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Original Article

Formulation and Development of Nanostructured Lipid Carrier for Glaucoma

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ABSTRACT

Glaucoma is a progressive optic neuropathy leading to irreversible blindness if left untreated. Conventional therapies often suffer from low bioavailability and frequent dosing, limiting their efficacy. Nanostructured lipid carriers (NLCs), a second-generation lipid-based Nano system, offer promising solutions by enhancing drug stability, bioavailability, and sustained release. This review discusses the potential of NLCs for antiglaucoma drug delivery, covering formulation techniques, characterization methods, drug release mechanisms, and recent advances in preclinical and clinical research. Over ten lakh persons worldwide are afflicted with glaucoma each year. It can impair vision and occasionally result in total blindness. Since the conjunctiva, cornea, iris-ciliary body, and retina of the eye contain multiple barriers that prevent drug doses from reaching the site and result in limited drug bioavailability, drug administration through the ocular route has always been difficult. Conventional dosing forms of treatment frequently have the drawback of having a short drug retention period since the medicine exits the ocular cavity through tear production and nasal discharge. The creation of a novel medication delivery technology that would bypass the eye's barrier channels and perhaps improve drug absorption at the site is urgently needed to address these issues.

Keywords: Bioavailability,Glaucoma, Nanostructured lipid carrier, Optic nerve

INTRODUCTION

Glaucoma is a complex visual disorder characterized by an increase in intraocular pressure (IOP), which can eventually lead to progressive vision loss. [1] This condition is occurs by gradual degeneration of retinal cells and optic nerve fibers, leading to vision impairment. [2] A key characteristic of glaucoma is the gradual narrowing of peripheral vision, which distinguishes it from other visual disorders. In many cases, glaucoma remains asymptomatic until routine eye examinations reveal early signs. [3] Acute angle-closure glaucoma, however, can manifest rapidly, resulting in a sudden and severe loss of vision, often accompanied by symptoms such as headache, nausea, vomiting, corneal swelling, and intense eye pain. Secondary glaucoma, on the other hand, is usually caused by an underlying eye injury or medical condition that increases intraocular pressure [4] There are several types including congenital, pigmentary, neovascular, exfoliative, traumatic, and uveitic variants. [5] While elevated IOP is commonly associated with glaucoma, some individuals may experience vision loss without significant IOP changes, a condition known as normal-tension glaucoma. The majority of glaucoma cases are diagnosed in individuals aged 40 and above, while congenital, developmental, and juvenile forms typically impact younger populations. [6] [7] Glaucoma management typically involves a combination of medication, laser therapy, or surgical intervention, all aimed at lowering intraocular pressure and slowing disease progression. Although these treatments cannot reverse existing optic nerve damage or restore lost visual fields, they can effectively reduce further deterioration. By actively treating affected individuals, healthcare providers strive to minimize vision loss and preserve quality of life. [8]

Epidemiology: [9]

In 2010, an estimated 2.1 million individuals, accounting for 6-5% of the 32.4 million blind people worldwide, were blind due to glaucoma. This

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condition, primarily affecting older adults, displayed a lower prevalence in younger regions but was more commonly observed in high-income areas with aging populations. Among individuals aged 40 to 80 years, the global prevalence of glaucoma was approximately 3-5%. Specifically, primary open-angle glaucoma affected around 3.1% of this age group, making it nearly six times more common than primary angle-closure glaucoma, which had a prevalence of approximately 0.5%. Demographically, individuals of African descent were more likely to develop primary open-angle glaucoma compared to those of European ancestry, with an odds ratio of 1.36. Gender also played a role, with men having a higher likelihood (OR 2.80) of developing the condition compared to women. Additionally, bilateral blindness caused by glaucoma was observed more frequently in individuals with primary angle-closure glaucoma than those with open-angle glaucoma, suggesting a potentially worse prognosis for the former.

What is Glaucoma: [10] [11][12][13][14]

Glaucoma is a chronic, progressive eye disease characterized by damage to the optic nerve, usually caused by increased intraocular pressure (IOP). This damage leads to gradual loss of peripheral vision, and if left untreated, it can result in permanent blindness. Glaucoma is often called the "silent thief of sight" because it typically develops without noticeable symptoms until advanced stages. Early detection and treatment are crucial to prevent vision loss.

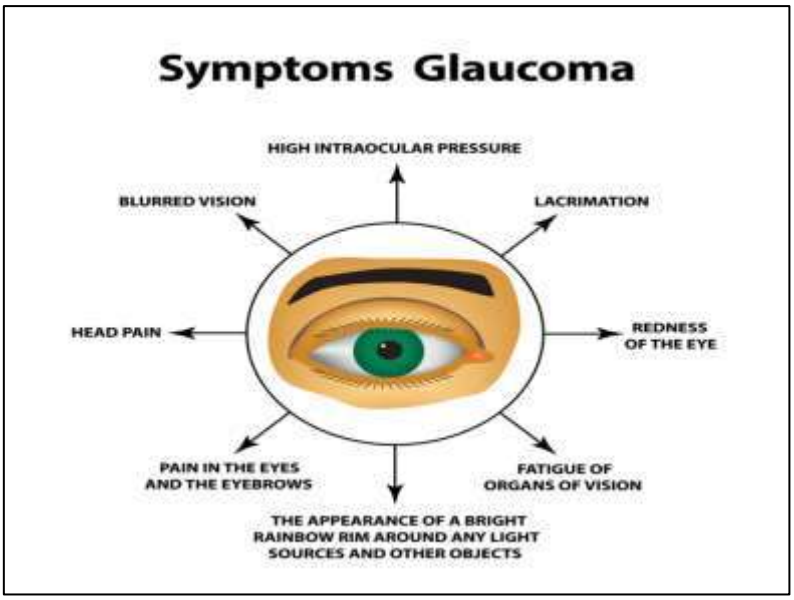


Fig .1.1: Symptoms of glaucoma

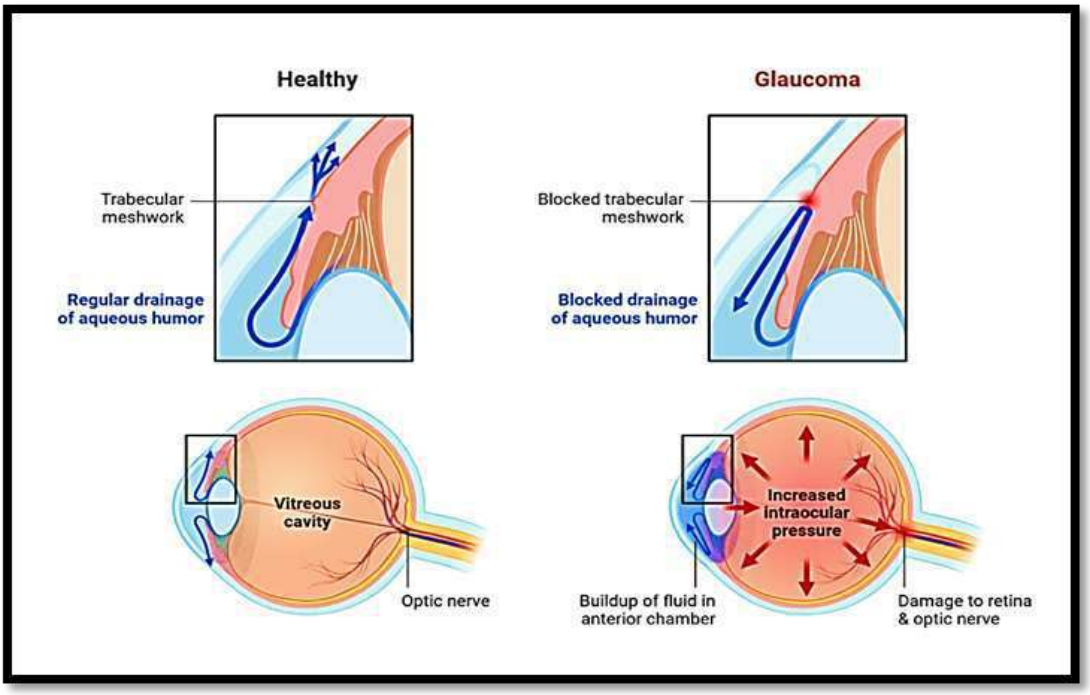


Fig. 1.2: Development of glaucoma

Types and Mechanism of Glaucoma:

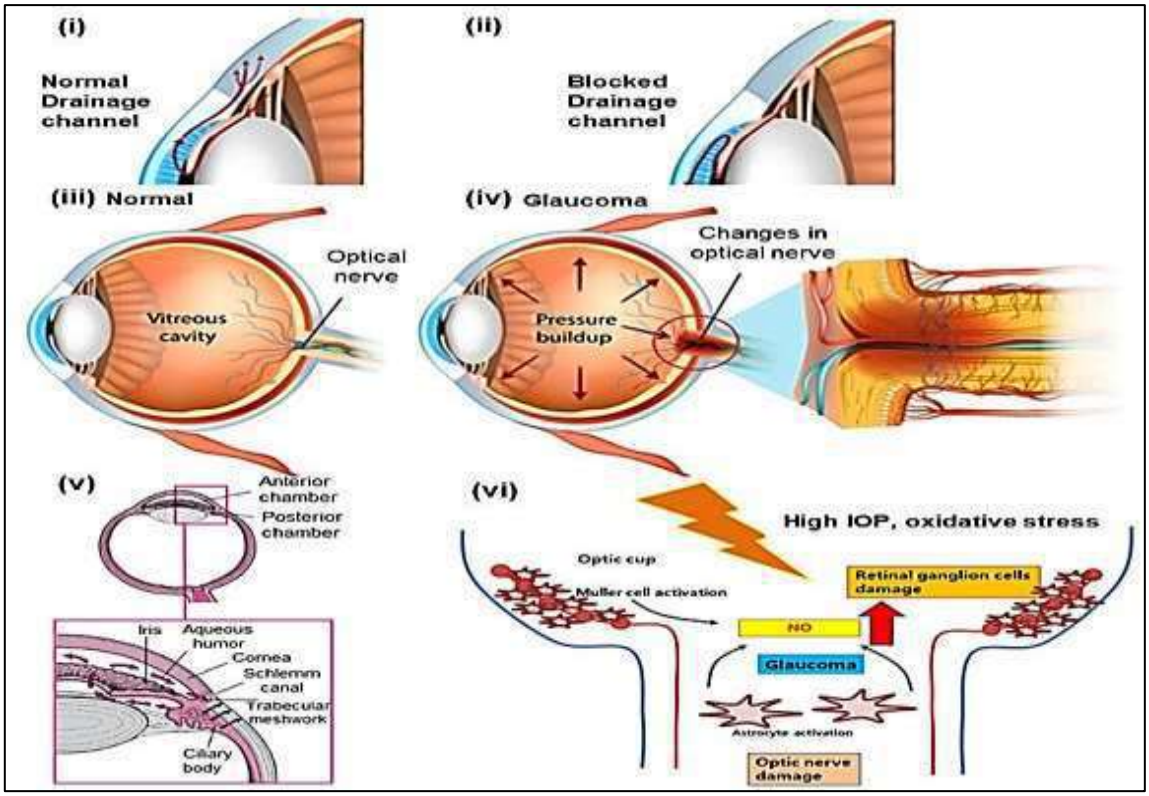
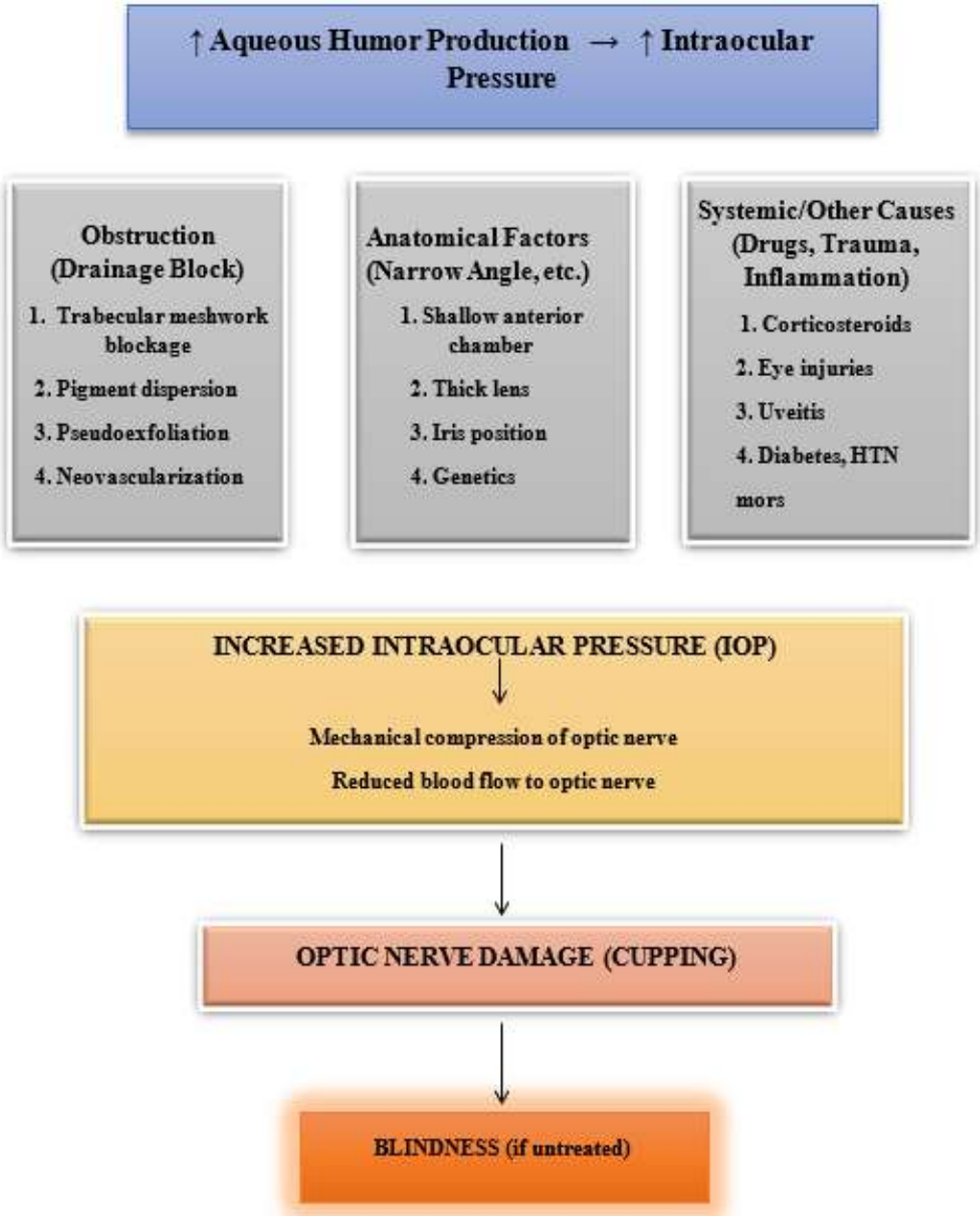


Fig. 1.3: Mechanism of glaucoma

Table 1.1: Types of glaucoma with its pathophysiology

Type of Glaucoma	Mechanism	Pathophysiology	Result
Primary Open-Angle Glaucoma (POAG)	Gradual blockage of trabecular meshwork drainage	Increased resistance to aqueous humor outflow through trabecular meshwork	Increased IOP → Optic nerve damage
Primary Angle-Closure Glaucoma (PACG)	Narrow or closed anterior chamber angle prevents aqueous humor drainage	Pupillary block → Iris bows forward → Closes angle → Sudden rise in IOP	Acute IOP spike → Severe optic nerve damage
Normal-Tension Glaucoma	Optic nerve damage without elevated IOP	Vascular dysregulation or increased optic nerve susceptibility	Optic neuropathy despite normal IOP
Secondary Glaucoma	Due to other ocular/systemic conditions	Causes: trauma, uveitis, steroid use, neovascularization → blocks trabecular meshwork or angle closure	Variable increase in IOP → Glaucoma symptoms
Congenital Glaucoma	Developmental anomaly of anterior chamber angle	improper formation of trabecular meshwork → Decreased outflow	High IOP in infants → Corneal enlargement
Pigmentary Glaucoma	Pigment dispersion from iris clogs trabecular meshwork	Pigment granules block drainage pathway	Increased IOP over time → Optic nerve damage

Glaucoma: Cause and Effect: [15-22]



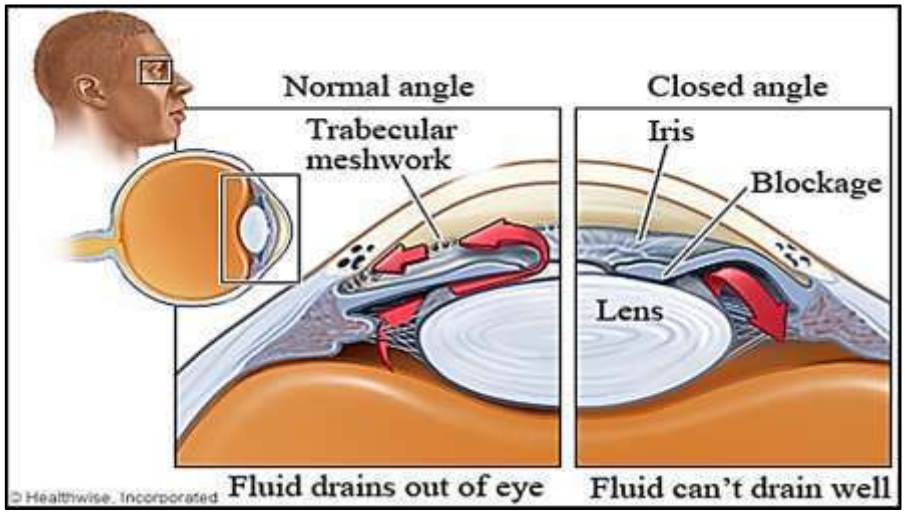
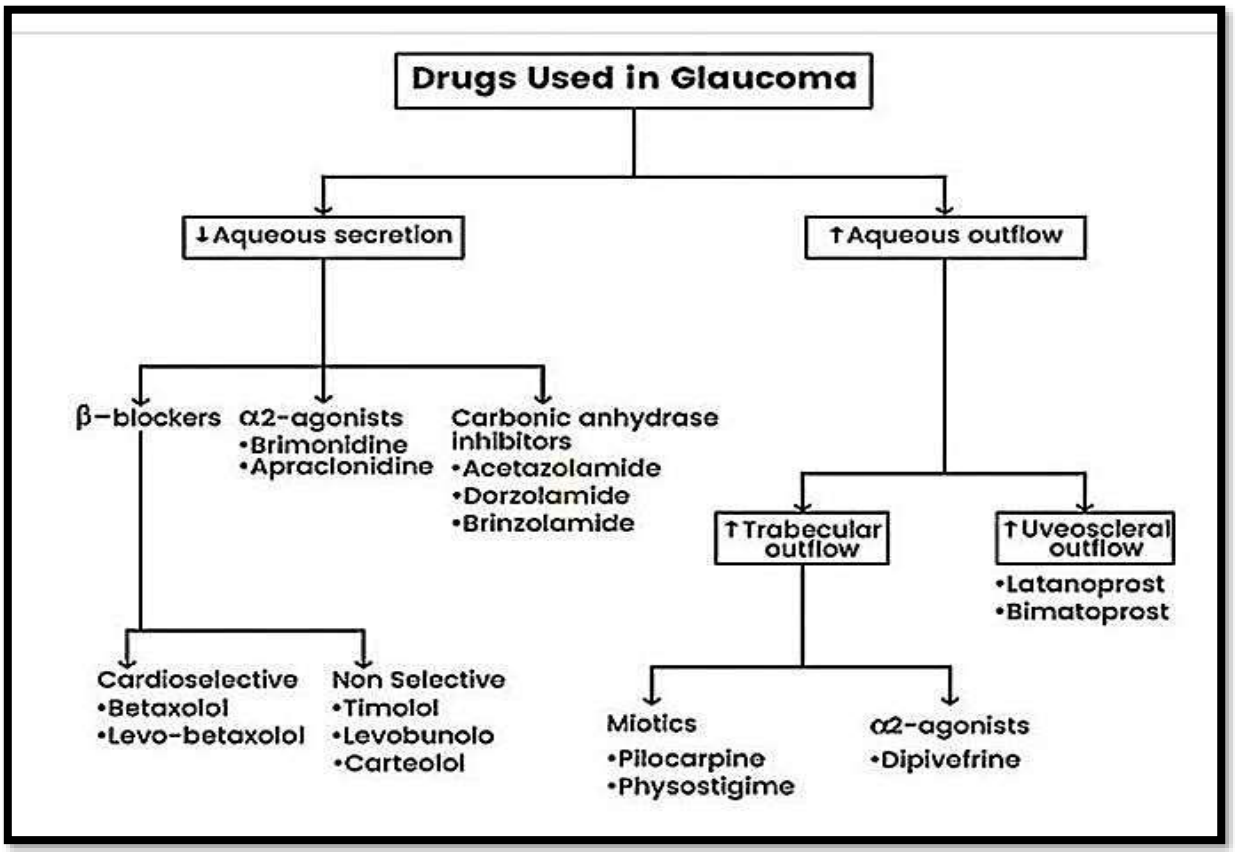


Fig. 1.4: Difference between normal angle and closed angle glaucoma

Treatment of Glaucoma:

Treatment options for glaucoma aim to lower intraocular pressure (IOP) to prevent optic nerve damage. Prostaglandin analogs such as latanoprost are commonly used as first-line agents; they increase the outflow of aqueous humor through the uveoscleral pathway. Alpha-adrenergic agonists like brimonidine work by both reducing aqueous humor production and enhancing its outflow. Carbonic anhydrase inhibitors, such as dorzolamide and acetazolamide, lower IOP by inhibiting the enzyme carbonic anhydrase, thereby reducing fluid formation in the eye. Additionally, cholinergic agents like pilocarpine promote aqueous humor drainage through the trabecular meshwork by contracting the ciliary muscle. Timolol maleate is a non-selective beta-adrenergic blocker used effectively in the management of glaucoma, particularly primary open-angle glaucoma and ocular hypertension. Its primary mechanism of action involves the reduction of intraocular pressure (IOP) by decreasing the production of aqueous humor in the eye. Timolol achieves this by blocking both β1- and β2-adrenergic receptors located in the non-pigmented epithelial cells of the ciliary body. Normally, stimulation of these receptors activates adenylate cyclase, leading to an increase in cyclic adenosine monophosphate (cAMP), which enhances aqueous humor secretion. By inhibiting beta receptor activity, timolol reduces cAMP levels, thereby suppressing aqueous humor formation. Importantly, timolol does not significantly affect aqueous humor outflow, distinguishing it from other classes of antiglaucoma drugs like prostaglandin analogs. The result is a significant reduction in intraocular pressure, typically observed within 30 minutes of administration, with peak effects around 1–2 hours and lasting up to 24 hours. This pressure-lowering action helps prevent further damage to the optic nerve, which is crucial in managing glaucoma and preserving vision. However, since timolol can be systemically absorbed, it may cause side effects such as bradycardia, hypotension, or bronchospasm, especially in patients with asthma, cardiac conditions.

Table.1.2: Drugs used for glaucoma



Nanocarriers for ocular delivery: [26-34]

Benefits compared to conventional drug delivery:

- Nanoscale size
- Controlled and sustained drug release
- Enhanced bioavailability and absorption in eye therapies
- Biocompatible, biodegradable, and non-immunogenic

Table. 1.3: Nanocarriers for ocular delivery

System	Structure	Size Range	Advantages	Applications
Liposomes	Phospholipid bilayers enclosing aqueous core	0.08–10 µm (SUV: 10–100 nm, LUV: 100–300 nm)	Biocompatible, encapsulates both hydrophilic/lipophilic drugs	Front & back of the eye drug delivery
Niosomes	Bilayered vesicles	Variable (Discosomes: 10–14 µm)	Chemically stable, low toxicity, easy storage	Ophthalmic drug delivery
Nanomicelles	Self-assembled Nano systems	Nanometer range	Enhances solubility, prolongs ocular retention, increases BA	Clear aqueous formulations
Microemulsion	Isotropic oil/water systems	10–100 nm (typically)	High stability, improved solubility & permeability	Timolol, Sirolimus, Chloramphenicol
Hydrogels	Cross-linked polymer networks	Swellable matrices	Sustained release, high ocular compatibility	Mucoadhesive ocular delivery
Nanoparticles	Solid colloidal carriers	10–1000 nm	High drug loading, multiple routes, stability	Topical, ocular, systemic
Lipid Nanoparticles (LNPs)	Solid lipid core systems	50–1000 nm	Stable, controlled release, better than liposomes & emulsions	Advanced ocular & systemic delivery

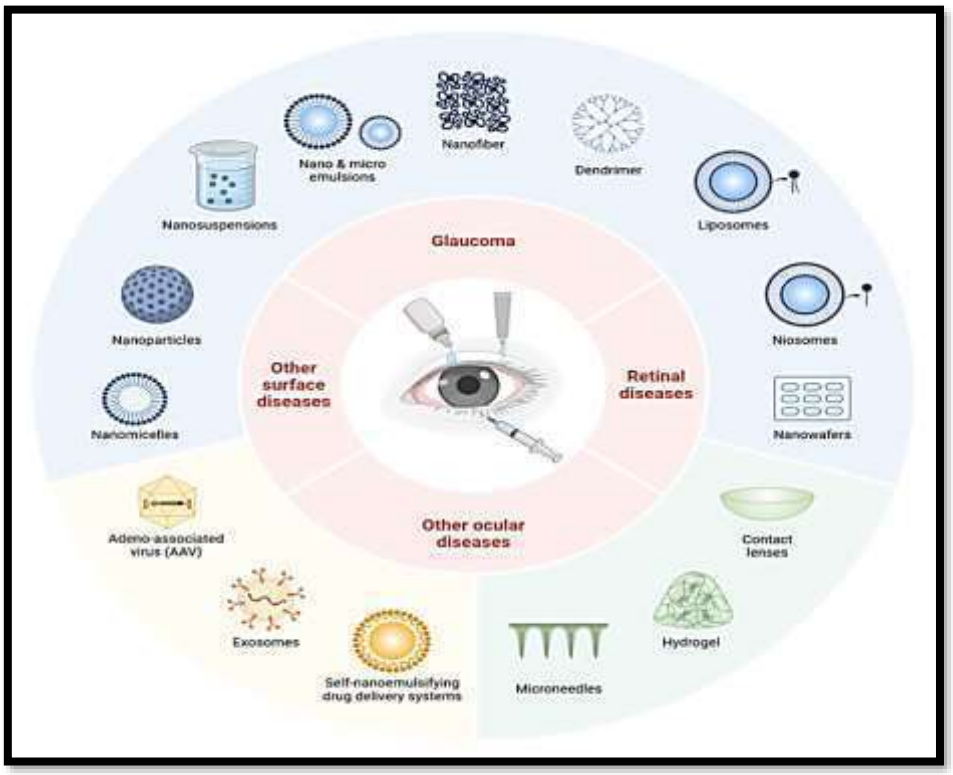


Fig. 1.5: Nanocarriers for ocular delivery

Nanostructured lipid carrier: [35, 36]

The dual complex of solid or liquid lipids makes up NLC, the second generation of LNPs, which have a mean size between 10 and 500 nm. Solid-lipid and liquid-lipid should ideally be mixed at a ratio of 70:30 to 99.9:0.1. They contain certain nanostructures that increase drug loading and tighten the medication's internal binding, increasing shelf life. Patients may get NLCs intravenously, topically, orally, or through their eyes. Additionally, it helps us transport the medication to the intended location and reduce adverse effects and dosage. Because NLCs resemble bodily lipids, they are widely used in the health zone. The small size of the lipid particle ensures close exposure to the stratum corneum, enabling medication administration to the skin or mucous membranes. In order to get around the drawbacks of first-pass metabolism, low bioavailability, and low solubility, NLCs have been created.

Advantages of Nanostructured Lipid Carriers (NLCs): [37]

- Increased solubility of drugs in aqueous environments
- Superior physical stability and durability
- Simple production process with ease of scaling up for industrial manufacturing
- High encapsulation efficiency for both hydrophilic and hydrophobic compounds
- Controlled and uniform particle size distribution
- Efficient delivery vehicle, especially suited for hydrophobic drugs
- Sustained and prolonged drug release profiles

Limitations of NLCs

NLC has some disadvantages despite its significant potential for targeted and chosen drug delivery, including:

- Cytotoxic effects associated with the kind and concentration of intercellular substances;
- Irritating effects of different surfactants
- More research is required to fully utilize the applications and efficacy of gene delivery systems and peptide and protein medications.

Structural type of NLCs:

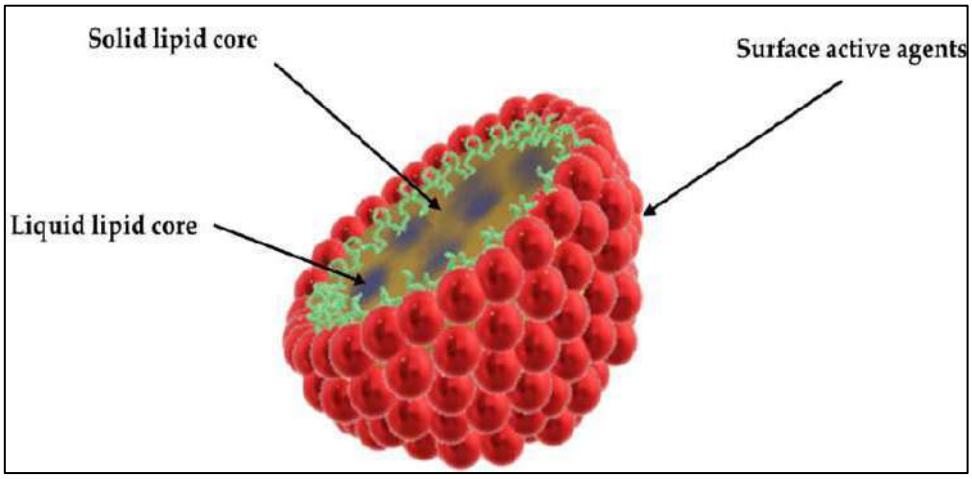


Fig. 1.6: Structure of NLC

NLCs have three quite different characteristics from SLNs, despite their somewhat similar topologies. Depending on the content of the lipid blend and the different production techniques, several types of NLCs are created. To optimize the payload for active compounds and reduce compound ejection during storage, the basic idea is to impart a particular nanostructure to the lipid matrix. The following is a summary of the three types of NLCs: The specification of particular type of NLCs has beed described in Table

Table. 1.4: Features of types of NLCs

Sr.No.	NLC type	Nature of matrix	Comments
1	Imperfect	Imperfectly structured solid matrix	Contains a mixture of spatially distinct lipids, creating imperfections in the crystal structure, resulting in high drug loading capacity
2	Amorphous	Structure less solid amorphous matrix	Developed by blending solid lipids with specialized lipids like hydroxyoctacosenyl hydroxystearate, isopropyl myristate, or medium-chain triglycerides (e.g., Miglyol 812). This prevents drug expulsion and offers a moderate drug loading capacity
3	Multiple	Multiple oil in fat in water	During cooling after homogenization, the drug's solubility in the lipid phase reduces, leading to crystallization and stability concerns during storage

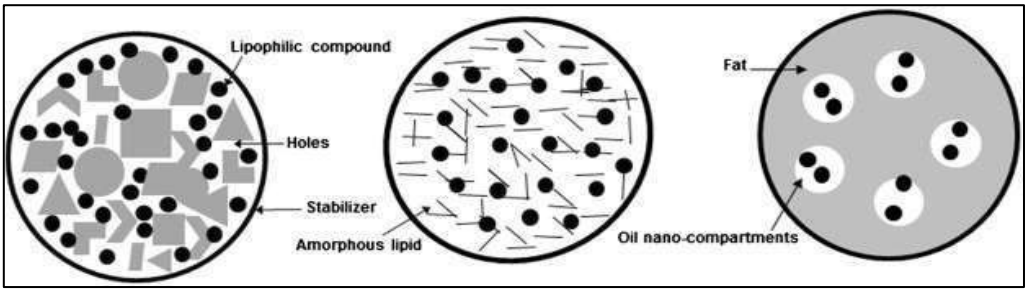


Fig .1.7: 1) Imperfect NLC 2) Amorphous NLC 3) Multiple NLC

Methods used for the fabrication of NLCs:

Table 1.5: Method of preparation of NLC

Energy Level	Method	Principle/Process	Advantages	Limitations
High Energy	High Pressure Homogenization (HPH)	Molten lipid + drug homogenized at high pressure (cold or hot technique).	Solvent-free, scalable, fast process.	Equipment cost, heat may degrade thermolabile drugs.
	High Shear Homogenization	Drug in molten lipid (10°C above melting point) + aqueous surfactant, homogenized at high speed.	Simple method, creates microemulsions for further processing.	Less control over particle size.
Low Energy	Micro-emulsion Technique	Mix molten lipid with surfactant/co-surfactant aqueous phase → transparent emulsion → cooled for NLC formation.	Suitable for thermolabile drugs, no special equipment needed.	Stability dependent on surfactant choice.
	Double Emulsification	Forms o/w/o emulsions using solvent evaporation method; ideal for hydrophilic drugs.	Good for water-soluble drugs, useful for lipospheres.	Larger particle size, less stable than SLNs.
	Phase-Inversion Method	Drug + lipid + surfactant heated above phase inversion temp → rapid cooling → phase reversal leads to nanoparticle formation.	No organic solvent, low energy, eco-friendly.	Less stability, requires temperature cycling.
Very Low/No Energy	Emulsification -Solvent Evaporation	Lipid + drug in organic solvent → dispersed in aqueous phase → sonication → solvent evaporation → cooling to form NLCs.	Simple, rapid technique.	Requires organic solvents, extra purification steps.
	Emulsification -Solvent Diffusion	Lipid dissolved in partially water-miscible solvent → emulsified in water → solvent diffuses and solidifies to form NLCs.	Fine particle size, avoids high energy.	Use of solvents, less eco-friendly.

Characterization and evaluation of the NLC [42, 45]

Evaluating nanostructures is essential for ensuring their quality and suitability for in vivo applications. Due to their small size, complex lipid composition, and dynamic behavior, NLCs present unique challenges in characterization. Key parameters for assessing NLC quality and stability include drug concentration, particle size, size distribution, zeta potential, surface charge, entrapment efficiency, and in vitro drug release.

Table. 1.6: Characterization and evaluation of the NLC

Parameter	Method	Key Insights
Particle Size, PDI & Zeta Potential	Measured via Dynamic Light Scattering (DLS).	Indicates particle uniformity and stability. Zeta potential > ±30 mV suggests strong repulsion, reducing aggregation.
Morphology	TEM, SEM, and AFM imaging.	Provides visual confirmation of shape, surface, and structural integrity. TEM is preferred, using stained, dried samples on copper grids.
Entrapment Efficiency (EE%)	NLCs are disrupted using solvents, and drug content is measured via UV-spectroscopy.	EE (%) = (Total drug – Free drug) / Total drug × 100. High EE is common with hydrophobic drugs due to lipid entrapment. [46,47]
In Vitro Drug Release	Typically done using dialysis method at 37°C with stirring; samples collected at intervals and analyzed by UV/HPLC.	Reveals drug release profile over time. Free drug solution serves as control.
Thermal Behavior (Crystallinity)	Evaluated via Differential Scanning Calorimetry (DSC).	Assesses melting points, crystallinity, and polymorphism; involves heating 10 mg sample under nitrogen with data analyzed using DSC software. [51,52,53]
Crystal Structure Analysis	X-ray Diffraction (XRD) of freeze-dried samples.	Determines crystalline or amorphous nature by interpreting diffraction patterns from 20° to 80° (2θ range). [54,55]
Drug Release Kinetics	Analyzed through in vitro and controlled release studies.	Affected by lipid type, surfactants, and drug positioning (core vs surface). Initial burst followed by sustained release is common. [56,57,58]
Ex Vivo Corneal Permeation	Delta diffusion cells with goat corneas and simulated tear fluid at 37°C.	Measures permeation and retention. Drug is quantified using UV spectrophotometry, and flux is calculated from the slope of permeation curve. [71]

Applications of NLC in ocular delivery:

Creating a revolutionary delivery system that can effectively target the ocular tissue that is diseased, deliver high quantities of the treatment, and maintain the drug's effects with few to no side effects [59] Because of certain physiological and anatomical characteristics of the eyes, ocular medication administration has numerous disadvantages and is still difficult. The eyes are a sensitive, intricate organ with many barriers. These obstacles can be addressed by innovative drug delivery methods like SLNs and NLCs, which improve ocular bioavailability. Its capacity to encapsulate hydrophobic medications, protect unstable components, and alter release behavior are further benefits. For the past several decades, 61 SLN has been used for ocular administration. Numerous research employing NLC as an ocular delivery mechanism is now well-known. NLC has been used to deliver some medications, like ciprofloxacin or amphotericin B, into the eyes. [62,63,64] The numerous ocular disorders that can affect both the front and back of the eye make it difficult to manage ophthalmic disease effectively. To get the medication to the intended location, a variety of ocular administration techniques are employed, including topical, intraocular, periocular, and in conjunction with ocular devices. Nanotechnologies

were used to improve eye retention time, medication penetration, and ocular bioavailability while reducing duration of drug consumption and side effects. This method improved the drug's efficacy and demonstrated good biocompatibility, suggesting that it will be widely utilized to treat eye infections. [65]

Recent Studies on NLCs: [66, 67, 68, 69]

Table. 1.7: Recent Studies on NLCs

Study	Drug	Lipid Components	Method	Key Findings
Cavalli et al.	Tobramycin	Not specified	Not specified	six hours of continuous medication release as opposed to the shorter time frame of traditional eye drops.
Attama et al.	Diclofenac Sodium	Lipid nanoparticles + Phospholipids High-	High-pressure homogenization	Enhancing ocular delivery, phospholipid coating increased corneal permeability.
Araujo et al.	Triamcinolone Acetonide	Precirol ATO5 (solid lipid), Squalene (liquid lipid), Lutrol F68 (surfactant)	High-pressure homogenization	The drug is mainly trapped in an amorphous NLC matrix; the Draize test shows little eye harm.
Zhang et al.	Genistein	Eudragit-modified NLC	Melt emulsification	enhanced ocular permeability, increased AUC by 1.22×, and Draize and cytotoxicity tests revealed no harm.
E. Gonzalez-Mira et al.	Flurbiprofen	Optimized lipid quantities	High-pressure homogenization	Long-term stability, controlled release, and lack of discomfort have all been verified.

Other Applications [70,71]

NLCs in chemotherapy for cancer:

Numerous chemotherapeutic medications have been encapsulated or integrated into NLCs within the last two to three years, and their effects have been assessed both in vitro and in vivo. These research' findings have been demonstrated to enhance pharmacokinetics, decrease adverse effects, boost potency, and improve medication stability, making them useful tools for clinical settings. The use of NLCs for delivery can help to partially address some of the issues that are frequently encountered with antibodies, such as tissue toxicity, poor quality, and stability.

NLC in peptide and protein delivery:

Other carriers for the treatment of proteins, peptides, and antigens include lipid nanoparticles and lipid microparticles, such as NLC and SLN. Lipid products contain peptides that are presently being studied, including somatostatin, insulin, calcitonin, and cyclosporine A.

NLC in CNS targeting:

Pharmaceutical applications may benefit from NLC's modest size (less than 50 nm). Reticuloendothelial disorders tend to be considerably less harmful to small people. Additionally, NLCs can be utilized medicinally. NLC is a promising medication targeting system for the treatment of organ illnesses and can enhance a medicine's capacity to cross the blood-brain barrier. NLCs have superior efficiency, greater drug

loading, and less cytotoxicity than polymeric nanoparticles.

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