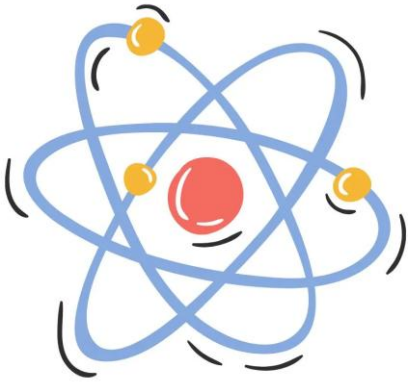

ISSN: 1672 - 6553

JOURNAL OF DYNAMICS AND CONTROL

VOLUME 10 ISSUE 07: P114-156

A COMPREHENSIVE REVIEW OF NANO-EMULSION BASED OPHTHALMIC TREATMENT FOR DRY EYE DISEASE

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JOURNAL OF DYNAMICS AND CONTROL
https://doi.org/10.71058/jodac.v10i0707

A COMPREHENSIVE REVIEW OF NANO-EMULSION BASED OPHTHALMIC TREATMENT FOR DRY EYE DISEASE

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Abstract: *Dry Eye Disease (DED) is a multifactorial disorder of the ocular surface characterised by tear film instability, inflammation, and ocular discomfort, leading to impaired vision and reduced quality of life. Conventional treatment approaches, primarily topical eye drops, are limited by poor bioavailability, rapid precorneal elimination, and the need for frequent administration, all of which affect patient compliance. In recent years, nano-emulsion-based drug delivery systems have gained significant attention as an advanced strategy to overcome these limitations. Nano-emulsions, due to their nanoscale droplet size, enhance drug solubility, improve corneal permeability, and prolong ocular residence time, thereby enabling sustained drug release and improved therapeutic outcomes. This review highlights the pathophysiology of DED, discusses the limitations of conventional therapies, and provides a comprehensive overview of nano-emulsion formulation strategies, mechanisms of action, and recent advancements in ocular drug delivery. Overall, nano-emulsion systems demonstrate considerable potential in improving drug efficacy, reducing dosing frequency, and enhancing patient compliance in the management of dry eye disease.*

Keywords*: Dry eye disease; Nano-emulsion; Ocular drug delivery; Tear film instability; Bioavailability; Corneal permeability; Sustained release; Patient compliance*

1. Introduction

Upwards of 217 million persons worldwide who are 18 years of age or older suffer from eye disorders that could impair their vision and ultimately result in permanent blindness, according to World Health Organisation (WHO) data from 2015(Nagaraj R et al. 2019). Over the past ten

https://doi.org/10.71058/jodac.v10i0707

years, numerous preclinical and clinical studies have been conducted to develop therapies for a range of eye disorders, including cataracts, diabetic retinopathy, glaucoma, age-related macular degeneration, and uveitis (Gorantla S et al. 2020). Dry eye is one of the most common ocular conditions worldwide, characterised by a preocular tear film anomaly that affects about 1 in 7 individuals aged 48 years and older. Women have a higher incidence of DED above the age of 50, and the sex difference in prevalence becomes more prominent with age. The rate rises with age, especially higher than the age of 40 for both sexes (Barabino S et al. 2016, Moss SE et al. 2000, Arita R et al. 2019). Topical eye drops constitute in excess of 90 of the ophthalmic formulations now available on the market. However, the eye's multiple protective mechanisms limit the therapeutic value of topically applied formulations, diminishing drug bioavailability and necessitating regular administration of eye drops over lengthy periods. The effectiveness of treatment is further limited by a decrease in patient compliance. The continual application of multiple eyedrops, which is frequently required to treat DED, may make therapy more difficult and lower patient compliance. (Abdelkader et al. 2012). The majority of the medication has been eradicated via enzymatic breakdown and tear fluid, or it might not be absorbed owing to the physiological eye barrier (Akhter et al. 2022). As a very potent anti-inflammatory and antibacterial biopharmaceutical that prevents bacterial and ocular inflammation, dexamethasone has been used extensively (N. Ren et al. 2019). However, due to ocular obstacles, the clinical efficacy of drug delivery by eye drops or intravitreal administration is limited by inherent shortcomings such as poor absorption, inefficient distribution, and inadequate bioavailability (H. Zierden et al. 2021). Furthermore, recombinant proteins and peptides, particularly anti-vascular endothelial growth factor (VEGF) medications with high potency and activity (such as aflibercept and ranibizumab), reduce drug-drug interactions and are frequently advised to prevent neovascular fundus disorders.(X. Liu et.al

https://doi.org/10.71058/jodac.v10i0707

2020) Nevertheless, because of their high molecular weight and strong hydrophilicity, which prevent them from passing through intricate cell membranes and tissue barriers, these medicines must be administered intravitreally. Additionally, their quick chemical and physical deterioration pose serious problems for long-term therapeutic efficacy, necessitating recurrent intravitreal interventions that may cause intraocular haemorrhage, infection, and discomfort, all of which could result in low patient compliance (A. Mandal et al. 2018). The limitations of self-assembled polymeric micelles include a lack of potential and adequate utilisation in gene delivery, limited entrapment of macromolecule agents, and unsuitable scale-up methods (A. Mandal et al. 2017). Although the problems of low encapsulation efficiency, poor stability, and burst release of pharmaceuticals have not yet been addressed, the microspheres show promise as a delivery mechanism for DED medications (Ratay et al. 2018). Microparticles have limitations, such as large particle size and irritation (Wadhwa S et al. 2009). Exosomes' limitations are Challenges of separation and purification, Low output yield, Low efficiency of cargo loading, and problems with stability and storage. Possibility of unintended immunological reactions, Absence of standardised procedures, unknown long-term safety (Kalluri R et al. 2020). Conjugates have limitations, such as problematic manufacture and formulation, restricted ability to penetrate bigger substances, possibility of toxicity or ocular irritation, the tear film's short retention time, and reactions of the immune system to big conjugates (Kickova E et al .2021). The constraints of microemulsions stabilising droplets in a microemulsion require a high concentration of surfactant and cosurfactant. The system's high-melting chemicals have a limited solubilising ability. When used in pharmaceutical applications, the surfactant needs to be non-toxic. Temperature and pH are two external elements that impact the stability of microemulsions and can change when they are administered to patients (Madhav S et al .2011). Nanomicelles have limitations such as

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potential stability concerns (Torchilin VP et al.2001). Nanosuspensions have limitations, such as surfactant addition may result in physical instability issues, including sedimentation and even toxicity. Particle size irregularities could lead to non-homogeneous particles and poor reproducibility. Additionally, there is a chance that the solvent will have negative effects, and scaling up the procedure is difficult. Nanosuspensions encounter significant challenges due to sedimentation and compaction (Coco G et al .2024). Limitations of liposomes include the possibility of aggregation and fusion, as well as the substance's poor stability during storage (Wu Y et al. 2024). Through nasal routes, Tyrvaya® (varenicline nasal spray) promotes the production of tears. restricted to DED that is aqueously deficient and may result in nose pain (Frampton et al.2022). In evaporative DED, NOV03 stabilises the tear lipid layer. Biomarker Testing: InflammaDry for MMP-9 is accessible and is currently reasonably priced, although there are still restrictions on long-term clinical accessibility and long-term safety findings. (Tauber et al.2023) In terms of corneal regeneration, mesenchymal stem cell (MSC) therapy exhibits promise. Long-term research is necessary to assess the safety, effectiveness, and regulatory clearance (Kato T et al. 2023). Lipi Flow® improves lipid secretion by unclogging the meibomian glands. Affordability and accessibility continue to be obstacles for many adoptions (Tauber et al. 2023). PROSE scleral lenses promote surface healing and distribute medications, but they are expensive and difficult to use in low-resource environments (Nakhla et al., 2024). The effectiveness of omega-3 supplementation in lowering tear evaporation is inconsistent. Definitive findings are limited by inconsistent study designs.

(Lopez I et al. 2023). Cataract surgery is the most common ocular treatment in modern clinical practice, and prior eye surgery is another risk factor (Kelly et al.2018). Although many patients have had outstanding results from developments in cataract surgery techniques over the past two decades, some still have post-operative problems, including DED, which can cause patient

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discontent and a lower quality of life (Miura et al.2022).30.3% of patients treated with CyclA sol reported emergent adverse effects. 30.9% of the eyes in the control groups (vehicle or 0.05% cyclosporine) experienced TEAEs. This conclusion implies that there is inadequate information to support a higher level of safety. CyclA Sol's profile is in contrast to commercially available Cyclosporine, or CsA (Wirta DL et al.2019). Whether SNEDDS preparations are more effective than C-CsA at suppressing T cell responses and IL-2 expression is unclear (BarbosaFL et al .2017). The Winsor type IV nanoemulsion is made up of one phase, so that CsA's activity remains constant throughout the nanoemulsion. These preparations were optically transparent and had very little turbidity in the current study. They were also chemically and thermodynamically stable, as shown by low instability indices and steady pH levels across time. SNEDDS is prepared utilising a low-energy technique, in contrast to the high-energy process for C-CsA (AntonN et al.2011). Because of this, several therapy approaches used to treat dry eye illness seem to be ineffective for several reasons and have not met safety and efficacy standards. Numerous risk factors, such as demographic, environmental, dietary, systemic, and ocular problems, as well as the use of specific drugs, are associated with DED (Stapleton et al.2025). Inflammatory modulation is a common aspect in the pathogenesis of a number of systemic illnesses linked to dry eye disease, such as migraine, thyroid disease, and connective tissue disorders (Stapleton et al. 2017). Air pollutants such as smoke and nitrogen oxide (Hwang et al 2016, Berg et al. 2020), low humidity (Galor et al. 2014), and high altitude (Hwang et al 2016) are environmental factors that can raise the incidence of dry eye illness. It is complicated how hereditary risk factors relate to dry eye illness. According to twin studies, dry eye is moderately influenced by hereditary variables (Vehof et al. 2014). Rapid drug clearance and low bioavailability are caused by several biological barriers on the ocular surface, including the tear film barrier and the corneal and conjunctival barrier. In particular,

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the thick conjunctival epithelium prevents drug entrance, and the tear film causes fast drug loss (Awwad et al.2017). In order to address DED within a public health framework, clinical evidence must be translated into scalable population-level policies that connect preventive medicine with ophthalmologic care. Through the use of digital health technology, comprehensive education, and the integration of ocular-surface health into It is feasible to lessen the burden of DED, enhance the quality of life, and reap long-term financial rewards through occupational and community health efforts. This strategy highlights the need for a multidisciplinary approach that includes clinical practice, public health policy, and health technology innovation and places an emphasis on proactive prevention as opposed to reactive therapy (Farrand et al. 2017; Divy Mehra et al .2020). An even greater financial burden on society and individuals is anticipated when newer, more expensive treatments become available (Chen EM et al .2016). Additionally, dry eye is still underdiagnosed while being a major threat to public health, suggesting that there may be a substantial unexplored burden of illness (Farrand KF et al .2017). Dry eye disease has been classified into two main entities: evaporative (EDE) and aqueous-deficient (ADDE) DED [38]. (ADDE), which is characterised by the lacrimal glands' incapacity or inefficiency to generate tears, and evaporative dry eye (EDE), which is usually linked to excessive tear fluid evaporation. ADDE is typically linked to a compromise in the integrity of the lacrimal functional unit and may or may not have an autoimmune aetiology. The more prevalent type of DED, known as EDE, is often linked to meibomian gland dysfunction (MGD), which is characterised by altered or decreased tear fluid lipids, potentially compromising the integrity and quality of the tear fluid (Nichols et al. 2011, Baudouin et al.2016). DED currently has no known cure, so treatment must be continued (Jones L et al .2017).Drug development for DED has been marked by a poor success rate and comparatively few compounds reaching the approval stage, even though there

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are many promising candidates in the pipeline (Chao W et al.2016, Novack GD et al. 2017) The variability of the patient group in terms of origins and clinical presentation, as well as the lack of correlation between symptoms and objective indicators of the disease, may be the reason of this (Chao W et al.2016, Wolffsohn JS et al.2017). It is estimated that 11.59% of people globally suffer from dry eye condition (Vehof J et al.2021). A "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface" is the definition of dry eye disease. It is associated by subacute ocular surface inflammation and elevated osmolarity of the tear film [46]. According to recent research, dry eye is an inflammatory condition that shares many characteristics with autoimmune diseases (Stern ME et al.2013, Stevenson W et al.2012, e1). The pathogenetic triggering mechanism is thought to be stress to the ocular surface caused by environmental stimuli, infection, endogenous stress, antigens, and genetic factors. Autoreactive T helper cells proliferate and invade the lacrimal gland and ocular surface as a result of proinflammatory cytokines, chemokines, and matrix metalloproteinases (Stern ME et al.2013). Loss of eyesight will follow from a vicious cycle of inflammation and damage to the ocular surface. Corneal problems or conjunctival scarring may develop in advanced or severe forms of dry eye illness. Apart from filamentary keratitis, the course may be complicated by ulceration, corneal perforation, and persistent epithelial abnormalities. Rarely, serious repercussions of dry eye disease are seen in conjunction with xerophthalmia, ichthyosis, Stevens-Johnson syndrome, graft-versus-host disease, and primary or secondary Sjögren's syndrome (e14–e21). They may cause functional blindness or even blindness (Turgut B et al. 2009. DED can have disastrous clinical repercussions. DED is accompanied by ocular surface inflammation, which in severe cases can result in corneal ulcers and blindness. (Swilem AE et al.2020) . In women over 80, the incidence is 30.1%, while in those between the ages of 20 and

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29, it is 2.7%. Women have a greater rate of DED over the age of 50, and the sex difference in prevalence becomes more pronounced with age. The rate rises with age, especially after the age of 40, in both sexes (Paulsen AJ et al. 2014). Owing to the ocular surface's dynamic nature, foreign substances are quickly removed from the eye through blinking, nasolacrimal drainage, reflex tears, and basal tears (Järvinen et al.1995). The characteristics of the ocular tissues and tear fluid, which combined, provide a strong obstacle to the intraocular transfer of medications (Duvvuri et al.2004). Dry eye has been demonstrated to result from surgical procedures for ocular refractive imperfections such as laser-assisted in situ keratomileusis (LASIK), photorefractive keratectomy (PRK), and tiny incision lenticule extraction (SMILE) (Shtein RM et al. 2011). This is because these surgical treatments have a downside of inevitably damaging the sensory nerves on the surface of the eye (Wong AHY et al. 2019). Only 10–15% of patients with DED are thought to have aqueous-deficient dry eye alone, whereas the majority of DED cases (more than 85%) contain an evaporative component (Lemp MA et al.2012). Explaining the chronic nature of EDE, its pathophysiology, and the negative consequences of frequent doctor visits or "doctor shopping" without adhering to treatment is crucial. If a patient is diagnosed with MGD, they should be open to changing their lifestyle and have reasonable expectations (e.g., symptoms may somewhat improve but are rarely removed) (Downie LE et al.2017). The development of dry eye disease (DED), a multifactorial disease of the ocular surface marked by a loss of tear film homeostasis and accompanied by ocular symptoms, is influenced by inflammatory damage to the ocular surface, tear film instability, neurosensory abnormalities, and hyperosmolarity (Craig JP et al. 2017). One of the most frequent issues that ophthalmologists deal with is EDE brought on by MGD in India, hospital-based. According to research, its prevalence ranges from 42.5% to 57.2% (Chatterjee S et al.2020). Quick clearance from tears poses a significant barrier to the delivery of drugs to even the ocular surface; access

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and penetration seem to be more facile for the ocular surface, followed by the (meibomian gland) MGs and then the (lacrymal glands) LGs (Hsueh PY et al. 2015). Ophthalmology has made significant advancements with nanomedicines as delivery technologies. By overcoming ocular physiological barriers through mucoadhesive capabilities, they boost ocular medication bioavailability with the ultimate objective of delivering pharmaceuticals to the target site with a sufficient concentration (Gote et al.2019, Weng et al.2017). By enabling sustained as well as trustworthy medication delivery by employing nanocarriers, such as nanospheres and nanoparticles, recent advances in nanotechnology have shown promise in the rejuvenation and healing of sick and injured corneas. Nanotechnology solves many of the obstacles encountered with earlier drug delivery technologies by shielding medicines from degradation during transport, improving corneal absorption, and enhancing corneal bioavailability and half-life on the ocular surface (Janagam DR et al.2017). Nanotechnology may be beneficial to DED. Nanotechnology evolved quickly during the last three decades, providing intriguing novel approaches to alleviating DED (Mitchell MJ et al.2021). Numerous scientific disciplines, including engineering, electronics, physics, material science, and molecular manufacturing, use nanotechnology (Savvidou et al.2024). Nanomedicine is a new area that applies nanoscience knowledge and methods to medical biology and illness. both remediation and prevention (Haba Y et al.2017). A material with a size range of 1 to 100 nm that affects the frontiers of nanomedicine, including biosensors, microfluidics, drug delivery, microarray testing, and tissue engineering, is known as a nanomaterial (Arayne MS et al .2007). The emergence of a novel carrier that is 100 nm or smaller is referred to as nanomedicine. Nanomedicine uses spatially ordered, complex, and flexible nanomaterials to deliver a range of medicinal benefits at the molecular level (Rahamathulla M et al. 2021). Topical medication (eye drops) absorption is impacted by conjunctival blood circulation. When all of the obstacles

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are taken into account, topical medication loss is approximately 95%. The ocular epithelial barrier is encountered by the remaining portion of the medication (Boddu et al.2010). Drug molecules have to move beyond the physiological barriers that protect tissue in order to have the best feasible therapeutic effect. (Cholkar et.al 2013). Drug bioavailability is decreased by a number of ocular barriers that control and restrict the rate of absorption in the anterior and posterior portions of the eye. The tear film, cornea, conjunctiva, sclera, blood-aqueous barrier, and blood-retina barrier are some of these barriers. (Del Amo et al. 2017). To conquer the limitations of traditional means of administration, nanomedicine makes use of an assortment of nanomaterials, including organic (like liposomes, micelles, and dendrimers), inorganic (like metal nanoparticles and silica), and biological (like exosomes) (Tang Z et al.2022). Nanomedicines have the potential to boost drug ocular bioavailability and provide patients with safe products by extending drug retention and controlling drug release (Lallemand F et al. 2017). The optimum sizes of nanoparticulate drug delivery systems (DDSs) for polymeric nanoparticles, liposomes, and micelles are 40–100 nm, 80–200 nm, and 20–60 nm, respectively; dendrimers are the smallest of these, having a diameter of just 10 nm or less (Que H et al.2022). Currently, a lot of research is being done on innovative drug delivery methods based on nanotechnology. Several nanotherapeutics, including nanoemulsions, nanosuspensions, microemulsions, liposomes, and nanomicelles, are in clinical trials, and some have received FDA approval as novel treatments for DED (Nagai et al.2022). Digital surroundings, environmental circumstances, nutrition, cosmetics use, elective medicine and surgeries, contact lenses, sociological factors, and general lifestyle are just a few of the numerous facets of our existence that can affect the ocular surface. (Galor A et al.2023) As a result, all of these must be taken into account when managing the illness, and the best course of action will probably involve many approaches or treatments. Furthermore, it has been

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discovered that hereditary factors contribute to DED. (Hsu CC et al.2024). Medication is quickly removed from the surface of the eyes when the eye drop is administered by the start of lacrimal fluid secretion. Because of the increased liquid volume in the cul-de-sac, precorneal variables such as tear turnover and reflex blinking, the elimination mechanism restricted the anterior eye segment's drug retention. (Weng et al.2016)] This is regarded as the primary roadblock to applying a medication topically. The variegated layer of squamous and columnar epithelial cells, coupled with the intercellular. Tight junctions serve as therapeutic permeation barriers via paracellular routes. The epithelial tight junctions are clogged by different protein molecules and calcium ion concentrations. Nevertheless, the drug permeability is enhanced in some way by the breakdown of the tight junction membrane or the complexation of calcium ions with EDTA. (Gaudana et al.2010). According to reports, 90% of eye drops on the market only increased the drug's bioavailability by 5%. The remaining drug has been eliminated through a variety of processes, including tear fluid, nasolacrimal secretion, protein binding, enzymatic degradation, or metabolism by the enzyme’s protease and esterase. Despite this, several physiological barriers, such as the corneal barrier, blood–retinal barrier, and blood–aqueous barrier, significantly contribute to poor drug retention (Nayak et al.2020). For pharmaceutical chemists, delivering medications to the eye remains one of their toughest undertakings (Macha S et al.2021). The primary hurdle to topical medication uptake is the corneal epithelium. (Klyce et al. 1985). Although the corneal epithelium's pores are negatively charged at physiological pH, negatively charged molecules penetrate more slowly than positively charged molecules (Rojanasakul et al. 1989). The eye has an intricate set of physiology and is a highly susceptible organ (Krishnaswami V et al.2018). Given the distinct and vital pharmacokinetic environment in the eye, ocular drug delivery is one of the most thrilling and difficult projects for a pharmaceutical scientist (Sahoo SK et al.2018). Artificial

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tears (ATs), which imitate tears and enhance their durability and traits, are the major therapy for DED. All DED subtypes, including evaporative and aqueous-deficient DED, have been shown to benefit from ATs in terms of symptoms and indicators of illness. Nonetheless, it is not unexpected that ATs do not work for every patient, given the distinct characteristics of DED. It is crucial to determine the underlying causes of the illness and appropriately escalate treatment when AT has no way to alleviate DED symptoms and/or indications (Kim et al. 2021). Due to the multifactorial and complex nature of dry eye disease, conventional approaches, surgical interventions, and traditional drug formulations have limited effectiveness, according to multiple reports. Novel therapeutics are being developed to improve diagnosis and treatment, enhance targeted drug delivery, and minimise toxicity. In this context, drug delivery systems based on nanotechnology have emerged as a viable method for the efficient treatment of dry eye illness.

This review article provides insight regarding recently designed nanomedicine for dry eye disease. We also retrieved data on the recent advancement in the arena of nano medicines. Their current challenges encountered in the practical field for efficacious industrial production and clinical translation have been provided, along with prospects that are also embedded in this article. Finally, nanomedicine is expected to help the early diagnosis and treatment of dry eye disease.

1.1. Overview of dry eye disease

Dry Eye Disease is defined as a multifactorial disease of the ocular surface characterised by a loss of tear film homeostasis accompanied by ocular symptoms. The prevalence of DED ranges from 5% to 50% worldwide, depending on environmental conditions and age groups. Risk factors include ageing, hormonal imbalance, prolonged exposure to digital screens,

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environmental pollution, and contact lens use. The condition significantly affects daily activities such as reading and driving, reducing overall quality of life (Craig et al., 2017).

1.2 Anatomy and Physiology of the Human Eye

The human eye is a highly organised sensory organ essential for vision, consisting of three main anatomical layers: the outer fibrous layer (cornea and sclera), the middle vascular layer or uvea (iris, ciliary body, and choroid), and the inner neural layer (retina). The cornea and lens are responsible for refracting and focusing light onto the retina, where photoreceptor cells (rods and cones) convert light into neural signals transmitted to the brain through the optic nerve. Physiologically, ocular surface homeostasis is maintained by the tear film, aqueous humour, and intraocular pressure. The tear film, composed of lipid, aqueous, and mucin layers, plays a critical role in lubrication, protection against pathogens, and maintaining a smooth optical surface. Any disruption in tear film composition or stability can result in dry eye disease, leading to irritation, inflammation, and visual impairment (Bron et al., 2017; Willcox et al., 2017). Figure 1 illustrates the basic anatomical structure of the human eye, highlighting key components involved in vision and ocular surface maintenance.

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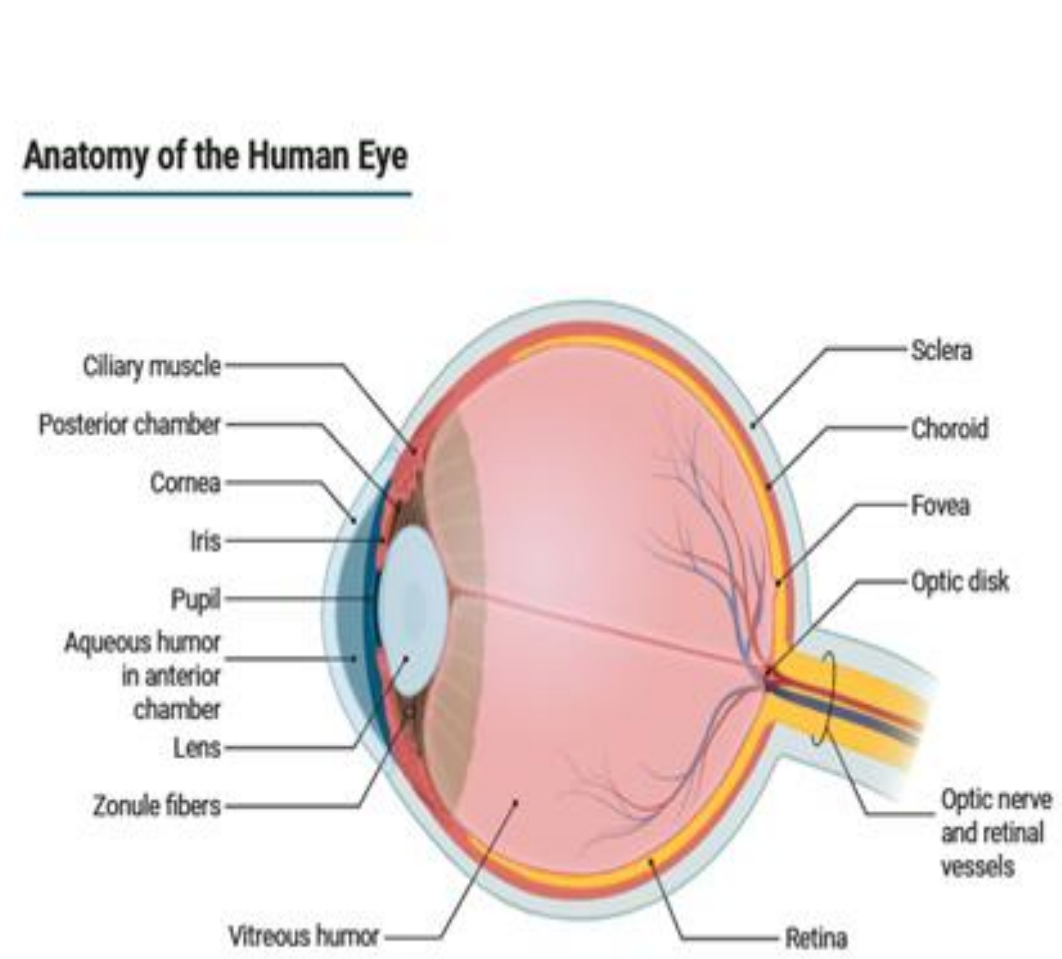

Figure 1: Anatomy and physiology of the eye. This figure was created with Biorender.com

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1.3 Anatomy and Physiology of Tear Film

The tear film is a thin, multilayered structure that covers the ocular surface and plays a vital role in maintaining ocular lubrication and optical clarity. Fig 2. It consists of three layers: the lipid layer, aqueous layer, and mucin layer. The lipid layer prevents tear evaporation, the aqueous layer provides nutrients and antimicrobial components, and the mucin layer ensures uniform spreading of tears over the corneal surface. Disruption in any of these layers can lead to tear film instability and dry eye disease (Willcox et al., 2017).

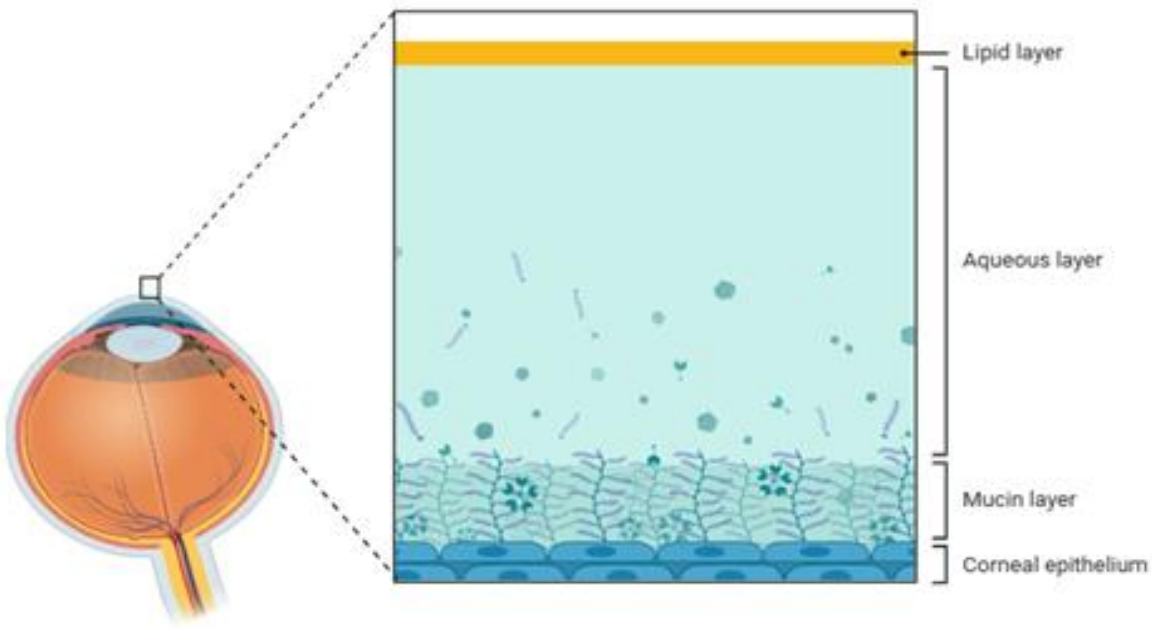

Figure 2: Eyes have 3 layers, which are affected by environmental and genetic factors. This figure was created with Biorender.com

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4. Patents

The various patents are filled for dry eye disease. However, a limited number of patents are filed or approved based on nanoformulations for dry eye disease, as listed in Table 1.

Table 1: Patents assessing therapeutic benefits of nanoformulations for dry eye disease therapy

S. No.	Product / Technology	Drug	Patent No.	Year	Inventors	Key Patent Claim	Referecnes
1	Restasis® (anionic nanoemulsion)	Cyclosporine A	US 5,474,979	1995	Sall K.; Stevenson D.	Stable oil-in-water emulsion for ocular CsA delivery	Sall K., Stevenson D.. Ophthalmic emulsion containing cyclosporine. US Patent 5,474,979, 1995.

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2	Restasis® improved formulation	Cyclosporine A	US 6,254,860	2001	Ding X.; Sall K.	Enhanced stability and bioavailability	Ding X., Sall K.. Stable ophthalmic cyclosporine emulsion compositions. US Patent 6,254,860, 2001.
3	Ikervis® (cationic nanoemulsion)	Cyclosporine A	US 7,927,613	2011	Daull P.; Garrigue J.S.	Cationic emulsion increases ocular surface retention	Daull P., Garrigue J.S.. Cationic oil-in-water emulsions for ophthalmic use.

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							US Patent 7,927,613, 2011.
4	Cyclokat®	Cyclosporine A	EP 1648456	2006	Benita S.	Cationic lipid-based ocular drug delivery	Benita S.. Cationic emulsions for ocular delivery of cyclosporine. EP Patent 1648456, 2006.
5	Cequa® (OTX-101 nanomicelle)	Cyclosporine A	US 9,066,843	2015	Lallemand F.; Daull P.	Nanomicellar solubilization of CsA	Lallemand F., Daull P.. Nanomicellar formulations for ophthalmic cyclosporine

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							delivery. US Patent 9,066,843, 2015.
6	CyclASol® (EyeSol technology)	Cyclosporine A	US 12,059,449	2024	Müller-Goymann C.	Water-free ocular drug delivery system	Müller-Goymann C.. Water-free ophthalmic compositions for dry eye disease. US Patent 12,059,449, 2024.
7	Eysuvis® (KPI-121 nanoparticles)	Loteprednol	US 8,796,353	2014	Schaus J.; Srinivasan S.	Mucus-penetrating nanoparticle system	Schaus J., Srinivasan S.. Mucus-penetrating particle

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							drug delivery systems. US Patent 8,796,353, 2014
8	Lacrisek® liposomal spray	Vitamins A & E	EP 2233035	2010	Gupta P.	Liposomal tear film stabilization	Gupta P.. Liposomal compositions for ocular surface lubrication. EP Patent 2233035, 2010
9	Artelac Rebalance®	Vitamin B12	EP 2062735	2009	Baudouin C.	Liposome-based tear substitute	Baudouin C.. Liposomal tear substitutes for dry

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							eye treatment. EP Patent 2062735, 2009
10	General nanoemulsion system	Multiple	US 20070110729	2007	Sall K	Oil-in-water nanoemulsion for ocular delivery	Sall K.. Oil-in-water nanoemulsion systems for ophthalmic delivery. US Patent 20070110729, 2007
11	Liposomal ocular delivery	Multiple	US 20090297488	2009	Lasic D.D.	Phospholipid vesicle-based drug delivery	Lasic D.D.. Liposome-based drug delivery systems.

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							US Patent 20090297488, 2009.
12	Nanomicelle delivery	Multiple	US 8,318,195	2012	Ocular Therapeutix	Polymeric micelle ocular drug delivery	Kumar V.. Polymeric micelle formulations for ophthalmic drugs. US Patent 8,318,195, 2012.
13	Hydrogel ocular system	Multiple	US 8,252,327	2012	Peppas N.A.	Hydrogel-based sustained release system	Peppas N.A.. Hydrogel systems for sustained ophthalmic drug delivery. US Patent

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							8,252,327, 2012.

5. Mechanism of Tear Film Erosion and Epithelial Cell Damage in Dry Eye Disease

Dry eye disease is driven by tear film instability and excessive evaporation, leading to progressive erosion of the tear film layers. The initial compromise of the lipid layer increases evaporative loss, resulting in tear hyperosmolarity and subsequent cellular stress on the ocular surface. This hyperosmolar environment activates inflammatory pathways, including the release of cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), along with matrix metalloproteinases (MMPs), which degrade epithelial cell junctions. As a result, corneal epithelial cells undergo damage and apoptosis, while goblet cell density decreases, reducing mucin production and further destabilising the tear film. As shown in Figure 3, erosion of the tear film exposes the corneal epithelium, leading to epithelial cell damage and surface irregularities, thereby sustaining a vicious cycle of inflammation and tear film disruption (Pflugfelder & de Paiva, 2017; Baudouin et al., 2016).

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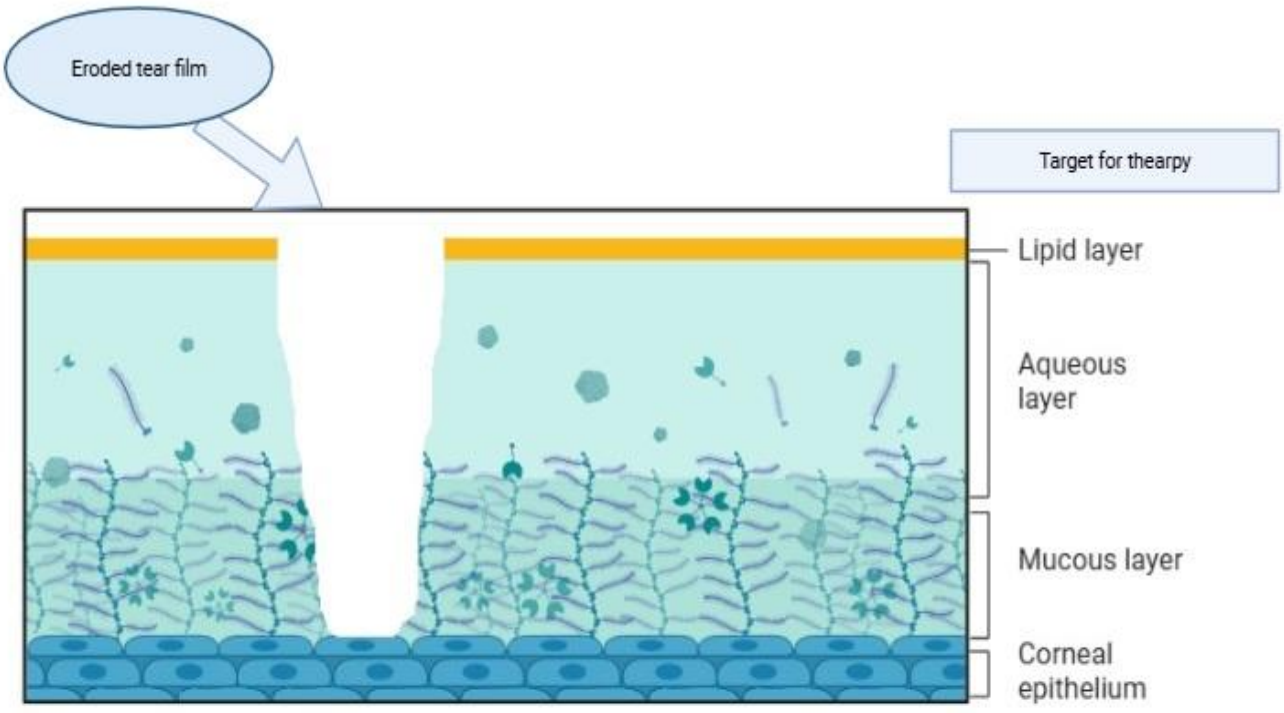

Figure 3: Tear film erosion and epithelial cell damage. This figure was created with Biorender.com

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5.5 Pathophysiology of Dry Eye Disease

The pathophysiology of DED involves tear film instability, hyperosmolarity, inflammation, and damage to the ocular surface. Increased tear osmolarity triggers inflammatory pathways that lead to epithelial cell damage and reduced tear production. Meibomian gland dysfunction is another major contributor to evaporative dry eye, resulting in increased tear evaporation and ocular surface irritation (Bron et al., 2017).

5.6 Factors Contributing to the Vicious Circle of Dry Eye Disease (DED)

Dry eye disease (DED) is influenced by a combination of extrinsic and intrinsic factors that contribute to the initiation and progression of the vicious cycle of tear film instability and ocular surface damage. Extrinsic factors such as environmental conditions (low humidity, air pollution, prolonged screen exposure), contact lens wear, and topical medications can disrupt the tear film by increasing evaporation and reducing tear stability. In contrast, intrinsic factors, including ageing, hormonal imbalances, autoimmune disorders, and meibomian gland dysfunction, impair tear production and alter tear composition. These factors collectively promote tear hyperosmolarity and trigger inflammatory responses, leading to epithelial cell damage and further destabilisation of the tear film. As shown in the figure 4, both extrinsic and intrinsic factors interact to amplify inflammation, tear film erosion, and ocular surface damage, thereby sustaining the self-perpetuating vicious cycle of DED (Nelson et al., 2017; Stapleton et al., 2017).

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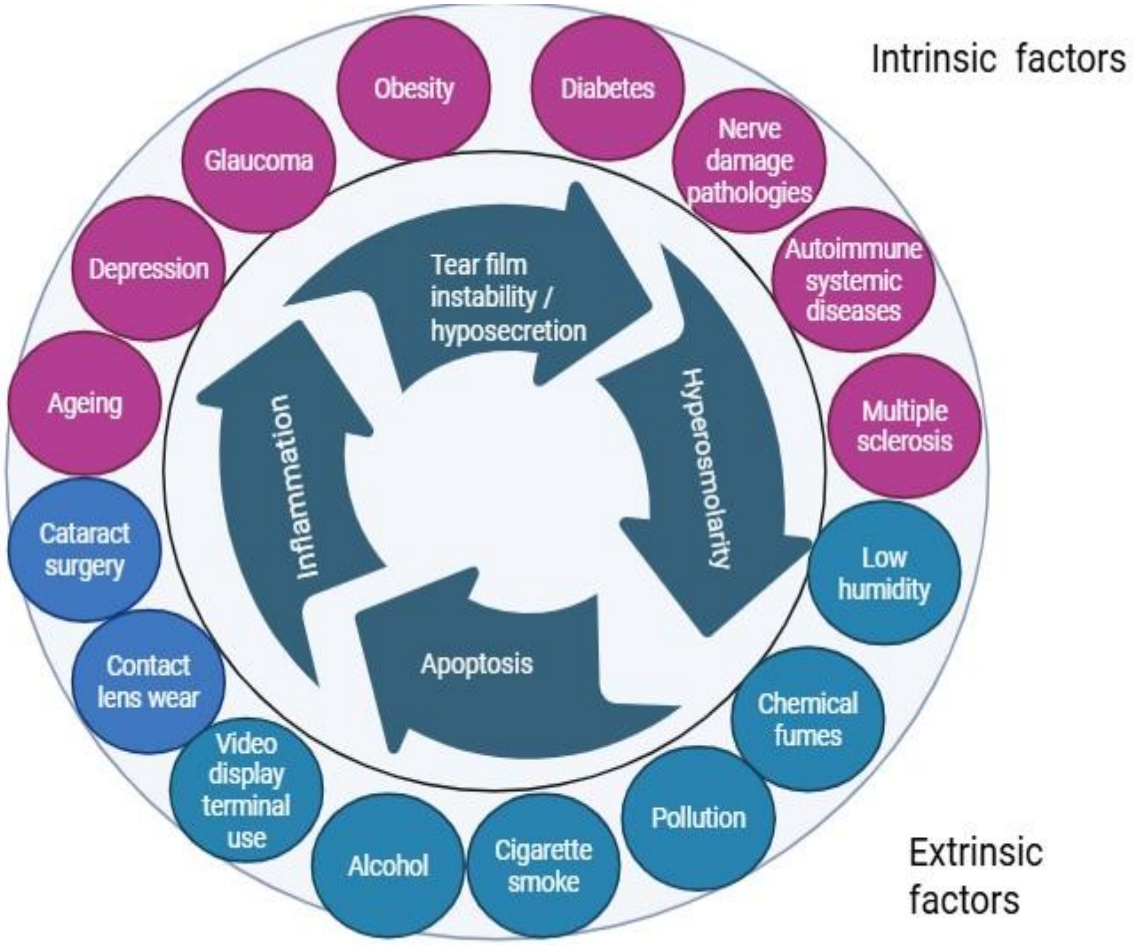

Figure 4 : Extrinsic and intrinsic factors that contribute to the vicious circle of dry eye disease (DED) .This figure was created with Biorender.com. Reproduced from

6. Conventional Treatment Approaches

The management of dry eye disease commonly involves artificial tears, anti-inflammatory drugs, corticosteroids, and immunomodulators such as cyclosporine. Artificial tears provide temporary lubrication but do not address underlying inflammation. Anti-inflammatory agents help reduce ocular surface inflammation, but conventional eye drops often require frequent administration due to rapid clearance from the eye (Baudouin et al., 2016).

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6.1 Challenges in Ophthalmic Drug Delivery

Several physiological barriers, including the corneal epithelium, conjunctival absorption, and rapid tear turnover, limit ocular drug delivery. These barriers significantly reduce drug absorption, resulting in less than 5% ocular bioavailability for most conventional formulations. As a result, frequent dosing is required to achieve therapeutic effects (Gaudana et al., 2010).

6.2 Nano emulsion: Concept and Characteristics

Nano emulsions are colloidal dispersions consisting of oil droplets dispersed in water with droplet sizes typically ranging from 20–200 nm. They are stabilised by surfactants and co-surfactants that reduce interfacial tension. Nano emulsions possess unique properties such as high surface area, improved drug solubility, and enhanced stability, making them suitable for ophthalmic drug delivery applications (Sharma et al., 2019).

6.3 Methods of Nano emulsion

Nanoemulsions can be prepared using high-energy and low-energy techniques. High-energy methods include ultrasonication and high-pressure homogenization, which use mechanical energy to reduce droplet size. Low-energy methods such as phase inversion temperature and spontaneous emulsification rely on changes in temperature or composition to form nano-sized droplets (Solans & Solé, 2012).

6.4 Methods of Nanoemulsion Preparation

Nanoemulsions are typically prepared using high-energy and low-energy methods, both of which aim to produce stable dispersions with droplet sizes in the nanometer range suitable for

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ophthalmic delivery. High-energy methods involve the application of external mechanical forces to break down coarse emulsions into nanosized droplets. Techniques such as high-pressure homogenization, ultrasonication, and microfluidization are commonly employed, where intense shear stress and turbulence reduce droplet size and improve uniformity. These methods are widely used due to their reproducibility and ability to produce kinetically stable nanoemulsions, although they may require specialised equipment and higher energy input (Gupta et al., 2016; McClements, 2012).

In contrast, low-energy methods rely on the intrinsic physicochemical properties of the system, such as phase behaviour and interfacial tension, to form nanoemulsions without significant external energy. These include spontaneous emulsification, phase inversion temperature (PIT), and phase inversion composition (PIC) methods. Such approaches utilise changes in temperature or composition to induce the formation of fine droplets, offering advantages like lower energy consumption and better suitability for thermostable drugs. (Solans & Solé, 2012; Tadros et al., 2004).

6.5 Characterisation of Nano emulsion

Characterisation of nano emulsions is essential to ensure formulation stability and effectiveness. Important parameters include particle size distribution, zeta potential, viscosity, drug loading efficiency, and stability studies. Particle size influences drug penetration, while zeta potential indicates electrostatic stability of the formulation (Gupta et al., 2016).

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7. Advantages of Nanoemulsion in Ophthalmic Drug Delivery

Nanomemulsions provide several advantages, including enhanced drug solubility, improved ocular penetration, increased retention time, and controlled drug release. Their small droplet size allows better interaction with the ocular surface, leading to improved therapeutic outcomes and reduced dosing frequency (Agarwal et al., 2013).

7.1 Application of Nanoemulsion in Dry Eye Disease

Nanoemulsion formulations are particularly useful for delivering anti-inflammatory drugs and lubricants to the ocular surface. These formulations help stabilize the tear film, reduce inflammation, and improve patient comfort. The nanoscale droplets increase drug penetration and prolong residence time on the ocular surface (Sharma et al., 2019).

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8 Recent Advances and Research

Recent research has focused on nanoemulsion formulations containing cyclosporine, tacrolimus, and other anti-inflammatory agents for the treatment of DED. Studies have demonstrated improved drug bioavailability, prolonged ocular residence time, and enhanced therapeutic efficacy compared with conventional formulations (Fialho & da Silva-Cunha, 2004).

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9 Marketed Nano emulsion Ophthalmic Products

Several nanoemulsion-based ophthalmic products have been developed for dry eye treatment. Restasis® (cyclosporine ophthalmic emulsion) is one of the most widely used nanoemulsion formulations for moderate to severe dry eye disease. Other products such as Cequa® and

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Ikervis® also utilize advanced nanoformulation technologies to improve drug delivery (Lallemand et al., 2012).

10 Challenges and Limitations

Despite their advantages, nanoemulsions face challenges such as long-term physical stability, surfactant toxicity, manufacturing complexity, and regulatory approval requirements. These factors must be carefully addressed during formulation development to ensure safety and effectiveness (Gupta et al., 2016).

11 Future Perspectives

Future research in nanoemulsion technology focuses on improving stability, targeting ocular tissues more effectively, and developing multifunctional formulations that combine anti-inflammatory and lubricating agents. Advances in nanotechnology may lead to more efficient treatments for dry eye disease in the coming years (Sharma et al., 2019).

12 Conclusion

Nanoemulsion-based ophthalmic drug delivery systems represent a promising strategy for improving the treatment of dry eye disease. Their ability to enhance drug solubility, stability, and ocular bioavailability makes them superior to conventional formulations. Continued research and technological advancements will likely expand their application in ophthalmic therapy.

https://doi.org/10.71058/jodac.v10i0707

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

https://doi.org/10.71058/jodac.v10i0707

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