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Review Article

PRONIOSOMES: A NOVEL VESICULAR CARRIER FOR OCULAR DRUG TARGETING

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ABSTRACT

The human body is one of the most fascinating and complex structures present on this earth. It has five sensory organs that allow a human to feel, understand, and respond according to their surroundings. Among these five organs, one is the eye. The eye is considered one of the most important sensory organs of the human body. It helps us in seeing this beautiful and colorful world, present around us. In case any kind of disease or disorder occurs in the eye, then the treatment may take a long time for the condition to return to normal. Ocular drug delivery presents unique challenges in the field of pharmaceutical sciences. This is due to the presence of numerous protective barriers and the complex anatomy of the human eye. Conventional formulations present in the market include eye drops, ointments, creams, and gels. These formulations often suffer from various limitations, such as low bioavailability, short drug residence time, and even rapid drug elimination. This results in decreased therapeutic efficacy of traditional formulations. To overcome these problems, vesicular systems such as proniosomes have emerged in the healthcare field as promising drug delivery carriers in ocular pharmacotherapy. Proniosomes are dry, free-flowing, and non-ionic surfactant-based formulations. Proniosomes convert into niosomes when hydrated. Proniosomes offer numerous advantages in ocular drug delivery. These advantages include enhanced drug stability, increased permeability, and prolonged drug release across the ocular barriers, thus providing increased therapeutic results. This article provides a detailed overview of the anatomy of the human eye, focusing on its structural complexity and barriers which are responsible for alterations in the effective absorption of administered drugs. It even highlights the potential of proniosomal formulations and how they revolutionize ocular pharmacotherapy. Furthermore, this article also elaborates about the various formulation methods of proniosomes, which include the coacervation-phase separation method, slurry method, ether injection method, spray drying method, and thin-film hydration method. This review emphasizes the enhanced drug delivery efficiency and the sustained therapeutic effects offered by proniosomal formulations. The future perspectives of proniosomal formulations for research have also been explored in this review while focusing on various innovative strategies that may improve drug targeting and bioavailability. This article mainly aims to serve as a comprehensive source of information about the potential and need for advanced proniosomal formulations in the treatment of ocular diseases.

Keywords: Ocular, Permeability, Barriers, Proniosomes, Nanocarriers.

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INTRODUCTION

The eye is one of the most integral parts of the human body. It acts as one of the sensory organs and is very sensitive [1]. The human eye consists of various parts, and they work together to provide a proper image of the object or surroundings, which is further sent to the human brain, and hence, the individual can see. The eye is also one of the most complex organs of the human body, and it consists of various protective barriers and defense mechanisms. This is the main reason why drug delivery in various compartments of the eyes is very difficult [2]. There are various infections due to microbial transmission which may affect the normal functioning of the human eye. These microbes may be transferred into the eye at different stages and factors such as at birth, due to environmental exposure, disease state, and many more. The pathogen may invade the eye through the conjunctiva or eyelid, or any other vulnerable ocular tissues [3]. The causative agents for infections in the eye include bacteria, viruses, fungi, and parasites. The treatment is given based on the causative agents and infection types using antibacterial, antiviral, antifungal, anti-helminthic, antiseptics, etc. Any kind of infection or disease in the eye may pose a threat to normal vision [4]. The drug delivery in the ocular system is considered to be the most challenging issue, mainly due to its anatomy and physiology [5]. The structure of the human eye is unique and complex. It consists of various barriers such as the conjunctiva, corneal epithelium, and the blood-ocular barrier. All these barriers are responsible for restricting the absorption and distribution of the drug [6].

The human eye is a complex sensory organ mainly responsible for vision. It is protected by multiple anatomical structures that facilitate its function while also serving as a barrier to drug delivery [7]. The eye primarily consists of three layers, which include the fibrous layer, vascular layer, and nervous layer. The fibrous layer (also known as fibrous tunic layer) includes cornea and sclera, which provide shape and protection to the eye [8]. The cornea is transparent and avascular, thus playing a crucial role in light refraction. Sclera, on the other hand, is an opaque and protective outer layer [9]. The vascular tunic (also known as uvea) is comprised of the iris, ciliary body, and choroid. They are responsible for the regulation of light entry and supplying nutrients to the ocular tissues. The third layer is called the nervous tunic; it mainly consists of the retina and is responsible for capturing visual information and transmitting it toward the human brain through the optic nerves [10]. In addition, the intraocular structures such as aqueous humor, vitreous humor, and lens play a huge role in maintaining the intraocular pressure while focusing light onto the retina. This ultimately leads to a clearer vision [11].

An ideal ocular drug delivery system should be long-lasting on the ocular surface and ensure maximum absorption of the drug while decreasing its loss through tear turnover [12]. It should also be non-irritating and comfortable to improve patient compliance, since discomfort often correlates with treatment non-compliance [13]. Sterility should reasonably be ensured against infection and make it safe for the eye [14]. Further, the formulation should ensure the controlled release of the drug predictably to maintain an optimum therapeutic level while avoiding both subtherapeutic

and toxic doses. Facilitation in administration is also essential, wherein the patient himself can use it without advanced techniques [15]. It should also have stability sufficient to maintain its efficacy over time with minimal loss. Thereby, they convert themselves seamlessly into the promising method of improving ocular medication delivery. They do not provide longer retention and even cause poor vision and irregular drug liberation as well. Ointments reduce patient compliance. Gels may increase retention, but these often cause discomfort to patients and unpredictable gelation behavior [15]. The eye drops have a short residence time [16].

Nanoformulations play a major role in current drug delivery. They are mainly involved in improving solubility, providing stability, and increasing bioavailability [13]. This makes them ideal for providing targeted therapy to the patient. They have proven to provide an effective percentage in encapsulating drugs in the vesicles [17]. Nanoformulations, being a broad category, include liposomes, niosomes, proniosomes, cubosomes, bilosomes, chitosomes, terpesomes, discome, spanlastics, ethosomes, transethosomes, and transferosomes [18]. Liposomes are formulations comprising phospholipid bilayers and are good carriers [19]. Niosomes are made of non-ionic surfactants and are wiser and cheaper than liposomal forms because they also face fewer problems with fusion and sedimentation [20]. Cubosomes are novel vesicular formulations, formed by dispersing self-assembled lipid molecules (amphiphilic), as a liquid crystalline phase [21]. Bilosomes are formulations that break in the gastric region, which allow the oral delivery of drugs that are given through injectables [22]. Chitosomes are microvesicular formulations that have chitin-synthetase activity at higher concentrations [23]. Terpesomes are terpenes containing liposomes [24]. Discomes are the disc-shaped niosomes with a diameter of about 20 μm [25]. Spanlastics are surfactant-based nanovesicle formulations that contain span and edge activators [26]. Ethosomes are ethanolic liposomes. They are non-invasive vehicles allowing medications to enter the transdermal layer easily and effectively [27]. Transethosomes are the modified form of ethosomal formulations containing edge activators and penetration enhancers [28]. Transferosomes are lipid-based vesicles that contain edge activators and phosphatidylcholine. These are mainly used for transdermal delivery of the drug [29]. Table 1 provides a comprehensive knowledge about various nanoformulations involved in the treatment of ocular diseases over the past years.

Proniosomes are a dry, free-flowing vesicular system, which on hydration converts to niosomes, thus overcoming the stability problems and enhancing drug administration [15]. These vesicular systems are especially helpful as ocular medication therapies, wherein conventional formulations such as eye drops, ointments, and gels have dire limits. Eye drops have low retention at the eye surface due to their rapid precorneal clearance due to the effect of blinking and tear turnover [19]. Proniosomes alleviate the above-mentioned problems by providing extended ocular residence duration through mucoadhesive features with sustained drug release and increased corneal penetration [30]. These encapsulating indirect features provide more controlled drug release, allowing less frequent dosing, reducing systemic side effects, and generally enhancing therapeutic performance for ophthalmic therapy. During the research, proniosomes-based formulations have emerged as promising vesicular carriers. They are designed to overcome various limitations of the conventional ocular formulations, by offering them controlled release, improved drug stability, and also enhanced permeation of the drug across the ocular barriers present [31]. This review mainly focuses on providing an overview of proteasomes and the current status of proniosomal formulations in the treatment of ocular diseases by targeting the ocular drug delivery system.

Barriers in ocular drug delivery

The unique anatomy of the human eye presents various barriers that are responsible for protecting it from external agents and, hence, prevent them from entering systemic circulation, but these barriers are also responsible for hindrance in drug delivery [32]. The corneal barrier is mainly composed of epithelium, stroma, and endothelium. It is the primary route meant for topical drug absorption [33]. The lipophilic nature of epithelium restricts hydrophilic drugs from penetrating into the eye, whereas the stroma, due to its hydrophilic nature, prevents the diffusion of lipophilic drugs [6]. The conjunctival barrier of an eye covers the sclera and inner eyelids, offering an alternate absorption pathway, but this pathway has low permeability and a large surface area. This leads to dilution of the drug [34]. The blood-aqueous barrier together with the blood-retinal barrier plays a huge role in maintaining the ocular immune privilege and homeostasis, hence preventing systemic drugs from reaching the intraocular tissues [11]. All these barriers together pose significant challenges toward effective ocular drug delivery and necessitate innovative ocular drug delivery systems like proniosomes.

Traditional ocular drug delivery methods include eye drops, gels, and ointments. These often face challenges such as rapid precorneal elimination with limited and low drug residence time, further leading to poor patient compliance [35]. Hence, the researchers have introduced the advanced form of drug delivery systems, such as nanoparticles, *in situ* gels and vesicular carriers. [36]. These are developed to overcome the issues faced by the traditionally used formulations for ocular disease treatment [37]. Among these, the proniosomal formulations have stood out due to their ability to provide enhanced drug stability, increased bioavailability, and sustained release of the drug in the system [38]. Fig. 1 below provides a more specified comparison between the traditional and proniosomal formulations for better understanding.

PRONIOSOMES-BASED FORMULATIONS

Proniosomes are free-flowing formulations that are dry in nature. They convert into niosomes on hydration [65]. These non-ionic surfactant-based vesicles offer several advantages, which include ease of storage, increased drug encapsulation efficiency, and higher trans-corneal permeation [66]. Proniosomes can be used for ocular applications by proper selection of appropriate surfactants, stabilizers, and methods for hydration. This ensures optimal drug delivery to the eye's anterior and posterior segments [67]. Fig. 2 below shows an elaborated and structural representation of proniosomes.

There are various proniosomal formulations which have been formulated for the treatment of ocular diseases; Table 2 focuses on those formulations. The table below includes proniosmal formulations made for the treatment of various ocular complications.

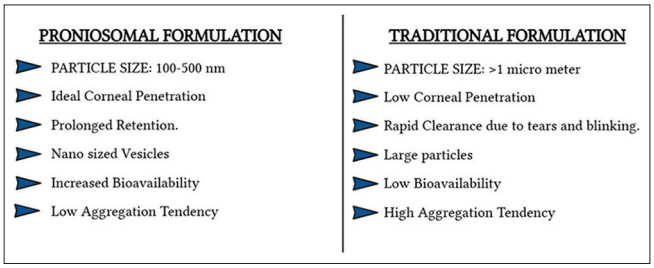

Fig. 1: Comparison between traditional and proniosomal formulation

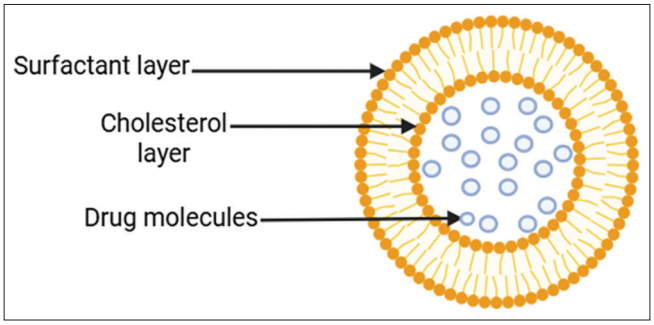

Fig. 2: Structural representation of proniosomes

Table 1: Nanoformulations for the treatment of ocular diseases in past years

Nanoformulations	Drug	Targeted disease	Polymers used	Method of preparation	Key findings	References
Biliosomes	Terconazole	Fungal infections	Span 60, Cholesterol	Ether- injection method	Entrapment efficiency: 96.59±0.42% Zeta Potential: −46.35±0.77 to−59.15±0.21 mV. Polydispersity Index: 0.24±0.01	[39]
Biliosomes	Acetazolamide	Glaucoma	Span 60, Cholesterol	Thin film hydration method	Entrapment efficiency: 69.03–74.24% Particle diameter: 350–735 nm Zeta potential: <−43.3mV. Polydispersity Index: 0.218–0.476 The *in-vitro* test showed a release profile of 78.06–97.71% for 8 h.	[40]
Biliosomes	Natamycin	Fungal Keratitis	Span 60, Cholesterol	Thin film hydration method	Entrapment efficiency: 70.12±3.66%–93.75±4.32% Particle size: 235.03±05.29 nm–380.43±27.94 nm Polydispersity index: 0.20±0.01–0.43±0.23, Zeta Potential: −45.41±4.54 mV−−69.03±1.57 mV.	[41]
Cubosomes	Acetazolamide	Glaucoma	Glyceryl monooleate (GMO) or Poloxamer (407)	Emulsification technique	Entrapment efficiency: 25.3±0.87%–59.8±0.82% Polydispersity index: 0.18±0.03 and Zeta potential: −10.8±3.2 mV Hydration Level of Corneal: 76–89% Enhancement permeability: Increase of about 4 folds when compared toconventional formulation.	[42]
Cubosomes	Voriconazole	Fungal infections	Pluronic F127 (F127), DL-ά-Monoolein (MO)	Melt dispersion emulsification method	Entrapment efficiency: 21.90–90.60% Polydispersity index: 0–1 Zeta potential: −19.45−−32.78 mV. Hydration level of corneal: 89% Permeability enhancement showed an increase of about 4 folds on comparison to conventional formulation.	[43]
Cubosomes	Latanoprost	Glaucoma	Phytantriol (3,7,11,15-tetramethyl-1,2,3-hexadecanetriol)/Pluronic F127	Bottom-up and top-down method	Entrapment efficiency: 87–94% Zeta potential: −25 mV Polydispersity index: 0.1 Particle size: 200 nm *In-vivo* assay shows 20% less irritability when tested on rabbit eye model.	[44]
Chitosomes	Ciprofloxacin	Bacterial conjunctivitis	Cholesterol, Span 60	Thin film hydration method	Entrapment efficiency: 78.32±4.49% Particle size: 180.34±5.13 nm *In-vitro* drug release showed 82.87±4.01% drug release (in 12 h)	[45]
Chitosomes	Carteolol	Glaucoma	Cholesterol, Span 60	Thin film hydration method	Entrapment efficiency: 70.45±0.87% Vesicle size: 235±3.54 nm. Permeation flux: 1.13-fold higher permeation than conventional formulation	[46]
Terpesomes	Fenticonazole nitrate	Fungal infection	L-α phosphatidylcholine	Thin film hydration method	Entrapment efficiency: 79.02±2.35% Zeta potential: 36.15±1.06 mV Polydispersity index: 0.46±0.01 Particle size: 287.25±9.55 nm	[24]
Flexomes	Tolnaftate	Fungal Infection	Tween 80, L-α phosphatidylcholine	Ethanol- injection method	Entrapment efficiency: 66.08±11.38% Zeta potential: 42.95±0.64 mV Particle size: 154.99±29.11 nm	[47]
Phytocubosomes	L-carnosine	Ocular Inflammation and Glaucoma	Phospholipid S100, Poloxamer 407, Glyceryl monooleate	Hydrotrope technique	Entrapment efficiency: 96% Positive charge: +49±6.09 mV *In-vitro* test showed a drug release profile was 38 % over 24 h	[48]

(Contd...)

Table 1: ***(Continued)***

Nanoformulations	Drug	Targeted disease	Polymers used	Method of preparation	Key findings	References
Nanoemulsions	Acyclovir	Herpes simplex keratitis	Poloxamer 407 as surfactant and Transcutol® 100 P	Low-energy method	Refractive index of ophthalmic drops: 1.340 Osmolarity: 1087–1276 mOsmol/kg Particle size: 28–34 nm Polydispersity index: 0.38±0.04–0.47±0.05 *In-vitro* test showed that that the release of the nanoemulsion formulation was between 74.44% and 80.78% after 6 h.	[49]
Nanoemulsions	Terbinafine hydrochloride	Fungal infection	Polyethylene glycol, Tween 80	Water titration method	Mean droplet size: <30 nm Transmittance: 90–96.5% *In vitro* test showed 10% release of drug at every hour and followed a zero order kinetics.	[50]
Nanosuspensions	IBU sodium salt	Conjunctivitis	Tween 80, Benzalkonium chloride	QESD technique	Entrapment efficiency: >90% Zeta potential: −12 mV *In-vitro* tests showed a sustained release profile for 24 h.	[51]
Dendrimers	Timolol maleate	Glaucoma	Polyethylene glycol diacrylate, Span 80, Tween 80	Inverse emulsion method	Enhanced corneal drug permeability by 17 folds and zero order drug release was reported.	[52]
Dendrimers	Anti-Vascular endothelial growth factor	Choroidal Neovascularization	Poly-L-lysine	Solid-phase Boc-chemistry	A sustained release profile was reported for up to 48 h	[53]
Solid-lipid nanoparticles	Cyclosporine	Corneal graft rejection	Tween 80	Hot homogenization technique	Zeta potential: 50.30±0.78 mV Particle size: 248.00±0.33 nm Polydispersity index: 0.25±0.00 *In-vitro* test showed sustained release drug profile.	[54]
Niosomes	Timolol maleate	Glaucoma	Span 20, Span 40, Span 60, Tween 20, Tween 40, Cholesterol	Thin- film hydration method	Entrapment efficiency: 94.6–98.8% IOP: decreased to 21.77 mmHg in & hours. Bioavailability: Increase of about 1.5–1.6 times than conventional formulation *In-vitro* test showed a sustained release profile of 96% and 97.10% for 24 h.	[55]
Niosomes	Lomefloxacin HCI	Conjunctivitis	Span 20, Span 60, Span 80 Tween 40, Tween 60, Tween 80, Cholesterol	Thin film hydration method	Entrapment efficiency: 68.41±0.07 Zeta potential: -40.70±2.20mV Particle size: 176.0±0.98 nm Polydispersity index: 0.11 ± 0.21 to 0.64 ± 0.23 *In-vitro* test has shown a sustained release profile of 8 h	[56]
Niosomes	Dorzolamide HCl	Glaucoma	Span 60, Cholesterol	Thin film hydration method	Entrapment efficiency: >30% Particle size: 150–300 nm In vitro test showed that 90.3±7.6% drug was released after 8 h.	[57]
Niosomes	Natamycin	Fungal Keratitis	Span 60, Cholesterol, Diacetyl phosphate, N-Trimethyl chitosan	Thin film hydration method	Entrapment efficiency: 81.76% Zeta potential: 30.72mV Particle size: 1034.14 nm Corneal permeability was increased up to 29.391±1.76%	[58]
Niosomes	Cyclosporine A	Corneal graft rejection	Span 60, Tween 80	Solvent injection method	Entrapment efficiency: 92–95% Zeta potential: −15.5±2.3 mV–−25.2±1.6 mV Particle size: 308.9±8.8 nm Polydispersity index: 0.264	[59]

(Contd...)

Table 1: ***(Continued)***

Nanoformulations	Drug	Targeted disease	Polymers used	Method of preparation	Key findings	References
					Osmolarity: 252–254 mOsmol/kg *In-vitro* test showed 30–50% of the drug content to be released after 24 h.	
Niosomes	Doxycycline hyclate	Corneal ulcers and keratitis	Span20, Span 80, Span 60, Cholesterol, Tween 60	Reverse-phase evaporative method	Entrapment efficiency: 51–56% Particle size: 117 nm Zeta potential: −27.4±2.2–−25.8±2.3 mV *In-vitro* test showed a sustained release profile for 20 h.	[60]
Liposomes	Edaravone	Age-related macular degeneration	Cholesterol	Calcium acetate gradient method	Entrapment efficiency: 41.4%±0.3%. Zeta potential: 7.4±0.4mV Particle size: 92.6±1.5nm	[61]
Liposomes	Lantoprost	Glaucoma	Not specified	Thin film hydration method	Entrapment efficiency: 75–88% Zeta potential: −2.6–−9.3 mV Particle size: 80–140 nm Polydispersity index: 0.09–0.2 The sustained release was recorded for up to 50 days	[62]
Liposomes	Diclofenac	Age-related macular degeneration	Cholesterol, PVA	Calcium acetate gradient method	Entrapment efficiency: >97% PDI: 0.037–1.00 Zeta Potential: −0.5–−2.5 mV	[63]
Liposomes	Triamcinolone acetonide	Macular edema	Chitosan, Cholesterol	Hydration method	Entrapment efficiency: 95–98% Zeta potential: +31.2–+32.9 mV Particle size: 103–105 nm	[64]

FORMULATION METHODS OF PRONIOSOMES

Proniosomal formulations can be prepared using different methods. They all offer unique advantages in terms of drug stability, encapsulation efficiency, and production ease. The most common methods for the formulation of proniosomes are coacervation phase separation, spray drying, slurry method, ether injection method, and thin-film hydration [74].

These methods mainly involve careful selection of surfactants, stabilizing agents, and carriers for optimized vesicle formation and drug encapsulation in them. Fig. 3 below provides a summary about the polymers used with their comparative amounts used in different proniosomal formulations:

APPLICATIONS IN OCULAR DISEASE TREATMENT

Proniosomal formulations have demonstrated their potential in treating various ocular conditions, by enhancing the drug penetration into the system and also providing sustained release of the drug. This is one of the major advantages of proniosomes and is also a need in current situations. Some well-known conditions where proniosomal formulation can be used in treatment include:

Glaucoma

Glaucoma (also known as motiyabind) is a progressive optic neuropathy condition. It is characterized by high intraocular pressure and damaged optic nerve, which leads to loss of vision. It is often asymptomatic during the early stages, which makes its timely diagnosis and treatment very crucial [73]. In the research conducted by Emad *et al*. [68], it was shown that the proniosomes-based formulations of brimonidine tartrate, prepared by the coacervation-phase separation method, are highly effective for the treatment of glaucoma due to their improved bioavailability and prolonged reduction of intraocular pressure. It was also tested that there was no irritation produced over the administration of the formulation, unlike the conventional ones. Optimization variables of the formulation showed the desirability of 0.732. This indicated that the formulation has demonstrated a sustained release profile of over 24 h.

Conjunctivitis

Conjunctivitis, also known as "pink eye disease," is a conjunctival inflammation caused by bacteria, viruses, or allergies that cause redness, irritation, and discharge. The proniosomal formulations can improve corneal penetration, sustain release, and increase drug stability. According to a study conducted on the curcumin-loaded proniosomal gel to treat ocular inflammation. It was found that the *ex vivo* permeability was 3.22 times higher, the mean particle size was 212.0 nm, and the entrapment effectiveness was 96%. Within 24 h, the gel showed a 40% decrease in inflammation, and after 4 days, it fully recovered [75]. Adding to this, in the Sprague-Dawley rat model, the tacrolimus-loaded proniosomes had shown prolonged corneal transplant survival till 13.86 days while also delaying corneal allograft rejection [68]. In research, it was found that the brimonidine-tartrate proniosomal gel demonstrated no eye discomfort with a 5.024-fold increase in bioavailability. The entrapment efficiency was also found to be about 79.23% [72]. The results have proven, proniosomal formulations can increase the bioavailability of ocular drugs, maintain drug release, and lower the frequency of dosage. This can further lead to improved and desirable outcomes for conjunctivitis treatment.

Age-related macular degeneration

Age-related macular degeneration is one of the most common causes of vision loss in old people. This condition is characterized by the degeneration of the macula and impairment of central vision [76]. In a study conducted by Del Amo *et al*. [9], it was found that proniosomal delivery of the anti-vascular endothelial growth factor agents ensures targeted release of drug in the posterior segment of the eye. This decreases systemic exposure and also reduces drug side effects. A study indicated that ranibizumab-loaded proniosomes had demonstrated a

Table 2: Proniosomes-based formulations for treatment of ocular diseases

Drug	Method of preparation	Targeted disease	Polymers used	Key findings	References
Brimonidine Tartrate	Coacervation phase separation	Glaucoma	Span 60, Brij 52, Cholesterol, Soybean α-lecithin	Entrapment efficiency (in %) was found to be79.23 and particle size (in nm) was 810.95. *In-vitro* release was determined to be 91.11% over 24 h. According to the *in-vivo* studies conducted, it was found that the bioavailability of the drug was improved to about 7.90-fold in mean residence time.	[68]
Ketoconazole	Coacervation phase separation	Fungal Keratitis	Span 60, Cholesterol, Lecithin	Entrapment efficiency (in %) was found to be as 51.40–70.70. Enhanced corneal permeation compared to conventional formulations. According to the *in vivo* studies, the formulation was effective in treating fungal keratitis in rabbit models.	[69]
Dorzolamide HCl	Coacervation phase separation	Glaucoma	Span 60, Cholesterol	Entrapment efficiency (In %) was 84.5±1.5. The analysis of the *in vitro* release profile has shown 58.51±1.00% over 8 h. Furthermore, the *in vivo* study has demonstrated a significant reduction in intraocular pressure when administered in rabbit models.	[70]
Timolol Maleate	Coacervation phase separation	Glaucoma	Span 60, Cholesterol, Lecithin	Entrapment efficiency (in %) was found to be higher than the conventional formulation. The *in vitro* release has demonstrated a sustained drug release profile for over 12 h and the *in vivo* studies have shown a significant reduction in intraocular pressure, in rabbit models.	[71]
Curcumin	Coacervation phase separation	Ocular inflammation	Pluronic P123, D-α-tocopheryl polyethylene glycol succinate (TPGS)	Entrapment efficiency (in %) was 91.5±1.5 and the *in vitro* release profile was 85.3±1.2% release for 24 h	[19]
Tacrolimus	Coacervation phase separation	Corneal Graft Rejection	Span 60, Cholesterol, Lecithin	entrapment efficiency (in %) was 89.7±1.3 and the *in-vivo* release profile was determined to be as 93.5±1.1% release for 24 h.	[72]
Levofloxacin	Coacervation phase separation	Bacterial Conjunctivitis	Cholesterol, Lecithin, Span 40, Span 60, PEO	Entrapment efficiency (in %) was determined to be as 88.2±1.4. The *in vivo* release profile was found as 90.7±1.3% release for 12 h.	[19]
Acetazolamide	Coacervation phase separation	Glaucoma	Poloxamer 407, Glyceryl Monooleate	Entrapment efficiency (in %) was 85.4±1.6 and the *in vivo* test release profile was determined to be as 87.9±1.2% release for over 8 h	[73]
Betaxolol Hydrochloride	Slurry method	Glaucoma	Cholesterol, Span 60	Entrapment Efficiency (in %) was 90.1±1.3. The *in vivo* release profile was determined to be 92.4±1.1% release over 12 h.	[19]
Lomefloxacin HCl	Coacervation phase separation	Bacterial conjunctivitis	Cholesterol/Brij 35 (Polyoxyethylene (23) lauryl ether), Brij 72, Brij 98 Span 20, Span 40 Span 60, Tween 40, Tween 60, Tween 80	Entrapment efficiency (in %) was determined to be87.6±1.5. The *in vivo* tests showed 89.8±1.2% release for over 12 h.	[19]

mean particle size of 183.2 ± 0.3 nm, a zeta potential of −27.6 ± 1.2 mV, and an entrapment efficiency of 92.4%. Its *in vivo* tests in rats showed that the therapeutic effect was present for 14 days [77]. In addition, when compared with traditional ocular formulations, dexamethasone-loaded proniosomal gels were showed an increase in their bioavailability of up to 4.8-fold. This has led to a prolonged anti-inflammatory effect with no discomfort to the eye. These results confirm that the proniosomal formulations are a viable as well as non-invasive option for the treatment of age-related macular degeneration [78]. They also guarantee prolonged drug release which ultimately increases the drug's bioavailability.

Ocular hypertension

The condition of ocular hypertension mainly refers to elevated intraocular pressure, occurring without any detectable glaucomatous damage. This increases the risks of having glaucoma. A study by Fouda *et al*. showed that dorzolamide hydrochloride is a carbonic anhydrase inhibitor. It is used to reduce the intra-ocular pressure. Proniosomal gels of dorzolamide HCl have been formulated with the intention of sustaining its effect and lowering the dosing frequency. Gel was developed by the coacervation phase separation method, using L-α-lecithin, cholesterol, and Span 40. According to *in vivo* studies, the regular formulation was significantly less effective than the formulated ones, which has shown the maximal IOP reduction of 45.4±8.2% within 6 h. The percentage drop in IOP was found to be 19.5±9.2%, after 8 h of administration, which suggests extended release of the medication. These findings mainly imply, that the proniosomal gel formulation of dorzolamide HCl offers prolonged drug release, which may lower the frequency of doses and increase patient adherence [70].

Cytomegalovirus (CMV)

CMV is one of the biggest health risks, particularly for newborns and individuals with weakened immune systems. Yadav *et al*. [79], in their study, found that the antiviral medications cidofovir and ganciclovir are

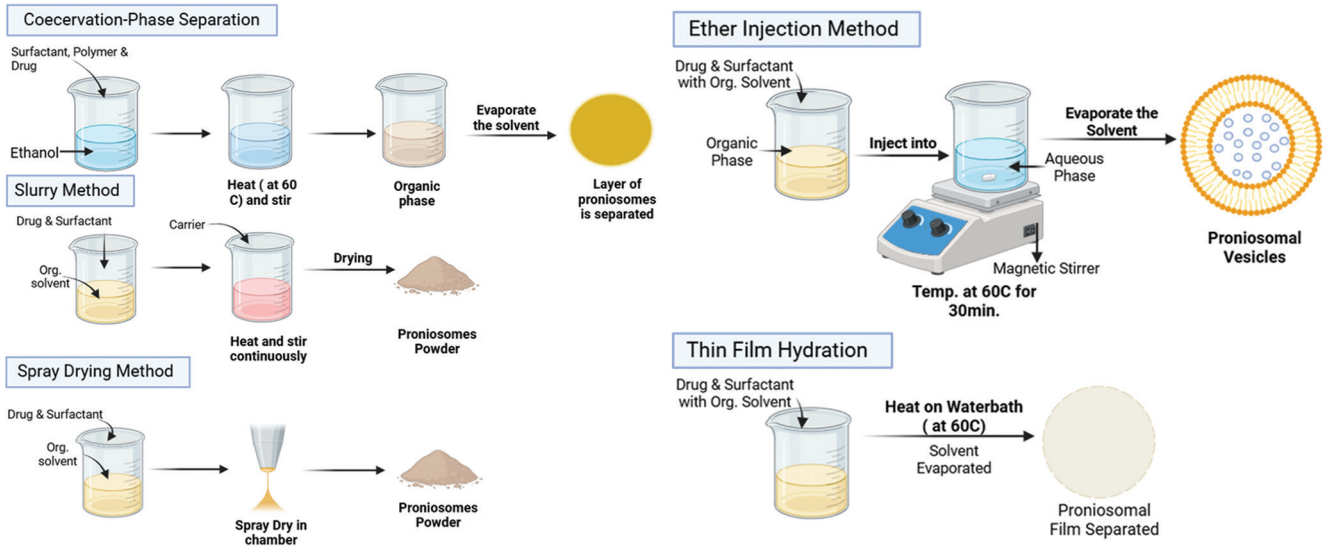

Fig. 3: Diagrammatic representation of proniosomal formulation methods

no longer used to treat CMV due to their severe adverse effects, and their bioavailability is restricted. Recent studies have shown the efficiency of proniosomal gels in ocular drug delivery. A study conducted on timolol maleate proniosomal gel reported, that the entrapment efficiency of the drug was about 99.98% and the *in vitro* release of the drug extended up to 12 h. This indicates the sustained release of the drug [71]. Research on a proniosomal gel loaded with etodolac showed that the drug's *in vitro* release was between the range of 71.86 and 97.16% for a 24-h period. The entrapment efficiency was between 74.36% and 90.85%. In comparison with the formulations present in the market, the *ex vivo* permeation studies and anti-inflammatory tests in animal models demonstrated a considerable decrease in paw edema. This indicates the anti-inflammatory efficacy of the formulation [80]. Proniosomal formulations have become a viable option due to their benefits in targeted distribution, bioavailability, and drug stability.

Corneal graft rejection

The graft immunological rejection at the cornea happens while the host's immune system attacks the transplanted cornea. This immune-mediated process can cause graft rejection. According to Durak *et al.* [2], it can be mainly due to HLA mismatches, previous graft failures, corneal vascularization, infections, and poor adherence to medication regimens in the patients. This condition is followed up by the symptoms of redness, sensitivity to light, vision impairment or loss, and pain. Zeng *et al.* [81] and Li *et al.*, [72] in their work on proniosomes-based formulations of tacrolimus have found that they show prolonged drug residency, low clearance rate of the drug in aqueous humor, and increased precorneal permeation. This makes them an ideal choice for the treatment of the condition.

Fungal keratitis

Fungal keratitis is one of the most severe corneal infections which are caused by fungal pathogens. This leads to corneal damage and even vision loss. For this, El-Emam *et al.* [82], in their study, found that proniosomal gels loaded with voriconazole have been made, to enhance the delivery of antifungal agents in the ocular system. With a particle size of 209.7±8.13 nm, a zeta potential of −33.5±1.85 mV, and an entrapment efficiency (EE%) of 87.4±2.55%, the voriconazole formulation demonstrated significant stability. Studies on *in vitro* release showed a biphasic release pattern, consisting of a continuous release phase after an initial burst release. According to the microbiologists, the 5% natamycin eye drops had shown a zone of inhibition (ZI) of 33.9 mm against Candida albicans, which is much lower. These results simply indicate that proniosomal formulations have better antifungal activity than traditional therapies.

Ocular inflammation

Ocular inflammation includes various conditions which are characterized by inflammation in different parts of the eye. This mainly leads to redness and pain which might even extend to vision impairment. Aboali *et al.*, [75] in their study, found that curcumin being an anti-inflammatory agent of natural origin has been incorporated into the proniosomal gels to enhance its ocular delivery. The formulation revealed an entrapment efficiency of 96.0±0.1%, a zeta potential of −5.1±0.2 mV, a polydispersity index of 0.3±0.1, and a mean particle size of 212.0±0.1 nm. Studies on the formulation's permeability showed a 3.22-fold increase, over curcumin dispersion. The *in vivo* tests conducted in rabbits showed a 40% decrease in the inflammatory symptoms on the 1st day and full recovery on the 4th day of drug administration. The ability of proniosomal gels to reduce inflammation was validated by the histopathological investigation. As a biocompatible substitute, the curcumin-loaded proniosomal gel has shown potent anti-inflammatory effects with lesser adverse effects.

Chorioretinitis

Chorioretinitis is characterized as the condition of inflammation in the uveal tract, which leads to redness and pain in the eye. It may also lead to potential vision loss. Li *et al.* [72], in their study, mentioned that proniosomal formulations of tacrolimus have been developed by the researchers to manage this condition. The optimized formulation achieved an entrapment efficiency of about 83.5±1.2% with a particle size of 162.3±2.8 nm. A 24-h sustained release profile was seen in *in vitro* release tests. In comparison to the drug solution, the *ex vivo* permeation studies employed rabbit corneas showing a 2.5-fold increase in the drug penetration. The *in vivo* ocular irritation testing on rats revealed no irritation with acceptable corneal biocompatibility. These findings imply that the proniosomal formulation of tacrolimus has shown improved medication release and corneal penetration, which may lower dosage frequency and also increase patient adherence.

CHALLENGES AND FUTURE PERSPECTIVES

Even though proniosome and nanoparticle development has been successful overall, there are still a lot of challenges to be solved, including reproducibility, scale-up feasibility, and complex regulatory difficulties. Consequently, large-scale production of nanomaterials may be challenging. New techniques and technology transfer must be incorporated to produce proniosomes on an industrial scale for commercial use. However, due to process limitations in small-scale preparation, any preparation method may not transfer from a laboratory scale to an industrial scale. Particle size, drug encapsulation, residual

components from the process, stability, and surface characteristics are the features of pronisomes that are most impacted by scaling up. Furthermore, the drug loading in the proniosomes might be reduced by the scale-up procedure.

Particle size, drug encapsulation, residual components from the process, stability, and surface characteristics are the features of pronisomes that are most impacted by scaling up. Some of the process restrictions include the use of hazardous solvents (such as dichloromethane or chloroform as an organic phase) and the stability of the components utilized for manufacturing. Therefore, for the pharmaceutical industry to generate nanomedicines, new methods that use aqueous solvents or solvents with low toxicity must be developed. To produce large batch sizes under good laboratory practices and eventually good manufacturing practices conditions, it is imperative to show that the technology can be transferred to a development facility or contract manufacturing company where a workable, scalable, and economical process can be established.

Proniosomes have the potential to be produced on a big scale due to their straightforward manufacturing process and adaptable drug delivery. For entrapping both hydrophobic and hydrophilic, or polar and non–polar pharmaceuticals, the proniosomes were studied as substitutes for liposomes and other carrier systems. Due to their non-ionic structure and the absence of any particular production or processing needs, proniosomes also offer the benefit of low toxicity. Proniosome production can be challenging to scale up from the lab to the large scale, and maintaining product quality is a crucial aspect of regulatory approval. To develop and implement proniosomes for ocular drug delivery mechanisms, there are certain obstacles that need to be overcome.

CONCLUSION

The delivery of drugs in ocular system is one of the most challenging processes due to its complex structure and multiple protective barriers. These barriers are responsible for limiting the drug absorption. Traditional methods include eye drops, ointments, gels, and creams. These formulations often encounter issues such as rapid drug clearance and low bioavailability. In the case of traditional formulations, frequent applications are needed which makes them less effective and patient compliance is also low in such cases. Proniosomal formulations are a promising solution for these issues. They work by enhancing drug stability, providing better corneal penetration, and also ensuring sustained drug release. Proniosomes are vesicular systems, which are made from non-ionic surfactants and are dry in nature. These on hydration get converted into niosomes. Studies have indicated that the proniosomes can be effectively used in the treatment of various ocular conditions, such as glaucoma, conjunctivitis, chorioretinitis, ocular inflammations, and age-related macular degeneration. The success of proniosomal-formulations depends on various factors such as the surfactant is chosen and preparation methods. By optimizing these aspects, proniosomes can further enhance drug delivery and therapeutic outcomes. In the end, we conclude by mentioning that proniosomal formulations have marked a significant step toward ocular drug delivery. Their capability to improve drug penetration, and provide prolonged therapeutic effects, has led to enhanced patient compliance. This makes them a potential alternative to conventional treatments for ocular disease treatment. Future research and clinical trials will come forward as the key sources to prove their potential in the field of medical science.

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AUTHOR'S CONTRIBUTIONS

Shalu Verma: Investigation, Conceptualization, drafting, Supervision. Alka Singh: Review, editing, and visualization. Arjeeta Singh Rathore: Writing review and editing. Khushi Kumari: writing and analysis.

CONFLICTS OF INTEREST

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REFERENCES

1. Peter M, Panonnummal R. A review on newer ocular drug delivery systems with an emphasis on glaucoma. Adv Pharm Bull. 2021;11(3):399-413. doi: 10.34172/apb.2021.048, PMID 34513615
2. Durak S, Esmaeili Rad M, Alp Yetisgin A, Eda Sutova H, Kutlu O, Cetinel S, *et al*. Niosomal drug delivery systems for ocular disease-recent advances and future prospects. Nanomaterials (Basel). 2020 Jun;10(6):1191. doi: 10.3390/nano10061191, PMID 32570885
3. Kaushik A, Mazumder R, Padhi S, Mazumder A, Budhori R, Manorma *et al*. Novel approaches in ocular drug delivery-a revolution. Int J Appl Pharm. 2022 May;14:1-11. doi: 10.22159/ijap.2022v14i3.44045
4. Bremond-Gignac D, Chiambaretta F, Milazzo S. A European perspective on topical ophthalmic antibiotics: Current and evolving options. Ophthalmol Eye Dis. 2011 Jan;3:29-43. doi: 10.4137/OED.S4866, PMID 23861622
5. Suri R, Beg S, Kohli K. Target strategies for drug delivery bypassing ocular barriers. J Drug Deliv Sci Technol. 2020 Feb;55:101389. doi: 10.1016/j.jddst.2019.101389
6. Ahmed I. The noncorneal route in ocular drug delivery. In: Mitra A, editor. Ophthalmic Drug Delivery Systems. 2nd ed. United States: CRC Press; 2003. p. 335-63. doi: 10.1201/9780203912072.ch11
7. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: A comprehensive review. AAPS PharmSciTech. 2023 Feb;24(2):66. doi: 10.1208/s12249-023-02516-9, PMID 36788150
8. Bryar PJ, Gu D, Agron S, Eichinger SE. Eye. In: Ernst LM, Ruchelli ED, Carreon CK, Huff DS, editors. Color Atlas of Human Fetal and Neonatal Histology. Cham: Springer International Publishing; 2019. p. 311-23. doi: 10.1007/978-3-030-11425-1_30
9. Del Amo EM, Urtti A. Current and future ophthalmic drug delivery systems A shift to the posterior segment. Drug Discov Today. 2008 Feb;13(3-4):135-43. doi: 10.1016/j.drudis.2007.11.002, PMID 18275911
10. Pardridge WM. The blood-brain barrier: Bottleneck in brain drug development. NeuroRx. 2005 Jan;2(1):3-14. doi: 10.1602/neurorx.2.1.3, PMID 15717053
11. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006 Mar;3(2):275-87. doi: 10.1517/17425247.3.2.275, PMID 16506953
12. Kishor RC, Dhewale S, Pawar AA, Vir DK. A review in the vision an novel innovation towards ocular drug delivery system with medication. Int J Creat Res Thoughts. 2025 Jan;13(1):1-2.
13. Tiwari S, Talreja S. Proniosome: A contemporary extension in drug delivery and specific target. J Interdisip Cycle Res. 2020 Nov;12:126-33.
14. Wadavkar SD, Khandre RA. Ocular drug delivery system: A review. Int J Creat Res Thoughts. 2022;7(11):9-24.
15. Ajrin M, Anjum F. Proniosome: A promising approach for vesicular drug delivery. Turk J Pharm Sci. 2022 Aug;19(4):462-75. doi: 10.4274/tjps.galenos.2021.53533, PMID 36047601
16. Dubald M, Bourgeois S, Andrieu V, Fessi H. Ophthalmic drug delivery systems for antibiotherapy-a review. Pharmaceutics. 2018 Jan;10(1):10. doi: 10.3390/pharmaceutics10010010, PMID 29342879
17. Mithra MM, Krishnakumar K, Nair SK. Herbal nanosuspension: *In vitro* cancer study against different cell lines. Asian J Pharm Clin Res. 2020 Jun;13:25-9. doi: 10.22159/ajpcr.2020.v13i7.37764
18. Li S, Chen L, Fu Y. Nanotechnology-based ocular drug delivery systems: Recent advances and future prospects. J Nanobiotechnology. 2023 Jul;21(1):232. doi: 10.1186/s12951-023-01992-2, PMID 37480102
19. Kandpal N, Nainwal N, Ale Y, Semwal Y, Jakhmola V, Padiyar N. Proniosomes: A pro vesicular system in ocular drug delivery. J Adv Biotechnol Exp Ther. 2023;6(3):622. doi: 10.5455/jabet.2023.d154
20. Hu C, Rhodes DG. Proniosomes: A novel drug carrier preparation. Int J Pharm. 1999 Aug;185(1):23-35. doi: 10.1016/S0378-5173(99)00122-2, PMID 10425362
21. Scriven LE. Equilibrium bicontinuous structure. Nature. 1976 Sep;263(5573):123-5. doi: 10.1038/263123a0
22. Gupta DK, Ahad A, Waheed A, Aqil Mohd, Al-Jenoobi FI, Al-Mohizea AM. Bilosomes: A novel platform for drug delivery. In: Systems of Nanovesicular drug Delivery. Netherlands: Elsevier; 2022. p. 293-309. doi: 10.1016/B978-0-323-91864-0.00004-8

23. Ruiz-Herrera J, Bartnicki-Garcia S, Bracker CE. Dissociation of chitosomes by digitonin into 16 S subunits with chitin synthetase activity. Biochim Biophys Acta. 1980 May;629(2):201-6. doi: 10.1016/0304-4165(80)90094-X, PMID 6446324
24. Albash R, Elmahboub Y, Baraka K, Abdellatif MM, Alaa-Eldin AA. Ultra-deformable liposomes containing terpenes (terpesomes) loaded fenticonazole nitrate for treatment of vaginal candidiasis: Box-Behnken design optimization, comparative *ex vivo* and *in vivo* studies. Drug Deliv. 2020 Jan;27(1):1514-23. doi: 10.1080/10717544.2020.1837295, PMID 33108907
25. Abdelkader H, Wu Z, Al-Kassas R, Alany RG. Niosomes and Discomes for ocular delivery of naltrexone hydrochloride: Morphological, rheological, spreading properties and photo-protective effects. Int J Pharm. 2012 Aug;433(1-2):142-8. doi: 10.1016/j.ijpharm.2012.05.011, PMID 22595640
26. Khan A, Varshney C, Chaudhary T, Singh B. Spanlastics: An innovative formulation strategy in pharmaceutical drug delivery. World J Pharm Res. 2023 Dec;12(20):219-34.
27. Pawar S, Shashikant D, Shivarkar R. Ethosome: A novel carrier used in transdermal and topical drug delivery. *Int J Pharm Res Appl.* 2024 May;9(3):2442-552.
28. Raj A, Dua K, Nair RS, Sarath Chandran C, Alex AT. Transethosome: An ultra-deformable ethanolic vesicle for enhanced transdermal drug delivery. Chem Phys Lipids. 2023 Sep;255:105315. doi: 10.1016/j.chemphyslip.2023.105315, PMID 37356610
29. Muthangi S, Pallerla P, Nimmagadda S. Transdermal delivery of drugs using transferosomes: A comprehensive review. J Adv Sci Res. 2023 Aug;14(6):30-5. doi: 10.55218/JASR.202314604
30. Antil D, Sharma R, Bhushan B. Formulation and *in vitro* characterization of thiocolchicoside proniosomes for oral delivery. Asian J Pharm Clin Res. 2023 Apr;16:114-21. doi: 10.22159/ajpcr.2023.v16i4.46456
31. Maiti S, Paul S, Mondol R, Ray S, Sa B. Nanovesicular formulation of brimonidine tartrate for the management of glaucoma: *In vitro* and *in vivo* evaluation. AAPS PharmSciTech. 2011 Jun;12(2):755-63. doi: 10.1208/s12249-011-9643-9, PMID 21671199
32. Cholkar K, Dasari SR, Pal D, Mitra AK. Eye: Anatomy, physiology and barriers to drug delivery. In: Ocular Transporters and Receptors. Netherlands: Elsevier; 2013. p. 1-36. doi: 10.1533/9781908818317.1
33. Eghrari AO, Riazuddin SA, Gottsch JD. Overview of the cornea: Structure, Function, and Development. Prog Mol Biol Transl Sci. 2015;134:7-23. doi: 10.1016/bs.pmbts.2015.04.001, PMID 26310146
34. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharm Res. 2009 May;26(5):1197-216. doi: 10.1007/s11095-008-9694-0, PMID 18758924
35. Rathore KS, Nema RK. An insight into ophthalmic drug delivery system. Int J Pharm Sci Drug Res. 2009 Apr; 1:1-5. doi: 10.25004/IJPSDR.2009.010101
36. Ahmad MZ, Mohammed AA, Mokhtar Ibrahim M. Technology overview and drug delivery application of proniosome. Pharm Dev Technol. 2017 Apr;22(3):302-11. doi: 10.3109/10837450.2015.1135344, PMID 26794727
37. Edsman K, Carlfors J, Petersson R. Rheological evaluation of poloxamer as an *in situ* gel for ophthalmic use. Eur J Pharm Sci. 1998 Apr;6(2):105-12. doi: 10.1016/S0928-0987(97)00075-4, PMID 9795025
38. Solanki A, Parikh J, Parikh R. Solanki proniosomes. Iran J Pharm Res. 2008 Nov;7(4):237-46. doi: 10.22037/ijpr.2010.772
39. Abdelbary AA, Abd-Elsalam WH, Al-Mahallawi AM. Fabrication of novel ultradeformable bilosomes for enhanced ocular delivery of terconazole: *In vitro* characterization, *ex vivo* permeation and *in vivo* safety assessment. Int J Pharm. 2016 Nov;513(1-2):688-96. doi: 10.1016/j.ijpharm.2016.10.006, PMID 27717916
40. Mohsen AM, Salama A, Kassem AA. Development of acetazolamide loaded bilosomes for improved ocular delivery: Preparation, characterization and *in vivo* evaluation. J Drug Deliv Sci Technol. 2020 Oct;59:101910. doi: 10.1016/j.jddst.2020.101910
41. Janga KY, Tatke A, Balguri SP, Lamichanne SP, Ibrahim MM, Maria DN, *et al*. Ion-sensitive *in situ* hydrogels of natamycin bilosomes for enhanced and prolonged ocular pharmacotherapy: *In vitro* permeability, cytotoxicity and *in vivo* evaluation. Artif Cells Nanomed Biotechnol. 2018 Oct;46:1039-50. doi: 10.1080/21691401.2018.1443117, PMID 29475386
42. Teba HE, Khalil IA, El Sorogy HM. Novel cubosome based system for ocular delivery of acetazolamide. *Drug Deliv*. 2021 Jan;28(1):2177-86. doi: 10.1080/10717544.2021.1989090, PMID 34662264
43. Said M, Aboelwafa AA, Elshafeey AH, Elsayed I. Central composite optimization of ocular mucoadhesive cubosomes for enhanced bioavailability and controlled delivery of voriconazole. J Drug Deliv Sci Technol. 2021 Feb;61:102075. doi: 10.1016/j.jddst.2020.102075
44. Bessone CD, Akhlaghi SP, Tártara LI, Quinteros DA, Loh W, Allemandi DA. Latanoprost-loaded phytantriol cubosomes for the treatment of glaucoma. Eur J Pharm Sci. 2021 May;160:105748. doi: 10.1016/j.ejps.2021.105748, PMID 33567324
45. Ameeduzzafar, Alruwaili NK, Imam SS, Alotaibi NH, Alhakamy NA, Alharbi KS, *et al*. Formulation of chitosan polymeric vesicles of ciprofloxacin for ocular delivery: Box-Behnken optimization, *in vitro* characterization, HET-CAM irritation, and antimicrobial assessment. AAPS PharmSciTech. 2020 Jul;21(5):167. doi: 10.1208/s12249-020-01699-9, PMID 32504176
46. Zafar A, Alruwaili NK, Imam SS, Alsaidan OA, Alharbi KS, Yasir M, *et al*. Formulation of carteolol chitosomes for ocular delivery: Formulation optimization, *ex-vivo* permeation, and ocular toxicity examination. Cutan Ocul Toxicol. 2021 Oct;40(4):338-49. doi: 10.1080/15569527.2021.1958225, PMID 34340615
47. Aziz D, Mohamed S, Tayel S, Makhlouf A. Flexosomes as a promising nanoplatform for enhancing tolnaftate ocular delivery: Formulation, *in vitro* characterization, statistical optimization, *ex vivo* and microbial *in vivo* studies. Int J Pharm. 2023 Nov;646:123471. doi: 10.1016/j.ijpharm.2023.123471, PMID 37793467
48. Omran S, Elnaggar YS, Abdallah OY. Controlled release, chitosan-tethered luteolin phytocubosomes; Formulation optimization to *in-vivo* antiglaucoma and anti-inflammatory ocular evaluation. Int J Biol Macromol. 2024 Jan;254(3):127930. doi: 10.1016/j.ijbiomac.2023.127930, PMID 37944733
49. Mahboobian MM, Mohammadi M, Mansouri Z. Development of thermosensitive in situ gel nanoemulsions for ocular delivery of acyclovir. J Drug Deliv Sci Technol. 2020 Feb;55:101400. doi: 10.1016/j.jddst.2019.101400
50. Tayel SA, El-Nabarawi MA, Tadros MI, Abd-Elsalam WH. Promising ion-sensitive in situ ocular nanoemulsion gels of terbinafine hydrochloride: Design, *in vitro* characterization and *in vivo* estimation of the ocular irritation and drug pharmacokinetics in the aqueous humor of rabbits. Int J Pharm. 2013 Feb;443(1-2):293-305. doi: 10.1016/j.ijpharm.2012.12.049, PMID 23333217
51. Pignatello R, Bucolo C, Ferrara P, Maltese A, Puleo A, Puglisi G. Eudragit RS100® nanosuspensions for the ophthalmic controlled delivery of ibuprofen. Eur J Pharm Sci. 2002 Jul;16(1-2):53-61. doi: 10.1016/S0928-0987(02)00057-X, PMID 12113891
52. Wang J, Li B, Huang D, Norat P, Grannonico M, Cooper RC, *et al*. Nano-in-Nano dendrimer gel particles for efficient topical delivery of antiglaucoma drugs into the eye. Chem Eng J. 2021 Dec;425:130498. doi: 10.1016/j.cej.2021.130498, PMID 34121919
53. Parekh HS, Marano RJ, Rakoczy EP, Blanchfield J, Toth I. Synthesis of a library of polycationic lipid core dendrimers and their evaluation in the delivery of an oligonucleotide with hVEGF inhibition. Bioorg Med Chem. 2006 Jul;14(14):4775-80. doi: 10.1016/j.bmc.2006.03.029, PMID 16603365
54. Başaran E, Demirel M, Sırmagül B, Yazan Y. Cyclosporine-A incorporated cationic solid lipid nanoparticles for ocular delivery. J Microencapsul. 2010 Jan;27(1):37-47. doi: 10.3109/02652040902846883, PMID 19545226
55. Ramadan AA, Eladawy SA, El-Enin AS, Hussein ZM. Development and investigation of timolol maleate niosomal formulations for the treatment of glaucoma. J Pharm Investig. 2020 Jan;50(1):59-70. doi: 10.1007/s40005-019-00427-1
56. Khalil RM, Abdelbary GA, Basha M, Awad GE, El-Hashemy HA. Enhancement of lomefloxacin Hcl ocular efficacy via niosomal encapsulation: *In vitro* characterization and *in vivo* evaluation. J Liposome Res. 2017 Oct;27(4):312-23. doi: 10.1080/08982104.2016.1191022, PMID 27241274
57. Hashemi Dehaghi M, Haeri A, Keshvari H, Abbasian Z, Dadashzadeh S. Dorzolamide loaded niosomal vesicles: Comparison of passive and remote loading methods. Iran J Pharm Res. 2017;16(2):413-22. PMID 28979296
58. Verma A, Sharma G, Jain A, Tiwari A, Saraf S, Panda PK, *et al*. Systematic optimization of cationic surface engineered mucoadhesive vesicles employing Design of experiment (DoE): A preclinical investigation. Int J Biol Macromol. 2019 Jul;133:1142-55. doi: 10.1016/j.ijbiomac.2019.04.118, PMID 31004631
59. Liu Y, Wang Y, Yang J, Zhang H, Gan L. Cationized hyaluronic acid coated spanlastics for cyclosporine a ocular delivery: Prolonged ocular retention, enhanced corneal permeation and improved tear production. Int J Pharm. 2019 Jun;565:133-42. doi: 10.1016/j.ijpharm.2019.05.018, PMID 31075435

60. Gugleva V, Titeva S, Rangelov S, Momekova D. Design and *in vitro* evaluation of doxycycline hyclate niosomes as a potential ocular delivery system. Int J Pharm. 2019 Aug;567:118431. doi: 10.1016/j.ijpharm.2019.06.022, PMID 31207279
61. Shimazaki H, Hironaka K, Fujisawa T, Tsuruma K, Tozuka Y, Shimazawa M, *et al*. Edaravone-loaded liposome eyedrops protect against light-induced retinal damage in mice. Invest Ophthalmol Vis Sci. 2011 Sep;52(10):7289-97. doi: 10.1167/iovs.11-7983, PMID 21849425
62. Natarajan JV, Chattopadhyay S, Ang M, Darwitan A, Foo S, Zhen M, *et al*. Sustained release of an anti-glaucoma drug: Demonstration of efficacy of a liposomal formulation in the rabbit eye. PLoS One. 2011 Sep;6(9):e24513. doi: 10.1371/journal.pone.0024513, PMID 21931735
63. Fujisawa T, Miyai H, Hironaka K, Tsukamoto T, Tahara K, Tozuka Y, *et al*. Liposomal diclofenac eye drop formulations targeting the retina: Formulation stability improvement using surface modification of liposomes. Int J Pharm. 2012 Oct;436(1-2):564-7. doi: 10.1016/j.ijpharm.2012.07.024, PMID 22828072
64. Cheng T, Li J, Cheng Y, Zhang X, Qu Y. Triamcinolone acetonide-chitosan coated liposomes efficiently treated retinal edema as eye drops. Exp Eye Res. 2019 Nov;188:107805. doi: 10.1016/j.exer.2019.107805, PMID 31526807
65. Khatoon M, Shah KU, Din FU, Shah SU, Rehman AU, Dilawar N, *et al*. Proniosomes derived niosomes: Recent advancements in drug delivery and targeting. Drug Deliv. Nov. 2017;24(Suppl 1):56-69. doi: 10.1080/10717544.2017.1384520, PMID 29130758
66. Patel NN, Vikran RK, Gupta A. Proniosomes for improved transdermal drug delivery - a review. Pharm Res 2013 Jan;8:62-82.
67. Baranowski P, Karolewicz B, Gajda M, Pluta J. Ophthalmic drug dosage forms: Characterisation and research methods. ScientificWorldJournal. 2014;2014:1-14. doi: 10.1155/2014/861904
68. Emad Eldeeb AE, Salah S, Ghorab M. Proniosomal gel-derived niosomes: An approach to sustain and improve the ocular delivery of brimonidine tartrate; formulation, *in-vitro* characterization, and *in-vivo* pharmacodynamic study. Drug Deliv. 2019 Jan;26(1):509-21. doi: 10.1080/10717544.2019.1609622, PMID 31090464
69. Abdelbary GA, Amin MM, Zakaria MY. Ocular ketoconazole-loaded proniosomal gels: Formulation, *ex vivo* corneal permeation and *in vivo* studies. Drug Deliv. 2017 Jan;24(1):309-19. doi: 10.1080/10717544.2016.1247928, PMID 28165809
70. Fouda NH, Abdelrehim RT, Hegazy DA, Habib BA. Sustained ocular delivery of dorzolamide-HCl via proniosomal gel formulation: *In-vitro* characterization, statistical optimization, and *in-vivo* pharmacodynamic evaluation in rabbits. Drug Deliv. 2018 Jan;25(1):1340-9. doi: 10.1080/10717544.2018.1477861, PMID 29869516
71. Lokapur JS, Goudanavar PS, Lokapur AJ, Acharya A, Murtale SA. Formulation and evaluation of timolol maleate proniosomal gel for ocular drug delivery. Int J Pharm Investig. 2022 Jul;12(3):386-90. doi: 10.5530/ijpi.2022.3.65
72. Li Q, Li Z, Zeng W, Ge S, Lu H, Wu C, *et al*. Proniosome-derived niosomes for Tacrolimus Topical ocular delivery: *In vitro* cornea permeation, ocular irritation, and *in vivo* anti-allograft rejection. Eur J Pharm Sci. 2014 Oct;62:115-23. doi: 10.1016/j.ejps.2014.05.020, PMID 24905830
73. Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. Int J Pharm. 2005 Feb;290(1-2):155-9. doi: 10.1016/j.ijpharm.2004.10.026, PMID 15664141
74. Parvez Baig R, Wais M. Formulation and development of proniosomal gel for topical delivery of amphotericin B. Int J Pharm Pharm Sci. 2022 Jan; 14(1):37-49. doi: 10.22159/ijpps.2022v14i1.43237
75. Aboali FA, Habib DA, Elbedaiwy HM, Farid RM. Curcumin-loaded proniosomal gel as a biofreindly alternative for treatment of ocular inflammation: *In-vitro* and *In-vivo* assessment. Int J Pharm. 2020 Nov;589:119835. doi: 10.1016/j.ijpharm.2020.119835, PMID 32890654
76. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. N Engl J Med. 2008 Jun;358(24):2606-17. doi: 10.1056/NEJMra0801537, PMID 18550876
77. Shokrolahi F, Latif F, Shokrollahi P, Farahmandghavi F, Shokrollahi S. Engineering atorvastatin loaded Mg-Mn/LDH nanoparticles and their composite with PLGA for bone tissue applications. Int J Pharm. 2021 Sep;606:120901. doi: 10.1016/j.ijpharm.2021.120901, PMID 34293469
78. Azimjonov J, Özmen A, Varan M. A vision-based real-time traffic flow monitoring system for road intersections. Multimed Tools Appl. 2023 Feb;84:1-20. doi:10.1007/s11042-023-14418-w, PMID 36789012
79. Yadav AV, Murthy MS, Shete AS, Sakhare S. Stability aspects of liposomes. Ind J Pharm Edu Res. 2011 Sep;45:402-13.
80. Patil M, Pandit P, Udavant P, Sonawane S, Bhambere D. Development and optimization of proniosomal gel containing etodolac: *In-vitro*, *ex-vivo* and *in-vivo* evaluation. Ars Pharm (Internet). 2021 Jun;62(3):290-304. doi: 10.30827/ars.v62i3.17944
81. Zeng W, Li Q, Wan T, Liu C, Pan W, Wu Z, *et al*. Hyaluronic acid-coated niosomes facilitate tacrolimus ocular delivery: Mucoadhesion, precorneal retention, aqueous humor pharmacokinetics, and transcorneal permeability. Colloids Surf B Biointerfaces. 2016 May;141:28-35. doi: 10.1016/j.colsurfb.2016.01.014, PMID 26820107
82. El-Emam GA, Girgis GN, El-Sokkary MM, El-Azeem Soliman OA, Abd El Gawad AE. Ocular inserts of voriconazole-loaded proniosomal gels: Formulation, evaluation and microbiological studies. Int J Nanomedicine. 2020;15:7825-40. doi: 10.2147/IJN.S268208, PMID 33116503