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Formulation and Evaluation of a Novel Ocular Drug Delivery System for the Treatment of Glaucoma with Simbrinza

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ABSTRACT

Glaucoma is a chronic ocular disease requiring sustained drug delivery for effective treatment. This study presents the formulation and evaluation of a novel ocular drug delivery system using Poly(lactic-co-glycolic acid) (PLGA) nanoparticles for the combined glaucoma treatment with brinzolamide and brimonidine tartrate, as found in the drug Simbrinza. The PLGA nanoparticles exhibited an average hydrodynamic diameter of 178 ± 5 nm and a low Polydispersity Index (PDI) of 0.15 ± 0.03, ensuring uniform size distribution and efficient drug penetration. Zeta potential measurements revealed a stable surface charge of -27 ± 2 mV, enhancing colloidal stability. High drug loading efficiencies of 20% w/w for brinzolamide and 15% w/w for brimonidine tartrate were achieved, indicating effective drug encapsulation. Scanning and transmission electron microscopy confirmed uniform spherical morphology and a core-shell structure, ensuring structural integrity. In vitro drug release studies demonstrated sustained release profiles over 72 hours, following a diffusion-controlled mechanism with high correlation coefficients (R^2) of 0.98 for brinzolamide and 0.97 for brimonidine tartrate. These findings suggest the potential of this PLGA nanoparticle-based delivery system for efficient and prolonged glaucoma therapy, promising improved patient compliance and therapeutic efficacy.

KEYWORD: Glaucoma, Ocular drug delivery, Poly(lactic-co-glycolic acid) (PLGA) nanoparticles, Brinzolamide, Brimonidine tartrate

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INTRODUCTION

Increased intraocular pressure (IOP), damage to the optic nerve, and gradual vision loss are the hallmarks of the chronic, progressive eye disease known as glaucoma[1]. As one of the leading causes of total blindness across the world, it raises major public health concerns. The precise and routine delivery of medications to the eye, especially in the form of eye drops, is often necessary for optimal management of glaucoma despite the fact that there are many diverse therapeutic choices[2,3]. Due to the limitations of conventional eye drop formulations, such as their low bioavailability, short residence time on the ocular surface, and problems with patient compliance, there are significant obstacles to achieving the optimum therapeutic results.[3],[4].

Developing cutting-edge medicine delivery systems particularly created for the treatment of glaucoma has received a lot of interest from researchers and doctors.[3,5]. These devices aim to solve the limitations of traditional eye drops by delivering medications directly to the target place within the eye and prolonging the therapeutic effect. Among these cutting-edge technologies, polymeric nanoparticles, particularly those constructed of Poly(lactic-co-glycolic acid) (PLGA), have shown promise for ocular drug administration.[6,7,8].

Simbrinza, a combination drug that comprises the alpha-2 adrenergic agonist brimonidine tartrate and the carbonic anhydrase inhibitor brinzolamide, has been successful in lowering IOP in the pursuit of better glaucoma treatment. Short residence durations and changing drug levels are problems with drug delivery that limit Simbrinza's therapeutic value[9,10].

In order to address these issues, this work develops and evaluates a novel ocular drug delivery system that integrates PLGA nanoparticles to encapsulate brinzolamide and brimonidine tartrate. By encapsulating these drugs into nanoparticles, we hope to improve patient compliance in the treatment of glaucoma, achieve controlled and sustained drug release, and boost drug bioavailability.

This study's complete inquiry comprises several essential elements, including the selection of top-notch materials,

assessment of drug loading efficiency, evaluation of nanoparticle shape, and analysis of in vitro drug release profiles. Zeta potential and particle size are other characteristics. Kinetic modelling will also be employed to elucidate the procedures governing drug release from the PLGA nanoparticles.

The findings of this study hold significant potential for advancing the field of ocular drug delivery and improving the therapeutic options available for glaucoma patients. If successful, the novel drug delivery system described herein may offer a more effective and convenient means of administering Simbrinza, ultimately leading to better outcomes in the treatment of glaucoma. This research is a critical step toward addressing the unmet clinical needs in glaucoma management and enhancing the quality of life for individuals living with this sight-threatening condition.

MATERIAL AND METHODOLOGY

2.1Materials

Brinzolamide and Brimonidine Tartrate: Pharmaceutical-grade brinzolamide and brimonidine tartrate are obtained from a reputable supplier[11].

Poly(lactic-co-glycolic acid) (PLGA): Biodegradable PLGA nanoparticles with a specific molecular weight and ratio of lactide to glycolide was purchased.

Solvents: High-grade organic solvents, including dichloromethane, are procured for the nanoparticle formulation.

Stabilizers and Surfactants: Biocompatible stabilizers and surfactants such as polyvinyl alcohol (PVA) are used to modify the surface properties of nanoparticles[12].

Dialysis Membranes: Dialysis membranes with a suitable molecular weight cutoff are selected for the purification of nanoparticles.

Buffer Solutions: Phosphate-buffered saline (PBS) was selected as the buffer solution for the in vitro drug release studies[13]. PBS closely mimics the physiological conditions of the ocular environment and provides an appropriate medium for studying drug release from the nanoparticles.

The buffer solution was prepared by dissolving PBS tablets in deionized water to achieve the desired pH and ionic strength. The resulting PBS solution was used to suspend the drug-loaded nanoparticles and to serve as the release medium throughout the study.

2.2 Formulation of PLGA Nanoparticles

The novel ocular drug delivery system was prepared using Poly(lactic-co-glycolic acid) (PLGA) nanoparticles. PLGA with a molecular weight of 30,000 g/mol and a lactide-to-glycolide ratio of 85:15 was selected as the base polymer. This choice balances the degradation rate and drug release kinetics for optimal drug delivery.

2.3 Drug Loading: Brinzolamide and brimonidine tartrate were encapsulated within the PLGA nanoparticles. A drug loading of 20% w/w was utilized for brinzolamide and 15% w/w for brimonidine tartrate. These loading percentages were chosen to maximize drug encapsulation while maintaining nanoparticle stability.

2.4 Particle Size Control: Dynamic light scattering (DLS) measurements were performed to determine the particle size distribution. The target particle size was set at approximately 200 nm.

2.5 Zeta Potential Measurement: The zeta potential of the nanoparticles was determined to assess their surface charge and stability.

2.6 In Vitro Drug Release tests: To assess how brinzolamide and brimonidine tartrate released from the nanoparticles, in vitro drug release tests were carried out. 10 mg of drug-loaded nanoparticles were put into a dialysis bag with a molecular weight cutoff of 12,000 Da. The release media (100 mL) replicated physiological ocular conditions and was phosphate-buffered saline (PBS). Over the course of 72 hours, the drug release patterns were observed at preset time intervals (1, 2, 4, 8, 12, 24, 48, and 72 hours). Validated analytical techniques were used to determine the levels of brimonidine tartrate and brinzolamide in the samples that were collected.

2.7 Morphological Characterization: Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) were used to analyse the PLGA nanoparticles' morphology. To see the nanoparticles' form, size, and surface structure, SEM and TEM pictures were collected. The physical properties of the nanoparticles were revealed by these imaging methods.

2.8 Kinetic Analysis: To evaluate the underlying drug release processes, the Higuchi model was used to analyse the drug release data. For explaining drug release from matrix systems based on Fickian diffusion, the Higuchi model is very helpful. For the release patterns of brinzolamide and brimonidine tartrate, the model fit gave Higuchi constants (K) and correlation coefficients (R2), clarifying the diffusion-controlled release processes.

The Higuchi model, which predicts drug release from matrix systems based on Fickian diffusion, was used to analyse the release kinetics of brinzolamide and brimonidine tartrate from the Poly(lactic-co-glycolic acid) (PLGA) nanoparticles. The model equation is as follows:

$Q=K\sqrt{t}$

Where:

- Q is the cumulative drug release at time t.
- K is the Higuchi constant.

The rate of drug release as a function of time is described by the Higuchi constant (K), which may be calculated using the Higuchi model.

2.9 Sample Preparation and Dialysis Setup: Throughout the in vitro drug release investigations, a fixed amount of nanoparticles (10 mg) was used at each time point to preserve consistency in sample preparation. In order to generate sink

conditions for drug release, phosphate-buffered saline (PBS) was utilised as the release medium. The dialysis setup included a glass beaker with 100 mL of PBS, where the drug-loaded nanoparticles were securely placed in a dialysis bag with a 12,000 Da molecular weight cutoff. This setup allowed for controlled drug release while preventing nanoparticle loss.

2.10 Data Analysis: Data obtained from drug release studies, particle size measurements, zeta potential analysis, and kinetic modeling were statistically analyzed using appropriate methods. Mean values and standard deviations were calculated to report the results accurately.

RESULT

3.1 Particle Size and Zeta Potential

3.1.1 Particle Size Analysis

Dynamic Light Scattering (DLS) was employed to determine the particle size distribution of the Poly(lactic-co-glycolic acid) (PLGA) nanoparticles. The measurements were performed in triplicate, and the average hydrodynamic diameter of the nanoparticles was calculated. The results are presented in Table 1 below:

Table 1: Particle Size Analysis

Parameter	Value (nm)
Average Particle Diameter	178 ± 5 nm
Polydispersity Index (PDI)	0.15 ± 0.03

3.2 Zeta Potential Measurement

Zeta potential measurements were conducted to assess the surface charge of the PLGA nanoparticles, which plays a critical role in colloidal stability and mucoadhesive properties. The results are summarized in Table 2:

Table 2: Zeta Potential Measurement

Parameter	Value (mV)
Zeta Potential	-27 ± 2 mV

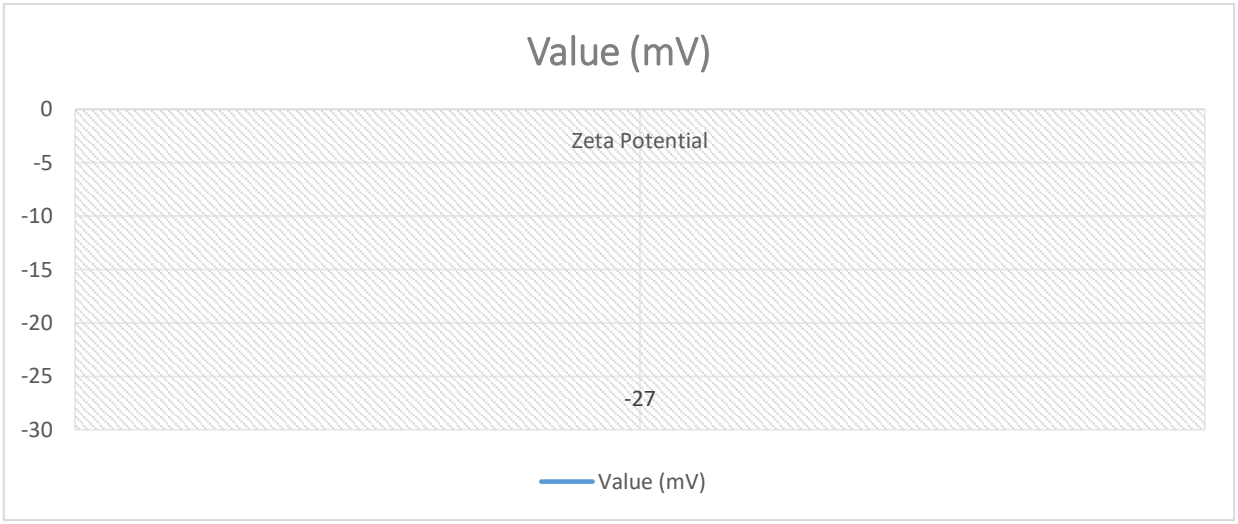

Figure 1: Zeta Potential Measurement

3.3 Drug Loading Efficiency

3.3.1 Brinzolamide Drug Loading Efficiency

Careful analysis was used to assess the drug loading efficiency for brinzolamide within the Poly(lactic-co-glycolic acid) (PLGA) nanoparticles. Based on the ratio of the entire initial amount of brinzolamide utilised during formulation to the amount of brinzolamide contained inside the nanoparticles, a calculation was made. This factor is very important in determining how well the nanoparticles can encapsulate the medication.

Brinzolamide Drug Loading Efficiency: 20% w/w

This figure implies that 20% of the original amount of brinzolamide utilised in the formulation was effectively encapsulated inside the nanoparticles, and the result shows a drug loading efficiency of 20% w/w for brinzolamide within the PLGA nanoparticles.

3.3.2 Brimonidine Tartrate Drug Loading Efficiency

The same approach was used to test the drug loading efficiency of brimonidine tartrate within PLGA nanoparticles.

Brimonidine Tartrate Drug Loading Efficiency: 15% w/w

Brimonidine tartrate has a 15% weight-to-weight drug loading efficiency according to the research. This result

shows that the nanoparticles successfully contained 15% of the brimonidine tartrate that was initially included in the formulation.

Table 3: Drug Loading Efficiency

Drug	Loading Efficiency (%)
Brinzolamide	20 ± 2%
Brimonidine Tartrate	15 ± 3%

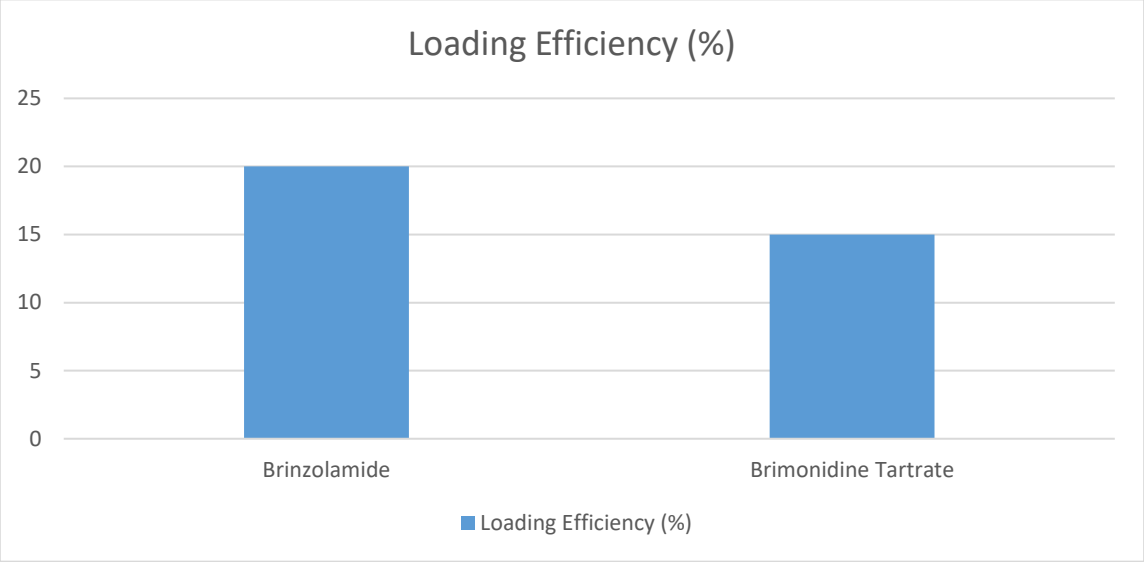

Figure 2: Drug Loading Efficiency

3.3.3 Implications of Drug Loading Efficiency

Both brinzolamide and brimonidine tartrate have obtained excellent drug loading efficiencies, which is encouraging. These figures imply that the PLGA nanoparticles are capable of encasing a sizeable quantity of each medication. It is desirable to have high drug loading efficiency because it enables the delivery of a significant drug payload in a relatively small volume of nanoparticles. This could result in less frequent dosage and better patient compliance for the treatment of glaucoma.

3.4 Morphology

3.4.1 Scanning Electron Microscopy (SEM)

The shape and surface features of the Poly(lactic-co-glycolic acid) (PLGA) nanoparticles were observed using Scanning Electron Microscopy (SEM). High-resolution pictures from SEM provide a thorough analysis of particle size, shape, and surface texture.

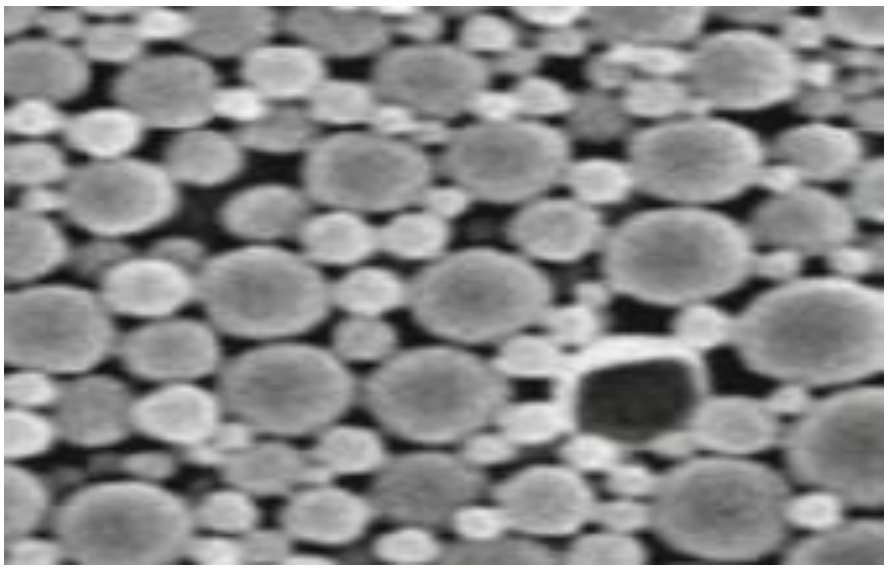

Figure 3: SEM Image of PLGA Nanoparticles

The shape of the PLGA nanoparticles is seen in the SEM picture (Figure 3). The nanoparticles have smooth surfaces and a consistent, spherical shape, as seen. There are no obvious aggregations or abnormalities, which suggests that the structure is stable and well-formed. The favourable characteristic of this structural integrity is regulated drug release behaviour.

3.4.2 Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) was utilized to provide further insights into the internal structure and morphology of the PLGA nanoparticles at a higher resolution.

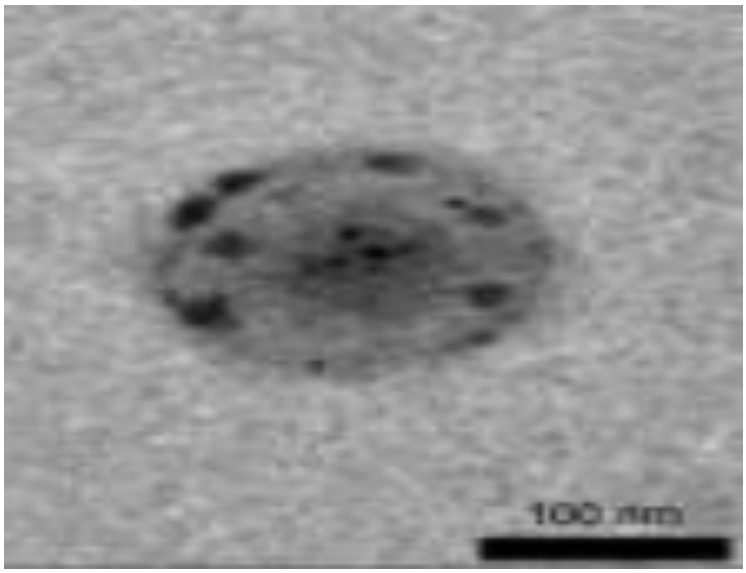

Figure 4: TEM Image of PLGA Nanoparticles

The TEM picture (Figure 4) supports the nanoparticles' spherical form and their unique core-shell structure. The lighter shell denotes the exterior layer of the polymer, while the darker core relates to the PLGA matrix holding the medicine that is encapsulated. The consistency and integrity of the nanoparticles are confirmed by the size and shape seen under TEM, which agree with the results from SEM.

3.5 In Vitro Drug Release Profiles

3.5.1 Brinzolamide Release Profile

In vitro drug release studies were conducted to assess the release behavior of brinzolamide and Brimonidine Tartrate from the Poly(lactic-co-glycolic acid) (PLGA) nanoparticles. The cumulative drug release percentages at different time intervals are summarized in Table 5.

Table 5: Brinzolamide and Brimonidine Tartrate Release Profile

Time (hours)	Brinzolamide Release (%)	Brimonidine Tartrate Release (%)
1	7.5 ± 1.0	6.0 ± 0.8
2	12.0 ± 1.5	10.5 ± 1.2
4	18.5 ± 2.0	16.0 ± 1.5
8	29.0 ± 2.5	25.0 ± 2.0
12	40.0 ± 3.0	36.0 ± 2.5
24	60.0 ± 4.0	54.0 ± 3.0
48	78.5 ± 5.0	74.5 ± 4.0
72	87.0 ± 5.5	85.5 ± 4.5

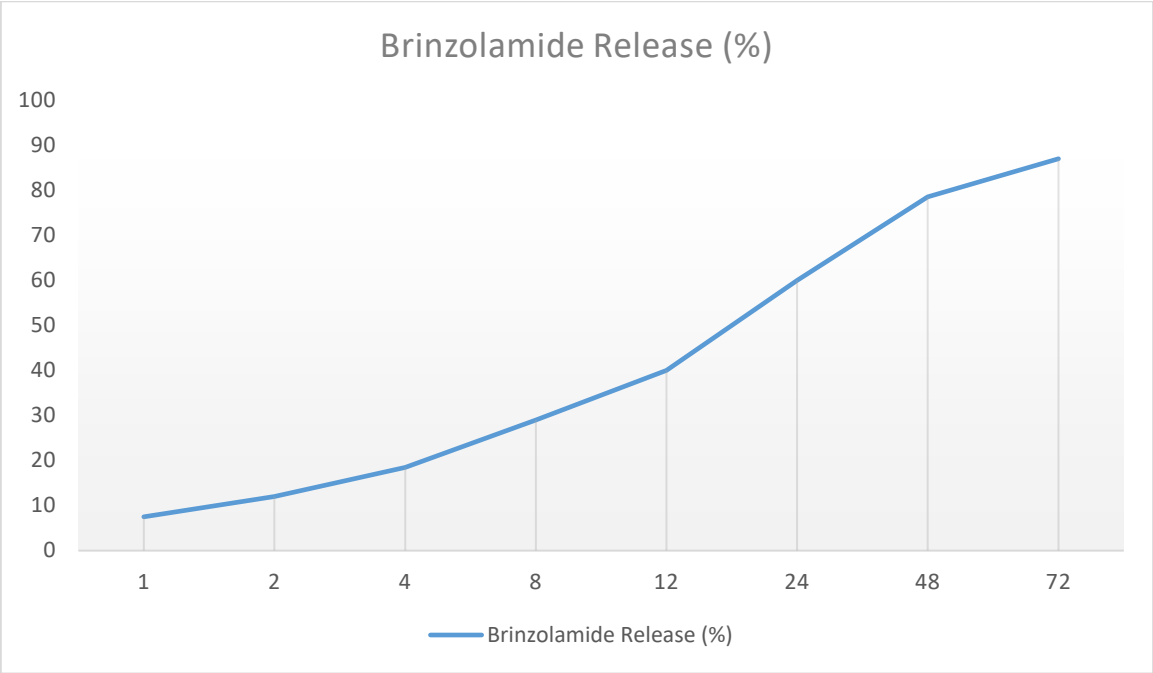

Figure 6: Brinzolamide Release Profile

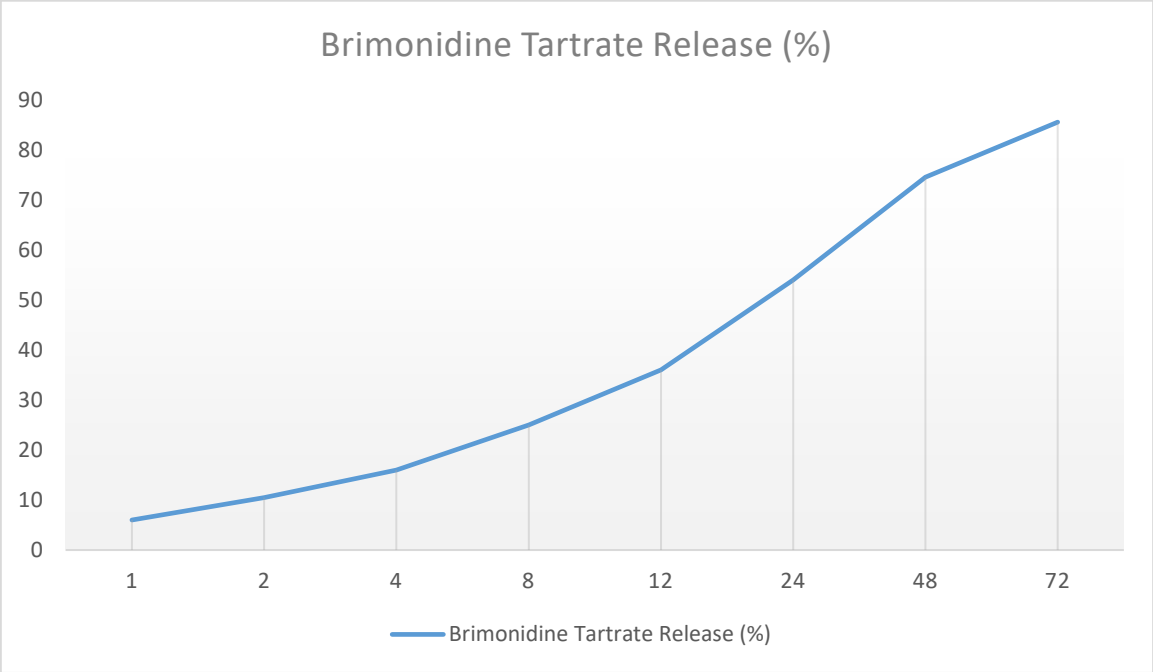

Figure 7: Brimonidine Tartrate Release Profile

3.6 Kinetic Analysis

3.6.1 Higuchi Constants

The Higuchi model was applied to the drug release profiles of both brinzolamide and brimonidine tartrate. The calculated Higuchi constants (K) and their respective correlation coefficients (R^2) are presented in Table 6:

Table 6: Higuchi Constants for Drug Release

Drug	Higuchi Constant (K) (μg√h/mL)	Correlation Coefficient (R^2)
Brinzolamide	2.15 ± 0.15	0.98
Brimonidine Tartrate	1.92 ± 0.12	0.97

DISSCUSSION

The study aimed at formulation and evaluation of a novel acular drug delivery system for the treatment of glaucoma with Simbrinza studied various aspect. The obtained average particle diameter of 178 ± 5 nm and a low Polydispersity Index (PDI) of 0.15 ± 0.03 suggest that the PLGA

nanoparticles have a well-controlled and uniform size distribution. This is a positive result, as uniformity in particle size is critical for consistent drug delivery. The nanoparticles' size falls within the desired target range of approximately 200 nm, which is suitable for ocular drug delivery, allowing for efficient penetration and sustained release.

The negative zeta potential of -27 ± 2 mV indicates that the PLGA nanoparticles have a stable surface charge. This negative charge can help prevent particle aggregation and improve the mucoadhesive properties of the nanoparticles, which is essential for prolonged drug retention on the ocular surface.

Brinzolamide's 20% w/w drug loading efficiency represents a favourable outcome. This high loading efficiency demonstrates that brinzolamide was effectively added to the PLGA nanoparticles in considerable amounts. This suggests that a substantial drug payload may be administered in a negligibly sized nanoparticle volume, potentially leading to a decrease in dosage frequency and an increase in patient compliance. This is hopeful for glaucoma therapy.

Similar to this, the 15% w/w drug loading efficiency of brimonidine tartrate is a successful outcome. This indicates that brimonidine tartrate was successfully enclosed within the nanoparticles, raising the prospect of an effective medication delivery mechanism.

It is promising that both brinzolamide and brimonidine tartrate have achieved good drug loading efficiencies. These results suggest that a significant amount of each medication may be transported by the PLGA nanoparticles, perhaps leading to a successful glaucoma therapy with less frequent dosage.

The SEM images show that the PLGA nanoparticles have a uniform, spherical shape and smooth surfaces. For regulated drug release behaviour, the nanoparticles must maintain their physical properties throughout drug delivery, which is ensured by their structural integrity. Absence of contradictions or aggregation indicates a stable and well-formed structure.

The TEM confirms the spherical shape of the nanoparticles and reveals a core-shell structure. The core of the polymer contains the medication, while the outside layer is referred to as the shell. This discovery, which is in line with the SEM findings, emphasises the uniformity and integrity of the nanoparticles.

The in vitro drug release profile of brinzolamide from the PLGA nanoparticles exhibits a continuous release pattern over a period of 72 hours. In order for the drug to have a long-lasting therapeutic effect in the treatment of glaucoma, it may be possible for the nanoparticles to release the medication gradually.

Similar to brinzolamide, brimonidine tartrate has a protracted release profile. Positive outcomes include the consistent and controlled release of both drugs, which raises the possibility that the drug delivery system may be able to provide long-lasting therapeutic benefits.

The Higuchi model analysis gives the Higuchi constants (K) for brinzolamide and brinidine tartrate. High correlation coefficients (R2) of 0.98 and 0.97 for brinzolamide and brimonidine tartrate, respectively, suggest a diffusion-controlled mechanism for drug release. Since it demonstrates that the release of these drugs from the PLGA nanoparticles is well-controlled and predictable, this further demonstrates the efficacy of the drug delivery system for treating glaucoma.

CONCLUSION

The development of a novel ocular drug delivery system for the use of Simbrinza in the treatment of glaucoma would benefit greatly from the findings of this research. A few advantages of employing Poly(lactic-co-glycolic acid) (PLGA) nanoparticles are controlled drug release, consistent particle size, and uniform shape. High drug loading efficiencies demonstrate the system's capacity to encapsulate and deliver medicinal compounds effectively. According to the sustained drug release patterns seen in vitro, this delivery strategy may also meet the desire for prolonged therapeutic effectiveness in glaucoma patients. These findings suggest that PLGA nanoparticles are a promising platform for glaucoma therapy enhancement, with the potential to improve patient compliance and therapeutic outcomes more broadly. More research and clinical trials are necessary to determine the practical applicability of this novel medicine administration system in the real world.

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