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Review Article

Nanotechnology-based Therapeutic Strategies for Dry Eye Disease

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Abstract

Dry eye disease (DED) is a prevalent ocular condition affecting a significant proportion of the global population. Characterized by disruption of tear film homeostasis, DED results in dryness, discomfort, impaired visual clarity, and potential corneal damage. Despite its severe consequences, consistently effective treatments for DED remain elusive, leaving the majority of patients with persistent symptoms. This review aims to examine recent advancements in DED therapy, emphasizing the role of nanotechnology-based delivery systems in the development of novel treatments. By harnessing the potential of cutting-edge nanotechnology, we aspire to unveil innovative therapeutic strategies that address the unmet needs of patients with DED. Furthermore, we will discuss the current challenges, limitations, and future associated with these novel nanotechnology-based therapies for managing DED.

Introduction

DED, a general ocular condition, disrupts tear film homeostasis and affects the ocular surface, leading to desiccation, discomfort, impaired visual acuity, and potential corneal deterioration.[1] Contemporary treatments for DED include ocular lubricants, anti-inflammatory medications, and punctal occlusion (closure of tear ducts).[2] Additionally, lifestyle adjustments and environmental modifications can be employed as therapeutic strategies to mitigate the risk of tear film destabilization.[3]

A strong association has been established between the onset of DED and an increased propensity for depressive symptoms, which were prevalent in 50–82% of the examined cases.[4,5] Supporting evidence from other studies also suggests that depression and anxiety frequently coexist in patients with DED.[6] These findings indicate that addressing depressive symptoms is a crucial and often-overlooked aspect of DED management, warranting comprehensive attention to achieve satisfactory outcomes. Moreover, the co-occurrence of anxiety may further aggravate DED symptoms, underscoring the need for a holistic approach to treatment that considers both ocular and psychological factors.

Keywords: Dry eye disease; Nanoformulations; Tear film; Cubosomes; Niosomes.
Abbreviations: DED, dry eye disease; HA, hyaluronic acid; HSP, heat shock protein; MGD, meibomian gland dysfunction; PG-HPG, Propylene Glycol and Hydroxypropyl Guar; SH, sodium hyaluronic; TBUT, tear film break-up time.
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Dry eye has been postulated to be a localized autoimmune disease, as evidenced by various sources. This claim is supported by studies involving a mouse model of dry eye induced by environmental stress.[7] Further evidence includes clinical and biological markers observed in non-Sjögren's dry eye patients,[8] as well as the characterization of dry eye as a localized autoimmune disease.[9] Research findings further corroborate the theory that dry eye syndrome arises because of a disproportion between the protective immunoregulatory and pro-inflammatory pathways of the ocular surface, thus strengthening its autoimmune character.[10] Nonetheless, it is crucial to acknowledge the involvement of other factors in DED pathogenesis, such as environmental and hormonal influences,[8] mucosal tolerance disruption,[9] and toll-like receptor subtype TLR4.[11] Moreover, some limitations of this hypothesis have been highlighted.[12]

An intriguing association has been identified between the peptide LL37 and DED through a research investigation focusing on ocular fatigue-related phenomena.[13] Scientific investigations have observed LL-37's interaction with extracellular DNA, a potential contributor to inflammation in DED, which facilitates its translocation into ocular surface cells. This process activates the TLR9-MyD88 signalling pathway, subsequently eliciting a type 1 interferon response and triggering the adaptive immune response,[14] thereby implicating it in the pathogenesis of DED. However, it is important to note that the study investigating the correlation between LL37, and DED involved a small sample size of patients.[13] Consequently, further research with larger sample sizes is warranted to confirm the role of LL37 in the development of DED.

The tear film (Fig. 1) consists of three separate layers (mucus, aqueous, and lipid layers).[15] Each layer, in its unique way, plays an

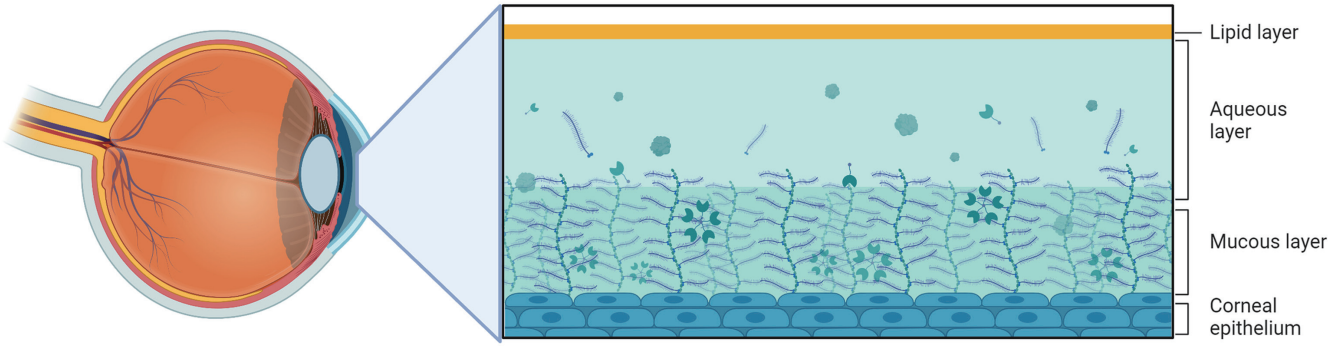

Fig. 1. The three distinct layers of the tear film: The outer lipid layer, the middle aqueous layer and the inner mucin layer.

important role in maintaining the integrity and stability of the tear film. Factors such as tear film production, evaporation, absorption, and drainage continuously influence the tear film.[16] Overall, the three layers work in tandem to protect and provide essential eye lubrication, which helps to prevent dryness and irritation of the eye. The thin inner mucin layer secreted by the lacrimal gland and conjunctiva goblet cells contains proteins, growth hormones, and antimicrobials. These contents help stick the tear film to the surface of the eye. The middle aqueous layer (7–8 µm thick) is composed of water, electrolytes, and various substances secreted by the lacrimal gland. The secreted components provide moisture and nutrients to the cornea and the conjunctiva. The outer lipid layer (0.1 µm thick) is composed of meibomian oil secreted by the meibomian glands. The layer reduces the tear surface tension and acts as a barrier to tear evaporation (reduced evaporation up to 95%).[17] A retrospective study found that 86% of patients with DED had meibomian gland dysfunction (MGD).[18] This relationship was supported by other studies,[19–21] whereas DED and MGD were reported to be prevalent among type 2 diabetes, with a prevalence of 72.3% and 55.3%, respectively.[22] However, one potential bias in this study is that only included confirmed a small population type 2 diabetes patients, which may not be representative of all diabetes patients in Ghana. The current consensus in scientific literature is that MGD plays a significant role in the etiology of DED. The pathophysiology of MGD involves a reduction in the secretion of meibum from the meibomian gland, which is the primary causative factor behind the functional abnormalities observed in MGD.[23,24]

For treating the mucin, aqueous, and/or lipid tear film inadequacies, along with the damage to ocular surface linked with DED, various novel therapeutic approaches have been proposed.[25] Studies on patients with Sjögren's syndrome have compared dry eye evaluation tests and presented major treatment conclusions.[26] Another study has shown that hyaluronic acid (HA) can hinder the dehydration of human corneal epithelial cells both in vitro and in vivo.[27] This discovery has the potential to speed up the advancement of more effective treatments for DED. On the other hand, a research has indicated that HA may lead to the counterintuitive outcome of causing the formation of haze and a reduction in the thickness of the epithelium.[28]

DED can be caused by a number of factors, such as medication (both systemic and topical), skin conditions, eye surgeries, exposure to chemicals or heat, prolonged device usage, vitamin A deficiency, wearing contact lenses, environmental elements, and more. Diagnosing DED requires a combination of symptoms and indicators such as tear volume, meniscus evaluation, tear film break-uptime (TBUT), Schirmer test, fluorescein staining, phenol red test, tear film osmolarity, lissamine green staining, matrix metalloproteinases, and eyelid examination.[29] Research has also demonstrated that DED may be caused by genetic factors, such as those related to immune response, tear film stability and corneal sensitivity. Recent genetic studies have identified new genetic regions associated with DED, further emphasizing its complex genetic makeup.[30] A study shows that Human Leukocyte Antigen-C1 alleles group is strongly associated with 108.30% increase in the odds of having DED.[31] A study on twins carried out by Vehof *et al*., discovered that the heritability of DED was around 30% for symptoms and 40% for diagnosis, and there was a range of heritability of 25% to 80% for selected signs.[32] The findings suggested that identifying specific genes associated with DED could lead to better treatments and prevention strategies. Other studies have also indicated that genetic factors could contribute to the onset of DED, alongside environmental influences.[33]

In the US, DED occurs in approximately 6.8% of adults (16 million individuals aged 18 or older). Unfortunately, its incidence increases with age and women are more likely to be affected than men.[34] A study focusing on men (50 years and older) estimated that 4.34% had DED (approximately 1.68 million men). Furthermore, it was predicted that the number of patients with this condition will exceed 2.79 million by 2030.[35] One potential bias is that the study only included male physicians, which may not be representative of the general population. Additionally, the study relied on self-reported data, which may be subject to recall bias or social desirability bias. A cross-sectional study conducted in 16 towns in the Northern West Bank of Palestine to assess the prevalence of DED and potential associated risk factors found that the prevalence of DED was 64% in the study population, with older age and female gender being associated risk factors for its development.[36] However, a limitation of the study is the sampling method. The authors used a multistage sampling method based on the Palestinian central bureau of statistics sampling frame to identify the Palestinian towns participating in the study. While this approach may have helped ensure that a representative sample was obtained, it is possible that some groups were underrepresented or excluded from the study. Similarly, Germany saw an increase in DED prevalence from 20.24 per 1,000 patients in 2008 to 23.13 per 1,000 in 2014. Cataracts were the most frequent ocular comorbidity. The study concluded that these individuals used more healthcare resources and associated costs than their normal cohort.[37] One limitation of the study was that it relied on administrative claims data, which may not accurately reflect actual patient outcomes or treatment patterns. Overall, DED is a common ocular condition affecting a significant portion of the global population, with women and older

individuals being at higher risk. The incidence of DED is predicted to increase in the coming years, leading to increased healthcare resource utilization and associated costs. However, studies assessing the prevalence of DED and associated risk factors may be subject to limitations, such as sampling bias and reliance on self-reported or administrative claims data. Therefore, further research is needed to accurately assess the burden of DED and its risk factors in diverse populations to inform effective prevention and management strategies.

Diagnosis and management of DED

Generally, the DED diagnostic evaluation includes a thorough patient history, a detailed slit-lamp examination, and additional tests as deemed necessary.[38] Moreover, patient-reported outcomes (PRO) questionnaires are often utilized to measure the severity of DED symptoms. However, it is important to note that not all PRO questionnaires have been validated and, thus, should be utilized with caution.[39] Ultimately, a precise diagnosis of DED requires a combination of tests and PRO questionnaires while ruling out other potential ocular surface conditions such as allergies and infections. The International Dry Eye Workshop (DEWS) report has furnished a comprehensive guide for diagnosing DED. However, with recent advances in diagnostic techniques, certain aspects of the DEWS findings and recommendations require revaluation.[40] The diagnostic criteria for DED remain a matter of contention, and there is a lack of agreement on disease classification and interpretation of diagnostic tests. Therefore, standardization of disease terminology and diagnostic tools is necessary to enhance the utility of epidemiological and clinical research on DED. Further research and consensus-building efforts are essential to improve our understanding and management of DED.[41]

The identification of DED involves utilizing both subjective and objective assessments. Patients' self-reported symptoms are taken into consideration as a subjective measure, while objective tests entail examining tear film stability through methods like TBUT and fluorescence staining (FTBUT) using a slit-lamp microscope. Although tear film instability tests involve a variety of procedures, some of which may be intrusive, not easily reproducible, and less precise.[19] TBUT has been reported to be associated with a 1,200% increase in the odds of severe DED.[42] The corner fluorescent staining was introduced after suggestions by the Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) for DED diagnostic procedures. In situations where there is a disagreement between the patient's reported symptoms and the clinical signs, further assessment using additional diagnostic criteria was advised.[43] Back in 2006, a group of experts in the field of DED reached a consensus using the Delphi approach. They suggested the use of the term "dysfunctional tear syndrome " instead of DED in their report.[44] The ODISSEY scoring algorithm serves as a straightforward tool for evaluating ocular surface damage in cases of severe DED, making the diagnosis process more accessible.[43] In DEWS II, a wide range of diagnostic procedures were identified, which included questionnaires, tests for tear film stability, abnormalities in the epithelium, and other methods. Although specific diagnostic criteria were not proposed in the report, it did suggest the most effective tests for diagnosing and tracking DED.[44] Some new techniques for diagnosing dry eye disease involve developing devices that rely on visual acuity to monitor patients' symptoms.[45] Reduced FTBUT (tear film instability) is another means of diagnosing DED,[46] although there is a weak association between dry eye tests and a lack of agreement between subjective symptoms and clinical signs.[47]

To treat DED, the patient must receive proper education, and management techniques such as using ocular lubricants, modifying the environment (i.e., adding moisture), maintaining good hygiene of the eyelids, employing autologous tears, and tear preservation are recommended.[48] To manage the disease, palliative treatments such as antimicrobial and anti-inflammatory therapy, along with warm compresses, are also utilized.[49] Healthcare providers and patients typically opt for topical ocular preparations to help alleviate the symptoms of DED.[50] Previous investigations had delved into examining the viability of P2Y (purinergic) family receptor agonists as a prospective treatment for DED.[51] Recent studies have revealed that P2Y family receptor agonists show potential as a prospective treatment for DED by increasing tear and mucin production.[52] Diquafosol, a topical $P2Y_2$ agonist, is already being used as a drug to treat the disease.[53,54] Moreover, antagonists of $P2Y_{12}$ receptors, and potentially $P2Y_1$ receptors, are being tested as anti-thrombotic agents, while a $P2Y_2/P2Y_4$ receptor agonist has been found to be effective in treating DED symptoms. Furthermore, TRPM8 receptor agonists such as cryosim-3 are also being studied for their potential to act as a viable treatment for DED.[55–58] A summary of important findings from the development and clinical trials of diquafosol, another P2Y2 receptor activator, revealed its effectiveness in treating DED in short-term studies.[59] Dinucleoside polyphosphates, created by combining two nucleotides with varying numbers of phosphates, have been suggested as a potential DED treatment. However, the FDA has not approved oral pilocarpine and cevimeline, which activate the muscarinic acetylcholine receptor, for the treatment of DED.[60] $P2Y_2$ receptors may also be a target for future trials aimed at treating tumors,[61] and therapies targeting $P2Y_1$ have been proposed as a new approach to treating drug-resistant status epilepticus.[62] Despite the development of many treatments, some patients seek more straightforward or efficient remedies.[63] Currently, no specific curative measures for DED are mentioned in modern medicine.[64] Nonetheless, essential fatty acids are being suggested as a new treatment method for patients with dry eye syndrome.[65] In addition, the use of novel eye drops that contain n-3 eicosapentaenoic and docosahexaenoic acids has been shown to effectively manage mild cases of DED.[66,67] Other recently developed eye drops such as Trimix eye drops,[68] cord blood serum eye drops,[69] HA and trehalose ophthalmic solution (Thealoz® Duo),[70] corticosteroids, MC2-03 0.18% sodium hyaluronate (SH) eye drops,[71] propylene glycol/hydroxypropylguar (PG-HPG) nanoemulsion-based eye drops,[72] and SH/chondroitin sulfate, preservative-free, ophthalmic solution, have demonstrated efficacy in managing mild cases of DED.[73] Trimix eye drops, a combination of viscosity-enhancing HA trehalose, and cationic liposomes comprising stearylamine and phospholipids, showed promising results in improving objective signs and subjective symptoms in patients with DED.[74] However, potential biases and limitations exist. The study for Trimix eye drops was conducted by a single center with a small sample size (25 patients), which limits its generalizability. Also, there was no control group or comparison to other available tear substitutes. Although the article mentions a shift towards complex multi-action combined formulas for DED, it provides no evidence to support this claim, raising questions about their effectiveness.

Additionally, randomized clinical trials have shown that water-based eye drops containing SH, carboxymethylcellulose, or carbomers can also alleviate symptoms associated with DED. Moreover, the new-generation Intense Pulsed Light has been found to be safe and effective in relieving symptoms and signs of MGD-

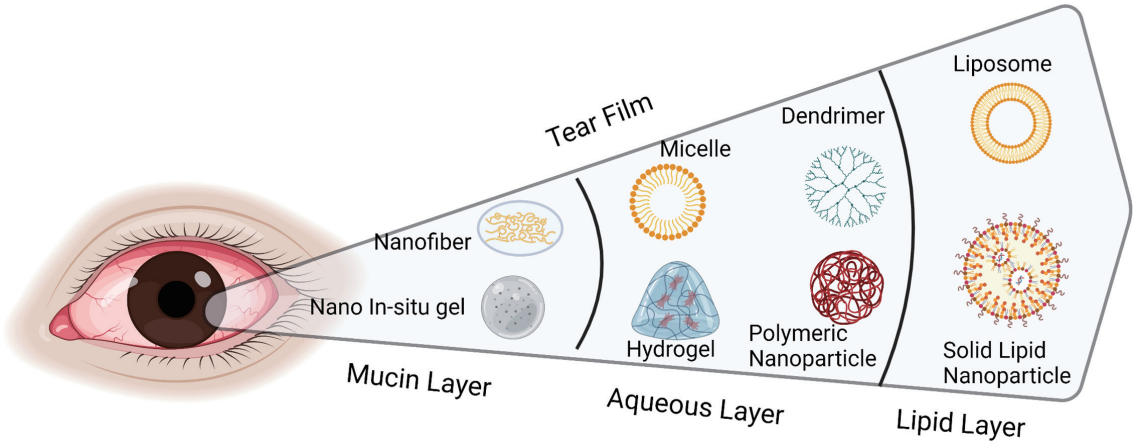

Fig. 2. Different nanotechnology drug delivery systems applied to the three distinct layer of the tear film. Certain formulations will have the best bioavailability if they are placed in the right tear film.

related dry eye.[75,76] Automation of diagnostic methods for DED can improve accuracy and ease of acquisition, with semi-automated and fully automated methods showing promise in quantifying DED characteristics.[19] An example of an effective approach to enhance diagnostic accuracy is the utilization of 3D ultrasound, which facilitates evaluation in three orthogonal planes and enables scrutiny of the external appearance of facial features.[77] Additionally, cross-checking may heighten diagnostic accuracy by allowing human experts to apply their information processing heuristics, reasoning methods, and pattern recognition techniques, which automated systems may not possess.[78] Therefore, the implementation of automated noninvasive workup is a promising instrument for the accurate diagnosis of DED.[74]

Nanotechnology: a cutting-edge approach to DED drug delivery

The burgeoning field of nanotechnology has been making waves in the realm of DED therapy, offering a multitude of innovative possibilities (Fig. 2). By harnessing the power of nanoparticles, researchers have successfully crafted drug carriers that can efficiently penetrate and enhance bioavailability within the anterior segment of the eye.[79] Despite the myriad of promising applications for nanoparticles in ophthalmology, their potential toxicity to ocular tissues, including the cornea, conjunctiva, and retina, under specific conditions warrants careful consideration. As such, elucidating the ocular toxicity of nanoparticles is of paramount importance to ensure the safety and efficacy of these innovative treatments. Further, although there is a strong interest in the use of nanoformulations for delivering phytochemicals to the eye, but this technology has been reported to be a hindrance to the clinical translation of new products due to scalability issues.[80]

To address this challenge, researchers have turned to advanced in vitro cell culture techniques that can closely simulate the human organism. One such technique involves the use of human organoids, which are three-dimensional, self-organizing cell structures derived from pluripotent stem cells. Organoids can accurately mimic the complexities of human tissues and have been employed in various fields of study, including toxicology.[81] Another groundbreaking approach in this domain involves the utilization of nanotechnology to create novel drug delivery systems, such as inhalation-based modalities. Central to the development of these inhalable powders is the art and science of particle engineering, a pivotal aspect that ensures the successful delivery of drugs with augmented therapeutic effects and precision targeting. By tailoring particle size, morphology, and surface properties, researchers can optimize the performance of inhalable formulations and maximize their clinical benefits.[82] However, potential toxicity issues still remain largely unanswered.

This pioneering area of nano-ophthalmology is currently in its infancy, but it holds immense promise in overcoming the ocular barriers that have long hindered effective drug delivery.[83] The advent of sophisticated nanotechnology-based delivery methods holds the potential to fundamentally transform the landscape of DED management. By providing heightened efficacy and pinpoint accuracy, these techniques promise to elevate therapeutic outcomes and improve patient experiences. Moreover, the dual-capability of nanotechnology to transport both pharmaceutical agents and antigens has piqued the interest of researchers, who are diligently investigating its diverse applications. As the development of this versatile technology advances, the scientific community eagerly awaits the emergence of novel treatment modalities and their potential impact on DED therapy.[84,85]

Liposomes

The management of DED is witnessing a paradigm shift with the advent of liposome-based therapies (Fig. 3). These innovative strategies offer new hope for the effective treatment of this prevalent ocular ailment. The development of liposome eye spray, for instance, has been heralded as a big advancement.[86] Utilizing vitamin A-coupled liposomes (VA-lip) containing heat shock protein 47 (HSP47) for a formulation (VA-lip HSP47), researchers have identified a novel antifibrotic topical therapy for DED. The liposome has been shown to be effective in DED in a mouse model of chronic graft-versus-host disease (GVHD). In GVHD, the HSP47 has been identified to play a role and DED is the most common manifestation. The ocular instillation of VA-lip HSP47 distributed to the lacrimal glands, knocked down HSP47 expression in fibroblasts, reduced collagen deposition, and restored tear secretion after allogeneic stem cell transplantation. Additionally, ocular instillation of VA-lip HSP47 also ameliorated established lacrimal gland fibrosis and DED.[87] However, studies in humans still need to establish the above claims. Similarly, the potential of thymoquinone loaded liposomes as a therapeutic agent in DED has been

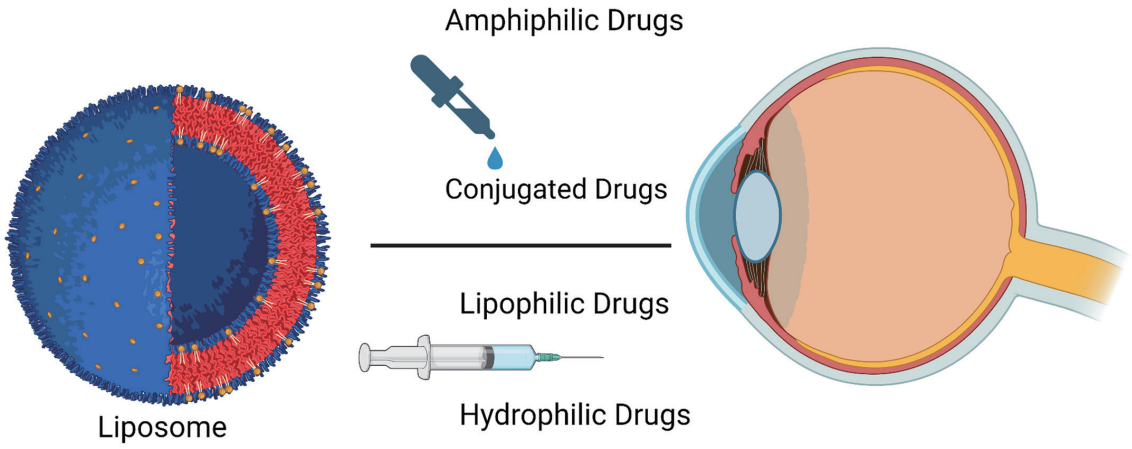

Fig. 3. Liposome delivery to the eye. Different properties of the drug which can be formulated as a liposome for the best action are depicted in the figure. Some of the them can be given as eye drops, and some as injections.

identified. This effect may be attributed to the anti-inflammatory properties of the encapsulated vitamins and the protective barrier formed by liposomes.[88] Another promising approach involves the use of liposomes loaded with 1-bromoheptadecafluorooctane and tetrandrine, which exert anti-inflammatory effects without substantially impacting intraocular pressure, offering an alternative therapeutic strategy for DED.[89]

Niosomes

Niosomes are a novel drug delivery system that can be used to treat a variety of ocular diseases, including DED. Studies have shown that niosomes have a high encapsulation efficiency and prolonged drug-release rate for drugs such as doxycycline hyclate and gentamycin sulfate, making them an effective and promising treatment option. Compared to liposomes, niosomes have several advantages, such as their ability to entrap both lipophilic and hydrophilic drugs, their improved drug permeation in corneal cells, their small size which allows for better drug retention on the ocular surface, and their cost effectiveness for production in the pharmaceutical industry. Furthermore, niosomes are more convenient for handling and storage than liposomes. As such, due to their advantageous properties, niosomes offer a promising drug delivery system for treating DED.[90]

According to a preclinical study conducted by Durak *et al*. niosomes loaded with timolol maleate demonstrated high encapsulation efficiency and were found to be more effective at reducing eye pressure compared to other delivery systems.[91] This finding suggests that niosomes loaded with timolol maleate could be used as an effective treatment option for glaucoma, a condition that causes damage to the optic nerve and can lead to vision loss if left untreated. Moreover, a study by Cvenkel *et al*. found that the reduction in intraocular pressure achieved by niosomes loaded with timolol maleate was comparable to other commonly used glaucoma medications such as latanoprost and bimatoprost.[92] There have been studies that demonstrate the successful use of niosomes as ocular drug delivery carriers, which significantly improve the ocular bioavailability of various drugs. For example, one study reported 2.5 times increase in the ocular bioavailability of timolol maleate (a water soluble drug) encapsulated in niosomes compared to a timolol maleate solution. Niosomes are preferred over other vesicular systems for ocular drug delivery due to their chemical stability, low toxicity, biodegradability, biocompatibility, and non-immunogenicity. Surfactants used in niosomes can act as penetration enhancers to improve the performance and availability of the drug.[93] It is important to note that the success of niosomes as ocular drug delivery carriers may depend on factors such as the specific drug being encapsulated, the formulation and composition of the niosomes, and patient-specific factors.

Graphene nanocomposites

A recent study focuses on a new antioxidant nanocomposite created from pterostilbene and carboxyl-chitosan modified graphene to control oxidative stress of human corneal epithelial cells. Pterostilbene (PS), found in blueberries, is an antioxidant with potential for medical applications. However, poor hydrophobicity, poor cellular permeability and retention limit its use. Carboxyl-chitosan functionalized graphene (CG) was used to address these limitations as it has good hydrophilicity and ocular biocompatibility. The resulting nanocomposite, PS-CG, had a good antioxidant effect due to its synergistic effects. The activation of the Keap1-Nrf2-ARE signalling pathway enhances the expression of various antioxidative enzymes and detoxification enzymes, preventing oxidative stress that causes dry eye. The synthesis process involved a ball milling method followed by the centrifugation and dialysis process to obtain CG. PS was covalently linked to CG via a π-π stacking interaction, resulting in a PS-CG dispersion that can be used to treat dry eye caused by oxidative stress.[94]

Micelles

Micelles are a type of colloidal drug delivery system that emerges when the concentration of polymer/surfactant exceeds the critical micellar concentration. This solution is commonly used to enhance the drug's solubility and bioavailability, thereby improving its therapeutic efficacy.[95] Micelles are formed by the spontaneous self-assembly of amphiphilic surfactants or diblock polymers at a specific concentration or temperature in a solution, and they can have varied shapes like spheres, cylinders, or star shapes with dimensions that range from 10–200 nm.[96] The morphology of the micelles can have increased circulation time.[97] Other studies also support the claim with their measurement of polymeric micelles in the blood to have a retention at 24 h above 20 % ID/g, which indicates that a large percentage of the micelles are still in circulation.[98]

Micelles are useful in transporting hydrophobic drugs in wa-

ter, with normal micelles being the carriers of choice, while hydrophilic drugs can be delivered using reversed micelles.[99] This makes them ideal for targeting ocular tissue and increasing corneal permeability when applied topically. Micelles, despite their challenges in drug loading, scalability, and potential toxicity from surfactant use, offer notable benefits for DED treatment. Cyclosporin A, a hydrophobic and potent immunosuppressive agent, is used to address DED and prevent corneal transplant rejection. To improve its solubility and ocular bioavailability, researchers have explored nanoparticulate drug delivery systems for cyclosporine A. Polymeric micelles were successfully created utilizing a diblock polymer, specifically Methoxypoly(ethylene glycol)-poly(lactic acid), which was loaded with cyclosporine A via a thin film dispersion method. This micellar approach boosted the drug's retention on the precorneal surface by 4.5 times and decreased its elimination compared to a cyclosporine emulsion. These results highlight the potential of cyclosporine A micelles to enhance the drug's effectiveness in treating DED.[80]

In a study, nanomicelles were formed, which were small, self-assembling particles that can have the potential to improve the bioavailability of drugs by protecting them from precorneal elimination and promoting drug uptake into the eye. These nanomicelles have a better activity than those produced with Ikervis, and their stability and acceptability in patients are improved. Clinical studies will be necessary to identify the effective dose in the treatment of ocular pathologies such as DED.[100]

Among all the discussed nanoformulations, nanomicelles have shown promise in treating DED. This is because of their ability to improve the solubility and stability of drugs, prolong their release, and enhance their penetration into the target tissues. By encapsulating the therapeutic agents within nanomicelles, their bioavailability and efficacy can be increased, leading to improved treatment outcomes for DED.

Nanoemulsions

Dry eye symptoms have been effectively addressed using a nanoemulsion eye lubricant comprising Propylene Glycol and Hydroxypropyl Guar (PG-HPG). This innovative formulation serves to enhance tear film stability, increase lipid layer density, alleviate dryness and discomfort associated with contact lens use, and provide preventive benefits for maintaining ocular moisture in arid environments. Demonstrating sustained efficacy and tolerability, PG-HPG eye drops have become a widely adopted treatment for DED, and show potential for application in other ocular conditions as well.[2]

Both preclinical and clinical investigations have confirmed the effectiveness of PG-HPG nanoemulsion lubricants in mitigating DED symptoms.[101] The HPG nanoscale droplets promote the optimal distribution of phospholipids within the tear film, thereby contributing to its stability. Results from studies comparing lipid and non-lipid-based aqueous drops have consistently reported sustained relief from dry eye symptoms, reduced severity of superior lid wiper epitheliopathy, and improved tear film consistency and ocular surface properties. These findings have been corroborated by Phase IV clinical trial data, emphasizing the utility of PG-HPG nanoemulsion in the management of DED.[72]

Despite these promising results, there remains a need for more comprehensive clinical trials to establish robust evidence supporting the effectiveness of PG-HPG nanoemulsion lubricants in addressing DED symptoms.[74] Future research should focus on further elucidating the therapeutic potential and efficacy of this novel formulation.

Cubosomes

Cubosomes, a distinct class of lipid-based nanostructured carriers with dimensions ranging from 100 to 300 nm, offer an expansive surface area and minimal viscosity, rendering them suitable candidates for various drug delivery systems.[102–104] These versatile carriers encapsulate hydrophilic, lipophilic, and amphiphilic drugs, thereby demonstrating a promising potential for diverse administration routes, including oral, ocular, and transdermal applications. Notably, drug absorption is generally facilitated through the transcellular pathway.[105]

An in vivo study investigating the anti-inflammatory effects of fexofenadine hydrochloride in rabbits substantiated the superiority of a cubosomal carrier over an aqueous drug dispersion.[105] Huang *et al*. reported the successful implementation of a cubosome-based drug delivery system for glaucoma treatment using timolol maleate (TM). Ex vivo corneal permeability experiments revealed an elevated penetration of TM cubosomes compared to commercially available eye drops, indicating an enhancement in corneal permeability, increased retention time, and improved bioavailability of ocular drugs for ocular disease treatment.[106]

Moreover, numerous investigations have posited the promise of cubosomes as drug delivery systems for ocular disease therapy, including DED. Eldeeb *et al*. discovered that brimonidine tartrate-loaded cubosomes exhibited augmented corneal permeability and sustained release patterns, culminating in a heightened intraocular pressure-lowering effect relative to commercial eye drops.[107] Nasr *et al*. demonstrated that fluconazole-loaded cubosomes enhanced antifungal activity in the treatment of keratomycosis in rats.[108]

Despite these promising findings, no study has yet directly investigated the efficacy of cubosomes in treating DED. Additionally, the large-scale production of cubosomes presents a significant challenge.[109] Consequently, further research is warranted to explore the potential of cubosomes as a therapeutic strategy for DED and address the obstacles related to their large-scale manufacturing.

Mucoadhesive nanoparticles

Mucoadhesive nanoparticles are promising drug delivery systems for treating DED. They have been shown to effectively target and deliver drugs to the ocular surface with prolonged retention, resulting in enhanced therapeutic efficacy.[110] The use of phenylboronic acid-modified mucoadhesive nanoparticles has facilitated weekly treatment of experimentally-induced dry eye syndrome, providing a potential solution for patients suffering from this chronic condition.[111] Furthermore, Cyclosporin A, a widely used immunosuppressant drug for treating DED and preventing corneal transplant rejection, can be delivered using mucoadhesive nanoparticle eye drop formulations, increasing the drug's ocular retention and reducing dosage frequency.[80] Chitosan mucoadhesive nanoparticles have the potential to improve ocular drug delivery due to their ability to promote mucoadhesion and enhance corneal penetration, therefore, providing a promising alternative for treating ocular diseases such as dry eye syndrome. However, safety concerns still persist regarding the cross-linked chitosan formulations.[112]

Future directions

The diagnosis and treatment of DED pose significant challenges due to the multifactorial etiology, lack of consensus on diagnostic criteria, and limitations in current therapeutic approaches.[113] The

inadequacy of commonly used clinical signs and symptoms for diagnosis, along with the challenge of determining disease severity using biomarkers, surrogates, or outcomes, further complicates the management of DED.[114] Addressing the low bioavailability of drugs and the risk of systemic side effects is crucial for enhancing the efficacy of existing treatments, such as topical administration of eye drops, surgery, and contact lens use.

Future studies should focus on the development of reliable diagnostic criteria and the identification of new biomarkers for DED, which will enable more accurate disease classification and monitoring. Additionally, research should continue to explore the potential of nanotechnology-based delivery systems, with particular attention to overcoming the current limitations and paving the way for their successful clinical translation. Ultimately, such advancements will lead to improved management and treatment of DED, enhancing the quality of life for millions of patients worldwide.

Conclusions

Nanotechnology-based delivery systems have emerged as a promising alternative to conventional ocular delivery systems for the treatment of anterior segment diseases, including DED. These systems have the potential to overcome the challenges associated with current treatment modalities by increasing drug bioavailability, reducing side effects, and enabling targeted drug delivery. However, before these novel delivery systems can be translated into clinical use, further research is needed to address the existing challenges, optimize their performance, and establish their safety and efficacy profiles.

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Conflict of interest

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Author contributions

Anil K. Philip is the sole author of this work.

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