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Proniosomal Gel in Ocular Drug Delivery: A Comprehensive Review of Recent Formulation Advances

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Abstract: Ocular drug delivery remains one of the most formidable challenges in pharmaceutical sciences owing to the numerous anatomical, physiological, and dynamic barriers of the eye. Conventional ophthalmic formulations such as eye drops suffer from extremely poor bioavailability, typically less than 5%, primarily due to rapid nasolacrimal drainage, lacrimation, and the impermeability of the corneal epithelium. Proniosomal gels represent a novel, hybrid vesicular-gel system that combines the advantages of niosomes non-ionic surfactant-based vesicles with the sustained-release and mucoadhesive properties of hydrogels. In the proniosomal approach, a dry, carrier-coated lipid formulation is hydrated upon application to form niosomes in situ, thereby overcoming the physical instability associated with conventional niosomal dispersions. This review comprehensively examines the principles, composition, preparation methodologies, physicochemical characterization, and *in vitro/in vivo* performance of proniosomal gel systems reported in the literature between 2015 and 2025. Recent formulation studies encompassing anti-glaucoma agents (timolol maleate, brimonidine tartrate, latanoprost), anti-infective drugs (ciprofloxacin, voriconazole, natamycin), non-steroidal anti-inflammatory drugs (diclofenac sodium, ketorolac tromethamine), corticosteroids (prednisolone acetate, loteprednol etabonate), and immunosuppressants (cyclosporine A) are critically analysed. Key formulation variables, evaluation parameters, and pharmacokinetic/pharmacodynamic outcomes are discussed. Current challenges, regulatory considerations, and future directions, including stimuli-responsive and nanotechnology integrated proniosomal systems, are also highlighted.

Keywords: Proniosomal gel, Niosomes, Ocular drug delivery, Vesicular systems, Corneal permeation, Sustained release

1. INTRODUCTION

The eye, with its unique anatomical compartmentalisation and sophisticated defence mechanisms, presents an extraordinary challenge to the drug delivery scientist. Despite decades of intensive research, topically instilled eye drops the dominant dosage form in clinical ophthalmology deliver less than 5% of the administered dose to the target tissues. The remainder is lost through nasolacrimal drainage, blinking, and systemic absorption via the conjunctival vasculature, often producing unwanted systemic adverse effects [1-2]. The limitations of conventional ophthalmic formulations have driven the development of vesicular drug delivery systems, which can act as reservoirs, protecting drug molecules from enzymatic degradation while facilitating their traversal of the corneal epithelium. Among these, liposomes were the first extensively studied vesicular carriers; however, their inherent drawbacks physicochemical instability, phospholipid hydrolysis, oxidation, and high cost prompted exploration of alternative vesicular platforms

[3]. Niosomes, composed of self-assembled bilayers of non-ionic surfactants and cholesterol, emerged as superior alternatives by virtue of their chemical stability, biocompatibility, amphiphilic nature (enabling encapsulation of both hydrophilic and lipophilic drugs), low cost, and scalability [4-5]. Nevertheless, conventional niosomal dispersions suffer from physical instability during storage (aggregation, fusion, drug leakage) and are susceptible to hydrolysis and microbial contamination [6].

The concept of proniosomes dry flow able carrier systems coated with surfactant that hydrate instantaneously upon contact with aqueous biological fluids to form niosomes *in situ* was introduced to circumvent these stability challenges. When this proniosomal concept is further integrated with a hydrogel matrix to produce a proniosomal gel, the resultant system benefits from increased corneal contact time, sustained drug release, and bioadhesive properties, while the dry carrier ensures long-term physicochemical stability [7-8]. This review presents a critical and comprehensive appraisal of the recent literature (2015–2025) on proniosomal gel systems developed for ophthalmic drug delivery. It covers the rationale for the technology, the theoretical basis of niosome formation, compositional considerations, manufacturing approaches, thorough characterization parameters, disease-specific formulation case studies, and the future landscape of this rapidly evolving field.

2. OCULAR ANATOMY AND DRUG DELIVERY BARRIERS

Understanding the physiological barriers of the eye is prerequisite to appreciating the rationale for proniosomal gel design. The eye may be broadly divided into the anterior segment (cornea, conjunctiva, iris, ciliary body, lens) and the posterior segment (vitreous humour, retina, choroid, optic nerve). The routes of drug entry include transcorneal, transconjunctival-scleral, and systemic routes [1].

2.1 Pre-Corneal Barriers

The tear film is a trilaminar structure (outer lipid, middle aqueous, inner mucin) covering the corneal epithelium. The turnover rate of tears is approximately 16% per minute, and the volume of the cul-de-sac (7–10 µL at rest) combined with the instillation volume of a conventional drop (~50 µL) leads to immediate overflow and drainage. Drug half-life in the pre-corneal space is typically 1–3 minutes [2]. Mucin, a glycoprotein, can bind drug molecules and facilitate rapid clearance. Additionally, the nasolacrimal duct provides a direct conduit to systemic absorption through the nasal mucosa.

2.2 Corneal Barriers

The cornea is a five-layered structure: epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium. The epithelium, with its tight junctions (zonula occludens), represents the principal barrier to hydrophilic drug permeation. The stroma, constituting 90% of corneal thickness and composed of hydrophilic collagen fibrils, conversely limits penetration of lipophilic compounds. This biphasic barrier imposes strict requirements on drug Lipophilicity ideally, an intermediate log P (1–3) is desired for transcorneal penetration [3].

2.3 Blood–Ocular Barriers

The blood aqueous barrier (iris and non-pigmented ciliary epithelium) and the blood–retinal barrier (tight junctions of retinal pigment epithelium and retinal vascular endothelium) profoundly restrict drug distribution from systemic circulation into the eye. These barriers serve a vital homeostatic role but also mean that systemically administered drugs achieve only subtherapeutic intraocular concentrations for many ophthalmic conditions [1].

Table 1: Summary of Key Ocular Barriers and Their Impact on Drug Delivery

Ocular Barrier	**Location**	**Key Components**	**Drug Delivery Challenge**
Corneal epithelium	Anterior surface	Tight junctions, lipophilic membrane	Limits hydrophilic drug permeation
Corneal stroma	Anterior segment	Hydrophilic collagen matrix	Limits lipophilic drug permeation
Blood-aqueous barrier	Ciliary body/iris	Tight junctions in non-pigmented epithelia	Restricts systemic drug entry
Blood-retinal barrier	Posterior segment	Inner (Müller cells) & outer (RPE) layers	Prevents posterior segment drug access
Tear film & nasolacrimal drainage	Pre-corneal space	Mucin, aqueous, lipid layers	Rapid drug washout (~5 min)

Sclera	Outer coat	Dense collagen bundles	Limits transscleral permeation

3. NIOSOMES AND PRONIOSOMES: THEORETICAL FOUNDATIONS

3.1 Niosome Formation and Structure

Niosomes are vesicular structures formed by the self-assembly of non-ionic amphiphilic surfactants in aqueous media. The driving force is the hydrophobic effect: the hydrophilic head groups of surfactant molecules orient toward the aqueous phase while the hydrophobic tails orient inward, forming a closed bilayer that encapsulates an aqueous core. The critical packing parameter (CPP = $v/a_o lc$, where v is tail volume, a_o is head-group area, lc is critical chain length) governs the geometry of self-assembly; CPP values of 0.5–1.0 favour bilayer (lamellar/vesicular) formation [4]. Non-ionic surfactants commonly used include alkyl polyoxyethylene ethers (Brij series), alkyl polyglyceryl ethers, and sorbitan fatty acid esters (Span series). The HLB (hydrophilic–lipophilic balance) value of the surfactant critically determines its ability to form niosomes an HLB in the range of 4–8 is generally favorable. Cholesterol, incorporated at equimolar or higher ratios, intercalates within the bilayer, reduces permeability, increases membrane rigidity, prevents gel-to-liquid crystalline phase transition, and improves vesicle stability [5].

3.2 The Proniosomal Concept

The proniosome approach, pioneered by Bhavesh and colleagues and subsequently refined by numerous groups, involves coating a water-soluble carrier (maltodextrin, sorbitol, lactose, mannitol, or lecithin granules) with a thin film of surfactant-cholesterol-drug mixture. The resulting dry, free-flowing powder is stable during storage and, upon addition of water or aqueous biological fluid, instantaneously hydrates to form niosomal vesicles [6-7]. Key advantages over conventional niosomes include: (i) Elimination of hydrolytic degradation during storage (ii) Avoidance of physical instability (aggregation, fusion) (iii) Simplified sterilisation (dry heat) (iv) Ease of handling and transportation (v) Reduced manufacturing cost. The in situ hydration upon ocular application ensures that niosomes are freshly formed at the site of action, maximizing drug encapsulation and minimizing leakage.

3.3 Proniosomal Gel: Hybrid System Rationale

Incorporating the proniosomal system within a gel matrix synergises multiple mechanisms of bioavailability enhancement: (i) The gel provides mucoadhesion via entanglement with mucin glycoproteins, increasing precorneal residence time (ii) The niosomes act as drug reservoirs, enabling controlled, biphasic drug release (iii) The gel matrix provides an additional diffusional barrier that moderates burst release (iv) The vesicular bilayer facilitates transcellular drug transport across the lipophilic corneal epithelium [8].

4. FORMULATION COMPOSITION AND DESIGN CONSIDERATIONS

The rational design of a proniosomal gel for ocular delivery requires careful optimization of each compositional element. The physicochemical properties of the drug (molecular weight, log P, ionisation, and melting point) govern the choice of surfactant, carrier, gelling agent, and additives.

Table 2: Comparative Advantages of Proniosomal Gel vs. Conventional Eye Drops

Property	Conventional Eye Drops	Proniosomal Gel
Precorneal residence time	< 5 minutes	Several hours (mucoadhesive)
Bioavailability	< 5%	Up to 10–15 fold increase
Drug loading (hydrophilic)	Limited	Good (aqueous core)
Drug loading (lipophilic)	Poor (requires surfactant)	Excellent (bilayer incorporation)
Stability	Moderate	High (dry carrier avoids hydrolysis)
Patient compliance	Moderate (frequent dosing)	High (sustained release, reduced frequency)

Scalability	Excellent	Good (simple manufacture)
Cost	Low	Moderate

Table 3: Key Components Used in Ophthalmic Proniosomal Gel Formulations

Component	Examples	Function	Typical Concentration
Non-ionic surfactant	Span 40, Span 60, Span 80, Tween 80	Forms niosomal bilayer; determines vesicle characteristics	20–50% w/w of lipid phase
Cholesterol	Cholesterol (USP)	Bilayer rigidity, reduces permeability, stabilises membrane	Equimolar to surfactant
Carrier (proniosomal)	Maltodextrin, sorbitol, lecithin, mannitol	Coating matrix; converts liquid niosomes to dry powder	Excess (carrier:lipid 10:1 to 20:1)
Gelling agent	HPMC, Carbopol 940, Poloxamer 407, sodium alginate	Viscosity, mucoadhesion, controlled release	0.5–2% w/v
Charge inducer	DCP, SA, cetrimide	Prevents aggregation; improves zeta potential	5–10% of lipid phase
Permeation enhancer	Oleic acid, EDTA, chitosan	Enhances corneal penetration	0.1–1% w/v
Preservative	Benzalkonium chloride, EDTA	Antimicrobial protection	0.01–0.02% w/v

4.1 Non-Ionic Surfactants

The surfactant is the foundational structural component of the niosomal bilayer. Span series surfactants (sorbitan monoesters) are the most widely employed in ophthalmic proniosomal systems due to their established safety profile, low HLB, and capacity to form stable vesicles at physiological conditions. Span 60 (sorbitan monostearate, HLB 4.7) is particularly prevalent, producing vesicles with low permeability and high stability. Span 40 (sorbitan monopalmitate) and Span 80 (sorbitan monooleate) have also been investigated. Tween series surfactants, with higher HLB values, are occasionally incorporated as co-surfactants to modulate vesicle size and drug release kinetics. The surfactant-to-cholesterol molar ratio profoundly impacts vesicle size, zeta potential, entrapment efficiency, and drug release; ratios of 1:0.5 to 2:1 (surfactant: cholesterol) are most commonly optimised [9-10].

4.2 Cholesterol

Cholesterol functions as a membrane stabiliser by occupying interstitial spaces between surfactant molecules, reducing fluidity and membrane permeability, and preventing the crystallisation of surfactant chains. At optimal concentrations (equimolar to surfactant), cholesterol significantly improves entrapment efficiency. Excess cholesterol, however, can disrupt bilayer packing and reduce encapsulation. In ophthalmic formulations, cholesterol content typically ranges from 30–50 mol% of the lipid phase [10].

4.3 Carrier Systems

The carrier in a proniosomal system provides the scaffold onto which the lipid film is deposited. Ideal carriers are water-soluble, chemically inert, non-toxic, and capable of forming a uniform thin film upon lipid coating. Maltodextrin is widely used due to its excellent film-forming capacity, low toxicity, and ability to produce a fine powder with good flow properties. Sorbitol and mannitol (polyols) provide osmotic compatibility with ocular tissues. Lecithin granules (phosphatidylcholine-based) can serve a dual role carrier and co-emulsifier potentially enhancing bilayer stability and corneal permeation [6, 11].

4.4 Gelling Agents

The gelling agent imparts the viscoelastic properties necessary for prolonged ocular retention. HPMC (hydroxypropyl methylcellulose) at various viscosity grades (E4M, E15, K4M, K15M) is widely employed for its optical clarity, non-irritating nature, and pseudoplastic flow. Carbopol 940/934 (cross-linked polyacrylic acid) provides excellent bioadhesion through ionic interactions with corneal mucin at

physiological pH, but requires neutralisation. Poloxamer 407 (Pluronic F127) confers thermogelling behaviour—liquid at room temperature and gel at ocular temperature (34–35°C) enabling easy administration followed by in situ gelation. Sodium alginate and chitosan offer mucoadhesion and, in the case of chitosan, permeation-enhancing properties through transient tight junction modulation [8, 12].

5. PREPARATION METHODOLOGIES

5.1 Slurry Method

The slurry method is the most commonly employed technique for preparing proniosomes. The drug, surfactant, and cholesterol are dissolved in a minimum volume of organic solvent (chloroform, methanol, or their mixtures). The carrier (maltodextrin, sorbitol) is added to the lipid solution with continuous stirring, forming a slurry. The organic solvent is removed by evaporation (using a rotary evaporator or spray dryer) at controlled temperature and vacuum, leaving a dry, carrier-coated powder. The proniosomal powder is then dispersed in the hydrogel matrix by incorporating it into a pre-swollen polymer solution under gentle stirring or vortex mixing [7, 13].

5.2 Coacervation–Phase Separation Method

This method involves dissolving the surfactant and drug in a minimum volume of warm cyclohexane or hexane, adding the carrier under agitation to precipitate the lipid as a thin coating upon cooling. The solvent is removed by lyophilisation. This approach yields particularly uniform proniosomal granules but requires careful control of precipitation conditions [14].

5.3 Spray Drying

Spray drying offers the advantage of scalability and continuous processing. The drug-surfactant-cholesterol-carrier solution (aqueous or hydroalcoholic) is atomised into a heated chamber, yielding spherical, free-flowing microspheres. Process parameters (inlet temperature, feed rate, atomiser speed) must be optimised to prevent thermal degradation of heat-labile drugs and to control particle size and morphology [15].

5.4 Supercritical Fluid Technology

Supercritical CO_2 has been investigated as an alternative, solvent-free approach to produce proniosomal powders. The surfactant-cholesterol-drug mixture is processed in $scCO_2$ at defined pressure and temperature conditions, yielding nano-structured proniosomal systems with narrow size distribution. While environmentally advantageous, the high capital cost limits widespread adoption [16].

5.5 Gel Incorporation

Following preparation of the proniosomal powder, incorporation into the gel base involves hydration and gelation. For HPMC and Carbopol systems, the polymer is first hydrated in phosphate buffer (pH 7.4) or simulated tear fluid, the proniosomal powder is added under gentle mixing, and pH adjustment is performed if required. For poloxamer-based gels, a cold mixing technique (4°C) is employed, followed by storage; gelation occurs upon warming to body temperature. The final gel is filled into sterile ophthalmic containers under aseptic conditions [12].

6. CHARACTERISATION PARAMETERS

Thorough physicochemical and biological characterisation of proniosomal gels is essential to ensure product quality, efficacy, and safety. Regulatory agencies (USFDA, EMA) mandate extensive characterisation prior to clinical evaluation.

Table 4: Recent Proniosomal Gel Formulations for Ophthalmic Drug Delivery (2015–2025)

Drug	Carrier/Surfactant	Gelling Agent	Entrapment %	Key Finding	Reference
Timolol maleate	Span 60/Chol/Mal	HPMC E15	73.2%	2.5-fold IOP reduction vs drops	[7]
Acetazolamide	Span 60/Chol/Sor	Carbopol 934	68.9%	Sustained release >12 h; reduced systemic absorption	[9]
Ketorolac	Span 40/Chol/Lec	HPMC	81.3%	Enhanced anti-	[11]

tromethamine		K4M		inflammatory effect in rabbit model	
Brimonidine tartrate	Span 60/Chol/Mal	Poloxamer 407	78.6%	Thermosensitive; improved corneal permeation 3.1-fold	[13]
Ciprofloxacin HCl	Span 80/Chol/Man	Carbopol 940	65.4%	MIC maintained >24 h; excellent ocular tolerance	[15]
Voriconazole	Span 60/Chol/Sor	HPMC + Carbopol	70.2%	Enhanced antifungal activity vs Vfend® eye drops	[17]
Loteprednol etabonate	Span 60/Chol/Lec	Sodium alginate	84.7%	Mucoadhesive; prolonged anti-inflammatory action	[20]
Diclofenac sodium	Span 40/Chol/Mal	Poloxamer 188	72.5%	Reduced corneal inflammation score vs marketed gel	[22]
Cyclosporine A	Span 60/Brij 72/Chol	HPMC	88.1%	Increased tear production in dry eye rabbit model	[24]
Natamycin	Span 60/Chol/Mal	Carbopol 940	76.3%	Superior fungal keratitis treatment vs Natacyn®	[26]
Latanoprost	Span 60/Chol/Sor	Poloxamer 407	79.8%	Once-daily dosing; IOP reduction comparable to drops	[28]
Prednisolone acetate	Span 40/Chol/Man	HPMC K15M	71.9%	Enhanced bioavailability; lower systemic side effects	[30]

Table 5: Evaluation Parameters for Ophthalmic Proniosomal Gel Systems

Parameter	Method / Equipment	Acceptable Range	Significance
Vesicle size	Dynamic light scattering (DLS)	100–500 nm	Affects penetration, bioavailability
Zeta potential	Laser Doppler anemometry	±20 to ±60 mV	Colloidal stability indicator
Polydispersity index	DLS	< 0.3	Homogeneity of vesicle population
Entrapment efficiency	Ultracentrifugation / dialysis + UV-Vis	> 60%	Drug loading capacity
pH	Calibrated pH meter	6.5–7.5	Ocular compatibility, comfort
Viscosity	Brookfield / cone-plate viscometer	1000–40,000 cPs	Spread, retention, patient comfort
In vitro drug release	Dialysis bag / Franz diffusion cell	Sustained >8 h	Release kinetics, therapeutic window
Corneal permeation	Excised bovine/rabbit cornea, Franz cell	Flux > marketed formulation	In vitro bioavailability surrogate
Ocular irritation	HET-CAM / Draize test	Score 0–4 (non-irritant)	Safety for ophthalmic use
Stability	ICH Q1A: 25°C/60% RH, 40°C/75% RH	No significant change at 6 months	Shelf-life prediction
Morphology (TEM/AFM)	Transmission electron microscopy, AFM	Spherical, unilamellar	Confirms vesicle structure

6.1 Vesicle Size and Size Distribution

Dynamic light scattering (DLS) is the gold-standard technique for determining the hydrodynamic diameter and polydispersity index (PDI) of niosomal vesicles formed upon proniosome hydration. For ophthalmic applications, vesicle sizes in the range of 100–500 nm are generally targeted; submicron vesicles facilitate corneal penetration while avoiding lacrimation-induced clearance. A PDI < 0.3 is indicative of a monodisperse, homogeneous population [17]. Transmission electron microscopy (TEM) and atomic force microscopy (AFM) provide direct morphological confirmation of vesicle shape (typically spherical and unilamellar) and surface topology.

6.2 Zeta Potential

Zeta potential is a measure of the electrostatic charge on the vesicle surface and is a key predictor of colloidal stability. Vesicles with $|\zeta| > 30$ mV are considered electrostatically stable due to inter-particle repulsion. For ophthalmic proniosomal gels, most formulations target zeta potentials in the range of −20 to −60 mV for anionic systems (using DCP dicetyl phosphate as charge inducer) or +20 to +50 mV for cationic systems (using cetrimide or stearyl amine). Cationic niosomes may interact favourably with the negatively charged corneal surface, enhancing bioadhesion, but must be evaluated carefully for toxicity [18].

6.3 Entrapment Efficiency

Entrapment efficiency (EE%) is determined by separating free drug from encapsulated drug via ultracentrifugation (100,000 × g, 1 h) or membrane dialysis, followed by quantification of unentrapped drug in the supernatant/dialysate by UV–Vis spectrophotometry or HPLC. EE% for ophthalmic proniosomal gels typically ranges from 60–90%, depending on drug properties, surfactant type, drug-to-lipid ratio, and preparation method. Lipophilic drugs partition preferentially into the bilayer and achieve higher EE% [17, 19].

6.4 *In Vitro* Drug Release

Drug release from proniosomal gels is most commonly evaluated using a dialysis bag method or a Franz diffusion cell with a synthetic membrane (cellulose acetate or polycarbonate). Simulated tear fluid (pH 7.4, containing 0.9% NaCl, 0.2% $NaHCO_2$, 0.02% $CaCl_2$) is used as the receptor medium at 34 ± 0.5°C to mimic physiological conditions. Release profiles are typically biphasic an initial burst release from surface-adsorbed drug (0–2 h) followed by sustained release from the vesicular reservoir (2–24 h). Release kinetics is analysed using zero-order, first-order, Higuchi matrix, and Korsmeyer–Peppas models to characterize the dominant release mechanism [20].

6.5 *Ex Vivo* Corneal Permeation

Corneal permeation studies using excised bovine or rabbit corneas mounted in Franz diffusion cells represent the most predictive in vitro surrogate for in vivo ocular bioavailability. The apparent permeability coefficient (Papp), cumulative amount permeated per unit area, and flux are calculated from permeation data. Proniosomal gels consistently demonstrate 2–8-fold increases in corneal flux compared to conventional eye drops or unformulated solutions, attributable to the combination of prolonged contact time and the ability of niosomes to intercalate with and transiently disorganize the corneal lipid bilayers [21, 22].

6.6 Mucoadhesion and Rheological Properties

Mucoadhesive strength is evaluated using a texture analyser (measuring detachment force from bovine ocular tissue) or a rheological method (measurement of viscoelastic properties in the presence of mucin). Viscosity measurements are performed using a Brookfield viscometer or an oscillatory rheometer; pseudoplastic (shear-thinning) behaviour is advantageous for ophthalmic gels as it allows easy instillation while maintaining adequate post-application viscosity. For thermogelling systems (poloxamer), sol-gel transition temperature is measured by oscillatory temperature sweeps [12].

7. DISEASE SPECIFIC FORMULATION STUDIES: A CRITICAL REVIEW

7.1 Anti-Glaucoma Agents

Glaucoma, characterized by elevated intraocular pressure (IOP) leading to progressive optic nerve damage, is the world's second leading cause of blindness. Timolol maleate, a non-selective β-blocker, remains a cornerstone of glaucoma therapy but is associated with systemic cardiovascular adverse effects due to

nasolacrimal drainage and conjunctival absorption. Proniosomal gel formulations of timolol maleate using Span 60 and maltodextrin as carrier, incorporated into HPMC-based gels, demonstrated a 2.5-fold reduction in IOP in normotensive rabbits compared to marketed eye drops, with a duration of action extending beyond 12 hours and significantly lower plasma concentrations, indicating reduced systemic exposure [7]. Brimonidine tartrate, an α_2-adrenoceptor agonist used as monotherapy or adjunct in glaucoma, was formulated into thermosensitive proniosomal gels using Poloxamer 407. The *in situ* gelling system achieved a 3.1-fold increase in corneal permeation compared to the aqueous solution, with IOP reduction maintained for 10 hours post-application in rabbit models. The thermosensitive approach facilitated instillation as a liquid followed by in situ gelation at ocular temperature, eliminating the need for preservatives that may cause ocular surface disease with chronic use [13]. Latanoprost, a prostaglandin $F_2\alpha$ analogue and first-line IOP-lowering agent, presents formulation challenges due to its thermal and photochemical lability. Proniosomal gel systems using Span 60 and Poloxamer 407 demonstrated equivalent IOP reduction to commercial once-daily Xalatan® drops in rabbit models, with the additional benefit of improved stability at 25°C over 6 months compared to the commercial formulation [28].

7.2 Anti-Infective Agents

Bacterial keratitis and conjunctivitis represent ophthalmic emergencies requiring prompt and effective drug delivery. Ciprofloxacin hydrochloride proniosomal gels prepared using Span 80 and mannitol carrier, incorporated in Carbopol 940 gels, demonstrated sustained minimum inhibitory concentration (MIC) against *Staphylococcus aureus* and *Pseudomonas aeruginosa* over 24 hours in vitro, compared to less than 6 hours for commercial ciprofloxacin eye drops. Ocular irritation scoring (HET-CAM assay) confirmed excellent biocompatibility [15]. Voriconazole, the drug of choice for fungal keratitis, poses solubility challenges (aqueous solubility 0.7 mg/mL at physiological pH) that limit its formulation as eye drops. Proniosomal gel systems achieved drug entrapment up to 70.2%, providing significant improvement in aqueous drug concentration at the corneal surface. In vitro antifungal activity against *Fusarium solani* and *Aspergillus fumigatus* demonstrated superior zones of inhibition compared to commercially available Vfend® eye drops [17]. In vivo pharmacokinetic studies in rabbits showed 3.8-fold higher drug concentrations in aqueous humour at 4 hours post-application for the proniosomal gel compared to the aqueous suspension. Natamycin, the only FDA-approved antifungal specifically indicated for fungal keratitis, has poor corneal penetration due to its macrolide structure and hydrophilicity. Proniosomal gel formulations demonstrated substantially improved corneal permeation and antifungal efficacy in a *Candida albicans* keratitis rabbit model compared to Natacyn® 5% suspension [26].

7.3 Anti-Inflammatory Agents

Post-operative ocular inflammation and uveitis require potent anti-inflammatory therapy. Ketorolac tromethamine proniosomal gels (Span 40, HPMC K4M) demonstrated 4.2-fold higher aqueous humour concentrations in rabbits at 4 hours compared to marketed 0.5% ketorolac eye drops, with a significant reduction in prostaglandin E_2 levels as a biomarker of inflammation [11]. Diclofenac sodium proniosomal gels using Poloxamer 188 as the gelling agent demonstrated superior clinical scores in an endotoxin-induced uveitis rabbit model compared to the reference Voltaren® ophthalmic solution [22]. Corticosteroids remain the gold standard for severe ocular inflammation. Loteprednol etabonate, a 'soft' corticosteroid with reduced IOP-raising propensity, was formulated in proniosomal gels using sodium alginate as the mucoadhesive gel former. The formulation demonstrated an 84.7% entrapment efficiency and significantly higher bioadhesive strength than HPMC-based comparators, with sustained anti-inflammatory effects over 12 hours in a carrageenan-induced ocular inflammation model [20]. Prednisolone acetate proniosomal gels showed enhanced bioavailability with a 3.6-fold increase in AUC (0–24h) compared to commercial Pred Forte® 1% suspension, attributed to improved corneal permeation and reduced precorneal drainage [30].

7.4 Immunosuppressants

Cyclosporine A (CsA), a cyclic polypeptide immunosuppressant, is indicated for dry eye disease (DED) and severe anterior segment inflammatory conditions. Its extreme hydrophobicity (log P 2.92) renders aqueous formulation extraordinarily difficult. CsA proniosomal gels using Brij 72 as co-surfactant with Span 60 achieved entrapment efficiencies exceeding 88%, the highest reported for this highly lipophilic drug. In a rabbit model of DED induced by benzalkonium chloride, the proniosomal gel restored tear production, goblet cell density, and corneal integrity to near-normal levels after 4 weeks of twice-daily application, demonstrating superior outcomes compared to Restasis® 0.05% emulsion [24].

8. *IN VIVO* PHARMACOKINETICS AND PHARMACODYNAMICS

Rabbit models have been the most widely used preclinical species for ocular pharmacokinetic evaluation of proniosomal gels, owing to their anatomical similarity to the human eye, large ocular surface area, and established bioanalytical methods. Drug concentrations in aqueous humour, cornea, iris-ciliary body, and vitreous are typically determined at defined time points following ocular instillation by HPLC-UV or HPLC-MS/MS after tissue homogenisation and protein precipitation. Pharmacokinetic analysis of proniosomal gel formulations consistently demonstrates significantly higher maximum drug concentrations (Cmax) and area under the concentration-time curve (AUC) in target ocular tissues compared to conventional eye drops or solutions. The time to maximum concentration (Tmax) is generally delayed (2–4 h vs. 0.5–1 h for drops), consistent with the controlled-release mechanism. The elimination half-life ($t_1/_2$) from aqueous humour is substantially prolonged, supporting reduced dosing frequency [7, 13]. Importantly, several studies have demonstrated significantly reduced plasma concentrations of drug following proniosomal gel application compared to conventional drops, indicating that the sustained ocular residence and controlled permeation reduces nasolacrimal-mediated systemic absorption. This has particular relevance for drugs with narrow therapeutic indices or significant systemic toxicity (e.g., timolol maleate in patients with cardiovascular disease) [7].

The pharmacodynamic advantages of proniosomal gels are well-documented in disease-specific models. IOP-lowering studies for anti-glaucoma agents, MIC maintenance studies for anti-infectives, and inflammatory scoring for anti-inflammatory agents all demonstrate statistically superior outcomes for proniosomal gels compared to marketed formulations, corroborating the pharmacokinetic data [11, 13, 22].

9. STABILITY AND SAFETY CONSIDERATIONS

9.1 Physical and Chemical Stability

One of the primary advantages of the proniosomal approach is its superior stability profile compared to conventional niosomal dispersions. Stability studies conducted in accordance with ICH Q1A guidelines (25°C/60% RH and 40°C/75% RH over 6 months) have consistently confirmed that proniosomal gels exhibit minimal changes in vesicle size, zeta potential, entrapment efficiency, drug content, and pH under storage conditions. The dry proniosomal carrier is inherently protected from hydrolytic degradation, while the gel matrix provides physical protection against vesicle aggregation and coalescence [19]. Some studies have reported improved photostability for photolabile drugs (e.g., latanoprost) encapsulated within the opaque gel matrix [28].

9.2 Ocular Biocompatibility and Toxicity

Safety evaluation of ophthalmic formulations is paramount given the sensitivity of ocular tissues. The HET-CAM (hen's egg test on the chorioallantoic membrane) assay is widely used as a pre-screening test for ocular irritation potential. Draize rabbit eye tests (assessment of corneal, iris, and conjunctival changes) provide regulatory-grade irritation data. The majority of published proniosomal gel formulations produce Draize scores in the non-irritating to minimally irritating category (scores 0–4), attributable to the use of Generally Recognised As Safe (GRAS) excipients (non-ionic surfactants, cholesterol, HPMC, Carbopol) and isotonic, physiological pH formulations [15, 20]. Corneal histopathology following repeated ocular application in rabbits has generally confirmed the absence of significant morphological changes. However, certain charge-inducing agents (e.g., cetrimide at high concentrations) and permeation enhancers (e.g., EDTA) require careful concentration optimization to balance efficacy against toxicity [18].

10. CHALLENGES, REGULATORY ASPECTS, AND FUTURE DIRECTIONS

10.1 Current Challenges

Despite the compelling preclinical evidence, no proniosomal ophthalmic gel has yet progressed to clinical trials or regulatory approval, highlighting the translational gap between bench and bedside. Key challenges include: (i) Scale-up and manufacturing reproducibility the organic solvent-based slurry method requires rigorous solvent removal validation (ii) Sterilization compatibility filtration sterilisation of vesicular systems requires careful evaluation to avoid vesicle disruption (iii) The complex in vitro–in vivo correlation (IVIVC) for ophthalmic vesicular systems remains incompletely characterized (iv) Regulatory pathway ambiguity proniosomal gels may be classified as drug device combination products in certain jurisdictions, complicating approval strategy (v) Patient acceptability studies (blurring, comfort, tolerability) are largely absent from the current literature [8].

10.2 Future Directions

Several emerging strategies are being explored to further advance proniosomal gel technology. Stimuli-responsive systems incorporating temperature-sensitive (poloxamer), pH-sensitive (Carbopol, alginate), and light-responsive (azobenzene-modified surfactants) components offer the prospect of triggered drug release in response to pathological changes in the ocular microenvironment. Surface-functionalized proniosomal gels with targeting ligands (transferrin, folate, hyaluronic acid) directed at specific corneal or retinal receptors represent another frontier [8]. The integration of proniosomal systems with other nanotechnology platforms such as nanoparticles (polymeric, lipid, gold), nanoemulsions, and dendrimers may enable combinatorial drug delivery for complex ocular diseases such as diabetic macular oedema and age-related macular degeneration. Three-dimensional-printed contact lens inserts incorporating proniosomal layers offer a wearable drug delivery platform. Finally, the application of Quality by Design (QbD) methodologies, including Design of Experiments (DoE), response surface methodology, and Artificial Intelligence-based predictive modelling, will accelerate optimisation and reduce the development timeline for these systems [9].

11. CONCLUSION

Proniosomal gels represent a technologically sophisticated, pharmacologically rational, and economically viable approach to the persistent challenge of ocular drug bioavailability. By harnessing the stability of dry proniosome carriers, the controlled-release kinetics of niosomal vesicles, and the mucoadhesive and viscosity-enhancing properties of hydrogel matrices, these systems offer a multi-pronged solution to the formidable barriers of the eye. The extensive body of literature reviewed herein demonstrates consistent superiority of proniosomal gels over conventional ophthalmic formulations across a diverse range of pharmacological classes' anti-glaucoma, anti-infective, anti-inflammatory, and immunosuppressant agents. Key formulation variables surfactant type and HLB, cholesterol ratio, carrier nature, gelling agent, and charge-inducing agents have been systematically investigated and their influence on critical quality attributes (vesicle size, entrapment efficiency, drug release, corneal permeation, and mucoadhesion) well characterized. The safety profile, as assessed by Draize and HET-CAM testing, is generally favorable. The primary imperatives for future research are the development of robust scale-up processes, resolution of regulatory classification challenges, conduct of formal pharmacokinetic studies with validated bioanalytical methods, and ultimately, initiation of clinical trials to translate the compelling preclinical evidence into patient benefit. With continued interdisciplinary effort at the interface of pharmaceutical sciences, materials science, and clinical ophthalmology, proniosomal gels are poised to significantly advance the landscape of ophthalmic drug therapy.

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