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REVIEW ARTICLE

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NIOSOMAL GEL BASED OCULAR DRUG DELIVERY SYSTEMS FOR CONTROLLED RELEASE OF PILOCARPINE IN GLAUCOMA THERAPY

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ABSTRACT: Glaucoma is a chronic ocular disorder characterized by elevated intraocular pressure (IOP), leading to progressive optic nerve damage and irreversible vision loss. Pilocarpine, a well-established cholinergic agent, lowers IOP by enhancing aqueous humor outflow; however, its conventional ocular delivery is limited by poor corneal permeability, rapid precorneal elimination, and the need for frequent dosing. These limitations significantly reduce therapeutic efficacy and patient compliance. To overcome these challenges, niosomal gel-based ocular drug delivery systems have emerged as an innovative and effective strategy. Niosomes are non-ionic surfactant-based vesicular carriers capable of encapsulating drugs and providing sustained release, improved stability, and enhanced penetration across ocular barriers. When incorporated into gel systems, they further increase precorneal residence time, reduce drug drainage, and allow prolonged drug–cornea interaction. This dual delivery approach enhances bioavailability, minimizes dosing frequency, and improves patient compliance. Additionally, niosomal gels can be engineered using biocompatible polymers to achieve controlled and targeted drug delivery with minimal irritation. This review highlights recent advances in formulation strategies, preparation methods, characterization parameters, and in vitro and in vivo evaluation of niosomal gel systems for pilocarpine delivery. Furthermore, it discusses therapeutic advantages, limitations, and future perspectives, including the development of stimuli-responsive and targeted systems. Overall, niosomal gel-based delivery represents a promising approach for improving the efficacy and safety of glaucoma therapy. Such systems may also reduce systemic exposure, enhance ocular retention, and support sustained pharmacological action over extended periods, thereby offering a more reliable and patient-friendly therapeutic alternative for long-term glaucoma management and improved clinical outcomes overall.

Keywords: Niosomes, Pilocarpine, Glaucoma, Ocular drug delivery, Controlled release, Gel systems

I. INTRODUCTION

Glaucoma is a long-term, progressive eye disease, and also one of the major causes of irreversible blindness in the world. It is associated with destruction of the optic nerve which is usually accompanied by an increase in intraocular pressure (IOP), and leads to progressive loss of vision. Glaucoma is a serious health issue in the world as the number of elderly people is increasing and people are not diagnosed early enough. Unattended, the disease may result in permanent visual disability and lower quality of life [1]. High IOP is regarded as the most significant risk factor that can be modified in glaucoma. It is caused by a disbalance between the generation and elimination of aqueous humor in the eye. Prolonged elevation of IOP results in mechanical tension and vascular impairment of the optic nerve, which finally results in the loss of retinal ganglion cells. Thus, the main approach to glaucoma treatment is the IOP reduction to avoid or slow down the disease process [2].

Pilocarpine is a conventional antiglaucoma medication that is a cholinergic agonist. It works by activating muscarinic receptors in the eye resulting in the contraction of ciliary muscle and enhanced excretion of aqueous humor via the trabecular meshwork. Although effective, pilocarpine by conventional eye drops has a number of constraints, such as low corneal permeability, high rate of precorneal excretion owing to turnover in tears, low bioavailability, and frequent dosing regimen that decreases patient compliance [3].

In a bid to solve these shortcomings, there is exploration of advanced ocular drug delivery systems to enhance drug retention, penetration and controlled release. Of these, niosomal gel-based systems have come out as one of the promising methods. Niosomes are vesicles formed by non-ionic surfactants and cholesterol, which enhance the stability of a drug and its prolonged release. Included in gel formulations, they also increase precorneal residence time and therapeutic efficacy and provide a new and effective approach to managing glaucoma [4].

2. Literature Search Methodology

To gather the necessary scientific data on the niosomal gel-based ocular drug delivery systems to control the release of pilocarpine in the treatment of glaucoma, a thorough

systematic literature search was carried out to obtain the necessary information. Various electronic databases such as PubMed, ScienceDirect, and Google Scholar were thoroughly searched to allow wide coverage of peer-reviewed articles, research papers and review studies [5].

Keywords and their combinations that were used as the search strategy included: niosomes, ocular drug delivery, pilocarpine, glaucoma, and controlled release. Refining the search results to enhance relevance was done using Boolean operators (AND, OR). The literature search was mainly restricted to articles in the English language with a special interest given to the recent developments to capture up-to-date scientific understanding [6].

The inclusion criteria were well-defined to include those studies which were straight to the point. These were research articles and reviews that dealt with niosomal formulations, gel-based ocular delivery systems and articles that assessed pilocarpine both *in vitro* and *in vivo*. The articles that included formulation development, the parameters of characterization, drug release, and pharmacological assessment were prioritized to provide the complete picture of the topic [7].

The exclusion criteria were used to remove the studies that were not directly related to ocular delivery systems, had insufficient experimental information, and/or were of low quality. Other publications that were duplicated, which were not peer-reviewed, and studies with unclear or inconclusive findings were also rejected. The chosen literature was critically evaluated and systematized to avail a consistent and scientifically sound review [8].

3. Glaucoma and Ocular Drug Delivery Challenges

3.1 Pathophysiology of Glaucoma

Glaucoma is a chronic progressive optic neuropathy that is linked to structural degeneration of the optic nerve head and a disruption in visual field. It is regarded as one of the most widespread causes of irreversible blindness in the world and in its initial stages, it is normally asymptomatic and therefore hard to be detected. The high intraocular pressure (IOP) is the most prevalent disease-related issue, and the primary risk factor that can be altered during the disease progression [9].

Pathophysiology of glaucoma is closely related to the dynamics of aqueous humor. The aqueous humor is constantly produced by the ciliary body which is emptied through the trabecular meshwork (conventional pathway) and ureoscleral route (non-conventional pathway). During glaucomatous diseases the resistance to efflux of aqueous humor, particularly through the trabecular meshwork, leads to the accumulation of the aqueous humor in the anterior chamber, which leads to high IOP. This extra force results in mechanical stress of lamina cribrosa and optic nerve fibers [10].

In addition to mechanical injury, high IOP can also lead to ocular blood flow impairment, that is, ischemia and optic nerve oxidative stress. The phenomenon leads to the death of retinal ganglion cells that are essential in transmitting visual information to the brain. The degeneration causes irreversible and progressive vision loss over time. Other factors that may aggravate the situation are genetic predisposition, age, vascular dysregulation, and neuroinflammatory processes. In such a way, the best strategy of glaucoma treatment will be the reduction of IOP and maintenance of the integrity of optic nerves [11].

3.2 Challenges in Ocular Drug Delivery

Drug delivery by eye is very challenging as the eye has some very specific anatomical, physiological, and biochemical barriers. The eye is a very well-defended organ and its defense mechanisms tend to hamper the action of drugs that are applied topically. Among the major ones is the rapid tear turnover, which constantly removes instilled formulations off the ocular surface. Mean tear turnover rate, reflex blinking and lacrimal drainage lead to the rapid excretion of drugs in minutes after administration [12].

The other significant obstacle is the corneal epithelium which is a lipophilic membrane that has tight junctions that limit diffusion of hydrophilic and large molecular weight drugs. Below it is the stromal layer that contains a hydrophilic barrier, complicating drug penetration further. This dual barrier greatly limits the drug quantity that arrives intraocular tissues [13].

Besides, conjunctival absorption and systemic drainage via the nasolacrimal duct further reduces the availability of drugs to the eye and increases the chances of systemic side effects. These factors have resulted in the extremely low bioavailability of the conventional ocular dosage forms (e.g. eye drops) which is typically less than 50 percent of the dosage delivered to the target site [14].

Poor drug retention and absorption may necessitate high frequency dosing, which may result in low patient compliance, particularly in older populations with glaucoma. In addition, when administered repeatedly, it can lead to local irritation and blurred vision, among other undesirable effects. These issues underscore the importance of a high-order system of ocular drug delivery to increase residence time, enhance drug penetration, offer controlled release and ultimately improve therapeutic effects [15].

4. Pilocarpine: Drug Profile and Limitations

4.1 Pharmacological Action

Pilocarpine is a naturally-derived, naturally-occurring alkaloid and an established antiglaucoma agent that is a direct-acting cholinergic agonist. It has its main effect on stimulating muscarinic receptors (M3 subtype) located in the iris sphincter and ciliary muscles of the eye. When applied topically, pilocarpine causes the ciliary muscle to contract resulting in the opening of the trabecular meshwork and causing the aqueous humor to drain through the normal outflow system (Table 1) [16].

Intraocular pressure (IOP) decreases substantially, leading to significant effects of pilocarpine especially in the treatment of open-angle glaucoma as well as acute angle-closure glaucoma. Also, pilocarpine induces miosis (constriction of the pupil) and this effect also helps to enhance aqueous humor dynamics, since it enlarges the anterior chamber angle. Pilocarpine has been extensively used as a first line or adjunctive in the treatment of glaucoma, since it has a quick action and has been utilized in clinical practice over many decades [17].

4.2 Limitations

Although pilocarpine is therapeutically effective, it has a number of shortcomings when used as traditional ocular dosage, e.g., eye drops. Its main disadvantage lies in the fact that it has a short precorneal half-life; the drug is eliminated quickly through the ocular surface, by tears, blinking, and nasolacrimal drainage. It results in a decrease in the duration of action and requires regular dosing to sustain therapeutic drug levels [18]. Inadequate penetration of corneas is another significant weakness. Pilocarpine is not very lipophilic and the corneal lipophilic epithelium and thus limits its penetration into the lipophilic corneal tissue. Consequently, low bioavailability is due to the fact that very little of the administered dose gets into the intraocular tissues (Table 1) [19]. Moreover, the constant use of pilocarpine eye drops is linked with various side effects, such as blurred vision, irritation of the eyes, pains in eyebrows, and poor night vision since the miosis is persistent. These side effects may have detrimental effects on patient compliance particularly in the long-term glaucoma treatment [20]. Thus, the development of new drug delivery systems that will help address these shortcomings and enhance the therapeutic efficacy of pilocarpine is required.

Table 1: Drug Profile of Pilocarpine [21]

S. No.	*Parameter*	*Description*
1	Drug name	Pilocarpine
2	Chemical class	Alkaloid
3	Pharmacological class	Cholinergic (parasympathomimetic) agonist
4	Mechanism of action	Stimulates muscarinic (M_3) receptors
5	Primary effect	Increases aqueous humor outflow
6	Indication	Glaucoma (open-angle and angle-closure)
7	Route of administration	Topical ocular (eye drops, gels)
8	Molecular formula	$C_{11}H_{16}N_2O_2$
9	Molecular weight	208.26 g/mol
10	Solubility	Water-soluble
11	pKa value	~7.1
12	Bioavailability	Low (<5% in conventional eye drops)
13	Half-life	Short (approximately 1–2 hours ocularly)
14	Side effects	Blurred vision, irritation, brow ache, miosis
15	Limitations	Poor corneal penetration, rapid precorneal loss, frequent dosing requirement

5. Niosomes as Ocular Drug Delivery Systems

5.1 Structure and Composition

Niosomes are microscopic vesicles that are produced by self-assembly of non-ionic surfactants in an aqueous medium and thus have a bilayer structure akin to that of liposomes. These vesicles are mainly made of non-ionic surfactants like Span, Tween or Brij which offer structural integrity and flexibility to the bilayer. The formulation includes cholesterol to increase the rigidity of the membranes, stability, and their permeability in order to avoid leakage of the drug encapsulated [22]. Niosomes have a hydrophilic core and one or more concentric bilayers as a structural component. This special vesicular system enables the entrapment of hydrophilic drugs (in the aqueous core) and lipophilic drugs (in the bilayer membrane). Due to the amphiphilic properties of the surfactants, the interactions with biological membranes are facilitated, and niosomes are especially effective in ocular drug delivery. Their nano- or microscales also promote better penetration and retention of drugs in ocular tissues [23].

5.2 Advantages

Niosomes have a number of benefits compared with the traditional ocular drug delivery system and hence they make a good carrier of drugs such as pilocarpine. Among the main advantages are their superior biocompatibility and low toxicity since they are made of non-ionic surfactants, which are generally well-tolerated by ocular tissues [24]. They offer sustained and controlled drug delivery, thus contributing to the maintenance of therapeutic drug levels over a long period of time and decreasing the number of dosing. This can help especially in chronic diseases like glaucoma. Moreover, niosomes improve the permeation of drugs through the corneal barrier because it can interact with lipid membranes, and thus the bioavailability of the drug to the eye is increased [25].

Other benefits are that it enhances drug stability, prevents degradation of the drug, it is versatile in formulation and can be easily modified on the surface to deliver to the target. All these properties lead to better treatment effects and adherence to the treatment [26].

5.3 Methods of Preparation

Niosomes may be made by different methods based on the required size, lamellarity, and the drug entrapment capacity. The most widely used technique is the thin film hydration technique, in which the surfactants and cholesterol are dissolved in an organic solvent, and the solvent is evaporated to create a thin film. The aqueous phase containing the drug is then added to this film causing multilamellar vesicles to form [27]. Reverse phase evaporation is also another technique that is commonly used, and in this process a water-in-oil emulsion is created and the organic solvent is taken off in low pressure that results in the formation of large unilamellar vesicles with a high drug entrapment rate (Fig. 1) [28].

Another technique that is used is the ether injection technique in which the surfactant solution in ether is gradually injected into a heated aqueous solution containing the drug. Niosomal vesicles are formed as the ether is evaporated. All approaches have certain benefits in vesicle properties and are used depending on the demands of formulations [29].

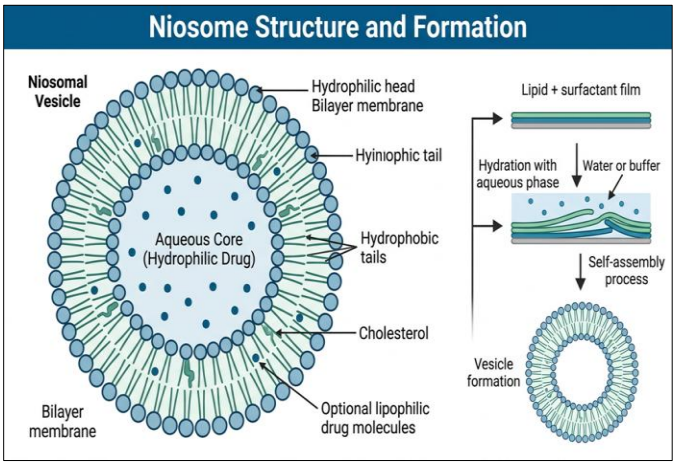

Figure 1: Structure and Formation of Niosomes [30]

6. Niosomal Gel Formulation for Ocular Delivery

6.1 Need for Gel Incorporation

Despite the ability of niosomes to deliver drugs in a controlled manner, direct ocular delivery can still be limited by the rapid precorneal clearance caused by tears turnover and blinking. To improve the therapeutic performance of niosomes, it is thus necessary to incorporate them in a gel matrix. The gel systems enhance the viscosity of the formulation that is highly effective in extending the residence time of the drug at the ocular surface. This prolonged contact period enables the drug to enter the cornea more, hence enhancing bioavailability [31].

Also, the gel-based systems aid in decreasing nasolacrimal drainage, which contributes to the primary losses of drugs in traditional eye drops. The gel also serves as a reservoir by creating a semi-solid layer on the corneal surface which releases the drug over time. This translates to long-lasting delivery of the drug, lower dose frequency and compliance, particularly in chronic diseases like glaucoma [32].

6.2 Types of Gelling Agents

Depending on the desired viscosity, stability and drug release properties, different polymers are employed in the preparation of niosomal gels. Carbopol is a synthetic polymer with very high usage because it has a great gelling capacity, bioadhesive properties, and is compatible with ocular tissues. It will form clear gels and give sustained drug release [33].

Another commonly used semi-synthetic polymer is hydroxypropyl methylcellulose (HPMC) which increases viscosity and enhances ocular retention. It is reputed to be non-irritant with good film-forming properties. The thermoresponsive polymer Poloxamer is especially effective in in situ gel, where the formulation is in liquid form at room temperature and turns into a gel when exposed to the temperature of the ocular surface. This characteristic increases the retention and ease of administration of the drug further [34].

6.3 Preparation Method

The niosomal gel formulations are prepared in two steps. To make niosomes, first of all, appropriate procedures are employed to make them through thin film hydration, reverse phase evaporation or ether injection. The niosomal suspension is prepared and then the vesicle size, entrapment efficiency and stability are characterized [35].

The niosomal dispersion is then added in a pre-prepared gel base that contains the chosen polymer (e.g., Carbopol or HPMC) in the second step. The mixture is stirred, so that the niosomes are evenly distributed in the gel matrix. The pH of the formulation is then corrected to correspond to physiological ocular pH (about 6.87.4) to prevent irritation [36].

Lastly, the viscosity is also optimized to be easy to apply and at the same time sufficiently sticky on the ocular surface. The resultant niosomal gel formulation offers a stable, controlled-release delivery system that has a high therapeutic effect in ocular drug delivery (Table 2) [37].

Table 2: Components of Niosomal Gel Formulation [38]

S. No.	*Component*	*Category*	*Example*	*Function*
1	Non-ionic surfactant	Vesicle former	Span 60	Forms niosomal bilayer
2	Non-ionic surfactant	Vesicle former	Tween 80	Improves vesicle flexibility
3	Cholesterol	Membrane stabilizer	Cholesterol	Enhances rigidity and stability
4	Drug	Active ingredient	Pilocarpine	Antiglaucoma effect
5	Hydration medium	Aqueous phase	Distilled water	Vesicle formation medium
6	Organic solvent	Solvent	Chloroform	Dissolves lipids during preparation
7	Organic solvent	Solvent	Methanol	Used in thin film formation
8	Gelling agent	Polymer	Carbopol 934	Provides viscosity and gel structure
9	Gelling agent	Polymer	HPMC	Enhances ocular retention
10	Gelling agent	Polymer	Poloxamer 407	Thermoresponsive gel formation
11	Neutralizing agent	pH adjuster	Triethanolamine	Adjusts gel pH
12	Buffer system	pH stabilizer	Phosphate buffer	Maintains physiological pH
13	Preservative	Antimicrobial	Benzalkonium chloride	Prevents microbial growth
14	Penetration enhancer	Permeation aid	Propylene glycol	Enhances corneal penetration
15	Stabilizer	Additive	EDTA	Improves stability and shelf life

7. Mechanism of Controlled Drug Release

The niosomal gel system provides a dual-controlled release mechanism that significantly enhances the therapeutic efficiency of pilocarpine in ocular delivery. This system integrates the advantages of vesicular carriers (niosomes) with a polymeric gel matrix, resulting in sustained and targeted drug delivery [39].

Sustained Release from Vesicles

Niosomes act as microscopic reservoirs that encapsulate pilocarpine within their aqueous core or lipid bilayer. The drug is released gradually from these vesicles through processes such as diffusion, bilayer erosion, and vesicle destabilization. The presence of cholesterol within the bilayer enhances membrane rigidity, thereby slowing drug leakage and ensuring prolonged release. This sustained release helps maintain consistent drug levels in ocular tissues over an extended period [40].

Diffusion through Gel Matrix

Once released from the niosomes, the drug must diffuse through the surrounding gel matrix before reaching the ocular surface. The gel acts as an additional barrier, controlling the rate of drug diffusion. The viscosity and polymer concentration of the gel (e.g., Carbopol or HPMC) play a crucial role in regulating this process. Higher viscosity results in slower diffusion, thereby extending the duration of drug release and minimizing burst release effects [41].

Increased Corneal Contact Time

The gel formulation enhances the residence time of the drug on the ocular surface by adhering to the corneal and conjunctival tissues. This prolonged contact reduces drug loss due to tear turnover and nasolacrimal drainage. As a result, more drug is available for absorption across the cornea, leading to improved bioavailability. The combined effect of sustained vesicular release, controlled diffusion, and enhanced retention makes niosomal gel systems highly effective for controlled ocular drug delivery (Fig. 2) [42].

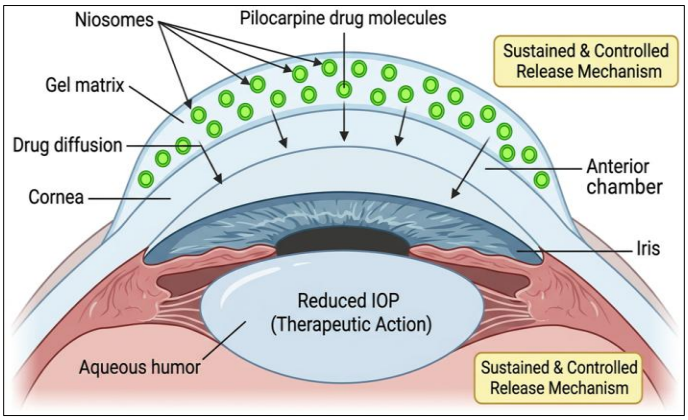

Figure 2: Mechanism of Controlled Release of Pilocarpine from Niosomal Gel [43]

8. Evaluation and Characterization

Evaluation and characterization of niosomal gel formulations are essential to ensure their stability, efficacy, safety, and suitability for ocular application. A combination of physicochemical, in vitro, and in vivo studies is performed to comprehensively assess formulation performance (Table 3) [44].

8.1 Physicochemical Properties

The physicochemical characterization of niosomal gels plays a crucial role in determining formulation quality and consistency.

Vesicle Size and Size Distribution: Vesicle size significantly influences drug release, ocular penetration, and stability. It is typically measured using dynamic light scattering (DLS). Smaller and uniformly distributed vesicles enhance corneal permeation and provide better therapeutic outcomes [45].

Zeta Potential: Zeta potential indicates the surface charge of vesicles and is an important parameter for predicting stability. Higher absolute zeta potential values prevent aggregation of vesicles due to electrostatic repulsion, thereby improving formulation stability [46].

Entrapment Efficiency: Entrapment efficiency determines the amount of drug successfully encapsulated within the niosomes. It is usually measured by centrifugation or dialysis methods. High entrapment efficiency is desirable for achieving sustained drug release and improved bioavailability [47].

8.2 *In Vitro* Studies

In vitro studies provide preliminary insight into drug release behavior and permeation characteristics.

Drug Release Studies: These studies are conducted using diffusion cells (*e.g.*, Franz diffusion cell) to evaluate the release profile of pilocarpine from the niosomal gel. A sustained and controlled release pattern is typically observed compared to conventional formulations [48].

Permeation Studies: Permeation studies assess the ability of the drug to cross the corneal barrier. Excised animal cornea or synthetic membranes are used to simulate ocular conditions. Enhanced permeation indicates improved bioavailability and therapeutic effectiveness [49].

8.3 *In Vivo* Studies

In vivo studies are essential to confirm the safety and pharmacological efficacy of the formulation.

Intraocular Pressure (IOP) Reduction: The primary objective of pilocarpine therapy is to reduce IOP. In vivo studies are conducted on suitable animal models to evaluate the extent and duration of IOP reduction, demonstrating the therapeutic performance of the formulation [50].

Ocular Irritation Test: Safety assessment is performed using standard tests such as the Draize test to evaluate any signs of redness, irritation, or damage to ocular tissues. A well-formulated niosomal gel should be non-irritant and well tolerated [51].

Table 3: Evaluation Parameters of Niosomal Gel [52]

S. No.	*Parameter*	*Method/Instrument*	*Purpose*
1	Vesicle size	Dynamic Light Scattering (DLS)	Determines size for penetration and stability
2	Polydispersity index (PDI)	DLS	Indicates uniformity of vesicle distribution
3	Zeta potential	Zeta analyzer	Assesses surface charge and stability
4	Entrapment efficiency	Centrifugation method	Measures drug encapsulation capacity
5	Morphology	Transmission Electron Microscopy (TEM)	Determines shape and structure of vesicles
6	Surface morphology	Scanning Electron Microscopy (SEM)	Evaluates surface characteristics
7	pH measurement	Digital pH meter	Ensures ocular compatibility
8	Viscosity	Brookfield viscometer	Determines gel consistency and retention
9	Spreadability	Glass slide method	Assesses ease of application
10	Drug content uniformity	UV-Visible spectrophotometer	Ensures uniform drug distribution
11	*In vitro* drug release	Franz diffusion cell	Evaluates release kinetics
12	Ex vivo permeation	Excised cornea study	Assesses drug penetration ability
13	Stability studies	ICH guidelines	Determines shelf-life and formulation stability
14	Ocular irritation test	Draize test	Evaluates safety on ocular tissues
15	In vivo IOP reduction	Animal model study	Confirms therapeutic efficacy

9. Advantages over Conventional Systems

Niosomal gel-based ocular drug delivery systems offer several significant advantages over conventional formulations such as eye drops and ointments [53]. These benefits arise from the combined effects of vesicular encapsulation and gel-based retention, making them highly effective for glaucoma therapy.

Prolonged Drug Action

One of the major advantages of niosomal gel systems is their ability to provide sustained and controlled drug release. Niosomes act as drug reservoirs that release pilocarpine gradually over an extended period, while the gel matrix further slows down drug diffusion. This dual mechanism ensures prolonged therapeutic action and maintains effective drug concentration at the site of action for longer durations [54].

Reduced Dosing Frequency

Due to sustained drug release and enhanced ocular retention, the need for frequent administration is significantly reduced. Conventional eye drops often require multiple doses per day, whereas niosomal gel formulations can maintain therapeutic levels with fewer applications. This not only improves treatment efficiency but also minimizes the risk of missed doses [55].

Improved Patient Compliance

Frequent dosing and associated side effects of conventional formulations often lead to poor patient adherence, especially in elderly patients with glaucoma. Niosomal gel systems improve compliance by reducing dosing frequency and providing better comfort during application. The gel formulation also reduces drug washout, leading to a more convenient and effective therapy [56].

Enhanced Bioavailability

Conventional ocular formulations typically exhibit very low bioavailability due to rapid precorneal elimination and poor corneal permeability. Niosomal gels enhance drug absorption by increasing residence time on the ocular surface and facilitating better penetration through the cornea. This results in higher drug availability at the target site and improved therapeutic outcomes [57].

10. Limitations and Challenges

Despite the promising advantages of niosomal gel-based ocular drug delivery systems, several limitations and challenges must be addressed before their widespread clinical application.

Stability Issues

One of the major concerns associated with niosomal formulations is their physical and chemical stability. Niosomes may undergo aggregation, fusion, or leakage of the encapsulated drug during storage, which can affect their performance. Factors such as temperature, pH, and composition of surfactants can influence vesicle integrity. Additionally, gel formulations may experience changes in viscosity or phase separation over time. Therefore, careful optimization of formulation components and storage conditions is required to maintain stability [58].

Scale-up Difficulties

While niosomal gels show excellent results at the laboratory scale, their large-scale manufacturing presents challenges. Techniques such as thin film hydration and reverse phase evaporation may be difficult to reproduce consistently on an industrial scale. Maintaining uniform vesicle size, entrapment efficiency, and batch-to-batch reproducibility requires advanced equipment and strict process control. These challenges can increase production costs and limit commercial feasibility [59].

Limited Clinical Data

Although numerous in vitro and in vivo studies demonstrate the potential of niosomal gel systems, there is a lack of well-designed clinical trials to confirm their safety and efficacy in humans. Most available data are based on experimental or preclinical studies, which may not fully predict clinical outcomes. Regulatory approval also requires extensive clinical validation, which is currently limited.

Overall, addressing these challenges through formulation optimization, advanced manufacturing techniques, and

comprehensive clinical studies is essential for the successful translation of niosomal gel systems into clinical practice [60].

11. Future Perspectives

Niosomal gel-based ocular drug delivery systems have demonstrated significant potential in improving the therapeutic efficacy of pilocarpine; however, further advancements are required to translate these systems into routine clinical use. Future research is expected to focus on the development of more precise, efficient, and patient-friendly delivery strategies [61].

Targeted Ocular Delivery

Future approaches may involve surface modification of niosomes with ligands, antibodies, or bioadhesive polymers to achieve targeted delivery to specific ocular tissues such as the trabecular meshwork or ciliary body. This can enhance drug localization, reduce systemic exposure, and improve therapeutic outcomes while minimizing side effects [62].

Advanced Nanocarriers

The integration of niosomes with other advanced nanocarrier systems, such as nanoparticles, nanoemulsions, or dendrimers, may further enhance drug loading, stability, and penetration. Hybrid systems combining multiple delivery technologies could offer improved control over drug release and better interaction with ocular tissues [63].

Clinical Trials and Translation

A major focus for future development is the conduction of well-designed clinical trials to evaluate the safety, efficacy, and long-term performance of niosomal gel formulations in human subjects. Successful clinical validation will be essential for regulatory approval and commercialization of these systems [64].

Smart Stimuli-Responsive Gels

Emerging research is exploring the use of smart gels that respond to physiological stimuli such as temperature, pH, or ionic strength. These in situ gelling systems can undergo sol-to-gel transition upon administration, providing enhanced retention and controlled drug release. Such innovative systems have the potential to further improve patient compliance and therapeutic efficiency [65].

Conclusion

Niosomal gel-based ocular drug delivery systems represent a promising and innovative approach for the effective management of glaucoma. By combining the advantages of vesicular carriers and gel matrices, these systems significantly enhance the delivery of pilocarpine to ocular tissues. The incorporation of pilocarpine into niosomes enables sustained and controlled drug release, improved stability, and better penetration across ocular barriers. Furthermore, embedding these vesicles within a gel base increases precorneal residence time, reduces drug loss due to drainage, and enhances overall bioavailability.

Compared to conventional eye drop formulations, niosomal gels offer prolonged therapeutic action, reduced dosing frequency, and improved patient compliance. These benefits are particularly important in chronic conditions like glaucoma, where long-term treatment adherence is critical. Despite these advantages, challenges such as formulation stability, large-scale manufacturing, and limited clinical data remain significant barriers to their widespread clinical application.

Therefore, further research focusing on formulation optimization, advanced delivery strategies, and well-designed clinical trials is essential to establish their safety, efficacy, and commercial feasibility. With continued advancements, niosomal gel systems have the potential to emerge as a next-generation ocular drug delivery platform for improved glaucoma therapy.

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