The Effect of Freezing on the Elution of PVA from Contact Lenses

by

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Contact lenses are widely used, with over 140 million wearers globally. Wearing contact lenses can cause symptoms of discomfort and dryness, which affect nearly half of all wearers. To address this concern, this thesis explores the release of polyvinyl alcohol (PVA) from contact lenses, aiming to improve comfort through controlled elution. PVA forms a protective film when placed on the ocular surface and serves to reduce ocular discomfort. This research specifically studies the impact of freezing on PVA interaction with various contact lens materials and its subsequent release kinetics. This thesis hypothesizes that freezing enhances the hydrogen bonding of PVA to lens materials, enabling the formation of a surface layer on contact lenses and increasing PVA elution. To investigate this hypothesis, commercial lenses (Acuvue® Oasys – senofilcon A, DAILIES® AquaComfort PLUS® - nelfilcon A, 1-Day Acuvue® Moist® - etafilcon A) were soaked in 2.5% w/v high molecular weight PVA solutions at 37°C for 48 hours, followed by 1 hour at either room temperature or freezing at -80°C. The results demonstrate a significant ($p<0.05$) increase in the cumulative PVA release from nelfilcon A lenses after 24 hours following freezing at -80°C for one hour, with 55.07 ± 2.46 µg of high molecular weight PVA released in comparison to lenses kept at room temperature which showed 46.16 ± 6.94 µg of PVA release. In contrast to nelfilcon A, etafilcon A and senofilcon A did not show a significant ($p>0.05$) change in the amount of PVA released after freezing. Etafilcon A lenses released 17.03 $\pm$ 3.03 µg and 20.21 $\pm$ 2.51 µg ($p>0.05$), and senofilcon A showed 20.33 $\pm$ 6.60 µg and 24.14 $\pm$ 2.58 µg ($p>0.05$) at room temperature and after freezing at -80°C for one hour, respectively, suggesting that freezing enhances these

effects only for nelfilcon A lenses. To further explore the impact of PVA with lenses, experiments with synthesized lenses (pHEMA and PVA loaded pHEMA) were performed, which demonstrated that the presence of PVA inside the lens significantly ($p<0.05$) impacts subsequent PVA loading and release and the freezing effect. The cumulative release of PVA over 24 hours from pHEMA lenses were 32.64 ± 5.48 µg and 36.25 ± 6.11 µg ($p>0.05$), at room temperature and after freezing at -80°C for one hour, respectively. PVA loaded pHEMA lenses, in contrast, showed a significant ($p<0.05$) increase in the cumulative PVA release over 24 hours after freezing, rising from 42.88 ± 4.96 µg to 47.39 ± 6.26 µg after one hour at -80°C. The study emphasizes the importance of PVA incorporation within contact lenses to observe a substantial impact on release after soaking or freezing. The findings suggest that the freezing technique has potential applications in enhancing the release of comfort agents such as PVA from contact lenses, especially those containing PVA internally. In conclusion, this research provides insights into optimizing contact lens design for improved comfort by utilizing PVA release. The demonstrated impact of freezing on nelfilcon A lenses indicates a promising avenue for enhancing the release of comfort agents.

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Dedication

I dedicate this thesis to my loving parents Smt. Usha devi Shukla and Shri. Rajendraprasad Shukla whose vision and sacrifices helped me reach this milestone, my supportive brother Ashish Shukla, and to Anamika Desai, whose encouragement and inspiration have been invaluable throughout this journey.

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List of Abbreviations

ATRP	atom transfer radical polymerization
CAF	caffeine-contained
CL	soft contact lenses
CLD	contact lens discomfort
DD	daily disposable
DMA	N,N-dimethylacrylamide
EGDMA	ethylene glycol dimethacrylate
F/T	freeze-thaw
GMA	glycerol methacrylate
HA	hyaluronic acid
HEMA	2-hydroxyethyl methacrylate
HPMC	hydroxypropyl methylcellulose
IPN	interpenetrating polymer network
LBL	layer-by-layer
MAA	methacrylic acid
MPC	2-(methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate
MW	molecular weight
NMR	nuclear magnetic resonance
NVP	1-vinyl-2-pyrrolidinone
PDMS	polydimethylsiloxane
PEG	polyethylene glycol
pHEMA	poly(2-hydroxy ethyl methacrylate)
PLTF	post-lens tear film
PVA	polyvinyl alcohol
PVC	polyvinyl chloride
RGP	rigid gas permeable
RPM	revolution per minute
SAMs	self-assembled monolayers
TRIS	3-[tris(trimethylsiloxy)silyl] propyl methacrylate
UV	ultra-violet
UV-B	ultraviolet-B radiation
Vit. E	vitamin E

List of Symbols

µL	microlitre
°C	degree Celsius
mg	milligrams
mL	millilitre
KI	potassium iodide
I_2	Iodine
hr	hour
kDa	kilodalton
%	percentage
w/v	weight/volume

Chapter 1
Literature review

1.1 Introduction

Soft contact lenses (CL) are thin, transparent, flexible, curved discs used by approximately 140 million wearers across the world[1] and around 40 million in the US.[2] They were first developed by Wichterle and Lim[3] in 1960 and can be either hydrogel or silicone hydrogel based depending on the underlying composition. Unfortunately, wearing contact lenses can cause symptoms of discomfort and dryness, with almost half of the wearers experiencing these issues which can lead to temporary or permanent lens wear discontinuation.[4]

The TFOS International Workshop on Contact Lens Discomfort defined contact lens discomfort (CLD) as “a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear”.[5] This definition of CLD itself highlights the potential consequence of contact lens wear, where the ocular surface can show an impairment that resembles mild to moderate dry eye conditions and increases lens wear dropout rates.[4] This highlights the need for careful diagnosis and management of symptoms in contact lens wearers if they are to remain wearing these lenses, or pre-emptively managing CLD to prevent its occurrence.

1.2 Contact lens discomfort

Contact lens discomfort is a common issue reported by wearers, affecting their overall experience and satisfaction, and potentially leading to discontinuation of lens use.[4] Contact lens comfort is influenced by both bulk and surface material properties. Bulk properties enc

ompass oxygen transmissibility, ion permeability, modulus, and water content.[6] Earlier studies suggested that silicone hydrogel lenses could be used to reduce CL dropout due to improved comfort.[6] However, more recent studies and reviews suggest that no substantial comfort difference exists between silicone hydrogel and hydrogel controls.[7, 8] Lysozyme deposition has been shown to play a role in discomfort.[9] Lens replacement frequency also plays a role,[10] with silicone hydrogel lenses generally yielding higher comfort levels when used as a daily disposable modality compared to when they are replaced on a reusable format.[11] Surface properties, including friction, wettability, and surface water contact, also impact comfort.[7] Lower friction coefficients might correlate with enhanced end of day comfort.[12-14] Understanding the interplay between these properties and discomfort is crucial for improving lens design and enhancing wearer satisfaction.

1.2.1 Bulk properties affecting contact lens comfort

1.2.1.1 Oxygen transmissibility

Oxygen transmissibility refers to the ability of a contact lens material to allow oxygen to pass through to the cornea.[15] Insufficient oxygen supply can lead to corneal hypoxia, resulting in a wide variety of complications, including corneal neovascularization.[16] High-oxygen-permeable materials, such as silicone hydrogels, mitigate these issues by ensuring adequate oxygen supply to the cornea, reducing the risk of hypoxic complications.[17, 18] Silicone hydrogel have more oxygen permeability compared to conventional hydrogels, but unfortunately did not appreciably increase comfort in most wearers without hypoxic complications. Furthermore, insufficient oxygen levels can lead to corneal swelling, affecting the lens fit and causing discomfort during wear.[6]

1.2.1.2 Ion permeability

The movement of ions through contact lenses is crucial for maintaining proper hydration and flexibility, which are essential for lens comfort and stability on the eye.[19] Poor ion permeability can disrupt the delicate balance of ions on the ocular surface, leading to discomfort and dryness.[19] Contact lenses designed with optimal ion permeability can uphold a balanced ionic environment in the eye, lowering the risk of discomfort and irritation.[19] There is a minimum level of ion permeability that is required for successful contact lens wear, however, surpassing this critical threshold does not result in additional movement of the lens on the eye.[19]

1.2.1.3 Modulus

Modulus refers to the stiffness or rigidity of a material. High modulus contact lenses may exert excessive pressure on the cornea, causing mechanical irritation and discomfort.[10, 20] Conversely, low-modulus materials offer greater flexibility and conformability, enhancing wearer comfort. Although it might be anticipated that contact lens materials with a lower modulus would conform more easily to the cornea and settle faster compared to lenses with a higher modulus, this hypothesis was not supported by the outcomes observed by Dumbleton et al.[21] Designing lenses with an appropriate modulus and design ensures optimal fit and comfort, minimizing the risk of discomfort-related issues.

1.2.1.4 Bulk water content

Water content plays an important role in influencing the hydration and lubrication of contact lenses, impacting comfort during wear.[22] Low water content hydrogel contact lenses have been shown to be more comfortable compared with medium and high water content contact lenses.[7, 23] Low water content contact lenses may offer advantages such as enhanced durability and resistance from protein deposition.[7, 24]

High water content lenses have been shown to reduce friction and irritation, leading to enhanced comfort, particularly during extended wear or overnight wear.[25] Some high-water content lenses are designed with advanced materials that not only offer increased moisture but also ensure optimal oxygen permeability.[26] This allows for improved oxygen delivery to the cornea, promoting ocular health and reducing the likelihood of discomfort.[27] Despite their benefits, high water content lenses are not without drawbacks. One significant concern is the potential for dehydration during wear.[28] These lenses may lose moisture more rapidly than lower water content counterparts, especially in dry or windy environments.[10] This can lead to discomfort, dryness, and fluctuations in vision quality throughout the day. Maintaining optimal water content is essential for ensuring long-term comfort and wearability of contact lenses.[28]

1.2.2 Surface properties affecting contact lens comfort

1.2.2.1 Friction

Friction plays a pivotal role in contact lens discomfort, potentially causing irritation and abrasions on the delicate ocular surface if not optimized.[10] As the lens moves with blinking or eye movements, excessive friction can occur, leading to discomfort for the wearer. Factors contributing to friction include the fit of the lens, material properties, and tear film condition.[1, 10, 29-32] Poorly fitting lenses with uneven surfaces or edges can rub against the cornea or eyelids, heightening friction, and discomfort. Optimal lens fitting by an eye care professional is essential to minimize friction-related issues. Additionally, the material composition of the lens influences its surface characteristics, with certain materials having higher coefficients of friction,[1, 29, 31, 32] necessitating the development of materials with lower friction properties to enhance wearer comfort. Moreover, maintaining a stable and healthy tear film acts as a

lubricating barrier, reducing friction and preventing dryness.[28] Factors such as insufficient tear production or r[10, 29, 31, 32]

Material scientists have endeavored to enhance contact lens comfort by devising strategies to diminish friction through augmenting surface lubricity. Various methodologies have been employed, encompassing alterations to the lens surface, incorporation of wetting agents within the material, and controlled release mechanisms.[26] These approaches aim to mitigate friction-induced discomfort experienced by wearers. For instance, nelfilcon A, a material employed in daily disposable lenses, integrates polyvinyl alcohol (PVA) into its matrix, facilitating either gradual elution or surface release upon blinking, thereby fostering a smoother interaction between the lens and the ocular surface.[26]

1.2.2.2 Wettability

Contact lens wettability, crucial for contact lens comfort, refers to the surface's ability to retain a thin, even layer of tear film, facilitating smooth interactions with the ocular surface.[33] When wettability is compromised, contact lens wearers may experience heightened discomfort due to factors such as increased friction, dryness, and irritation.[28] Surface properties play a pivotal role in wettability, with hydrophobic surfaces repelling water and diminishing wettability, leading to discomfort. To counteract this, manufacturers employ hydrophilic components or surface treatments to enhance wettability and ensure tear film stability, promoting a more comfortable wearing experience.[10]

Silicone hydrogels also face challenges regarding wettability, due to their inherent hydrophobic nature, which can lead to decreased surface wettability, increased lipid interaction, and lens-binding issues.[34] Objective measurements have shown that silicone hyd[34] However, researchers have employed various strategies to address these challenges successfully. Incorporating wetting agents into the core of silicone hydrogels has shown

promise, particularly in materials such as narafilcon A and senofilcon A.[35] Additionally, efforts to modify the surface properties of hydrogels, including strategies to enhance surface wettability, have been explored.[36] These approaches aim to improve the interaction between the lens surface and tear film, thereby enhancing comfort and reducing the risk of complications associated with poor wettability.

Moreover, the interaction between the contact lens and the tear film significantly impacts wettability. A well-wetting lens facilitates the uniform spreading of the tear film, ensuring adequate coverage and lubrication of the ocular surface. Environmental factors such as low humidity or exposure to pollutants can further exacerbate wettability issues, leading to decreased comfort.[37] To address these concerns, strategies such as surface modifications, lubricating solutions, and proper lens care regimens are employed to enhance wettability, alleviate discomfort, and optimize the overall contact lens wearing experience. However, a clear association of wettability with the comfort has not yet been established.[33]

1.2.2.3 Surface water content

Surface water content of a contact lens refers to the amount of water present on the outermost layer or surface of the lens. It directly influences the lens's interaction with the tear film and ocular tissues, affecting comfort and visual performance. This measure differs from the overall (or bulk) water content of a lens, which represents the total amount of water within the lens matrix, including both surface and bulk water content.[34] Understanding both surface and overall water content is essential for optimizing contact lens design and performance. The surface water content of contact lenses plays a crucial role in maintaining hydration, lub[10]

Lenses with high water content may be prone to dehydration, especially in dry or windy environments. As water evaporates from the lens surface, it can lead to dryness, protein

deposits, and discomfort for wearers.[38] In comparison, lenses with low water content may have reduced protein deposition and enhanced durability. Additionally, low water content traditional hydrogel materials may be less permeable, leading to reduced oxygen transmission and potential hypoxic effects on the cornea.[28]

Balancing surface water content is essential to ensure optimal comfort and ocular health for contact lens wearers. Manufacturers utilize advanced materials and hydration technologies to achieve the ideal balance between moisture retention, oxygen permeability, and surface lubrication.[10]

1.3 Management of contact lens discomfort

CLD remains a significant challenge despite advancements in contact lens technology.[5] Managing CLD involves various strategies, including refitting lenses, altering lens materials, and employing lubrication methods. Understanding these strategies and their effectiveness is crucial for optimizing contact lens wear. This section explores different approaches to managing CLD and evaluates their efficacy based on existing literature.

1.3.1 Fitting

One of the primary reasons for discomfort in contact lens wearers is poor lens fit.[39] Ill-fitting lenses can cause mechanical irritation, leading to sensations of scratching, burning, or foreign body sensation. Refitting lenses, which involves adjusting parameters to better match the curvature of the cornea and the size of the eye, can reduce friction and improve com[22] Studies have shown that optimizing lens fit can alleviate symptoms and enhance the wearer's overall comfort. This process involves adjusting various parameters of the contact lenses, such as base curve, diameter, and material composition, to optimize fit and reduce factors contributing to discomfort.[39]

Arroyo-del Arroyo et al.[39] found that refitting monthly CL wearers with daily disposable (DD) contact lenses significantly reduced symptoms of CLD, highlighting the importance of selecting appropriate lens types for individual patients. Additionally, Navascues-Cornago et al.[40] observed a continual and significant decline in discomfort over a 12-hour wearing period among symptomatic DD contact lens wearers, further supporting the efficacy of refitting interventions in improving comfort. However, it is essential to note that the success of refitting interventions may vary depending on factors such as the underlying cause of discomfort, individual eye physiology, and patient compliance. Therefore, a thorough assessment of the patient's symptoms, ocular health, and lifestyle factors is crucial in determining the most appropriate refitting approach.

1.3.2 Material modifications

Material modifications play a crucial role in managing contact lens discomfort by addressing factors such as dehydration, and lens surface interactions. Silicone hydrogel lenses, a notable advancement in contact lens technology, offer enhanced oxygen permeability and water retention properties compared to traditional hydrogel lenses.[41] These attributes contribute to maintaining corneal health and reducing discomfort associated with hypoxia and dryness. However, concerns regarding increased lipid deposition on silicone hydrogel surfaces have prompted further investigation into surface modifications to mitigate these issues.[42] Studies have explored surface coatings, such as those incorporating hyalur[43] PVA,[44] and polyethylene glycol (PEG),[45] to enhance lubricity and reduce friction between the lens and ocular surface.

1.3.3 Comfort agents

The role of comfort agents in managing ocular discomfort is highlighted in various studies. Dryness symptoms related to CL surface wettability have led practitioners to advise patients

to use wetting drops before lens application. For instance, pre-lubrication with substances such as methylcellulose or guar can enhance comfortable wearing time.[46] Additionally, using a carboxymethyl cellulose-based conditioning solution on the contact lens before inserting a DD lens improves comfort.[47] During continuous wear, rewetting drops containing surface-active surfactants have demonstrated benefits in terms of comfort, visual quality, and reduced mucous discharge compared to saline solutions.[48]

Surface-active agents aid in removing protein deposits on continuous-wear silicone hydrogel lenses, potentially improving wearer comfort.[48] Tear breakup time enhancement can be achieved by using wetting drops proactively.[48] Incorporating the ocular lubricant hydroxypropyl methylcellulose (HPMC) into multipurpose contact lens solutions conditions the lens surface, leading to enhanced comfort through improved wetting.[48, 49] PVA, a tear film stabilizer, is used in comfort drops and some soft contact lens materials. An approach involving additional non-functional PVA as an internal wetting agent in a PVA-containing lens (nelfilcon A) has shown consistent sustained release onto the ocular surface.[26] This approach improves lens surface wettability and comfort initially and throughout the day.[26, 50] However, while most other external wetting agents enhance comfort, their benefits are most pronounced during the early phase of daily lens wear. Further details about PVA are provided in section 1.6.

It is thus clear that the manufacture and components of contact lenses can have an impact on comfort, and thus an understanding of the methods to synthesize lenses is important.

1.4 Contact lenses: materials and synthesis

1.4.1 Materials

A polymer consists of repeating monomer units linked by covalent bonds. Polymerization, the process of polymer formation, starts with initiators that induce radical formation.[51] These radicals initiate polymerization by reacting with neighboring monomer functional groups. This propagation continues until all monomers are consumed. Polymerization terminates when radicals are quenched, often chosen practically for CL manufacturing, such as ultra-violet (UV) or thermal initiators.[51] The polymers used in contact lens production are crucial for comfort, biocompatibility, and optical properties. Hydrogel-based polymers have revolutionized contact lens materials due to their water retention and silicone hydrogels with increased oxygen permeability, minimizing discomfort and allowing longer wear times. These polymers are synthesized using techniques such as photo-polymerization or heat polymerization.[51] Furthermore, the synthesis process involves copolymerization of monomers to achieve desired properties such as flexibility and durability.

Hydrophilic monomers such as 1-vinyl-2-pyrrolidinone (NVP), methacrylic acid (MAA), N,N-dimethylacrylamide (DMA), 2-hydroxy ethyl methacrylate (HEMA), and glycerol methacrylate (GMA) are commonly used in the synthesis of contact lenses. These monomers contribute to the material's water retention and biocompatibility.[52] Poly(2-hydroxy ethyl methacrylate) (pHEMA) is a polymer which forms a three-dimensional hydrogel when soaked in water and is one of the most common backbone polymers for contact lenses.[3] It is synthesized by polymerization of 2-hydroxy ethyl methacrylate and can be made into a contac

t lens when co-polymerized with other monomers such as ethylene glycol dimethacrylate (EGDMA), methyl methacrylate (MMA), and MAA. Because of its hydrophilic pendant group, pHEMA is a biocompatible,[53] non-biodegradable, and optically transparent hydrophilic polymer that swells and forms a hydrogel upon absorption of water or biological fluids. In contrast, in a dry state pHEMA is a hard and brittle material.[54] Optical properties, mechanical strength, oxygen permeability, and water content can be changed by altering cross-linking rate, polymerization type, adding copolymers, etc.[55] It can be polymerized by either photo-polymerization or thermal methods,[56] and has a wide variety of applications.[57]

Silicone-based hydrogel contact lenses involve monomers such as polydimethylsiloxane (PDMS) and 3-[tris(trimethylsiloxy)silyl] propyl methacrylate (TRIS).[58] Zwitterionic monomers, such as 2-(methacryloyloxy)ethyl 2-(trimethylammonio)ethyl phosphate (MPC), are also studied for their unique properties. TRIS is often a key component in silicone-based contact lens materials.[52, 59] It enhances oxygen permeability by integrating siloxane functional groups during synthesis. This improved oxygen flow ensures wearer comfort and eye health by reducing the risk of hypoxia and enhancing overall lens performance.[51] These diverse monomers enable the development of contact lenses with varying characteristics to cater to different user needs.

1.4.2 Synthesis

The synthesis of contact lenses involves several methods tailored to produce lenses with optimal biocompatibility, mechanical properties, and optical clarity. These include cast molding, lathe cutting and spin casting. All these methods allow for precise control over lens geometry and optical properties to be formulated.

1.4.2.1 Cast molding

Cast molding is a versatile method used for manufacturing both rigid and soft contact lenses. This process involves pouring liquid monomer material into molds and allowing it to solidify, forming the desired lens shape. Cast molding offers several advantages, including flexibility in lens design, customization for individual prescriptions, and scalability for mass production.[60]

The process of cast molding begins with the selection of appropriate monomer materials, which may include silicone hydrogels or hydrogel polymer-based compositions. These materials undergo polymerization, where monomer molecules crosslink to form a solid network structure. During the molding phase, the liquid monomer mixture is poured into precision-engineered molds, which define the final shape and dimensions of the lenses.[60] After pouring the monomer mixture into the molds, it undergoes a curing process to initiate polymerization. This step may involve exposure to UV light, heat, or chemical initiators to promote crosslinking and ensure uniformity in lens composition and properties. Once solidified, the lenses are carefully removed from the molds and subjected to post-processing steps, including surface polishing, inspection, and packaging.[60]

1.4.2.2 Lathe cutting

Lathe cutting is a precision manufacturing method predominantly used for manufacturing rigid gas permeable (RGP) contact lenses. This process involves the mechanical shaping of small, hard disks of contact lens material on a spinning lathe. Lathe cutting offers several advantages, including high precision, excellent optical clarity, and the ability to produce lenses with complex geometries for specialized applications.[61]

The process of lathe cutting begins with the selection of suitable lens materials, typically RGP polymers or other rigid materials with excellent optical properties. These materials are machined into small, disk-shaped blanks, which serve as the starting point for lens fabrication. The blanks are securely mounted onto the lathe, where they undergo precise machining operations to shape the lens surfaces and edges according to the desired prescription and design specifications.[61] During lathe cutting, the spinning motion of the lathe and the precision cutting tools remove material from the lens blanks, gradually forming the final lens shape. The cutting tools are carefully controlled to achieve the desired curvature, thickness, and optical power, ensuring consistent performance across all lenses. Specialized polishing and finishing processes may be employed to further refine the lens surfaces and optimize optical clarity.[61]

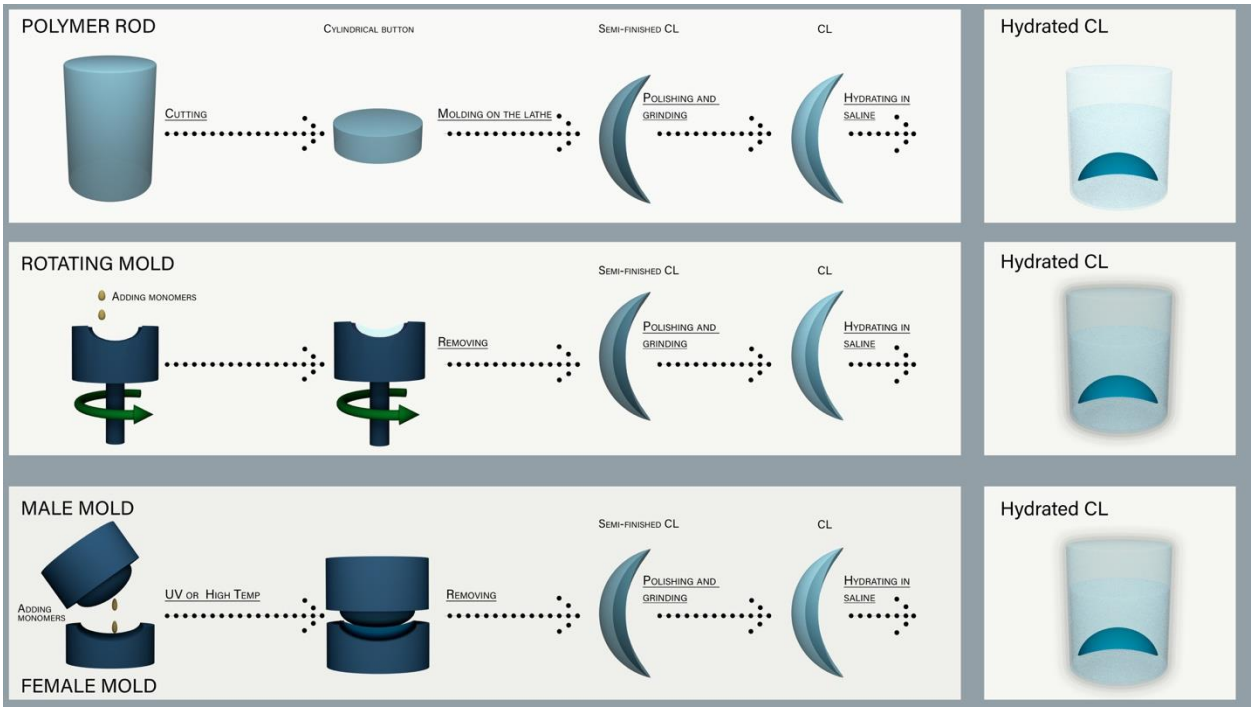

Figure 1: Manufacturing processes of contact lenses: (a) lathe-cut, (b) spin casting, and (c) cast molding

1.4.2.3 Spin casting

Spin casting is a sophisticated manufacturing process utilized in the production of contact lenses. The process begins with the fabrication of a convex stainless-steel tool, commonly known as an 'insert,' using high-precision engineering lathes. Alternatively, modern non-ferrous materials can also be employed for crafting the mold tool, with nano-accurate single point turning lathes ensuring exceptional surface finishes without the need for polishing.[60] Once the mold tools are prepared, they are pressed against heated liquid polypropylene or polyvinyl chloride, which cools and solidifies to form concave female molds. This injection cast molding process is conducted in a controlled environment to minimize potential contaminants, ensuring the quality and integrity of the lenses.[60]

The xerogel lens form is then created by pouring liquid monomers into the concave molds, which rotate at controlled rates about the central mold axis. The rotation speed, along with the mold tool shape and monomer dosage, determines the final lens parameters. The lens's back surface shape is primarily influenced by centripetal force, surface tension forces, and gravity effects. Higher rotation speeds result in more polymer mass shifting towards the lens periphery, leading to a more negative lens power.[60] Subsequently, ultraviolet radiation and/or heat are introduced to initiate polymerization, after which the lens is extracted from the mold. While some spinning systems may require additional processes such as lens edge polishing, inspection, hydration, reinspection, packaging, and autoclaving.[60]

Amid the backdrop of advancing contact lens manufacturing techniques, they are also being investigated as a potential drug delivery platform. Traditionally, ophthalmic drugs are administered via eye drops, which exhibit a low bioavailability, ranging from only 1% to 5% of the administered drug and a limited drug residence time.[62] Thus, there remains an

opportunity for the development of novel ophthalmic drug delivery systems aimed at enh[63, 64]

1.5 Drug delivery

Drug delivery refers to the process of administering pharmaceutical compounds to achieve therapeutic effects in humans or animals.[65] This field aims to improve the efficacy, safety, and convenience of drug administration while minimizing side effects. Various drug delivery systems have been developed, ranging from conventional oral tablets to advanced nano-based formulations.[66] These systems control the release rate, target specific sites, and enhance drug stability, bioavailability, and patient compliance.

The choice of drug delivery system depends on factors such as the physicochemical properties of the drug, the desired route of administration, and the therapeutic indication. Conventional systems include oral, intravenous, and topical routes, while advanced systems utilize nanotechnology, microparticles, liposomes, and implants.[66] These technologies offer precise control over drug release kinetics, enabling sustained, controlled, or targeted delivery.

Ophthalmic drug delivery focuses on administering pharmaceuticals to treat ocular diseases and conditions. The unique anatomy and physiology of the eye present challenges such as poor drug bioavailability, rapid clearance, and the blood-eye barrier.[67] To address these challenges, various strategies have been developed, including eye drops, ointments, inserts, implants, and nanoparticles.[68]

Eye drops are the most common form of ophthalmic drug delivery but suffer from low ocular retention and high tear turnover rates.[69] Ointments provide prolonged drug release but may cause blurred vision and patient discomfort. Inserts and implants offer sustained release but

req[67] Nanoparticles, such as liposomes and dendrimers, enhance drug stability and penetration while minimizing systemic side effects.[66]

Recent advancements in ophthalmic drug delivery include nanotechnology-based formulations, hydrogels, and contact lenses as drug carriers.[70-73] These innovations improve drug bioavailability, prolong residence time on the ocular surface, and enhance patient comfort and compliance.[74] However, challenges such as scalability, safety, and regulatory approval remain, necessitating further research and development in this field.

1.5.1 Contact lens based drug delivery

Contact lenses represent an advantageous medical device for ocular drug delivery owing to several key factors. Firstly, contemporary contact lenses offer prolonged, comfortable wear ranging from daily to extended periods of weeks.[75, 76] Secondly, the drug residence time in the very thin post-lens tear film (PLTF) between the cornea and the back surface of the lens is approximately 30 minutes, significantly surpassing the mere 5-minute duration observed with eye drop administration.[71] This extended residence time is facilitated by the diffusion of drugs into the PLTF, where the drug remains before being drained by the natural tear drainage mechanism.[71] Moreover, contact lenses, composed of cross-linked gels, provide facile drug entrapment within the gel matrix, achievable through either soaking in a drug solution or incorporation during the polymerization process.[64]

The exploration of contact lenses as a prominent platform for ocular drug delivery has stimulated considerable research interest. In recent decades, various novel methodologies have been devised for the controlled delivery of ophthalmic drugs via contact lenses, encompassing soaking techniques, molecular imprinting, vitamin E integration, and nanoparticle-based technologies.[77]

1.5.1.1 Soaking technique

Drug uptake into the lens by the so-called “soaking method” is a simple and very common approach in contact lens based drug delivery.[64] This method entails the immersion of contact lenses into solutions containing drugs, drug-polymer complexes, nanoparticles, or microemulsions for a specified duration. Solution volumes range from 2 mL to 15 mL or even more,[72, 78] while soaking times span from 24 hours to 7 days until saturation is attained.[64, 79] Soaking contact lenses into a drug solution creates a layer of the molecule on its surface, along with a minimal amount being absorbed. Within a particular range, the higher the concentration of the drug in the soaking solution, the greater the concentration of the drug loaded onto the contact lens, and the faster the release.[80] The soaking method offers advantages in terms of cost-effectiveness and formulation simplicity.[64] Several studies to deliver ketotifen,[81] ciprofloxacin,[80] PVA[44] and natamycin[82] among others using soaking technique have been performed.

Coating of the surface of contact lenses has been attempted and one such study was undertaken by Zhang et al.[83] They designed and synthesized novel tri-branched PEG-substituted hydrazides for surface modification of poly(2-hydroxyethyl methacrylate) (pHEMA)-based hydrogels.[83] Various surface coating and modification methods employing antifouling polymers were explored, including physical adsorption, layer-by-layer (LbL) deposition, self-assembled monolayers (SAMs), surface-initiated atom transfer radical polymerization (ATRP), interpenetrating polymer network (IPN), and specific group reactions between polymers and substrates.

1.5.1.2 Vitamin-E integration

Vitamin E, a hydrophobic molecule with antioxidant properties, has shown promising effects against a number of eye diseases such as keratocyte apoptosis after surgery and

corneal apoptosis.[84, 85] Vitamin E acts as a barrier to the small molecules loaded in the contact lenses due to its hydrophobicity, low solubility and biocompatibility.[73] In this method, contact lenses are soaked into an ethanol-vitamin E solution for 24 h and then incubated into a drug-polymer solution.[86]

Chauhan et al. were the first to demonstrate the use of vitamin E as a diffusional barrier into commercial contact lenses.[76] They soaked timolol,[73] dexamethasone,[76] and fluconazole[73] into commercial contact lenses using different approaches and studied their in-vitro release using 2 mL of PBS. This series of studies has demonstrated the capability of the system to deliver hydrophilic drugs, and additionally providing a UV-B blocking effect.[73] Further optimizing the system for dexamethasone delivery, they found that with 30% of Vit. E loading, drug release time can be prolonged to 7-9 days, proposing it to be a thin layer over the lens.[76, 87] They further used the concept to deliver cyclosporine over an extended period to treat dry eye.[88] The study showed that with 24 h soaking into the ethanol-Vit. E solution, 15 days release was obtained, rendering the release rate near concentration independent (zero-order) kinetics.[88]

1.5.1.3 Molecular imprinting

Molecular imprinting in hydrogels involves a method in polymer synthesis that utilizes template-induced polymerization mechanisms.[89] This approach results in the formation of synthetic macromolecular networks that possess specific affinities, capacities, and selectivity towards a particular template molecule.[89] By utilizing molecular imprinting, it becomes possible to embed a "memory" of a therapeutic agent within a flexible polymer matrix. This embedding process can effectively slow down the release of the drug from the matrix by leveraging interactions between the drug molecules and the organized functional groups present within the network.[90]

Timolol delivery via molecularly imprinted hydrogels has been reported by Alvarez-Lorenzo et al.[90] It was found that the maximum loading of the drug occurs within 8 hours of soaking, and MAA increases swelling as well as loading capacity, demonstrating a 48-hour release.[90] Molecular imprinting has shown 2-3 times increase in the loading capacity compared to the soaking method and the drug release was not dose-dependent, as was the case with the eye drops.[91]

1.6 Polyvinyl alcohol (PVA)

1.6.1 Properties

PVA is a synthetic, non-ionic, water-soluble, and biocompatible polymer used in many medical applications.[92] PVA is made up of $-(C_2H_4O)_n-$, where the "n" varies from 500 to 5000, which changes the molecular weight from 20,000 to around 200,000 Daltons.[93]. The tacticity (spatial arrangement of monomer units) of PVA plays a crucial role in its structural properties, determined by the starting materials and synthesis method, often analyzed via NMR spectroscopy.[94] PVA derived from vinyl acetate polymerization and hydrolysis is typically atactic i.e. random arrangements of the polymer chain, while syndiotactic PVAs are produced from radical polymerization of vinyl formate, vinyl pivalate, and vinyl trifluoroacetate, which arranges the polymer chain in alternate positions.[94, 95] Isotactic PVAs are synthesized through cationic polymerization of benzyl vinyl ether and have a uniform arrangement of the polymer chain.[95] The properties of PVA polymers are influenced by preparation method, molecular weight, tacticity, degree of polymerization, and hydrolysis level.[96] Enhanced characteristics such as viscosity, solvent resistance, adhesive and tensile strength, and film-forming ability are observed with increasing molecular weight and hydrolysis degree.[96] Increasing vinyl acetate hydrolysis leads to a more crystalline polymer structure, resulting in heightened intermolec[93]

PVA hydrogels exhibit favorable properties such as biocompatibility, drug compatibility, water solubility, film forming ability, and good mechanical and swelling properties, making them promising candidates for drug delivery systems.[97-99] They have been extensively researched for various administration routes, including ocular,[26] oral,[100] transdermal,[101] buccal,[102] and rectal[103] routes as a carrier. PVA hydrogels can be tailored as matrix or reservoir drug delivery platforms. Manipulating gel properties, solubility, and incorporating copolymers are strategies employed to regulate drug release from PVA hydrogels.[98, 100, 102] These characteristics make PVA hydrogels versatile and promising for controlled drug delivery applications in various medical fields.

1.6.2 Ocular applications

PVA is a lubricant which has demonstrated comfort to contact lens wearers.[50] PVA lubricates the eye by forming a thin, protective film on the ocular surface, which helps retain moisture and reduce friction, prevent rapid tear evaporation and breakup, thus alleviating dry eye discomfort.[26, 104] PVA also aids in tear film stability by improving the spreading and retention of the tear film on the ocular surface. When added to the contact lenses, it increases the material water content as well as the tensile strength compared to pHEMA.[105]

A ”pure” PVA based contact lens material (nelfilcon A) has been commercialized and has shown a significant increase in comfort compared to “conventional” contact lenses.[50] Since PVA is a polymer, with increase in the molecular weight there is an increase in viscosity which could keep the surface lubricated for a longer time due to longer retention.

In 1998, Tighe et al.[106] observed that the packaging saline solution of CIBA Vision Focus® DAILIES® (nelfilcon A) contact lenses exhibited a lower surface tension than expected, mea[26] It was determined that a small but considerable quantity of PVA macromer remained uninvolved in the cross-linking process that generates the nelfilcon A hydrogel during the

manufacturing process, allowing it to migrate from the lens into the packaging solution after packaging.[26]

This literature suggests that by increasing the amount of PVA release from the contact lens, it could potentially enhance the comfort. One of the aspects through which the loading of PVA on a contact lens can be increased is through exploring the freezing of the PVA, the very process through which PVA hydrogels are made.

1.7 The influence of freeze-thaw cycles on PVA release

Researchers have explored a physical approach to gelation of PVA as an alternative to conventional chemical cross-linking methods to avoid potential component leaching.[107] This method entails casting hydrogels from dilute aqueous solutions of PVA, followed by multiple cycles of cooling to -20°C and subsequent thawing to room temperature.[107] The resulting hydrogels exhibit stability through physical cross-linking facilitated by crystalline regions. This process leads to the aggregation of PVA chains, promoting hydrogen bonding and crystallization, resulting in a stable gel structure.[108, 109] The number of cycles, durations, and temperatures significantly influence the hydrogel properties as the intermolecular hydrogen bonding becomes stronger.[110] These freeze/thawed hydrogels have shown enhanced mechanical properties, which could be particularly beneficial for biomedical applications due to their non-toxic nature, high mechanical strength, and elasticity, rendering them suitable for applications in artificial tissue and contact lens development.[111]

Gupta et al.[110] investigated the impact of freeze-thaw (F/T) cycles on the properties of transparent PVA hydrogel films synthesized from aqueous solutions with varying concentrations. Preparation involved dissolving PVA powder in distilled water, cooling to remove bubbles, pouring into molds, and subjecting this mixture to freeze-thaw cycles. The study showed a cyclic F/T method within a temperature range of 0°C to 37°C, demonstrated significant variations in transparency, crystallinity, wettability, swelling, and mechanical properties of the hydrogels based on solution concentration and the number of F/T cycles, all while maintaining a constant average molecular weight of 95 kDa. They revealed a strong correlation between the number of F/T cycles and the structural-property relationships of the synthesized hydrogels, indicating the potential to tailor structural and process parameters for applications such as cell-gel interactions. Increasing polymer concentration led to reduced swelling and increased crystallinity, consequently enhancing mechanical properties.

Another study by Chee et al.,[112] highlights the impact of stretching hydrogels between F/T cycles on their properties, particularly for drug delivery systems. PVA hydrogels and caffeine-contained (CAF) PVA hydrogels were subjected to freeze-thaw cycles followed by stretching cycles, revealing that hydrogels with two F/T cycles and two stretching cycles exhibited improvement in its properties. These hydrogels demonstrated increased crystallinity and stiffness, fitting into the Hixson-Crowell drug release model with a rapid release rate and high swelling degree. Overall, the study suggested that oriented PVA/CAF hydrogels could serve as promising biomaterials for drug release applications due to their reproducible synthesis method and enhanced properties.[112]

However, when considering the use of these freeze-thawed gels in pharmaceutical and medical contexts, it becomes imperative to assess their long-term stability. Challenges associated with PVA gels produced through F/T techniques include the dissolution of PVA

chains, melting of crystallites, and secondary crystallization over extended periods.[108] However, the multi-freeze-thaw process is more complicated, time-consuming, and arduous, and the hydrogel strength obtained at lower PVA concentration (10% w/v) is typically inadequate, resulting in challenges in application.[113] These insights into freeze/thawed PVA gels underscore the ongoing need for a deeper understanding of the structure-property relationships governing the overall morphology of these hydrogels.

This thesis focuses on the delivery of PVA through contact lenses, leveraging the advantages of the soaking technique. This methodology is favored for its simplicity and feasibility in exploring the incorporation of additional molecules, such as lubricants, post-manufacturing. Additionally, freezing at -80 °C for one hour was utilized along with the soaking technique to enhance the loading of the PVA. Through this approach, we propose to develop a drug delivery system by incorporating PVA into the contact lenses and facilitating its release while preserving the intrinsic properties of the lenses.

Chapter 2

Aim and objectives

2.1 Aim

This thesis aimed to develop a hydrogel platform capable of delivering a significant amount of PVA for a one-day wear schedule.

2.2 Objectives

The objective of this thesis was to explore how freezing influences the interaction between PVA and contact lenses. By understanding these dynamics, it seeks to optimize PVA-based drug delivery for ophthalmic use. Through rigorous experimentation, it aims to uncover insights into temperature-dependent PVA-contact lens interactions, advancing ocular drug delivery technology.

It will achieve these objectives by:

- Soaking commercial lenses in PVA and subjecting them to room and freezing temperatures to explore how this factor is associated with PVA loading and sustained release
- Synthesizing custom materials which will have increased or exaggerated temperature sensitive PVA effects

2.3 Hypothesis

The thesis hypothesizes that by freezing, intermolecular bonding within PVA molecules and between PVA and contact lens materials is enhanced. This hypothesis suggests that such an enhancement could lead to increased loading and sustained release levels of drugs or substances, leading to greater amounts of PVA released from such materials for longer periods of time.

Chapter 3
Materials and methods

3.1 Fabrication of contact lenses

In this thesis, two types of contact lenses have been used. 1.) Commercial contact lenses and 2.) Synthesized or fabricated contact lenses. In the initial segment of this research, exploration was undertaken to scrutinize the loading and release of PVA from commercial contact lenses. After this comprehensive analysis, a methodical approach was adopted to engineer customized contact lenses within the confines of our laboratory setting, based on the results observed with commercially available lenses. This custom manufacturing process was designed specifically with the intent of faithfully replicating the characteristics observed in commercial lenses.

Commercial contact lenses used included 1-Day Acuvue® Moist® (etafilcon A), Acuvue® Oasys (senofilcon A), DAILIES® AquaComfort PLUS® (nelfilcon A), and PureVision® (balafilcon A) to investigate a broad range of lens materials and water contents as listed in table 1. For laboratory synthesized lenses, the monomer mixture used to prepare the contact lenses was composed of 2-hydroxyethylmethacrylate (HEMA) as a backbone monomer and ethylene glycol dimethyl acrylate (EGDMA) as a crosslinker, which also increases the modulus of the material. 2-hydroxy-2-methylpropiophenone was used as the photo-initiator and water as the co-solvent to dissolve PVA. HEMA and EGDMA in the amount of 80 and 5 %v/v, respectively, were mixed to form the monomer mixture which are referred as pHEMA lenses. In another set, 1.4% w/v PVA solution in MilliQ water was prepared and then 50 µL was added into this mixture to prepare a PVA loaded 527.5 µL contact lens monomer mixture, which are referred as PVA loaded pHEMA lenses.

Table 1: List of commercial contact lenses used in the experiments

Brand name	1-Day Acuvue® Moist®	Acuvue® Oasys	DAILIES® AquaComfort PLUS®	PureVision®
Manufacturer	Johnson & Johnson	Johnson & Johnson	Alcon	Bausch & Lomb
Material	etafilcon A	senofilcon A	nelfilcon A	balafilcon A
Material type	Hydrogel	Silicone hydrogel	Hydrogel	Silicone hydrogel
Principal monomer	HEMA, MA	HEMA, NVP, MA	PVA	NVP, TPVC, NCVE, PBVC
Wetting agent	-	PVP	HPMC, PEG, PVA	-
Water content (%)*	58	38	69	36
Surface charge	Highly negative	No charge	No charge	Mild negative charge

*As per packaging label

HEMA: 2-hydroxyethylmethacrylate; MA: methacrylic acid; NVP: N-vinyl pyrrolidone; TPVC: tris-(trimethylsiloxysilyl) propylvinyl carbamate; NCVE: N-carboxyvinyl ester; PBVC: poly[dimethylsiloxyl] di [silylbutanol] bis[vinyl carbamate]; PVP: polyvinyl pyrrolidone; PVA: polyvinyl alcohol; HPMC: hydroxypropyl methylcellulose; PEG: polyethylene glycol

Contact lenses in the laboratory were synthesized with the cast molding technique using polypropylene molds. The monomer mixture solution of 65 µL was added to the mold, and then the cover was placed on top. As shown in figure 2., the assembly was moved to an UV transilluminator for 11 min for photopolymerization. The removal of un-reacted monomers after the fabrication of the contact lenses is required to prevent eye irritation. To remove the un-reacted monomers after the curing process, the contact lenses were individually placed in a 5 mL boiling water for 15 min[90] before using further.

Figure 2: Contact lens synthesis

3.2 PVA loading into commercial contact lenses

PVA loaded contact lenses were prepared by soaking the commercial contact lenses into PVA (99% hydrolyzed) solutions at different concentrations. Two different molecular weights of PVA were used in this experiment; a lower molecular weight (MW) PVA in the range of 31 – 50 kDa (average – 40.5 kDa) and higher molecular weight PVA in the range of 146 – 186 kDa (average – 166 kDa) to explore the effect of molecular weight on the PVA loading and release.

First, the lenses were rinsed using 5 mL MilliQ water in a vial and kept for at least 24 h to remove all the residues of packaging solution so that we only have the contact lens material

to work with. Then the PVA solution was meticulously prepared by gradually dissolving the specified quantity of PVA into MilliQ water. This process was conducted using a water bath equipped with a magnetic stirrer set to rotate at 300 RPM at the temperature range of 120 – 140°C.

These lenses were then soaked in a 5 mL solution of 5% w/v (50 mg/mL) or 2.5% w/v (25 mg/mL) PVA of low MW and high MW and kept in a vial for 48 h at 37°C in an orbital shaker. A layer of PVA is expected to be created on the surface of the contact lenses by soaking. After 48 h, the contact lenses and soaking solution containing vial were subjected to one of two different temperatures: room temperature (control), and -80°C for one hour. Lenses at room temperature did not require further processing. For the lenses which were frozen for one hour, the vials were taken out and kept in a water bath for 15 min at 30°C to thaw. This will be referred as freeze-thaw (F/T) cycle. After thawing, these lenses were subject to in-vitro release testing, as described in section 3.4. Another set of experiments with 5 cycles of freeze-thaw at -80°C was conducted to understand the effect of multiple cycles on freezing the PVA solution with the contact lenses. All the experiments were performed with a sample size of six.

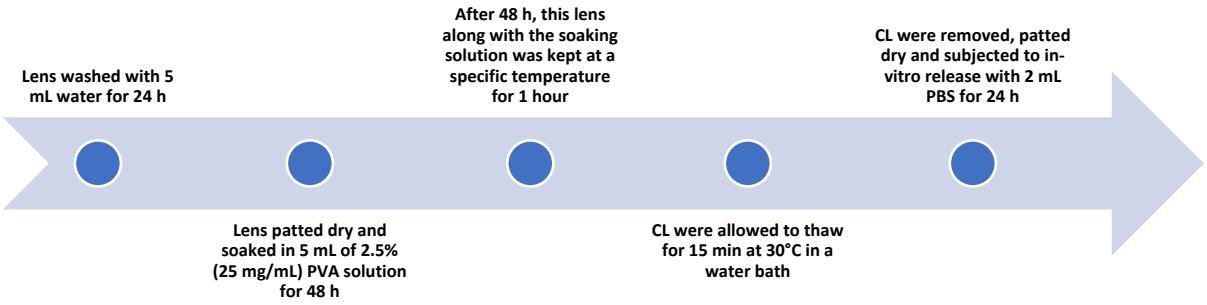

Figure 3: Preparation and treatment protocol for PVA-coated contact lenses

3.3 Freeze-thaw cycle of PVA

PVA layering on the contact lens surface were prepared using the F/T cycle, which could increase the amount of loading as well as release from the contact lenses. After soaking the contact lens in the PVA solution for 48 h, the contact lenses along with the PVA soaking solution in the vial were frozen at -80°C for one hour and then thawed in a water bath for 15 min at 30°C to create the bonding among the PVA polymer and PVA with the contact lens material. PVA is known to form gels by multiple freeze-thaw cycles at temperatures lower than -20°C [108] and the same technique has been utilized to investigate the effect on loading and release after exposing to extreme conditions.

3.4 In-vitro release methods

To understand the PVA release kinetics from these loaded lenses of various types, an *in-vitro* release study was performed. The contact lens were kept in a vial containing 2 mL PBS at 34°C in an orbital shaker at 50 RPM.[114] Samples of 200 µL were withdrawn at regular time intervals and replaced with fresh 200 µL PBS to maintain the sink conditions. The amount of PVA released from the lenses was determined using the analytical method described in section 3.5. The amount of PVA released was calculated using the slope-intercept of the cal

ibration curve as shown in Figure 4. First, the amount of PVA in the 200 µL sample was calculated and then converted for the total volume of the medium i.e. 2 mL. Subsequently, the amount of PVA at each time point was calculated and added into the earlier one to produce a cumulative release amount. All the experiments were conducted with a sample size of six.

3.5 Analytical method of PVA

PVA was quantified using a UV spectrophotometry method.[115] This method is based on the complex formation between iodine-boric acid and PVA. A Boric acid (40 mg/ml) and Iodine solution (25 mg/ml KI + 12.7 mg/ml I_2) was freshly prepared in water. A sample of 200 µL PVA was taken and mixed with 750 µL boric acid solution along with 150 µL iodine solution. The mixture was kept for 20 min and then analyzed using UV at 630 nm. A calibration curve was prepared by plotting the absorbance on Y-axis and the concentration of PVA (µg/mL) on X-axis. The range if calibration curve was from 10 – 100 µg/mL. The concentration of the PVA will be determine in the unknown samples by measuring their absorbance and interpolating from the curve.

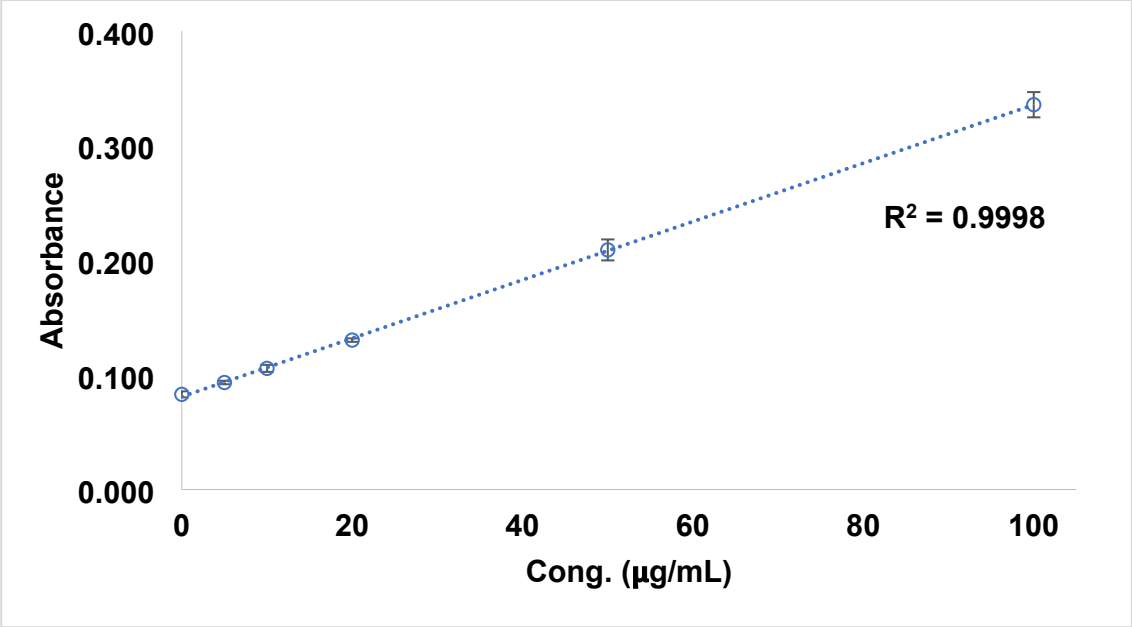

Figure 4: Calibration curve of PVA in water using UV spectroscopy

3.6 Statistics

A standard deviation was calculated for each time point and plotted in the graph using GraphPad Prism software. A two-sample paired student's t-test was conducted to determine any significant differences between within one type of contact lens under two conditions, otherwise a One-way ANOVA was performed to determine differences across testing groups. Post hoc Tukey analysis was performed where necessary. A probability value (p-value) of less than 0.05 was utilized to evaluate whether a significant change was present.

Chapter 4
Elution of PVA from commercial contact lenses after incorporation at freezing temperatures

4.1 Introduction

In this chapter, the interaction between PVA and commercially available contact lenses following exposure to freezing is examined. The primary aim is to investigate the effects of soaking these lenses in PVA and exposing them to freezing and room temperature, shedding light on the variables influencing PVA absorption and its sustained release in response to temperature fluctuations. This exploration serves to enhance understanding of how temperature impacts PVA loading and subsequent release dynamics in contact lenses, providing valuable insights for potential applications in controlled drug delivery systems.

It is hypothesized that by applying a layer of PVA onto the surface of contact lenses using a freeze-thaw cycle, the loading capacity and subsequent release of PVA could be significantly improved. Stauffer and Peppas[107] demonstrated that subjecting a 10 – 15% w/v PVA solution to freezing at -20°C for one hour results in the formation of a robust gel with increased mechanical properties. The strength of this hydrogel is directly influenced by the number of freeze-thaw cycles applied. Applied to a contact lens, a loosely bound gel coating of PVA on the surface material would offer both a smooth texture, increased loading, and a gradual release due to its surface erosion. This experimental approach aims to optimize the interaction between the PVA and the contact lens material via subjecting them to different temperatures. To execute this methodology, contact lenses along with a prepared packaging solution containing PVA, are placed in a freezing environment at -80°C for one hour. This process outlined in Section 3.3 offers consistent treatment across all lenses, minimizing variability in the experimental setup and allowing for differences due to materials and their int

eractions with PVA at different temperatures to be highlighted. Following the completion of the freeze cycle, the lenses are carefully thawed, initiating the evaluation phase. In the subsequent *in vitro* analysis, the kinetics of PVA release are examined. By assessing the rate and extent of PVA release from the contact lenses, the factors associated with successful PVA incorporation and release can be evaluated to provide insight into the efficiency and effectiveness of PVA materials in novel drug delivery systems.

4.2 Materials and methods

4.2.1 Incorporation of PVA in commercial contact lenses

To investigate a broad range of material types, four commercial contact lenses - 1-Day Acuvue® Moist® (etafilcon A), Acuvue® Oasys (senofilcon A), DAILIES® AquaComfort PLUS® (nelfilcon A), and PureVision2® (balafilcon A) were used in this experiment. To study the effect of molecular weight the experiment involved the application of two different molecular weights of PVA. One variant had a lower MW within the range of 31 – 50 kDa (average – 40.5 kDa), while the other had a higher MW ranging from 146 – 186 kDa (average – 166 kDa). Prior to the experiment, the lenses underwent a thorough rinsing in MilliQ water for a minimum of 24 h. Subsequently, they were soaked in 2 mL of either a 5% w/v (50 mg/mL) or 2.5% w/v (25 mg/mL) PVA solution and placed in vials for incubation at 37°C on an orbital shaker for 48 h to facilitate creation of a surface coating. After 24 h, the contact lenses, along with the soaking solution containing vial, underwent treatment at either room temperature (control), or -80°C for one hour. Subsequently, the vials were taken out and placed in a water bath for 15 min at 30°C to facilitate thawing. Additionally, a separate experiment involving 5 cycles of freeze-thaw at -80°C was conducted for nelfilcon A lenses to evaluate the impact of repeated cycles on freezing the PVA solution with the contact lenses. Each experiment was carried out with a sample size of n=6.

4.2.2 In-vitro release

After thawing, the contact lens was removed, gently pressed with Kimwipes® to remove any excess surface liquid and transferred to a separate vial with 2 mL of PBS. It was then maintained at 34°C on an orbital shaker for the *in vitro* release investigation outlined in section 3.4. Subsequently, all samples underwent analysis to detect PVA concentrations released using UV spectroscopy, following the procedures described in section 3.5.

4.3 Results

For the initial experiments, both low and high molecular weight PVA were used in a 5% w/v soaking solution. These experiments investigated the impact of molecular weight of the PVA on the release from commercial contact lenses at room temperature and after exposure to freeze thaw cycle. The total release of PVA from nelfilcon A, etafilcon A, and balafilcon A lenses following 48 hours of soaking in 5% w/v solution at room temperature are shown in table 2.

Upon exposure to a freeze-thaw cycle, nelfilcon A lenses exhibited increased release profiles for both low and high molecular weight PVA, showing a statistically significant ($p<0.05$) increase in release compared to lenses soaked only at room temperature. In contrast, etafilcon A lenses did not exhibit any significant ($p>0.05$) change in release amount after undergoing the freeze-thaw cycle, as shown in table 2. Similarly, balafilcon A did not show any significant ($p>0.05$) effect of PVA release amount after freezing for one hour at -80°C.

Table 2: Amount of PVA released from commercial contact lenses after soaking in 5% w/v PVA solution

Lens materials	Total amount of PVA release (µg)			
	After room temperature		After freezing at -80°C for one hour	
	Low molecular weight PVA	High molecular weight PVA	Low molecular weight PVA	High molecular weight PVA
nelfilcon A	94.15 ± 10.73	95.35 ± 14.06	127.90 ± 31	144.37 ± 28.48
etafilcon A	69.49 ± 6.56	71.23 ± 5.78	71.58 ± 11.27	74.29 ± 7.43
balafilcon A	62.13 ± 9.83	63.98 ± 6.72	66.42 ± 8.32	68.98 ± 9.74

Furthermore, it was noted that the 5% w/v PVA soaking solution displayed high viscosity, leading to reduced polymer mobility, and consequently limiting its binding capacity with the lenses. To address this concern, subsequent investigations centered on utilizing a 2.5% w/v PVA soaking solution comprising solely high molecular weight PVA. After decreasing the soaking concentration by 50%, nelfilcon A lenses exhibited approximately 66% decrease in the released amount, whereas etafilcon A lenses demonstrated about 76% reduction.

Table 3: Amount of PVA released from commercial contact lenses after soaking in 2.5% w/v PVA solution

Lens materials	Total amount of PVA release (µg)	
	After room temperature	After freezing at -80°C for one hour
nelfilcon A	32.40 ± 8.47	58.53 ± 17.26
etafilcon A	17.03 ± 3.03	20.21 ± 2.51
senofilcon A	20.33 ± 6.60	24.14 ± 2.58

The amount of PVA released after soaking at 2.5% w/v showed a similar trend as with soaking at 5% w/v. After soaking at 2.5 w/v for 48 hours and subsequent freezing, nelfilcon A lenses showed significantly ($p<0.05$) increased release of PVA compared to lenses exclusively soaked at room temperature. Conversely, etafilcon A lenses displayed no significant ($p>0.05$) change in release amount following the freeze-thaw cycle, as shown in table 3. Similarly, senofilcon A did not exhibit any significant ($p>0.05$) impact on PVA release amount after undergoing freezing for one hour at -80°C.

The kinetics of PVA release from these materials after loading with a 2.5% solution and freezing at -80°C for one hour were performed at the time intervals as stated in section 3.4. As shown in figure 5, the majority of the PVA is released in the first two hours, which is expected with typical soaking techniques with contact lenses. A student's t-test between etafilcon A and senofilcon A suggests that there is no significant difference ($p>0.05$) in the release of PVA when loaded at room temperature, while nelfilcon A lenses release significantly ($p<0.05$) more compared to both lens types. Similar trends of release were observed with the freezing of the lenses at -80°C for one hour, as shown in figure 6. nelfilcon A lenses did not show any significant difference in the release of PVA after 5 cycles of freeze-thaw, suggesting that there is only a one-time opportunity for coating over the lenses, and additional cycles in this system did not confer additional benefit.

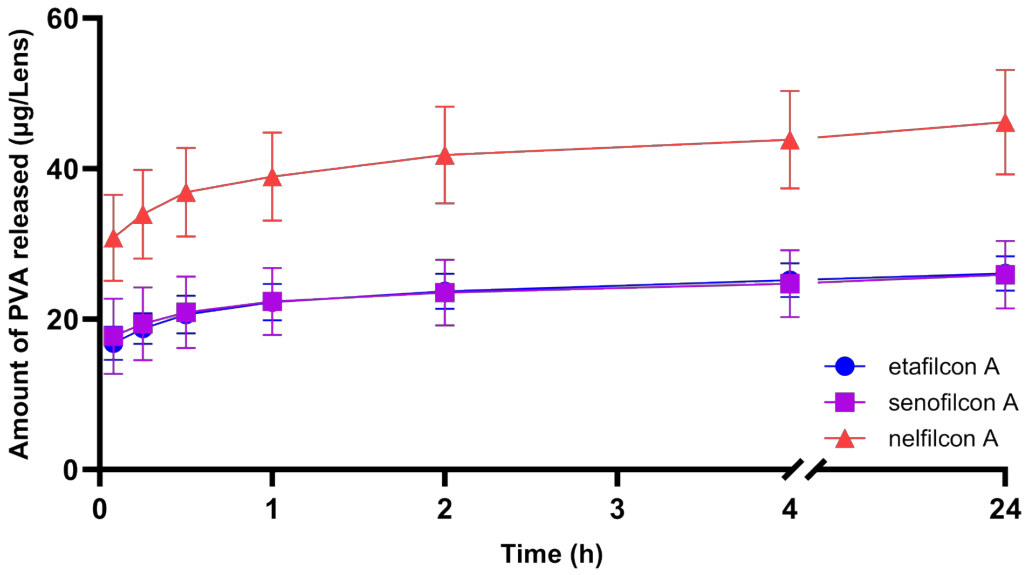

Figure 5: Cumulative release of PVA from commercial contact lenses soaked in 2.5% w/v PVA at room temperature

Figure 5 illustrates the release profile of PVA from the various contact lenses over time. The majority of PVA is released within the first two hours, consistent with standard soaking techniques. A student's t-test indicates no significant difference ($p > 0.05$) in PVA release between etafilcon A and senofilcon A lenses when loaded at room temperature. However, nelfilcon A lenses release significantly more PVA ($p < 0.05$) compared to both etafilcon A and senofilcon A lenses.

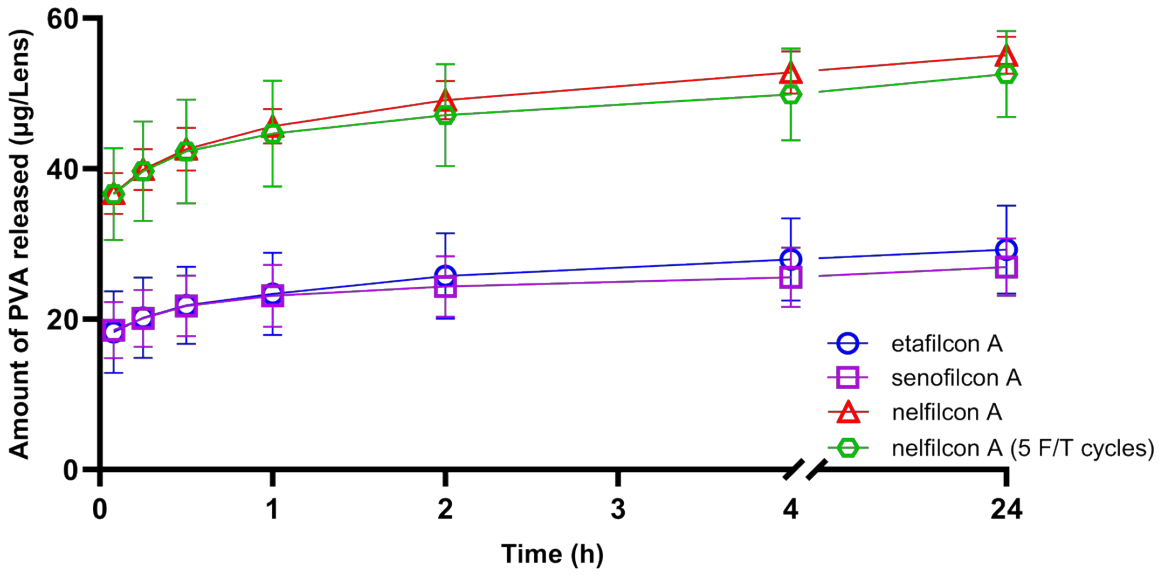

Figure 6: Cumulative release of PVA from commercial contact lenses soaked in 2.5% w/v PVA after freezing at -80°C for one hour and for nelfilcon A after 5 F/T cycles

Figure 6 shows the cumulative release of PVA from contact lenses after freezing at -80°C for one hour and subsequent thawing. Similar trends in release were observed across the different lens types. nelfilcon A lenses showed a significantly ($p<0.05$) increase in the release of PVA compared to other lens types. However, nelfilcon A lenses exhibited no significant ($p>0.05$) difference in PVA release after undergoing 5 cycles of freezing compared to 1 cycle of freezing.

4.4 Discussion

Contact lenses possess the capacity to absorb molecules when immersed in a drug solution. The efficacy of their reservoir capability is influenced significantly by several factors, including the water content of the lens, the molecular weight of the drug, the concentration of the drug in the soaking solution, the drug's solubility in the gel matrix, and the thickness of the lens. Understanding the release of PVA from contact lenses is crucial for the development of a potential PVA releasing lens for improved lens comfort. Two key aspects are considered in interpreting the results of this experiment. First, the initial experiments aimed to investigate any influence of molecular weight on the release of PVA from commercial contact lenses.

Results indicate no statistically significant difference ($p>0.05$) in the release of low versus high molecular weight PVA when lenses were exclusively soaked at room temperature with a 5% PVA solution. However, a shift occurred when exposed to freezing, where high molecular weight PVA exhibited a statistically significant increase ($p<0.05$) in PVA release compared to low molecular weight, with nelfilcon A lenses.

The expected difference in release amount between low and high molecular weight PVA from contact lenses, due to their molecular weight, did not occur, for the molecular weights used in this experiment. Low molecular weight PVA was anticipated to release more due to higher polymer mobility. However, both exhibited similar release amounts, indicating the independence of PVA release from contact lenses based on molecular weight.

Second, the observation of significantly higher PVA release from nelfilcon A lenses compared to etafilcon A lenses raises the question of material properties between these two lenses which may explain this difference in PVA release. Despite both materials being hydrogel-based, potential factors such as difference in water content (69% vs 58%), surface charge (neutral/non-ionic vs ionic) or the base material composition were explored (PVA vs pHEMA-MAA). In addition, to understand the potential impact of the base material, the silicone hydrogel material balafilcon A was included, which has a similar water content (36%) to that of pHEMA (38%), as etafilcon A (58%) is based on a pHEMA backbone. Also, balafilcon A is slightly negatively charged (compared with the large negative charge on etafilcon A). Results from balafilcon A lenses were similar to that of the etafilcon A lenses. Given the substantial differences between these two materials, it appears unlikely that factors such as water content, surface charge, or the distinction between conventional hydrogel and silicone hydrogel lenses significantly contribute to PVA release. Therefore, the superior

performance of nelfilcon A lenses for PVA release is likely attributed to their unique characteristics as a lens material, notably in that it contains bound PVA.

Based on these findings, it was deemed appropriate to concentrate on investigating the hypotheses exclusively using the high molecular weight PVA. The choice was motivated by the similarity in results between low and high molecular weight PVA release during soaking at room temperature, while also potentially emphasizing the freezing effect due to an increased entanglement of the PVA monomers resulting from longer chains. It was additionally observed that the 5% PVA soaking solution exhibited high viscosity, which in turn decreases the polymer movement, thereby limiting the binding capacity to the lenses. To mitigate this issue, further investigations focused on using a 2.5% PVA soaking solution containing high molecular weight PVA only.

With these new parameters, nelfilcon A, etafilcon A, and senofilcon A lenses underwent further investigation to investigate the influence of freezing and thawing on PVA uptake and release. The data suggests that there is a significant increase in the amount of PVA released following exposure to freezing at -80°C for one hour, specifically for nelfilcon A lenses, as a similar effect with the etafilcon A or senofilcon A lenses was not observed. This observation suggests that the material type, and potentially something specific regarding the nelfilcon A material, plays a crucial role in both the uptake and release of PVA from contact lenses. These findings align with those reported by Phan et al.,[44] demonstrating that nelfilcon A lenses exhibit higher release rates compared to etafilcon A lenses.

This was further investigated by measuring and plotting the release kinetics of PVA through samples taken at various time intervals, as detailed in section 3.4. Figure 5 illustrates that the majority of PVA is released within the initial 30 minutes, aligning with the anticipated behavior

of contact lens soaking techniques as shown by other studies.[81] A student's t-test showed that there was no significant difference in the release rate of PVA from etafilcon A and senofilcon A lenses, while nelfilcon A lenses showed an increase in the amount of release at room temperature. Similar trends of release were observed with the freezing of the lenses at -80°C for one hour, as shown in figure 6. Notably, nelfilcon A lenses show consistent PVA release after 5 cycles of freeze-thaw, suggesting that there is no significant benefit to repeated cycles, and a single cycle is sufficient to allow for greater amount of PVA to be loaded and subsequently released from this material.

As only nelfilcon A materials demonstrated an impact with freezing in this experiment, it is hypothesized that there is potentially a greater interaction between the PVA solution and the PVA within this lens type, which is not found in either of the other two lenses. The observed phenomenon may also be explained by the strengthening of the PVA hydrogel with each freeze-thaw cycle, as suggested by Stauffer.[107] This process could result in enhanced attraction between the PVA polymers and the PVA hydrogel, leading to increased loading of PVA onto the lens and subsequent release.

In conclusion, release of PVA from contact lens materials typically follows a similar pattern across various lens types, unless there is a presence of PVA within the lens itself, which was seen with the nelfilcon A lens. The presence of PVA inside the lenses appears to significantly increase loading. These results also support the hypothesis that freezing the contact lenses with PVA solution enhances loading and release, but only for certain lens types, as this effect was observed solely with nelfilcon A lenses and not with other lens types tested.

Chapter 5
Elution of PVA from synthesized contact lenses after incorporation at freezing temperatures

5.1 Introduction

This chapter explores the interaction between PVA and synthesized contact lenses following exposure to freezing. The chapter draws upon observations from the interaction of PVA with commercially available contact lenses such as nelfilcon A, etafilcon A, and senofilcon A. A hypothesis has been formulated in Chapter 4 suggesting the importance of the presence of PVA within the contact lens material for further PVA enhanced uptake and release. Thus, the current chapter endeavors to validate this hypothesis by synthesizing pHEMA-based contact lenses with embedded PVA. The objective is to ascertain the importance of PVA presence within the pHEMA lenses regarding its potential implications for uptake and release dynamics and freeze-thaw cycles for PVA release.

The study involved synthesizing contact lenses similar to commercial pHEMA-based lenses. Additionally, another set of lenses was created by incorporating PVA into the pHEMA based monomer during synthesis, forming PVA-loaded pHEMA lenses, as mentioned in section 3.1. Both sets of lenses underwent similar treatment to commercial contact lenses, including washing, soaking, and a freeze-thaw cycle. The hypothesis of creating a PVA layer on the lens surface using the freeze-thaw cycle to enhance loading was investigated. All the contact lenses went through the freeze-thaw cycle as described in section 3.3. Following the freeze-thaw cycle, all lenses were subjected to in-vitro analysis.

5.2 Materials and methods

5.2.1 Incorporation of PVA into synthesized contact lenses

In this experiment, high molecular weight PVA was used, ranging from 146 to 186 kDa (average – 166 kDa). The synthesis of contact lenses was carried out utilizing the cast molding technique, as elaborated in section 3.1. The lenses were composed of a monomer mixture containing 2-hydroxyethylmethacrylate (HEMA) as the backbone monomer and ethylene glycol dimethyl acrylate (EGDMA) as a crosslinker, enhancing the material's modulus. The photo-initiator used was 2-hydroxy-2-methylpropiophenone, and water as a co-solvent dissolved PVA. A monomer mixture of 80% HEMA and 5% EGDMA formed the pHEMA lenses. Additionally, 50 µL, of 1.4% w/v PVA solution in MilliQ water was combined resulting in a PVA-loaded 527.5 µL contact lens mixture, designated as PVA-loaded pHEMA lenses. Following polymerization, materials were immersed in boiling water for a duration of 15 minutes. This step aimed to remove any unreacted monomer residues, thereby finalizing the synthesis process, and ensuring the integrity of the resulting contact lenses.

Following the synthesis process they underwent a rinsing process, where the lenses were kept in 5 mL MilliQ water for a minimum of 24 h at 37°C in an orbital shaker at 50 RPM to remove any unbound PVA from the PVA loaded pHEMA lenses, and any further unreacted monomer from the pHEMA lenses. Subsequently, the lenses were soaked in 5 mL of 2.5% (25 mg/mL) PVA solution in MilliQ water and placed in a vial for 24 h at 37°C in an orbital shaker at 50 RPM. A surface coating of PVA is expected to be created by soaking the synthesized contact lenses. Both synthesized pHEMA and PVA loaded pHEMA lenses were subject to treatment similar to commercial contact lenses in the previous experiment, as detailed in section 4.2.1. After incubation, the lenses and the soaking solution in the vials were subjected to treatment at either room temperature (control) or -80°C for one hour.

Subsequently, the vials were removed and placed in a water bath at 30°C for 15 minutes to thaw. All the experiments were conducted with a sample size of 6.

5.2.2 In-vitro release

After the thawing process, the contact lens underwent a series of steps. Firstly, it was carefully taken out and carefully blotted using Kimwipes® to eliminate any excess liquid. Following this, the lens was placed into a separate vial containing 2 mL of phosphate-buffered saline (PBS). It was then subjected to a controlled temperature of 34°C on an orbital shaker, as outlined in section 3.4, to investigate the in vitro release of PVA. After this incubation period, all samples were analyzed using UV spectroscopy, following the procedures detailed in section 3.5 of the study.

5.3 Results

To determine the influence of PVA presence in the base material on subsequent PVA release, two types of lenses were synthesized: a pHEMA based lens and a PVA loaded pHEMA lens. Upon investigation, significant differences in PVA release were observed between the two types of lenses. Table 4 shows that at room temperature, the PVA loaded pHEMA lenses released significantly ($p<0.05$) higher amount of PVA compared to pHEMA lenses. Similarly, after freezing at -80°C, the PVA loaded pHEMA lenses exhibited a significantly higher ($p<0.05$) PVA release compared to the pHEMA lenses as shown in table 4.

Table 4: Amount of PVA released from synthesized contact lenses after soaking in 2.5% w/v PVA solution

Lens	Cumulative release (µg)	
	Room temperature	After freezing at -80°C for one hour
pHEMA	32.64 ± 5.48	36.25 ± 6.11
PVA loaded pHEMA	42.88 ± 4.96	47.39 ± 6.26

Figures 7 and 8 illustrates the release kinetics of both pHEMA and PVA loaded pHEMA lenses at room temperature and after freezing. It must be noted that they follow the similar trend as the commercial lenses in terms of burst release, as the majority of the PVA is released within the first 30 minutes, which is on the expected line with the soaking technique of contact lenses. A student's t-test showed that there was a significant difference ($p<0.05$) in the release of PVA from pHEMA and PVA loaded pHEMA lenses at room temperature. A similar trend of release was observed with the freezing of the lenses at -80°C for one hour, suggesting the difference in release amount based on the material involved.

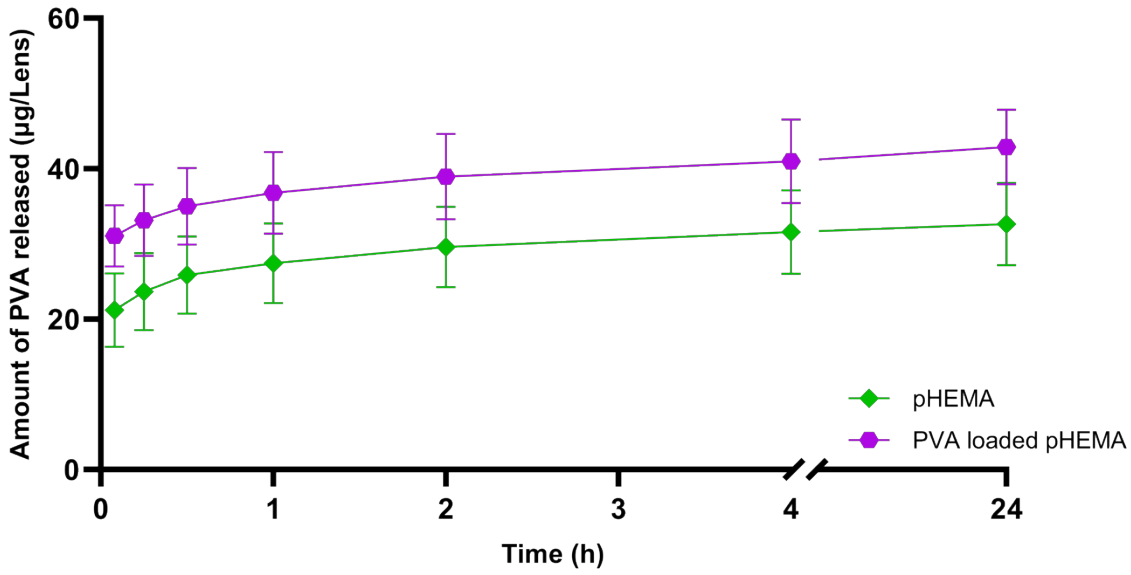

Figure 7: Cumulative release of PVA from synthesized contact lenses soaked in 2.5% w/v PVA at room temperature

Figure 7 shows the release kinetics of pHEMA and PVA-loaded pHEMA lenses at room temperature. Similar to commercial lenses, there is a burst release, where most PVA is released within 30 minutes. A significant difference ($p < 0.05$) in PVA release between pHEMA and PVA-loaded pHEMA lenses at room temperature was observed.

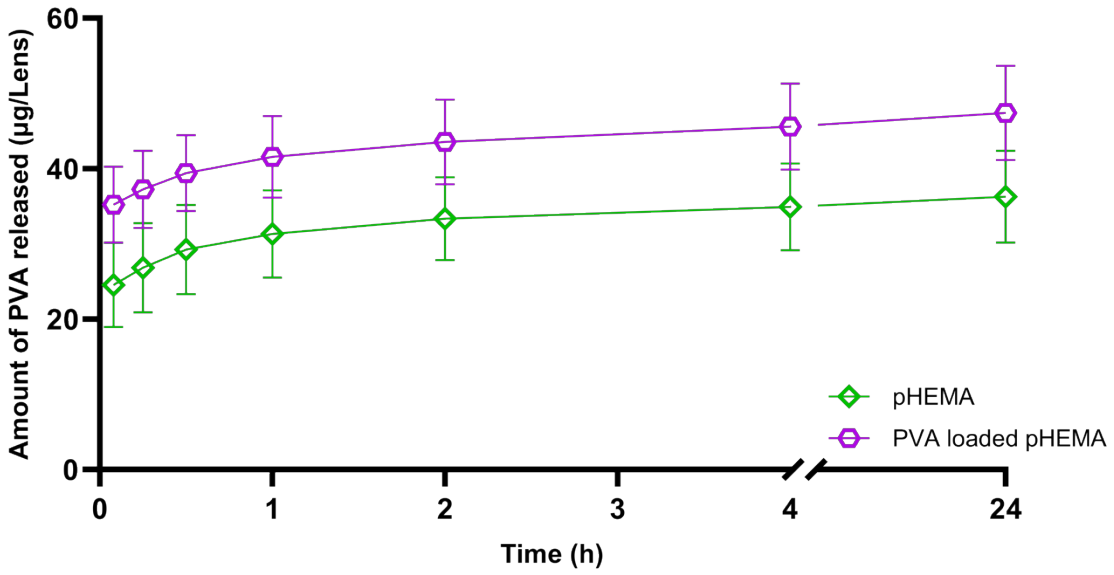

Figure 8: Cumulative release of PVA from synthesized contact lenses soaked in 2.5% w/v PVA after freezing at -80°C for one hour

Figure 8 shows that after freezing the pHEMA and PVA loaded pHEMA lenses at -80°C for one hour, a comparable release trend that of the room temperature is observed. This suggests differences in release amount based on the material involved.

5.4 Discussion

The investigation embarked upon in this chapter aimed to corroborate the hypothesis proposed in Chapter 4, which underscores the pivotal role of PVA within contact lens materials for an increased PVA uptake and release capabilities. To validate this conjecture, pHEMA-based contact lenses were synthesized, with an additional focus on embedding PVA within them.

Incorporating PVA into pHEMA lenses poses challenges due to PVA's heat requirement for dissolution in water and pHEMA's gelation at elevated temperatures. Thus, a co-solvent technique was employed, where a 1.4% w/v PVA solution in water was added to the mixture of HEMA and EGDMA. Increasing the concentration resulted in an opaque lens, indicating saturation, marking the maximum PVA loading capacity in pure pHEMA lenses.

The results suggest that there was a significant ($p<0.05$) difference in the amount of PVA released from the PVA loaded pHEMA lenses compared to the pHEMA lenses at room temperature, where PVA loaded pHEMA lenses released a higher amount of PVA. Furthermore, a similar trend was observed when comparing PVA release from PVA-loaded pHEMA lenses to pure pHEMA lenses after undergoing freezing at -80°C for one hour. These outcomes strongly imply that the incorporation of PVA within the contact lens material significantly influences both its loading capacity and the augmentation of loading post-freezing.

Table 5: Amount of PVA released from contact lenses

Lens	Cumulative release (µg)	
	Room temperature	After freezing at -80°C for one hour
pHEMA	32.64 ± 5.48	36.25 ± 6.11
PVA loaded pHEMA	42.88 ± 4.96	47.39 ± 6.26
etafilcon A	26.08 ± 2.31	29.24 ± 5.86
nelfilcon A	46.16 ± 6.94	55.07 ± 2.46

Moreover, as listed in table 5, the difference in results between pHEMA and PVA-loaded pHEMA lenses in contrast to commercial lenses such as etafilcon A and nelfilcon A, which are pHEMA and PVA based, warrants attention. This variation in release of PVA can be attributed to the composition disparity, as commercial lenses encompass additional monomers beyond pHEMA. For example, etafilcon A consists of additional MAA, while nelfilcon A is completely made of bound and unbound PVA. As a result, the study highlights

the pivotal importance of PVA within contact lenses to boost their ability to load PVA externally, especially after being subjected to extreme temperatures.

In the PVA loaded pHEMA lenses there is only 1.4% PVA, as a limit of its solubility in the HEMA, while nelfilcon A lenses are made of PVA only, which highlights and accounts for the differences in PVA release between these two lenses. However, the increase in PVA release and observed impact of freezing for synthesized lenses with PVA incorporation suggests that even a small amount of PVA tightly bound inside the lenses left after washing is enough to increase the loading of PVA after soaking. This further establishes that the presence of PVA inside the lenses in bound form is important to observe any effect on release either after soaking or after freezing.

In conclusion, this study validates the hypothesis proposed in Chapter 4, affirming the pivotal role of PVA within contact lens materials for increased PVA uptake and release capabilities. Synthesizing pHEMA-based lenses and embedding PVA within them revealed significant differences in PVA release compared to pure pHEMA lenses, both at room temperature and after freezing.

Chapter 6
General discussion

Contact lens wearers often feel discomfort and dryness, which increases dropout rates.[28] To address this concern, this thesis investigated the development of a method through which PVA can be released from contact lenses, aiming to improve comfort through controlled and increased elution. This thesis has demonstrated that a high molecular weight polymer such as PVA can be successfully loaded into a contact lens by using a simple soaking technique, which can be further used to alleviate contact lens discomfort. The study also contributes to the field of ocular drug delivery by providing a template of incorporating this polymer within a contact lens.

This research aimed to develop a hydrogel platform for efficient PVA delivery over a one-day period, for use in a daily disposable contact lens. The objective was to investigate how temperature affects PVA's interaction with contact lenses to optimize ophthalmic drug delivery. Methods included soaking commercial lenses in PVA at various temperatures to explore loading and release factors. Additionally, custom materials with enhanced temperature sensitivity were synthesized. The hypothesis proposed that lowering PVA solution temperature strengthens intermolecular bonds within PVA and with lens materials, enabling the formation of a surface layer on commercial contact lenses, with potentially increasing drug loading and release durations.

Two sets of experiments were conducted to investigate the hypothesis; First, commercial contact lenses were used to explore the interaction between PVA and contact lens materials, analyzing the potential factors involved in those interactions. Second, model contact lenses were fabricated in the lab to mimic the materials involved in the first experiment, namely pHEMA and PVA, and the inference from first experiment was tested.

For the first set, four commercial contact lenses (PureVision® - balafilcon A; Acuvue® Oasys – senofilcon A; DAILIES® AquaComfort PLUS® - nelfilcon A; 1-Day Acuvue® Moist® - etafilcon A) were used. Initially, nelfilcon A and etafilcon A lenses were soaked in low and high molecular weight PVA solutions at different temperatures. The lower molecular weight PVA was in the range of 31 – 50 kDa (average – 40.5 kDa) and higher molecular weight PVA was in the range of 146 – 186 kDa (average – 166 kDa). The PVA solution was prepared by gradually dissolving the specified quantity of PVA (99% hydrolyzed) into water within the temperature range of 120 – 140°C. This process was conducted using a water bath equipped with a magnetic stirrer set to rotate at 300 RPM.

The results from this set of experiments suggested that there was no statistically significant difference in the loading amount of the PVA between low and high molecular weight if loaded at only room temperature, among the contact lens types tested. However, nelfilcon A showed a higher amount of PVA release compared to etafilcon A.

In the investigation of factors influencing PVA release from hydrogel-based materials, differences in water content, surface charge, and base material composition were considered. A silicone hydrogel lens, balafilcon A, with a water content (36%) similar to pHEMA (38%) which is the base material of etafilcon A, was employed to probe the potential impact of base material on PVA release dynamics. Noticeably, findings from balafilcon A lenses mirrored those of etafilcon A lenses. This result suggests that factors such as water content, surface charge, and the differentiation between conventional hydrogel and silicone hydrogel compositions may not exert significant influence on the release of PVA. It was inferred that due to the presence of the PVA inside nelfilcon A lenses, they showed a higher amount of PVA loaded and subsequently released from those lenses. Additionally, results indicated a significant increase in PVA release from nelfilcon A lenses after freezing compared to

etafilcon A and balafilcon A contact lenses. This can be attributed to the lens material involved in each of these lenses.

Further, it was hypothesized that an increase in the loading of PVA can be observed if that material is also exposed to a lower temperature along with the PVA solution. However, this held true only for nelfilcon A lenses, as there was no statistically significant increase in the other lens types. nelfilcon A lenses showed a synergistic effect in the amount of PVA released after they were soaked in the PVA solution for 24 h and then exposed to -80°C for one hour along with the same soaking solution. This emphasizes the inference observed earlier that the presence of PVA inside the lenses is important in the loading and release of the PVA from contact lenses.

This was further investigated in the second set of experiments through the synthesis of pHEMA-based lenses and the incorporation of PVA in those lenses, which showed a statistically significant difference in PVA release compared to pure pHEMA lenses, both at room temperature and after freezing at -80°C for one hour. The findings support the hypothesis that the presence of PVA within contact lens materials plays a pivotal role in increasing PVA uptake and release capabilities. Notably, even a small amount of tightly bound or incorporated PVA inside lenses can increase external PVA loading after soaking and further when subjected to freezing. This can be attributed to the hydrogen bonding between the carboxyl group of the bound PVA present inside the lens material and the unbound PVA forming a layer on the contact lenses. The findings suggest that the freezing technique has potential applications in enhancing the release of comfort agents such as PVA from contact lenses, especially those containing PVA.

Furthermore, the in-vitro analysis of PVA release from both experimental sets showed no evidence of controlled release. Release kinetics from figures 5-8 suggests that the majority of the PVA was released within the first hour, irrespective of the lens type or the treatment

condition. This observation suggests that while an increased release of PVA was observed post exposure to lower temperature, it did not control the release to provide the benefit to an extended period.

To achieve extended release of PVA, a potential next experiment could involve incorporating sustained-release agents or modifying the hydrogel composition to prolong the release kinetics. One approach could be to encapsulate PVA within biodegradable microspheres or nanoparticles dispersed throughout the hydrogel matrix. Encapsulating PVA within biodegradable microspheres or nanoparticles dispersed in the hydrogel matrix could create a barrier around PVA molecules, slowing their diffusion out of the hydrogel as developed for other macromolecules such as proteins.[116] This sustained-release system could gradually release PVA over time, prolonging its release kinetics compared to direct incorporation into the hydrogel matrix. Conducting in-depth studies on the influence of these modifications on PVA release kinetics would provide valuable insights for optimizing controlled and extended-release formulations. The objective should be to ensure a prolonged presence of PVA on the surface of the contact lenses to establish a continuous barrier between the lens and the corneal surface, thereby minimizing discomfort.

It is essential to acknowledge the limitations of this research. The study focused primarily on in-vitro analysis, and further studies involving in-vivo experiments would provide a more comprehensive understanding of the practical implications of PVA incorporation in contact lenses. Based on the findings, it is recommended that future research explores additional parameters such as PVA concentration and a combination of molecular weights to optimize PVA release from contact lenses. Furthermore, investigations into the long-term effects of PVA incorporation on lens performance and wearer comfort would be valuable.

It is crucial to recognize situations where a specific type of lens is necessary, despite low PVA loading, as seen with etafilcon A or senofilcon A lenses. The results showed that adding

PVA to pHEMA increased the amount of PVA the lenses could hold. So, even lenses mostly made of pHEMA could contain some PVA, benefiting from this. This could lead to making hybrid lenses that combine PVA with pHEMA, unlike nelfilcon A lenses, which are purely made of PVA.

As observed in the results that by incorporating PVA into pHEMA, a higher loading capacity was achieved. Consequently, even lenses made primarily of pHEMA could incorporate some PVA, thereby benefiting from this effect and enabling the creation of PVA-based hybrid lenses, in contrast to nelfilcon A's pure PVA lenses.

In conclusion, this research provides insights into optimizing contact lens material design for improved comfort by utilizing PVA release. The demonstrated impact of freezing on nelfilcon A lenses indicates a promising avenue for enhancing the release of comfort agents.

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