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High Precision Deposition and Controlled Release of High Molecular Weight Hyaluronic Acid from Contact Lens Surfaces Using Nanoelectrospray

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Abstract

Using additive manufacturing processes to selectively modify soft and wet polymer surfaces, such as soft contact lenses, with micrometer levels of precision for applications, including controlled delivery of active ingredients, can be challenging. This study demonstrated the use of a novel nanoelectrospray (nES) process as a technical solution to deposit accurate amounts of high molecular weight hyaluronic acid (HA), a highly water-soluble anionic glycosaminoglycan, on the surface of soft contact lenses, and subsequently release it in a sustained manner. nES allows precise deposition of nano- to micrometer-thick layers outside the central optical zone. To achieve the sustained release of HA from the lens, a chemical modification of the polymer surface was developed to allow the lens surface to be covalently linked with a semi-interpenetrating network (IPN) layer containing entrapped HA after being deposited by nES. Additional zein barrier layers applied by nES over the HA layer led to further reduction of the release rate of HA from the lenses. The results confirmed that the selective nES deposition allowed modification of the lens surface without affecting optical properties in the central vision zone of the soft contact lenses. The results suggested that the HA release kinetics can be strongly affected by multiple factors including the degree of crosslinking, molecular size of crosslinker, the addition of photo-initiator and the polymeric barrier layer. This study demonstrated the potential of nES as an alternative approach for surface modification and drug loading to commercially available contact lenses for treating ocular conditions.

Keywords: photopolymerisation; nanoelectrospraying; controlled release; surface modification; contact lens; ocular drug delivery.

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Introduction

Hyaluronic acid (HA) is a naturally occurring linear polymer, a component of vertebrate extracellular matrix, that has been found to have an array of physiological/pharmacological functions[1]. It is a glycosaminoglycan with repeating units of D-glucuronic acid and N-acetylglucosamine disaccharides[2]. HA is found throughout the tissues of the eye, including the tear film[2] where it acts as a natural lubricant for the eye and contributes to stabilization of the tear film[3].

HA is a component of many commercially available eye drops which can be used in conjunction with contact lenses aiming to provide soothing effects and improve comfort. Despite mucoadhesive properties, the residence time of HA at the ocular surface is limited, with effects reported for up to 30 minutes after instillation[4-6] via eye drops. Enhanced comfort therefore has a limited time span and frequent application of HA-containing eye drops is needed. A contact lens that released HA has therefore been proposed[7] which would be anticipated to improve the contact lens wearing experience by enhancing surface water retention[8], reducing protein adsorption[9], and improved wearer comfort. Furthermore, HA has been shown to be effective in improving the signs and symptoms of dry eye disease[10]. Therefore, contact lenses capable of providing sustained release of HA would offer significant benefits to wearers who experience dry eye symptoms. This study aims to achieve this by developing a novel type of contact lens with an HA coating.

Controlled drug release by soft contact lenses, also known as drug eluting contact lenses (DECLs), is seen as a highly promising drug delivery method to the eye[11, 12] due to, for example, improved bioavailability caused by the extended residence time in the post-lens tear film and low dosing needed to achieve therapeutic effects. Various approaches to load contact lenses that deliver HA to the eye have been reported[13-15], including methods such as soaking[7], molecular imprinting[16], implant-laden contact lenses[17], physical entrapment of HA in the contact lens[7, 18, 19] and semi-circular ring-implanted contact lenses[20, 21]. However, achieving sustained release kinetics of HA from contact lenses is highly challenging[8, 18, 22-26]. This is mainly due to the extremely high aqueous

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solubility of HA which leads to the rapid diffusion and release of the loaded HA from the bulk of the lens material to the external aqueous environment.

A new additive manufacturing method, nanoelectrospray (nES) additive coating, for precision deposition of drug onto commercially available contact lenses was reported recently and was used in this study to develop controlled release of HA from contact lenses[27-29]. Using a custom-built-nES printing system, mask-free deposition on the lens surface can be carried out, enabling patterned coating of the peripheral region of the contact lens to ensure that the central optical area of the lens remains unaffected. The contact lenses with formulations deposited on their inner surface via nES exhibited optical transmittance above the acceptable threshold (>95%) at 600 nm. This confirms that nES deposition provides high spatial precision, enabling targeted coating while preserving the clarity of the optical zone[27-29].

The present study explored an alternative approach of chemical modification, which enables permanent linking *via* chemical bonding between the surface and the grafted polymer to form stable systems[30-35]. Chemically linking the lens surface to the nES printed HA-loaded polymer aimed to avoid delamination and allow extended release of HA. Among chemical modifications, photo-induced grafting is known to be a useful technique for the modification of polymeric materials[1, 36-38]. Poly (2-hydroxyethyl methacrylate) (pHEMA)-based soft contact lenses were surface modified with benzophenone before HA-acrylic monomer-based coatings were deposited on the lens. Photo-polymerisation by UV light enabled formation of a cross-linked semi-interpenetrating (semi-IPN) polymer network on the lens surface that traps the HA and provides sustained release of HA. A similar approach has been used which reported a modest 2% reduction in optical acuity was observed for HA-grafted pHEMA, yet transparency remained above >92%, indicating that HA grafting does not significantly impact the optical properties of pHEMA[39].

Burst release is a common issue of drug eluting contact lenses which is particularly challenging for water soluble actives, such as HA[15]. While simple soaking methods result in a rapid initial release within hours, advanced techniques such as embedding HA-modified nanoparticles, micelles, or polymeric implants within the lens structure are necessary for true sustained release,

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with studies demonstrating controlled delivery for over 12 days to several weeks[16, 40-43]. In this study, we evaluated nES's application of rapidly depositing a double-layer coating to slow down the diffusion and release of HA from the lens. UV-induced grafting was used due to its low cost, easy operation and mild reaction conditions[44-46]. The biological effect of HA is molecular weight (Mw) dependent[47-50]. HA with high Mw (average 2M Da) is reported to have greater anti-inflammatory activity as well as higher water binding capacity to provide better lubricating and soothing effects[51-53]. It was therefore used in this study. In the double-layer coating, the base coat contained HA and the top-coats chosen in this study, serving as the barrier layer, were zein and poly lactic-co-glycolic acid (PLGA). Both polymers have excellent biocompatibility and biodegradability, as well as effective film-forming properties, which make them commonly used in tablet and therapeutic product coatings[27, 54, 55]. Zein is considered amphiphilic, but more specifically as a hydrophobic protein with high concentration of non-polar amino acids[51]. It has been used previously for controlled drug delivery[52, 53]. PLGA is hydrophobic biodegradable polymer that has been widely used for controlled and sustained drug delivery in long-acting injectables and implants, mostly in the form of microparticles[54, 55]. We hypothesize that as a top coat over the HA formulations on contact lenses, its hydrophobic properties may prevent rapidly water diffusion into the PLGA coat, thereby restricting the diffusion of HA polymers and resulting in a sustained HA release.

Experimental

Materials

Sodium hyaluronate (average Mw of 2M Da) (HA) and Biomedics 38 soft contact lenses (Poly(2-hydroxyethyl methacrylate) based), with center thickness range from approximately 0.03–1.00 mm, were supplied by CooperVision Inc. (polymacon, San Ramon, USA; product no longer commercially available). The chemicals used to modified the lenses surface are: 2-hydroxyethyl methacrylate (HEMA) (≥99 %), 2-(diethylamino)ethyl methacrylate (DEAEMA) (99 %), poly(ethylene glycol) diacrylate (PEGDA) (average Mw 575 and 700 Da), benzophenone (BP),

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2,2-dimethoxy-2-phenylacetophenone (DMPA), and PLGA Resomer® RG 756 S (M_w 76-115 kDa, lactide:glycolide 75:25). These chemicals and phosphate buffer saline (PBS) tablets (pH 7.3) were purchased from Merck Life Science UK (Haverhill, UK). Purified zein was obtained from Thermo Scientific (Loughborough, UK). Ethanol, acetone, and sodium nitrate were purchased from Fisher Scientific (Loughborough, UK). Milli-Q (Merck Millipore, Watford, UK) ultra-pure water was used for all aqueous solutions. The chemical structures of the monomers, crosslinker and photo-initiators used are shown in **Figure 1**.

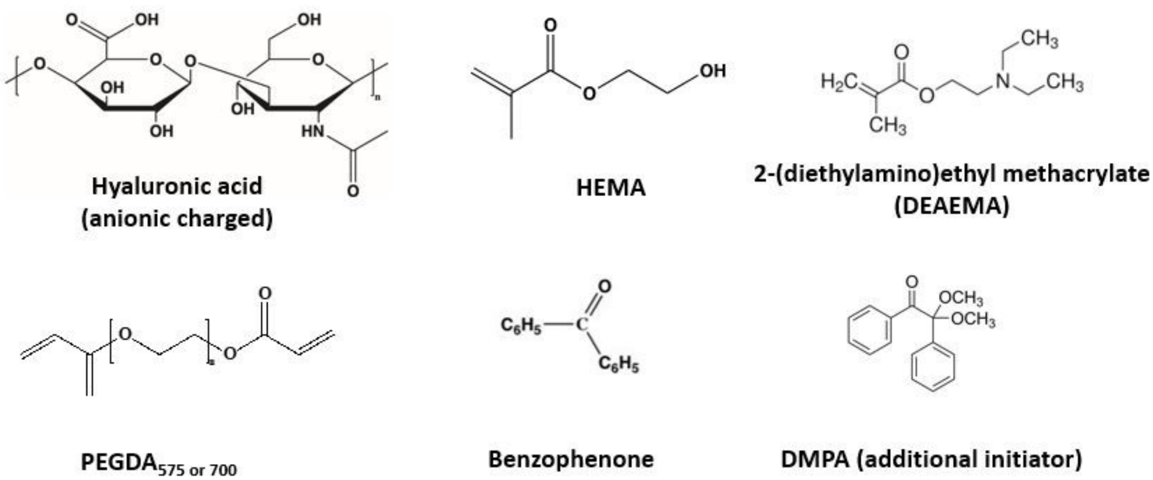

Figure 1. The structures of chemicals used to create the semi-IPN network on the lens surface.

Chemical surface modification of contact lenses with HA trapped in semi-IPN layer

The process involved two steps as depicted in **Figure 2**. In the first step, the contact lens was surface modified with Norrish type photo-initiator, benzophenone (BP). The lens was rinsed with Milli-Q water before transferring into a glass vial containing BP (10 mg/mL) in acetone and the solution with lens degassed with nitrogen for 10 minutes to remove the oxygen. After degassing, the solution with lens was placed under UV light (New Iradifire 48W UV LED floodlight with true 365 nm wide beam (100-degree beam angle), UV Gear, Surrey, UK) for 45 – 60 minutes. Although the light intensity was not measured, the height of the UV light sources was fixed for all experiments to ensure no fluctuation of light intensity caused by height. The lens was removed

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and washed with acetone and ethanol several times to remove excess unreacted BP and then washed with PBS media three times to remove the solvent from the lens. The BP-modified lenses were stored in the hydrated condition in the dark until further use.

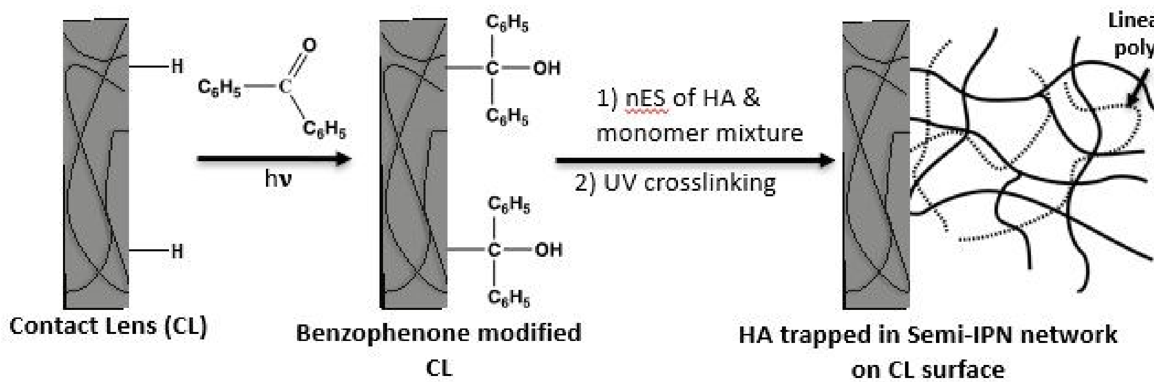

Figure 2. Schematic illustration of semi-IPN formation on the lens surface under UV light.

Nanoelectrospray (nES) coating of contact lenses

Figure 3a shows a schematic of the custom-made experimental setup for the nES used in this study (PCE Automations, Beccles, UK). The system features a 2.5 mL Luer lock syringe, equipped with a metal nozzle with a 100 µm internal diameter (Nordson EFD, Dunstable, UK). This syringe is mounted on a motorized z-translation stage (EGSC-BS-KF-32-100-8P, Festo SE & Co. KG, Ostfildern, Germany) that allows for vertical movement. Pneumatic pressure, adjustable via an in-line pressure gauge, facilitates the nES printing of highly viscous liquids. A high-magnification digital camera (MVL6X12Z, Thorlabs LTD, Ely, UK) monitors the spraying process. A custom-made contact lens holder, as described in previous studies[27-29] is mounted on a 2D motorized x-y translation stage (5155-1000A, Festo SE & Co. KG, Ostfildern, Germany), enabling simultaneous circular movements. All x, y, and z movements, as well as spraying parameters, are controlled via the machine's built-in digital control panel.

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Externally connected components include high voltage power supplies (HCP 146500 model, FuG Elektronik GmbH, Schechen, Germany) linked to a high voltage switch (PVX-4140 model, Direct Energy, Houston, TX, USA), which switches the voltage to pulsation mode. A function generator (TG 1000 model, Aim-TTi, Huntingdon, UK) controls the frequency and amplitude of the generated square waves. A current amplifier (DLPCA-200, Laser Components, Chelmsford, UK) amplifies the voltage and connects to a digital storage oscilloscope (TBS1104, Tektronix UK, Bracknell, UK) to monitor the waveform. The amplifier's measurement resistance is set to 10^6 Ω.

A power supply capable of up to 6 kV provides a voltage range of 1.5 - 3.5 kV to maintain a stable cone-jet. The contact lens is positioned on a motorized xy-translational stage, 3 mm beneath the cone-jet, to enable circular movement. The number of rotations was 90 with 10 mm/s rotation speed for all the coating formulations, including the top and base coats of the double-layer coated lenses. A 100 µm nozzle was used for the spraying with a nozzle to substrate distance (NSD) of 3 mm. A voltage ranges from 1.5-3.5 kV was applied to produce a stable cone-jet for all the formulations. **Figure 3b** shows the schematic illustration of printed polymer layer (grey colour) at the periphery of the contact lens with no coating in the vision zone of the lens for both single layer and double-layer deposition. For lenses coated with UV-curing treatment, the lenses were washed with Milli-Q water after nES to remove excess unreacted material.

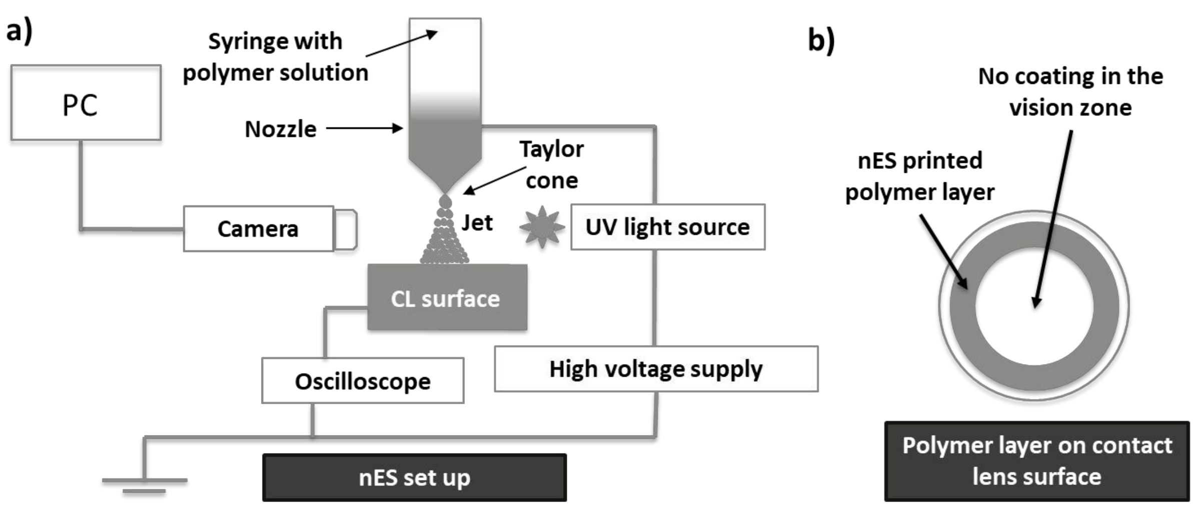

Figure 3. nES setup was used for depositions on contact lenses. Schematic illustration (a) of the nES setup; (b) polymer layer printed at the periphery of contact lens via nES.

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In the second step of the chemical surface modification of contact lenses with monomers HEMA (for hydrogen bonding with HA) and DEAEMA (cationic charged for electrostatic interaction with HA), crosslinkers ($PEGDA_{700}$ and $PEGDA_{575}$), an additional surface curing photo initiator DMPA (to induce the polymerisation process and reduce the polymerisation time), and HA (Mw, 2M Da, 2 mg/ml, dissolved in water) were mixed in different ratios and deposited on the BP modified contact lens via nES which was kept hydrated after step 1 described earlier. The HA loadings of the lenses were assessed prior to the UV light exposure. After nES, the coated contact lens was exposed to UV light for 15-45 minutes to create the semi-IPN network with trapped HA.

For the double-layer coated lenses, the lenses were coated with a base layer as described above. The single-layer coated lenses were returned to a petri-dish containing water to allow the lenses to relax for 2 hours to its original shape prior to the top layer coating. The PLGA (20 mg/ml in acetone) and zein (25 mg/ml in ethanol/H_2O (70/30) mixture) solutions used for coating were prepared for double layer coated lens as in previous studies [27,28].

Attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy

A FTIR spectrophotometer (VERTEX 70, Bruker Optics, Ettlingen, Germany), equipped with a Golden Gate, ATR accessory (Specac Ltd., Orpington, UK) and a diamond internal reflection element, was used to examine the contact lens before and after modification. The spectra were collected over a wavenumber range of 500–4000 cm^{-1} with a resolution of 4 cm^{-1} and 64 scans at room temperature.

In vitro HA release from HA-loaded contact lenses

HA was assayed by a high-performance liquid chromatography (HPLC) 200 series system (Perkin Elmer, MA, USA) with RI detector set at 35 ˚C and Waters HSPgel AQ MB-H, 6.0 x 150 mm, Part# 186001790 column (Waters, MA, USA). 0.2 M sodium nitrate dissolved in Milli-Q water

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was used as mobile phase. The column temperature was 65 ˚C and all methods were operating at 0.5 mL/min flow rate. The sample volume was 100 μL and the measurement time was 10 minutes. The HA calibration assay was carried out by using HA-2M from 3.05 - 54.13 μg/mL in PBS (pH 7.3). The retention time for HA (Mw 2M Da) was 3.8 min and area under the peak was used to plot the concentration calibration of HA.

The total amount of HA deposited on nES-coated lenses was quantified using HPLC. Each HA-loaded lens was subjected to ultrasonication for 2 minutes in a 6 mL glass vial containing 2 mL of phosphate-buffered saline (PBS, pH 7.3). The vials were sonicated for 2 minutes and then incubated in a shaking incubator for 24 hours to ensure complete delamination and dispersion of the HA polymer from the lens surface into the PBS medium. Triplicate lenses were used for average to determine the amount of HA loading on the lens.

The *in vitro* HA release tests from HA-loaded lenses was performed in 6 mL glass vials containing 2 mL of PBS and placed in a shaking incubator (125 rpm at 35 ˚C; IKA, Staufen, Germany). At each sampling time point, a 500 μL of the releasing medium sample was extracted and replaced with fresh PBS pH 7.3 to maintain the perfect sink condition throughout the release experiment. All samples were filtered through a 0.45 μm filter (to remove any large fragments delaminated from the lens) prior to HPLC analysis, and the HA release profile is plotted as the cumulative HA release (%) over time. The HA release experiments were carried out in triplicate for each sample. Statistical analysis of the drug release data at each time point was performed using one-way ANOVA followed by Tukey's post-hoc test, with $p \leq 0.05$ considered statistically significant.

Cryogenic-scanning electron microscopy (Cryo-SEM)

Cryo-SEM studies were used to examine the surface of nES printed polymer coats on different substrates using a Gemini 300 series microscope (Zeiss, Ostfildern, Germany), operating at 2-10 kV acceleration voltage. To perform cryo-SEM on contact lenses, the coated hydrated lens was

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cut into quarters using a scalpel. All the cryo-SEM samples were sublimated for 2 minutes and sputtered with platinum for 60s at 10 mA.

Viscosity and electrical conductivity measurements

As the viscosity and electrical conductivity of the formulation used for top- and base-coats can significantly affect the nES performance, both properties were measured for all formulations used in this study. The viscosity of each formulation used for nES was measured on a Discovery Hybrid Rheometer (TA Instruments, Delaware, USA) using a 40 mm steel cone plate across an increasing range of shear (0.01–200 1/s) at 25 ˚C. Data was analysed using TRIOS software (TA Instruments, Delaware, USA). The Carreau model was used to calculate the zero shear viscosity values of the formulations. Electrical conductivity measurements of all the nES formulations were performed by using a Jenway 4510 conductivity meter (Jenway Ltd, Stone, UK) with a microvolume conductivity probe. All measurements were performed at room temperature of 22±2 ˚C.

Results and discussion

Loading HA on benzophenone (BP)-modified contact lens using nES

The soft contact lenses were modified with the photoinitiator BP under UV light to create an active site for photo-polymerisation. **Figure 4a** illustrates the appearance of a contact lens after modification with BP which remained fully transparent. In this study, it is assumed that the chemical modification and nES coating did not introduce significant changes to the thickness, mechanical properties, or wearability of the contact lenses. These parameters will be systematically evaluated in follow-up experiments beyond the scope of the present study. ATR-FTIR spectra of the modified lens shows a new carbonyl peak at 1650 cm^{-1} and two benzene peaks (C=C stretches) at 1595 and 1577 cm^{-1} (**Figure 4b**), indicating the successful modification of photoinitiator on the lens surface[38, 56, 57].

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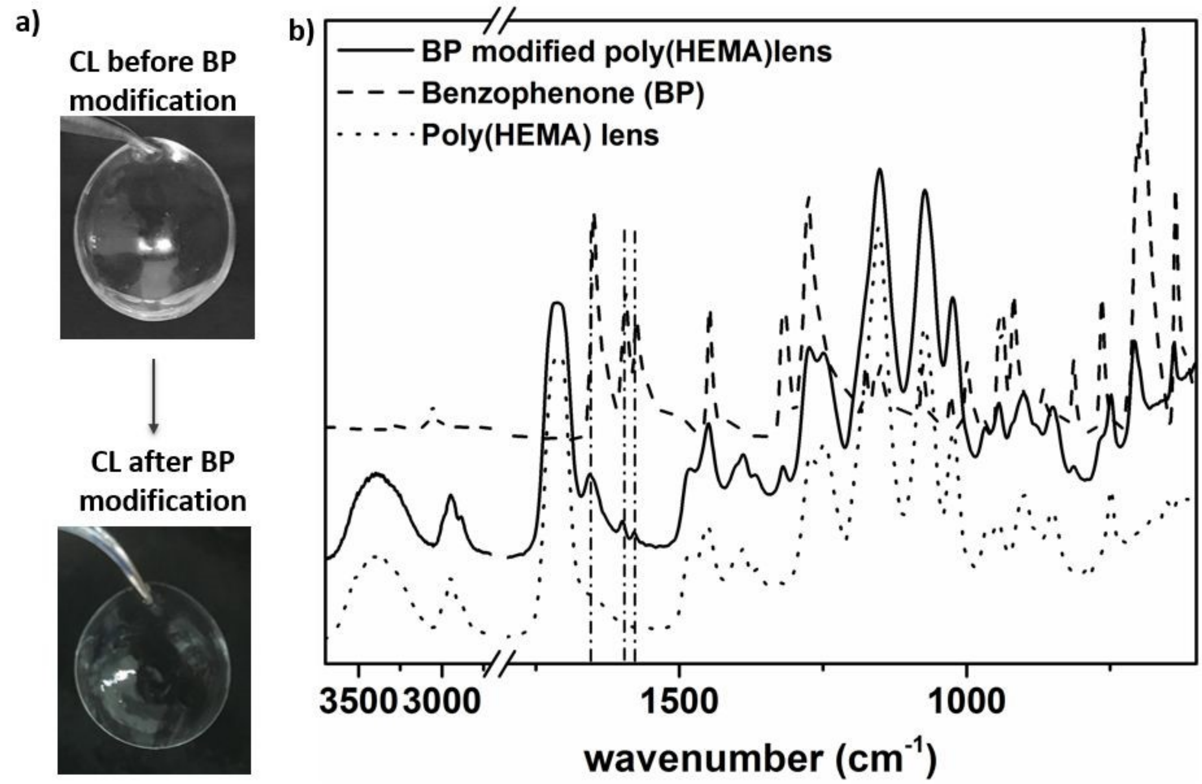

Figure 4. (a) Contact lens appearance before and after modification with BP; (b) ATR-FTIR spectra of lens before and after modification with BP (new peaks on BP modified lens indicated by vertical dotted lines).

The HA-acrylic monomer-based mixture containing monomers HEMA, cationic charged DEAEMA, crosslinkers $PEGDA_{700}$ and/or $PEGDA_{575}$ with HA were successfully deposited on the BP modified lens via nES at the periphery of the contact lens surface. Through UV exposure, the goal was to create a semi-IPN network with HA entrapped in the network, thus slowing down the diffusion and release of HA from the lens.

A range of HA-acrylic monomer-based mixture formulations for nES coating were tested. The detailed the amounts of monomers (HEMA and DEAEMA or mixture of both) and crosslinker ($PEGDA_{700}$) of each formulation are shown in **Table 1**. The zero shear viscosity and conductivity of all formulations were measured and were in the range of 50-80 cP and 30-55 μS/cm, respectively. All coating formulations contained HA, with HA-2M lenses without monomer or crosslinkers serving as a control (no UV curing was performed on the control lenses). The control

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lenses and the lenses with a code containing 'UV' were all BP-modified lenses. The HA loadings of the lenses were assessed prior to UV-curing. The loading values ranged from 11.55 to 14.84%µg/lens, as seen in **Table 1**. No significant difference in HA loading was observed in the control lenses and those containing monomer/crosslinker (UV-01 to UV-05).

Table 1. nES coating formulations of HA-acrylic monomer-based mixtures containing different volume ratio of monomers and crosslinker ($PEGDA_{700}$ and/or $PEGDA_{575}$) with HA

Lens code	HA* (mL)	$PEGDA_{700}$ crosslinker (mL)	$PEGDA_{575}$ crosslinker (mL)	HEMA monomer (mL)	DEAEMA monomer (mL)	Amount of HA deposited on CL (µg)
HA-2M*	1.0	-	-	-	-	14.84 ± 1.17
UV-01	1.0	0.7	-	0.3	-	12.01 ± 2.60
UV-02	1.0	0.9	-	0.1	-	12.85 ± 3.37
UV-03	1.0	0.9	-	0.05	0.05	11.55 ± 2.16
UV-04	1.0	0.9	-	-	0.1	14.73 ± 2.35
UV-05	1.0	-	0.9	0.1	-	12.08± 1.40

* HA (Mw of 2M Da, 1mL, 2 mg/mL concentration) further diluted with 1 mL water to make the final concentration of 1 mg/mL for spraying; HA deposited presented as mean±SD; n = 3.

In vitro HA release from HA-loaded contact lenses

Release profiles of HA from the lenses coated with the formulations UV-01 to UV-04 (**Table 1**) are shown in **Figure 5a**. The control lenses coated with HA without any chemical modification showed that over 95% of the HA was released within the first 60 minutes (**Figure 5a**). UV-01 showed a higher level of initial burst release compared to the other three formulations on the chemically modified lenses (UV-02, UV-03 and UV-04).

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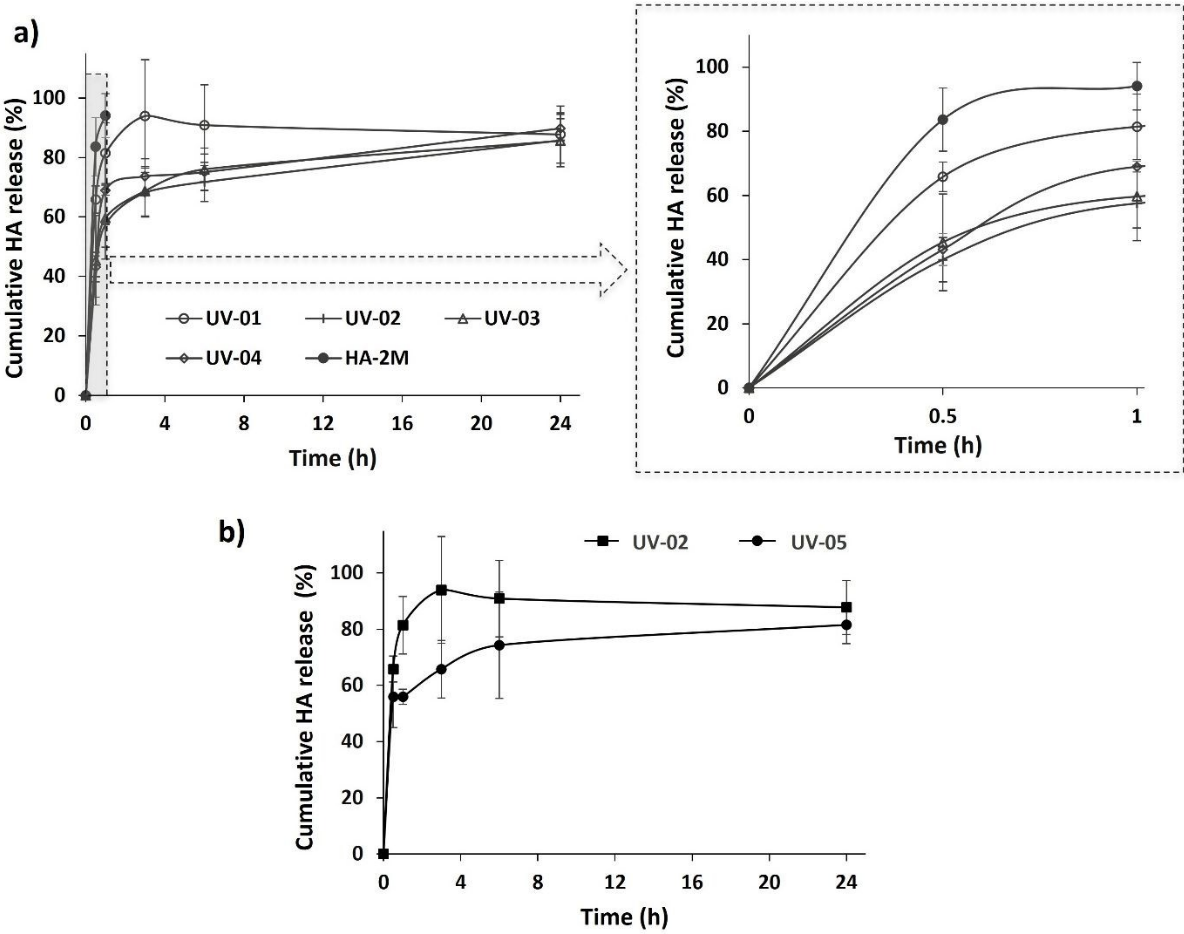

Figure 5. (a) Cumulative HA release (%) of the lenses with printed semi-IPN polymer ring using different monomers (HEMA and DEAEMA or mixture of both) and crosslinker ($PEGDA_{700}$) ratio, with the enlarged display of the release profile of the first hour (insert on the right); (b) HA release of lens UV-05 with a lower MW crosslinker, $PEGDA_{575}$, in comparison to UV-02. (Data is presented as mean ± SD; n = 3)

The diffusion of macromolecules such as HA through a crosslinked polymer network is mainly affected by the size and configuration of the molecule and the crosslinked network, respectively. The surrounding crosslinked polymer network acts as a steric barrier for HA to diffuse. A larger mesh size of the polymer network results in faster diffusion. In addition, HA, being a long-chain molecule, diffuses differently compared to simple particles. It behaves like a sequence of interconnected particles, with each segment of the chain needing to follow the one in front of it. This chain-like structure restricts movement, leading to what is known as the reptation model of

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diffusion.[16, 58, 59] These may have contributed to the reduced release rate observed for HA in the chemically modified lenses.

Two different monomers, two types of crosslinkers and two crosslinker to monomer ratios were used in these formulations. As seen in **Figure 5a**, the order of the HA release rate is UV-01>UV-04>UV-02 ≈ UV-03 in the first 4 hours of the tests. UV-01, as expected, has the fastest HA release among the tested formulations since it has the lowest crosslinker to monomer ratio (7:3) among all other formulations in **Table 1**, leading to a less crosslinked polymer network with, therefore, a larger mesh-size. UV-02 and UV-04 have the same crosslinker to monomer ratio (9:1), but different monomer. With a tertiary amine group, DEAEMA (UV-04) is positively charged which introduces ionic character to the polymer network and provides electrostatic interaction with negatively charged carboxyl groups of HA. Although electrostatic interaction is stronger than the hydrogen bonding occurring between HEMA (UV-02) and HA, the difference seen in the HA release rate is not significant. UV-03 used high crosslinker to monomer ratio and HEMA-DEAEMA mixed monomers. It showed a similar HA release rate to UV-04 and UV-02. The overall HA release for these formulations is still relatively fast, reaching 80% release within 14 hours for UV-02, UV-03 and UV-04, with a notable burst release in the first 4 hours.

To attempt to further reduce the HA release rate from the lenses, a lower molecular weight of the crosslinker, $PEGDA_{575}$, was used (UV-05). This was expected to produce a less porous polymer IPN structure on the lens surface[60, 61]. The $PEGDA_{575}$ crosslinker resulted in a slower HA release compared to $PEGDA_{700}$ **(Figure 5b)**. UV-05 exhibited an initial burst release of 55% HA within the first 30 minutes, which is likely dominated by the HA on the surface of the polymer matrix that is not fully entrapped within the bulk of the IPN network. However, after the first 30 minutes, the release rate of HA from UV-05 treated lenses was notably slower than the lenses treated with $PEGDA_{700}$-based crosslinker, indicating that the shorter-chain $PEGDA_{575}$ crosslinker created a less porous IPN network which slowed down the diffusion and release of the HA from the polymer matrix.

Table 2. nES coating formulations with the addition of DMPA initiators

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Lens code	HA* (mL)	$PEGDA_{575}$ (mL)	HEMA (mL)	DEAEMA (mL)	DMPA* (µL)	UV time (mins)	Amount of HA deposited on CL (µg)
UV-06	1.5	0.9	0.05	0.05	20	10	22.98 ± 3.88
UV-07	1.5	0.9	0.1	-	-	45	18.80 ± 2.25
UV-08	1.5	0.9	0.1	-	50	10	19.13 ± 1.55

* HA (Mw of 2M Da) has a concentration of 2 mg/mL, and DMPA has a concentration of 50 mg/mL; HA deposited presented as mean±SD; n = 3.

To accelerate the polymerisation process for nES HA coating, the photoinitiator DMPA (50 mg/mL) was incorporated with the monomers (HEMA and DEAEMA) and the crosslinker ($PEGDA_{575}$) **(Table 2)**. DMPA was selected due to its fast reaction rate and efficiency, even at low concentrations[62, 63]. The addition of the DMPA initiator further shortened the needed polymerisation time under UV light from 45 minutes to 10 minutes for UV-06 and UV-08. In contrast, UV-07, which did not include DMPA, required 45 minutes to achieve a crosslinked polymer network on the lens surface.

The HA release profile showed a significantly slower initial release in UV-06 and UV-08 than UV-07 **(Figure 6)**. In UV-07, BP on the lens surface, through the modification process prior to nES, is the only available initiator for the reaction at the contact lens/HA coat interface, leading to longer polymerisation time and a crosslinked grafted polymer network[64, 65]. In contrast, DMPA, through its radical formation and rapid curing process, allowed for faster photo-polymerisation of the sprayed HA ink from the surface to the bottom of the coating in UV-06 and UV-08. Taking into consideration the effects on sustaining the HA release and reducing the curing time, including DMPA in the formulation was carried forward for further formulation optimisation.

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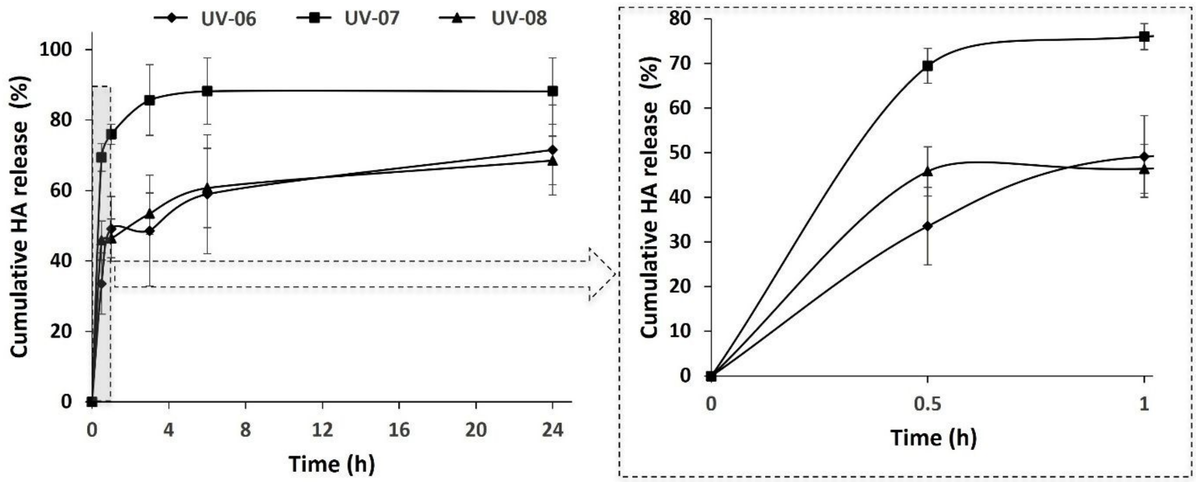

Figure 6. Cumulative HA release profiles of the lenses with printed semi-IPN polymer rings with the additional initiator DMPA in the ink formulations. (Data is presented as mean ± SD; n = 3)

To further reduce the HA release rate, a barrier coating of either PLGA or zein was added to the semi-IPN HA layer, creating a bilayer coating (**Table 3**). These formulations have a HA-2M semi-IPN base-coat (UV-09 with no topcoat), and either zein (UV-10) or PLGA (UV-11) as the top-coat.

Table 3. nES coating formulations of single and double-layer coated contact lenses

Base-coat (for single and double-layer coated lenses)							
Lens code	**HA* (mL)**	**$PEGDA_{575}$ (mL)**	**HEMA (mL)**	**DEAEMA (mL)**	**DMPA* (µL)**	**UV time (mins)**	**Amount of HA deposit on CL (µg)**
UV-09	1.5	0.9	0.05	0.05	50	10	18.26 ± 4.56

Top-coat (for double-layer coated lenses)				
Lens code	**Polymer used**	**H_2O (%)**	**Ethanol (%)**	**Acetone (%)**
UV-10	Zein (25 mg/mL)	30	70	0

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UV-11	PLGA (20 mg/mL)	0	0	100

* HA (Mw 2M Da) has a concentration of 2 mg/mL concentration, and DMPA has a concentration of 50 mg/mL; HA deposited presented as mean±SD; n = 3.

Both HEMA and DEAEMA monomers were included with the cross-linker $PEGDA_{575}$ in the base-coat of UV-10 and UV-11. Photo-initiator (DMPA) was included, and a 10-minute exposed to UV light was used to facilitate photo-polymerisation. For UV-09, the HA-monomer formulation was applied to the lens and cured under UV light for 10 minutes. For UV-10 and UV-11, after the 10 minutes curing of the base-coats, a topcoat of zein or PLGA was deposited on top to act as a secondary barrier to HA release. Cryo-SEM images revealed the morphology of different locations of the contact lens surface with a bilayer nES coating. **Figure 7a** shows a top-coat at the peripheral region of the contact lens as illustrated in **Figure 7b**, while the central region (optical zone diameter ~8mm) remained uncoated (**Figure 7c**).

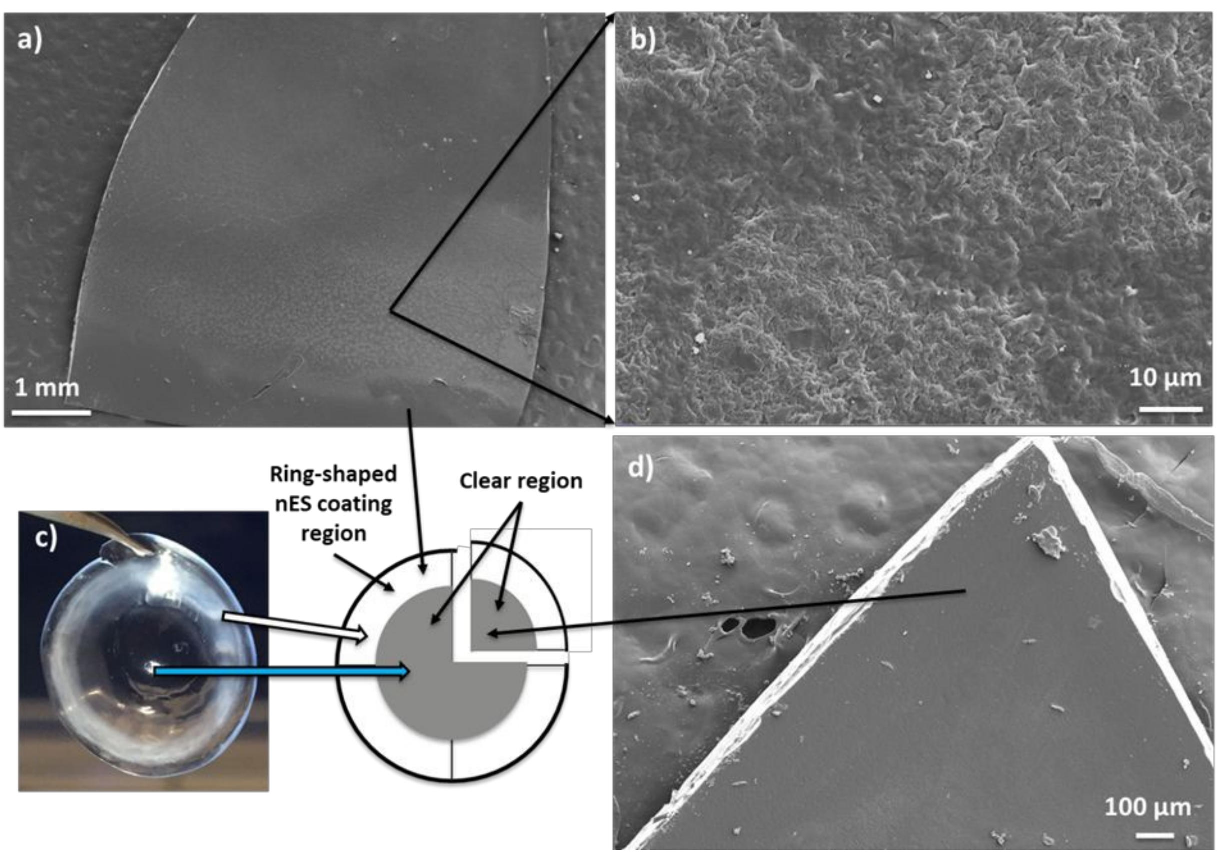

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Figure 7. a) A representative cryo-SEM image of the bilayer (semi-IPN as basecoat and zein as topcoat) deposited layer at the periphery on BP modified lens; b) higher resolution of the surface of the bilayer coated lens; c) visual appearance of a bilayer coated lens and schematic diagram to show the cryo-SEM sampling location; d) cryo-SEM image of the center of contact lens (not coated) having smooth surface with no polymer coating.

The release of HA was evaluated from the double-layer coated lenses (UV-10 and UV-11) and compared to the results of single-layer coated lenses (UV-09) (**Figure 8**). The single-layer coated lenses (UV-09) exhibited a rapid initial burst of HA within the first hour of over 50% and over 80% within 5 hours. The double-layer coated UV-11 lenses with PLGA top-coat showed no statistically significant difference in the cumulative release and release rate of HA compared to UV-09. This may be attributed to the higher hydrophobicity of PLGA which led to some level of delamination of the coating during the HA release experiment.

The double-layer coated lenses with zein being the top-coat (UV-10) showed a significant reduction of the total HA release to 35% within 24 hours (**Figure 8a**) in comparison to UV-09 and UV-11. HA in the base-coat can have dual-directional diffusion, leading to release from both the front of the lens and across the zein top-coat at the back of the lens, as illustrated in **Figure 8b**. There is almost no release within the first 30 minutes which could be attributed to the lag time for the HA to diffuse across the zein layer as well as the full thickness of the lens. This is followed by 18% release in 1 hour and an additional 17% release between 1-6 hours. Between 6-24 hours, the HA release rate significantly reduced and resulted in 35% cumulative release by 24 hours. The reason for the incomplete HA release within 24 hours could be attributed to the interaction between HA and zein within the hydrated zein network. It has been reported that in the hydrated or film form of zein, it can form a cross-linked or semi-interconnected network[66-69]. While HA is diffusing through the hydrated zein network, it could interact with zein through electrostatic attraction, hydrogen bonding between NH_2 of HA and C=O of glutamine in zein, and hydrophobic interactions[66]. These interactions could retain HA within the zein layer, leading to the slow and incomplete release observed.

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There are two main limitations of nES as a surface deposition method. In the context of contact lens coating, while nES can successfully deliver active ingredients to the surface of both high-water content hydrogel lenses and silicone hydrogel lenses, these compounds are prone to rapid bidirectional diffusion through the lens material, as illustrated in **Figure 8b**. This presents a particular challenge for highly hydrophilic molecules such as HA, which may require chemical modification or advanced formulation strategies to achieve sustained release. More broadly, nES delivers relatively small volumes of formulation per application. Although this is generally sufficient for ocular therapeutics, where drug doses are typically low, it may limit the applicability of nES for other medical devices with small surface areas that require high drug loading.

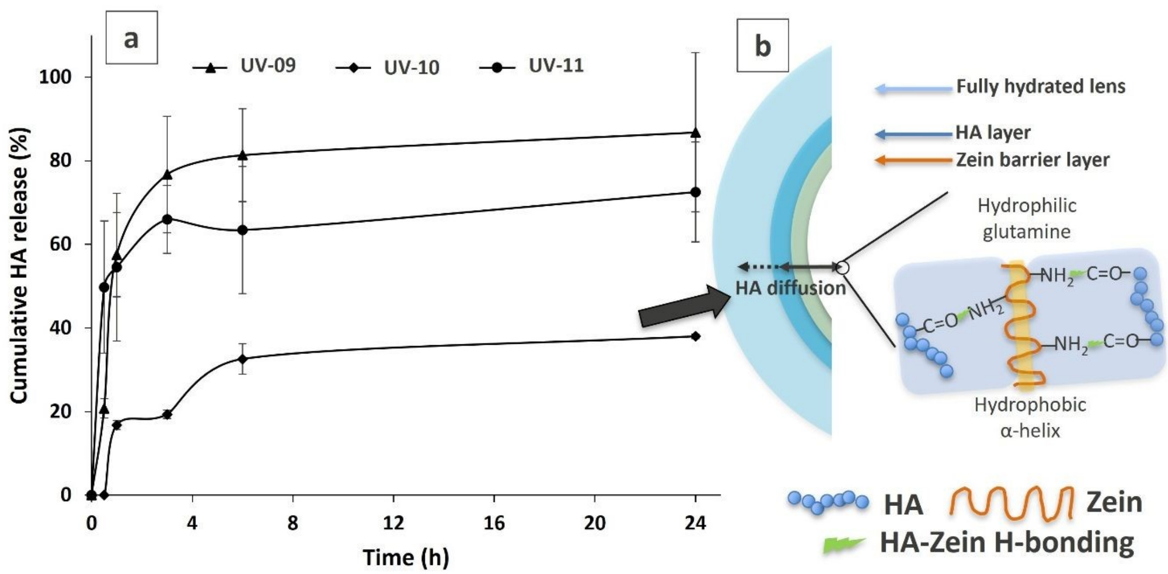

Figure 8. (a) Cumulative HA release from single- (semi-IPN) and double-layer coated (semi-IPN as base-coat and polymers like zein and PLGA as top-coat) BP modified lens (Data is presented as mean ± SD; n = 3), (b) graphic illustration of the possible mechanism of sustained and incomplete HA release within 24 hours.

Conclusions

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This study used high molecular weight HA (2M), which is an ocular surface comfort agent used in eye drops and has clinically been used for treating dry eye syndrome, to demonstrate the capability of nES for material deposition on contact lens surfaces with high precision. An IPN approach was developed to 'dock' HA at the peripheral section of the contact lens surface. The selection of monomer type (for hydrogen bonding and electrostatic interaction) with different length of crosslinker (M_w of 700 and 575) and the additional rapid cured photo-initiator impacted on the density of IPN formed and the speed of the curing process. The different mesh-sized IPN network slowed down the HA release from the lens surface after an initial burst release. The deposition of an additional zein or PLGA coat to act as a release barrier on top of HA trapped in IPN base-layer led to further sustained HA release beyond 24 hours from the zein top-coated lenses. nES can be employed to selectively coat the peripheral regions of soft contact lenses, enabling sustained release of HA from the lens. The results of this study demonstrate the potential of nES as a versatile technique for precise surface deposition of active ingredients, with broader applicability across a range of medical devices.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest:

There are no conflicts to declare.

Data availability

Data is available upon request.

Acknowledgement

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Data availability

Data is available upon request.