

A COMPREHENSIVE REVIEW OF ANTIGLAUCOMA DRUGS: MECHANISMS, EFFICACY, AND FUTURE PERSPECTIVES

Jayatheertha S. Lokapur^{*1}, Ramesh V. Kinhal², Ravi Sondur¹, Arpitha J. Lokapur¹, Pradeep B. Mirje¹ and Ravi Sondur¹

¹Department of Pharmaceutics, K. L. E Society's College of Pharmacy, Gadag – 582 101, Karnataka, India.

²Department of Pharmaceutical Chemistry, K. L. E Society's College of Pharmacy, Gadag – 582 101, Karnataka, India.

Article Received on: 27/04/2025

Article Revised on: 17/05/2025

Article Accepted on: 07/06/2025



*Corresponding Author

Jayatheertha S. Lokapur

Department of Pharmaceutics, K.

L. E Society's College of

Pharmacy, Gadag – 582 101,

Karnataka, India.

ABSTRACT

Glaucoma, a leading cause of irreversible blindness worldwide, is primarily managed by reducing intraocular pressure (IOP). Pharmacologic intervention remains the first line of treatment, with several classes of drugs available to lower IOP. This review explores the pharmacodynamics, pharmacokinetics, clinical efficacy, side effects, and future directions of antiglaucoma medications, including prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors, and rho-kinase inhibitors. We also discuss combination therapies and emerging drug delivery systems that aim to enhance compliance and therapeutic outcomes. The only sense organ needed for vision is the eye. Conditions that impair the eyes' ability to function properly, such as glaucoma, cataracts, diabetic retinopathy, etc., can occasionally result in blindness. The peculiar anatomy of the eye makes treating eye problems extremely difficult. Good ocular bioavailability is not achieved with the conventional therapy modalities. The proovesicular systems are next-generation delivery methods that can increase medication bioavailability and deliver therapeutic effects throughout the specified length of time in a regulated way. Although liposomes were the first of this type of delivery system, niosomes were developed instead because of their instability and expensive cost.

KEYWORDS: Antiglaucoma, Proniosomes, Niosomes, Intraocular pressure, Timolol maleate.

INTRODUCTION

The most exquisite and delicate organ in our body, the eye aids in our ability to see and comprehend the world around us.^[1,2] It is located in the skull's orbital cavity.^[3,4] The anterior diameter of the eye is 24 mm, giving it a spherical form. Four target areas may be identified for medication administration in the eye (a) the cornea (b) the anterior and posterior chambers and related tissue (c) the posterior eye segment, which includes the posterior cavity and retina and (d) the preocular structure (conjunctiva and eyelids).^[5,6] The anterior portion of the eye is composed of the cornea,^[7] crystalline lens,^[8] iris, and pupil. Both the front and posterior chambers are filled with aqueous fluid.^[9]

The number of individuals with ocular illnesses is rising globally. HIV infections, glaucoma, diabetes retinopathy, and age-related macular degeneration (AMD) are a few pathological disorders of the eyes that may cause serious visual issues or even cause total blindness.^[10] Drugs are either systemically or topically used to treat or manage eye problems. While administering medication via the systemic route has the benefit of more readily reaching the eye, it also carries the risk of unanticipated side effects and inadequate therapeutic effectiveness.^[11] For

ocular administration, the different delivery strategies listed in Table 1 have been employed. Figure 1 presents a diagrammatic depiction that compares the use of innovative and standard drug delivery technologies for ocular administration.^[12]

Several traditional drug delivery methods, such as ocular gels, solutions, suspensions, etc., have serious side effects, such as poor corneal permeability, drug loss on the eyelids and lashes, nasolacrimal drainage, blinking, and blurred vision.^[13]

The aforementioned difficulties have increased the need for novel methods of medication delivery to the eyes.

The most popular and extensively utilised ocular dose forms are eye drops. But because of the several ocular barriers that exist in the eye, the main disadvantage of traditional dosage forms for ocular distribution is that only 5% of the medicine reaches the target region.^[14]

Additionally, it is generally accepted that using nanotechnology and other cutting-edge medication delivery methods can help overcome the shortcomings of

traditional dosage forms and get around the several roadblocks that are present in the eye.^[15]

The medication is enclosed in surfactant vesicles by the vesicular system, which allows for targeted drug administration at the corneal surface and increased bioavailability.^[16]

Vesicular ocular drug delivery is ideal when the drug easily penetrates the corneal membrane, stays in the eye for a longer period of time to produce the intended therapeutic effect, requires fewer doses, has little drug

loss, doesn't cause blurred vision, and has few negative reactions or side effects.^[17]

In recent years, a novel kind of drug delivery system called promethiosomes has drawn a lot of interest for a variety of uses.^[18]

Because of their superior bioavailability and outstanding stability, promiosomes have become more and more popular than liposomes and niosomes.^[19]

This current review discussed various aspects of proniosomes in ocular drug delivery.

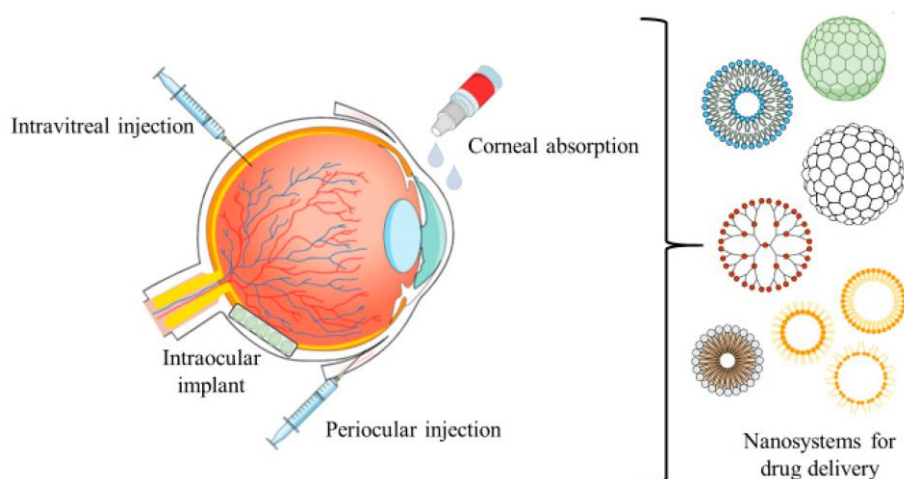


Figure 1: Conventional versus novel approaches for ocular drug delivery.^[20]

Table 1: Formulation approaches for ocular delivery.

Sl. No.	Strategies	Advantages	References
1	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.	[21]
2	Ocular implants	The systemic side effects of the drug get reduced. Avoids restrictive blood ocular barrier. Releases medication for an extended period.	[22]
3	Nanosuspension	Improve drug solubility and bioavailability, negligible irritant property	[23]
4	Microemulsion	Increase drug solubility and corneal membrane permeability	[24]
5	Niosomes	Chemical stability, improve bioavailability, and lower toxicity	[25]
6	Viscosity modification	Improve ocular residence time	[26]
7	Liposomes	Enhance corneal absorption of the drug	[27]
8	Soluble inserts	Prolonged drug release and increased residence time.	[28]
9	Intravitreal injections	Highest retinal and vitriol bioavailability.	[29]

Proniosomes

A lipid-based medication delivery device called a proneosome is made up of a dry combination of cholesterol and surfactants that congeal into vesicles in an aqueous phase. Proniosomes are solid colloidal particles that may be readily hydrated in order to produce aqueous niosome dispersions that are on par with those produced by more time-consuming conventional methods.^[30] Proniosomes mitigate the physical stability problems associated with niosomes, such as leakage,

fusion, and aggregation. They also improve the convenience of dose, distribution, storage, and transportation.^[31] Proniosome-derived niosomes exhibit improved shape, particle size, particle size distribution, and drug release in comparison to conventional niosomes. Protosomes can be characterised as liquid crystalline or dry granular depending on how they are processed.^[32] A surfactant is applied to a water-soluble carrier (sorbitol or maltodextrin) to create dry granular proteosomes. Dry granular proniosomes are further

divided into two types: sorbitol dry granular proniosomes and maltodextrins, depending on the type of carrier that is utilised.^[33] Benefits of dry granular proniosomes include enhanced stability and easy storage. However, the highly ordered liquid crystalline structure of liquid crystalline proniosomes improves drug encapsulation, sustained release, and penetration across biological membranes.^[34]

Proniosomes are designed to improve the solubility and bioavailability of drugs and were investigated for a range of applications, including ocular delivery. Because non-ionic surfactant inclusion makes proniosomes stable, inexpensive, easy to produce, and nontoxic, they have favourable properties for gene delivery.^[35] Drug targeting is one of the most advantageous properties of proniosomes. Proniosomes are employed in transdermal drug delivery systems to deliver hypertension drug captopril.^[36] Furosemide is also delivered non-invasively by Proniosomes. In hormonal therapy, levonorgestrel, an emergency contraceptive, has been tested for transdermal distribution using Proniosomes. Peptide delivery is also possible with proniosomes.^[37] Oral peptide breakdown by gastrointestinal enzymes is problematic. Nevertheless, peptides were shielded successfully using niosomes against peptide degradation in the digestive tract. An entrapment inside the vesicles considerably boosted the stability of the peptide when it was given orally as a vasopressin derivative in niosomes. Proniosomes have been widely used to deliver antibiotics and anti-inflammatory agents.^[38] Proniosomes may be produced using a variety of techniques, such as the slow spray coating method, coacervation phase separation method, and slurry approach.^[39] The medicine is added to a slurry created by dissolving a non-ionic surfactant in a volatile organic solvent, and then a carrier substance such as lactose or mannitol is added.^[40] Reduced pressure causes the organic solvent to evaporate, producing dry

proniosomal powder. By first combining a non-ionic surfactant and carrier in a solvent, proniosomes are created using the coacervation method.^[41] Next, a coacervation-inducing substance, such as calcium or magnesium ions, is added, causing coacervate to form. The proniosomes are coated with a thin layer of a polymer or other coating material using a spray drier in the slow spray coating process. The spray coating approach yields stable proniosomes. It takes a lot of time and effort, though. Every approach has benefits, and the best one to choose will depend on the particulars of the formulation.^[42]

Proniosomes in ocular drug delivery

The ocular medication delivery system is a difficult field because of the distinct physiological and anatomical characteristics of the eye. The blood-retinal barrier and the tear film restrict the amount of medications that may enter the eye due to its small surface area.^[43] Thus, developing a drug delivery system that can overcome these barriers and deliver drugs effectively to the eye is critical. Proniosomes offer a promising solution for ocular drug delivery due to their unique properties.^[44] 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.^[45] Niosomes can then be further processed to form proniosomes by lyophilization or spray drying. Proniosomes have the potential to shield medications from the body's enzymes and pH fluctuations, extending their stability and shelf life. Additionally, the surfactant in proniosomes aids in increasing the drug's solubility, which can enhance its bioavailability.^[46]

Table 2: Commonly used excipients.

Sl. No.	Excipients used	Uses	Examples	References
1	Hydration medium	Affect shape and size of vesicles and selfassembly of non-ionic surfactant into vesicles.	Phosphate buffers of different pH ranges	[47]
2	Carriers	Alters the drug distribution and imparts flexibility.	Spray dried lactose, Maltodextrin, Sorbitol Sucrose stearate, Lactose monohydrate, Glucose monohydrate	[48]
3	Aqueous phase	For hydration and penetration enhancement	Butanol, Ethanol, Propanol, Phosphate buffer, Isopropanol	[49]
4	Lecithin	Act as a membrane stabilizer and penetration enhancer.	Soya lecithin, Egg lecithin	[50]
5	Cholesterol	Provides stability and rigidity to proniosomes.	Cholesterol	[51]
6	Surfactant	Increases cell membrane permeability of drugs and their bioavailability.	Span 20, Span 40, Tween 20, Brij 72	[52]

Proniosomes are a novel drug delivery system composed of non-ionic surfactants and cholesterol that form a vesicular structure when hydrated. Several factors can influence the formulation of proniosomes.

- a. **Choice of Surfactant:** The type and concentration of non-ionic surfactant used in proniosome formulation significantly affect vesicle size, stability, and drug entrapment efficiency. Common surfactants include Span and Tween series.
- b. **Lipid Composition:** Besides surfactants, the type and concentration of lipids like cholesterol or other additives play a crucial role in vesicle formation and stability. Lipid composition impacts the rigidity and permeability of proniosomes.
- c. **Drug Loading:** The physicochemical properties of the drug being loaded into proniosomes influence formulation parameters such as drug entrapment efficiency, release kinetics, and stability.
- d. **Hydration Medium:** The type and pH of the hydration medium used during proniosome preparation can affect vesicle size, stability, and drug encapsulation efficiency.
- e. **Hydration Temperature:** The temperature at which hydration occurs can influence the size and stability of proniosomes. Higher temperatures may lead to faster hydration and larger vesicles.
- f. **Hydration Time:** The duration of hydration affects the size, uniformity, and stability of proniosomes. Longer hydration times may lead to better encapsulation efficiency but may also increase the risk of aggregation.
- g. **Methods of preparation:** Different methods such as thin-film hydration, slurry method, and coacervation techniques can be employed for proniosome preparation. The choice of method can impact the physicochemical properties of proniosomes.
- h. **Sonication:** Sonication or other forms of mechanical energy input during proniosome preparation can affect vesicle size, homogeneity, and drug entrapment efficiency.
- i. **Freeze-drying Conditions:** If proniosomes are intended for storage as dry powder, freeze-drying conditions such as freezing rate, temperature, and pressure can influence the stability and reconstitution properties of proniosomes upon rehydration.
- j. **Addition of Stabilizers or Excipients:** Addition of stabilizers or other excipients such as antioxidants, cryoprotectants, or lyoprotectants may enhance the stability and shelf-life of proniosomes.^[53]

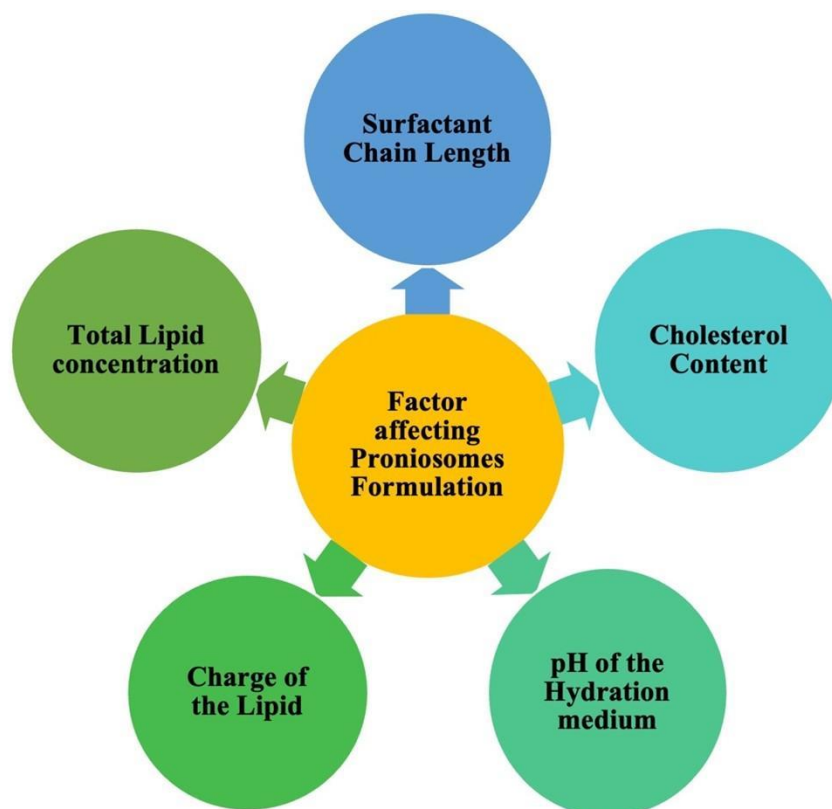


Figure 2: Factors affecting the formulation of proniosomes.^[54]

Evaluation of Parameters of ocular Proniosomes

In order to guarantee proniosomes' efficacy, safety, and quality in administering medications to the eyes, they must be evaluated. via order to assess how well

proniosomes function via the ocular pathway, a number of critical factors are included in Table 3.

Table 3: Evaluation parameter of Proniosomes.

Sl. No.	Characteristics	Ideal Requirement	Methods	Significance	Reference
1	Surface morphology	Smooth surface, Spherical shape.	SEM, TEM, Electron microscopy, Optical microscopy, Photon correlation microscopy.	To access uniformity of particle size and surface characteristics.	[55]
2	Vesicle size	Globular in shape, <10 µm	Malvern master sizer, Dynamic light scattering	Analyses variation in scattered light intensity.	[56]
3	Entrapment efficiency	>50 %	Ultrafiltration centrifugation, HPLC.	Important for accessing drug loading capacity	[57]
4	Zeta potential	+30 mv	Malvern zeta sizer.	For proniosomes stability	[58]
5	Polydispersity index	0.1-0.4 (<0.5)	Dynamic light scattering	Measure of homogeneity	[59]
6	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	[60]
7	Viscosity	Between 2 and 3 mPa.s	Brookfield viscometer	Viscosity should be optimized to provide residence, not blurred vision.	[61]
8	pH	6.5-8.5	pH meter	Reduces eye irritability	[62]
9	Surface tension	Between 40-50 mN/m	Tensiometer	Important to measure the performance of the formulation	[63]

CONCLUSION

Proniosomal gel represents a promising and environment friendly vesicular drug transport machine that enhances the stability, bioavailability, and managed launch of therapeutic agents. Its ease of preparation, scalability, and non-leakage houses provide widespread benefits over traditional liposomes and niosomes. The capability to convert proniosomes into niosomes upon hydration ensures extended shelf-life and enables drug transport throughout organic membranes, making it mainly appropriate for transdermal, topical, and oral shipping systems. Overall, proniosomal gels show practicable for enhancing affected person compliance and therapeutic efficacy, particularly for poorly soluble or unstable drugs.

Future Aspects

Further lookup on proniosomal gels need to focal point on the optimization of system parameters to enhance entrapment effectivity and drug launch profiles for a wider vary of energetic compounds. Advanced characterization methods and in vivo research are quintessential to higher apprehend their pharmacokinetics and pharmacodynamics. Additionally, integrating novel polymers, penetration enhancers, or focused ligands should lengthen their utility in customized medication and centered drug delivery. Regulatory critiques and medical trials will additionally be indispensable to facilitate the transition of proniosomal

gel structures from the laboratory to industrial pharmaceutical markets.

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