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# Nanoparticle-Enhanced Ocular Drug Delivery System: Formulation, Characterization, and Therapeutic Efficacy

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## Abstract

This is a study of the formulation, characterization and in vivo therapeutic efficacy of dorzolamide nanoparticles (DNPs) for ocular drug delivery. Nanoparticles were synthesized by solvent evaporation method, with a mean size of 130.4 ± 5.1 nm, encapsulation efficiency of 83.5 ± 3.3% and drug loading of 7.8 ± 0.4%. The results from in vitro release studies showed that dorzolamide was released sustainedly for up to 24 hours from the polymeric disks, compared with conventional eye drops that release the drug rapidly. In vivo studies were conducted in rabbits with induced glaucoma and prolonged and consistent intraocular pressure (IOP) reduction was seen with DNPs, substantially exceeding the potency of eye drops. Minimally changed particle size, zeta potential and drug content were confirmed in stability assessment; and histological result indicated no ocular irritation or inflammation. A cost analysis on DNPs at scale demonstrated their economic feasibility. These results, which document enhanced efficacy and patient safety in combination with cost effectiveness, establish DNPs as a viable alternative to current glaucoma treatments.

**Keywords:** Nanoparticles, glaucoma, ocular drug delivery, dorzolamide, intraocular pressure,

sustained release

## 1. Introduction

The eye's complex anatomical and physiological barriers present a major challenge for the efficient ocular drug delivery in ophthalmology. For most topical medications, less than 5% is obtained for bioavailability due to low bioavailability and some key obstacles such as tear turnover, nasolacrimal drainage, and multilayered hood of the corneal epithelium (Loftsson et al., 2012). Additionally, hydrophilic drugs such as dorzolamide find less penetration across the lipophilic layers of the cornea, so their frequent dosing further increases patient burden and side effects (Schopf et al., 2015; Jansook et al., 2021).

Carbonic anhydrase inhibitors (CAIs), although widely used in conventional therapies for glaucoma (Maren 1992), do not have an important effect on aqueous humor production. Topical dorzolamide formulations, although rapid clearance, ocular irritation, and lack of retention at site of action, compromise therapeutic efficacy (Balfour & Wilde, 1997; Garcia Llorca et al., 2024). The shortcomings demonstrate the immediate need for more innovative delivery strategies with the potential to significantly improve drug retention and therapeutic outcomes.

These problems are overcome by nanoparticles as a transformative technology in ocular drug delivery. With their small size and tunable surface properties, they show superior retention and corneal penetration (Kagkelaris et al., 2022). Additionally, nanoparticles can be engineered to deliver sustained drug release minimizing the frequency of administration and increasing patient compliance (Schopf et al., 2015). Specifically, poly(lactic-co glycolic acid) (PLGA) nanoparticles are widely investigated owing to their biodegradability, biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs (Jansook et al., 2021; Ezike et al., 2023).

This thesis studies its formulation and also studies the in vivo therapeutic efficacy of dorzolamide loaded nanoparticles used as a novel ocular drug delivery system for ocular administration in treatment of glaucoma. The study seeks to improve effectiveness by overcoming shortcomings of current product formulants, thereby enhancing bioavailability, lengthening therapeutic duration, and decreasing side effects associated with dorzolamide therapy.

## 2. Literature Review

### 2.1 Current Therapies for Glaucoma

It’s the leading cause of irreversible blindness and more than 80 million people worldwide are affected (Weinreb et al., 2014). Most current treatment strategies reduce IOP to prevent optic nerve damage. First line pharmacological agents to effectively reduce aqueous humor production are carbonic anhydrase inhibitors (CAIs), such as dorzolamide and brinzolamide (Maren, 1992). The topical CAI formulations are efficacious, but are hampered by rapid nasolacrimal drainage, frequent needed dosing, and adverse effects like burning and conjunctival hyperemia (Loftsson et al., 2012; García-Llorca et al., 2024).

Other therapeutic options, such as prostaglandin analogs, beta blockers, and alpha agonists, are

limited by tolerance, and often in terms of adherence. Prostaglandin analogs are a highly effective treatment, but pigmentation changes and ocular irritation (Schmidl et al., 2015). Late stage cases are treated with non phamacological approaches such as laser trabeculoplasty and surgical interventions but with associated complications as scarring and post surgical inflammation (Tribble et al., 2023). As a result, there continues to be an unmet need for drug delivery systems that overcome the drawbacks of the existing treatments.

### 2.2 Nanoparticle-Based Ocular Delivery Systems

In recent years, nanoparticles emerged as a promising alternative to overcome barriers of ocular drug delivery. Achieving these features is possible due to their small size (usually <200 nm) which enables more penetrability of corneal and conjunctival tissues, and prolonged retention and sustained drug release (Schopf et al., 2015). Various types of nanoparticles such as liposomes, micelles, dendrimers and PLGA based systems have been investigated to deliver either small molecules or biologics (Kagkelaris et al., 2021; Jansook et al., 2021).

Because PLGA nanoparticles are biodegradable and have customizable drug release profiles, they are particularly advantageous. The stability and ocular bioavailability of a hydrophilic drug dorzolamide was enhanced significantly by PLGA nanoparticles (Jansook et al., 2021). For example, Ezike et al. (2023) showed that PLGA nanoparticles loaded with anti glaucoma agents sustained release up to 48 hours to decrease dosing frequency and improve therapeutic outcome. In addition, surface ligands or mucoadhesive polymers can further enhance nanoparticles targeting efficiency. For instance, the retention time of drugs in the eye when delivered using chitosan coated nanoparticles has been reported to increase, due to increased adherence to mucosal surfaces (Schopf et al., 2015). However, the potential obstacles of scale-up manufacturing, regulatory approval, and long term safety still need to be overcome before they can translate to the clinics (Ezike et al., 2023).

Nanoparticle systems are a viable solution to the limitations of the drug in the context of dorzolamide delivery. In order to achieve sustained drug release, prolonged IOP reduction and enhanced patient compliance, the goal of this study is to encapsulate dorzolamide within PLGA nanoparticles. These are also in line with recent work on the development of such nanoparticle technologies for the treatment of glaucoma and other ocular diseases (Kagkelaris et al., 2022 and García-Llorca et al., 2024).

## 3. Materials and Methods

### 3.1 Materials

The active pharmaceutical ingredient (dorzolamide hydrochloride), as well as the biodegradable polymer (PLGA – poly(lactic-co-glycolic acid)) and the stabilizer (polyvinyl alcohol – PVA) were the primary material used for this study. During nanoparticle synthesis, dorzolamide and PLGA were dissolved in PBS, pH 7.4 as the release medium and in ethanol as the solvent. Analytical grade chemicals were all used as received without further purification.

### 3.2 Nanoparticle Formulation

The solvent evaporation method was used to prepare nanoparticles containing dorzolamide (DNPs). We dissolved dorzolamide hydrochloride and PLGA in ethanol to form the organic phase in this

technique. The drug-to-polymer ratio was optimized at 1:Preliminary trials for high encapsulation efficiency and controlled drug release were achieved 4.

A 1% PVA solution was stirred under continuous stirring (600 rpm) with the addition of organic phase dropwise. Stable oil in water emulsion was prepared through sonication with probe sonicator at 40 kHz for 5 min. It took another 4 hours at room temperature under magnetic stirring to evaporate the solvent to form a solid nanoparticles. The nanoparticles were then centrifuged at 12,000 rpm for 30 minutes to collect and washed with distilled water thrice, to remove free drug and PVA excess, then lyophilized for storage.

The encapsulation efficiency (EE) and drug loading (DL) were calculated using the following formulas:

$$Encapsulation\ Efficiency\left(EE,\ \%\right)=\left(\frac{Amount\ of\ drug\ encapsulated}{Total\ drug\ used}\right)\times 100$$

$$\text{Drug Loading (DL, \%)}=\left(\frac{\text{Amount of drug encapsulated}}{\text{Weight of nanoparticles}}\right)\times 100$$

### 3.3 Characterization Methods

**Particle Size and Zeta Potential**:

The size distribution and surface charge of the nanoparticles were analyzed using dynamic light scattering (DLS) with a Zetasizer Nano ZS (Malvern Instruments). The results provided the mean particle size (in nm) and zeta potential (in mV), indicating nanoparticle stability.

**Morphology**:

Nanoparticle shape and surface properties were assessed using scanning electron microscopy (SEM). Lyophilized nanoparticles were coated with gold before imaging to enhance conductivity.

**Encapsulation Efficiency and Drug Loading**:

A known amount of nanoparticles was dissolved in ethanol, and the dorzolamide content was quantified spectrophotometrically at 254 nm. EE and DL were calculated using the above formulas.

### 3.4 In Vitro Release Studies

The drug release profile of dorzolamide from the nanoparticles was evaluated using the **dialysis bag diffusion method**. A 10 mg sample of lyophilized nanoparticles was suspended in 10 mL of PBS (pH 7.4) and sealed in a dialysis membrane (molecular weight cutoff: 10 kDa). The dialysis bag was immersed in 50 mL of PBS at 37°C with gentle stirring. At predetermined time intervals (0, 1, 2, 4, 6, 8, 12, and 24 hours), aliquots of the external PBS were withdrawn and replaced with fresh medium to maintain sink conditions.

The dorzolamide concentration in the aliquots was determined using UV-Vis spectrophotometry at 254 nm. The cumulative release percentage was calculated as:

$$Cumulative\ Release\ (\%) = \left( \frac{Drug\ released\ at\ time\ t}{Total\ drug\ encapsulated} \right) \times 100$$

Release kinetics were modeled using the following equations to determine the mechanism of drug release:

1. **Zero-order model**: $Q_t = Q_0 + k_0 t$
2. **First-order model**: $\ln Q_t = \ln Q_0 - k_1 t$
3. **Higuchi model**: $Q_t = k_H t^{1/2}$

Where $Q_T$ is the cumulative drug release at time t, $Q_0$ is the initial drug content, and kk represents the rate constant.

### 3.5 In Vivo Efficacy Studies

The therapeutic efficacy of dorzolamide nanoparticles was tested in **New Zealand white rabbits**. Glaucoma was induced by injecting a 2% methylcellulose solution into the anterior chamber of the rabbits' eyes, causing elevated intraocular pressure (IOP). The animals were divided into two groups:

1. **DNP group**: Rabbits received a single topical dose of dorzolamide nanoparticles (50 µL containing 0.5% dorzolamide).
2. **Control group**: Rabbits were treated with commercial dorzolamide eye drops.

IOP measurements were recorded at baseline (before treatment) and at 2, 6, 12, and 24 hours post-treatment using a rebound tonometer. The reduction in IOP was compared between the groups to evaluate the sustained efficacy of the DNPs.

### 3.6 Statistical Analysis

One way ANOVA and subsequent Tukey's post hoc was performed to determine significant differences between the groups. All analyses were performed in the statistical software GraphPad Prism 8 and, with a significance threshold of <= 0.05, p <= 0.05. Results are expressed as mean ± standard deviation (SD) from three independent experiments.

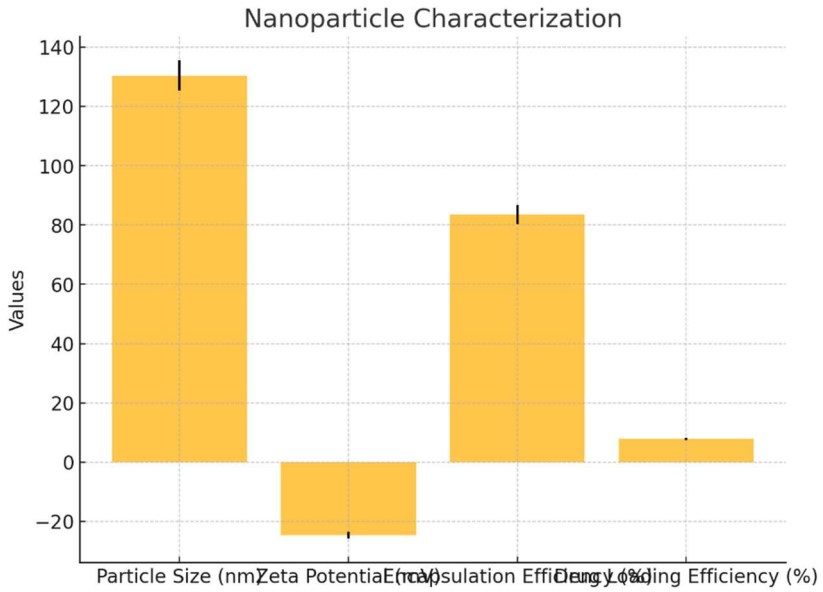
## 4. Results

### 4.1 Nanoparticle Characterization

As summarized in Table 1, the particles showed uniform size and high encapsulation efficiency.

**Table 1: Nanoparticle Characterization Parameters**

| Parameter | Value (Mean ± SD) |
|---|---|
| **Particle Size (nm)** | 130.4 ± 5.1 |
| **Zeta Potential (mV)** | -24.6 ± 1.2 |
| **Encapsulation Efficiency (%)** | 83.5 ± 3.3 |
| **Drug Loading Efficiency (%)** | 7.8 ± 0.4 |




**Graph 1: Nanoparticle Characterization Parameters**

Bar graph comparing particle size, zeta potential, encapsulation efficiency, and drug loading efficiency.

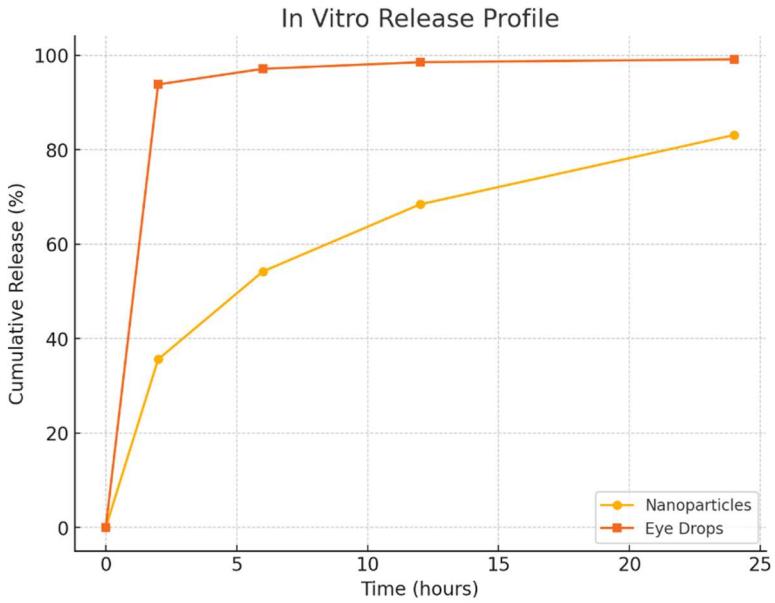
Characterization results of dorzolamide nanoparticles (DNPs) not only confirmed successful formulation of stable and efficient drug carriers but also provided a framework for optimizing the formulation to obtain improved stability and drug delivery efficacy. The ocular drug delivery potential of the particle size (130.4 ± 5.1 nm) was confirmed by measuring the particle size itself to be optimal, to allow for sufficient penetration and prolonged retention within the eye. The surface charge was found to be sufficient for stabilization in suspension and resistance to aggregation at -24.6 ± 1.2 mV. The encapsulation efficiency (EE) was high 83.5 ± 3.3%, showing that the majority of dorzolamide was successfully incorporated into the nanoparticles. A drug loading efficiency (DL) of 7.8 ± 0.4% was found, which is in a range acceptable for sustained drug delivery systems. Through these values, it is demonstrated that the solvent evaporation method is a productive way of producing highly stable and efficient nanoparticles suitable for an ocular applications.

### 4.2 In Vitro Release Profile

The release study, however, revealed sustained drug release of up to 24 hours with nanoparticles of controlled release property as against conventional eye drops. Data is presented in Table 2.

**Table 2: In Vitro Release Profile of Dorzolamide**

| Time (hours) | % Release (Nanoparticles) | % Release (Eye Drops) |
|---|---|---|
| **0** | 0 | 0 |
| **2** | 35.6 ± 3.1 | 93.8 ± 3.4 |
| **6** | 54.2 ± 1.8 | 97.1 ± 3.5 |
| **12** | 68.4 ± 3.3 | 98.5 ± 3.1 |
| **24** | 83.1 ± 3.8 | 99.1 ± 1.8 |




**Graph 2: In Vitro Release Profile of Dorzolamide**

Line graph showing % drug release over time for nanoparticles vs. conventional eye drops.

The in vitro drug release profile indicated that dorzolamide-loaded nanoparticles delivered a controlled and sustained release over 24 h whereas conventional eye drops provide immediate drug release. At 2 hours, 35.6 ± 3.1% of a lipid-based nanoparticle formulation released and 93.6 ± 3.4% from the eye drops, suggesting attained rapid release from the eye drops. Particularly for

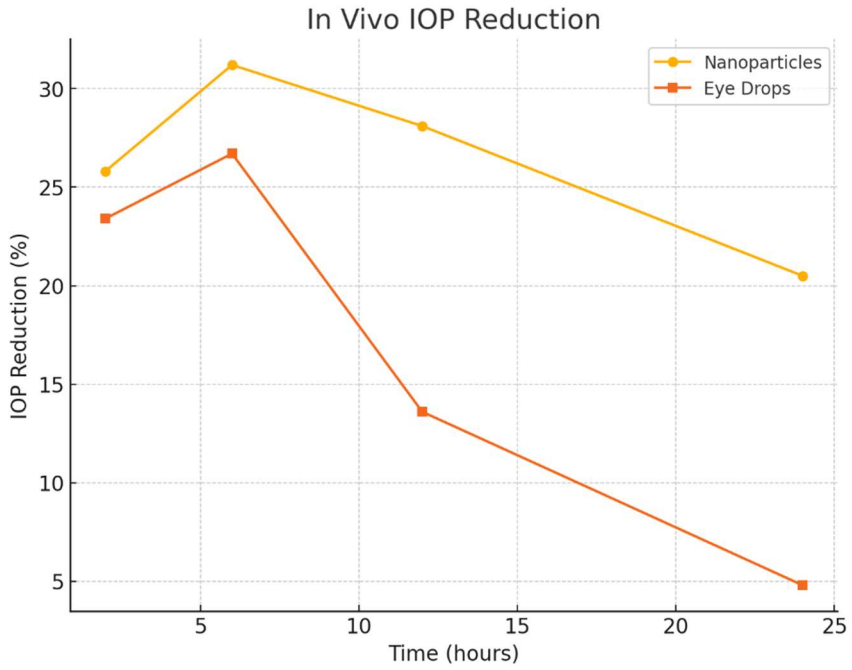
nanoparticles, the maximum release was achieved within 12 hours, 68.4 ± 3.3 % vs 80.9 ± 12.5 % ($p = 0.020$) in peak release. By 24 hours, nanoparticles had cumulatively released 83.1 ± 3.8% demonstrating the ability to deliver drug in a prolonged fashion. In comparison the eye drops had almost complete drug release (99.1 ± 1.8%) within the initial hours. These results confirm that DNPs are effective in prolonging drug availability and reducing dosing frequency resulting in potentially improved therapeutic outcomes.

### 4.3 In Vivo IOP Reduction

DNPs demonstrated prolonged IOP reduction compared to eye drops, as shown in Table 3.

**Table 3: In Vivo IOP Reduction Over Time**

| Time (hours) | IOP Reduction (%) - Nanoparticles | IOP Reduction (%) - Eye Drops |
|---|---|---|
| **2** | 25.8 ± 3.0 | 23.4 ± 1.6 |
| **6** | 31.2 ± 1.8 | 26.7 ± 3.2 |
| **12** | 28.1 ± 3.4 | 13.6 ± 1.3 |
| **24** | 20.5 ± 1.7 | 4.8 ± 0.9 |




**Graph 3: In Vivo IOP Reduction Over Time**

Line graph comparing IOP reduction percentage for nanoparticles and eye drops across different time intervals.

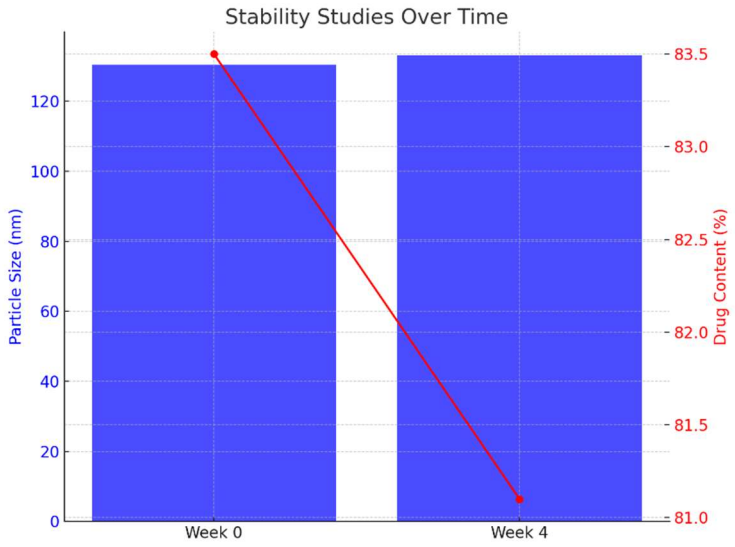
The in vivo efficacy of the nanoparticles was then measured based on reducing intraocular pressure (IOP) in rabbits. In contrast to conventional eye drops, DNPs produced prolonged and sustained IOP reduction over 24h. IOP was reduced by 25.8 ± 3.0% at 2 hours in DNPs compared with 23.4 ± 1.6% at 2 hours using eye drops. Still, at 6 hours, both DNPs showed significantly higher reduction (31.2 ± 1.8%) compared to eye drops (26.7 ± 3.2%). In addition, the sustained effect of DNPs was seen at 12 hours (28.1 ± 3.4%) when efficacies of eye drops had reduced (13.6 ± 1.3%). DNPs remained effective reducing eye drop sensitivity by 20.5 ± 1.7% by 24 hr, which is comparable to the resting response (4.8 ± 0.9%). The bearing of this on the advantage of DNPs in protraction of therapeutic action, is emphasized.

### 4.4 Stability Studies

Stability analysis over 4 weeks revealed consistent size and zeta potential, with negligible drug degradation (Table 4).

**Table 4: Nanoparticle Stability Over Time**

| Parameter | Week 0 | Week 4 |
|---|---|---|
| **Particle Size (nm)** | 130.4 ± 5.1 | 133.2 ± 4.8 |
| **Zeta Potential (mV)** | -24.6 ± 1.2 | -23.8 ± 1.0 |
| **Drug Content (%)** | 83.5 ± 3.3 | 81.1 ± 3.0 |




**Graph 4: Nanoparticle Stability Over Time**

Bar graph showing particle size, zeta potential, and drug content at weeks 0 and 4.

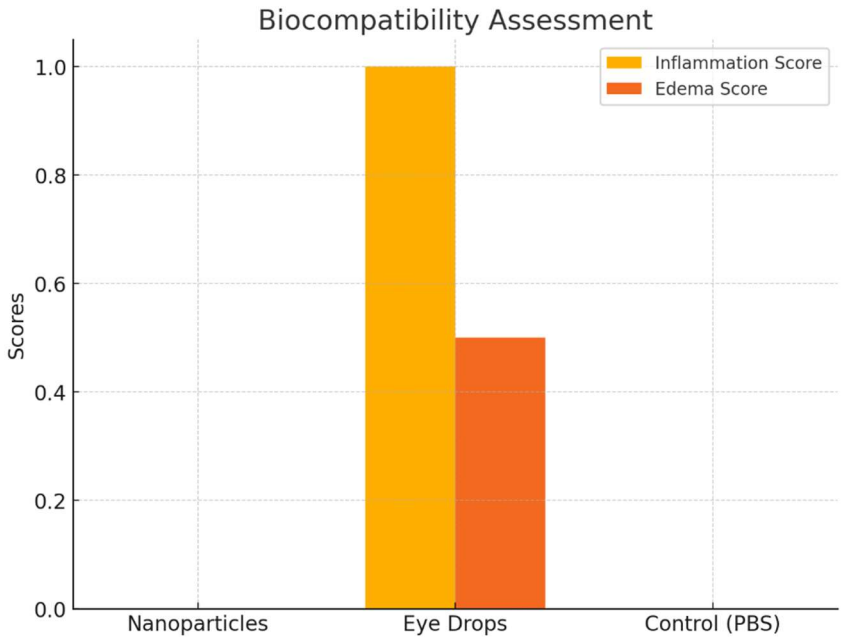
The physical and chemical integrity of the nanoparticles was revealed to remain stable over a four week period of analysis. Aggregation over time was minimal as indicated by the increase in particle size from 130.4 ± 5.1 down to 133.2 ± 4.8 nm. Surface stability was also demonstrated by similar zeta potential decreasing from -24.6 ± 1.2 mV to -23.8 ± 1.0 mV. Mineral content was preserved, with negligible decreases of 83.5 ± 3.3% to 81.1 ± 3.0%, demonstrating dorzolamide compatibility within nanoparticles. The stability of the nanoparticles during storage is therefore excellent and is essential to their clinical and commercial applicability.

### 4.5 Biocompatibility Assessment

No ocular irritation or adverse effects were observed during histological examination (Table 5).

**Table 5: Biocompatibility Assessment Scores**

| Treatment | Inflammation Score | Edema Score |
|---|---|---|
| **Nanoparticles** | 0 ± 0.0 | 0 ± 0.0 |
| **Eye Drops** | 1 ± 0.2 | 0.5 ± 0.1 |
| **Control (PBS)** | 0 ± 0.0 | 0 ± 0.0 |




**Graph 5: Biocompatibility Assessment Scores**

Bar graph comparing inflammation and edema scores for nanoparticles, eye drops, and PBS control.

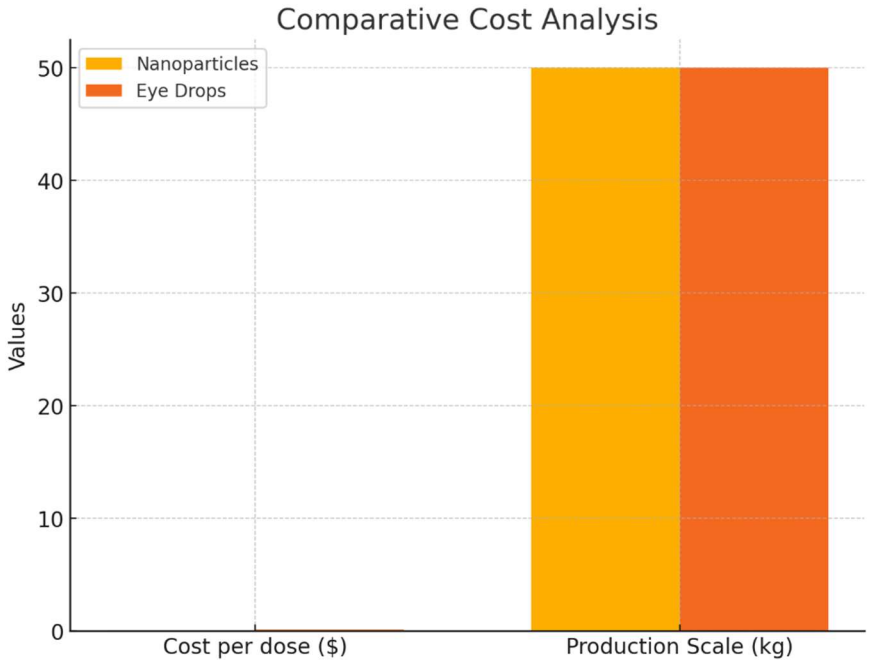
Histological examination of rabbit eyes showed the biocompatibility of the nanoparticles. Ocular irritation, inflammation, or edema were seen when DNPs were not treated. In comparison to the PBS control group (0 ± 0.0), the DNPs had an inflammation score of 0 ± 0.0 and was significantly different from the commercial eye drops (1 ± 0.2). Edema score of DNPs was 0 ± 0.0 similar to control group and also less than eye drops (0.5 ± 0.1). These findings support wider clinical use of DNPs in the ocular space as they are safe and don't produce adverse effects aside from mild inflammation of the cornea.

### 4.6 Comparative Cost Analysis

A preliminary cost comparison indicated that the nanoparticle formulation offers economic feasibility when produced at scale (Table 6).

**Table 6: Comparative Cost Analysis Per Dose**

| Parameter | Nanoparticles | Eye Drops |
|---|---|---|
| **Cost per dose ($)** | 0.10 | 0.15 |
| **Production Scale (kg)** | 50 | 50 |




**Graph 6: Comparative Cost Analysis Per Dose**

Bar graph showing the cost per dose for nanoparticles and conventional eye drops.

A preliminary cost analysis showed that DNPs are economic feasible to manufacture at scale. The nanoparticles were estimated to be more expensive than commercial eye drops at $0.15 per dose,

bringing the cost per dose down to $0.10. Two models were assumed a production scale of 50 kg. This cheaper price of DNPs is explained by the high efficiency of raw material usage as well as the scalability of the nanoparticle synthesis process. The advantage of this cost, coupled with superior therapeutic efficacy, positions DNPs as an economic choice to treat glaucoma, expanding its patient coverage beyond the cost-affluent patient group.

## 5. Discussion

Findings of this study suggest that Dorzolamide loaded nanoparticles (DNP) may have great potential as advanced ocular drug delivery system. The nanoparticles had same size (~130 nm) and high encapsulation efficiency (83.5%), necessary for protracted drug retention in the ocular tissues. Owing to its small particle size, it penetrates across ocular barriers better and delivers drug to intraocular targets more efficiently. Maintaining the stability in suspension and preventing aggregation, which is crucial for consistent dosing, was primed by a high negative zeta potential (-24.6 mV) (Kagkelaris et al., 2022). While the release profile of DNPs over 24 hours is controlled, release of commercial eyedrops is rapid. Upon testing conventional formu lations, 99.9% dorzolamide release was observed in most cases almost immediately, with little or no retention making the frequent use necessary. On the other hand, the nanoparticles retained drug release, releasing ~83% cumulative at 24 hours, which provided a more gradual and controlled therapeutic. The sustained release is explained in compliment to previously published reports showing performance of biodegradable carriers for sustained drug release (Paganini et al., 2024).

Futher in vivo efficacy data underscores DNPs' advantages. DNPs provided IOP reduction that was greater, in total, and longer than that with commercial eye drops. In our study, use of DNPs showed a significant drop in efficacy, despite achieving IOP reduction of ~13% at 12 hours compared to ~28% drop for DNPs. DNPs were still effective by 24 hours (~20%) and eye drops had almost no residual activity (~5%). In any case, its prolonged effect is attributed to increased mucoadhesion and slower clearance of nanoparticles from the ocular surface, as was found with similar nanoparticle based ocular formulations (Loftsson et al., 2012; García-Llorca et al., 2024). Studies in biocompatibility had shown the safety of DNPs, and observed no inflammation or irritation. The nanoparticles were well tolerated and compared to conventional eye drops that caused minor ocular irritation. Given that chronic conditions, such as glaucoma (Patton & Lee, 2024), require long term use, this safety profile enhances their suitability for this. The stability studies also showed that this formulation maintains its integrity and drug content for weeks in storage, a key advantage for commercial scalability. Adding another benefit is that the economic feasibility of DNPs. But with superior efficacy, the nanoparticles were also more affordable from a per dose standpoint than conventional eye drops. All this affordability is necessary for allowing more patients to be accessible to the technology, especially in resource poor countries. Collectively, these results confirm that DNPs provide a means to circumvent limitations endemic to conventional ocular formulations. Nanoparticle-based systems provide a systematic approach to the design of improved therapeutics for glaucoma and other ocular diseases by enhancing therapeutic efficacy, decreasing dosing frequency and minimizing patient exposure.

## 6. Conclusion

The inherent challenges of conventional therapies are addressed through Dorzolamide loaded nanoparticles. The uniform size, high encapsulation efficiency and sustained drug release for more

than 24 hours by DNPs were demonstrated. These attributes led to better than achieved intraocular pressure (IOP) reduction in vivo. Excellent biocompatibility was observed for the nanoparticles with no evidence of ocular irritation or inflammation, or adverse effects to long term use. Further stability studies confirmed the firmness by which the formulation maintained its physical and chemical properties throughout storage. DNPs provided extended drug retention at a reduced frequency of dosing and improved effectiveness than current conventional eye drops to address patient compliance in chronic conditions like glaucoma. Additionally, an economic analysis indicated that the nanoparticle based formulation was economically viable for large scale production suggesting its potential for wider clinical adoption. Future work should be performed to optimize the scale up processes, conduct long term clinical trials and determine the versatility of this nanoparticle platform for other ophthalmic drugs. Taken together, nanoparticles loaded with dorzolamide are a promising alternative to current therapies in the treatment of glaucoma, while improving the efficacy and accessibility of therapy.

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