVA22007 (Ciclosporin 0.1%) ▪ Drug: NOVA22007	III	A Phase III, Multicenter, Randomized, Controlled, Double-Masked Study in Patients with Moderate to Severe DES.
Efficacy of Cyclosporine Ophthalmic Emulsion in the Treatment of Dry Eye Syndrome in Contact Lens Wearers	NCT00335114	▪ Drug: cyclosporine ophthalmic emulsion	Not Applicable	Dry eye syndrome is presently treated with cyclosporine ophthalmic emulsion. People who wear contact lenses often have dry eye syndrome. This study aims to compare the effectiveness of cyclosporine ophthalmic emulsion and rewetting drops in treating contact lens wearers' dry eye complaints.
Evaluating Safety and Efficacy of FID 112903 Post Discontinuation of Long-term Use of RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%	NCT01198782	▪ Other: FID 112903 (SYSTANE® ULTRA Lubricant Eye Drops)	IV	This study aims to assess the safety and effectiveness of FID 112903 when used as a treatment substitute right away in dry eye patients who stop using RESTASIS for at least six months.
A Study of TL-925 as a Treatment for DED	NCT05745064	▪ Drug: TL-925 ▪ Drug: Placebo	II	Approximately 100 participants with moderate to severe DED will be randomly assigned (1:1) to receive either TL-925 or a placebo.

Title	Identifier	Study Type --- Intervention / Treatment	Phase	Summary of the Invention
Study of Two Formulations of Cyclosporine Ophthalmic Emulsion in Healthy Volunteers and in Patients With Dry Eye	NCT01319773	▪ Drug: cyclosporine ophthalmic emulsion Formulation A ▪ Drug: cyclosporine ophthalmic emulsion Formulation B ▪ Drug: cyclosporine ophthalmic emulsion Formulation A; cyclosporine ophthalmic emulsion 0.05%	I	In the parallel-group phase, this study assesses the pharmacokinetics, safety, and tolerability of two cyclosporine ophthalmic emulsion formulations in healthy individuals. A paired-eye phase that compares the safety and tolerability of two cyclosporine ophthalmic emulsion formulations to cyclosporine ophthalmic emulsion (RESTASIS®) in patients with dry eye will come after the parallel-group phase.
The Comparison of 50% AS Versus PFAT+ 0.05 % COE in Severe Dry Eye Syndrome	NCT03666884	▪ Drug: COE 2*1 (Restasis) + PFAT Refresh Single dose) 8*1 ▪ Biological: AS 50% eye drops 8*1	IV	Based on a comparison of OSDI scores before and after therapy, Schirmer's test findings, TBUT values, and OXFORD scale scores, all patients showed good response to both treatments following the initial one-month treatment period.
The Effect of a New Emulsion in Dry Eye Patients on Tear Layer Aberrometry, Contrast Sensitivity, and Reading Ability	NCT01013077	▪ Drug: Optive ▪ Drug: Soothe ▪ Drug: New Emulsion	Not Applicable	Optical aberrations were reduced when dry eye patients' tear layers were treated with an artificial tear (such as Vismed). Only the short-term effects (less than 10 minutes) of a single artificial tear delivery were investigated in this earlier investigation.
Efficacy of Cyclosporine for the Prevention and Treatment of Dry Eye Symptoms Following LASIK or Photorefractive Keratectomy	NCT00349440	▪ Drug: Cyclosporine, Refresh Plus	IV	This study aims to assess how topical cyclosporine ophthalmic solution 0.05% (Restasis, Allergan) affected dry eye symptoms and indicators in patients having photorefractive keratectomy (PRK) or laser eye surgery (LASIK).
Safety and Efficacy Study of Cyclosporine Ophthalmic Emulsion in Post-LASIK Patients	NCT00611403	▪ Drug: Cyclosporine Ophthalmic Emulsion 0.05% (RESTASIS®) ▪ Drug: Artificial Tears REFRESH ENDURA®	II	The safety and effectiveness of cyclosporine ophthalmic emulsion given twice daily after LASIK surgery were assessed in this study.

Title	Identifier	Study Type --- Intervention / Treatment	Phase	Summary of the Invention
Comparing the Treatment of Dry Eye With Intracanalicular Dexamethasone, Restasis, and/or Lotemax	NCT04555694	▪ Drug: Cyclosporine ▪ Drug: Loteprednol Etabonate ▪ Drug: Dexamethasone Ophthalmic 0.4 Mg Ophthalmic Insert	IV	For the treatment of DED signs and symptoms, this six-month study compared the use of Intracanalicular Dexamethasone in combination with Restasis (cyclosporine ophthalmic emulsion) to Restasis with Lotemax (loteprednol etabonate ophthalmic suspension 0.5%) and Restasis monotherapy.
NOVA22007 0.05% and 0.1% Cyclosporine Versus Vehicle for the Treatment of Dry Eye	NCT00739349	▪ Drug: NOVA22007 ''Cyclosporine'' ▪ Drug: NOVA22007 ''Cyclosporine'' ▪ Drug: vehicle/placebo	II	Following a three-month treatment period, the study evaluated the safety and effectiveness of NOVA22007 0.05% and 0.1% Cyclosporine Ophthalmic Cationic Emulsions QD in comparison to the vehicle for the treatment of dry eye symptoms.
Comparison of Efficacy, Safety and Anti-Inflammatory Effect Between Topical 0.05%Cyclosporine A Emulsion and REFRESH® in Patients With Moderate to Severe Dry Eyes	NCT00704275	▪ Drug: 0.05% cyclosporin eye drop	IV	To assess the effectiveness, safety, and tolerability of Refresh against 0.05% topical cyclosporin eye drop in individuals with moderate to severe dry eye.
Piiloset Trehalose Emulsion Eye Drop Study in Moderate or Severe Dry Eye	NCT03569202	▪ Device: Piiloset Trehalose Emulsion Eye Drops ▪ Device: Control Eye Drops	Not Applicable	The research assessed the effectiveness, safety, and ocular tolerability of emulsion eye drops containing hyaluronic acid, trehalose, and sacha inchi seed oil in treating moderate to severe dry eye in adult patients. For a maximum of 30 days, the experimental gadget compared to control eye drops that include hyaluronic acid.
Comparison of Tolerability and Clinical Performance of Two Emulsion-type Artificial Tears	NCT01335126	▪ Other: Emulsion type artificial tear	III	This study aims to compare two artificial tears of the emulsion kind in terms of performance.
A Study of TL-925 Ophthalmic Emulsion as a Treatment for DED	NCT06225973	▪ Drug: TL-925 ▪ Other: Placebo	II	Approximately 670 participants with moderate to severe DED will be randomly divided (1:1) to receive either TL-925.
Evaluation of Extended Tear Film Break up Time (TFBUT) With an Ocular Emulsion	NCT01368198	▪ Other: Systane Balance Lubricating Eye Drops ▪ Other: OPTIVE™	Not Applicable	This study's main goal was to measure the increase in tear film break-up time (TFBUT) that occurs when dry eye patients receive a single eyedrop of an ocular emulsion.

Clinical trials on emulsions for dry eye disease and ocular surface inflammation

The current clinical trials for emulsion-based dry eye drug delivery products are summarized in Table 6. For example, Ousler et al. evaluated the effectiveness of Retaine™ ophthalmic emulsion in reducing the signs and symptoms of dry eye in a single-center, open-label study lasting approximately two weeks [97]. This study demonstrated that Retaine™, when combined with Novasorb® technology, effectively alleviates the symptoms and signs of dry eye. The findings indicate that Retaine™ provides a therapeutic effect on dry eye symptoms and signs after two weeks of treatment, along with an immediate, short-term improvement in tear film stability. Reductions in mean breakup area (MBA) and corneal fluorescein staining, both indicators of ocular surface protection, as well as improvements in quality of life (QoL) and clinical symptom relief, show complete dry eye relief [57, 97]. As the first commercially available ophthalmic emulsion for dry eye disease (DED), Restasis® (Allergan, Waco, TX, USA) is an oil-in-water (O/W) anionic nanoemulsion that contains cyclosporine. It is formulated using polysorbate as an emulsifier to dissolve cyclosporine in castor oil. After instillation, Restasis® medication droplets quickly disperse across the ocular surface, facilitating rapid drug absorption and the onset of action [7]. Santen Pharmaceutical (Osaka, Japan) developed the O/W cationic nanoemulsion of cyclosporine, known as Ikervis®. Ikervis® features the highest drug concentration in clinical use and is prescribed to patients with severe DED who do not benefit from artificial tears. The emulsion droplets of Ikervis® are smaller than those of Restasis®, enhancing cyclosporine's ability to penetrate the cornea [7]. Bang et al. developed self-emulsifying nano drug delivery systems, specifically Cyporin-N (SNEDDS-N; Taejoon Pharma, Seoul, Republic of Korea) and T-sporin (SNEDDS-T; Taejoon Pharma, Seoul, Republic of Korea), to enhance drug bioavailability and improve eye comfort. SNEDDS (self-nanoemulsifying drug delivery systems) are anhydrous, homogenous mixtures of oils, drugs, surfactants, and cosurfactants [98, 99]. Compared to Restasis®'s high turbidity and unstable pH, SNEDDS offers more consistent particle sizes, improved light transmission, and a more stable pH. Additionally, SNEDDS is more effective than Restasis® at restoring tear film stability [7, 100]. In addition to drug-loaded emulsions, drug-free emulsions have also been developed for dry eye disease (DED). Cationorm® (Santen Pharmaceutical) is a drug-free oil-in-water (O/W) cationic nanoemulsion. Because Cationorm® contains benzylcetyldimethylammonium chloride, a cationic surfactant with inherent antibacterial properties, it is a preservative-free formulation. This design improves the safety profile of Cationorm®. According to pharmacodynamic studies, Cationorm® is a safe and effective tear supplement, as it stabilizes the tear film with its oily components while providing moisturizing and lubricating benefits [101, 102]. A study by Srinivasan et al. examined the formulation components and mechanism of action and summarized preclinical and clinical data for a lipid-based formulation—propylene glycol-hydroxypropyl guar (PG-HPG) nanoemulsion lubricating eye drops (Systane™ Complete) [103]. When exposed to the tear film, hydroxypropyl guar (HPG) forms a thin, soft, cross-linked in situ gel matrix with borate ions, which extends lubricant retention and protects the ocular surface. Dimyristoyl phosphatidyl glycerol, an anionic phospholipid, helps regenerate the lipid layer of the tear film. Additionally, the nanoemulsion formulation improves ocular surface coverage by acting as a depot for delivering dimyristoyl phosphatidyl glycerol. Regardless of the subtypes of dry eye disease (DED), preclinical and clinical data indicate that PG-HPG nanoemulsion lubricating eye drops are safe and effective in temporarily alleviating symptoms. Specifically, these drops enhance the lipid layer grade, improve tear film durability, enhance ocular surface properties, and reduce dry eye symptoms over time [103]. In another study, Yeu et al. assessed the clinical effectiveness and safety of PG-HPG-based nanoemulsion (Systane® Complete) lubricant eye drops in individuals with dry eye disease (DED) [104]. The results demonstrated that PG-HPG nanoemulsion-based lubricant eye drops were well tolerated by participants, regardless of DED subtype, and improved tear film stability and DED signs and symptoms [104]. Additionally, in a separate study, the PRO-176 score evaluation revealed a significant reduction in DED-related symptoms reported by users, as indicated by the Ocular Surface Disease Index (OSDI) score evaluation. These findings support the idea that ocular ophthalmic 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC)-based nanoemulsion (PRO-176) could be beneficial in alleviating symptoms and clinical characteristics of DED. Furthermore, it showed no significant differences compared to a well-known commercially available eye drop, offering a new approach to treating patients with mixed or evaporative DED [105]. The clinical effectiveness of topical 0.05% cyclosporine

nanoemulsion in treating meibomian gland dysfunction (MGD) and DED was also evaluated by Yeon Ji Jo et al. [106]. Compared to the control group, cyclosporine, and nano-cyclosporine significantly improved DED with MGD. The nano-cyclosporine group showed statistically greater improvements in conjunctival injection (CI) and corneal staining (CS) at 4 weeks, with particularly notable improvements in lipid layer thickness (LLT) at 4, 8, and 12 weeks [106]. Other emulsion-based treatments, such as the ophthalmic DMPC-based nanoemulsion, have also demonstrated safety and effectiveness in improving clinical parameters and symptoms in DED patients [107]. Additionally, cationic emulsion (CE)-based eye drop technology has been shown to restore ocular surface homeostasis and tear film stability, leading to better management of DED [108]. These findings highlight the potential of emulsion-based treatments in providing relief for patients with DED.

Nano-niosome drug delivery system in treating DED and ocular surface inflammation

Non-ionic surfactant vesicles, commonly known as niosomes, gained prominence in the 1970s through the efforts of the cosmetic giant L'Oréal [109]. These vesicles subsequently transitioned into the pharmaceutical industry as potential drug delivery agents, offering versatility across various administration routes, including oral, buccal, dermal, intravenous, and ocular pathways. Niosomes are primarily composed of nonionic surfactants, lipids such as cholesterol, and a hydration medium [110].

The self-assembly of nonionic surfactants in water, which forms closed bilayer structures, is a fundamental aspect of niosome structure in drug delivery. This interaction is driven by the high interfacial tension between the hydrophobic amphiphilic tails and water molecules. The hydrophilic termini of the surfactants face outward, maintaining contact with water molecules due to the hydrophilic and steric repulsion between the head groups of nonionic surfactants. Typically, mechanical or thermal energy inputs are required to form closed bilayers. Niosomes can be classified into three types based on their size and number of bilayers: small unilamellar vesicles (SUVs) (10–100 nm), large unilamellar vesicles (LUVs) (100–3000 nm), and multilamellar vesicles (MLVs), which contain multiple bilayers. The number of lamellae, composition, surface charge, and size of niosomes can be tailored and optimized to enhance their performance in drug delivery [111, 112].

Niosomes have garnered significant interest due to their ability to form bilayer vesicles similar to liposomes, offering distinct advantages for drug delivery. One key advantage is that the materials used to fabricate niosomes—non-ionic surfactants—are more cost-effective compared to the phospholipids employed in liposomes. Additionally, non-ionic surfactants exhibit more excellent stability and resistance to oxidation than phospholipids. From a formulation perspective, niosomes also achieve higher drug encapsulation efficiency than liposomes [112, 113]. Recent studies have focused on optimizing drug encapsulation methods and understanding the kinetics of drug/protein loading and release. Researchers are particularly interested in liposomal drug delivery systems for their potential to treat severe inflammatory conditions, including various types of cancer [113]. For example, a recent study by Moghassemi et al. involved BSA-loaded niosomes, demonstrating controlled and gradual drug release. The release profile of these niosome-based complexes can be modulated by adjusting the cholesterol content in the formulation [114]. Compared to other nanostructures used in ocular drug delivery, niosomes exhibit advanced chemical stability and excellent surface spreading on the eye, resulting in high bioavailability. However, there is limited information on the ocular delivery of niosomal formulations. Elastic nano-sized niosomes (ethoniosomes), prepared using thin film hydration (TFH) and ethanol injection (EI) methods, were evaluated for ocular delivery of prednisolone. These ethoniosomal vesicles (EV) demonstrated physical stability, good ocular tolerability, and significantly enhanced ocular bioavailability compared to conventional suspension and solution eye drops, as shown by the modified Draize test [114]. The healing time for clove oil-induced severe ocular inflammation was reduced by half with Pred A and Pred P EVs. Notably, the side effect of elevated intraocular pressure (IOP) associated with Pred A and Pred P EVs was much less severe than that of traditional suspension and solution eye drops [115]. In a study by Ozdemir & Uner, niosomal systems loaded with loteprednol etabonate (LE) were shown to increase the drug's bioavailability and efficacy in treating DED. Due to LE's limited bioavailability, niosomes were created using a design of experiments (DoE) method. The optimal niosomal formulation exhibited an encapsulation efficiency of 89.6% and a particle size of 89.22 nm. In vitro, ex vivo, and in vivo studies demonstrated that niosomes could improve drug distribution and release in the eye. With increased bioavailability and fewer side effects, these LE-loaded niosomes appear to be a promising treatment for DED [116].

Nanomaterials' safety and toxicity

Nanomaterials have recently been developed as a promising approach for treating various ophthalmic disorders. These materials possess unique physicochemical properties and improved bioavailability, potentially transforming ocular therapeutics. However, concerns about the safety and toxicity of nanomaterials in ophthalmology remain [1-3]. Given the potential risks associated with nanotoxicity the toxicity of nanomaterials typically used for therapeutic purposes—conducting in vivo toxicity studies is crucial for evaluating the safety of formulated nanomaterials. The size and shape of nanomaterials can significantly impact their efficacy when applied to the eyes, potentially causing unexpected effects. While small materials can easily penetrate ocular barriers and sensitive tissues, their form and size can influence cellular uptake and biodistribution [4]. Key factors such as surface charge, hydrophobicity, and functional groups are critical in nanomaterials' biocompatibility and interaction with ocular tissues. Surface modification techniques can enhance biocompatibility and reduce potential toxicity [3, 5, 6]. Moreover, nanomaterials' tendency to accumulate in physiological environments may lead to complications, such as occlusion of ocular blood vessels and inflammatory responses. The rate at which nanomaterials degrade and are eliminated from the body also significantly impacts their overall toxicity. Rapidly degrading materials may release harmful byproducts, while slow-degrading materials may accumulate in tissues, leading to prolonged damage [7, 8]. Recent disease treatment strategies have aimed to enhance pharmaceutical efficacy and selectivity while minimizing toxicity to normal tissues. Nanoscale liposomes and niosomes have emerged as drug delivery systems to meet these requirements. Liposomes hold great promise for gene and drug delivery due to their biocompatibility and modular properties. However, their toxicity is context-dependent, influenced by exposure time, dosage, and surface properties [9].

Niosomes, which combine the advantages of liposomes while overcoming challenges related to drug encapsulation, have been investigated for ocular drug delivery. Toxicity studies and immune responses associated with these formulations are crucial considerations. Achieving a balance between therapeutic efficacy and safety is paramount. A neutral liposomal formulation containing low cholesterol levels is essential for an adequate drug delivery system [10]. Niosomes represent an emerging class of drug delivery systems that retain the targeting benefits of liposomes while addressing issues related to low drug encapsulation and instability [11, 12]. Alyami et al. studied nonionic surfactant vesicles (niosomes) for ocular drug delivery, specifically investigating the toxicity of optimized niosomes using the HCE-2 cell line, which serves as a model for the corneal epithelium. Interestingly, the ethanol injection (EI) method produced smaller niosomes than the thin-film hydration (TFH) method, although the latter exhibited better stability over time. Incorporating pilocarpine HCl into the organic phase during niosome preparation significantly enhanced drug entrapment. Optimal Span-60 niosomes exhibited no corneal cellular toxicity and demonstrated high drug encapsulation. This study provides valuable insights into the design, evaluation, and toxicological screening of niosomes, emphasizing their potential for ocular drug delivery, particularly for older people [12].

CONCLUSION AND PROSPECTS

Due to the complex structure of the eye, pharmaceutical researchers face significant challenges in delivering drugs to targeted locations using various administration methods. Topical drug prescription, the most commonly used method, often proves ineffective due to the low bioavailability of medications. The intricate anatomy of the eye creates barriers to effective drug delivery via conventional routes. Although topical administration remains widely used, its limitations in bioavailability hinder therapeutic efficacy. However, nanomaterials, such as liposomes and niosomes, present promising solutions. These nanoformulations can provide sustained drug delivery, enhancing bioavailability and targeting at the desired site. Liposomes, in particular, offer an efficient means of encapsulating compounds, improving their solubility and bioavailability. The protective encapsulation provided by liposomes prevents rapid degradation and enables controlled drug release. Both niosomes and liposomes have emerged as valuable tools in therapeutics. Studies have shown that niosomes enhance drug stability, reduce dosage requirements, and improve delivery to targeted tissues. The properties of niosomes can be further optimized for specific routes of administration by applying novel preparation methods, loading techniques, and structural modifications. Since niosomes comprise surfactants, selecting the appropriate surfactant and optimizing the surfactant-to-cholesterol ratio is critical to minimizing toxicity, maximizing stability, and achieving optimal drug delivery efficiency.

However, evaluating whether extended retention times could lead to systemic side effects is essential. Although in vivo ocular toxicity studies of niosomal formulations have indicated no significant complications or inflammation, further toxicity assessments are needed for upcoming preclinical and clinical studies. The ongoing refinement of nanomaterials—such as niosomes and liposomes—holds great promise for advancing ocular drug delivery, particularly in managing inflammatory eye diseases. These innovative approaches may pave the way for significant breakthroughs in treating inflammatory conditions of the eye.

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CONFLICTS OF INTEREST

There are no conflicts to declare.

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