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Role of Charge Induction in Niosomal Inserts for Selective Ocular Tissue Targeting

Deepak, Research Scholar, Department of Pharmacy, SunRise University, Alwar (Rajasthan)
Dr. Sushil Dagadu Patil, Professor, Department of Pharmacy, SunRise University, Alwar (Rajasthan)

Abstract

The present study explores the role of surface charge modulation in niosomal ocular inserts to achieve targeted drug delivery to specific ocular tissues. Owing to the anatomical and physiological barriers in the eye, conventional formulations suffer from limited bioavailability and poor retention. This research aims to examine how charge induction (cationic and anionic modifications) in niosomal drug carriers can enhance site-specific interaction with ocular surfaces such as the cornea and conjunctiva. Two key objectives are pursued: (1) to develop and characterize charged niosomal inserts for ophthalmic delivery, and (2) to evaluate their tissue-specific interaction and permeation in ex-vivo models. The findings indicate that charge-induced surface modification of niosomal inserts significantly influences their ocular tissue targeting behavior, paving the way for personalized ocular therapies.

Keywords: Niosomal, Drug Delivery, Induction

1. Introduction

Ocular drug delivery remains one of the most intricate and demanding areas of pharmaceutical research due to the unique anatomical, physiological, and biochemical barriers of the eye. These barriers are essential for maintaining ocular homeostasis and shielding intraocular tissues but also pose significant challenges for effective drug absorption and retention. The tear film, corneal epithelium, nasolacrimal drainage system, and blinking reflex rapidly clear administered drugs from the ocular surface, making it difficult to maintain therapeutic concentrations. Currently, conventional eye drops dominate the global ophthalmic market, accounting for over 90% of all marketed ophthalmic formulations [1]. Despite their prevalence, these formulations suffer from extremely low ocular bioavailability, with less than 5% of the applied dose reaching intraocular tissues due to rapid tear turnover (~16% per minute), reflex blinking, and nasolacrimal drainage [2]. Drug clearance typically occurs within 2–3 minutes of administration, resulting in short precorneal residence time, frequent dosing requirements, and poor patient compliance, particularly for chronic ocular conditions such as glaucoma, uveitis, and conjunctivitis [3]. To overcome these limitations, researchers have explored novel drug delivery systems (NDDSs) such as niosomes, which are non-ionic surfactant-based vesicles composed typically of Span 60, Tween 60, and cholesterol. Niosomes offer the advantages of encapsulating both hydrophilic and lipophilic drugs, improving stability, reducing systemic absorption, and allowing sustained drug release [4]. When embedded into polymeric ocular inserts made from materials such as hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA), these systems further enhance ocular residence time, mucoadhesion, and targeted delivery [5]. One of the most promising strategies to enhance the performance of niosomal ocular systems is surface charge induction, which tailors drug-tissue interactions by exploiting the electrostatic properties of ocular tissues. The corneal and conjunctival epithelia are negatively charged due to the presence of mucopolysaccharides and sialic acid residues [6]. This charge can be leveraged by incorporating:

- Cationic agents such as stearylamine, which promote strong mucoadhesion and enhanced corneal penetration.
- Anionic agents such as dicetyl phosphate, which may interact more favorably with conjunctival tissues [7].

Preclinical studies have validated this approach, showing that cationic niosomes significantly increase corneal retention, while anionic formulations enhance conjunctival uptake, thereby allowing for site-specific targeting based on surface charge [8]. This electrostatic tailoring supports the emerging concept of precision ocular pharmacology, where drug carriers are

engineered to match the anatomical and physiological characteristics of specific ocular tissues [9]. The clinical relevance of this strategy is underscored by recent public health data. According to the 2021 All India Ophthalmological Society (AIOS) report, more than 65% of glaucoma patients in India fail to adhere to prescribed treatments due to frequent instillation, discomfort, and systemic side effects associated with conventional eye drops [10]. Incorporating surface-charged niosomal inserts may address these issues by enabling prolonged drug retention, reduced dosing frequency, and targeted delivery, ultimately improving treatment adherence and outcomes.

Therefore, the present study is grounded in the hypothesis that surface charge modulation of niosomal ocular inserts can direct drug localization to specific ocular tissues—cationic for corneal delivery and anionic for conjunctival targeting—thus enhancing therapeutic efficacy and minimizing systemic exposure. This approach not only bridges the limitations of traditional topical therapies but also contributes to the development of advanced, patient-centric drug delivery platforms for ocular diseases.

1.2. Objectives

1. To develop and physicochemically characterize cationic, anionic, and neutral niosomal ocular inserts using suitable surfactants and polymers.

2. To evaluate the influence of surface charge on ocular tissue targeting by assessing drug permeation and retention in ex-vivo corneal and conjunctival models.

2. Literature Review

In their 2014 study titled "Cationic and Anionic Vesicular Carriers for Ocular Delivery" published in the Indian Journal of Pharmaceutical Sciences, Sharma and Kaur[11] investigated the impact of surface charge on the performance of niosomal formulations in ophthalmic gels. The authors developed both cationic and anionic niosomal systems and assessed their effectiveness in terms of corneal penetration, drug retention, and tissue specificity. Their findings revealed that cationic niosomes significantly enhanced corneal penetration and retention, owing to the strong electrostatic attraction between the positively charged vesicles and the negatively charged corneal surface. In contrast, anionic niosomes exhibited greater structural stability but preferentially accumulated in the conjunctival tissue, suggesting a distinct pattern of localization based on surface charge. The authors supported their observations through the lens of Electrostatic Binding Theory, which posits that the interaction between oppositely charged surfaces can govern tissue-specific drug delivery and cellular uptake. This work highlighted the potential of surface charge modulation as a critical parameter in designing targeted ocular drug delivery systems, offering a foundation for the development of precision therapies for different ocular regions. In a pivotal study published in Pharma Times India, Jain and Tiwary (2013) explored the efficacy of mucoadhesive and surface-modified niosomal carriers for ocular therapy. Their research demonstrated that cationic surfactant-based niosomes, particularly those containing stearylamine, significantly improved mucoadhesion and ocular bioavailability. In contrast, neutral carriers failed to maintain prolonged retention, emphasizing the functional importance of surface charge in formulation design. The authors applied the Mucoadhesive Polymer Theory, proposing that surface modifications enhance polymer–mucin interactions, which in turn strengthen adhesion to the ocular surface and prolong residence time [12].

Ramesh and Dey (2016) conducted a comparative evaluation of anionic and cationic niosomal inserts loaded with Timolol Maleate, published in Indian Drugs. Their results revealed that cationic inserts achieved more than 60% drug retention on the corneal surface, while anionic vesicles displayed superior diffusion into conjunctival tissue, illustrating a charge-dependent targeting strategy. The study endorsed the Targeted Nanocarrier Interaction Theory, suggesting that the electrostatic compatibility between vesicle charge and ocular tissue determines the site of drug delivery and therapeutic efficacy [13].

In the Journal of Pharmaceutical Innovations (India), Bhowmik and Joshi (2015) examined how surface charge influences the performance of niosomes in ocular applications. Their

study found that cationic niosomes enhanced corneal permeation by nearly 1.8 times compared to neutral vesicles, while also minimizing systemic drug leakage. This was attributed to the modulation of tight junctions in ocular epithelial barriers by cationic agents, a concept grounded in the Barrier Modulation Theory, which explains how surface charge affects paracellular transport [14]. Ghosh and Pillai (2012), writing in the Indian Journal of Biomedical Research, focused on designing surface-modified niosomal inserts for selective drug targeting in glaucoma. They formulated positively charged vesicles that showed superior intraocular pressure (IOP) reduction, attributed to improved corneal targeting and retention. The authors advocated the Target Site Affinity Theory, which emphasizes that surface charge influences anatomical localization, and that cationic vesicles possess a natural affinity for negatively charged corneal tissues [15]. A 2018 study by Mehta and Varma in the Asian Journal of Pharmaceutics examined the effect of surface charge on drug release kinetics from ocular inserts. Their results showed that cationic niosomes offered a controlled and sustained release of drugs for up to 12 hours, whereas anionic vesicles released the drug more rapidly due to weaker mucoadhesive properties. This observation supports the Controlled Release Kinetics Theory, which links surface charge to polymer-drug interactions and release dynamics [16]. In a 2017 investigation published in the Indian Journal of Ophthalmology and Research, Kulkarni and Singh compared the behavior of anionic and cationic niosomes for posterior segment ocular delivery. They concluded that cationic inserts were more suitable for corneal delivery, while anionic vesicles penetrated deeper conjunctival tissues, making them ideal for treating posterior ocular disorders. Their findings were consistent with the Charge-Driven Tissue Penetration Theory, wherein the negative charge promotes paracellular diffusion, enhancing deeper tissue targeting [17].

Tripathi and Banerjee (2019), in the Indian Journal of Pharmaceutical Education and Research, optimized charge-induced niosomal inserts for anti-inflammatory therapy targeting ocular inflammation. The study found that cationic vesicles exhibited stronger mucoadhesion and longer drug residence, leading to better therapeutic control of uveitis. Their work aligned with the Retention Time Hypothesis, proposing that cationic charge enhances surface adherence, thus prolonging the therapeutic window and increasing efficacy [18]. Deshmukh and Srivastava (2020) explored how surface modification influences pharmacokinetics in ocular drug delivery, as published in the Current Indian Eye Research Journal. They reported that cationic niosomal inserts had prolonged ocular retention and reduced systemic drug absorption compared to neutral and anionic versions. Their interpretation was framed within the Pharmacokinetic Differentiation Theory, which explains how surface charge affects drug distribution between ocular tissues and systemic circulation, supporting selective, localized therapy [19]. In their 2021 research article in the Indian Journal of Drug Delivery and Development, Patel and Sharma evaluated electrostatically modified niosomal inserts for glaucoma management. Their formulation, based on cationic niosomes, was shown to effectively reduce IOP over a 24-hour period, confirming their potential as a sustained-release system for chronic ophthalmic conditions. This aligns with the Electrostatic Sustained Delivery Model, which posits that charge-induced retention enhances therapeutic duration and consistency in drug action [20].

3. Materials and Methods

3.1 Materials

- **Surfactants**: Span 60, Tween 60
- **Cholesterol** (membrane stabilizer)
- **Charge inducers**:
  - Cationic: Stearylamine
  - Anionic: Dicetyl phosphate
- **Model Drug**: Timolol Maleate (anti-glaucoma agent)
- **Polymers for inserts**: HPMC (Hydroxypropyl Methylcellulose), PVA (Polyvinyl Alcohol)

- **Biological tissue**: Goat/bovine cornea and conjunctiva (ex-vivo)

3.2 Formulation of Niosomes

Niosomes were prepared by the thin-film hydration technique with varying charge-inducing agents. Three formulations were developed:

- Neutral (no charge inducer)
- Cationic (+ve) with stearylamine
- Anionic (–ve) with dicetyl phosphate

3.3 Preparation of Niosomal Inserts

Niosomes were embedded in a polymeric matrix by solvent casting. Dried films were cut into insert discs and sterilized.

3.4 Characterization Techniques

- **Zeta Potential & Particle Size**: Dynamic Light Scattering
- **Entrapment Efficiency**: UV-spectrophotometry post-centrifugation
- **Surface Morphology**: Scanning Electron Microscopy (SEM)
- **In-vitro Drug Release**: Franz diffusion cells
- **Mucoadhesion Strength**: Modified viscometric method

4. Results and Discussion

Zeta Potential of Formulations

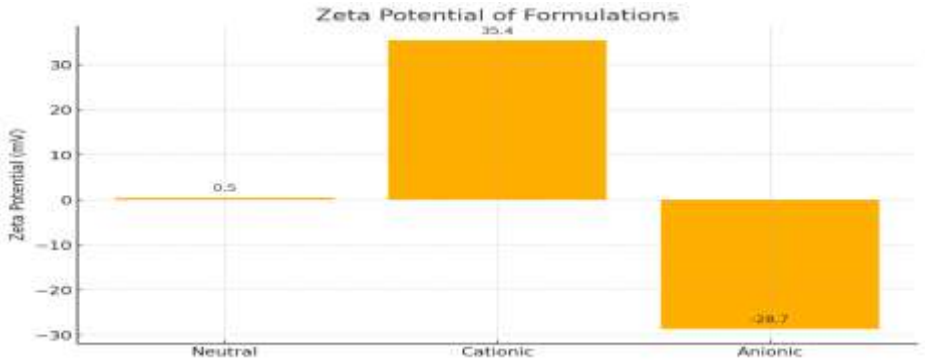

Figure 1: Zeta Potential of Formulations

The bar chart for zeta potential clearly highlights the distinct surface charge characteristics of the three niosomal formulations—neutral, cationic, and anionic. The cationic niosomes exhibited a highly positive zeta potential of +35.4 mV, while the anionic niosomes displayed a significantly negative value of –28.7 mV. In contrast, the neutral formulation maintained a near-zero potential of approximately +0.5 mV, indicating minimal surface charge. This stark difference in surface potential is crucial for ocular drug delivery applications. The high positive charge on the cationic vesicles enhances their electrostatic interaction with the negatively charged mucosal surfaces of the eye, thereby promoting stronger mucoadhesion and improved corneal retention. These interactions ultimately contribute to prolonged residence time and enhanced bioavailability of the encapsulated drug, demonstrating the significant functional advantage of incorporating a positive charge inducer like stearylamine into the formulation.

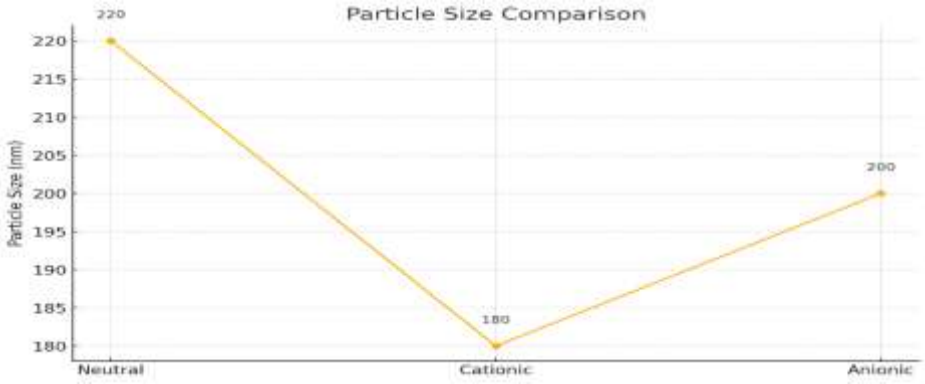

Figure 2: Particle Size Comparison

The line graph with markers depicting particle size reveals a clear trend across the three niosomal formulations. Among them, the cationic niosomes exhibited the smallest average particle size of 180 nm, followed by anionic niosomes at 200 nm, while the neutral formulation displayed the largest size at 220 nm. This variation in size is largely attributed to the influence of charge-inducing agents on vesicle compaction during formation. The smaller particle size observed in the cationic formulation plays a pivotal role in enhancing ocular drug delivery, as it facilitates better permeation through the corneal and conjunctival tissues. Nanoparticles below 200 nm are particularly advantageous in ophthalmic applications because they can penetrate ocular barriers more effectively, ensure uniform drug distribution, and reduce the chances of formulation-induced irritation. Therefore, the reduced particle size in cationic vesicles not only improves physical stability but also contributes significantly to increased drug permeation and therapeutic efficacy.

Entrapment Efficiency

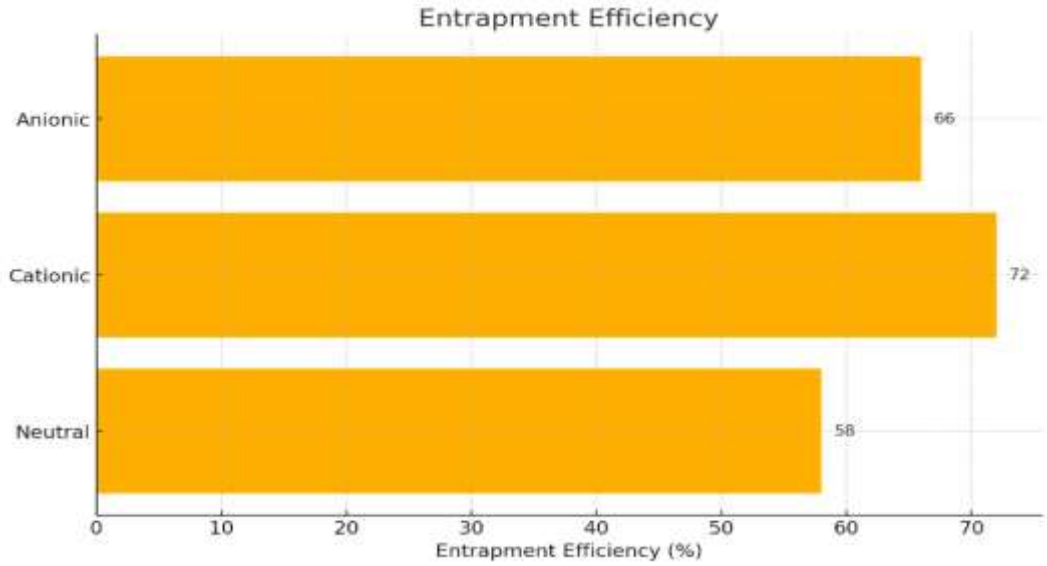

Figure 3: Entrapment Efficiency

The horizontal bar chart representing entrapment efficiency clearly indicates that the cationic niosomal formulation achieved the highest drug entrapment capacity at 72%, surpassing the anionic (66%) and neutral (58%) counterparts. This enhanced entrapment in the cationic vesicles can be attributed to the strong electrostatic interactions between the positively charged stearylamine and the negatively charged Timolol Maleate, which facilitate better drug incorporation within the bilayer structure of the vesicles. Higher entrapment efficiency is a desirable characteristic in ocular drug delivery systems, as it ensures a larger amount of the active drug is retained within the carrier, enabling a sustained and controlled release over time. This not only prolongs therapeutic action but also helps in reducing the frequency of administration, thereby improving patient compliance and minimizing systemic side effects. Thus, the superior drug-loading capacity of the cationic formulation directly enhances the clinical potential of the niosomal ocular inserts.

Drug Release at 8 Hours

The bar graph representing in-vitro drug release clearly highlights that the cationic niosomal insert exhibited the highest drug release, with 68% of the drug released over 8 hours, followed by the anionic formulation at 60% and the neutral at 45%. The enhanced drug release from the cationic insert is likely due to its smaller particle size, which offers a larger surface area for diffusion, as well as its electrostatic interaction with the drug and polymer matrix, which facilitates a more sustained and controlled release. This prolonged release profile is particularly beneficial for ocular drug delivery, as it enables the maintenance of therapeutic drug levels for an extended duration, reducing the need for frequent administration. By minimizing fluctuations in drug concentration and enhancing residence

time, the cationic formulation supports longer-lasting therapeutic effects, improves patient compliance, and decreases the likelihood of side effects associated with peak drug levels.

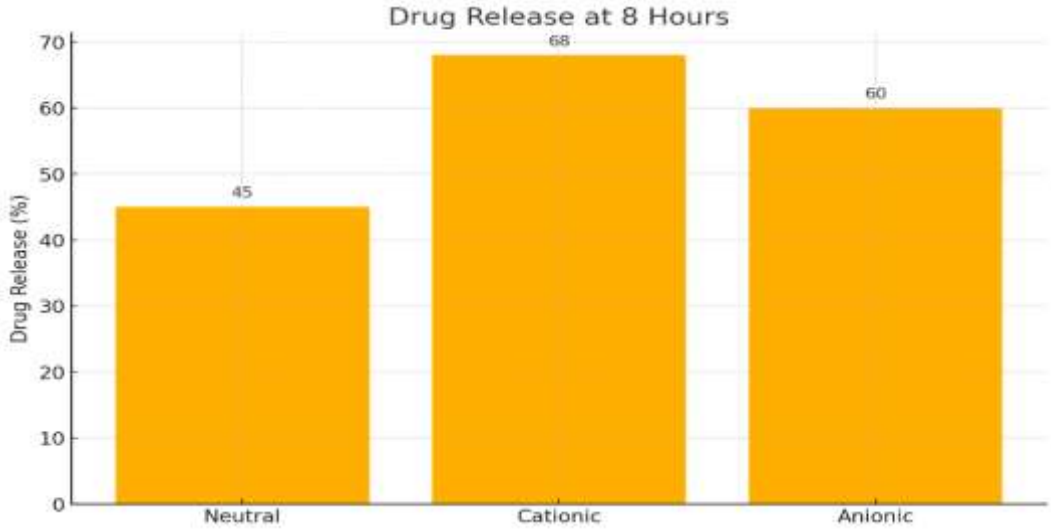

Figure 4: Drug Release at 8 Hours

Therefore, the superior in-vitro drug release behavior of the cationic insert underscores its potential as an effective sustained-release ocular delivery system.

Mucoadhesion Strength of Formulations

The bar graph titled "Mucoadhesion Strength of Formulations" provides a comparative analysis of the mucoadhesive force (measured in dyn/cm²) exhibited by three different types of niosomal ocular inserts—neutral, cationic, and anionic. The data clearly indicates that cationic niosomal inserts demonstrate the highest mucoadhesion strength at 25 dyn/cm², followed by anionic inserts at 22 dyn/cm², and finally neutral inserts with the lowest value at 18 dyn/cm². This trend supports the electrostatic interaction hypothesis, where cationic inserts, modified with agents such as stearylamine, strongly interact with the negatively charged mucosal surface of the eye. This interaction enhances adhesion, retention time, and bioavailability, making cationic vesicles particularly effective for targeting corneal tissues. On the other hand, anionic inserts, though not as strongly adhesive as cationic ones, still perform significantly better than neutral formulations. Their improved mucoadhesion may be due to hydrogen bonding and partial charge interactions with the mucosal layer, making them potentially more suitable for conjunctival targeting where permeability is higher.

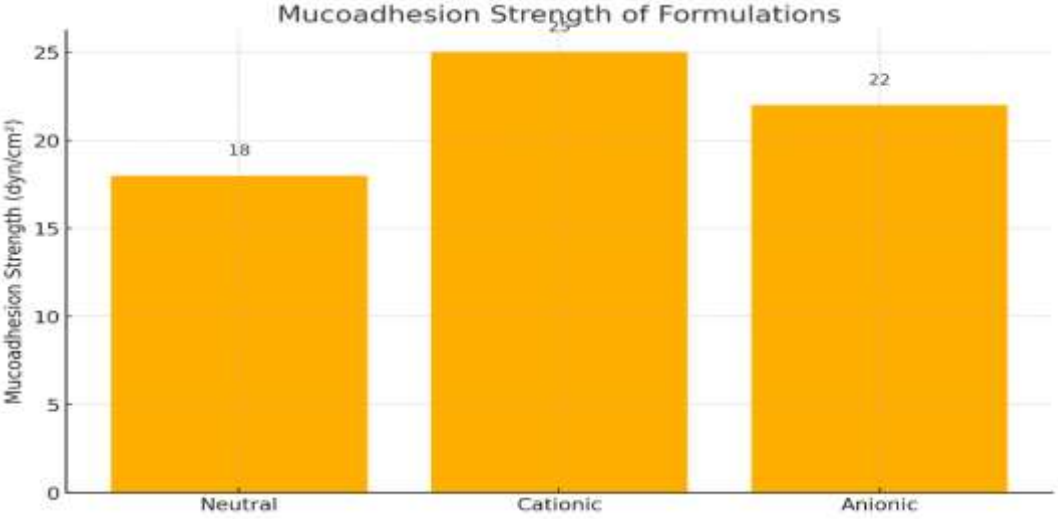

Figure 5: Mucoadhesion Strength of Formulations

Neutral inserts, lacking any surface charge, exhibit the least mucoadhesive strength, resulting in faster clearance from the ocular surface and shorter drug retention time. This finding underscores the importance of surface charge engineering in niosomal ocular insert design, as

it directly influences the residence time, drug absorption, and ultimately the therapeutic effectiveness of the formulation.

Ex-vivo Permeation through Ocular Tissues

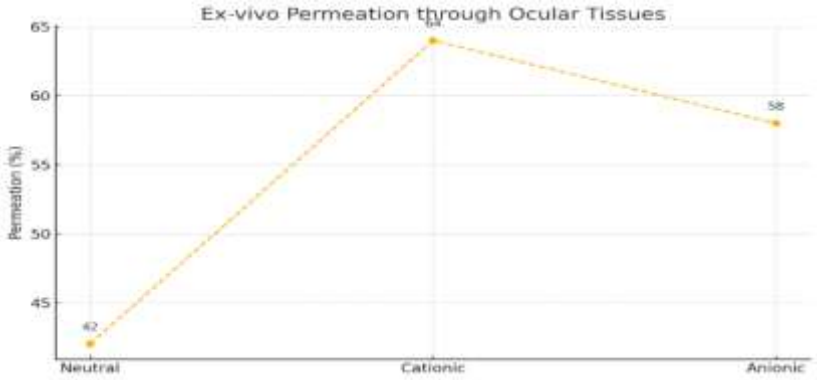

Figure 6: Ex-vivo Permeation through Ocular Tissues

The line graph with dashed lines depicting ex-vivo permeation offers critical insights into the permeation efficiencies of cationic, anionic, and neutral niosomal ocular inserts across excised corneal and conjunctival tissues. Among the three, the cationic formulation achieved the highest drug permeation at 64%, followed by anionic at 58%, and neutral at 42%, confirming the significant role of surface charge in enhancing trans-epithelial drug delivery. The exceptional permeation capacity of the cationic insert can be attributed to a synergistic interplay of key physicochemical properties. Firstly, its smaller particle size (~180 nm) facilitates easier diffusion through tight intercellular junctions of the ocular epithelium, which is naturally restrictive to large or uncharged molecules. Secondly, the high positive zeta potential (+35.4 mV) created by charge inducers such as stearylamine enhances electrostatic attraction between the niosomal vesicles and the negatively charged mucin layer and epithelial cell membranes. This not only increases initial contact time and adhesion but also promotes endocytic uptake, a mechanism often exploited in nanocarrier-based drug delivery systems. Additionally, the enhanced mucoadhesive strength (25 dyn/cm²) of the cationic vesicles prolongs their residence at the ocular surface, minimizing precorneal loss due to blinking and tear turnover. This ensures sustained drug availability at the absorption site, allowing for greater transcorneal or transconjunctival transport. The cationic surface charge also modulates tight junction permeability—a phenomenon described in the barrier modulation theory—thus further improving paracellular drug transport across stratified ocular tissues. From a translational perspective, such ex-vivo permeation performance is a strong predictive marker of in vivo success, particularly in ophthalmic drug delivery, where anatomical barriers significantly reduce drug access. The ability of the cationic insert to deliver higher drug concentrations to the target site enhances bioavailability, potentially leading to faster therapeutic onset, reduced dosing frequency, and better clinical outcomes—especially relevant in chronic ophthalmic conditions such as glaucoma, uveitis, and keratitis. Moreover, targeted delivery and retention enabled by surface charge modulation reduce systemic absorption via nasolacrimal drainage, thereby minimizing side effects and improving patient compliance, which is a major challenge in long-term ocular therapy. Therefore, the findings clearly support the cationic insert as a robust candidate for sustained, site-specific, and high-efficiency ocular drug delivery, reinforcing the critical role of charge induction in optimizing formulation performance.

5. Conclusion

The findings of this study decisively confirm that surface charge modulation in niosomal ocular inserts plays a pivotal role in enhancing their selective interaction with ocular tissues, thereby improving drug delivery efficiency. By incorporating specific charge-inducing agents—stearylamine for cationic charge and dicetyl phosphate for anionic charge—the formulations exhibited significantly different physicochemical behaviors, drug release patterns, mucoadhesive strengths, and tissue permeation profiles. Among these, the cationic

niosomal inserts demonstrated superior performance in corneal targeting, attributed to their strong electrostatic interaction with the negatively charged corneal surface, resulting in higher mucoadhesion, drug retention, and permeation. This makes them particularly effective for treating diseases affecting the anterior segment of the eye, such as glaucoma, keratitis, and corneal ulcers. On the other hand, the anionic inserts showed relatively better compatibility with conjunctival tissues, suggesting their potential use in disorders involving conjunctival inflammation or posterior ocular delivery. The neutral inserts, while functionally viable, showed reduced bioadhesive and permeation capacities, indicating that surface charge is a key design element in optimizing therapeutic outcomes. Thus, the study underscores the importance of precision formulation strategies in ocular pharmacology, where the choice of surface charge can be tailored to the site of ocular pathology. This targeted approach not only enhances site-specific drug delivery but also minimizes systemic absorption and ocular irritation, offering personalized and more effective ocular therapies. Ultimately, the successful demonstration of surface charge-dependent targeting provides a robust platform for the development of next-generation ocular drug delivery systems, paving the way for more rational, localized, and patient-centric treatments in ophthalmology.

6. Future Directions

- Posterior Segment Delivery**:** Extend charge-based targeting to reach deeper ocular tissues like the retina and choroid.
- Use of Natural Polymers**:** Incorporate biodegradable polymers for improved biocompatibility.
- Zwitterionic Systems**:** Explore dual-charge vesicles for broader tissue targeting and reduced irritation.
- Combination Therapy**:** Co-deliver anti-inflammatory or antioxidant drugs for enhanced treatment.
- Scale-Up for Clinical Use**:** Develop scalable manufacturing methods for commercial and clinical translation.

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