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Nanoelectrospray fabrication of pH-responsive double-layered drug-eluting contact lenses for ocular drug delivery

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ABSTRACT

Additive manufacturing approaches enable the rapid production of drug-eluting contact lenses (DECLs) directly from commercially available lenses. Nanoelectrospraying (nES) is a promising additive technique, capable of applying drug coatings within seconds per lens. However, DECLs made by nES share similar challenges to DECLs made by other methods, including minimising drug loss into the packaging solution and achieving controlled drug release. In this study, bimatoprost, a drug widely used in glaucoma therapy, was selected as a model compound to develop a double-layered, pH-responsive DECL system incorporating drug-loaded NPs. The bimatoprost-loaded NPs were prepared using flash nanoprecipitation with zein and hyaluronic acid (HA). They were characterised for size, zeta potential, and entrapment efficiency. A double-layer coating was applied using nES, with the base layer comprising NPs in polyvinyl alcohol (PVA) and the top layer using Eudragit L100 for pH-responsive drug release. DECLs were evaluated for coating uniformity, optical transmittance, and storage stability. Comparative *in vitro* drug release studies were performed under static conditions and with a custom 3D-printed tear flow simulating device (TFS) to simulate physiological tear dynamics. Bimatoprost-loaded NPs exhibited a reasonable colloidal stability and entrapment efficiency. Drug release from soaked lenses (as the control sample) or nES single-layer-coated lenses was rapid, highlighting the need for advanced coating approaches. Storage stability studies confirmed drug retention of the DECLs with the double-layer coating, with minimal loss over storage at pH 5.5. Under physiological pH (pH 7.4), sustained drug release was achieved, demonstrating a 34% reduction in burst release and a significant increase in sustained release to single-layer coatings and soaked lenses. In conclusion, the double-layered, nanoparticle-loaded DECLs with a pH-responsive coating effectively demonstrated sustained drug release at physiological pH, with significantly reduced drug loss during storage in packaging solution. This scalable platform has the potential for DECL manufacturing which provides an alternative ocular drug delivery solution for chronic conditions like glaucoma.

1. Introduction

Effective delivery of ocular drugs to the eye remains a significant challenge in clinical practice due to the natural protective mechanisms of the eye which limit drug absorption and retention (Raj et al., 2020). Traditional administration via eye drops is associated with bioavailability rates below 5% due to tear drainage and clearance from the eye, often requiring multiple daily applications to maintain efficacy (Agrahari et al., 2016, Davis et al., 2018, Gupta et al., 2012). This frequent dosing can lead to adherence challenges, particularly for patients with chronic conditions like glaucoma or allergic conjunctivitis (Gupta et al., 2012). Additionally, preservatives in eye drops may cause irritation, while dosing variability can impact treatment consistency and patient outcomes (Jansook and Loftsson, 2022). As a result, the field has been actively pursuing alternative delivery methods that can increase bioavailability, reduce administration frequency, and improve patient adherence, especially important for chronic conditions requiring long-term treatment (Ioniță et al., 2023). Although other self-administered dosage forms such as eye ointment and gels can sustain drug release and reduce dosing frequency in comparison to eye drops, the accuracy of the dose is highly affected by the application skills of the patient (Bisen et al., 2024).

Drug-eluting contact lenses (DECLs) address these limitations by allowing for continuous, controlled drug release directly to the eye with

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high precision dosing, representing a promising shift from conventional approaches (Ciolino et al., 2009; Hsu et al., 2014). Compared to eye drops, DECLs have demonstrated bioavailability improvements of up to ten fold, significantly increasing therapeutic efficacy (Fan et al., 2020). Initially conceptualised in the 1960s, DECLs have since evolved, with various fabrication techniques explored to optimise drug loading, retention, and release kinetics (Alvarez-Lorenzo et al., 2010). The first commercial DECL, Acuvue Theravision® with Ketotifen, daily disposable contact lenses developed by Johnson & Johnson Vision, was manufactured using conventional contact lenses soaked in ketotifen fumarate solution to alleviate ocular itch in contact lens wearers ("Johnson & Johnson Vision Care Receives FDA Approval for ACUVUE® TheravisionTM with Ketotifen – World's First and Only Drug-Eluting Contact Lens," 2022). However, while effective for specific conditions, soaking-based methods for drug loading of contact lenses are limited to drugs that can have specific surface interactions, for example ketotifen fumarate that has electrostatic interactions at the lens surface (Lanier et al., 2020). In addition, for hydrophilic drugs, unavoidable and continuous drug loss to the packaging solution is a consideration for DECLs made by soaking methods. The Acuvue Theravision® DECL was packaged in a plastic blister pack containing a buffered ketotifen solution to mitigate the drug loss if packed in a drug free buffer solution ("Acuvue Theravision with Ketotifen," 2022). For hydrophobic drugs, soaking lenses with ethanol–water solutions of Vitamin E has been widely reported in the literature to create a hydrophobic diffusion barrier and slow down the drug release rate (Sekar and Chauhan, 2019; Liu et al., 2022; Bodoki et al., 2021; Rykowska et al., 2021). However, this approach may alter lens mechanical properties and does not resolve the drug leaching during storage, potentially limiting its long-term clinical applicability (Liu et al., 2022).

In addition to soaking, a range of DECL fabrication methods, such as molecular imprinting (Bodoki et al., 2021), polymer film encapsulation (Rykowska et al., 2021), and immersion in supercritical fluids (Gungor et al., 2024) have been reported, but all require extensive modification to the existing contact lens mass manufacturing process (Lovrec-Krstič et al., 2023). In some cases, these methods may also compromise the comfort, vision correction properties, and structural integrity of contact lenses, posing challenges for clinical application (Lovrec-Krstič et al., 2023). Other additive processes, including electrospinning and inkjet printing, have been reported for producing DECLs (Pollard et al., 2023; Tetyczka et al., 2022). Drug coating through electrospinning requires masking techniques that adds additional processing steps during manufacturing (Mehta et al., 2017) and inkjet printing is constrained by the requirement that drug loaded inks maintain a specific viscosity range to achieve consistent and effective deposition (Tetyczka et al., 2022). Several innovative DECL strategies have been reported. Desai *et al.* developed implant-laden lenses incorporating timolol, bimatoprost, and hyaluronic acid, which achieved sustained release and reduced burst effects; however, this approach involved complex fabrication (Desai et al., 2020). Similarly, Maulvi *et al.* employed graphene oxide (GO) to modulate bimatoprost release in silicone hydrogel lenses, improving transmittance and pharmacokinetics, but requiring further optimization to achieve consistent therapeutic levels (Maulvi et al., 2021). In contrast, our nanoelectrospray-based double-layered DECLs offer a scalable, simpler fabrication platform that minimizes storage-associated drug loss while maintaining lens transparency and providing pH-responsive sustained release.

Nanoelectrospraying (nES) has been previously demonstrated as a novel approach for DECL fabrication that enables precise, additive coating without masking (Tam et al., 2022). This method allows consistent deposition of thin, drug-loaded material layers onto the surface of commercially available contact lenses, and can be readily integrated into the current industrial manufacturing process of contact lenses (Jaworek, 2006; Nguyen et al., 2016). This approach could provide a scalable and rapid manufacturing solution for DECLs. Furthermore, the process makes it feasible to achieve customised dosages based on therapeutic need. Compared with other additive manufacturing techniques such as inkjet printing and electrospinning, nES offers distinct advantages for drug deposition on contact lenses in DECL fabrication. Inkjet printing is limited by the narrow viscosity range of suitable formulations and is prone to nozzle clogging (Ghazi et al., 2025), while electrospinning generates fibrous coatings that can compromise lens transparency and require masking strategies to address this issue (Mishra et al., 2023). In contrast, nES enables rapid and precise deposition of accurate drug doses at predetermined sites on the lenses, making it highly adaptable for industrial-scale DECL production (Tam et al., 2024). However, the formulation of the coating is critical to the degree of control of drug release rate. Previously, a single drug-loaded poly(lactic-co-glycolic acid) (PLGA) layer was deposited as a ring on the peripheral region of lenses that enabled modified drug release without affecting optical clarity of the visual zone of the lenses (Tam et al., 2022). Building on these advances, this study investigates a strategy to enhance sustained release from nES coatings through the integration of drug-loaded NPs and a stimuli-responsive coating. Zein/HA nanoparticles were selected over conventional PLGA carriers due to their biocompatibility, sustainability, and ocular tolerance. Zein is a plant-derived protein with excellent biodegradability and biocompatibility (Hassan et al., 2022), while HA provides mucoadhesive and lubricating properties that may improve patient comfort (Guarise et al., 2023).

Stimuli-responsive delivery systems represent a transformative approach in ocular drug delivery, enabling precise, on-demand drug release in response to environmental triggers such as pH, temperature, or light (Berillo et al., 2021). Such systems are particularly attractive for ocular applications using DECLs, where minimising premature drug loss in storage solutions and achieving controlled release upon wear remain significant challenges. In this study, we investigate the capability of nES to produce stimuli-responsive double-layered DECLs that address a technology gap that currently is not fulfilled by other methods for producing DECLs, specifically to minimise drug loss in storage solution and trigger the sustained drug release when the lenses are being worn. In this study, a change in pH was employed as the stimulus for drug release, with lenses transferred from a storage solution at pH 5.5 to the tear film environment, which is reported to range between pH 6.5 and 7.6 (Abelson et al., 1981). This approach provides a practical pathway to reduce drug loss during storage and enable sustained drug release under physiological conditions.

Bimatoprost was used as the model drug, a synthetic prostaglandin analogue used in the form of eye drops to treat glaucoma (Curran, 2009). It is considered lipophilic with an aqueous solubility of 19 mg/L and log P of 3.2. Bimatoprost is known for its poor retention on the ocular surface when given as eye drops, leading to rapid loss of therapeutic concentrations (Wadhwa et al., 2022) and DECLs have previously been investigated using soaking and molecular imprinting loading methodologies (Wadhwa et al., 2022; Xu et al., 2019).

Eudragit L100, a pH-responsive polymer, remains intact in weak acidic environments, such as the pH 5.5 storage solution used in this study, while swells with increasing pH, enabling controlled release in physiological conditions (Dong et al., 2019; Jablan and Jug, 2015; Singh and Nayak, 2023). Eudragit L100 has previously been investigated as an excipient in ocular drug delivery, specifically in drug-loaded nanoparticle eye drops, to provide sustained release and *in vivo* studies suggested a lack of toxicity (Bucolo et al., 2004; Pignatello et al., 2006; Rosario Pignatello et al., 2002; Pignatello et al., 2002). In this study, Eudragit L100-based coating was applied to a base layer of polyvinyl alcohol (PVA) embedded with bimatoprost-loaded NPs (Fig. 1). By combining stimuli-responsive polymers with nanoparticulate carriers, the aim is to achieve highly efficient and patient-friendly drug delivery for ocular diseases offering a promising strategy for controlled drug release while minimising the initial burst effect (Hassan et al., 2022; Guarise et al., 2023). Maintaining therapeutic drug levels over an extended period would address limitations of conventional delivery

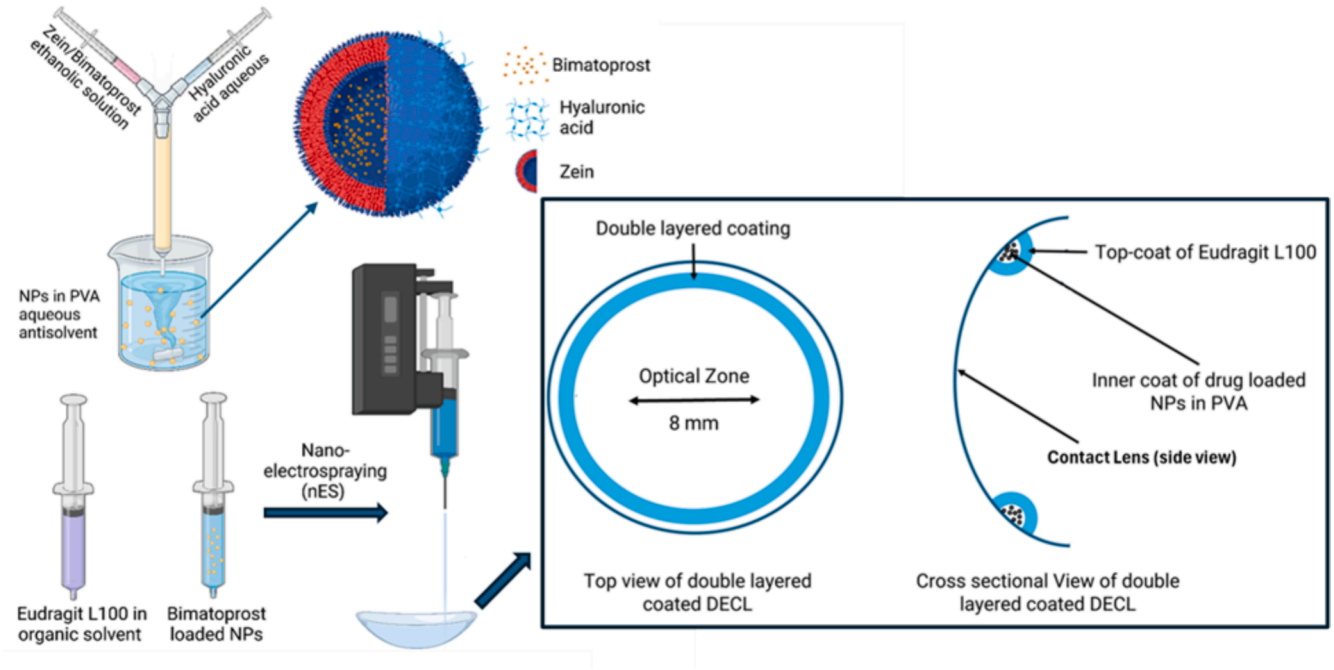

Fig. 1. Schematic illustrations of the formulation preparation and nES process to produce the DECLs.

methods for management of chronic ocular conditions (Maulvi et al., 2017; Pereira-da-Mota et al., 2022; Tieppo et al., 2012). This approach represents a novel improvement over conventional soaking methods, which often struggles to address burst release and prolonged drug retention (Baghban et al., 2023). Although both nanoencapsulation and nanoelectrospray have been reported individually for ocular applications, their integration into a pH-responsive, double-layered DECL platform has not previously been described. Our strategy integrates nanoencapsulation with nES deposition to construct double-layered DECLs that exhibit pH-responsive bimatoprost release. This approach reduces drug loss during storage, ensures reproducibility, and employs environmentally sustainable biopolymers (zein and hyaluronic acid), thereby offering a scalable and patient-oriented platform for long-term glaucoma therapy. This approach uniquely combines sustained, on-demand release, reduced drug loss during storage, and compatibility with industrially scalable fabrication processes, thereby addressing critical translational barriers to clinical adoption of smart contact lenses.

2. Materials and methods

2.1. Materials

Bimatoprost was purchased from Molekula (Darlington, UK). Phosphate buffered saline (PBS) solution tablets (pH 7.4), triethylamine (≥99.5 %), phosphoric acid (≥85 %), Hyaluronic acid (MW of 300,000–500,000), PVA and Zein were obtained from Merck (Gillingham, UK) and Eudragit L100 was kindly donated by Evonik (Darmstadt, Germany). Methanol and acetonitrile, high-performance liquid chromatography grade, were purchased from Fisher Scientific (Loughborough, UK). The ceramic MicroDot tips with a 50 μm inner diameter (P/N 7,364,054) were purchased from Nordson EFD (Dunstable, UK).

Commercial soft contact lenses, Biomedics® 1-day extra contact lenses (CooperVision Ltd, USA), with a composition of 45 % ocufilcon D/ 55 % water, were used as the model contact lens. Their characteristics are as follows, base curve 8.6 mm, diameter 14.2 mm, centre thickness 0.08 mm, water content 55 %, oxygen transmissibility Dk/t ≈ 24 × 10^{-9}, and refractive index 1.409. Biomedics contact lenses (HEMA-based hydrogel, 55 % water content) were selected due to their high hydration capacity, which ensures compatibility with nanoelectrospray deposition and allows uniform polymer coating. Their properties have been previously reported to support reproducible polymer deposition (Tam et al., 2022).

2.2. Preparation of bimatoprost-loaded zein and hyaluronic acid (HA) NPs

Bimatoprost-loaded nanoparticles (NPs) were prepared using flash nanoprecipitation, modified from the method of Jacinto et al. (Jacinto et al., 2022). Zein (2.5 %, w/v) was dissolved in 70 % ethanol to form the organic phase. Bimatoprost was dissolved in the zein solution at the desired concentration (25 mg/ml) under magnetic stirring at 350 rpm for 2 h. Separately, a 1 % (w/v) solution of hyaluronic acid (HA) was prepared in water. Zein-drug solution and HA solution were mixed at a 1:1 ratio using a V-mixer (Yus et al., 2020) to ensure rapid and homogeneous mixing, injecting into antisolvent aqueous phase at a rate of 1 ml/s. The combined mixture was immediately injected into antisolvent aqueous phase containing 1.5 % polyvinyl alcohol (PVA) in 35 % ethanol at a 9:1 ratio (PVA aqueous phase: Zein/HA organic phase), over magnetic stirring at 350 rpm. This rapid injection facilitated the precipitation of NPs as the organic solvent diffused quickly into the aqueous medium, leading to NPs formation. Following the rapid injection, the NP dispersion was removed from magnetic stirring. As required, a dialysis step of the drug-loaded NP formulation was performed to effectively reducing the amount of unencapsulated bimatoprost prior to deposition on the contact lenses. This was done by loading a dialysis bag (molecular weight cut-off of 10 kDa) with NP dispersion, followed by submerging in a receptor solution of phosphate-buffered saline (PBS) at pH 7.4 and kept at 4 °C for 2 h prior to use. This ensured removal of free drug while retaining HA nanoparticles (MW 300–500 kDa), which provide enhanced lubrication and ocular comfort (Zhang et al., 2021).

For dialysis studies, 0.5 mL of nanoparticle dispersion was sealed in each dialysis bag and immersed in 250 mL of PBS to maintain sink conditions. In this context, 0.5 mL nanoparticle dispersion (2.5 mg/mL) was placed in a dialysis bag and immersed in 250 mL PBS (pH 7.4). Considering the aqueous solubility of bimatoprost (20 mg/L), the theoretical minimal receptor volume to dissolve the donor dose is ~ 62.5 mL. A 250 mL receptor volume was therefore selected to provide a > 4-fold safety margin, ensuring sink conditions and avoiding solubility-

limited artefacts during release measurements.

2.3. Nanoparticle characterisation

The size distribution, surface charge and morphology of the NPs were assessed using transmission electron microscopy (TEM), and dynamic light scattering (DLS). TEM sample preparation involved placing a 5 μL drop of NP dispersion onto carbon-coated copper grids, followed by negative staining with 2 % uranyl acetate and drying. The samples were imaged using a Gemini 360 EM (Zeiss, Cambridge, UK) operating at 15 kV in NanoVP mode. Images were captured, and then analysed using ZEISS ZEN core software (Zeiss, Cambridge, UK). For TEM analysis, a minimum of three images were obtained per sample, with at least three independent samples analysed.

DLS analysis was performed to measure the particle size, polydispersity index (PDI) and zeta potential of the NPs using a Malvern Zetasizer Nano ZS (Malvern Panalytical Ltd, UK). For each measurement, a 1 mL aliquot of the nanoparticle dispersion was transferred into a disposable semi-micro cuvette (BRAND® cuvette, Brand GmbH + Co KG, Wertheim, Germany). DLS analysis was conducted at 20 °C, with an auto-attenuator, and a laser wavelength of 600 nm. Particle size outcomes were reported as Z-average average diameters. Each sample was analysed in triplicate (n = 3) for both size and zeta potential, and the results were presented as the mean ± standard deviation (SD).

2.4. Drug loading (DL) and entrapment efficiency (EE)

The DL and EE of bimatoprost within the NPs were assessed using a dialysis method. A known volume of the nanoparticle suspension (1 ml) was placed inside dialysis membrane bag with a molecular weight cut-off of 10 kDa. The dialysis bag was then submerged in a receptor solution of phosphate-buffered saline (PBS) at pH 7.4 and kept at 4 °C. Samples from the receptor solution were collected after 24 h to measure the amount of dialysed drug, related to the free unentrapped drug (n = 3). The concentration of free drug was analysed using high-performance liquid chromatography (HPLC) (Franca et al., 2014). Briefly, bimatoprost concentrations were measured using an HPLC system (Jasco, Tokyo, Japan) with a PU-1580 pump, an AS-2055 Plus autosampler, and a UV-1570 M 4-channel UV detector. Separation was achieved on a Waters C18 column (250 × 4.6 mm, 5 μm particle size) with an HC–C18 guard column (Agilent, California, USA) under ambient conditions. The mobile phase consisted of acetonitrile, methanol, and 0.1 % phosphoric acid (30:30:40, v/v/v), with a flow rate of 1 mL/min and detection wavelength set to 210 nm. Samples were analysed in triplicate, and the results were presented as the mean ± SD. The DL (%) and EE (%) were then calculated using the following Eq. (1) and (2):

$$EE\% = \left(\frac{Totaldrug - Freedrug}{Totaldrug}\right) \times 100 \quad (1)$$

$$DL\% = \left(\frac{Total\,drug - Free\,drug}{Weight\,of\,\text{used}\,polymers}\right) \times 100 \quad (2)$$

2.5. DECL preparation by nanoelectrospraying (nES)

DECLs were prepared using nES. Prior to coating, commercially available contact lenses were removed from their original packaging and equilibrated in phosphate-buffered saline (PBS) at pH 7.4 for 30 min to ensure hydration. After equilibration, excess PBS on each lens was removed using a lint-free dry wipe (RS Components, Corby, UK) to prevent interference during the coating process. To maintain lens hydration throughout the coating process, 10 μL of pH 7.4 PBS was added to the custom 3D-printed lens holder before positioning the contact lens onto it. The exact layout is described in detail in our previous work (Tam et al., 2024; Tam et al., 2022).

All types of lenses tested in the study are listed in the Table 1. Lenses were soaked in 2 mL of bimatoprost solution (2.5 mg/mL in 70 % w/v ethanol) for 24 h at 4 °C, serving as the control with a lens code of L-S. Excess solution was removed by gently blotting the lenses with lint-free tissue, followed by rinsing three times in pH 7.4 PBS prior to use. The L1-F lenses were prepared by nES of a single layer of Eudragit L100 1.5 % (w/v) in ethanol/acetone solvent mixture (70:30) solution containing 2.5 mg/ml dissolved bimatoprost. Lenses coated with a single layer of bimatoprost-loaded HA/Zein NPs in polyvinyl alcohol (PVA) solution (L1-NP) were also prepared by nES. The concentration of the PVA solution was optimised for stability and adhesion to the lens surface. For the double layer coated lenses (L2-NP-E), the full coating process involved a double-layered approach, with a first (inner) layer of NPs in PVA solution and a second (top) layer of drug-free Eudragit L100 (1.5 % (w/v) Eudragit L100 dissolved in a 70:30 ethanol/acetone solvent) for pH-responsive drug release.

Table 1
Codes for the lenses used in this study indicating the number of layers and the formulation of the coating.

Lens code	Number of layers	Layer composition (s)
L-S	0	No nES coating. The drug was loaded using the soaking method
L1-F	1	Bimatoprost (2.5 mg/ml) dissolved in Eudragit L100 in ethanol/acetone solvent mixture (70:30)
L1-NP	1	Bimatoprost-loaded HA/Zein NPs in PVA (1 % w/v) solution
L2-NP-E	2	Bimatoprost-loaded HA/Zein NPs in PVA solution as the inner layer and the drug-free Eudragit L100 as the outer layer

Our custom-built nES system (PCE Automation, Beccles, UK) was used to spray each layer onto the contact lenses. For double-layer coating, the NP-PVA solution was sprayed onto the lenses first, followed by the Eudragit L100 solution, ensuring an even coating without obscuring the optical zone. Spraying parameters, optimised in preliminary studies are shown in Table 2.

Following nES deposition, lenses were placed on sterile lint wetted with buffer and stored at 4 °C for 4 h to allow ethanol evaporation without lens dehydration. The deposited volume was controlled by nES parameters (rotation number, spray speed, nozzle–substrate distance), which were standardized across experiments.

The drug content of the DECLs was determined by replicating the deposition process using nES onto aluminium foil, to ensure uniform deposition (n = 3). The deposited mass was then dried, transferred into a vial, and dissolved in an ethanol/acetone solvent mixture. The resulting solution was analysed for drug content in triplicate using the HPLC method described previously. Deposition method on aluminium foil was performed only for parameter optimization. For all experimental lenses, drug content was quantified by extraction in 2 mL DMF, ensuring complete polymer digestion and accurate determination of loading. This was further confirmed by extracting the drug from the contact lenses in triplicate after double-layer deposition

2.6. Physical characterisation of nES-coated DECLs

The optical transmittance of the DECLs was measured using a UV–Vis spectrophotometer (Lambda 35, Perkin Elmer, Beaconsfield, UK) across

Table 2
Nes operational parameters applied to all nes-coated lenses.

Operational parameter (unit)	Value
Nozzle-substrate-distance (NSD) (mm)	2.99
Dosing speed (mm/s)	15
Spraying radius (mm)	5
Number of nozzle ration revolutions for 1st layer	70
Number of nozzle ration revolutions for 2nd layer	70

a wavelength range of 200–800 nm, according to previously described method (Wang et al., 2021). To maintain hydration, three coated contact lenses were immersed separately in a quartz cuvette filled with phosphate-buffered saline (PBS) at pH 7.4. Each lens was positioned with its convex side facing the incoming light beam. Uncoated contact lenses were used as a control to establish baseline transmittance, with an expected transmittance of at least 95 % for optimal clarity.

The thickness of the coating was measured using an electronic ET-3 thickness gauge (Createch Rehder, Inc., Greenville, USA) with an accuracy of 2 μm. Uncoated lenses were first equilibrated in PBS (pH 7.4) for 30 min. Baseline thickness measurements were taken at three predetermined locations in the peripheral region of each uncoated lens. After applying the double-layered nES coating, the thickness at the same locations was remeasured to determine the total coating thickness. Each measurement was repeated for three lenses to obtain an average thickness value.

A Stylus Profilometer (DektakXT, Bruker, MA, USA) was used to analyse the surface profile of the dried films on the lenses deposited by nES. For the measurements, the profilometer was set to the "Hills and Valleys" profile, with a 2 μm radius stylus applied at a force of 1 mg.

The surface morphology of the nES-coated contact lenses was observed at different levels of resolution using a FDSC196 optical microscope (Linkam Scientific, Salfords, UK) and cryo-scanning electron microscopy (cryo-SEM). Prior to cryo-SEM imaging, each lens was cut into quarters, and a single piece was rapidly frozen in nitrogen slush for cryo-preservation. The frozen sample was then transferred to a PP3010T cryo-chamber (Quantum Design AG, Marly, Switzerland) for sublimation of surface ice, followed by sputter coating with platinum under vacuum conditions. SEM imaging was conducted using a Gemini 360 SEM (Zeiss, Cambridge, UK) equipped with a cryo-chamber, and images were acquired on a cold stage to ensure high-resolution visualisation of the coating layers.

2.7. In vitro drug release of nES coated contact lenses

The *in vitro* drug release of DECLs was measured using two methods, a conventional method and using a tear flow simulating (TFS) device-based method. For the conventional method, the DECLs (after being washed 3 times to remove excess solution) were placed in glass vials containing 2 mL of either PBS at pH 7.4 or acetate buffer at pH 5.5, and the vials were placed in a shaking incubator set to 37 °C with a rotation speed of 300 rpm. At predetermined intervals, aliquots (300 μL) were removed from the release medium and replaced with fresh buffer. The amount of bimatoprost released was quantified using the HPLC method described earlier. Each aliquot was mixed with the appropriate mobile phase in a 1:1 ratio and filtered through a 0.2 μm PTFE syringe filter (Fisher Scientific, UK) before analysis.

A comparative release study was conducted using three different DECLs: (1) contact lenses soaked in an ethanolic solution of bimatoprost, used as control (L-S) (2) contact lenses coated with a single layer of drug loaded Eudragit film (L1-F), (3) contact lenses coated with a single layer of drug-loaded nanoparticle suspension (L1-NP), and (4) double-layer coated DECLs containing a bimatoprost-loaded NPs inner layer and Eudragit L100 top layer (L2-NP-E). Each formulation was tested in PBS at pH 7.4 and acetate buffer at pH 5.5 to evaluate the impact of pH on the drug release profile. Release studies were conducted in triplicate, with three independent lenses tested per condition. Results are presented as mean ± standard deviation (SD).

The drug content was confirmed by digesting drug-loaded contact lens and analysing the bimatoprost content using the HPLC assay method described previously. Drug stability post-digestion was verified by HPLC, confirming no degradation of bimatoprost. In brief, 1 mL of dimethyl formamide (DMF) was used to transfer each contact lens individually. After complete degradation of the lens, the solution was diluted 1:100 with the mobile phase. Drug content was quantified for all lens systems. For soaking-loaded lenses, the concentration of bimatoprost in the soaking solution was adjusted to yield drug contents comparable to nES-loaded lenses. Subsequently, HPLC was employed to quantify the bimatoprost content. Thus, the percentage cumulative drug release at each time point could be calculated using the following equation Eq. (3):

$$\%Cumulativerelease = \left(\frac{M_t}{M_\infty}\right) \times 100 \tag{3}$$

where: M_t is the amount of drug released at time t, and M_∞ is the total drug content in the contact lens determined by degradation analysis

To better simulate *in vivo* ocular conditions, an in-house custom-made tear flow simulating (TFS) device was used. The device was prepared according to a model designed by Bajgrowicz et al. (Bajgrowicz et al., 2015) to mimic the natural tear flow over contact lenses (Fig. 2). The TFS setup was fabricated by 3D printing using PLA. The device consisted of two interlocking parts designed for a secure fit without clamping. The release medium was pumped in via syringe pump through a side inlet and collected through a narrow outlet orifice. To minimize evaporation, the entire system was sealed with parafilm throughout the experiment. The contact lenses were placed on the surface of the device, and release medium was introduced at a flow rate of 250 μL/hour, replicating physiological tear flow. Samples were collected at regular intervals from the outflow of the device and analysed for bimatoprost content using HPLC as described previously. A comparative study was conducted to evaluate the difference between the drug release kinetics obtained from the conventional static release method and the TFS device.

Drug release data were fitted to a modified multi-exponential model to describe the change in drug amount released over time (Bebawy et al., 2025). A modified multi-exponential model was selected because the drug release profile exhibited multiple distinct phases, including an initial burst followed by intermediate and sustained release components, which could not be accurately captured by conventional single-phase models such as first-order, Higuchi, or Korsmeyer–Peppas (details are provided in the Supplementary Information SI Table S2). The modified exponential model (Bebawy et al., 2025) is expressed according to the following Eq.4:

$$M_t - M_0 = a_1 e^{-k_1 t} + a_2 e^{-k_2 t} + a_3 e^{-k_3 t} \tag{4}$$

where $M_t - M_0$ represents the amount of drug released at time (t) relative to zero-time, k is rate constant, and coefficients (a_1, a_2, a_3) correspond to the fractional contributions of each release phase. Model fitting was performed using nonlinear regression, optimising parameters to minimise residual sums of squares, and fit quality was assessed by R^2 and χ^2/DOF. Mean dissolution time (MDT) was calculated according to the statistical moment theory, as described by Möckel and Lippold (1993), and reflects the mean time for drug molecules to be released from the dosage form. The mean dissolution time (MDT) was determined from the empirical formula using Eq.5:

$$MDT = \frac{\sum_{i=1}^{n} t_i . \Delta M_i}{\sum_{i=1}^{n} \Delta M_i} \tag{5}$$

where t_i is the midpoint of the time interval i, ΔM_i is the amount of drug released in time interval i, and n is number of time points.

2.8. Drug loss study in pH 5.5 packaging solution

The DECLs were stored in packaging blisters, containing 2.5 ml of acetate buffer (pH 5.5) at 4 °C for 5 days. To calculate drug loss during storage, the amount of drug leached into the buffer was measured at different time points. After the storage period, the lenses were neutralised by washing three times with PBS at pH 7.4. The drug release profile was then evaluated and compared to that of the DECLs before storage. It is worth mentioning that in our approach, DECLs are expected to be

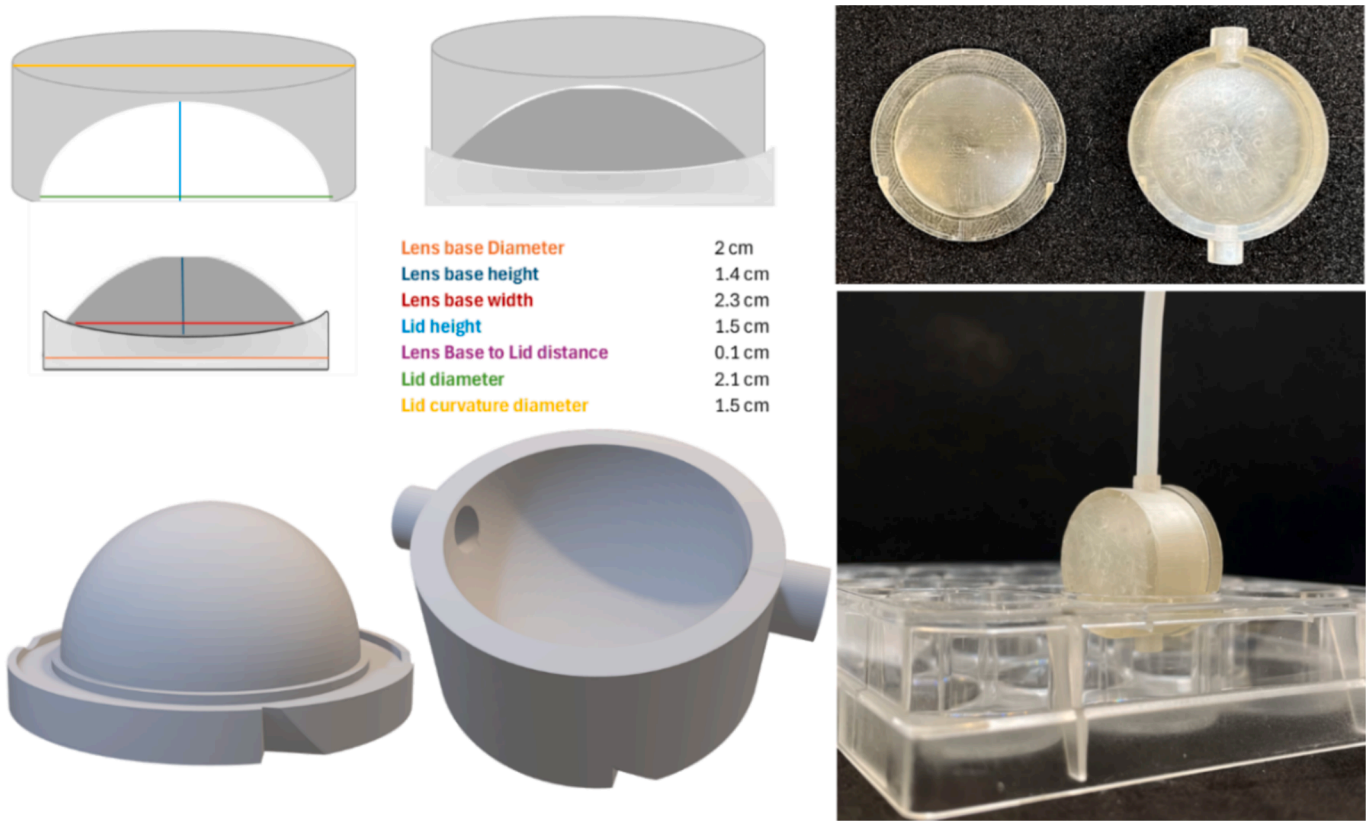

Fig. 2. Custom-made tear flow simulating (TFS) device, mimicking physiological conditions of tear flow for *in vitro* measurement of drug release. The device consisted of two interlocking parts designed for a secure fit without clamping. The release medium was pumped in via syringe pump through a side inlet and collected through a narrow outlet orifice. The coloured lines match the coloured text.

washed by commercial washing buffer before use.

2.9. Statistical analysis

Normality of datasets was assessed using GraphPad Prism®. Data meeting normal distribution criteria were analysed by ANOVA followed by Tukey's post-hoc test, with $p \leq 0.05$ considered statistically significant.

3. Results and discussion

3.1. Physicochemical characterisation of drug-loaded NPs

Particle size is crucial in influencing the release profile of drug molecules from NPs. Smaller particles have a high surface-area-to-volume ratio, which can accelerate drug release, whereas large particles generally provide a more sustained release due to the longer diffusion path of the encapsulated drug (Danion et al., 2007; Peng et al., 2010). The drug loaded NPs were characterised for particle size, polydispersity, and zeta potential to evaluate their stability and suitability for controlled drug release applications. The DLS data revealed a Z-average particle size of 367.7 ± 30.0 nm, with a polydispersity index of 0.34, indicating a narrow size distribution (Supplementary information Fig. S1). For optimising ocular delivery in glaucoma treatment, NPs smaller than 200 nm are typically favoured to enhance corneal penetration and maximise drug bioavailability (Pardeshi et al., 2024; Wang et al., 2025). However, larger particles, approximately 300 nm in size, have demonstrated advantages in sustaining drug release and prolonging therapeutic efficacy (Tieppo et al., 2012; Baghban et al., 2023; Yus et al., 2020). Therefore it is reasonable to expect that the bimatoprost-loaded NPs produced in this study are likely to provide a prolonged drug release profile (Lin et al., 2018; Öztürk et al., 2024). Although the average nanoparticle exceeds the commonly cited threshold for ocular penetration, this is not a limitation in our system, as the nanoparticles are immobilized within the lens coating and are not intended to penetrate corneal tissue. Instead, they function as a depot for controlled release at the tear-lens interface, reducing systemic exposure and ensuring localized delivery (Lin et al., 2018).

The average zeta potential was measured at −10.87 ± 1.27 mV, suggesting a moderate electrostatic colloidal stability against aggregation (Pochapski et al., 2021), which is beneficial during the process of nES, to avoid nozzle blockage. Despite the observed zeta potential (~−11 mV), the nanoparticles exhibited no visible aggregation as confirmed in TEM images, with size distribution remaining stable. Although the zeta potential is lower than typically considered highly stable (|≥30| mV), the presence of HA may also contribute steric stabilisation, which can help maintain dispersion and limit aggregation over time (Chiesa et al., 2021). Hyaluronic acid (HA) contains hydrophilic functional groups that form a protective layer around the NPs, providing steric repulsion that prevents particle–particle interaction and aggregation (Pakian et al., 2024). This steric barrier significantly enhances the colloidal stability of the NPs in dispersion. Furthermore, the use of nES ensures deposition of NPs directly onto the lens surface, which minimises concerns related to colloidal aggregation in solution and long-term storage.

The TEM images of the NPs revealed a relatively uniform and spherical shape (Fig. 3). Spherical NPs have a low surface-area-to-volume ratio, contributing to sustained release by slowing the initial burst effect (Tieppo et al., 2012; Baghban et al., 2023; Yus et al., 2020). Particle size analysis obtained from the TEM images of the drug-loaded NPs, using ImageJ software, showed an average particle diameter of 310.0 ± 23.4 nm, closely matching the values obtained from DLS.

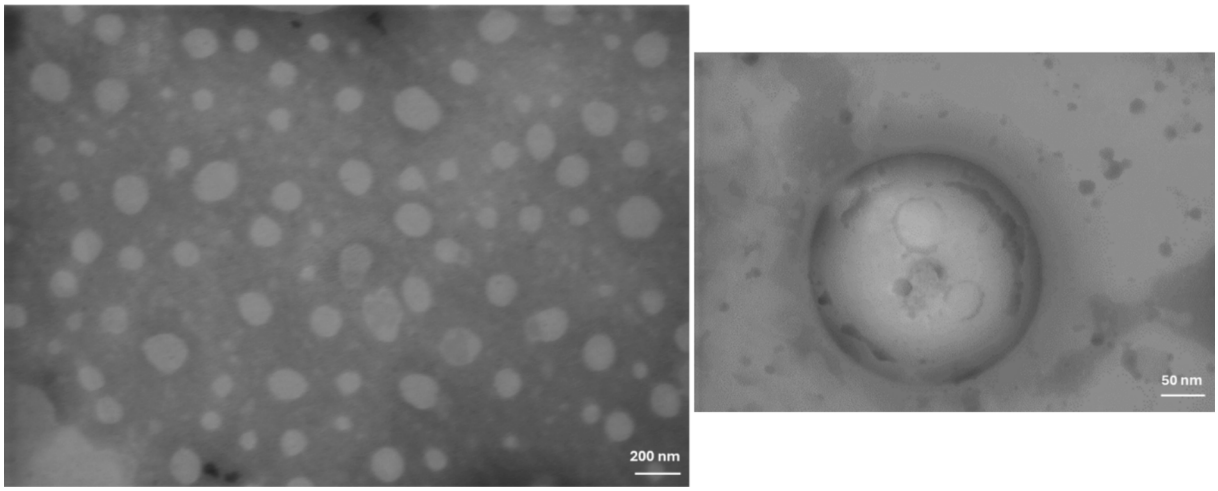

Fig. 3. TEM images of drug loaded Zein/HA NPs, showing spherical particles with no aggregations.

The EE% and DL % of bimatoprost within the NPs were measured to be 37 % ±2.4, and 53.3 ± 1.1 %, respectively. This EE can be attributed the hydrophilic nature of the encapsulating matrix. While the entrapment efficiency of zein/HA nanoparticles was relatively modest, the achieved drug loading remained pharmacologically relevant. This outcome highlights the trade-off between maximal EE% and the selection of biocompatible, patient-friendly carriers such as zein/HA, which also contribute to the ocular safety profile of the DECLs. In the literature, when hydrophobic matrices, such as solid lipid NPs or polymeric PLGA NP systems, were used, higher bimatoprost EE values, typically around 60 %, were reported (Mishra et al., 2009; Satyanarayana et al., 2023). In this study, hydrophilic polymers were used (zein/HA) in our formulation. Although this may contribute to a lower EE, using hyaluronic acid could be beneficial as it not only contributes to the nanoparticle structure, but is also beneficial for ocular applications, with properties that may reduce irritation and enhance comfort upon application of DECLs (Casey-Power et al., 2022). This added benefit may help mitigate some of the potential side effects associated with DECLs by improving the biocompatibility of the formulation with the ocular surface and help in patient tolerance of the treatment (Zhang et al., 2021).

3.2. Physical characterisation of DECLs prepared by nES

While the nES coating process of contact lenses is effective and straightforward, selecting the appropriate polymer matrix, optimising processing conditions, and investigating the necessary requirements for controlled drug release remain critical. Tam *et al.* (Tam et al., 2024) investigated the use of nES to prepare PLGA-coated lenses loaded with a range of model drugs. However, the release behaviour was not well controlled, particularly for bimatoprost, where over 75 % of the drug was released within the first hour. A similar rapid release was observed with latanoprost, although to a lesser extent (Tam et al., 2024). In this study, we implemented a double-layered coating, combining a NP-based inner layer and a pH-responsive polymer (Eudragit L100) top layer, aiming to mitigate burst release and achieve a more controlled drug release pattern. Additionally, this approach could help minimise drug loss during storage, thus ensuring enhanced stability and sustained therapeutic efficacy.

The coating thickness of the material deposited by nES can be influenced by processing parameters, such as nozzle size, spraying speed, and solution concentration. These parameters were maintained constant throughout the experiments to ensure uniformity of the coating. The thickness of the fully hydrated coating is impossible to be measured accurately using either profilometer or microscopic methods. The dried single layer coating was measured using profilometer (data can be found in Supplementary Information Fig. S2) which indicated a coating thickness of less than 1 μm, with the width of the coating band approximately of 230 μm. In the fully hydrated state, the thickness of the coating could be expected to swell to be a few μm in thickness. Fig. 4A is a representative image taken using optical microscopy, revealing a smooth, continuous coating with well-defined edges and an average width of 410 ± 12 μm.

High optical transmittance is crucial for DECLs to minimise interference to vision (Wu et al., 2021). Following the methodology established in the literature (Quesnel and Simonet, 1995), the minimal optical transparency was set at 95 % transmittance, and the measurement of uncoated reference lenses was 97.6 ± 0.3 %. L2-NP-E lenses demonstrated transmittance levels of 95.63 ± 0.3 % in the central zone, meeting the minimum requirement for transparency. The nES method facilitated the precise deposition of the polymer double layer around the periphery of the contact lens (Fig. 4B), aiming to minimise any impact on vision when wearing.

The changes in morphology of the coatings on the lenses after being exposed to solutions with different pHs were examined using cryo-SEM (Fig. 5). The surface of the Eudragit coating (L1-F) after being soaked at pH 5.5 for 2 h appears as an intact, continuous layer with minimal visible pores (Fig. 5A). This indicates that the Eudragit coating remained as a dense, cohesive film under weak acidic conditions (pH 5.5), which could provide a barrier for undesired drug release and premature release during storage at pH 5.5 (Patra et al., 2017).

After being soaked at pH 7.4 for 2 h the coating on L1-F lenses has a notable increase in surface porosity, with visible pores across the film (Fig. 5B). This increased porosity at pH 7.4 is consistent with the pH-responsive nature of Eudragit L100, which undergoes structural changes at higher pH levels due to increased solubility. This would allow for a more permeable coating that could facilitate drug release (Patra et al., 2017).

Fig. 5C shows the morphology of the coating on L2-NP-E lenses after being exposed to pH 7.4 for 2 h. The image reveals a distinct two-layer structure. The upper Eudragit coating is discontinuous due to the polymer dissolution at pH 7.4, exposing the underlying nanoparticle layer. The presence of the NPs beneath the Eudragit coating is evident, indicating successful formation of the double-layered structure. The upper Eudragit layer could act as a protective barrier at acidic pH, while the inner nanoparticle layer provides the primary drug reservoir.

Drug loading onto the contact lenses was determined to be 40 ± 2.6 μg per lens, as quantified by HPLC with no statistically significant differences observed across batches ($n = 3$, ANOVA, $p > 0.05$). The coefficient of variation (CV) was < 5 %, confirming uniform deposition and reproducibility of the nanoelectrospray process. This consistent and

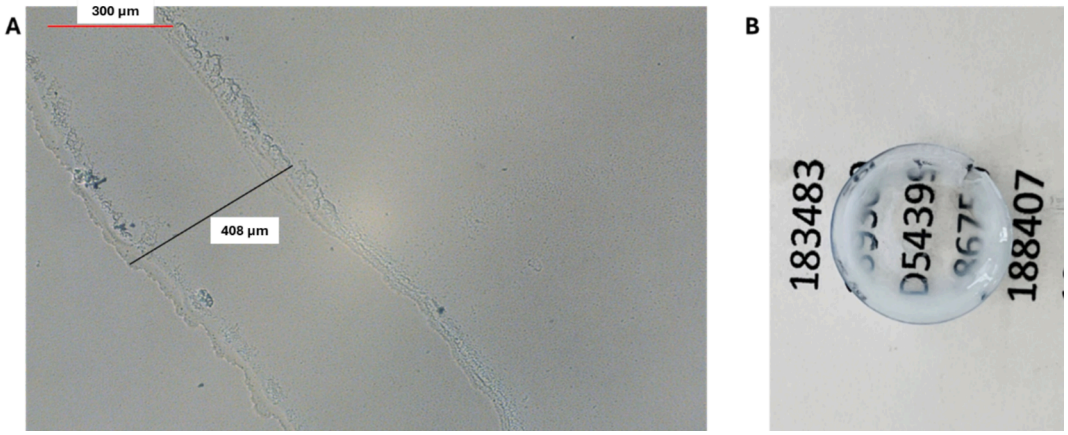

Fig. 4. Physical characterisation of coated DECLs using nES. A) light microscopy image of the double layered DECL (L2-NP-E), B) a photographic image of the L2-NP-E lens showing clarity of the central vision region of the lens.

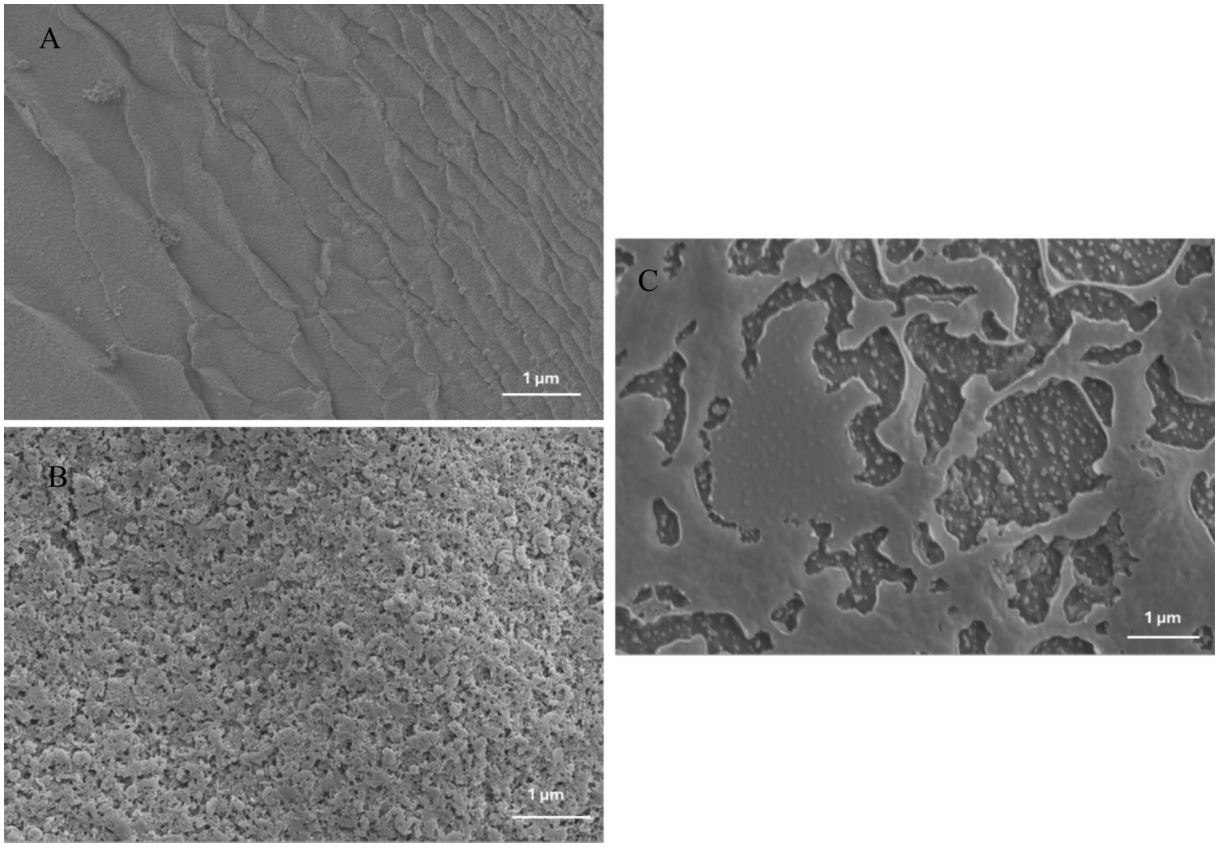

Fig. 5. Cryo-SEM image of DECL after being exposed to different media. The coating on L1-F lenses A) after soaked in pH 5.5 buffer for 2 h and B) after soaked in pH 7.4 buffer for 2 h. C) the coating on L2-NP-E lenses after soaking in pH 7.4 buffer for 2 h.

reproducible loading demonstrates the efficiency of the nES deposition technique in delivering a controlled amount of drug onto the lens surface (Tam et al., 2022). The therapeutic concentration range of bimatoprost in the aqueous humour has been reported to lie within ~ 2–45 ng/mL following topical instillation, depending on dose and time after administration (Camras et al., 2004; Ogundele and Jasek, 2010). Conventional eye drops can reach these levels but with low bioavailability (~5%) due to rapid elimination from the precorneal surface. By contrast, drug-eluting contact lenses offer extended residence and controlled drug release, potentially enhancing the bioavailable fraction and maintaining therapeutic concentrations over longer periods. Achieving precise drug loading is critical for ensuring therapeutic efficacy while minimising the risk of adverse effects associated with dose variability. Since this loading amount is within the therapeutic range required for ocular delivery, supporting the potential of the fabricated lenses as a viable platform for sustained drug delivery in glaucoma management (Easthope and Perry, 2002).

3.3. *In vitro drug release of DECLs*

To evaluate the drug release performance of the developed formulations, a series of *in vitro* studies were conducted under physiologically

relevant conditions. At first, drug-eluting contact DECLs were tested using a conventional static release method. The *in vitro* drug release tests were performed on individual lenses which means that it was not possible to accurately measure the total drug contents of each lens which requires the full extraction of drug from the coatings prior to the release test. Therefore, the cumulative drug release is presented as absolute quantity of drug released (Fig. 6) to capture differences in release kinetics, barrier function, and pH responsiveness. This aligns well with how other DECL studies present *in vitro* release data (Ciolino et al., 2014; Hiratani et al., 2005). Drug release profiles are presented both as absolute drug released (μg) and as cumulative percentage of the average total loaded amount (40 μg), to allow clearer comparison across different lens formulations. The cumulative release data presented as a percentage can be found in the Supplementary Information (SI, Fig. S3 and S4) where 100 % drug loading was calculated by taking the average value of the total drug content measured (40 ± 2.6 μg; n = 3).

PBS pH 7.4 media, mimicking the pH of human tear fluid, was used to study *in vitro* drug release. The release data (Fig. 6) revealed differences in drug release kinetics between bimatoprost-soaked lenses, L-S, as the control, single-layer coated lenses (L1-F and L1-NP), and the double layered DECL (L2-NP-E). The L-S exhibited a rapid burst release of 24 μg (~60 %) in the first 15 min, mostly due to the unencapsulated drug readily diffusing out from the lens matrix. The lack of sustained release from soaked lenses is expected as reported in the literature, where directly soaked lenses without an encapsulating or barrier layer show uncontrolled drug diffusion, often leading to suboptimal therapeutic profiles due to rapid depletion (Lovrec-Krstič et al., 2023). The drug release of L1-F at pH 7.4 showed burst release of 17.7 μg (~43 %) in the first 15 min. The L1-NP without Eudragit displayed a similar level of burst release to L1-F, with about 14 μg (~35 %) released in the first 15 min.

The double-layered lenses, L2-NP-E, exhibited the slowest release rate at pH 7.4 compared with the single-layer coated lenses. At pH 7.4, the amount drug released was 13 μg in the first 15 min, 17.1 μg in the first hour, 37.2 μg over 8 h and 40.03 μg within 24 h, corresponding to approximately 30 %, 43 %, 90 % and 100 %, respectively. This double-layered coating structure combines the encapsulating effects of NPs with Eudragit's pH-responsive polymeric matrix barrier, effectively modulating release over an extended period which is within the timeframe to achieve prolonged drug release for daily wear lenses, as well as mitigate the drug loss during storage if the lenses are stored in pH 5.5 solution. Since HA is a substrate for lysozyme in the tear film, some acceleration of drug release *in vivo* compared to buffer-based *in vitro* studies might be expected (Casey-Power et al., 2022). Nevertheless, the presence of the pH-responsive Eudragit L100 layer and the zein/HA complex matrix mitigates premature release. Moreover, enzymatic degradation ensures biodegradability and long-term safety. Future *in vivo* studies will be essential to confirm the influence of lysozyme activity on release kinetics.

Additionally, while direct deposition of pH-responsive nanoparticles onto contact lenses may achieve controlled release, our double-layer approach provides added benefits. The outer Eudragit L100 layer acts as a protective barrier, minimizing premature drug loss during storage, while the layered architecture enables finer modulation of release kinetics. This dual mechanism results in improved stability and sustained release performance. In contrast, applying a Eudragit layer directly onto soaked lenses failed to sustain release effectively (Fig. 6, L1-f).

Our release data aligns well with other literature reporting controlled release of bimatoprost from DECLs. For example, the use of microemulsion-laden contact lenses demonstrated the reduction of burst release of bimatoprost to 30–40 % in the first hour, as reported by Xu *et al.* (Xu et al., 2019). Gold nanoparticles either loaded with bimatoprost or gold nanoparticles laden lenses soaked in bimatoprost solution were tested by Li et al (2021). Their results revealed over 50 % drug release in the first hour which is slower than bimatoprost soaked lenses.

The initial burst release from formulations containing NPs could have been due to the nanocarrier's low entrapment efficiency causing significant amounts of free drug which contributed to the initial burst release. To remove the free drug, dialysis of the NPs was performed and utilised for L-NP and L2-NP-E lenses coating. The *in vitro* drug release profiles from these lenses are shown in Fig. 7. The results show reductions of the initial burst release at pH 7.4 for all lenses when the dialysed NPs were used. The drug release in the first hour was reduced from 27.0 μg to 19.5 μg and 17.2 μg to 12.6 μg, respectively for L1-NP and L2-NP-E which is equivalent to approximately 69 % to 48.8 % for L1-NP lenses, 43 % to 31.6 % for L2-NP-E lenses. This indicates that there was approximately 3–4 μg of free drug in the NP formulations.

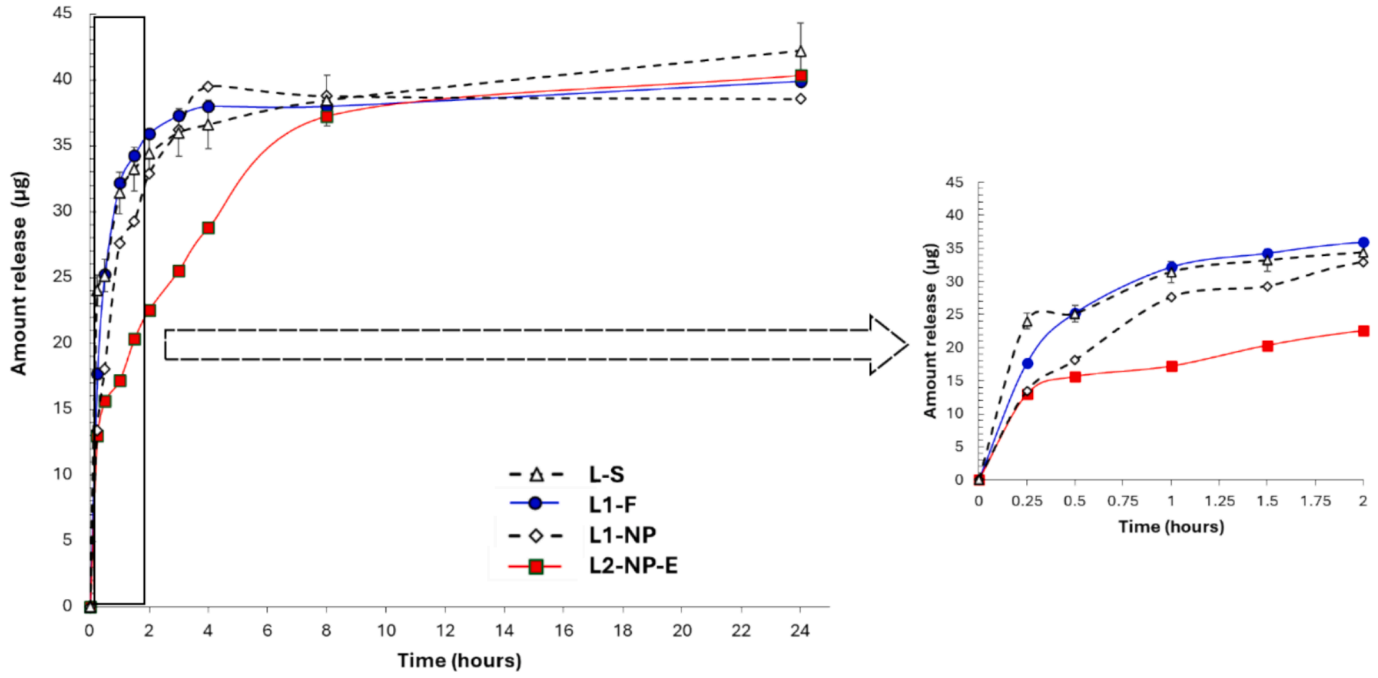

Fig. 6. Comparative *in vitro* drug release profile of L-S, L1-F, L1-NP, L2-NP-E measured using conventional static methods at 37° C and 300 rpm at pH 7.4.

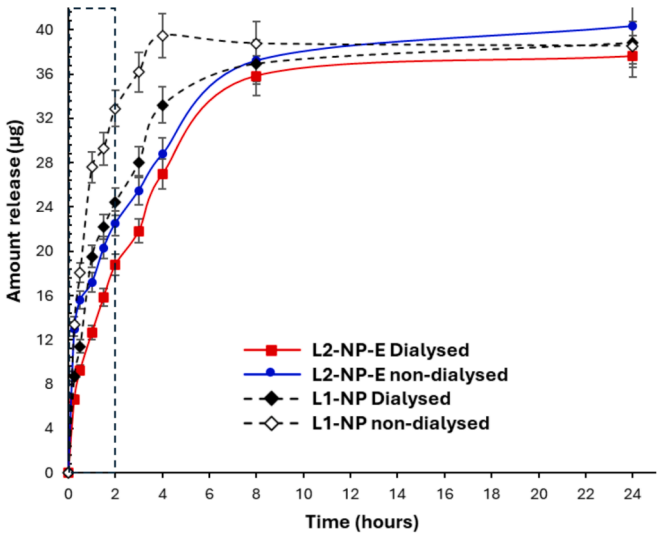

Fig. 7. Comparative drug release profile of double layered DECLs prepared by nES before and after dialysis to remove free drug from bimatoprost loaded Zein/HA NPs. Release media was at physiological pH 7.4.

3.4. Drug loss on storage of double layer coated DECLs

Prior to use in practice, DECLs would require storage. It was therefore investigated whether L2-NP-E lenses could retain bimatoprost in the coating if stored at pH5.5 for 5 days and whether the remaining drug could be released after this period on exposure to physiological pH 7.4. To assess release during storage L2-NP-E lenses were stored in blisters containing 2.5 ml acetate buffer at pH 5.5 and 4 °C for a storage period of 5 days. A gradual increase in the amount (µg) of bimatoprost released over time under storage conditions is seen in Fig. 8A, with the total drug loss plateauing around 11 µg after 2 days which is equivalent to a 26 % loss from the initial loading. Although approximately 26 % of drug loss was observed over 5 days of storage at pH 5.5, this value remains within pharmacologically acceptable limits for sustained therapeutic delivery. Future optimization strategies include tailoring the thickness of the Eudragit L100 layer, exploring alternative packaging buffers, and developing multilayered coatings to further minimize premature loss. These refinements will also support regulatory compliance and clinical translation of the DECL system.

Fig. 8B shows the drug release profile at physiological pH of 7.4 of L2-NP-E lenses that had been stored for 5 days in pH 5.5 compared to lenses not subjected to storage condition. A reduction in total drug release in the lenses being stored for 5 days was observed, likely to attributed to the drug loss during storage. The amount of reduction, approximately 10 µg, agrees well with the drug loss detected from the storage experiment (Fig. 8A). The retained, controlled release profile post-storage, however, suggests that the overall release mechanism remains functional, with Eudragit still effectively acting as a barrier layer. While storage stability was confirmed over a one-week period in this study, long-term stability studies spanning weeks to months under ICH-recommended conditions for clinical translation will be necessary to establish shelf life, an important perspective in future work.

It should be noted that the bimatoprost ophthalmic solution currently used in clinical practice (administered once daily) contains approximately 15 µg of bimatoprost per drop, assuming an average drop volume of 50 µL. Considering that the ocular bioavailability of conventional eye drop formulations is typically only 1–5 % (Curran, 2009), the effective therapeutic dose is estimated to be no more than 0.75 µg of bimatoprost. In comparison, the contact lenses developed in this study released a total of approximately 20 µg of bimatoprost. Thus, even if only 3.75 % of the released drug were bioavailable, this would correspond to the amount delivered by the conventional eye drop formulation. Although the exact bioavailability of drug released from the contact lenses cannot be determined without *in vivo* investigation, previous studies on DECLs have demonstrated that sustained release and prolonged residence time on the corneal surface can enhance ocular bioavailability by up to 50 % (Li and Chauhan, 2006; Rykowska et al., 2021). This means that potentially the dose loaded to the lens could be lowered and still attain the same level of therapeutic outcome achieved by eye drops.

The findings on drug loss over extended storage in controlled-release ocular systems are well-documented in the literature, with many systems showing significant drug loss over time. This loss is typically due to storage conditions, such as temperature and humidity, which affect the release of the drug in these delivery systems (Abdelkader et al., 2012). However, in the case of our double-layered pH-responsive DECLs, the drug loss during the 5-day storage was considerably lower. Our stability study was conducted until equilibrium was reached (5 days). While this does not reflect commercial shelf-life, it demonstrates the potential of the system. Future studies will focus on long-term storage stability under industry-relevant conditions. The *in vitro* drug release data showed that after storage no burst release was observed. In storage medium, the drug loss seems to reach a plateau of maximum drug loss after 2 days. It is likely that there may not be further drug loss, but this would need to be further investigated. This result suggests that the pH-responsive properties of the system, may provide enhanced stability compared to conventional controlled-release formulations.

3.5. Effect of in vitro testing method on drug release kinetics

The widely adopted *in vitro* drug release testing method for DECLs, referred to as the conventional method used to generate the data in the previous section, takes no consideration of the physiological features, such as extremely low tear volume and continuous perfusion. To understand how the *in vitro* method might impact on the *in vitro* drug release results, a tear flow simulating (TFS) method was used in this study to compare with the results generated by the conventional method.

This TFS method allowed a continuous flow of release medium at a physiological rate of 250 µL/hour, mimicking *in vivo* tear dynamics more closely than conventional methods. The confined spacing where the DECL is placed alters the fluid dynamic of the release medium running across the surface of the lens and may affect drug release from formulations on the DECL surface.

The comparison of bimatoprost release from L2-NP-E lenses under the conventional and the TFS methods is shown in Fig. 9A and B. Normality of the release datasets (n = 3 lenses per group) was assessed using the Shapiro-Wilk test, which confirmed that both the conventional method and tear flow simulation (TFS) groups followed a Gaussian distribution ($p > 0.05$). Statistical comparison was therefore performed using a two-way ANOVA, which demonstrated a significant effect of time on bimatoprost release ($p < 0.0001$). However, no significant difference was observed between the two release methods within the first 3 h or at the study endpoint ($p > 0.05$). At intermediate time points beyond 3 h, the TFS method exhibited a significantly more sustained release compared with the conventional method ($p < 0.05$).

This suggests that the dissolution and diffusion of the drug is sufficiently fast that it is not affected by the fluid dynamic difference of the testing methods. The rapid diffusion and release may be due to residual free drug that remained in equilibrium within the system, likely positioned near the surface of the coating despite efforts to remove it via dialysis. However, beyond 3 h, we hypothesised that the rate of diffusion of the drug from the NPs and outer coating is significantly slower than the rate of diffusion of free drug. The confined spacing with restricted flow rate of release medium becomes the rate limiting factor for the measured drug release.

Although conventional models, including first-order, Higuchi, and Korsmeyer-Peppas, were evaluated (the detailed analysis can be found

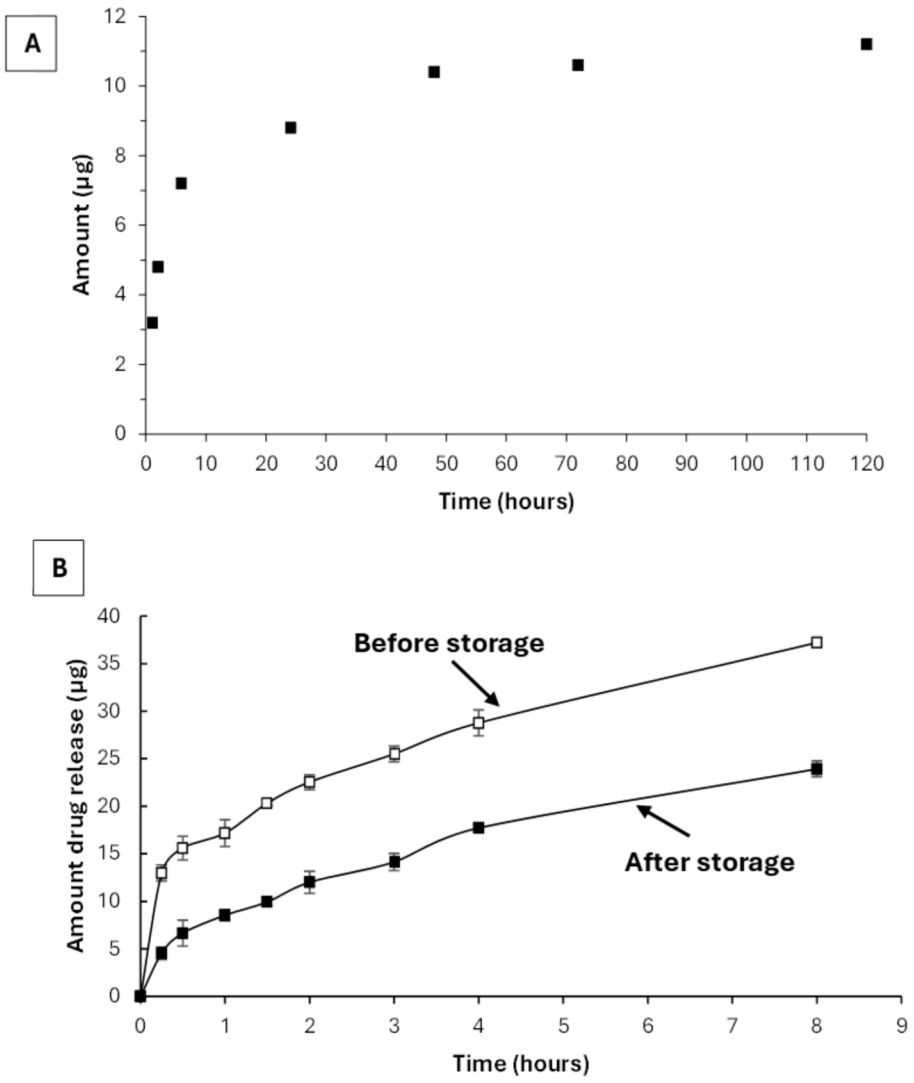

Fig. 8. Drug loss study from L2-Np-E lenses at pH 5.5, A) amount of bimatoprost lost during storage in 2.5 mL acetate buffer pH 5.5 at 4 °C for a period of 5 days; B) drug release of L2-NP-E lenses in pH 7.4 before and after storage for 5 days in pH 5.5 storage solution, measured using the conventional method at 37 °C and 300 rpm. Data are expressed as mean ± standard deviation (SD); error bars are present but not visible at this scale as they are smaller than the data point symbols.

in the Supplementary Information SI Fig. S5), the limited number of experimental time points restricted the reliability of mechanistic parameter estimation using these approaches. On the other hand, fitting the experimental release data to the modified multi-exponential model (Fig. 9 C and D) demonstrated that drug release from the contact lenses followed multiple kinetic pathways rather than a single homogeneous mechanism. The presence of three exponential terms revealed the existence of distinct release phases as expressed in Eq.6.

$$M_t - M_0 = 0.8104e^{-D\times 88.838t} + 0.090e^{-D\times 246.77t} + 0.32e^{-D\times 483.67t} \quad (6)$$

The first phase, which accounted for the largest contribution (coefficient ≈ 0.81, rate constant = 88.8D), represented a rapid initial release typically associated with drug loosely bound to or near the surface of the coating. The second phase (coefficient ≈ 0.09, rate constant = 246.77D) represented an intermediate release process, likely attributed to drug located in moderately accessible regions of the polymer matrix. The third phase (coefficient ≈ 0.32, rate constant = 483.67D) represented a slower, sustained release process likely associated with drug entrapped in denser or more strongly bound regions of the polymer network.

The kinetic study revealed that the TFS model produced lower mean dissolution time (MDT = 3.108 h) compared to the conventional dissolution method (MDT = 5.87 h) as calculated by Eq. (5). This reduction in MDT under dynamic conditions likely reflects the enhanced diffusion and reduced boundary layer resistance achieved by simulating physiological tear flow, thereby providing a more accurate prediction of *in vivo* drug release behaviour (Pereira-da-Mota et al., 2023; Phan et al., 2021). Incorporating the modified exponential model confirmed that diffusion remains the primary release mechanism. However, the dynamic conditions of the TFS model appear to slow down drug release, suggesting that this model could improve the predictability of therapeutic onset and sustained delivery in ocular formulations. These findings support the concept that employing physiologically relevant *in vitro* models is important to better replicate *in vivo* conditions for optimising ocular drug delivery systems.

4. Conclusions

This study demonstrates the potential of using nES to produce double-layered, pH-responsive DECLs for the controlled delivery of bimatoprost, addressing key challenges associated with DECL delivery of various drugs including burst release and drug loss during storage in the packaging solution. Although this study focused on bimatoprost, the nES platform is inherently versatile, enabling deposition of both

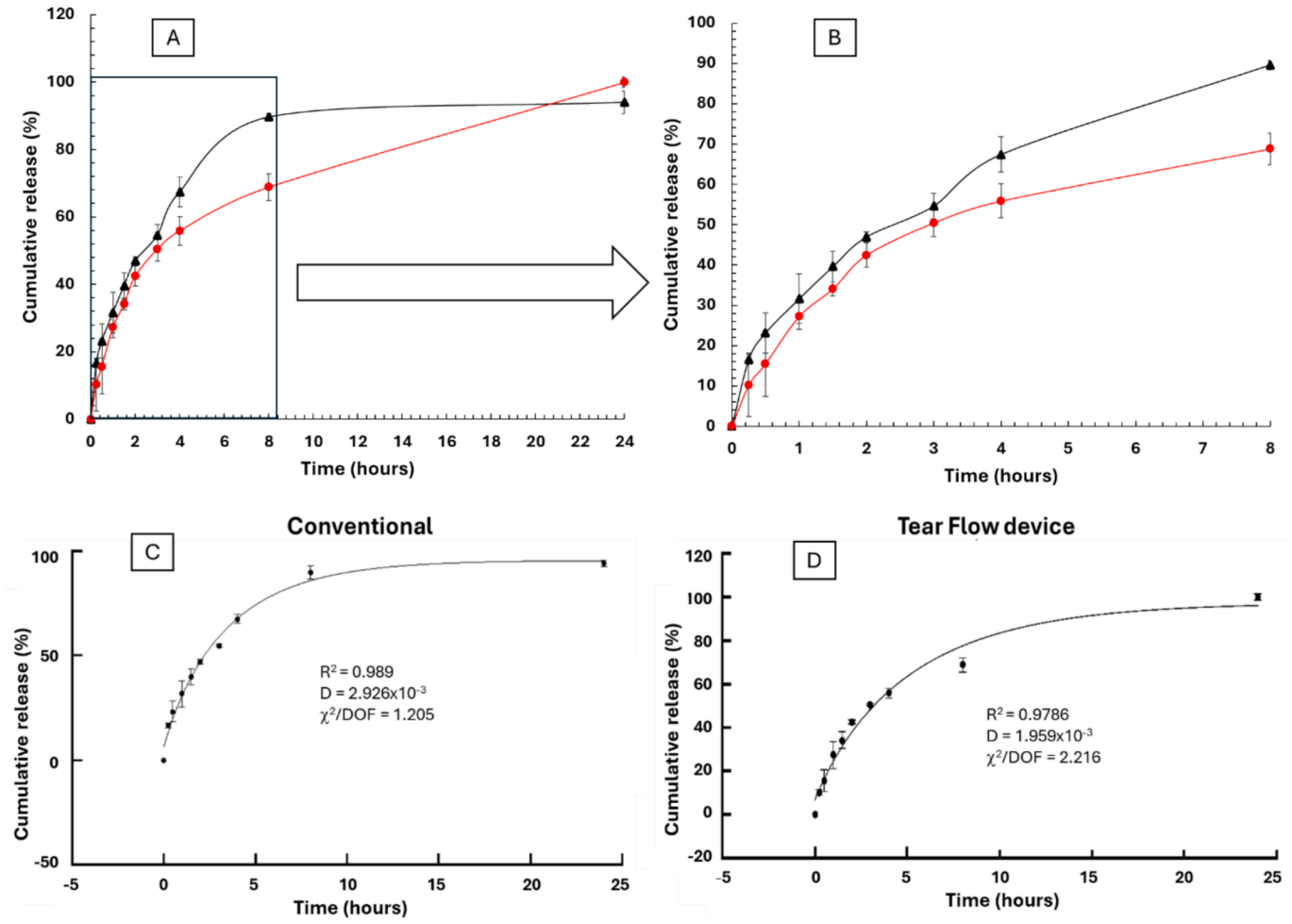

Fig. 9. (A) Comparative drug release profile of L2-NP-E lenses using two release methods, (▲) the conventional method and (●) the tear flow simulating device method (TFS), at pH 7.4, 37 °C and 300 rpm, with (B) the zoomed in for the first 8 h of release. Release kinetics model for L2-NP-E lenses employing the two different release methods tested using (C) the conventional, and (D) the TFS) model, fitted with modified multi-exponential model.

hydrophobic and hydrophilic drugs through direct spraying from appropriate solvents or incorporation into nanoparticle carriers. This adaptability supports the broader application of the platform across a range of ocular therapeutics. The combination of drug-loaded NPs and nES for precise lens coating allowed the fabrication of DECLs with excellent central optical transparency, uniform coating thickness, and controlled drug release properties. The inner NP layer, composed of zein and hyaluronic acid, provided effective drug encapsulation and reduced the burst release effect. The outer layer of Eudragit L100, a pH-responsive polymer, introduced a responsive mechanism that enhanced drug retention at weak acidic pH (5.5; the pH of the storing solution) and controlled drug release at physiological pH (7.4). In comparison to other DECLs and ocular drug delivery systems that only contain drug-loaded NPs, the double-layered system developed in this study offers a significant improvement by introducing a pH-responsive polymer, which adjusts drug release according to the pH at the ocular surface enabling triggered release when the lens is applied to the eye. Storage stability studies confirmed plateauing of drug loss after 2 days in acidic packaging solution. Dynamic tear flow simulating *in vitro* testing obtained a slower and more controlled drug release compared to the conventional *in vitro* method, indicating the impact of the testing method on the release kinetics of DECLs *in vitro*. The results of this study highlight the potential of double-layered DECLs as a scalable and patient-friendly solution for chronic ocular conditions such as glaucoma. This innovative approach enables sustained drug delivery, reduces dosing frequency, and could enhance therapeutic outcomes while maintaining user comfort and visual clarity. Future perspectives will include long-term stability testing under varied storage conditions, sterilisation optimisation, *in vitro* cytocompatibility assessment on ocular cell lines, and evaluation of oxygen permeability and mechanical performance to confirm clinical safety and functionality of the coated DECLs.

CRediT authorship contribution statement

George Bebawy: Writing – original draft, Investigation, Data curation. **Julie Sanderson:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Sheng Qi:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Funding

Medical Research Council (MRC) Impact Acceleration Account (IAA).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.126323.

Data availability

Data will be made available on request.

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