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NOVEL DRUG DELIVERY SYSTEMS FOR THE MANAGEMENT OF DRY EYE DISEASE

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ABSTRACT

Dry eye disease (DED) is a complex condition affecting the ocular surface, marked by tear film instability, inflammation, and irritation, which can considerably reduce a patient's quality of life. Traditional treatment options, including lubricating eye drops and anti-inflammatory medications, often provide only short-term relief due to rapid clearance from the ocular surface, low drug absorption, and limited retention time. To address these challenges, novel drug delivery systems (NDDS) have been developed to enhance the effectiveness of dry eye management. These innovative delivery approaches include nanoparticles, liposomes, niosomes, micellar systems, hydrogels, in situ forming gels, ocular inserts, and drug-eluting contact lenses. Such systems are designed to improve drug stability, increase residence time on the eye surface, and provide sustained and controlled drug release, thereby enhancing drug penetration across ocular tissues. Furthermore, they allow for targeted delivery, reduce dosing frequency, and improve patient adherence while minimizing adverse effects. Recent advancements also focus on stimuli-responsive and mucoadhesive delivery systems, along with nanotechnology-based formulations, which show great promise in targeting the underlying inflammatory and degenerative pathways of dry eye disease. Although these systems demonstrate encouraging results in research and clinical settings, issues related to stability, scalability, regulatory considerations, and long-term safety still need to be addressed. Overall, novel drug delivery systems offer a promising advancement in the treatment of dry eye disease, with the potential to provide more effective and sustained therapeutic outcomes than conventional therapies. Ongoing research and clinical validation are necessary to support their widespread application in ophthalmology.

INTRODUCTION

1.1 Background and Significance

The ocular surface is one of the most environmentally exposed and immunologically active tissues in the human body, perpetually dependent on a stable and functionally competent tear film for its integrity and transparency. Dry eye disease (DED), also referred to as keratoconjunctivitis sicca, represents a chronic, multifactorial disorder of the ocular surface characterised by loss of tear film homeostasis, accompanied by neurosensory abnormalities, inflammation, and damage to the ocular surface epithelium. The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), published in 2017, formally redefined DED as a condition in which tear film instability and hyperosmolarity, ocular surface inflammation, neurosensory abnormalities, and damage to the epithelium co-exist and mutually perpetuate a self-reinforcing cycle of disease progression.[1]

Globally, DED has emerged as one of the most prevalent ophthalmic conditions encountered in clinical practice, affecting an estimated 5% to 50% of the population depending on the diagnostic criteria and geographic region studied.[2] In South and Southeast Asia, prevalence estimates tend to be markedly higher than in Western populations, attributed to differences in environmental pollution, digital device usage, dietary patterns, and genetic susceptibility. Epidemiological studies from India report a prevalence ranging from 18.4% to 54.3% in various cohorts, underscoring the substantial burden this condition places on the Indian healthcare system.[3] Beyond the discomfort it causes, DED significantly impairs vision-related quality of life, interferes with activities requiring sustained visual attention such as reading and computer use, and is associated with a measurable reduction in work productivity comparable to that observed in patients with moderate-to-severe systemic conditions such as angina pectoris and dialysis-dependent renal disease.[4]

The pathophysiological basis of DED centres on a vicious inflammatory cycle. Tear film hyperosmolarity, arising from either aqueous-deficient or evaporative mechanisms, activates inflammatory signalling cascades on the ocular surface, triggering the release of pro-inflammatory cytokines including interleukin-1β (IL-1β), tumour necrosis factor-α (TNF-α), and matrix metalloproteinases (MMPs). These mediators damage the goblet cells and corneal epithelium, further destabilising the tear film and amplifying hyperosmolarity. Concurrent T-lymphocyte infiltration into the lacrimal gland accelerates secretory dysfunction, creating a self-sustaining cycle that is difficult to interrupt with transient pharmacological interventions .[5]

Conventional management of DED has largely relied upon topical instillation of artificial tear

substitutes, anti-inflammatory agents such as cyclosporine A (CsA) 0.05% ophthalmic emulsion (Restasis®) and lifitegrast 5% ophthalmic solution (Xiidra®), corticosteroids, and secretagogues. While these agents offer symptomatic relief or modest disease modification, they are fundamentally constrained by the formidable anatomical and physiological barriers of the ocular surface. Following conventional eye drop instillation, the precorneal residence time is typically less than five to seven minutes, with approximately 75% of the administered volume lost within the first 30 seconds through nasolacrimal drainage, blinking, and overflow.[6] Corneal bioavailability of most topically applied drugs consequently remains below 5%, necessitating frequent dosing regimens that adversely affect patient compliance and introduce the risk of preservative-associated epitheliotoxicity. Benzalkonium chloride (BAC), the most widely used ophthalmic preservative, has been demonstrated to induce dose-dependent apoptosis of corneal and conjunctival epithelial cells, paradoxically worsening the ocular surface disease it is intended to treat.[7]

Against this backdrop, novel drug delivery systems (NDDS) have garnered intense scientific interest as platforms capable of overcoming the dual challenges of ocular bioavailability and controlled drug release. NDDS encompass a diverse spectrum of formulation strategies including polymeric nanoparticles, solid lipid nanoparticles, liposomes, niosomes, nanoemulsions, in-situ gelling systems, hydrogels, dendrimers, cyclodextrin complexes, contact lens-based delivery, ocular inserts, and more recently, exosome-based and gene therapy approaches. These systems are designed to exploit mucoadhesive interactions with the conjunctival glycocalyx, prolong corneal contact time, protect encapsulated actives from enzymatic degradation, and deliver drug payloads in a sustained and controlled manner to anterior ocular tissues.[8] Several of these platforms have demonstrated markedly superior bioavailability, reduced dosing frequency, and improved therapeutic outcomes in preclinical and early clinical investigations compared to conventional formulations.

1.2 Objectives and Scope of the Review

The present review article has been undertaken with the following objectives: (i) to provide a thorough account of the anatomy of the ocular surface and the structural organisation of the tear film as it pertains to pharmacokinetic challenges unique to ophthalmic drug delivery; (ii) to present a consolidated overview of the pathophysiology, epidemiology, and clinical features of dry eye disease based on the most current consensus guidelines; (iii) to critically evaluate the mechanistic basis, formulation strategies, pharmaceutical advantages, and relevant preclinical and clinical evidence for each category of NDDS investigated for dry eye

management; (iv) to identify the outstanding formulation, regulatory, and clinical challenges that currently limit the translation of these systems into routine ophthalmic practice; and (v) to outline emerging and future-directed delivery strategies that hold promise for next-generation dry eye therapeutics.[9]

1.3 Literature Search Strategy

A systematic search of the published scientific literature was conducted using the electronic databases PubMed/MEDLINE, Scopus, ScienceDirect, and Google Scholar. The following MeSH terms and free-text keywords were employed in various Boolean combinations: 'dry eye disease,' 'keratoconjunctivitis sicca,' 'tear film,' 'ocular drug delivery,' 'novel drug delivery systems,' 'nanoparticles ophthalmology,' 'liposomes eye,' 'in-situ gel ocular,' 'hydrogel dry eye,' 'nanoemulsion ophthalmic,' 'ocular bioavailability,' 'cyclosporine nanoparticles,' and 'ocular surface inflammation.' Articles published between 2000 and 2024 were prioritised, with seminal older publications retained where their foundational contribution warranted inclusion. A total of 120 references were selected for citation in this review following qualitative screening for scientific rigour, relevance, and methodological soundness.[10]

ANATOMY, PHYSIOLOGY AND TEAR FILM

2.1 Ocular Surface Anatomy

The ocular surface constitutes a continuous, functionally integrated epithelial system encompassing the cornea, limbus, bulbar and palpebral conjunctiva, and the accessory structures that maintain its homeostasis, including the lacrimal gland, meibomian glands, goblet cells, and the nasolacrimal drainage apparatus. This anatomical unit operates as an interconnected functional complex, wherein disruption of any single component initiates a cascade of compensatory and pathological responses that ultimately compromise the transparency, integrity, and immune privilege of the ocular surface.[11]

The cornea is an avascular, transparent, dome-shaped structure approximately 11–12 mm in horizontal diameter and 500–540 μm in central thickness in the human adult. Histologically, it is composed of five distinct layers: the outermost stratified non-keratinised epithelium (five to seven cell layers, approximately 50 μm thick), Bowman's layer, the stromal compartment comprising approximately 90% of total corneal thickness and consisting of orthogonally arranged type I collagen lamellae interspersed with keratocytes, Descemet's membrane, and the inner corneal endothelium. The corneal epithelium functions as the primary physical barrier to transcorneal drug permeation and is rendered hydrophobic by the presence of tight

junctions (zonula occludens) between superficial squamous cells, rendering it selectively permeable to lipophilic compounds.[12]

The conjunctiva is a thin, highly vascularised mucous membrane lining the inner surface of the eyelids (palpebral conjunctiva) and reflecting onto the anterior sclera (bulbar conjunctiva). It contains mucus-secreting goblet cells, which are concentrated most heavily in the inferior nasal quadrant. Conjunctival goblet cells are the primary source of secretory mucin MUC5AC, a high- molecular-weight gel-forming glycoprotein that forms the innermost mucus layer of the tear film and mediates adhesion between the aqueous phase and the glycocalyx of corneal and conjunctival epithelial cells.[13] The meibomian glands are sebaceous glands embedded within the tarsal plates of both eyelids and synthesise meibum, composed of wax esters, cholesterol esters, phospholipids, and free fatty acids, which constitutes the outermost lipid layer of the tear film. Meibomian gland dysfunction (MGD) is recognised as the leading cause of evaporative dry eye, the most prevalent subtype of DED in clinical populations.[14]

2.2 Three-Layer Tear Film: Lipid, Aqueous and Mucin Layers

The preocular tear film is a thin, structured fluid layer approximately 3–10 μm in total thickness, interposed between the atmosphere and the corneal epithelial surface. It performs multiple indispensable physiological functions: it provides a smooth optical surface essential for high-quality vision, delivers oxygen and metabolic substrates to the avascular cornea, lubricates the ocular surface during blinking, maintains the appropriate osmotic and pH environment for epithelial cell survival, and constitutes the first line of immune defence against microbial pathogens and environmental antigens.[15]

The **lipid layer** is the most superficial component of the tear film, secreted by the meibomian glands onto the lid margins and spread across the tear surface with each blink. It serves two primary functions: retarding aqueous evaporation from the tear surface (reducing evaporative water loss by approximately 90–95% compared to an exposed aqueous surface), and lowering surface tension at the air–tear interface to facilitate tear spreading and film stability. Disruption of the lipid layer architecture, as occurs in MGD, results in accelerated evaporation, increased tear osmolarity, and evaporative DED.[16]

The **aqueous layer** constitutes the bulk of the tear film volume, accounting for approximately 98% of total tear volume at an average of 7–10 μL distributed across the ocular surface. It is secreted primarily by the main and accessory lacrimal glands and contains water, electrolytes (sodium, potassium, chloride, bicarbonate), proteins (lactoferrin, lysozyme, lipocalin,

secretory IgA, albumin), growth factors, mucins, and enzymes. The aqueous layer maintains a physiological tear osmolarity of 296–302 mOsm/kg in healthy eyes, and its pH ranges from 7.14 to 7.82.[17]

The **mucin layer** represents the innermost stratum of the tear film, formed by membrane-spanning mucins MUC1, MUC4, and MUC16 anchored to the apical surface of corneal and conjunctival epithelial cells. Their densely glycosylated extracellular domains create a net negative charge that repels pathogenic organisms and renders the otherwise hydrophobic corneal epithelial surface wettable by the overlying aqueous tear phase. The soluble gel-forming mucin MUC5AC, secreted by conjunctival goblet cells, lubricates the ocular surface during blinking. Loss of goblet cells, as occurs in DED, Stevens–Johnson syndrome, and chemical burns, results in mucin deficiency and tear film instability.[13,15]

2.3 Ocular Barriers Relevant to Drug Delivery

Understanding the biological barriers of the ocular surface is foundational to rationalising the design of NDDS for DED. These barriers operate simultaneously and collectively restrict the bioavailability of topically administered therapeutics to below 5% for most conventional formulations.[6] The precorneal space is a highly dynamic environment governed by tear production, drainage, and dilution. The normal tear turnover rate is approximately 16% per minute, meaning that a topically instilled drug solution is diluted and drained within three to five minutes of instillation. The blinking reflex, occurring 15–20 times per minute, generates shear forces that mechanically displace applied formulations from the ocular surface.[18]

The tight junctions of the stratified corneal epithelium represent the rate-limiting step in transcorneal drug permeation with an effective pore radius of approximately 2 nm, excluding most hydrophilic macromolecules from paracellular diffusion. The epithelial barrier also expresses efflux transporters such as P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRPs), which actively expel certain drug substrates from the epithelium back into the tear film, further reducing intracorneal drug concentrations.[19] The collective implications of these barriers are clear: an ideal drug delivery system for DED management must be capable of withstanding immediate precorneal clearance forces, establishing intimate contact with the mucin glycocalyx layer, releasing drug in a sustained and controlled manner, and delivering sufficient concentrations of therapeutic agent to the corneal and conjunctival epithelium while avoiding systemic exposure.[20]

DRY EYE DISEASE — OVERVIEW

3.1 Definition (TFOS DEWS II) and Classification

Dry eye disease is a complex, chronic disorder of the ocular surface that has undergone considerable refinement in its conceptual definition over the past two decades. The most widely accepted and clinically authoritative definition was established by the Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) in 2017, which characterised DED as a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.[1] This definition represented a significant conceptual advancement over earlier frameworks by explicitly incorporating neurosensory dysfunction and ocular surface inflammation as primary aetiological drivers rather than mere secondary consequences.

The TFOS DEWS II classification framework organises DED into two principal mechanistic subtypes. **Aqueous-deficient dry eye (ADDE)** arises from insufficient lacrimal gland secretion of the aqueous tear component, and is further subdivided into Sjögren syndrome dry eye (SSDE) and non-Sjögren syndrome dry eye (NSSDE). Sjögren syndrome, a systemic autoimmune exocrinopathy, results in lymphocytic infiltration and progressive destruction of the lacrimal and salivary glands, producing severe aqueous deficiency.[21] **Evaporative dry eye (EDE)**, which is aetiologically attributable to accelerated water loss from the tear surface, is by far the more prevalent form in clinical populations, accounting for approximately 65–85% of all DED cases. Meibomian gland dysfunction is the leading intrinsic cause of EDE.[22]

3.2 Epidemiology and Global Prevalence

Dry eye disease is recognised as one of the most prevalent chronic ophthalmic conditions worldwide. Reported prevalence rates range from as low as 5% in population-based studies applying stringent sign-and-symptom criteria to as high as 50% in clinic-based studies using broad symptom-only criteria.[2] The Women's Health Study reported a prevalence of 7.8% among women aged 45–84 years and 4.3% among men in the same age range in the United States, yielding an estimated 4.91 million Americans affected by DED.[23] In the Asia-Pacific region, a large multicentre study conducted across six Asian countries reported a prevalence of 27.5% based on symptom criteria, with individual country estimates ranging from 20.7% to 52.4%.[24] In India specifically, population-based studies have documented prevalence rates of 18.4% to 54.3% depending on the cohort studied.

Several modifiable and non-modifiable risk factors have been consistently identified across

epidemiological studies. Age is a robust independent risk factor, with prevalence increasing significantly beyond the fifth decade of life. Female sex is another well-established risk factor, with androgens playing a critical regulatory role in meibomian gland lipid synthesis and lacrimal gland secretory function; relative androgen deficiency in postmenopausal women is a recognised contributor to DED.[25] The estimated annual direct and indirect economic burden of DED in the United States alone exceeds USD 3.84 billion, encompassing costs of artificial tear purchases, prescription ophthalmic medications, clinical visits, and lost workplace productivity.[26]

3.3 Pathophysiology, Risk Factors and Diagnosis

3.3.1 Pathophysiology: The Vicious Cycle of DED

The pathophysiology of DED is best conceptualised as a self-perpetuating inflammatory cycle, in which an initiating insult generates tear film hyperosmolarity that serves as the pivotal amplifying mechanism for downstream ocular surface damage and glandular dysfunction.[27] Tear film hyperosmolarity, defined as an osmolarity exceeding 308 mOsm/L, activates multiple intracellular stress-response pathways in corneal and conjunctival epithelial cells, including the mitogen- activated protein kinase (MAPK) cascades —– specifically the p38 MAPK and c-Jun N-terminal kinase (JNK) pathways —– as well as the nuclear factor-kappa B (NF-κB) transcription factor network. Activation of these pathways drives upregulated expression and secretion of pro- inflammatory cytokines and chemokines, most notably interleukin-1α (IL-1α), IL-1β, IL-6, IL-8, IL- 17, and tumour necrosis factor-α (TNF-α), as well as matrix metalloproteinases MMP-9 and MMP- 3, which degrade components of the basement membrane and glycocalyx-associated mucins, particularly MUC16.[27,28]

The inflammatory cytokine milieu promotes the recruitment and activation of antigen-presenting dendritic cells in the corneal epithelium and conjunctiva, which migrate to regional lymph nodes and initiate adaptive immune responses. CD4+ T helper lymphocytes, particularly the Th1 and Th17 subsets, are preferentially activated and home to the lacrimal gland, where infiltrating T lymphocytes and macrophages release interferon-γ (IFN-γ), IL-17A, and additional TNF-α, which suppress acinar cell secretion and induce acinar cell apoptosis. Corneal nerve damage, resulting from chronic epithelial inflammation, reduces corneal sensitivity and blink reflex responsiveness. This neurogenic component of DED underlies the paradoxical disconnect observed in many patients between the severity of objective clinical signs and the intensity of subjective symptoms —– neuropathic ocular pain.[29]

3.3.2 Clinical Diagnosis of Dry Eye Disease

The clinical diagnosis of DED requires an integrated assessment of patient-reported symptoms and objective clinical signs. The Ocular Surface Disease Index (OSDI) is the most widely validated patient-reported outcome measure for DED, comprising 12 questions assessing ocular discomfort, visual function, and environmental triggers on a 0–100 scale, with scores of 13–22 indicating mild disease, 23–32 moderate disease, and 33–100 severe disease. The fluorescein tear break-up time (TBUT), measured as the interval between a complete blink and the appearance of the first dry spot in the fluorescein-stained tear film, is the most widely used clinical measure of tear film stability; a TBUT of less than 10 seconds is considered abnormal.[30] Tear osmolarity measurement using point- of-care osmometry demonstrates a threshold of ≥308 mOsm/L with a sensitivity of 73% and specificity of 92% for DED diagnosis. The Schirmer test measures basal and reflex aqueous tear secretion by quantifying the length of wetting on a standardised filter paper strip placed in the inferior conjunctival fornix over a five-minute period; wetting of less than 5 mm is diagnostic of severe aqueous deficiency.[30,31]

CONVENTIONAL THERAPY AND LIMITATIONS

4.1 Artificial Tears, Lubricants and Anti-Inflammatory Agents

4.1.1 Artificial Tears and Ocular Lubricants

Artificial tear preparations constitute the cornerstone of first-line DED management across all severity grades and represent the most widely used class of ophthalmic formulation globally. These preparations are designed to supplement, replace, or stabilise deficient components of the native tear film, providing transient symptomatic relief through lubrication, dilution of hyperosmolar tears, and supplementation of aqueous, mucin, or lipid components depending on their composition.[32] The viscosity-enhancing polymers employed in artificial tear formulations include hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose sodium (CMC), hydroxypropyl guar (HP-guar), hyaluronic acid (HA), polyvinyl alcohol (PVA), polyethylene glycol (PEG), and carbomers. Clinical studies have demonstrated that HA-based artificial tears at concentrations of 0.1%–0.4% significantly improve TBUT, reduce corneal staining scores, and alleviate OSDI symptom scores compared to non-HA-containing formulations.[35]

Lipid-based emulsion formulations, such as Systane Ultra® (PEG 400 and propylene glycol), and Cationorm® (a cationic oil-in-water nanoemulsion), specifically target the lipid layer deficiency characteristic of MGD-associated evaporative DED. The electrostatic attraction

between the positively charged droplets of cationic emulsions and the negatively charged mucin glycocalyx of the ocular surface prolongs retention and enhances lipid layer replenishment.[34] Despite their widespread use and established safety profile, artificial tears address only the symptomatic manifestations of DED without modifying the underlying inflammatory pathology. Their duration of action is limited by precorneal clearance, typically necessitating instillation four to eight times daily for adequate symptom control in moderate disease.[33]

4.1.2 Cyclosporine A

Cyclosporine A (CsA), a cyclic undecapeptide derived from the fungus *Tolypocladium inflatum*, is the most extensively studied and clinically established immunomodulatory agent for the treatment of moderate-to-severe DED. Its primary mechanism of action involves the formation of a complex with the intracellular receptor cyclophilin, which subsequently inhibits calcineurin, a calcium- dependent phosphatase required for the nuclear translocation of the nuclear factor of activated T cells (NFAT) transcription factor. Calcineurin inhibition prevents NFAT-mediated transcription of IL- 2 and other T cell activation cytokines, thereby suppressing CD4+ T lymphocyte activation and proliferation and attenuating the T cell-mediated lacrimal gland and ocular surface inflammation central to DED pathogenesis.[36] Restasis® (cyclosporine A 0.05% ophthalmic emulsion, Allergan), approved by the US FDA in 2003, was the first prescription pharmaceutical approved specifically for the treatment of DED. Clinical trials demonstrated that twice-daily instillation of CsA 0.05% emulsion significantly increased Schirmer test scores, reduced corneal fluorescein staining, and improved goblet cell density in patients with moderate-to-severe DED compared to vehicle-treated controls.[36] Cequa® (cyclosporine A 0.09% nanomicellar ophthalmic solution, Sun Pharmaceuticals), approved by the US FDA in 2018, employs a water-soluble nanomicellar formulation to enhance CsA solubility and corneal penetration.[37] A significant limitation of Restasis® is the delayed onset of clinical benefit, with meaningful improvements in objective signs typically requiring three to six months of consistent twice-daily use.

4.1.3 Lifitegrast, Corticosteroids and Secretagogues

Lifitegrast 5% ophthalmic solution (Xiidra®, Novartis), a small molecule integrin antagonist receiving US FDA approval in July 2016, selectively blocks the interaction between lymphocyte function- associated antigen-1 (LFA-1) and its counter-receptor intercellular adhesion molecule-1 (ICAM-1), preventing T lymphocyte adhesion and subsequent cytokine-

mediated inflammatory amplification at the ocular surface.[38] Topical corticosteroids including loteprednol etabonate, fluorometholone, prednisolone acetate, and dexamethasone exert broad anti-inflammatory effects through glucocorticoid receptor-mediated inhibition of NF-κB and AP-1 transcription factor pathways, representing the most rapidly acting pharmacological agents for DED-associated ocular surface inflammation but precluded from long-term use due to risks of steroid-induced ocular hypertension, posterior subcapsular cataract formation, and increased susceptibility to ocular infections.[39] Secretagogue agents including diquafosol tetrasodium (a P2Y2 purinergic receptor agonist) and rebamipide (a mucin secretagogue and reactive oxygen species scavenger) stimulate endogenous tear and mucin production and have demonstrated efficacy in improving TBUT and reducing corneal staining in clinical trials.[40]

4.2 Limitations: Bioavailability, Drainage and Ocular Toxicity

The bioavailability of topically instilled ophthalmic formulations at the corneal surface is remarkably low, typically estimated at less than 5% of the administered dose for most conventional drug solutions and suspensions.[6] Upon instillation of a conventional eye drop volume of 25–50 µL into a precorneal cul-de-sac with a maximal holding capacity of 7–10 µL, the excess volume is immediately expelled by reflex blinking and overflow onto the lid margins. The nasolacrimal drainage system efficiently channels drug-containing tear fluid into the nasal cavity within two to five minutes of instillation, delivering drug to the highly vascular nasal mucosa where rapid systemic absorption can occur.[18] Cyclosporine A exemplifies this physicochemical challenge particularly clearly: with a molecular weight of 1202 Da, extreme hydrophobicity (log P approximately 2.9), and near-complete water insolubility, its formulation in conventional aqueous vehicles is not feasible, necessitating the development of emulsion-based delivery systems that themselves suffer from rapid precorneal clearance limitations.[36]

Benzalkonium chloride (BAC), present in over 70% of multi-dose topical ophthalmic preparations at concentrations of 0.004%–0.025%, produces concentration-dependent cytotoxic effects on the corneal and conjunctival epithelium, including disruption of tight junctions, induction of oxidative stress, apoptosis of superficial epithelial cells, and suppression of conjunctival goblet cell function.[7,41] Patients with DED who instil preserved artificial tears four to eight times daily accumulate sufficient BAC exposure to produce measurable conjunctival squamous metaplasia, goblet cell loss, and increased ocular surface inflammation. Non-adherence rates of 30%–80% to topical ophthalmic therapy have been

consistently reported across chronic eye conditions, with DED patients demonstrating non-adherence patterns driven primarily by the inconvenience of frequent instillation, burning and stinging upon drop instillation, and perceived lack of efficacy.[42]

4.3 Need for Novel Drug Delivery Systems

The cumulative weight of pharmacokinetic limitations, preservative toxicity, poor patient compliance, and the inability of conventional formulations to sustain therapeutic drug concentrations at the ocular surface establishes an unambiguous and compelling clinical rationale for the development of novel drug delivery systems tailored specifically to the unique physicochemical and biological environment of the ocular surface in DED. An ideal drug delivery system for DED management would achieve a prolonged precorneal residence time through mucoadhesive interactions with the conjunctival glycocalyx, thereby circumventing rapid nasolacrimal drainage; encapsulate and protect the active pharmaceutical ingredient from premature degradation; release the drug in a controlled, sustained manner over hours to days; demonstrate biocompatibility with the corneal and conjunctival epithelium; and ideally be preservative-free or employ non-toxic alternative preservative systems.[8,32]

NOVEL DRUG DELIVERY SYSTEMS FOR DRY EYE DISEASE

The fundamental inadequacies of conventional topical ophthalmic formulations have catalysed intensive pharmaceutical research directed toward the design and development of novel drug delivery systems capable of overcoming the anatomical, physiological, and pharmacokinetic barriers unique to the ocular surface. NDDS represent a paradigm shift in ophthalmic drug delivery philosophy —— from simple solution-based instillation toward engineered particulate, colloidal, polymeric, and biological platforms that interact intelligently with the ocular surface environment to extend drug residence time, protect drug integrity, modulate release kinetics, and ultimately achieve therapeutic drug concentrations at target tissues with reduced dosing frequency and improved patient acceptability.

5.1 Nanoparticles (Polymeric, PLGA and Solid Lipid Nanoparticles)

5.1.1 Polymeric Nanoparticles

Polymeric nanoparticles represent one of the most extensively investigated and scientifically mature categories of NDDS for ophthalmic drug delivery. Defined as solid colloidal particles in the size range of 10–1000 nm, polymeric nanoparticles consist of a drug molecule entrapped, encapsulated, dissolved, or adsorbed within or onto a polymeric matrix composed

of either natural or synthetic biodegradable polymers. Their nanoscale dimensions confer several pharmacokinetic and biopharmaceutical advantages directly relevant to ocular drug delivery: particles in the size range of 100–500 nm demonstrate enhanced mucoadhesion to the conjunctival glycocalyx through non- specific hydrophobic and electrostatic interactions, and their polymeric matrix enables modulation of drug release kinetics from rapid burst to prolonged zero-order profiles depending on polymer composition, molecular weight, and surface functionalisation.[43]

Chitosan, a deacetylated derivative of chitin obtained from crustacean shells, has emerged as a particularly valuable polymer for ocular nanoparticle fabrication owing to its intrinsic mucoadhesive properties arising from electrostatic interaction between its positively charged amino groups and the negatively charged sialic acid residues of ocular mucins, its demonstrated capacity to transiently open tight junctions of the corneal epithelium thereby enhancing paracellular drug permeation, and its biocompatibility and biodegradability.[44] Chitosan nanoparticles loaded with cyclosporine A, prepared by ionic gelation with tripolyphosphate, have demonstrated significantly superior corneal Cs A concentrations compared to Restasis® emulsion in rabbit ocular pharmacokinetic studies, with a two- to threefold improvement in AUC and a sustained drug release profile extending beyond 24 hours.[45] Hyaluronic acid-coated nanoparticles exploit the specific interaction between HA and CD44 receptors, which are overexpressed on the ocular surface epithelium in inflammatory conditions including DED, to achieve receptor-mediated endocytosis and targeted intracellular drug delivery.[43]

5.1.2 PLGA Nanoparticles

Poly(lactic-co-glycolic acid) (PLGA) is an FDA-approved biodegradable copolymer that undergoes hydrolytic degradation in aqueous biological environments to yield lactic acid and glycolic acid, both normal metabolic intermediates that are eliminated via the Krebs cycle without accumulation or systemic toxicity. PLGA nanoparticles have been investigated more extensively than any other polymeric nanoparticle system for ophthalmic drug delivery, owing to their well-characterised biocompatibility, tunable degradation rates (from weeks to months depending on copolymer ratio, molecular weight, and terminal group), and regulatory acceptance.[46] PLGA nanoparticles encapsulating cyclosporine A, prepared by the nanoprecipitation or emulsion-solvent evaporation method, have consistently demonstrated encapsulation efficiencies exceeding 80%, sustained in vitro drug release over 14–30 days, and significantly superior ocular bioavailability compared to conventional CsA formulations

in multiple rabbit pharmacokinetic studies.[47] PLGA-PEG nanoparticles loaded with dexamethasone demonstrated a sustained drug release profile over 21 days in vitro and significantly reduced corneal fluorescein staining scores in a benzalkonium chloride-induced murine DED model compared to dexamethasone eye drops.

5.1.3 Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

Solid lipid nanoparticles (SLNs) represent a colloidal drug delivery system composed of a solid lipid matrix stabilised by surfactants and dispersed in an aqueous phase. SLNs offer particular biopharmaceutical advantages for ophthalmic delivery owing to their lipid composition, which closely mimics the meibomian lipid components of the tear film lipid layer, thereby facilitating integration into and stabilisation of the precorneal lipid film. Nanostructured lipid carriers (NLCs), the second-generation evolution of SLNs, incorporate a mixture of solid and liquid lipids in the matrix to create a less ordered, more amorphous lipid structure that accommodates higher drug loading capacities and produces more flexible and tailorable drug release profiles.[48] NLCs loaded with cyclosporine A have demonstrated encapsulation efficiencies of 85%–95% and sustained drug release over 24 hours in vitro, with significantly enhanced corneal permeation compared to CsA eye drops in ex vivo bovine corneal studies, and approximately 2.8-fold higher corneal drug concentrations compared to Restasis® emulsion in comparative pharmacokinetic studies in rabbits.

5.2 Liposomes and Niosomes

5.2.1 Liposomes

Liposomes are spherical, self-assembling colloidal vesicles composed of one or more concentric phospholipid bilayers enclosing an aqueous core, with diameters ranging from approximately 25 nm to several micrometres. Their unique structural architecture —— comprising both a hydrophilic aqueous compartment and a hydrophobic lipid bilayer —— enables simultaneous encapsulation of hydrophilic drugs within the aqueous core and hydrophobic drugs within the lipid bilayer, rendering them uniquely versatile drug carriers for the broad spectrum of therapeutic agents relevant to DED management.[49] The phospholipid composition of liposomal membranes closely resembles the polar lipid components of the inner meibomian lipid layer and the phospholipid-rich surface of the aqueous tear film, conferring good ocular biocompatibility, minimal corneal and conjunctival cytotoxicity, and the capacity to fuse with and integrate into the preocular lipid film.[50]

Cyclosporine A-loaded liposomes composed of DPPC and stearylamine have achieved a 3.5-

fold enhancement in corneal bioavailability compared to CsA oil solution in rabbit pharmacokinetic studies, attributable to the electrostatic attraction between positively charged liposomal surfaces and the negatively charged mucin glycocalyx. Chitosan-coated liposomes have demonstrated significantly prolonged precorneal retention with a retention half-life approximately 2.3-fold longer than uncoated liposomal preparations as assessed by gamma scintigraphy in human volunteers.[50] Liposomal eye drops commercially available for DED management include Liposic® (phosphatidylcholine liposomes, Bausch + Lomb) and Tears Again® (phospholipid-based liposomal spray), which function primarily as lipid layer supplements, demonstrating improvements in TBUT and symptom scores in randomised controlled trials comparing them to conventional artificial tear preparations.

5.2.2 Niosomes

Niosomes are non-ionic surfactant-based vesicular systems structurally analogous to liposomes but composed of non-ionic surfactants —— most commonly alkyl polyoxyethylene ethers (Brij series), polysorbates (Tween series), or sorbitan fatty acid esters (Span series) —— in combination with cholesterol or other membrane-stabilising lipids. Niosomes offer several practical and economic advantages over phospholipid-based liposomes: non-ionic surfactants are significantly less expensive than pharmaceutical-grade phospholipids, exhibit greater chemical stability against oxidative degradation, and do not require specialised cold-chain storage conditions.[51]

Niosomal formulations of cyclosporine A prepared with Span 60 and cholesterol have demonstrated encapsulation efficiencies of 70%–85% and sustained drug release profiles over 24 hours in vitro, with significantly enhanced ex vivo corneal permeation compared to CsA solution and comparable or superior bioavailability to Restasis® emulsion in rabbit ocular pharmacokinetic studies.

5.3 Nanoemulsions and Microemulsions

5.3.1 Nanoemulsions

Nanoemulsions are thermodynamically unstable but kinetically stable colloidal dispersions consisting of immiscible oil and water phases stabilised by appropriate amphiphilic surfactant and co-surfactant combinations, with dispersed droplet diameters in the range of 20–200 nm. Nanodroplets in this size range demonstrate enhanced penetration into the mucin gel layer of the tear film and establish more intimate contact with the corneal epithelial glycocalyx than larger emulsion droplets, facilitating drug transfer directly at the epithelial surface.[52] The oily

phase solubilises lipophilic drugs —— including cyclosporine A, tacrolimus, and omega-3 fatty acids —— at concentrations several orders of magnitude higher than achievable in aqueous vehicles, substantially increasing the thermodynamic activity and hence the diffusion driving force of the drug across the corneal epithelium.

Cationic nanoemulsions represent a particularly sophisticated application of the nanoemulsion platform. Cationorm® (Santen), a commercially available preservative-free cationic nanoemulsion containing cetalkonium chloride, has demonstrated significantly prolonged precorneal retention, superior tear film stabilisation, and improved TBUT in clinical studies compared to conventional anionic artificial tear preparations, and is approved for DED management in Europe.[53] Restasis® (cyclosporine A 0.05% ophthalmic emulsion, Allergan), technically a submicron emulsion with droplets approximately 100–200 nm, represents the most commercially successful ophthalmic emulsion globally. Next-generation CsA nanoemulsion formulations incorporating cationic surfactants and surface functionalisation with mucoadhesive polymers have demonstrated substantially superior corneal pharmacokinetics in preclinical studies.[52,53]

5.3.2 Microemulsions

Microemulsions are thermodynamically stable, optically isotropic, and transparent colloidal systems consisting of oil, water, surfactant, and co-surfactant phases, with dispersed domain sizes in the range of 10–100 nm. Unlike nanoemulsions, microemulsions form spontaneously upon mixing of their components at the appropriate ratio and remain indefinitely stable at a given temperature without energy input, representing a distinct and thermodynamically advantageous phase structure. The thermodynamic stability of microemulsions offers significant pharmaceutical advantages in terms of physical stability on storage, ease of manufacturing, and reproducible batch-to-batch quality.[54] Cyclosporine A microemulsions prepared with Cremophor EL, propylene glycol, and medium-chain triglycerides have demonstrated encapsulation of CsA at concentrations up to 0.5% with thermodynamic stability at room temperature and significantly enhanced ex vivo corneal permeation compared to CsA in castor oil or CsA emulsion.

5.4 In-Situ Gelling Systems

In-situ gelling systems exploit the physiological stimuli present at the ocular surface —— temperature, pH, and ionic composition —— to trigger a sol-to-gel phase transition of a liquid formulation immediately upon instillation into the conjunctival sac. This approach reconciles

two seemingly contradictory desiderata of ophthalmic drug delivery: the ease of accurate dosing associated with liquid eye drop formulations, and the extended precorneal residence time characteristic of viscous gel preparations, while avoiding the transient visual blurring associated with pre-formed viscous gels.[55]

5.4.1 Thermosensitive In-Situ Gels

Thermosensitive in-situ gels exploit the property of certain polymers to exist as low-viscosity solutions at room temperature and undergo sol-to-gel transition at or near physiological temperature (35–37°C at the ocular surface). Poloxamer 407 (Pluronic F-127), a triblock copolymer composed of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) units, undergoes concentration-dependent temperature-sensitive micellisation and gelation. Poloxamer- based in-situ gels encapsulating cyclosporine A have demonstrated significantly prolonged precorneal residence, as confirmed by gamma scintigraphy studies, with a mean precorneal half- life approximately threefold longer than for CsA eye drops.[56]

5.4.2 PH-Sensitive and Ion-Sensitive In-Situ Gels

pH-sensitive in-situ gelling systems exploit the acidic-to-physiological pH transition that occurs when a formulation buffered to a mildly acidic pH (approximately 4.0–5.5) contacts the tear film, which maintains a physiological pH of approximately 7.2–7.4. Carbopol (polyacrylic acid) and its derivatives are the most widely investigated pH-sensitive gelling polymers for ophthalmic use, with progressive ionisation of carboxylic acid groups upon contact with neutral tear film pH generating electrostatic chain repulsion that produces gel formation.[55] Ion-sensitive in-situ gelling systems such as gellan gum (Gelrite®) undergo gelation in response to the electrolytes present in the tear film, primarily calcium ions. Gellan gum-based in-situ gels for DED have been formulated with cyclosporine A and various lubricant polymers, demonstrating gel formation within seconds of contact with simulated tear fluid, prolonged drug release over 8–12 hours in vitro, and superior corneal drug concentrations compared to conventional eye drops in rabbit pharmacokinetic studies.[57]

5.5 Hydrogels and Mucoadhesive Systems

Hydrogels are three-dimensional, crosslinked hydrophilic polymer networks capable of absorbing and retaining large quantities of water —— typically 90%–99% of their total weight —— while maintaining a defined structural integrity. Their high water content renders them intrinsically biocompatible with the hydrated ocular surface environment and facilitates

diffusion of water- soluble drug molecules through the swollen polymer matrix. Polyacrylic acid (PAA), poly(2- hydroxyethyl methacrylate) (pHEMA), polyvinyl alcohol (PVA), poly(N-isopropylacrylamide) (pNIPAM), and hyaluronic acid-based hydrogels represent the most extensively investigated systems for ophthalmic drug delivery.[58] Hyaluronic acid hydrogels loaded with cyclosporine A demonstrated sustained drug release over 14 days in vitro and significant improvements in corneal epithelial integrity, goblet cell density, and lacrimal gland histopathology scores compared to vehicle-treated controls in a murine DED model.

Mucoadhesive drug delivery systems incorporating polymers capable of establishing prolonged adhesive interactions with the mucin glycocalyx of the ocular surface extend the drug contact time with the corneal and conjunctival epithelium. Thiomers —— polymers functionalised with thiol groups through chemical conjugation of cysteine, N-acetylcysteine, or thioglycolic acid to natural polymer backbones —— form covalent thiol-disulphide bonds with mucin cysteines that are significantly stronger and more durable than non-covalent mucoadhesive interactions, producing precorneal retention times three- to fivefold longer than those of unmodified polymer counterparts.[59] Chitosan- N-acetylcysteine conjugate nanoparticles encapsulating cyclosporine A demonstrated a mean precorneal residence time of 4.2 hours compared to 1.1 hours for unmodified chitosan nanoparticles in rabbit ocular retention studies, with a corresponding twofold improvement in corneal CsA bioavailability.

5.6 Dendrimers and Cyclodextrin Inclusion Complexes

5.6.1 Dendrimers

Dendrimers are highly branched, tree-like macromolecular architectures synthesised through iterative, stepwise chemical reactions from a central core molecule, with precisely controlled molecular weight, architecture, and peripheral functional group density determined by the number of synthetic iterations (generations). Polyamidoamine (PAMAM) dendrimers are the most extensively investigated dendrimer class for ophthalmic drug delivery. Lower-generation (G1–G2) dendrimers, with diameters below 2 nm, are capable of paracellular permeation through corneal epithelial tight junctions, providing a unique transcorneal absorption pathway inaccessible to larger nanoparticles; higher-generation (G4–G6) dendrimers demonstrate significant mucoadhesive properties through multivalent hydrogen bonding and electrostatic interactions with mucin glycoproteins.[60] Hydroxyl-terminated G4 PAMAM dendrimers complexed with pilocarpine hydrochloride achieved a 2.4-fold enhancement in corneal permeation compared to free pilocarpine solution in ex vivo rabbit

corneal permeation studies, with no significant cytotoxicity at therapeutic dendrimer concentrations.

5.6.2 Cyclodextrin Inclusion Complexes

Cyclodextrins are cyclic oligosaccharides forming a truncated cone-shaped molecular structure with a hydrophilic outer surface and a hydrophobic inner cavity of defined dimensions. The hydrophobic cavity of cyclodextrins enables the formation of non-covalent host-guest inclusion complexes with lipophilic drug molecules, effectively solubilising poorly water-soluble drugs in aqueous ophthalmic formulations without the use of organic solvents or surfactant systems.[61] 2-Hydroxypropyl-β- cyclodextrin (HPβCD) is the most widely investigated and regulatory-accepted cyclodextrin for ophthalmic drug formulation. Cyclosporine A-HPβCD complexes increase the aqueous solubility of CsA from approximately 6 μg/mL to greater than 1 mg/mL upon complexation with 10%–20% HPβCD, enabling formulation of CsA in a clear, preservative-free aqueous solution. Clinical studies of aqueous CsA-HPβCD eye drops have demonstrated comparable immunomodulatory efficacy to Restasis® with a more comfortable instillation experience and improved patient acceptability.

5.7 Contact Lens-Based and Ocular Insert Delivery

5.7.1 Contact Lens-Based Drug Delivery

Therapeutic contact lenses represent a conceptually compelling drug delivery platform that exploits the prolonged ocular surface contact time of contact lenses —– typically 8–16 hours of continuous wear —– to achieve extended and controlled drug release to the corneal and conjunctival surface.

Unlike conventional eye drops, drug-eluting contact lenses maintain direct contact with the corneal epithelium throughout the wearing period, enabling continuous drug exposure that more closely approximates the pharmacokinetic ideal of zero-order sustained release.[62] Vitamin E-loaded contact lenses incorporate hydrophobic vitamin E diffusion barriers within the hydrophilic HEMA matrix that create a tortuous diffusion path for lipophilic drugs such as cyclosporine A and dexamethasone, reducing the effective diffusion coefficient and producing sustained drug release profiles of 24–120 hours. Nanoparticle-laden contact lenses incorporating drug-loaded PLGA or liposomal nanoparticles directly into the contact lens polymer matrix during lens polymerisation have demonstrated maintenance of therapeutic CsA concentrations in simulated tear fluid for up to seven days in vitro.[63]

5.7.2 Ocular Inserts and Punctal Plugs

Ocular inserts are solid or semi-solid dosage forms designed for placement within the conjunctival sac or on the ocular surface, providing sustained drug release over periods ranging from days to months. The Lacrisert® (hydroxypropyl cellulose ophthalmic insert, Bausch + Lomb), a preservative-free soluble insert of pure HPC that dissolves over 24 hours in the inferior conjunctival sac, provides continuous tear film supplement in patients with moderate-to-severe aqueous- deficient DED, significantly reducing the frequency of artificial tear instillation required for symptom control.[64] Dextenza® (dexamethasone 0.4 mg intracanalicular insert, Ocular Therapeutix), FDA- approved in 2018, is a drug-eluting punctal plug composed of a PEG hydrogel matrix that releases dexamethasone in a sustained manner over approximately 30 days while simultaneously reducing tear drainage to conserve native tear volume —– a dual mechanism particularly well-suited to DED associated with ocular surface inflammation.[65] Cyclosporine A-eluting punctal plugs investigated in preclinical studies and early-phase clinical trials have demonstrated sustained CsA elution over 90 days and significant improvements in Schirmer test scores, corneal staining, and OSDI symptom scores compared to baseline.

5.8 Exosomes and Emerging Approaches

5.8.1 Exosomes and Extracellular Vesicle-Based Delivery

Exosomes are endosome-derived extracellular vesicles of 30–150 nm diameter secreted constitutively by virtually all cell types through fusion of multivesicular bodies (MVBs) with the plasma membrane. As naturally occurring biological vesicles, exosomes exhibit intrinsic biocompatibility, absence of immunogenicity when derived from autologous or immune-privileged cell sources, capacity to traverse biological membranes through membrane fusion and endocytosis, and inherent targeting specificity determined by their surface protein composition.[66] Exosomes derived from mesenchymal stem cells (MSC-Exos) have attracted the greatest research interest for DED applications, as MSCs are potent immunomodulatory cells whose paracrine anti-inflammatory signalling is mediated to a significant degree through exosomal transfer of anti-inflammatory miRNAs and proteins to target cells.

Topically administered MSC-derived exosomes have demonstrated remarkable therapeutic efficacy in murine DED models, significantly increasing goblet cell density, improving corneal epithelial integrity, reducing CD4+ T lymphocyte infiltration into the conjunctiva, and suppressing conjunctival IL-1β and TNF-α expression, with therapeutic effects comparable to those of topical CsA eye drops.[67] The anti-inflammatory mechanism was attributed to

exosomal transfer of miR-204-5p, which suppresses IL-1β-induced NF-κB activation in corneal epithelial cells by targeting the 3'-UTR of NLRP3 inflammasome components, providing molecular-level evidence for exosome-mediated disease modification in DED.

5.8.2 Stem Cell Therapy

Stem cell-based therapies for DED represent the most biologically ambitious and potentially transformative frontier in dry eye therapeutics, targeting the restoration of lacrimal gland secretory function, conjunctival goblet cell populations, and corneal epithelial homeostasis. Multiple stem cell populations have been investigated for lacrimal gland regeneration and ocular surface restoration in preclinical DED models, including mesenchymal stem cells (MSCs) from bone marrow, adipose tissue, and umbilical cord; limbal epithelial stem cells (LESCs); induced pluripotent stem cells (iPSCs); and lacrimal gland-specific progenitor cells.[68] Subconjunctival or systemic administration of bone marrow-derived MSCs has demonstrated significant improvements in lacrimal gland aqueous secretion, tear film stability, and ocular surface histopathology in murine and rabbit DED models. iPSC-derived lacrimal gland organoids, generated by directed differentiation of patient- derived induced pluripotent stem cells, have been successfully fabricated ex vivo and demonstrated capacity for fluid secretion upon cholinergic stimulation, suggesting their potential as autologous lacrimal gland tissue replacement constructs for patients with end-stage aqueous deficient DED.

CHALLENGES, FUTURE PERSPECTIVES AND CONCLUSION

6.1 Challenges in Ocular NDDS Development

6.1.1 Biological and Precorneal Barriers in NDDS Context

Despite the remarkable scientific progress documented in Chapter 5, the translation of novel drug delivery systems from the laboratory to routine clinical ophthalmic practice for DED management has proven considerably more challenging than the preclinical evidence base might suggest. The mucus layer of the tear film, rather than serving exclusively as a mucoadhesive anchor for nanoparticles as commonly assumed in formulation design, simultaneously functions as a dynamic clearance barrier that can trap and rapidly eliminate nanoparticles through mucociliary action and blinking-induced shear forces, particularly for particles larger than 500 nm or those with highly cationic surfaces that form irreversible electrostatic bonds with mucin fibrils.[71] The protein composition of the tear film —— comprising lactoferrin, lysozyme, secretory IgA, albumin, and a complex mixture of signalling proteins —— rapidly adsorbs onto nanoparticle surfaces to form a protein corona

that fundamentally alters the surface charge, hydrodynamic diameter, colloidal stability, mucoadhesive properties, and cellular uptake behaviour of the nanoparticles in ways that are rarely predicted by the clean aqueous buffer systems used in standard in vitro characterisation.[72]

6.1.2 Manufacturing, Scalability and Stability

The manufacture of NDDS for ophthalmic application must satisfy an exceptionally demanding set of quality requirements. The sterilisation of nanoparticulate formulations presents particular difficulties, as terminal heat sterilisation causes nanoparticle aggregation, polymer degradation, and drug leakage in most formulations, while gamma irradiation may degrade polymer matrices and chemically modify encapsulated drug molecules. Aseptic manufacturing under Grade A/ISO Class 5 cleanroom conditions using validated aseptic processing techniques represents the only generally applicable sterilisation strategy for most NDDS, but requires significant capital investment.[73] Physical stability during storage is a persistent challenge for most NDDS categories. Lyophilisation (freeze-drying) with appropriate cryoprotectants such as trehalose, mannitol, or sucrose is widely employed to convert aqueous nanoparticle dispersions into dry powder intermediates with extended shelf stability.[74] Liposomal formulations are additionally susceptible to phospholipid oxidation and hydrolytic degradation of ester bonds during aqueous storage, necessitating nitrogen overlay, antioxidant incorporation, and carefully controlled storage temperature regimens.

6.1.3 Regulatory Challenges and Patient Acceptability

The regulatory pathway for NDDS-based ophthalmic products is substantially more complex and resource-intensive than that for conventional ophthalmic formulations. Key regulatory requirements include comprehensive physicochemical characterisation (particle size distribution, zeta potential, morphology by transmission electron microscopy, crystallinity, drug loading and encapsulation efficiency, in vitro drug release kinetics), demonstration of ocular biocompatibility through standardised in vitro cytotoxicity assays, ex vivo corneal permeation studies, in vivo ocular toxicology studies in at least two animal species with full ocular histopathology, and comprehensive in vivo ocular pharmacokinetic studies.[75] The absence of established in vitro–in vivo correlation (IVIVC) models specifically validated for ophthalmic NDDS represents a significant regulatory gap.[76] Beyond regulatory challenges, the ultimate clinical success of ophthalmic NDDS for DED is contingent on their acceptability to patients as chronic, self-administered therapeutic agents —— nanoparticulate ophthalmic

formulations that produce transient visual blurring or ocular irritation following instillation are poorly tolerated by patients engaged in visually demanding occupations.

6.2 Future Directions and Emerging Technologies

6.2.1 Gene Therapy Approaches

Gene therapy for DED targets the correction of specific molecular defects in lacrimal gland secretory function, ocular surface epithelial homeostasis, or the inflammatory signalling cascades that perpetuate disease progression, through the delivery of therapeutic nucleic acid constructs —– including plasmid DNA, viral vectors, small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and microRNA mimics or inhibitors —– to relevant ocular surface cell populations. The potential of gene therapy approaches in DED lies in their capacity to achieve durable, potentially curative disease modification from a single administration.[77] Adeno-associated virus (AAV) vectors have demonstrated efficient transduction of lacrimal gland acinar cells and corneal epithelial cells following topical or subconjunctival administration in animal models, with transgene expression persisting for months to years. Topical siRNA targeting TNF-α, ICAM-1, or MMP-9 has demonstrated ocular surface anti-inflammatory efficacy in murine DED models when delivered in PLGA nanoparticle or lipid nanoparticle carriers that protect the nucleic acid payload from nuclease degradation.

6.2.2 Smart and Stimuli-Responsive Drug Delivery Systems

Stimuli-responsive or 'smart' drug delivery systems are designed to release their therapeutic payload in response to specific endogenous or exogenous stimuli. Reactive oxygen species (ROS)- responsive drug delivery systems are particularly well-suited to DED applications, as oxidative stress —– characterised by elevated tear film concentrations of hydrogen peroxide, superoxide, and other ROS —– is a well-established component of the inflammatory pathophysiology of DED and a direct mediator of corneal epithelial damage and goblet cell apoptosis. ROS-responsive nanoparticles incorporating thioketal, boronate ester, or peroxalate linkages that undergo oxidative cleavage in the presence of elevated ROS concentrations have been engineered to release encapsulated anti-inflammatory drugs selectively within the inflamed DED ocular surface environment, achieving disease activity-dependent drug release that self-regulates in proportion to the severity of local oxidative stress.[78] Matrix metalloproteinase (MMP)-responsive hydrogels crosslinked with MMP-9-cleavable peptide sequences progressively dissolve and release encapsulated CsA or anti-inflammatory peptides

in direct proportion to local MMP-9 activity, which is elevated tenfold or more in moderate-to-severe DED compared to healthy controls.

6.2.3 Three-Dimensional Bioprinting and Artificial Intelligence

Three-dimensional bioprinting technology enables the layer-by-layer deposition of cell-laden bioink constructs with precise spatial control of composition, architecture, and mechanical properties. Bioprinted corneal stroma constructs and conjunctival tissue equivalents incorporating goblet cells within an alginate-gelatin bioink matrix have demonstrated MUC5AC secretion and structural organisation comparable to native conjunctival epithelium, suggesting their potential utility as tissue-engineered conjunctival grafts for patients with severe goblet cell deficiency in advanced DED.[79] Artificial intelligence (AI) and machine learning (ML) methodologies are increasingly being applied to the rational design, optimisation, and clinical translation of ophthalmic drug delivery systems. Quantitative structure-property relationship (QSPR) models and deep learning neural networks trained on large datasets of physicochemical descriptors and experimental nanoparticle characterisation data have demonstrated capacity to predict PLGA nanoparticle encapsulation efficiency, particle size, and drug release kinetics from input formulation variables with mean absolute errors of less than 10%, enabling computational screening of formulation design spaces without exhaustive experimental synthesis.[80]

6.3 CONCLUSION

Dry eye disease represents one of the most prevalent, impactful, and therapeutically challenging chronic disorders of the ocular surface, affecting hundreds of millions of individuals globally and imposing a substantial burden of visual morbidity, reduced quality of life, and socioeconomic productivity loss that is disproportionate to its classification as a non-sight-threatening condition. The evidence base reviewed in this article unequivocally demonstrates that novel drug delivery systems represent a scientifically mature, mechanistically well-rationalised, and increasingly clinically validated paradigm for overcoming the pharmacokinetic and pharmacodynamic limitations of conventional ophthalmic formulations in DED management.[81]

Polymeric nanoparticles, particularly PLGA and chitosan-based systems, have demonstrated two- to fourfold improvements in corneal drug bioavailability compared to conventional eye drops across multiple preclinical species and drug payloads. Liposomal and niosomal formulations offer biomimetic lipid bilayer platforms that simultaneously supplement the tear

film lipid layer and deliver anti-inflammatory payloads with superior precorneal retention. Nanoemulsions —– particularly cationic platforms exemplified by the commercially approved Cationorm® —– have successfully demonstrated clinical efficacy in DED patients, validating the translational potential of the nanoemulsion approach. In-situ gelling systems provide a patient-friendly delivery strategy that prolongs precorneal drug residence without altering the familiar eye drop instillation format. Contact lens-based delivery and drug-eluting ocular inserts —– particularly the FDA-approved Dextenza® dexamethasone punctal insert —– achieve the most prolonged and controlled drug release of any topical delivery approach.[82,83]

Emerging platforms including exosome-based delivery systems, stem cell therapies, gene therapy approaches, stimuli-responsive smart nanoparticles, and AI-guided personalised nanomedicine represent the frontier of a rapidly evolving field that is progressively converging on the vision of disease-modifying, patient-personalised, and minimally burdensome ophthalmic therapeutics for DED. Continued interdisciplinary collaboration between pharmaceutical scientists, clinical ophthalmologists, materials scientists, molecular biologists, and regulatory scientists is essential to accelerate the translation of the extensive and growing preclinical evidence base into clinically available, patient-accessible, and disease-modifying therapeutics that fundamentally transform the treatment paradigm for this highly prevalent and significantly burdensome condition.[84]

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