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Original Article

Design Development and *ex vivo* Evaluation of Dorzolamide Nanoparticles Laden Contact Lens for Management of Glaucoma

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ABSTRACT

Background: The current study aimed to design dorzolamide hydrochloride nanoparticle (NP)-laden contact lenses to control drug release for the effective management of glaucoma. **Materials and Methods:** Ionotropic gelation technique, using chitosan and sodium tripolyphosphate as the polymer and cross-linking agent, respectively, was employed for the formulation of nanoparticles. The formulation trials were optimized using a factorial design with JMP Pro software. The ANOVA-supported optimum formula (S6) was evaluated for particle size, zeta potential, FTIR, drug entrapment efficiency, morphology, *in vitro* drug release profile, and ex vivo permeation. Optimized nanoparticles were loaded into the contact lens using the soaking method, and the loaded contact lens was characterized for appearance, optical clarity, swelling equilibrium, *in vitro* release, *ex vivo* transcorneal permeation, and short-term stability. **Results:** The optimized formulation S6 exhibited a mean particle size of 55.7 nm and zeta potential of 25.6 mV. Scanning electron microscopy revealed that the nanoparticles were irregularly shaped with uneven and dense surfaces. Furthermore, ex vivo permeation studies of the optimized nanoparticles exhibited a higher flux and permeability coefficient than the pure drug solution and marketed eye drops. The nanoparticle-laden contact lenses were visually transparent and had a transmittance of 94.10±30.21%, similar to that of the control lenses. In addition, it showed less swelling and exhibited drug release 71.79±0.17% in 12 h. The *ex vivo* permeation studies exhibited good permeation, and drug loss during the storage period was insignificant.

Keywords: Nanoparticles, Ionotropic gelation, Chitosan, Glaucoma, Dorzolamide.

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INTRODUCTION

Glaucoma is a group of multifactorial optical neurodisorders distinguished by the gradual degeneration of Retinal Ganglion Cells (RGCs) and a specific field-of-vision impairment pattern.[1] The leading cause of glaucoma is increased Intraocular Pressure (IOP), which occurs within the anterior chamber of the eye by opposing aqueous humor outflow from the Schlemm's Canal inner Surface (SC) and trabecular meshwork.[2] In addition, various factors that lead to glaucoma-related blindness are present if diagnosis occurs at later stages because patients are unaware of the constriction of their vision until their visual acuity declines. Second, medicine and surgery are ineffective for controlling this disorder. At present, the only approved treatment for glaucoma is lowering Intraocular Pressure (IOP) to a regular limit (16-18 mmHg). IOP can be lowered by reducing the production or boosting aqueous humour evacuation.[3]

Carbonic Anhydrase (CA) plays a fundamental role in glaucoma by facilitating the production of bicarbonate (HCO3-) ions, which are secreted into the posterior chamber of the eye by the ciliary process.[4] The inhibition of CA has been shown to lead to an increase in Intraocular Pressure (IOP)·Among the various treatments for glaucoma, Dorzolamide (DRZ) is the most widely utilized and falls under the category of Carbonic Anhydrase Inhibitors (CAI).[4]

Owing to their simplicity of administration and therapeutic compliance, eye drops are the most frequent and well-accepted delivery strategy for ocular illnesses. The main disadvantage of this dosage form is the frequency of administration (2-3 times per day), which causes inconvenience to the patient. In addition, the instilled drugs are systemically absorbed by the conjunctiva/ nasolacrimal duct, leaving only 5% of the drug dose available for action.[5]

The ideal dosage form for an effective therapeutic response has to retain the required dose in the visual region over an extended

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period of time.[6] Consequently, it decreases the number of drops each day, thereby facilitating better compliance.[7] To overcome these drawbacks, it is necessary to reformulate dorzolamide HCl to a novel dosage form for effective therapy. Several drug delivery technologies based on nanoparticulates, including nanoparticles, nanosuspensions, nanoemulsions, niosomes, liposomes, cyclodextrins and dendrimers, can enhance the efficiency of ocular drug administration.[8] Nanoparticles offer sustained medication release, with the drug dispersed within the matrix, enabling the achievement of necessary tear concentrations and therapeutic outcomes.[9] Consequently, an extended precorneal residence time can be attained by combining polymeric matrices with nanoparticles.[10]

Nanoparticles composed of other natural polymers, such as chitosan, also facilitate intraocular drug penetration due to their capacity to establish close contact with conjunctival and corneal surfaces.[11] Chitosan is a natural biodegradable polymer with excellent visual compatibility.[12] Its chemical structure contains positively charged amine groups that may interact with the negatively charged mucosal layer, providing mucoadhesive properties.[13]

Thus, cationic nanoparticles can be attracted to the surface by electrostatic interactions. This results in cationic nanoparticles retaining on negatively (-) charged ocular tissues, achieving delivery of drugs to the anterior eye region.[2] Furthermore, to maximize patient compliance and administer a lower dose of the medication for a prolonged period, nanoparticles must be loaded into an appropriate carrier.

Contact lenses are one of the newest strategies for retaining optical and physical properties, enhancing the improvement of eye care.[1] After a single instillation, contact lenses can provide medication for lengthy periods. Furthermore, to boost bioavailability and decrease side effects, using contact lenses for prolonged drug delivery may enhance patient adherence, resulting in better treatment and clinical outcomes in glaucoma.[14]

This study aimed to investigate the possibility of developing a Dorzolamide HCl nanoparticle-laden contact lens that remains over the corneal surface for an extended period, resulting in a decreased drug dose, drug penetration towards the anterior of the eye and increased overall patient compliance

MATERIALS AND METHODS

Materials

The pure drug (dorzolamide hydrochloride) (Assay 99.5%) was provided by Precise Chemipharma Pvt. Ltd., as a gift (free) sample. Chitosan (Molecular weight 161.16) was obtained from Indian Fine Chemicals, India. All other chemicals and reagents were procured from SD Fine Chemicals. Soft contact lenses (Omafilcon A) were purchased from the Lenskart Store in Bangalore, India. The remaining solvents were of analytical grade.

Methods

Compatibility study by FT-IR spectra

Fourier Transform Infrared Spectroscopy (FTIR) was used to examine the variations in the drug-excipient mixtures. A small quantity of the sample was placed on the sample holder and the IR spectra of the samples were collected in the range 4000-400 cm^{-1} using the attenuated total reflection method.

Preparation of drug loaded polymeric Nanoparticles

Dorzolamide-loaded chitosan nanoparticle were prepared using the ionotropic gelation method. The polymer used was chitosan and the cross-linking agent was Sodium Tripolyphosphate (STPP). First, chitosan was dissolved in 1% aqueous acetic acid. Sodium Hydroxide (NaOH) was added to the solution to adjust the pH to 4-6.[15] Previously, dorzolamide HCl was dissolved in chitosan solution. TPP was added to the solution in deionized water. Under magnetic stirring, the required amount of the TPP solution was added dropwise to the chitosan solution at room temperature. The solution was then homogenized for 30 min to produce nano-sized particles. The solution was further magnetically stirred for a reasonable periods (3-4 hr). The nanosuspension was loaded into a centrifuge tube and spun at 5300 rpm for 30 min. After draining the supernatant from the particles, it was filtered and washed thrice using distilled water.

Utilization of experimental full factorial design

In the JMP software, a full factorial design helped to screen the formulation and processing parameters on quality attributes such as drug entrapment (%) and drug release (%). Formulation variables such as chitosan (%) and STPP (%) were chosen as continuous factors. Drug entrapment efficiency and drug release were chosen as the dependent variables or responses. The design generated eight experimental trials, as listed in Table 1.

Drug entrapment efficiency determination

Total drug concentration was assessed from a 10 mg drug equivalent nanoparticle and diluted suitably. Further, the diluted sample was measured against phosphate buffer as blank. Further, the diluted sample was measured against phosphate buffer pH 7.4 as blank. In the same way a 10 mg drug equivalent nanoparticle was taken and centrifuged, the supernatant was analysed for free drug concentration spectrophotometrically after suitable dilution. The absorbance of the sample was studied by UV spectrophotometry using phosphate buffer pH 7.4 as blank.[15]

$$Entrapment\ efficiency = \frac{Total\ drug\ content - free\ drug\ content * 100}{Total\ drug\ content}$$

In vitro drug release studies from nanoparticles

The *in vitro* release patterns of the selected nanoparticle formulations were studied over 12 h. The *in vitro* release study was performed in a Franz Diffusion Cell using Simulated Tear Fluid at pH 7.4. Drug-loaded nanoparticles were placed on a dialysis

membrane between the donor and receiver compartments of the diffusion cell assembly. The donor compartment was wetted with 5 mL of simulated tear fluid. The covered end of the donor compartment was fitted to the receptor compartment, which contained 50 mL of simulated tear fluid. A magnetic stirrer was used to agitate the receptor fluid, which was maintained at a temperature of 37±1°C. 1 mL of the sample was withdrawn periodically and equal amounts of fresh simulated tear fluid were replaced. The withdrawn samples were then analyzed spectrophotometrically in terms of drug content at the observed λ_{max}.[16]

Evaluation of experimental design

The responses of the experimental study were inserted into the experimental design and the model fit was assessed. The design space and desirability functions were determined using this model. Surface response curves were also obtained. An optimum formulation was prepared and evaluated and the optimum formula was chosen for nanoparticle preparation.

Physiochemical characterization of optimum formulation:

Particle size determination

Horiba SZ-100 equipment was used to estimate the mean particle size of the formulation. The particle size was determined by Dynamic Light Scattering (DLS). A sample was diluted in double distilled water to provide an acceptable concentration for evaluation and the sample was tested three times at a scattering angle of 90° at 25°C.[16]

Zeta potential determination

The zeta potential is a fundamental physical property that characterizes the behavior of nanoparticles in colloidal solutions. It is necessary for nanoparticles to approach their surface charges. Zeta potential was determined using a Horiba SZ-100 instrument. A sample was diluted in double distilled water at a temperature of 25°C; particles were examined three times at a scattering angle of 90°.[16]

Surface morphology

The surface morphology of the particles was assessed using Scanning Electron Microscopy (SEM, Tescan Vega 3) and the device was set to operate at an acceleration voltage of 15 kV. A concentrated aqueous suspension was applied over a slab and vacuum drying was performed. The sample was then shadowed with a 20 nm in thickness gold layer in a cathodic evaporator. An image processing application was used to create photographs.[16]

Drug release kinetics

Several mathematical equations have been presented to characterize the drug release kinetics of controlled-release formulations. To determine the kinetics of drug release from nanoparticles, the data from *in vitro* release were fitted with a zero-order model and the Korsmeyerpeppas model using Free Open-Source Software, known as KinetDS 3.0 software. Zero order kinetic (Cumulative Drug Release (CDR) versus time (t)): Qt=Qo+Kot, Where, Qo is the starting quantity of drug, Qt is the total amount of drug released at time 't'; t is the time in h and the zero-order release constant is denoted by Ko. Korsmeyer-Peppas model (Log CDR Vs log t): n Q=kt, Where, K is rate constant, Q is quantity of drug release at time t and n is release exponent (indicative of drug release mechanism).[6]

Ex vivo permeation study

Transcorneal permeation experiments were conducted on freshly excised goat cornea procured from a local slaughterhouse. Before usage, from the ocular tissue, the cornea was gently removed and cleaned multiple times to eliminate any unwanted residue. On the Franz Diffusion Cell, the excised cornea was immediately inserted between the donor and receptor compartments so that the endothelial surface faced the receptor compartment and the epithelial surface faced the donor.[16] Fresh STF (pH 7.4) 50 mL was poured into the receptor compartment. A drug-loaded nanoparticle was placed on the cornea and the receptor containing STF was maintained at 37°C. Permeation studies lasted 12 hr and at periodic intervals. The samples were removed from the receptor compartment and replaced with the same amount of freshly prepared media. The samples were examined using a UV spectrophotometer set to 253.6 nm.

Loading of Dorzolamide-NPs into commercial contact lenses

Dorzolamide HCl-Nanoparticle was loaded into the contact lens via the lens soaking method. Initially, 30 mL of Millipore water was used to soak the contact lens for 10 min. It was then dipped into 10 mL of ethanol for another 10 min, resulting in swelling and an increase in thickness, which helped in promoting drug uptake. Furthermore, the lenses were soaked in 10 mg equivalent of Dorzolamide HCl-NPs solution for 24 hr. The lenses were wiped after the drug was loaded with clean filter paper (lint-free) to eliminate any residual surface drug solution before being used for further study.[17]

Visual appearance

The contact lens loaded with nanoparticles was visually evaluated for any change in color and transparency.[18]

Optical clarity

The optical characteristics of Dorzo-nanoparticle-loaded contact lenses should not change after loading the nanoparticles. Because more than 90% transmittance assures clear eyesight, the percentage transmittance through the contact lenses was determined. The control contact lens was soaked in simulated tear fluid for 24 hr before being scanned in a UV spectrophotometer

using a quartz cuvette at wavelengths between 200 and 1000 nm. Furthermore, the transmittance of Dorzo-NP loaded contact lenses was measured and the data was compared against the standard to check the significant differences that could affect normal vision compared to the commercially available contact lens.[18]

Equilibrium swelling study

The mass balance approach determines the percentage of swelling at equilibrium. This experiment was performed by immersing the contact lenses in Dorzo nanoparticles until an equilibrium was reached. The tissue was used to dry the lenses after they had swollen for 24 hr and then Weighed using a balance (Wwet) in air. Followed by drying out The lenses were dried to calculate the initial Dry Weight (Wdry). The equilibrium swelling index was calculated using the following equation;[19]

Wdry is the weight before he experiment. Wwet- Weight after the experiment.

In vitro release study

Contact lenses loaded with Dorzo-NP were placed in 5-mL glass tubes containing 3 mL of Simulated Tear Fluid (STF, pH 7.4) at ambient temperature. The tubes were then shaken in a shaking incubator at 100 rpm for the release study. The volume of the release medium was 3 mL, which is nearly equal to the *in vivo* condition of typical human tear turnover. The simulated tear fluid was refilled in the perfect sink condition at each interval using an equal volume (1 mL) of fresh simulated tear fluid. A UV-visible spectrophotometer was used to evaluate the dynamic drug concentration in the tear fluid by determining the absorbance at 253.6 nm. The plots of CDR (%) vs time h were used to examine the release profile of dorzolamide.[20]

Ex vivo permeation study

A modified Franz diffusion cell was used to conduct *ex vivo* permeation tests. The corneal surface was covered with a Dorzo NP-loaded contact lens. The procedure was the same as that described previously.[16]

Short term stability study

A short-term stability study was conducted to assess the drug that leached from nanoparticle-loaded contact lenses inside the packed liquid. The nanoparticle-loaded lens was kept in the packaging solution for 1 month at room temperature (25°C±2°C) and 65±5% relative humidity.[21] The amount of free drug in the packing solution was determined using UV spectroscopy.

RESULTS AND DISCUSSION

Drug excipients compatibility studies by FTIR

The characteristic peaks of the pure drug were preserved within the stretching range 1500-1650 for amine (NH bending), 3000-3100 for alkene (C=H), 2844-2954 for alkane (CH3), 1440-1625 for aromatic substitution (C=C), 1250-1360 for the cyano group (C=N), 1146-1168 for Sulfonyl compound (SO_2). The FTIR spectra of the physical mixture and wavenumber peaks were observed suggesting no interaction between the drug and excipients used.

Formulation of nanoparticles

The formulations were optimized by the factorial design approach using the JMP software, generating eight experimental runs. The prepared formulations were evaluated for drug entrapment efficiency (%) and cumulative drug release (%) and the results are shown in Table 1. The drug entrapment efficiency ranged from 84.09±0.15% to 93.990.12%. The drug release study for over 12 hr showed 80.08±0.12 to 87.94±0.21% release, as shown in Figure 1. The highest entrapment efficiency was found for the S6 formulation, which exhibited the highest drug release of 87.94±0.21 for 12 hr. The drug entrapment efficiency was initially found to be directly related to the STPP concentration, as it increased when the STPP concentration was increased to a certain extent. Similarly, when a higher amount of chitosan was incorporated, it showed higher gel-forming ability, preventing

Table 1: Experimental runs and responses.

Formulation code	Pattern	Chitosan (%)	STPP (%)	Drug release for 12 hr (%)	Drug entrapment efficiency (%)
S1	+2	0.5	0.75	83.6±0.22	90.09±0.13
S2	-3	0.75	0.25	82.9±0.19	88.05±0.18
S3	-2	0.5	0.25	86.06±0.15	92.03±0.23
S4	-1	0.25	0.25	86.66±0.11	92.97±0.20
S5	00	0.5	0.5	84.91±0.27	91.05±0.19
S6	+3	0.75	0.75	87.94±0.21	93.99±0.12
S7	00	0.5	0.5	83.96±0.23	90.27±0.31
S8	+1	0.25	0.75	80.08±0.12	84.09±0.15

the movement of dorzolamide to the external phase. The ionic interaction between the polymer and STPP may lead to increased entrapment of the drug in the nanoparticles. The drug release rate was possibly affected by factors such as the structure of the nanoparticles, concentration of chitosan and STPP.

Surface Response curves and desirability approach

ANOVA helped identify the significance of the model and factors. The chitosan concentration and STPP were the most influential factors. The desirability function helped select the optimum formulation with a maximum desirability of 0.84, as shown in Figure 2. An optimal formulation was prepared and evaluated based on the desirability function. The experimental data were the best-fitted quadratic model for drug release and entrapment.

Evaluation of optimised formulation

Particle size and Zeta potential of optimum formulation

Drug-loaded nanoparticles 50-400 nm in size are considered adaptable for ocular delivery because they can overcome physiological barriers and target the drug to a particular cell. The average particle size was 55.7 nm, which is considered adaptable for ocular delivery, as shown in Figure 3. The zeta potential gives an idea of the magnitude of electrostatic repulsion between nearby similarly charged particles in a dispersion. The higher the zeta potential, the better the stability of the dispersed system. A zeta potential of 25.6 mV suggests that positively charged cationic nanoparticles could interact with the negatively charged mucous layer, resulting in cationic nanoparticles being retained on negatively charged ocular tissues, thereby achieving drug delivery to the anterior eye segment.

Drug release kinetics

The release of the drug from the optimized formulation showed zero-order kinetics with an R2 value of 0.88. The Korsmeyer-Peppas model is a more precise, straightforward, semi-empirical equation for describing drug release mechanisms from polymeric systems. Formulation S6 showed a non-Fickian (Case-II) release pattern with n=1.09 and regression of R^2=0.99, as shown in Figure 4.

Surface morphology of optimum formula

Surface photographs of the nanoparticles were obtained at different magnifications (4000x and 5000x). The SEM images show that the nanoparticles had uneven and dense surfaces and irregular shapes. The nanoparticles showed slight aggregation or crevice-like structures on their surface. The effect of the high stirring speed on the disorient structure of chitosan might be one of the contributing factors to the unevenness.

Evaluation of nanoparticle loaded contact lens

Physical appearance, Optical clarity study and Equilibrium swelling index

The lens loaded with nanoparticles had similar visual properties to the control lens, which was examined visually. The optical clarity was determined by measuring the transmittance of the control and nanoparticle-loaded contact lenses at 630 nm using a UV-vis spectrophotometer. The lens loaded with nanoparticles was determined to be transparent, with the highest transmittance of 94.103±0.213%. The percentage transmittance of both the control contact lens and contact lenses loaded with NP showed almost identical transmittance, even after the loading of nanoparticles into the matrix of the lenses. Moreover, drug loading did not affect

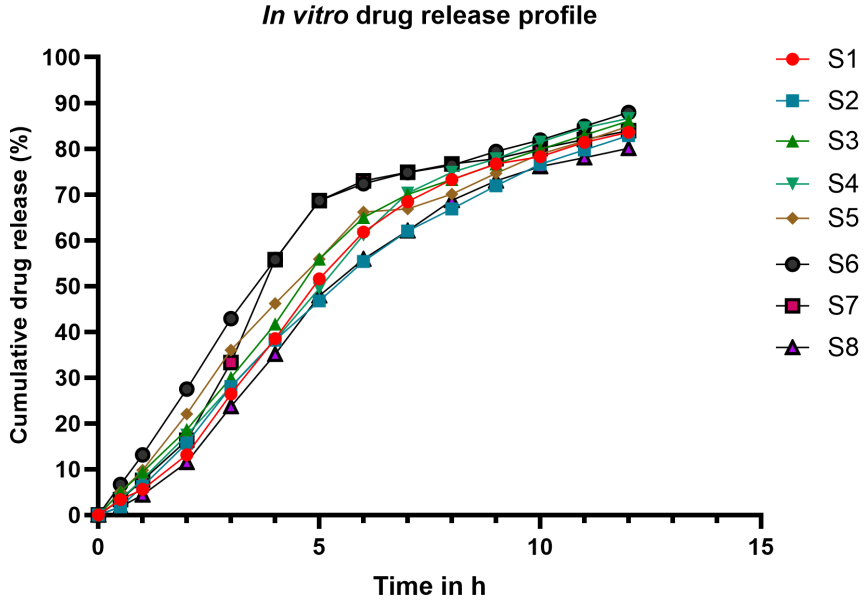

Figure 1: *In vitro* drug release profile from nanoparticle formulations S1-S8.

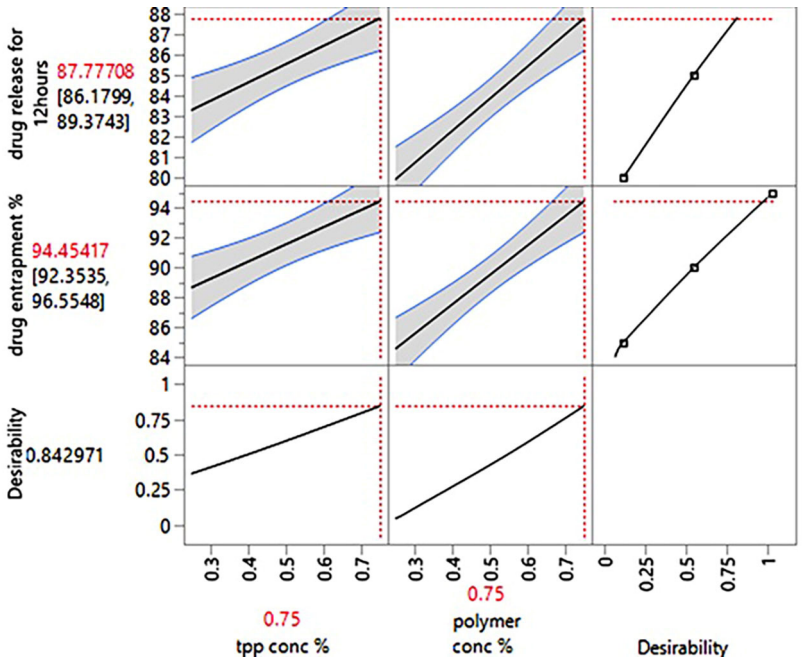

Figure 2: Selection of optimum formulation using maximum desirability function.

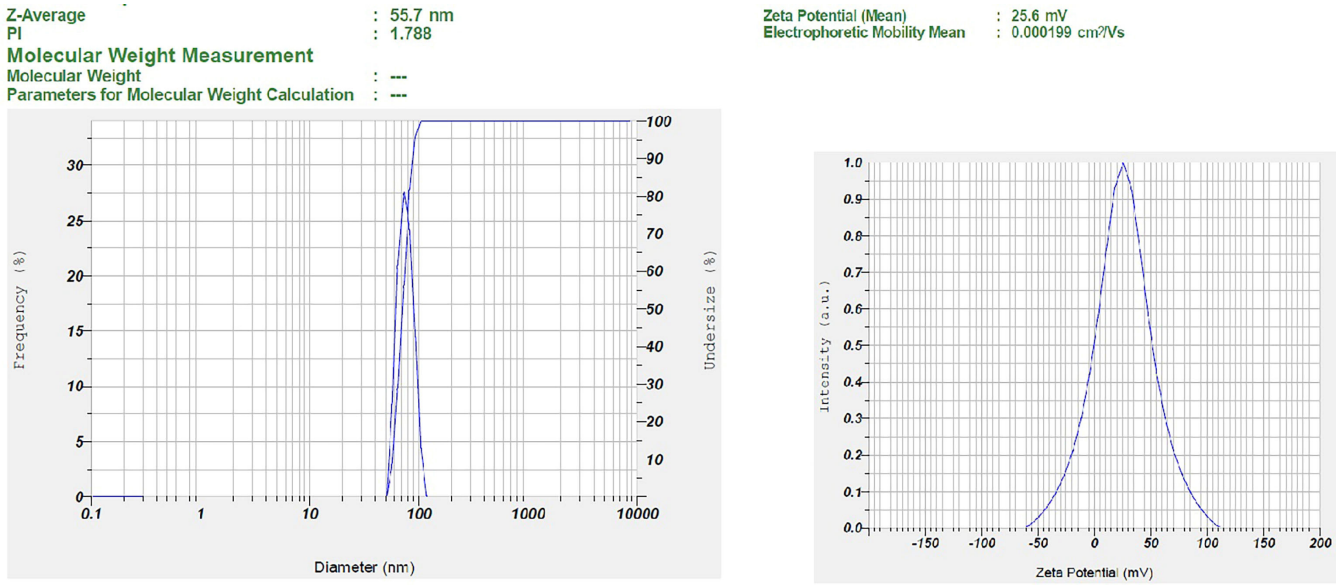

Figure 3: Particle size and zeta potential of the optimized nanoparticle. Formulation.

the physical and optical properties of the lens. The Nanoparticle (NP) contact lens showed almost 3% lower swelling than the control contact lens.

Comparative *in vitro* release study

The dorzolamide NP-loaded contact lens released 71.79±0.17% within 12 hr, compared to dorzolamide nanoparticles, pure drug solutions and marketed formulations, as shown in Figure 5. Dorzolamide nanoparticles released 89.37±0.34% within 12 hr. The % CDR of the pure drug was found to be 99.01±0.18 in just 5 hr and that of the marketed formulation was found to be 97.52±0.19 in just 7 hr. The release pattern indicates that the drug release from the nanoparticle-loaded contact lens was slow compared to the other formulations and the reason may be attributed to the slow swelling of the contact lenses and the polymer swelling within the system taking adequate time, unlike the pure drug solution and marketed drop.

Ex vivo permeation study

The drug permeation rate from the nanoparticle-loaded contact lens was 68.60%±0.62% compared to dorzolamide-loaded nanoparticles, which showed a permeation rate of 83.01% in 12 hr. In contrast, pure drug solution permeated 65.53±0.19% and marketed formulation permeated 60.63±0.27%. The rate of permeation of the drug from loaded nanoparticles was faster as it contained chitosan, which facilitates adhesion to the mucosal

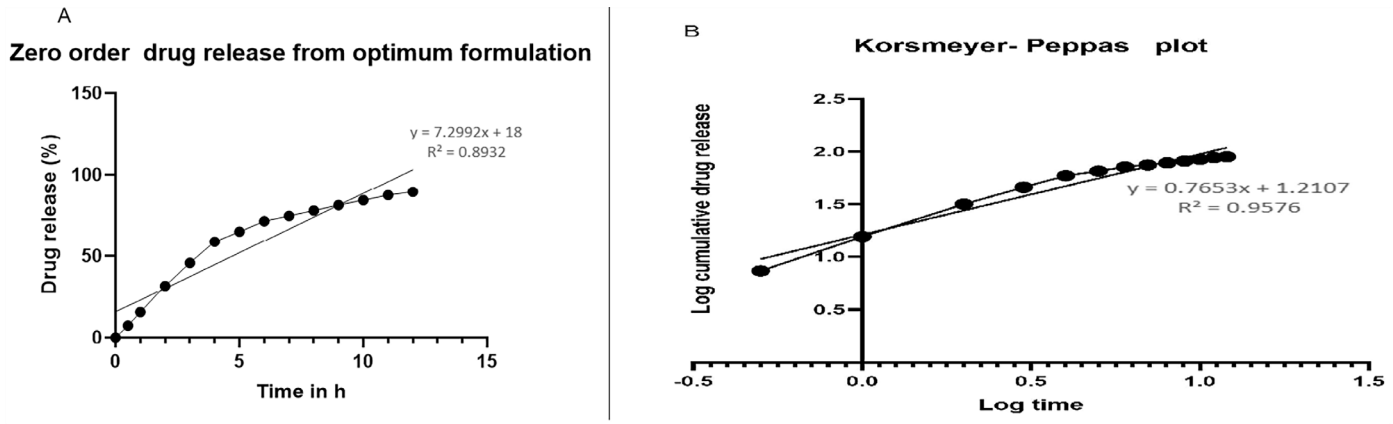

Figure 4: *In vitro* drug release kinetics of the optimised formulation. a) Zero-order model; b) Korsmeyer-Peppas model.

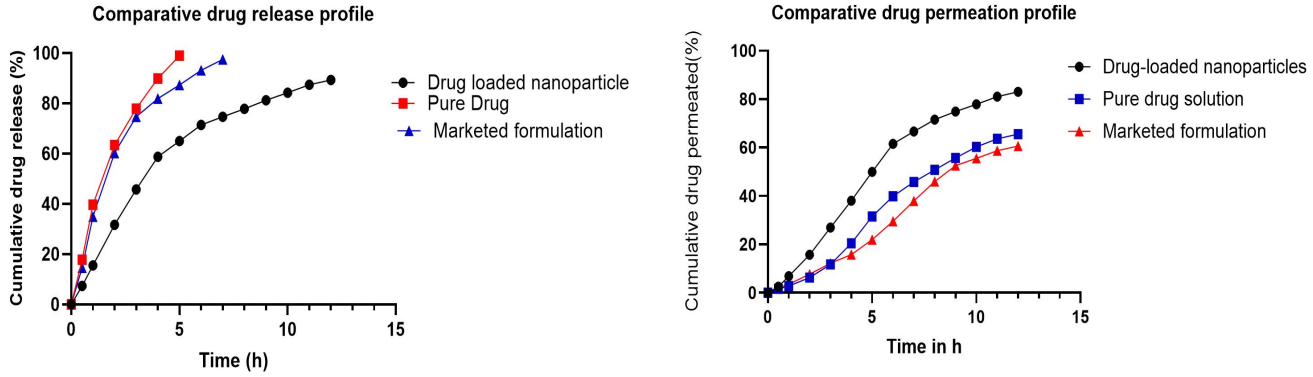

Figure 5: Comparative *in vitro* drug release and *ex vivo* drug permeation profile of nanoparticles vs. Marketed opthalmic drop and pure drug solution.

surface and momentarily opens tight junctions between cells, thereby enhancing the permeation of the drug.

Short term stability study

The drug content from the NP-loaded contact lens after 30 days was found to be 95.89±0.17% at room temperature. These data suggest that the loading and drug loss factors throughout the storage period were insignificant. Therefore, drug loss in the packed solution was prevented by chitosan nanoparticles during the shelf life of the therapeutic contact lens.

CONCLUSION

Treatment of glaucoma requires novel drug therapy via sustained drug action. Therefore, this study concentrated on converting dorzolamide into a nanoparticulate system and presented it as a contact lens for a convenient drug delivery system for prolonged therapy. The ionotropic gelation method was used to prepare nanoparticles. This simple soaking method resulted in the incorporation of nanoparticles into the contact lens. Visual clarity studies have recommended the optical clarity of the DNC. The *in vitro* and *ex vivo* studies suggested controlled drug release along with a higher permeation profile than that of the marketed formulation. This study concluded that DNC is a promising approach for treating glaucoma.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DNC: Dorzolamide hydrochloride nanoparticles-laden contact lens; **ANOVA:** Analysis of Variance; **NP:** Nanoparticle; **FTIR:** Fourier-transform infrared spectroscopy; **SEM:** Scanning electron microscope; **NP-CL:** Nanoparticle loaded contact lens; **RGCs:** Retinal ganglion cells; **IOP:** Intraocular pressure; **SC:** Schlemm's canal; **CA:** Carbonic anhydrase; **DRZ:** Dorzolamide; **CAI:** Carbonic anhydrase inhibitors; **HCl:** Hydrochloride; **STPP:** Sodium tripolyphosphate; **NaOH:** Sodium hydroxide; **DLS:** Dynamic light scattering; **CDR:** Cumulative drug release; **STF:** Simulated tear fluid.

SUMMARY

The study proposed a contact lens laden with nanoparticles as a drug delivery system for the management of glaucoma. Nanoparticles of chitosan were prepared using the ionotropic gelation method using TPP as a cross-linking agent. The formulation trials via the 2^3-factorial design approach led to the optimum formation and were evaluated for particle size, zeta potential, drug entrapment efficiency and drug release. The optimum formation incorporated contact lens showed good transmittance; *in vitro* drug release studies suggested a zero-order release kinetics with a diffusion-controlled drug release mechanism. The permeation profile via isolated sheep cornea shows a higher nanoparticle permeation profile than the marketed formulation. The stability studies suggested no apparent changes in drug loading at both temperatures studied.

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