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Proniosomes: A provesicular system in ocular drug delivery

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ABSTRACT

The eyes are the only sense organ required for vision. Diseases like glaucoma, cataract, diabetic retinopathy etc. affect the proper functioning of the eyes and sometimes lead to blindness. The treatment of eye disorders is very challenging because of the unique structure of this organ. The traditional treatment approaches are not effective in providing good ocular bioavailability. The provesicular systems are new-generation delivery systems that can improve drug bioavailability and provide therapeutic responses in a controlled manner for desired time. Among all, liposomes are the first such delivery vehicle but due to the lack of stability and the high cost, niosomes were formulated. Niosomes are nanosized vesicles composed of non-ionic surfactants that can encapsulate both lipophilic and hydrophilic drugs. The drawbacks associated with niosomes, like fusion, aggregation, sedimentation, difficulty in sterilization, leaking, etc., gave birth to proniosomes. Proniosomes are more stable and bioavailable than niosomes and liposomes. Proniosomes are dry formulations of hydrophilic carrier particles coated with a water-soluble non-ionic surfactant that, when hydrated, instantly transforms into niosomes. Proniosomes can be used as stable, non-toxic carrier carriers to improve the ocular residence and bioavailability of many drugs. This paper reviewed proniosomes, their biomedical applications and their toxicity in ocular drug delivery.

INTRODUCTION

The eye is the most beautiful and sensitive organ of our body that helps us to perceive and understand our surroundings. It is situated in the orbital cavity of the skull. The eye is spherical in shape, with 24 mm anterior diameter. In terms of drug delivery eye can be divided into four target sites: (a) cornea, (b) anterior and posterior chamber and associated tissue, (c) posterior eye segment (including the retina and posterior cavity), and (d) preocular structure (conjunctiva and eyelids). The cornea, crystalline lens, iris, and pupil make up the anterior part of the eye. Aqueous fluid fills both the anterior and posterior chambers [1].

A growing proportion of people worldwide suffer from ocular illness. Possible significant vision problems caused by some pathological conditions of the eyes, such as diabetic retinopathy, age-related macular degeneration (AMD), HIV infections, and glaucoma may cause complete loss of vision [2]. Eyes disorders are cured or managed using either a topical or systemic delivery of drugs. Although the administration of drugs through the systemic route offers the advantage of delivering the medicine to the eye more conveniently, it has the disadvantage of unexpected side effects and insufficient therapeutic efficacy. The various delivery approaches, as given in Table 1, have been used for ocular administration. The diagrammatic representation is given in Figure 1 depicting the comparison between conventional and novel drug delivery systems in ocular administration. Some conventional forms of drug delivery, like ocular

gels, solutions, suspensions, etc., have significant drawbacks in the form of tears turnover, poor corneal permeability, drug loss on eyelids and eyelashes, nasolacrimal drainage, inaccurate dosing associated with eye drops, blinking, and blurred vision. The above-mentioned challenges have raised the demand for innovative approaches to delivering drugs to the eyes [3]. Eye drops are the most common and widely used ocular dosage forms. However, the major drawback of conventional dosage forms in ocular delivery is that only 5% of the drug reaches the target site because of the various ocular barriers present in the eye [4]. Furthermore, the use of nanotechnology and other emerging drug delivery systems is widely regarded as a means of overcoming the drawbacks of conventional dosage forms and avoiding the various obstacles present in the eye [5–7]. The vesicular system encloses the drug within surfactant vesicles to achieve targeted drug delivery at the corneal surface resulting in enhanced bioavailability [8]. Ideal characteristics for vesicular ocular drug delivery include easy penetration of the drug through the corneal membrane, longer residence time in the eye to achieve a desired therapeutic effect, reduced dosing frequency, minimum drug loss, avoidance of blurred vision, and minimal adverse reaction/side effects [9]. Proniosomes are a novel class of drug delivery system that has gained considerable attention in various applications in recent years [10–13]. Proniosomes gained popularity over liposomes and niosomes because of their excellent stability and better bioavailability [14]. This current review discussed various aspects of proniosomes in ocular drug delivery.

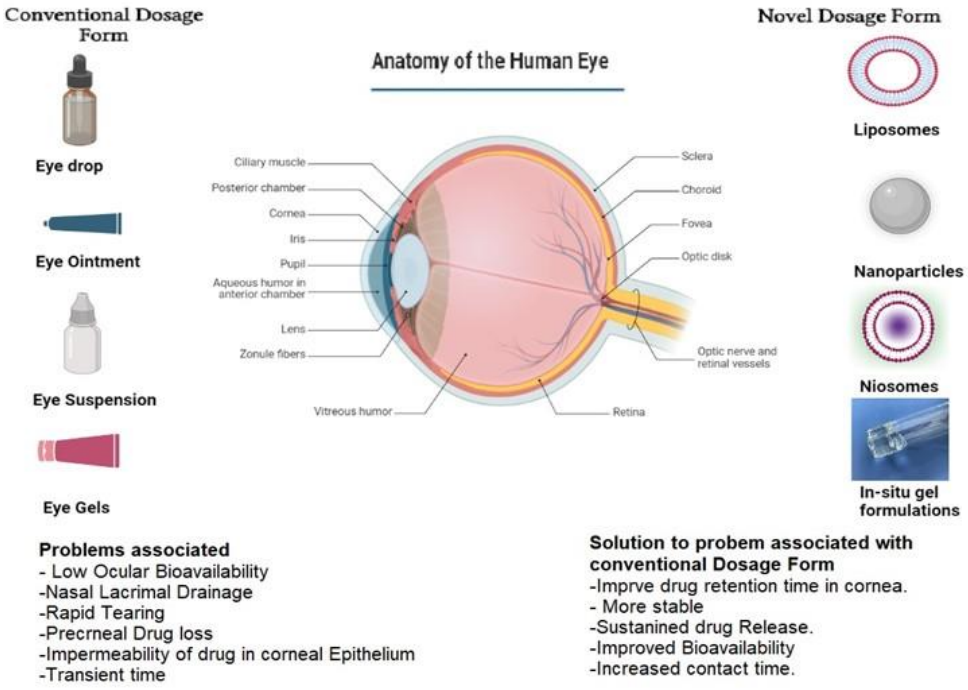

Figure 1. Conventional versus novel approaches for ocular drug delivery.

Table 1. Formulation approaches for ocular delivery.

Strategies	Advantages	Ref.
Liposomes	Enhance corneal absorption of the drug	[74]
Viscosity modification	Improve ocular residence time	[75]
Niosomes	Chemical stability, improve bioavailability, and lower toxicity	[76]
Microemulsion	Increase drug solubility and corneal membrane permeability	[77]
Nanosuspension	Improve drug solubility and bioavailability, negligible irritant property	[78]
Ocular implants	The systemic side effects of the drug get reduced. Avoids restrictive blood ocular barrier. Releases medication for an extended period.	[79]
Insoluble inserts	Increases ocular residence time. Targeted drug delivery to specific ocular tissues. Avoids sensitivity responses related to preservatives to reduce the need for them.	[80]
Soluble inserts	Prolonged drug release and increased residence time.	[81]
Intravitreal injections	Highest retinal and vitreal bioavailability.	[82]

PRONIOSOMES

Proniosomes are a form of lipid-based drug delivery system consisting of a dry mixture of surfactants and cholesterol that form vesicles in an aqueous phase. Proniosomes are solid colloidal particles that can be quickly hydrated before use to make aqueous niosome dispersions that are comparable to those made using more laborious traditional procedures [15]. The proniosomes reduce the issues with niosomes' physical stability, including aggregation, fusion, and leakage. Additionally, they make transportation, distribution, storage, and dosage more convenient. The shape, particle size, particle size distribution, and drug release of the proniosome-derived niosomes are superior to those of traditional niosomes [16]. Based on their processing, proniosomes can be classified as either dry granular or liquid crystalline. Dry granular proniosomes are prepared by coating a water-soluble carrier (maltodextrin or sorbitol) with a surfactant. Based on the type of carrier used, dry granular proniosomes are further classified into two types of maltodextrins and sorbitol dry granular proniosomes [17]. Dry granular proniosomes provide advantages such as improved stability and convenient storage. On the other hand, liquid crystalline proniosomes possess a highly organized liquid crystalline structure, which enhances drug encapsulation, sustained release, and permeation through the biological membranes [18].

Proniosomes are designed to improve the solubility and bioavailability of drugs and were investigated for a range of applications, including ocular delivery [19]. Proniosomes exhibit favorable characteristics for gene delivery as they are easy to formulate, economical, stable, and nontoxic because of non-ionic surfactant inclusion [20]. Drug targeting is one of the most advantageous properties of proniosomes. Proniosomes are employed in transdermal drug delivery systems to deliver hypertension drug captopril [21]. Frusemide is also delivered non-invasively by proniosomes [22]. In hormonal therapy, levonorgestrel, an emergency contraceptive, has been tested for transdermal distribution using proniosomes [23]. Peptide delivery is also possible with proniosomes. Oral peptide breakdown by gastrointestinal enzymes is problematic [24]. Nevertheless, peptides were shielded successfully using niosomes against peptide degradation in the digestive tract [25]. An entrapment inside the vesicles considerably boosted the stability of the peptide when it was given orally as a vasopressin derivative in niosomes [26]. Proniosomes have been widely used to deliver antibiotics and anti-inflammatory agents [27]. There are different methods available for the preparation of proniosomes, including the slurry method, coacervation phase separation method and slow spray coating method. In the slurry method, a non-ionic

surfactant is dissolved in a volatile organic solvent to form a slurry, to which the drug is added followed by carrier material like lactose or mannitol. The organic solvent is evaporated under reduced pressure resulting in dry proniosomal powder [28]. In the coacervation method proniosomes are prepared by mixing non-ionic surfactant and carrier in a solvent and then adding a coacervation-inducing agent such as calcium or magnesium ions which leads to the formation of coacervate [29]. The slow spray coating method involves the use of a spray dryer to coat the proniosomes with a thin layer of a polymer or other coating material. Proniosomes produced by the spray coating method are stable. However, it is a tedious and time-consuming process. Each method offers its advantages and can be chosen based on specific requirements of the formulation [30].

PRONIOSOMES IN OCULAR DRUG DELIVERY

The eye's unique physiological and anatomical features make the ocular drug delivery system a challenging field. The eye has a limited surface area, and the tear film and the blood-retinal barrier limit the penetration of drugs into the eye [31]. Thus, developing a drug delivery system that can overcome these barriers and deliver drugs effectively to the eye is critical [32]. Proniosomes offer a promising solution for ocular drug delivery due to their unique properties [33]. Proniosomes are formulated using a range of surfactants, including non-ionic, cationic, and anionic surfactants and other excipients, as given in Table 2. The physiochemical parameters of drugs and the intended proniosomes features determine the surfactant to be used. Surfactant and cholesterol mixture is typically dried and reconstituted with an aqueous phase to form Niosomes. Niosomes can then be further processed to form proniosomes by lyophilization or spray drying [34]. Proniosomes can protect drugs from degradation by enzymes and pH changes in the body, improving their stability and shelf-life. The surfactant in proniosomes also helps to increase the solubility of the drug, which can improve its bioavailability [35].

Table 2. Commonly used excipients.

Components used	Uses	Examples	Ref.
Surfactant	Increases cell membrane permeability of drugs and their bioavailability.	Span 20, Span 40, Tween 20, Brij 72	[83]
Cholesterol	Provides stability and rigidity to proniosomes.	Cholesterol	[14]
Lecithin	Act as a membrane stabilizer and penetration enhancer.	Soya lecithin, Egg lecithin	[14]
Aqueous phase	For hydration and penetration enhancement.	Butanol, Ethanol, Propanol, Phosphate buffer, Isopropanol	[83]
Carriers	Alters the drug distribution and imparts flexibility.	Spray dried lactose, Maltodextrin, Sorbitol Sucrose stearate, Lactose monohydrate, Glucose monohydrate	[84]
Hydration medium	Affect shape and size of vesicles and self-assembly of non-ionic surfactant into vesicles.	Phosphate buffers of different pH ranges	[83]

Factor affecting the formulation of proniosomes

The formulation of proniosomes depends on several processing factors such as surfactant chain length, cholesterol content, pH of the hydration medium, total lipid concentration and charge of the lipids as shown in Figure 2 and discussed below.

a) Surfactant chain length: A longer alkyl chain length results in greater drug entrapping effectiveness. For example, Spans are widely used in the production of

proniosomes. The order of entrapment efficiency for surfactant is Span 60(C18)>Span 40(C16) >Span 20(C12) [36].

b) Cholesterol content: Depending on the type of surfactant or its concentration in the formula, cholesterol either improves or decreases the percentage of encapsulation efficiency. A higher amount of cholesterol in the formulation increases the rigidity of the bilayer leading to a decrease in the drug release from the encapsulated formulation.

c) pH of the hydration medium: A decrease in the pH of the hydration medium leads to an increase in the percentage encapsulation efficiency.

d) Total lipid concentration: As the concentration of lipids rises, the fraction of lipids participating in encapsulation decreases.

e) Charge of the lipids: The incorporation of a positive charge (Stearyl amine and stearyl pyridinium chloride) or a negative charge (diacetyl phosphate and phosphatidic acid) decreases the percentage encapsulation efficiency of proniosomes [37].

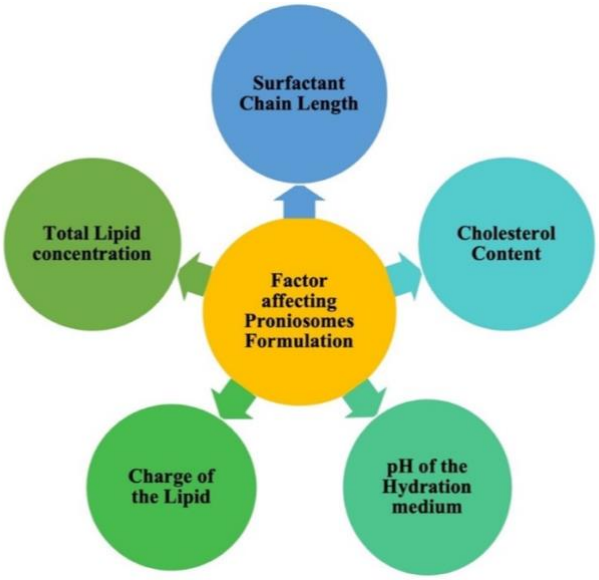

Figure 2. Factors affecting the formulation of proniosomes.

EVALUATION PARAMETERS OF OCULAR PRONIOSOMES

The evaluation of proniosomes is essential to ensure their quality, safety, and effectiveness in delivering drugs to the eyes. Several key parameters are mentioned in Table 3 and below, which are required in evaluating the performance of proniosomes in the ocular route**.**

Table 3. Evaluation parameter of proniosomes.

Characteristics	Ideal requirement	Methods	Significance	Ref.
Surface morphology	Smooth surface, Spherical shape.	SEM, TEM, Electron microscopy, Optical microscopy, Photon correlation microscopy.	To access uniformity of particle size and surface characteristics.	[85]
Angle of repose	Less than 30	Funnel method	To determine flow properties.	[86]
Vesicle size	Globular in shape, <10 μm	Malvern master sizer, Dynamic light scattering.	Analyses variation in scattered light intensity.	[87]
Entrapment efficiency	>50 %	Ultrafiltration centrifugation, HPLC.	Important for accessing drug-loading capacity.	[88]
Zeta potential	±30 mv	Malvern zeta sizer.	For proniosomes stability	[89]
Polydispersity index	0.1-0.4 (<0.5)	Dynamic light scattering	Measure of homogeneity	[90]
Refractive index	>1.476 as the refractive index of tear fluid ranges from 1.34 to 1.36.	Abbe refractometer	Detection of potential patient pain following administration due to impaired eyesight.	[91]
Viscosity	Between 2 and 3 mPa.s	Brookfield viscometer	Viscosity should be optimized to provide residence, not blurred vision.	[92]
pH	6.5-8.5	pH meter	Reduces eye irritability.	[93]
Surface tension	Between 40-50 mN/m	Tensiometer	Important to measure the performance of the formulation.	[94,95]
In vitro drug release	As per the need	Dialysis membrane or Franz diffusion cell	To determine the amount of drug release	[53]
Ocular irritation evaluation	The formulation should be safe and tolerable for ocular administration.	Draize test	To determine any congestions and or irritation of the cornea, iris, and conjunctiva caused by the formulation.	[96]
In vivo pharmacodynamic study	The formulation should provide the optimum therapeutic effect of the drug within the required time.	*In vivo* studies on living subjects	To evaluate the ocular bioavailability of the drug.	[97]
Stability	The formulation should be stable throughout its shelf life under the given storage condition.	As per ICH guidelines	To determine the effect of storage on the size, PDI, and zeta potential.	[53]

Surface morphology

It can be determined using various microscopy methods like scanning electron microscopy (SEM) or transmission electron microscopy (TEM). Such techniques allow visualization of the size, shape, and surface characteristics by providing high-resolution images of proniosomes [38]. The surface morphology of proniosomes can also be determined using fluorescence microscopy by incorporating fluorescent dyes in proniosomes to provide results of the size, shape, and distribution of proniosomes[39]. The vesicle size of proniosomes intended for ocular delivery is an important parameter that can influence their stability, drug release kinetics and ocular tissue penetration. Vesicle size range for proniosomes used in ocular delivery should be less than 10 μm. For example, Fouda *et al.* 2018 determined the surface morphology of dorzolamide proniosomes using TEM after negative staining with potassium phophotungustate [40]. TEM image showed that the proniosomes formed were spherical in shape [40].

Abaoli *et al.* (2020) investigated the surface morphology of curcumin proniosomes by SEM and TEM [41]. TEM image confirmed the smooth and spherical shape of proniosomes without aggregation. SEM results showed that the surface was smoother and more compact with no apparent pores suggesting good entrapment efficiency and a vesicle size of 212 nm [41].

Encapsulation efficiency

To determine encapsulated drugs in the formulation, it is necessary to isolate free drugs using methods like column chromatography, dialysis, ultra-centrifugation, freeze-thawing, gel filtration, etc. The effectiveness of trapped drugs can be assessed in two ways: proniosomal vesicle destruction with a triton (0.1%) or propane (50%) and identification of the drug trapped inside [42]. Alternatively, untapped drugs can be measured after the vesicle has been destroyed. The amount of drug entrapped can calculate by using the formula:

$$EE\ (\%) = [(Ct - Cf)/ Ct] \times 100$$

Where, Ct = the concentration of total drug

Cf= the concentration of the unentrapped drug

The ideal entrapment efficiency can vary depending on the specific drug, therapeutic goal, and formulation requirements. Generally, a higher entrapment efficiency (>50% or above) is desirable for effective ocular delivery. High entrapment efficiency ensures that a significant amount of drug is entrapped inside the vesicle leading to efficient drug delivery to the target ocular tissues and reducing potential drug loss or wastage.

Rheological Measurement

Rheological measurements of proniosomes for ocular delivery are valuable for understanding their physical behaviour, stability, and suitability for application to the ocular surface. Rheological measurements such as viscosity can provide information about the formulation's consistency and its ability to spread and adhere to the ocular surface. For ocular delivery, the viscosity should be low enough to facilitate easy spreading and administration on the ocular surface but high enough to ensure sufficient retention and contact time. Viscosity for ocular preparation should range between 2 to 3 mPa.s. [43,44].

Isotonicity and osmolarity

Isotonicity of the ocular formulations is important to minimize potential discomfort or irritation to the ocular surface. For ocular application, the ideal isotonicity range for proniosomes should be between 250-350 mOsm/kg as this range is close to the osmolarity of tears which is 308 mOsm/kg. Formulating proniosomes within this isotonic range help to minimize the risk of irritation or adverse effect on the ocular tissue. An osmolarity of less than 100 mOsm/kg or greater than 640 mOsm/kg is considered an eye irritant [44,45].

In vitro studies

The drug release from proniosomes can be determined using a dialysis membrane, Franz diffusion cell, reverse dialysis, and USP dissolution apparatus type 1. It is possible to analyze the drug release kinetics from the in-vitro drug release data. The release date is fitted into various kinetic models like- zero order, first order, Higuchi, Korsmeyer-Peppas, and Hixson Crowell models to find the order and mechanisms of drug release [46]. The "best-fit model" for drug release/dissolution can be selected based on a variety of factors like the coefficient of determination (R^2), $R^2_{Adjusted}$, Sum of squares of residue (SSR), Akaike information criteria (AIC), Mean square error (MSE), and Correlation coefficient (R)[47].

Ocular irritation

The Draize test is an effective and accurate method for accessing the irritation potential of proniosomes. It involves applying a test substance to the eyes of an animal, usually a rabbit (because of their wide eyes, ease of handling, and well-described anatomy). The responses are observed to determine any irritation caused due to proniosomes. The Draize test evaluates ocular irritation based on the study score. The score ranges from 0 to 3 for no irritation to redness and highest irritation. Nowadays, non-animal approaches such as computer modelling, and in-vitro experiments employing human cells and tissues are being used [48]. Eldeeb *et al.*, 2019 performed the Draize test on male albino rabbits which were subjected to Brimonidine Tartrate proniosomal formulation and marketed formulation (Alphagan) to evaluate irritancy [49]. The marketed formulation showed irritancy for the first 1 h whereas the test formulation showed no sign of irritation indicating the safety of the formulation for ocular delivery [49].

Zeta potential

The zeta potential determines both the stability of a colloidal system and a vesicle's surface charge. Zeta potential measures the electrical potential at the shear plane around a particle or vesicle [50]. The Zeta potential of proniosomes can affect drug loading, stability, and drug release characteristics. The ideal zeta potential for proniosomes used in ocular delivery should be around $\pm$30 mv. Higher zeta potential prevents particle aggregation and coalescence, ensuring dispersion stability. A low zeta potential indicates a risk of aggregation. Zeta potential can be measured using a Malvern zeta sizer [51].

Stability

According to ICH recommendations, Stability studies on proniosomes for dry powder meant for reconstitution should be conducted as per climatic conditions and climatic zones (WHO, 1996). For accelerated stability, a temperature and relative humidity (RH) of 40 ^{0}C/75% RH is required, and for long-term studies, 25 ^{0}C/ 60% RH is required for Zone 1 and Zone 2, respectively, whereas Zone 3 and Zone 4 must maintain a condition of 30 ^{0}C /65% RH and measured over time for in vitro drug release, poly dispersibility index (PDI), zeta potential, pH, sterility, pyrogenicity, etc[52]. Whereas stability studies for proniosomal gel should be conducted at a refrigeration temperature of 2-8^{0}C, room temperature of 25±0.5° and an elevated temperature of 45±0.50° for 90 days. Conduction stability studies are vital to ensure the safety and efficacy of the product during its shelf

life [53]. According to a stability study performed by Li *et al*. (2014) [54] on Tacrolimus-derived proniosomes for topical ocular delivery, studies were performed at 40 ± 2 ^{0}C/75 ± 5%RH; 4±2 ^{0}C/75 ± 5%RH; 25 ± 2 ^{0}C/60 ± 5%RH by storing proniosomes in a glass container. Physical stability studies were carried out to investigate the leakage of drug from the proniosomes during storage after 1,2 and 3 months of storage. Results indicated that proniosomes remain visually unchanged and entrapment efficiencies slightly reduce from 95% to 93% after 3 months of storing at 4 ^{0}C [54].

Toxicity of proniosomes

The eye is a very sensitive and very useful organ of humans. Therefore, attention should be given to the safety of any dosage form administered to the eye. There are limited research reports on the toxicity of proniosomes. Researchers need to assess the possible toxicity of ocular formulations and the materials utilized to prepare these formulations during repeated and prolonged application in the eye before their clinical use and commercial production. Most of the biocompatibility and safety studies of proniosomes are performed on animal eyes. However, the structure of animal eyes is quite different from human eyes. Unfortunately, the results of these preclinical studies are sometimes not validated in humans. Most preclinical findings concluded no signs of toxicity and altered pharmacological effects of proniosomes in the eyes. Proniosomes are composed of surfactants and cholesterol. Surfactants were used in proniosomal formulation to increase drug permeability through the cell membrane [55]. However, the chemical nature of surfactants imparts toxicity. Various studies have shown that the toxicity of proniosomes in ocular delivery depends on several factors, including the type of surfactant used, the concentration of surfactant, and the duration of exposure. A study by Govindarajan *et al*., 2022 [56] has shown that the ester derivative surfactant is harmful compared to the ether derivative. Surfactants like tween 80, can cause ocular irritation and damage to the cornea and conjunctiva when used at high concentrations [56]. CTAB (cetyltrimethylammonium bromide), a commonly used cationic surfactant, has been associated with cytotoxicity and disrupts cell membranes [57,58]. The most preferred constituents of proniosomes Span 60 and cholesterol are safe and do not produce any ocular toxic effect [59]. Overall potential toxicity of surfactants should be carefully considered, and at the same time, it is essential to conduct thorough safety evaluations of proniosomes before using them for ocular delivery in humans [60].

APPLICATION OF PRONIOSMOMES IN OCULAR DISEASES

Proniosomes have gained significant attention in the pharmaceutical field due to their potential application in various medical fields. One of those areas is the treatment of various ocular diseases as shown in Table 4.

Glaucoma

Glaucoma is an eye disorder marked by elevated intraocular pressure that eventually results in optic nerve damage, leading to vision loss or blindness. Glaucoma is the primary cause of blindness worldwide [61]. Dorzolamide (Carbonic anhydrase inhibitor) is used in the treatment of glaucoma. The proniosomes of dorzolamide showed decreased intraocular pressure with enhanced therapeutic efficacy in the *in-v*ivo studies in male albino rats [62,63]. Brimonidine tartrate (α-2 adrenergic agonist)

proniosomes decrease the production of aqueous humour and reduce the ischemia-induced optic nerve damage by enhancing the ocular bioavailability of the drug [49]

Conjunctivitis

Infection of the conjunctiva is known as conjunctivitis, commonly referred to as pink eyes. Conjunctiva is a thin transparent membrane covering the white part of the eyes. Proniosomes may use to encapsulate and deliver anti-inflammatory and antibiotic drugs directly to the eye to treat conjunctivitis[64,65]. Various studies have demonstrated the benefits of proniosomes conjunctivitis treatment. Lomefloxacin-proniosomal formulation was found effective in reducing the severity of bacterial conjunctivitis in rabbits [66]. In another study, Levofloxacin-loaded proniosomal formulation showed increased ocular residence time by providing sustained drug release [67].

Table 4. Application of proniosomes in ocular delivery.

Drug	Disease	Method of preparation	Key findings	Ref.
Dorzolamide HCl	Glaucoma	Coacervation phase separation method	An in-vitro investigation on male albino rabbit eyes demonstrated lower intraocular pressure and higher bioavailability than Trusopt eye drop.	[62]
Brimonidine tartrate	Glaucoma	Coacervation phase separation method	In-vivo studies on albino rabbits showed sustained drug release and an increase in mean residence time, which ultimately leads to an increase in bioavailability compared to the marketed formulation.	[49]
Voriconazole	Fungal infections like fungal keratitis	Coacervation phase separation method	The formulation was found to be stable and provide sustained release of formulation for the managing` of fungal infection when compared with the marketed formulation of voriconazole eye drops.	[98]
Ketoconazole	Ocular keratitis	Coacervation phase separation method	It shows a promising approach in increasing corneal contact, permeation, and retention time in the eye, resulting in sustained action and enhanced bioavailability than ketoconazole non-niosomal form.	[99]
Curcumin loaded proniosomal gel	Ocular inflammation	Coacervation phase separation method	The formulation showed enhanced permeability higher than curcumin dispersion and its lyophilized form.	[41]
Tacrolimus proniosomes	Corneal graft-versus-host disease, conjunctivitis, dry eye, uveitis	Coacervation phase separation method	In- vitro studies in rabbit cornea for 21 days showed enhanced precorneal permeation and retention of tacrolimus.	[71]
Timolol maleate	Glaucoma	Coacervation phase separation method	Proniosomes were found, an alternative to conventional eye drops as they exhibit good penetrability with sustained release action.	[100]
Levofloxacin proniosome gel	Bacterial conjunctivitis	Coacervation phase separation method	It enhances spread ability in the eye and increases ocular contact time by releasing the drug in a sustained manner.	[67]
Acetazolamide proniosomal gel	Glaucoma	Coacervation phase separation method	Acetazolamide proniosomal gel improved ocular medication delivery by prolonging drug release.	[101]
Betaxolol hydrochloride proniosomal gel	Glaucoma	Slurry method	The formulation showed good entrapment efficiency with an increase in ocular residence time.	[102]
Lomefloxacin HCl proniosomal gel	Bacterial conjunctivitis	Coacervation-phase separation method	In-vitro studies in rabbits found an increase in the therapeutic effectiveness of lomefloxacin by prolonging corneal retention and penetration.	[66]

Fungal infection

Fungal keratitis/mycotic/keratomycosis is a severe eye infection that affects the cornea of the eyes leading to corneal damage and vision loss. Candida parapsilosis, candida albicans, candida tropicalis, and candida glabrata mainly causes ocular fungal infections [68]. Proniosomes may be used to encapsulate and deliver antifungal medication for fungal keratitis. One of the studies indicated that proniosomes loaded with Amphotericin B were able to effectively treat fungal keratitis in rabbits [69].

Uveitis

Uveitis, or chorioretinitis, is an inflammation of the middle layer of the eyes causing inflammation of eyes. Proniosomes can be used to encapsulate and deliver anti-inflammatory medication, such as corticosteroids or NSAIDs, directly to the eye to treat uveitis [70]. Tacrolimus-loaded proniosomes gave higher precorneal permeation and retention in an *in vitro* study in rabbit cornea for 21 days [71].

SCALE-UP CHALLENGES OF PRONIOSOMES

Despite the development of proniosomes and nanoparticles in general being successful, there are still many obstacles to overcome, such as complicated regulatory issues, scale-up practicability, and reproducibility. As a result, producing nanomaterials on a large scale might be difficult [59]. To produce proniosomes on an industrial scale for commercial use, it is necessary to integrate new methods and technology transfer. However, any preparation procedure may fail to translate from a laboratory scale to an industrial scale due to process restrictions in small-scale preparation. Proniosomes' characteristics, such as particle size, drug encapsulation, process leftover materials, stability, and surface properties, are most affected by scaling up. Moreover, the scale-up process may decrease the drug loading in the proniosomes. Therefore, a well-designed scale-up procedure is required which can guarantee the effectiveness, affordability, and fast production of these nanomedicines [59]. The stability of the materials used for the production and the use of toxic solvents (such as the use of chloroform or dichloromethane as an organic phase) are some of the process limitations. Therefore, new techniques utilizing aqueous solvents or solvents with low toxicity must be developed for the pharmaceutical industry to produce nanomedicines.

It is critical to demonstrate the ability to transfer the technology to a development facility or contract manufacturing business where a practical, scalable, and cost-effective process can be established to produce large batch sizes under good laboratory practices (GLP) and ultimately good manufacturing practices (GMP) conditions [72].

Due to their simple fabrication method and flexibility in drug delivery, proniosomes have the potential to be manufactured on a large scale. Proniosomes were investigated as potential replacements for liposomes and other carrier systems for entrapping both hydrophobic and hydrophilic or polar and nonpolar pharmaceuticals. Proniosomes also have the advantage of minimal toxicity due to their non-ionic nature and the lack of any specific production or processing requirements. Additionally, it is an easy approach for producing proniosomes regularly and in big quantities without the use of undesirable solvents [73].

FUTURE PROSPECTS OF PRONIOSOMES

Proniosomes have been proven as an efficient delivery method that offers several benefits over conventional delivery methods in the form of better stability, bioavailability, and targeted delivery of therapeutic molecules. Further potential future applications of proniosomes include their use in gene therapy, vaccine delivery, and cancer treatment. Moreover, using proniosomes in combination with other drug delivery technologies, such as nanotechnology could lead to the formation of even more effective drug delivery systems. However, the formulation of proniosomes may present several challenges due to their complex nature and the need for precise control over their properties to ensure efficient drug delivery. Scaling up proniosomes from laboratory to large-scale production can be difficult, and it is important to ensure consistent product quality for regulatory approval. Tackling these challenges will be essential to developing and adopting proniosomes as a drug delivery system. Some patented formulations of proniosomes in various delivery systems are given in Table 5.

Table 5. Patented formulation of proniosomes.

Patent number	Title	Inventors	Country	Ref.
1288/DEL/2012	Curcumin proniosomal/niosomal Formulation, method for its preparation, and use thereof.	Yadav, *et al.*, 2012	INDIA	[103]
3228/DEL/2012	Novel proniosomal gel of *Withania somnifera*.	Garg *et al.*, 2012	INDIA	[104]
3231/DEL/2012	Novel ursolic acid loaded proniosomal gel and method of preparation thereof.	Garg, *et al.*, 2012	INDIA	[105]
WO2000042987A8	Targeted vesicular constructs for cryoprotection and treatment of *H. Pylori* infections.	Singh, *et al.*, 2000	WIPO	[106]
CN103340823A	Formulation of paeonol proniosomes and preparing method thereof.	Xiao *et al.*, 2013	CHINA	[107]
US20190083461A1	Methods and compositions for treating inflammatory diseases.	Etschmann, *et al.*, 2017	USA	[108]
WO2019038316A1 (2017)	Pharmaceutical composition for the prevention and treatment of cardiovascular and osteoarticular diseases.	Umberto Di Maio	WIPO	[109]

CONCLUSION

In conclusion, proniosomes represent a promising drug delivery platform for ocular drug delivery (Figure 3). These are essentially dry formulations that consist of a blend of surfactant and carrier material. The ability of proniosomes to improve drug absorption and retention in the eyes, along with their ease of handling and stability, makes them an attractive option for developing novel ocular therapies. These are widely applicable for the delivery of various drugs, including antibiotics, anti-cancer agents, and anti-inflammatory drugs. Furthermore, research is needed to optimize the formulation and delivery of proniosomes for clinical use.

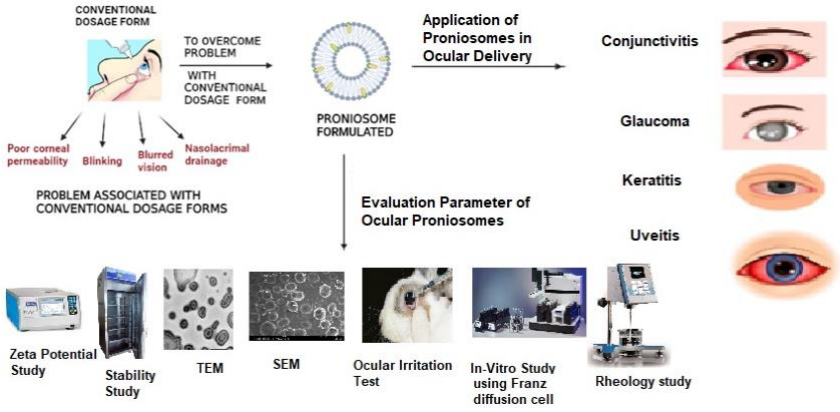

Figure 3. Proniosomes represent a promising drug delivery option for ocular drug delivery. The schema summarizes the potential application of proniosomes to overcome the problems associated with conventional dosage forms and their application in the treatment of various ocular conditions like conjunctivitis, glaucoma, keratitis, uveitis, etc.

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CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

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