Selectively coated contact lenses by nanoelectrospray (nES) to fabricate drug-eluting contact lenses for treating ocular diseases

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Abstract

Drug-eluting contact lenses (DECLs) incorporated with poly(lactic-co-glycolic acid) (PLGA) and various model drugs (ketotifen fumarate, bimatoprost and latanoprost) were fabricated by using nanoelectrospray (nES) approach. The resulting DECLs demonstrated outstanding optical transmittance within the optical zone, indicating that the employed coating procedure did not compromise visual acuity under the prescribed spraying parameters. *In vitro* drug release assessments of the model drugs (ketotifen fumarate (KF), bimatoprost (BIM), and latanoprost (LN)) revealed a strong correlation between the model drug's hydrophobicity and the duration of drug release. Changing the drug loading of the more hydrophilic model drugs, BIM and KF, showed no impact on the drug release kinetics of BIM and KF loaded DECLs, whereas for the hydrophobic model drug, LN, the highest LN loading led to the most extended drug release. The conventional steam sterilisation method was found to damage the PLGA coating on the DECLs fabricated by nES. An alternative sterilisation strategy, such as radiation sterilisation may need to be investigated in the future study to minimise potential harm to the coating.

Keywords: nanoelectrospray, drug-eluting contact lenses, ocular drug delivery, ketotifen fumarate, bimatoprost, latanoprost, poly(lactic-co-glycolic acid), controlled drug delivery

1 Introduction

Most ophthalmic drugs are administered as eye drops. Eye drops are self-administered directly to the eye, but many patients struggle to use them properly and causing poor patient adherence[1,2]. More importantly, the bioavailability of eye drops is often limited to less than 5%[3] due to drug loss via tear clearance and drainage from the eye[4]. The tear clearance leads to frequent instillation of eye drops to maintain the drug concentration at the therapeutic level[5]. Additionally, eye drops have been associated with preservative-induced eye irritation and intolerance for long-term usage[6] and highly variable dosing[7,8].

Innovative drug delivery systems are being explored to increase ophthalmic drug bioavailability and effectiveness. By prolonging the drug release in the eye, new drug delivery approaches also aim to reduce the administration frequency. Among the novel ocular drug delivery systems, drug-eluting contact lenses (DECLs) have drawn much attention as a non-invasive method to locally deliver ophthalmic drugs to the eye. DECLs have been reported to improve bioavailability to 50%, compared to 5% by eye drops[9].

The concept of DECLs was first established in the 1960s, and since then, various methods have been reported in the literature to fabricate DECLs[10,11]. The first commercially available DECLs, introduced by Johnson and Johnson Vision in 2022, was prepared by physically soaking the lens in saline solution containing ketotifen fumarate as a preventative measure to ocular itchiness in contact lens wearers[12].

Beyond physically soaking commercially available contact lenses in drug solution, many other methods to load ophthalmic drugs in contact lenses require significant modifications of the current contact lenses manufacturing method. These methods include molecular

imprinting[13], encapsulating drug-loaded polymer films within the polymer matrix of the contact lens[14], and immersing of contact lenses into supercritical fluid[15]. These methods require developing new polymer chemistry and/or implementing a new and complex multi-step contact lens manufacturing process. Many of these may also affect the intrinsic physical properties of contact lenses[16], in terms of comfort-for-wearing and vision correction functions. Direct coating of drugs and polymer onto contact lenses was demonstrated to be an alternative method to prepare DECLs[17–19]. The electrospinning method was adopted to unselectively coat the inner surface of dry contact lenses which the optical zone being clear by removing the applied mask[19]. The extensive coverage of polymer on the contact lens surfaces significantly affects the physical properties of the contact lenses, making them less suited for clinical applications.

We previously reported the development of a bespoke nanoelectrospraying (nES) process as an additive printing method to deposit thin layers of materials onto the surfaces of commercial contact lenses[17]. The nES method does not require masking for coating and holds the potential to fabricate DECLs with tailored dosages. By varying the drug loading while maintaining consistent spraying parameters, it is possible to construct a calibration curve for a specific range of drug loadings and prepare DECLs with tailored dose accordingly.

The drug-loaded spraying solutions comprise a model polymer and model drugs with a range of hydrophobicities. Poly(lactic-co-glycolic acid) (PLGA) was chosen as the model polymer because it is a biodegradable and biocompatible polymer that has been extensively studied and developed for numerous drug delivery systems and medical devices[20]. Several studies have reported using PLGA as the drug carrier to prolong the release of ocular medications[21,22]. The drug release kinetic from PLGA-based drug delivery systems was reported to be

controllable by employing PLGA of different molecular weights[23]. In this study, a PLGA with a relatively high molecular weight was chosen in an effort to achieve sustained drug release from the DECLs.

Model drugs with a range of hydrophobicities were tested in this study to demonstrate the drug delivery capability of DECLs manufactured using nES. The key physicochemical properties of the model drugs are summarised in **Table 1**. The hydrophilic model drug, ketotifen fumarate, is an anti-allergic medication prescribed for managing symptoms associated with allergic conjunctivitis. It is an H_1 histamine receptor antagonist and a mast cell stabiliser, alleviating symptoms such as ocular itching and tearing[24]. The other two hydrophobic model drugs used in this study, bimatoprost and latanoprost, are prostaglandin analogues licensed to treat open-angle glaucoma by reducing intraocular pressure[25]. They are also commonly prescribed as first-line medications for glaucoma treatment.

Table 1. *Physicochemical properties of the model drugs.*

Model drug	Log P	Aqueous solubility[#]	Melting point (°C)
Ketotifen fumarate	3.49[*] [26]	17.47 mg/ml [27]	201.24[22]
Bimatoprost	2.8 [28]	40 µg/ml [28]	63-67[29]
Latanoprost	4.3 [28]	6 µg/ml [28]	N/A liquid

** Of the free base. # At 25 °C and pH 7.0.*

This study aims to evaluate the feasibility and capability of using the nES system to fabricate DECLs. The study investigated three key performance areas of the DECLs: (1) The quality of the coating on commercially available contact lenses; (2) the *in vitro* release of the model drugs from DECLs prepared by nES; (3) the effect of sterilisation on DECLs prepared by nES. For

the *in vitro* drug release study, it was assumed that the drug release kinetics of the nES coating are diffusion-based. Different drug concentrations of the model drugs were employed to test against the assumption that the *in vitro* drug release kinetics can be controlled by altering the drug loading in the coating.

2 Materials and methods

2.1 Materials

Ketotifen fumarate (KF), bimatoprost (BIM) and latanoprost (LN) were purchased from Molekula (Darlington, UK). Phosphate buffer saline (PBS) solution tablets (pH 7.4), triethylamine (≥99.5%), phosphoric acid (≥85%) and PLGA Resomer® RG 756 S (M_w 76k-115k Da, lactide:glycolide 75:25) were obtained from Sigma-Aldrich (Gillingham, UK). Methanol and acetonitrile, high-performance liquid chromatography grade, were purchased from Fisher Scientific (Leicestershire, UK). The ceramic MicroDot tips with a 50 µm inner diameter (P/N 7364054) were purchased from Nordson EFD (Bedfordshire, 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. All materials were obtained from suppliers without further processing.

2.2 DECLs prepared by nanoelectrospray (nES)

The nES process is illustrated in **Figure 1**. Before the nES coating process, commercial contact lenses were removed from their original packaging and equilibrated in PBS pH 7.4 for 30 minutes. Excess PBS pH 7.4 on the lens was removed with a lint-free dry wipe (RS Components, Corby, UK) prior to the nES coating process. To maintain the hydration of the contact lenses during the coating process, 10 µl of PBS pH 7.4 was pipetted onto the silver

region of the 3D-printed lens holder before positioning the semi-dry contact lens on it (**Figure 1B**).

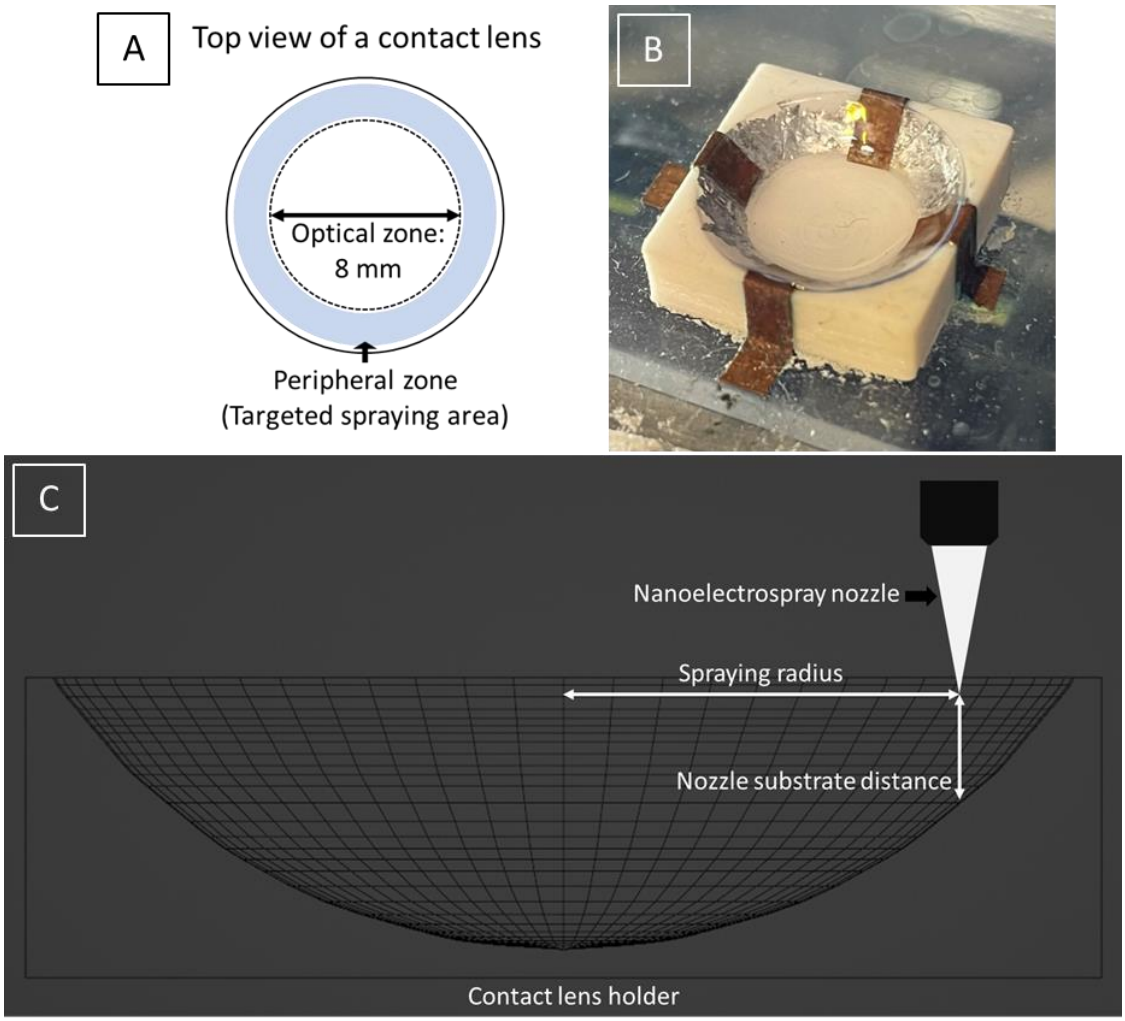


Figure 1. *(A): The targeted spraying area of the polymer-drug layer on contact lens by nES; (B): 3D-printed lens holder with a blank contact lens and (C): illustration of the 3D-printed lens holder and spraying parameters.*

The solvent system to solubilise PLGA alone was explored to assess the coating quality on contact lenses. The drug-loaded spraying solutions were then prepared as outlined in **Table 2**. The model drugs were dissolved individually in a 2.5% w/v PLGA solution using the optimised solvent system. The resulting solution was filtered through a PTFE syringe filter with 0.2 µm

pore size (Fisher Scientific, Loughborough, UK). Polymer-drug solutions with different drug loadings were prepared to evaluate the influence of drug loading on the *in vitro* drug release.

Table 2. *Composition of the nES spraying solutions and the associated spraying parameters.*

Spraying solutions	PLGA concentration (%w/v)	Model drug concentration (% relative to the polymer weight)			Applied voltage (kV)
		LN	BIM	KF	
KF1	2.5	-	-	1	2.7
KF2	2.5	-	-	3	2.7
KF3	2.5	-	-	5	2.7
BIM1	2.5	-	1.5	-	2.8
BIM2	2.5	-	5	-	2.8
BIM3	2.5	-	15	-	2.8
LN1	2.5	2.5	-	-	2.7
LN2	2.5	5	-	-	2.7
LN3	2.5	15	-	-	2.7
nES operational parameters (applied to all nES-coated lenses)					
Nozzle-substrate-distance (NSD) (mm)		2.99			
Dosing speed (mm/s)		15			
Number of revolutions		90			
Spraying radius (mm)		5			

A custom-made nES system (PCE Automation, Beccles, UK) was used to deposit the drug-loaded coating onto the contact lenses. Details of the nES system can be found in the published work [17]. Preliminary studies were carried out to determine the spraying parameter to ensure proper deposition of polymer and model drugs on the contact lenses without obscuring the vision zone. The theoretical vision zone, measured from the schematic is 8 mm in the diameter

of contact lens from the top view (**Figure 1A**). The polymer-drug solutions were sprayed onto the peripheral zone of the contact lenses (n=3) with the parameters specified in **Table 2**. The resulting DECLs were stored in a container with a lint-free dry wipe dampened with PBS pH 7.4 to maintain hydration prior to other measurements.

2.3 Physical characterisation of nES-coated DECLs

2.3.1 Optical transmittance

The method to measure the optical transmittance of the contact lenses was adopted from the literature [30]. The optical transmittance of the contact lens was determined at a 1 nm interval from 200 – 800 nm utilising a UV-Vis spectrophotometer (Lambda 35, Perkin Elmer, UK). According to the instrument specifications, the light beam has a dimension of 7.5 mm in height and 1 mm in width. Three contact lenses were coated as described above and immersed in a quartz cuvette filled with PBS (pH 7.4) solution to ensure the contact lenses remained hydrated during measurements. The convex side of the contact lens was oriented towards the incoming beam. The optical transmittance of blank contact lenses was used as the negative control. It is anticipated that the contact lenses exhibit at least 95% optical transmittance for clear vision[31].

2.3.2 Coating thickness

The coating thickness was measured by the electronic thickness gauge ET-3 (Rehder-dev, Greenville, USA) with an accuracy of ±2 μm. The instrument measures the sample thickness by lowering a sensor onto the sample, which is positioned on a steel ball carrier, and calculates the difference in distance relative to the zero point. Prior to measurement, the contact lenses were removed from their packaging and allowed to equilibrate in PBS pH 7.4 for 30 minutes. The thickness measurement was taken at three predetermined locations in the peripheral region

of each blanked contact lens. Following the application of the nES coating, the thickness of the marked locations was remeasured to calculate the difference in thickness. Three contact lenses were used for each spraying solution to calculate the average thickness.

2.3.3 Surface morphology of coatings

An optical microscope FDSC196 (Linkam Scientific, Tadworth, UK) was used to observe the morphology of PLGA coating on the contact lenses to optimise the solvent system for nES. The surface morphology of drug-PLGA coated contact lenses was imaged by the Gemini 300 scanning electron microscopy (SEM) (Zeiss, Cambridge, UK) equipped with the PP3010T cryo-chamber (Quantum Design AG, Marly, Switzerland). The nES coated contact lenses were stored in a container with a lint-free wipe moistened with PBS pH 7.4 before imagining. For the cryo-SEM imaging, the lens was cut to one-fourth of the whole lens, which was frozen rapidly by nitrogen slush. The frozen sample was transferred to the cryo-chamber for the sublimation of surface ice and sputter coating with platinum under vacuum before being sent to the SEM cold stage for image acquisition.

2.4 *In vitro* drug release of nES-coated contact lenses

The *in vitro* drug release of non-sterilised and sterile nES-coated contact lenses was performed in glass vials containing 2 ml of PBS pH 7.4. The vials were placed in a shaking incubator set at 35 °C with 125 rpm. All *in vitro* experiments were performed under the sink condition, except LN3 (15% latanoprost). A 1.5 ml aliquot was replaced at regular intervals with fresh PBS pH 7.4, followed by quantification of the model drugs using validated high-performance liquid chromatography (HPLC) methods [27,32,33]. Drug recovery was performed to calculate the amount of model drugs deposited onto the contact lenses. The drug-loaded coating was removed by pipetting 100 µl of acetone, followed by pipetting 1.9 ml PBS pH 7.4 to solubilise

the model drugs under sonication for 5 minutes. The amount of model drugs deposited onto the contact lenses was quantified by HPLC methods mentioned below.

The model drugs were assayed by a HPLC system (Jasco, Japan) consisting of a pump (PU-1580), an autosampler (AS-2055 Plus) and a 4-channel UV detector (UV-1570M). A Waters C_{18} column (250 x 4.6 mm i.d., 5 µm particle size) connected with a HC-C_{18} guard column (Agilent, California, USA) was used under ambient condition to assay all model drugs. All methods were operating at a flow rate of 1 ml/min. The mobile phase for KF included methanol to 0.2% triethylamine in water in an 80 to 20 ratio (v/v). The detection wavelength was set at 300 nm. Stock solutions of KF in PBS pH 7.4 were diluted with the mobile phase in 1:1 ratio to produce a calibration of 0.78 – 12.5 µg/ml. The mobile phase for BIM consisted of acetonitrile, methanol and 0.1% phosphoric acid (v/v/v) (30:30:40). The detection wavelength was set at 210 nm. Stock solutions of BIM in PBS pH 7.4 were diluted with the mobile phase in 1:1 ratio to produce a calibration of 0.63 – 10 µg/ml. The mobile phase for LN comprised acetonitrile and water (v/v) (60:40). The detection wavelength was set at 210 nm. Stock solutions of LN in mobile phase were diluted with the PBS pH 7.4 in 1:1 ratio to produce a calibration of 0.63 – 10 µg/ml.

The aliquots of all model drugs collected from *in vitro* experiment was mixed with the associated mobile phase in 1:1 ratio, followed by filtration through a 0.2 µm PTFE syringe filter (15141499, Fisher scientific, UK) before assay.

2.5 Steam sterilisation of nES-coated contact lenses

One spraying solution of each model drug was selected to investigate the influence of sterilisation on the drug loading and coating integrity on the DECLs. The DECLs prepared by

nES were stored in a glass vial containing 2 ml PBS pH 7.4 for steam sterilisation at 121 °C, 15 psi for 30 minutes (Systec DB-100, Deutschland, Germany) [34]. The *in vitro* release of the sterile DECLs and the amount of drug leaching were assayed by the abovementioned HPLC methods.

2.6 Statistical analysis

The mean value of coating thickness and *in vitro* drug release results were analysed by one-way ANOVA and Tukey test (SPSS 25, IBM, New York, USA). A p-value lower than 0.05 is considered to show statistical significance.

3 Results and discussion

3.1 Solvent system optimisation

With a relatively short NSD to limit the width of the liquid spray generated by the nES process, a solvent system containing fast-drying solvents was chosen. Acetone was selected as the primary solvent in the solvent system since it is an excellent solvent to solubilise PLGA. It also has high vapour pressure and is classified by FDA as a class III solvent, which is a relatively safe solvent that has lower risk to human health[35] in comparison to methanol and acetonitrile (class II). However, using acetone alone destabilised the spraying cone, leading to fragmented coating morphology generated by nES (**Figure 2A**). To achieve a uniform coating, additional solvent that has high boiling point is needed [36]. Ethanol was added to the solvent system to reduce the vapour pressure of the spraying solution. A range of acetone to ethanol (A:E) ratios, starting with A:E of 9:1, used in the spraying solution was investigated. The resulting PLGA film on the contact lens is shown in **Figure 2B.** The morphology of the PLGA film is improved, showing a smooth and continuous coating on the contact lens. Further increase of the acetone

to ethanol ratio to 8:2 led to precipitation of PLGA, thus the solvent ratio of acetone to ethanol was limited to 9 to 1.

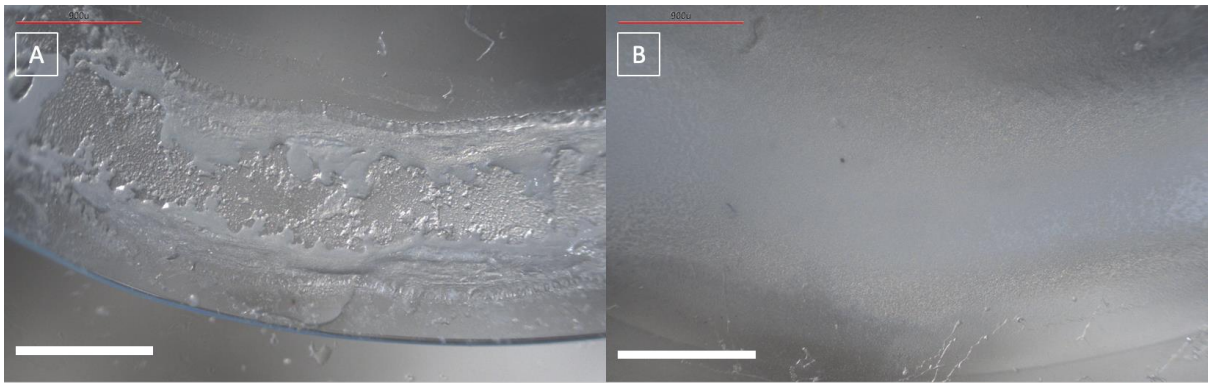


Figure 2. *Microscopic images of nES-coated contact lenses using 2.5 %w/v PLGA in acetone alone (A) and acetone to ethanol (9:1) (B). The scale bar is 1 mm.*

3.2 Physical characterisation of nES-coated DECLs

3.2.1 Optical transmittance

The nES system was designed to deposit materials precisely at the selected locations. **Figure 3A&B**. shows the typical contact lens before and after nES coating. The spraying radius was set to be 5 mm to coat the peripheral region of the contact lenses and remained the vision zone clear as intended. The high transmittance of the contact lenses is essential for providing clear vision to contact lens users. The optical transmittance of all coated lenses is above the acceptable target (>95%) at 600 nm, indicating the coating did not cover the vision zone, as shown in **Table 3**.

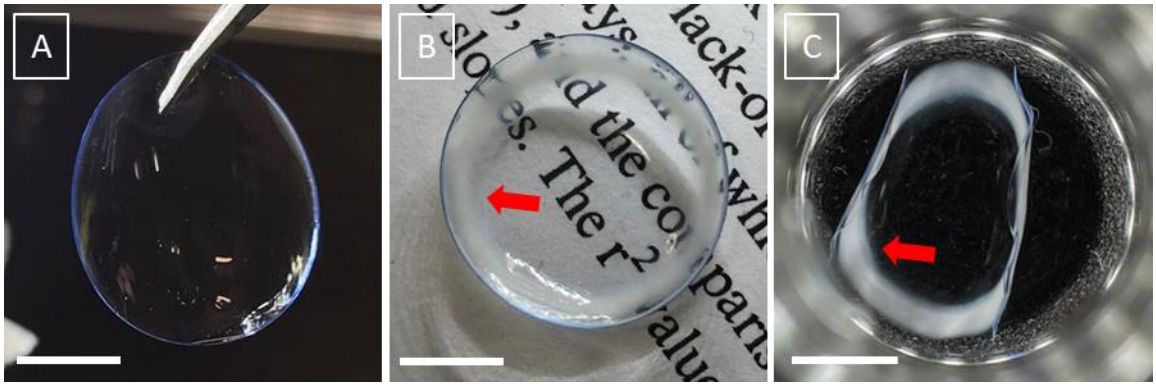


Figure 3. *Digital images of a contact lens before (A) and after nES (B) and immersed in PBS pH 7.4 solution after nES coating (C). Scale bar in the figure = 5 mm. The red arrows highlight the drug loaded PLGA coating.*

3.2.2 Coating thickness

Table 3 shows the coating thickness of all DELCs prepared by nES. The coating thickness across all spraying solutions varied between 41 and 45 µm, with no statistically significant difference observed ($p = 0.184 > 0.05$). The NSD, number of revolutions and dosing speed, which predominantly influence the coating thickness, were maintained constant throughout the experiments, and the observed outcomes were consistent with the anticipated results.

Table 3. *The optical transmittance of DECLs at the vision zone and the coating thickness.*

Spraying solution	Optical transmittance (%)	Coating thickness (µm)
Blank lenses	97.6 ± 0.3	-
KF1	96.4 ± 0.3	44 ± 4
KF2	95.9 ± 0.8	45 ± 4
KF3	96.2 ± 1.2	43 ± 5
BIM1	95.9 ± 1.6	41 ± 4
BIM2	96.3 ± 0.4	44 ± 3

BIM3	96.7 ± 0.4	41 ± 4
LN1	96.8 ± 0.3	45 ± 3
LN2	97.0 ± 0.4	44 ± 4
LN3	96.0 ± 0.5	43 ± 3

3.3 Morphology of coating on contact lenses

Figure 3C shows a representative appearance of a nES-coated contact lenses soaking in the PBS pH 7.4 solution before steam sterilisation. After being rehydrated in the saline solution, the DECLs show slight curling on the edges. The curling effect seen in nES DECLs is likely related to the hydrogel nature of soft contact lenses. The contact lenses were partially dehydrated during the nES process. Excess liquid on the blank contact lenses was blotted on a lint-free wipe before the nES coating process. The semi-wet contact lenses started to shrink with time during the nES coating process, which took about 2 minutes to complete. During the spraying process, the PBS pH 7.4 in the contact lens matrix may evaporate with time, leading to lens shrinkage. When the nES-coated lens was introduced into PBS pH 7.4, the lens swelled to the dimension before nES coating. However, the drug loaded PLGA coating ring may be more rigid and have lower degree of swelling than the lens material. As a result of this, the coating restricts the swelling of the contact lenses in the peripheral region, and the lens curled up. Therefore, the less dehydration of the lens, the less curling may be resulted. A closed spraying chamber with controlled humidity or reduced spraying time may reduce the curling issue.

Cryo-SEM images presented in **Figure 2** show the typical surface morphology of the drug loaded PLGA coatings on the contact lenses. Similar surface features were observed in the DECLs loaded with KF, BIM and LN. A dense and continuous layer of the drug-loaded

polymer film was deposited primarily on the peripheral region of the contact lens as, indicated by the dashed line in **Figure 4.** The area outside of the dashed line was free of nES particles. Given that the NSD remained constant, the observed film morphology suggests that the dosing speed was sufficient low, and the number of revolutions was sufficient high to enable fusion of nES PLGA particles on the contact lens surface to form solid films. The drug-loaded PLGA coating for all model drugs consisted of a mixture of fibres and particles. This suggested that the molecular weight of PLGA (M_w 76k - 115k Da) could be high enough to initiate formation of electrospun fibres[37].

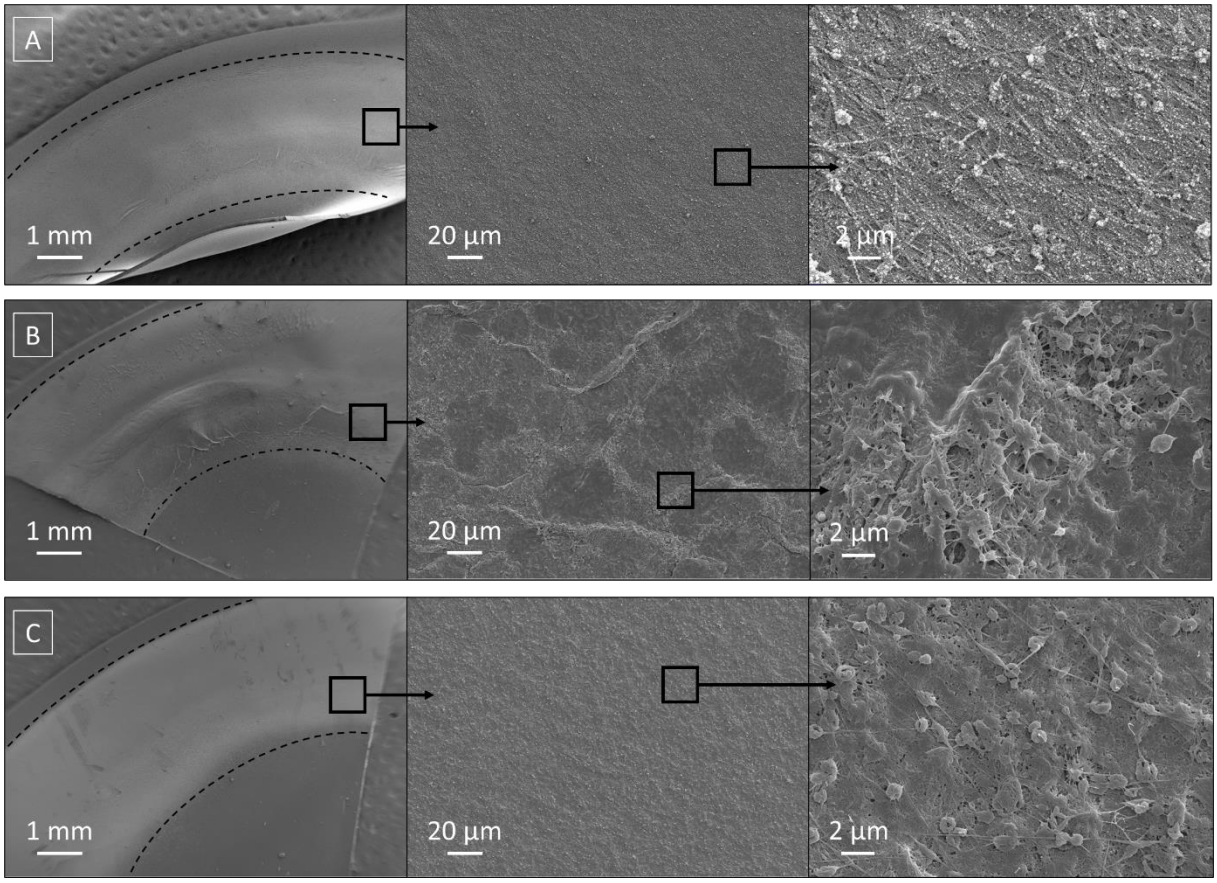


Figure 2. *Typical cryo-SEM images of DECLs with different model drugs, A: KF, B: BIM and C: LN. The dashed line indicates the coating region. The boxes in the figure show the images of higher magnifications of the area of interest.*

3.4 *In vitro* drug release of nES-coated lenses

To determine the amount of model drugs deposited onto the contact lenses, drug recovery from the coating was performed. The coating was completely dissolved and the total drug content in the coating was assayed. The correlations between the measured drug content and the drug concentration in the spraying solutions are presented in **Figure 5**. All model drugs demonstrate a linear relationship between the drug concentration and the total drug content to the contact lenses, with an excellent correlation factor. This indicates that the nES can controllably deposit desired amount of the drug accurately on the lens.

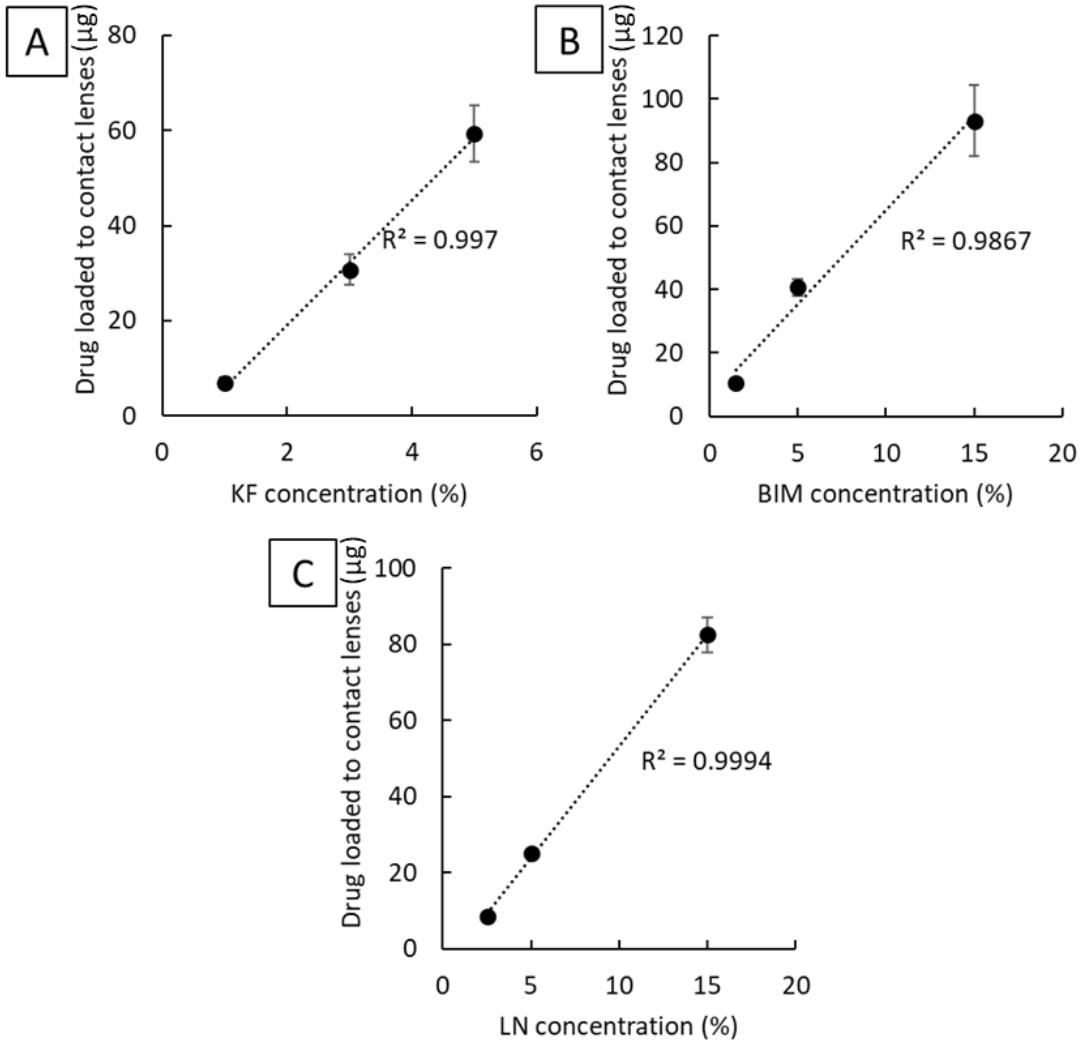
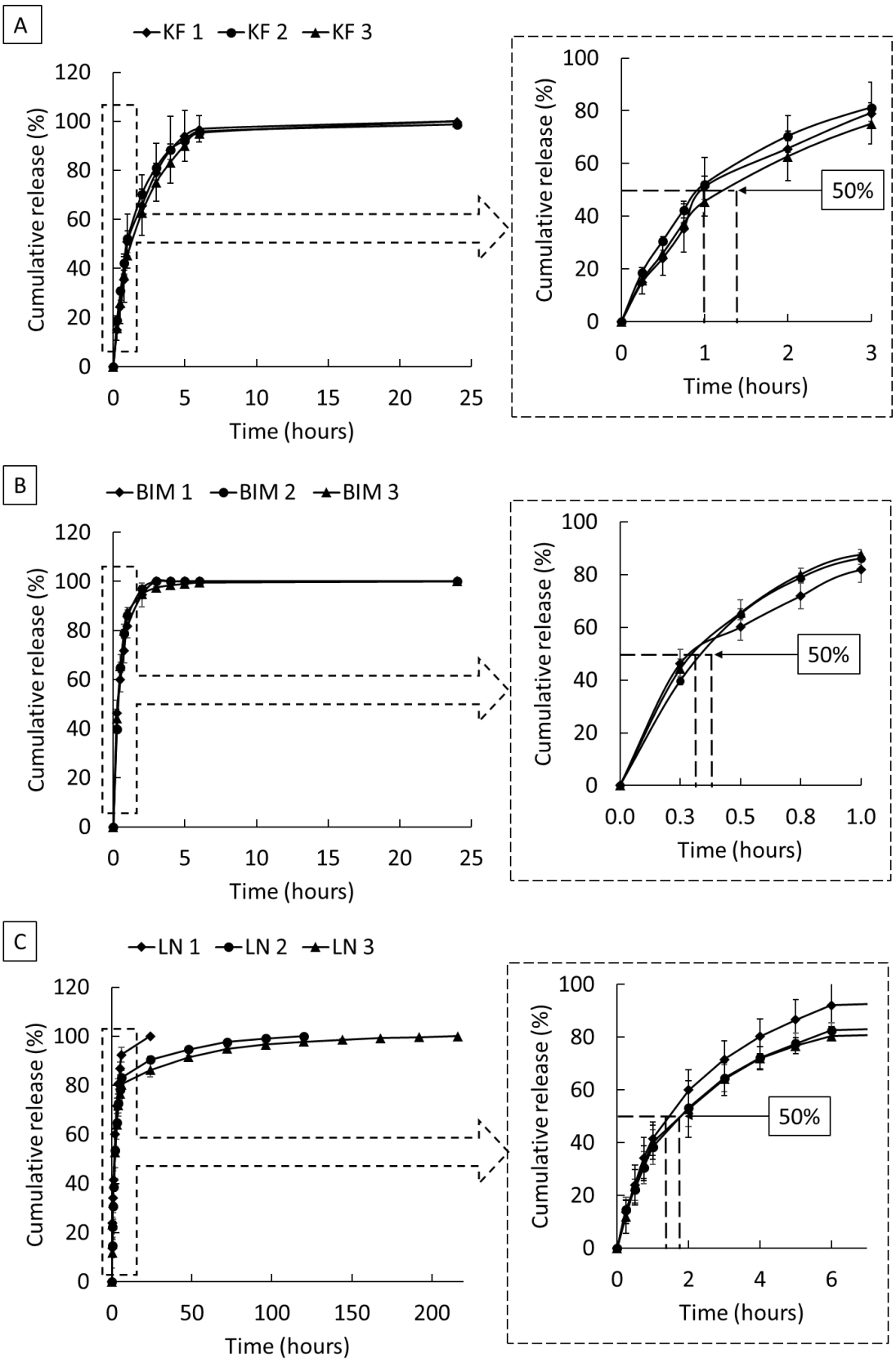


Figure 5. *Correlation of drug concentrations in the spraying solution to the drug-loaded onto contact lenses. A: KF, B: BIM and C: LN.*

The DECLs with three different drug concentrations in the spray solution were manufactured to test their *in vitro* drug release kinetics for each model drug. The rationale of selecting three different drug concentrations in the coating is to create different drug concentration gradients between the drug in the coating and the outer dissolution media environment. This will provide different thermodynamic driving force for drug release. In theory, the lenses with coatings that have highest drug loading should have the highest drug concentration gradient to the outer media, thus have the fastest *in vitro* drug release.

The *in vitro* drug release of the model drugs from DECLs prepared by the nES is presented in **Figure 6**. For the KF-loaded contact lenses, a rapid release of KF in the first 90 minutes was observed for all drug loadings (**Figure 6A**). The release of K1 - K3 reaches nearly the plateau at 6 hours and shows no further drug release after 24 hours. For BIM loaded lenses, the results showed that rapid release of BIM presented for all levels of drug loadings in the first 30 minutes (**Figure 6B**). No further drug release at 24 hours was observed for BIM1 – BIM3. Compared with KF and BIM, the *in* vitro drug release of LN shows a longer duration of drug release. A rapid release of LN lenses was observed within the first 2 hours for all drug loading levels (**Figure 6C**). The duration of drug release is dependent on the drug loading. The release of LN from LN1 and L2 stopped at 24 hours and 120 hours, respectively. LN3 shows extended drug release until 216 hours. The *in vitro* results suggested the hydrophobicity of the model drugs plays a role in the release duration.



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345 ***Figure 6.*** *Percentage cumulative in vitro drug release of KF (A), BIM (B) and LN (C) from*

346 *DECLs prepared by the nES method.*

KF and BIM are hydrophilic. With the low drug concentration used in the spraying solution, the PLGA-KF/BIM are highly likely to form a molecular dispersion, meaning the drug molecules are homogeneously distributed within the PLGA network. During the drug release experiments, the model drug molecules on the upper surface of the coating was rapidly released into the aqueous media. The coating thickness of all nES lens samples ranges between 41-45 µm on average without statistical significance ($p = 0.184$) (**Table 3**). The low thickness of the coating also allows the rapid diffusion of the drug molecules embedded in the coating to be release after diffused to the surfaces of the coating.

The *in vitro* results for the spraying solutions with all levels of KF and BIM loadings showed no difference in the release kinetic (**Figure 6A & B)**. In contrast, lenses coated with spray solutions LN1 – 3 show similar release kinetic in the first 5 hours but deviated afterwards. LN1 (1.5%) shows a faster drug release kinetic from 5 hours onwards in comparison to LN2 (5%) ($p = 0.036$) and LN3 (15%) ($p = 0.019$). LN is a hydrophobic drug with poor miscibility with PLGA. It is likely that the LN recrystallise after coating and storage. It is technically challenging to prove this as the wet coating was highly opaque and impossible to be inspected on the presence of small drug crystals using microscopic method. If drug recrystallises in the coating, the dissolution of the drug crystals would be rate limiting factor for the *in vitro* drug release. The coating with higher drug content would have higher amount of drug crystals, thus slower drug release.

The *in vitro* release data of DECLs should be carefully interpreted since currently there is no standardised method available. For the vial method reported in literature, the DECLs are placed in a vial containing a small volume (2 ml) of dissolution media (PBS pH 7.4 or simulated tear

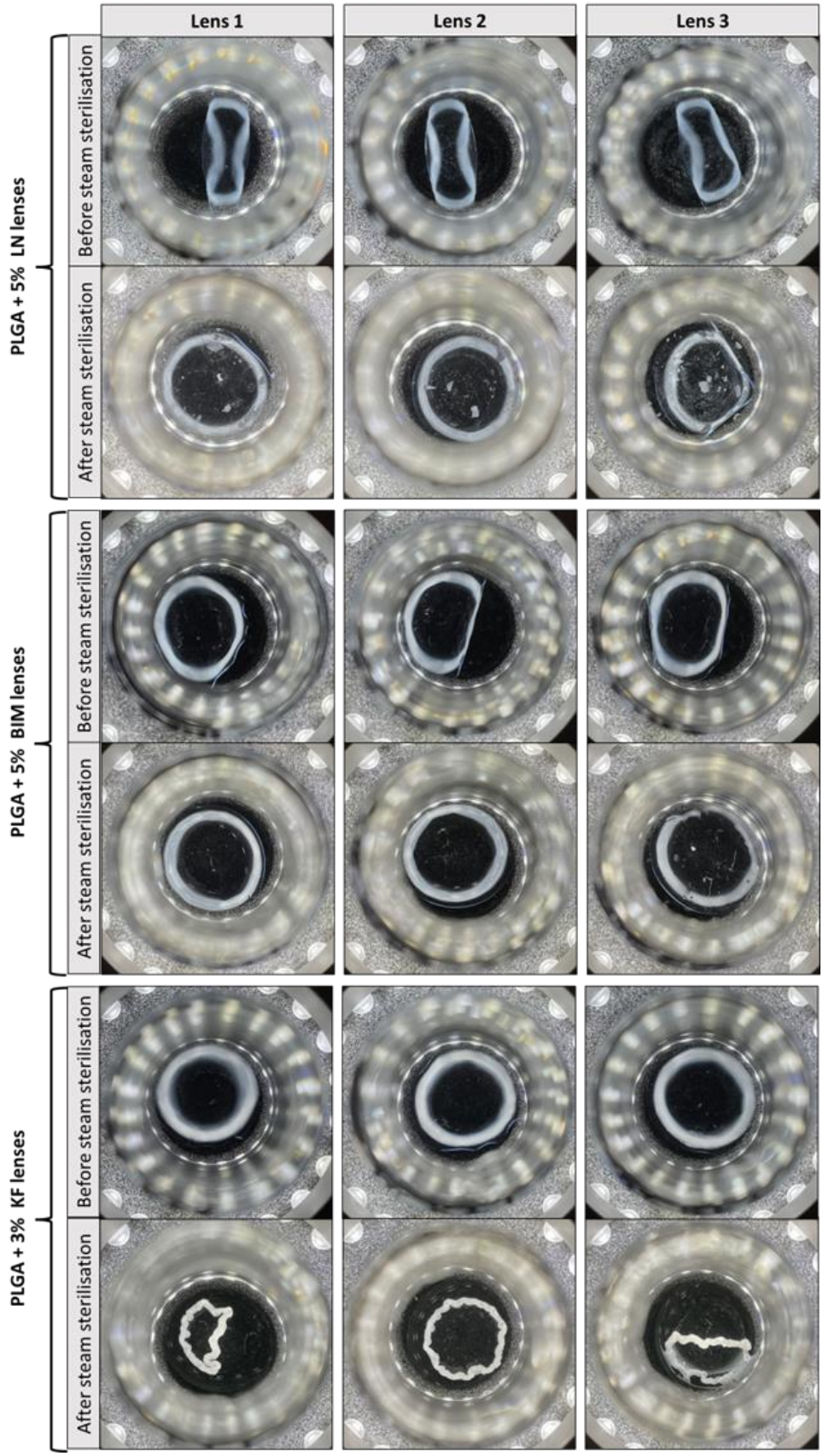
fluid) and introduced agitation by shaking[38,39]. The 2 ml of PBS pH 7.4 used in the *in vitro* release of this study was adapted from the literature as a simplified approach. The relatively large volume of release media used in this method (2 ml) provided the sink condition for the *in vitro* drug release set-up, thereby maintaining a sufficient concentration gradient to drive the drug molecules out from the coating. However, it should be noted that sink conditions are rarely achieved due to the low tear volume (7 - 30 μl) on the cornea[40]. Therefore, the *in vitro* result herein is limited to comparing the drug release kinetics for the tested spraying solutions. The *in vitro* results are expected to demonstrate a faster drug release kinetic, which were demonstrated from the comparison of *in vitro* and *in vivo* result of the same DECLs reported in the literature[41].

3.5 Effects of steam sterilisation on the nES coated DECLs

Steam sterilisation is the industrial standard for sterilising contact lens products after the lenses are manufactured and packaged into the blister packs and sealed with foil cover (in saline solution). The steam sterilisation was adopted to evaluate the influence of sterilisation on the nES coated contact lenses. Ideally, no coating delamination and significate drug loss should be observed after the sterilisation process. The images in **Figure 7** show the nES coated DECLs before and after steam sterilisation. The slight curling of all coated lenses after rehydration was discussed earlier, with LN lenses having the most apparent curling. After sterilisation, curling was absence in all nES-coated lenses indicating that the lenses returned to their original curvature. Delamination of the drug coating occurred in some DECLs after steam sterilisation. KF loaded lenses showed complete delamination of the coating.

The disappearance in the lens curling and the delamination may be attributed to the change in the expansion of the drug loaded PLGA coating during the heating and cooling cycle of the

steam sterilisation. The PLGA used in the study has a measured glass transition temperature (T_g) of 46.6 °C (data not shown). BIM has a low melting and LN is liquid at room temperature. If BIM and LN form amorphous molecular dispersion with PLGA, the presence of the drug could significantly plasticise the polymer coating and bring the T_g of the drug loaded PLGA coating to be below 46.6 °C. At elevated temperatures during steam sterilisation, the drug loaded PLGA coating would be in its rubbery state and more elastic than room temperature. This would allow the coating to be more flexible and match the expansion of the lens materials, thus disappearance of curling and little delamination. KF has a high melting and no measurable T_g reported in the literature. If using the rough rule of thumb of predicted T_g being 0.7 of melting temperature, the T_g of KF would be around 140 °C. If KF and PLGA formed amorphous molecular dispersion, the T_g of the coating would be much higher than the T_g of PLGA. This makes the KF loaded PLGA coating much more rigid than the ones loaded BIM and LN at the same temperature. This may explain the complete delamination of all KF coatings.



412

413 ***Figure 7.*** *Digital images of nES coated DECLs before and after steam sterilisation for all*

414 *three model drugs.*

The BIM and LN loaded DECLs were tested for their drug content (to identify any drug lose caused by sterilisation) and *in vitro* drug release post steam sterilisation. The KF loaded DELCs were not tested due to the complete delamination of the coating. BIM loaded lenses showed a total detectable drug content of 11.35 ± 2.1 µg on DECLs and 37.68 ± 8.68 µg in the PBS pH 7.4 solution post-sterilisation, indicating 76.4 ± 5.97% of BIM leached in PBS pH 7.4 during the steam sterilisation. The amount of LN detected on LN loaded DECLs was 9.71 ± 0.21 µg and the amount of LN found in the PBS pH 7.4 solution was 15.35 ± 1.21 µg, indicating 61.17 ± 1.79% LN leaching in the PBS during sterilisation.

The *in vitro* drug release results of LN and BIM loaded DECLs with and without steam sterilisation are shown in **Figure 8**. The *in vitro* drug release of LN-coated lenses after steam sterilisation showed faster release rate than the ones without being steam sterilised. The drug leaching also shorten the duration of drug release up to 24 hours. The release kinetic of BIM before and after the steam sterilisation showed no difference in that the rapid release happened in the first 0.25 hours and plateaued at 3 hours.

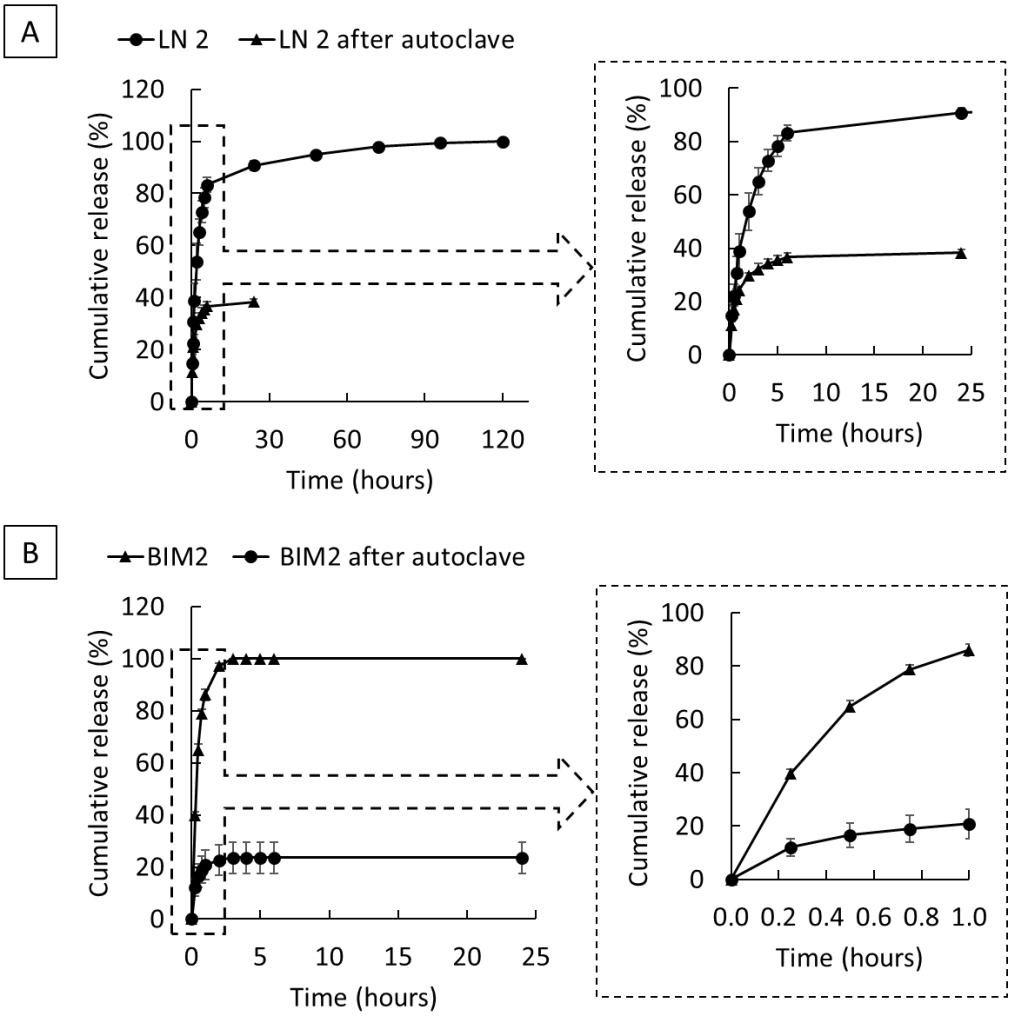


Figure 8. *The in vitro release of LN2 (A) and BIM2 (B) from nES-coated lenses before and after steam sterilisation.*

The sterilisation step of contact lenses is necessary to prevent potential microbes from causing eye infections during application. Although the nES could deposit the drug-loaded PLGA coating onto the lens surface, the steam sterilisation causing drug leaching and chemical degradation for thermolabile drug presents a significant technical barrier and alternative sterilisation method may need to be considered. Alternatively, gamma ray sterilisation could be used if the polymer has a low glass transition temperature and/or the drug is heat sensitive. The typical dose of gamma irradiation for medical devices is 25 kGy [42]. Gamma irradiation is reported to be an effective method for sterilising PLGA-based drug delivery systems [23].

The suitable dose of gamma irradiation is 25 kGy without significant change to the drug release kinetic [42].

4 Conclusions

In this study, DECLs with a range of drug loadings of the model drugs were prepared by nES. The rationale was based on using additive printing technology to prepare polymer-drug coated contact lenses on demand and produce a personalised drug delivery system. The drug loadings of all model drug were highly correlated to the drug concentration in the spraying solution, The established calibration curve enable personalised dosing under specific spraying parameters. All DECLs showed excellent optical transmittance at the optical zone, implying that the nES method does not interfere with the vision at the determined spraying parameters. It was found that the swelling of hydrogel contact lenses poses challenges in maintaining the original curvature of the contact lenses after the nES coating. Further study is needed to control the shrinkage during the nES process. The *in vitro* drug release of the model drug showed that the hydrophobicity of the model drug and the drug loading play a vital role in the duration of drug release, of which the 15% LN lenses showed the longest duration of drug release. The drug loadings showed no difference in the release kinetics for BIM and KF, except LN. Steam sterilisation is unsuitable for sterilising DECLs prepared by nES due to thermal damages on the PLGA coating. Gamma rays could be the alternative to minimise the damage to the coating.

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References

[1] P.A. Newman-Casey, A.L. Robin, T. Blachley, K. Farris, M. Heisler, K. Resnicow, P.P. Lee, The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey, Ophthalmology. 122 (2015) 1308–1316. https://doi.org/10.1016/j.ophtha.2015.03.026.

[2] P.A. Newman-Casey, L.M. Niziol, B.W. Gillespie, N.K. Janz, P.R. Lichter, D.C. Musch, The Association between Medication Adherence and Visual Field Progression in the Collaborative Initial Glaucoma Treatment Study, Ophthalmology. 127 (2020) 477–483. https://doi.org/10.1016/j.ophtha.2019.10.022.

[3] I.P. Kaur, S. Kakkar, Nanotherapy for posterior eye diseases, Journal of Controlled Release. 193 (2014) 100–112. https://doi.org/10.1016/j.jconrel.2014.05.031.

[4] V. Agrahari, A. Mandal, V. Agrahari, H.M. Trinh, M. Joseph, A. Ray, H. Hadji, R. Mitra, D. Pal, A.K. Mitra, A comprehensive insight on ocular pharmacokinetics, Drug Deliv Transl Res. 6 (2016) 735–754. https://doi.org/10.1007/s13346-016-0339-2.

[5] R. Kholdebarin, R.J. Campbell, Y.P. Jin, Y.M. Buys, G. Beiko, C. Birt, K. Damji, F. Feldman, C. Lajaoie, S. Kulkarni, J. Martow, T. Sakamoto, J. Spencer, G.E. Trope, Multicenter study of compliance and drop administration in glaucoma, Canadian Journal of Ophthalmology. 43 (2008) 454–461. https://doi.org/10.3129/I08-076.

[6] J. Thygesen, Glaucoma therapy: Preservative-free for all?, Clinical Ophthalmology. 12 (2018) 707–717. https://doi.org/10.2147/OPTH.S150816.

[7] S.A. Davis, B. Sleath, D.M. Carpenter, S.J. Blalock, K.W. Muir, D.L. Budenz, Drop instillation and glaucoma., Curr Opin Ophthalmol. 29 (2018) 171–177. https://doi.org/10.1097/ICU.0000000000000451.

[8] R. Gupta, B. Patil, B.M. Shah, S.J. Bali, S.K. Mishra, T. Dada, Evaluating Eye Drop Instillation Technique in Glaucoma Patients, J Glaucoma. 21 (2012).

[9] K.H. Hsu, S. Gause, A. Chauhan, Review of ophthalmic drug delivery by contact lenses, J Drug Deliv Sci Technol. 24 (2014) 123–135. https://doi.org/10.1016/S1773-2247(14)50021-4.

[10] O. Wichterle, O. Lim, Cross-linked hydrophilic polymers and articles made therefrom, 1965. https://doi.org/US3220960A.

[11] J. Xu, Y. Xue, G. Hu, T. Lin, J. Gou, T. Yin, H. He, Y. Zhang, X. Tang, A comprehensive review on contact lens for ophthalmic drug delivery, Journal of Controlled Release. 281 (2018) 97–118. https://doi.org/10.1016/j.jconrel.2018.05.020.

[12] J.& J. Vision, Johnson & Johnson Vision Receives Approval in Canada for World's First and Only Drug-Releasing Contact Lens for Vision Correction and Allergic Eye Itch: ACUVUE® Theravision™ with Ketotifen, (2021). https://www.jjvision.com/press-release/johnson-johnson-vision-receives-approval-canada-worlds-first-and-only-drug-releasing.

[13] C. Alvarez-Lorenzo, F. Yañez, A. Concheiro, Ocular drug delivery from molecularly-imprinted contact lenses, J Drug Deliv Sci Technol. 20 (2010) 237–248. https://doi.org/10.1016/S1773-2247(10)50041-8.

[14] A.R. Desai, F.A. Maulvi, D.M. Desai, M.R. Shukla, K.M. Ranch, B.A. Vyas, S.A. Shah, S. Sandeman, D.O. Shah, Multiple drug delivery from the drug-implants-laden silicone contact lens: Addressing the issue of burst drug release, Materials Science and Engineering C. 112 (2020) 110885. https://doi.org/10.1016/j.msec.2020.110885.

[15] J.H. Choi, Y. Li, R. Jin, T. Shrestha, J.S. Choi, W.J. Lee, M.J. Moon, H.T. Ju, W. Choi, K.C. Yoon, The Efficiency of Cyclosporine A-Eluting Contact Lenses for the Treatment of Dry Eye, Curr Eye Res. 44 (2019) 486–496. https://doi.org/10.1080/02713683.2018.1563702.

[16] O. L. Lanier, K.G. Christopher, R.M. Macoon, Y. Yu, P. Sekar, A. Chauhan, Commercialization challenges for drug eluting contact lenses, Expert Opin Drug Deliv. 00 (2020) 1–17. https://doi.org/10.1080/17425247.2020.1787983.

[17] Chak.Hin. Tam, M.S. Alexander, S. Qi, Precision coating of ocular devices/contact lenses by nanoelectrospray additive printing, Mater Des. 219 (2022) 110782. https://doi.org/10.1016/j.matdes.2022.110782.

[18] P. Mehta, A.A. Al-Kinani, R. Haj-Ahmad, M.S. Arshad, M.W. Chang, R.G. Alany, Z. Ahmad, Electrically atomised formulations of timolol maleate for direct and on-demand ocular lens coatings, European Journal of Pharmaceutics and Biopharmaceutics. 119 (2017) 170–184. https://doi.org/10.1016/j.ejpb.2017.06.016.

[19] P. Mehta, A.A. Al-Kinani, M.S. Arshad, M.W. Chang, R.G. Alany, Z. Ahmad, Development and characterisation of electrospun timolol maleate-loaded polymeric contact lens coatings containing various permeation enhancers, Int J Pharm. 532 (2017) 408–420. https://doi.org/10.1016/j.ijpharm.2017.09.029.

[20] M. Hirenkumar, S. Steven, Poly Lactic-co-Glycolic Acid (PLGA) as Biodegradable Controlled Drug Delivery Carrier, Polymers (Basel). 3 (2012) 1–19. https://doi.org/10.3390/polym3031377.Poly.

[21] J.B. Ciolino, T.R. Hoare, N.G. Iwata, I. Behlau, C.H. Dohlman, R. Langer, D.S. Kohane, A drug-eluting contact lens, Invest Ophthalmol Vis Sci. 50 (2009) 3346–3352. https://doi.org/10.1167/iovs.08-2826.

[22] S. Soltani, P. Zakeri-Milani, M. Barzegar-Jalali, M. Jelvehgari, Fabrication and in-vitro evaluation of ketotifen fumarate-loaded PLGA nanoparticles as a sustained delivery system, Iranian Journal of Pharmaceutical Research. 16 (2017) 22–34.

[23] Y. Xu, C.S. Kim, D.M. Saylor, D. Koo, Polymer degradation and drug delivery in PLGA-based drug–polymer applications: A review of experiments and theories, J Biomed Mater Res B Appl Biomater. 105 (2017) 1692–1716. https://doi.org/10.1002/jbm.b.33648.

[24] L. Bielory, K.W. Lien, S. Bigelsen, Efficacy and tolerability of newer antihistamines in the treatment of allergic conjunctivitis, Drugs. 65 (2005) 215–228. https://doi.org/10.2165/00003495-200565020-00004.

[25] K.S. Lim, C.B. Nau, M.M. O'Byrne, D.O. Hodge, C.B. Toris, J.W. McLaren, D.H. Johnson, Mechanism of Action of Bimatoprost, Latanoprost, and Travoprost in Healthy Subjects. A Crossover Study, Ophthalmology. 115 (2008) 790–795. https://doi.org/10.1016/j.ophtha.2007.07.002.

[26] Drugbank, Ketotifen, (2022). https://go.drugbank.com/drugs/DB00920 (accessed October 6, 2022).

[27] A.A. Abd El-Bary, H.F. Salem, R.M. Kharshoum, 2-Hydroxypropyl-ß-cyclodextrin complex with ketotifen fumerate for eye drops preparations, International Journal of Drug Delivery. 1 (2011) 228–240. https://doi.org/10.5138/ijdd.v3i2.217.

[28] P. Jansook, T. Loftsson, Aqueous Prostaglandin Eye Drop Formulations, Pharmaceutics. 14 (2022) 1–13. https://doi.org/10.3390/pharmaceutics14102142.

[29] National Center for Biotechnology Information., PubChem Compound Summary for CID 5311027, Bimatoprost, PubChem. (n.d.). https://pubchem.ncbi.nlm.nih.gov/compound/Bimatoprost. (accessed August 19, 2023).

[30] N.M. Quesnel, P. Simonet, Spectral transmittance of UV-absorbing soft and rigid gas permeable contact lenses, Optometry and Vision Science. 72 (1995) 2–10. https://doi.org/10.1097/00006324-199501000-00002.

[31] F.A. Maulvi, R.J. Patil, A.R. Desai, M.R. Shukla, R.J. Vaidya, K.M. Ranch, B.A. Vyas, S.A. Shah, D.O. Shah, Effect of gold nanoparticles on timolol uptake and its release kinetics from contact lenses: In vitro and in vivo evaluation, Acta Biomater. 86 (2019) 350–362. https://doi.org/10.1016/j.actbio.2019.01.004.

[32] J.R. Franca, L.D. Batista, T.G. Ribeiro, C. Fernandes, R.O. Castilho, A.A.G. Faraco, Development and Validation of a High Performance Liquid Chromatographic Method for Determination of Bimatoprost in Chitosan-Based Ocular Inserts, Anal Lett. 48 (2015) 531–540. https://doi.org/10.1080/00032719.2014.947533.

[33] P.P. Patel, P.P. Patel, P. Giram, Bioanalytical Method Development and Validation for Latanoprost Quantification in Pharmaceutical Opthalmic Microemulsion Formulation by RP-HPLC, J Anal Bioanal Tech. 6 (2015). https://doi.org/10.4172/2155-9872.1000284.

[34] F.A. Maulvi, H.H. Choksi, A.R. Desai, A.S. Patel, K.M. Ranch, B.A. Vyas, D.O. Shah, pH triggered controlled drug delivery from contact lenses: Addressing the challenges of drug leaching during sterilization and storage, Colloids Surf B Biointerfaces. 157 (2017) 72–82. https://doi.org/10.1016/j.colsurfb.2017.05.064.

[35] USFDA, Q3C — Tables and List Guidance for Industry, 2017.

[36] A. Jaworek, Electrospray droplet sources for thin film deposition, J Mater Sci. 42 (2007) 266–297. https://doi.org/10.1007/s10853-006-0842-9.

[37] D.N. Nguyen, C. Clasen, G. Van den Mooter, Pharmaceutical Applications of Electrospraying, J Pharm Sci. 105 (2016) 2601–2620. https://doi.org/10.1016/j.xphs.2016.04.024.

[38] M. Yang, Y. Yang, M. Lei, C. Ye, C. Zhao, J. Xu, K. Wu, M. Yu, Experimental studies on soft contact lenses for controlled ocular delivery of pirfinedone: in vitro and in vivo, Drug Deliv. 23 (2016) 3538–3543. https://doi.org/10.1080/10717544.2016.1204570.

[39] C. Wu, P.W. Or, J.I.T. Chong, I.K.K. Pathirage Don, C.H.C. Lee, K. Wu, M. Yu, D.C.C. Lam, Y. Yang, Extended delivery of pirfenidone with novel, soft contact lenses in vitro and in vivo, Journal of Ocular Pharmacology and Therapeutics. 37 (2021) 75–83. https://doi.org/10.1089/jop.2020.0058.

[40] A. Tieppo, K.M. Pate, M.E. Byrne, In vitro controlled release of an anti-inflammatory from daily disposable therapeutic contact lenses under physiological ocular tear flow, European Journal of Pharmaceutics and Biopharmaceutics. 81 (2012) 170–177. https://doi.org/10.1016/j.ejpb.2012.01.015.

[41] A.F. Pereira-da-Mota, C.M. Phan, A. Concheiro, L. Jones, C. Alvarez-Lorenzo, Testing drug release from medicated contact lenses: The missing link to predict in vivo performance, Journal of Controlled Release. 343 (2022) 672–702. https://doi.org/10.1016/j.jconrel.2022.02.014.

[42] C. Martínez-Sancho, R. Herrero-Vanrell, S. Negro, Study of gamma-irradiation effects on aciclovir poly(D,L-lactic-co- glycolic) acid microspheres for intravitreal administration, Journal of Controlled Release. 99 (2004) 41–52. https://doi.org/10.1016/j.jconrel.2004.06.004.