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Timolol maleate release from hyaluronic acid-containing model silicone hydrogel contact lens materials

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Abstract

This study was designed to assess the impact of a releasable wetting agent, such as hyaluronic acid (HA), on the release profile of timolol maleate (TM) from model silicone hydrogel contact lens materials. Polyvinylpyrrolidone (PVP) was used as an alternative wetting agent for comparison. The model lenses consisted of a hydrophilic monomer, either 2-hydroxyethyl methacrylate or N,N-dimethylacrylamide and a hydrophobic silicone monomer of methacryloxypropyltris (trimethylsiloxy) silane. The loading of the wetting and the therapeutic agent occurred during the synthesis of the silicone hydrogels through the method of direct entrapment. The developed materials were characterized by minimal changes in the water uptake, while lower molecular weight of HA improved their surface wettability. The transparency of the examined silicone hydrogels was found to be affected by the miscibility of the wetting agent in the prepolymer mixture as well as the composition of the developed silicone hydrogels. Sustained release of TM from 4 to 14 days was observed, with the drug transport occurring presumably through the hydrophilic domains of the silicone hydrogels. The release profile was strongly dependent on the hydrophilic monomer composition, the distribution of hydrophobic

(silane) domains, and the affinity of the therapeutic agent for the silicone hydrogel matrix. Noncovalent entrapment of the wetting agent did not change the in vitro release duration and kinetics of TM, however the drug release profile was found to be controlled by the simultaneous release of TM and HA or PVP. In the case of HA, depending on the HA:drug ratio, the release rate was decreased and controlled by the release of HA, likely due to electrostatic interactions between protonated TM and anionic HA. Overall, partitioning of the drug within the hydrophilic domains of the silicone hydrogels as well as interactions with the wetting agent determined the drug release profile.

Keywords

Contact lens, silicone hydrogel, ocular drug delivery, timolol maleate, wetting agent, hyaluronic acid, polyvinylpyrrolidone

Introduction

Ocular anatomy and physiology render the eye impermeable to exogenous substances, protecting the visual pathway from toxins. As a result, successful delivery of ocular therapeutics is challenging as the drug must penetrate the protective barriers without damaging any healthy tissue. Accounting for approximately 90% of all ophthalmic medications, the most common method of treating diseases of the anterior segment of the eye is instillation of topical formulations such as eye drops, emulsions, and suspensions.^{1–3} Their ease of application and noninvasive drug delivery to the targeted tissue, avoiding first pass of metabolism in the liver, render topical formulations advantageous vehicles for the treatment of ocular ailments. However, due to effective ocular clearance mechanisms, this method of administration suffers from inherent delivery inefficiencies leading to low drug bioavailability, thus limiting its efficacy of current treatment paradigms. More specifically, the short residence time of topically applied solutions (3–5 min) due to the reflex tearing and rapid tear turnover (0.5–2.2 ml/min)⁴ as well as the presence of highly impermeable corneal barriers are the main reasons for low drug bioavailability.^{3,5} As a result, only 1–5% of an instilled drop reaches the target tissue,⁶ with the rest being lost to nasolacrimal drainage, absorbed by the conjunctiva and spilled onto the cheek.⁵ This can lead to undesired adverse ocular and systemic side effects.^{7,8}

Since drug bioavailability and corneal penetration are low in the case of topical formulations, administration of frequent and/or high drug concentrations is necessary to achieve a therapeutically effective dose. Often, to maintain effective drug concentrations, eye drops must be instilled several times a day^{3,5} and in the case of some antimicrobials and corticosteroids, administration on an hourly basis is necessary.⁹ With this frequent dosing schedule, patient noncompliance is a major problem, particularly for chronic and age-related diseases like glaucoma that need constant management. As well,

administration in this manner is characterized by a rapid increase in drug concentration upon instillation, followed by a rapid decline. Therefore, better bioavailability and duration of action of ophthalmic medications can be achieved by increasing the residence time of the agent on the ocular surface, maximizing corneal drug absorption while minimizing precorneal drug loss.

Among the different strategies developed for improving the drug delivery efficacy to the front of the eye, contact lenses have been suggested as therapeutic devices with the potential to meet the above requirements.^{10,11} Contact lenses are one of the most successful and widely accepted biomaterials with over 140 million wearers worldwide.¹² Even though they were initially designed for vision correction, their unique properties make them potential candidates for ocular drug delivery vehicles. To date, contact lenses have been used as therapeutic devices for relief of postsurgery ocular pain, promotion of corneal healing along with mechanical protection and support.¹³⁻¹⁵ Upon contact lens insertion, the tear film is divided into two sections, the postlens tear film (PoLTF) and the prelens tear film. Drug diffusion occurs through the therapeutic contact lens to both sections of tear film and due to limited mixing in the PoLTF, the drug residence time between the lens and the cornea was found to be increased significantly from 2 min (eye drops) to 30min, with a potential to increase corneal bioavailability by at least 50%¹⁶⁻¹⁸ due to this fact alone. Increased drug bioavailability could lead to improved drug delivery efficacy allowing for lower therapeutically effective drug concentrations, reduced drug wastage, and reduced transfer to the systemic circulation. However, the drug release duration should match the wear duration of the therapeutic contact lens. The introduction of silicone hydrogel contact lenses, in the late 1990s, was the key to the application of lens materials for extended drug release as the superior oxygen permeability of these materials allows them to be worn continuously for periods of up to 30 days.¹⁹ Prolonged and sustained release would increase the potential of these materials as delivery vehicles. In addition, continuous wear of drug eluting contact lenses can possibly improve patient noncompliance by eliminating the need for frequent drug administration. As a result, contact lenses can be attractive candidates as ocular drug delivery vehicles.¹⁰

Many different material development strategies have been studied to design a contact lens-based drug delivery system that can provide controlled or sustained release profiles for extended periods of time while maintaining the original properties of the lens. Colloid and nanoparticle-laden contact lenses,²⁰⁻²⁴ incorporation of hydrophobic diffusive barriers,²⁵⁻²⁹ surface-coated drug-loaded layers³⁰ as well as biomimetic and molecularly imprinted contact lens materials³¹⁻³⁵ are some of the techniques investigated. Overall, results suggest that silicone hydrogel materials exhibit longer release durations than conventional materials.³⁶ In addition, there are two main approaches to incorporate the therapeutic agent into the lens matrix, postsynthesis either via soaking the lens into a drug solution^{9,36-38} or by applying drops while the lens is being worn,³⁹ and during hydrogel polymerization.⁴⁰ While soaking is convenient, release profiles are typically characterized

by an initial burst release followed by subtherapeutic dosing.^{9,30,41} Recently, Vistakon Pharmaceuticals, LLC (Jacksonville, FL, U.S.A) has completed a multicenter Phase III clinical trial in humans for contact lenses presoaked in a solution of an antihistamine drug, ketotifen, for the treatment of allergic conjunctivitis.^{42,43} The results of this study demonstrated increased bioavailability suggesting that a contact lens can perform as an ocular drug delivery system. Despite interesting results with the various materials, clinical trials remain limited however.

Hyaluronic acid (HA) has been suggested as a wetting agent for use in contact lenses to increase comfort. HA is a linear, nonsulfated glycosaminoglycan that occurs naturally throughout the body.⁴⁴⁻⁴⁶ In the eye, it can be found in the vitreous humor, lacrimal gland, conjunctiva, corneal epithelium, and tear film.³ It is biocompatible, nonimmunogenic, and biodegradable; and has been widely used in ophthalmic applications.⁴⁷⁻⁵¹ It has been also found to promote wound healing,⁵²⁻⁵⁴ provide better graft transparency,⁵⁵ and suppress inflammation.⁵⁶ Moreover, HA can interact with the ocular mucins when delivered on the surface of the eye, creating a ‘‘artificial mucin’’⁵⁷ that can cover the surface of the contact lens and counteract tear film destabilization that occurs during contact lens wear, leading possibly to higher degree of comfort. According to previous results, model silicone hydrogels containing HA as an internal nonreleasable wetting agent were characterized by improved water content, the surface wettability, and hydrophilicity, while the presence of HA also decreased lysozyme sorption and denaturation.⁵⁸⁻⁶¹ When these materials were examined in vitro for drug delivery, the presence of HA in the matrix led to higher and therapeutically effective levels of drug release for six days, suggesting promising properties for incorporated HA in ocular drug delivery.⁶² In another study, the presence of HA as a functional additive in model conventional and silicone hydrogel materials increased the loading and subsequent total release of timolol maleate (TM).⁶³ Conventional contact lenses loaded with releasable HA were also designed.^{44,64,65} Fagnola et al.⁶⁴ observed a five-day release from methafilcon 1B contact lenses, while Ali and Byrne⁴⁴ used the technique of molecular imprinting to develop nelfilcon contact lenses capable of releasing high molecular weight (MW) HA in a controlled manner for the treatment of dry eye.

The hypothesis of the present work is that improving the hydrophilicity of the polymer domains within a silicone hydrogel network, by incorporating a releasable wetting agent such as HA, can be used to tailor the release kinetics of a therapeutic agent, providing controlled and extended release. Given the relatively high MW of HA, drug release over prolonged time periods is anticipated by taking advantage of electrostatic interactions between anionic HA (pKa 1/4 3) and a positively charged drug such as TM (pKa 1/4 9.2). For comparison, the uncharged wetting agent polyvinylpyrrolidone (PVP) was examined.

Controlled and extended release of a single therapeutic agent or a wetting agent has been previously reported; however, this is the first report to our knowledge, of a multidrug

loaded contact lens-based drug delivery system. Such system shows simultaneous release of a therapeutic and a wetting agent that will potentially lead to a higher degree of comfort during wear and mitigation of undesired side effects caused by the long-term presence of the drug or the lens on the ocular surface during therapy.

Materials and methods

Materials

2-Hydroxyethyl methacrylate (HEMA, 97%), N,N-dimethyl acrylamide (DMA, 99%), ethylene glycol dimethacrylate (EGDMA, 98%), inhibitor remover for hydroquinone and monomethyl ether hydroquinone (MMEQ) removal, PVP (10 kDa), and TM 98% were all purchased from Sigma Aldrich (Oakville, ON, Canada). 3-Methacryloxypropyl-tris-(trimethylsiloxy) silane (TRIS, 95%) was supplied by Gelest (Morrisville, PA, USA). The photoinitiator 1-hydroxy-cyclohexyl-phenyl-ketone (Irgacure[®] 184) was generously donated by BASF Chemical Company (Vandalia, IL, USA). HA (sodium hyaluronate) of various MWs was purchased by LifeCore Biomedical (Chaska, MN, USA). Phosphate-buffered saline solution (PBS) 10^x was obtained from Bioshop[®] Canada Inc. (Burlington, ON, Canada). The UV-permeable acrylic mold (Plexiglass[®] G-UVT) used for casting the silicone hydrogels was kindly donated by Altuglass International (Bristol, PA, USA). All other reagents were purchased from Sigma Aldrich unless otherwise stated. The HA enzyme-linked immunosorbent assay (ELISA) kit was purchased from Echelon Bioscience Inc. (Salt Lake City, UT, USA).

Synthesis of p(HEMA-co-TRIS) and p(DMA-co-TRIS) hydrogels

Both p(HEMA-co-TRIS) (90:10 wt%) and p(DMA-co-TRIS) (50:50 wt%) hydrogels were prepared to model the properties of silicone hydrogel lenses. Initially, the monomers HEMA, DMA, and TRIS as well as the crosslinker EGDMA were purified to remove the polymerization inhibitor MMEQ, by passing each of the above chemicals through a separate column packed with inhibitor remover. In all cases, percentages are based on the total amount of the hydrophilic (HEMA or DMA) and hydrophobic (TRIS) monomers used. Initially, the hydrophilic monomer HEMA (90 wt%) or DMA (50 wt%), the hydrophobic TRIS (10 wt% for p(HEMA-co-TRIS) and 50 wt% for p(DMA-co-TRIS)) and EGDMA (5 wt% or 3.7 mol%) were mixed. The photoinitiator Irgacure[®] 184 (0.028wt%) was then added to the mixture under constant stirring. This prepolymer solution was then injected into a mold consisting of two acrylic plates lined with polyester sheets to prevent adhesion, bolted together and separated with a 1-mm thick Teflon spacer. The mold was then placed in a 400W UV chamber (Cure Zone 2 Control-cure, Chicago, IL, USA) for 10min for polymerization at a wavelength of 365nm. Upon removal from the mold, the materials were soaked in 100ml Milli-Q water to remove unreacted components and then punched into round discs of 7.94 mm (5/16⁰⁰) and 5.56

mm (7/32⁰⁰) diameter. The discs were placed in a 37^{°C} oven overnight and stored until use.

Synthesis of TM and/or wetting agent loaded silicone hydrogels

For the preparation of drug and/or wetting agent loaded materials, a similar procedure to above was used. Initially, the TM (0.5 or 2wt%) was dissolved in the hydrophilic monomer (HEMA or DMA) while stirring. The wetting agent HA or PVP of different MWs and concentrations, respectively, was then added to the monomer–drug mixture under vigorous stirring to ensure uniform dispersion. TRIS, EGDMA, and Irgacure[®] 184 were then added to the polymer mixture, and the resulting solution was polymerized as above. The different compositions of model silicone hydrogels synthesized for the current study are summarized in Table 1.

Table 1. Summary of materials and properties.

Material loading conditions	TM ^a (wt%)	Wetting agent (wt%)	Equilibrium water content—EWC (%)		Light transmittance (%)	
			D/T ^b	H/T ^c	D/T ^b	H/T ^c
1	–	–	31.1 ± 0.9	24.4 ± 0.7	97.1 ± 0.5	89.3 ± 4.7
2	0.5	–	30.4 ± 0.7	25.8 ± 1.0	92.0 ± 1.0	85.2 ± 5.0
3	0.5	0.1 (HA ^d , 7.5 kDa)	29.6 ± 0.9	25.7 ± 0.5	72.0 ± 5.7	52.6 ± 7.9
4	0.5	0.5 (HA, 7.5 kDa)	32.7 ± 1.1	25.7 ± 0.4	45.0 ± 5.5	15.0 ± 0.6
5	0.5	0.5 (HA, 132 kDa)	30.7 ± 0.5	24.6 ± 1.1	60.8 ± 2.7	51.3 ± 7.4
6	0.5	0.1 (PVP ^e , 10 kDa)	30.2 ± 0.9	24.4 ± 1.2	83.8 ± 2.4	79.2 ± 6.8
7	0.5	0.5 (PVP, 10 kDa)	30.4 ± 0.4	25.1 ± 1.0	46.7 ± 5.4	91.0 ± 3.4
8	2	–	31.0 ± 0.7	26.8 ± 0.5	86.9 ± 1.0	85.1 ± 6.0
9	2	0.1 (HA, 7.5 kDa)	32.1 ± 1.2	25.4 ± 0.7	76.8 ± 1.9	72.1 ± 2.8
10	2	0.5 (HA, 7.5 kDa)	31.9 ± 1.0	26.0 ± 1.2	34.7 ± 6.9	23.6 ± 1.6
11	2	0.5 (HA, 132 kDa)	30.6 ± 1.0	26.8 ± 0.8	69.2 ± 4.1	47.9 ± 1.2
12	2	0.5 (HA, 910 kDa)	29.7 ± 0.4	26.8 ± 0.7	61.7 ± 7.1	60.6 ± 4.0
13	2	0.1 (PVP, 10 kDa)	30.9 ± 0.6	26.7 ± 0.3	58.4 ± 3.9	93.2 ± 0.8
14	2	0.5 (PVP, 10 kDa)	32.5 ± 0.3	28.0 ± 0.4	11.6 ± 0.8	90.8 ± 1.9
15	2	10 (PVP, 10 kDa)	–	29.4 ± 0.8	–	75.2 ± 4.6

Note: TM, timolol maleate; EWC, equilibrium water content; HA, hyaluronic acid; PVP, polyvinylpyrrolidone.

^aTimolol maleate, ^bp(DMA-co-TRIS) (50:50 wt%), ^cp(HEMA-co-TRIS) (90:10 wt%), ^dhyaluronic acid, ^epolyvinylpyrrolidone.

Swelling behavior

The equilibrium water content (EWC) of the synthesized silicone hydrogels was determined. Discs were fully dried, weighed, and then soaked in 1 ml of MilliQ water for 48 h at ambient temperature. The swollen discs were removed, gently blotted with a Kimwipe to remove excess of water, and weighed to determine the wet mass. The EWC was calculated using equation (1), where M_H is the mass of the hydrated discs and M_D is the dry mass of the silicone hydrogel discs

$$\text{EWC}(\%) = \frac{M_H - M_D}{M_H} \cdot 100 \quad (1)$$

Optical transparency

The optical transparency of the discs was determined by measuring the light transmittance (%), using a UV–Vis spectrophotometer (Spectramax Plus 384, Molecular Devices, Corp, Sunnyvale, CA, USA). The swollen hydrogels were placed in 100ml MilliQ water and the light transmittance was measured over a wavelength range of 400–750nm. A water blank was used for all samples. For comparison purposes, the light transmittance of the studied silicone hydrogels is reported at a wavelength of 600 nm as a representative point of the visible spectrum range.

Surface wettability

The surface wettability was assessed by measuring the contact angles using the air captive bubble technique. Hydrated silicone hydrogel discs were gently blotted with a Kimwipe in order to remove any excess of wetting agent or drug from the surface before being immersed into a chamber filled with Milli-Q water. The contact angle (θ) between an air bubble and the surface was measured using a Rame-Hart NRL 100-00 Contact Angle Goniometer. Briefly, the air bubble (approximately 25ml) was dispensed manually from the tip of a U-shaped, stainless steel capillary that was tightly fastened to a 1-ml syringe. The capillary was then retracted from the chamber and the static contact angle was measured.

In vitro therapeutic and wetting agent release study

For release experiments, dry discs (7.94 mm in diameter and 1 mm thickness, n 1/4 4) with and without drug and/or wetting agent were weighed and then placed vertically into eppendorf tubes in 1 ml of PBS (pH 1/4 7.4) in order to have both sides exposed to the release medium. The eppendorf tubes were incubated in an orbital shaker (VWR International, West Chester, PA, USA) at 37°C at 90 r/min. The PBS was exchanged at every measurement to maintain sink conditions, in an attempt to mimic tear turnover. For TM detection, the absorbance of the releasates was measured by UV–vis spectrophotometry (Spectramax Plus 384, Molecular Devices, Corp, Sunnyvale, CA, USA) at a wavelength of 295nm and compared with a standard curve. An ELISA was conducted to quantify the concentration of HA in releasates. Release amounts were normalized and expressed as mass of TM or HA released per mass of dry disk.

Statistical analysis

Statistical analyses were carried out using a singlefactor analysis of variance and Tukey

honest significant difference (HSD) test in Statistica 10.0 (StatSoft Inc., Tulsa, OK, USA). In the cases where appropriate, student t-tests with two tail, unequal variance were used. In all cases, a value of $p < 0.05$ was used to establish statistical significance.

Results and discussion

In this study, the model materials were designed based on a combination of monomers that are commonly found in contact lenses aiming to mimic silicone hydrogel lenses. It is important to note that these hydrogels are silane based and do not include siloxane macromers, which are commonly incorporated in commercial silicone hydrogel contact lenses. However, in the current manuscript they will be referred as silicone hydrogels as their application is contact lens-based drug delivery. Since release in this case is expected to be via the hydrogel phase of the network, connectivity of the silicone phase is less critical to the evaluation of the potential of using wetting agents to facilitate drug release.

Swelling study—EWC

The ability of the silicone hydrogels to absorb and retain relatively high levels of water within their matrix is critical since the presence of water improves the on-eye movement of the lens, allowing higher degree of comfort. Typically, 24–38% is the acceptable range of EWC for overnight wear, depending on the constituent materials.⁶⁶ Swellability also has a significant impact on the release mechanism for both the therapeutic and wetting agent.

In order to determine the impact of both the therapeutic and wetting agent on the matrix of the drugloaded p(DMA-co-TRIS) and p(HEMA-co-TRIS) materials, the water content was determined using equation (1) and the results are shown in Table 1. Overall, p(DMA-co-TRIS) materials were found to swell more than p(HEMA-co-TRIS) despite the higher silicone monomer content (50 wt% vs. 10 wt%), with EWCs of 31.1% \pm 0.9 and 24.4% \pm 0.7, respectively ($p < 0.0005$). This is likely due to the higher degree of hydrophilicity of DMA (logP 0.14) compared to HEMA (logP 0.3).⁶⁷ The hydrophilic nature of TM did not seem to have an impact on the EWC of p(DMA-co-TRIS) hydrogels ($p > 0.2$), while for p(HEMA-co-TRIS) materials, a statistically significant increase in the water content was observed when the silicone hydrogels were loaded with 2wt% of TM (H/T materials 8 and 14, $p < 0.002$).

When HA was incorporated into TM-loaded p(DMA-co-TRIS) hydrogels, the water content increased slightly (7%) only when 0.5wt% of HA of 7.5 kDa MW was used (D/T material 4, $p < 0.03$). For p(HEMA-co-TRIS) hydrogels, the presence of releasable HA had negligible effect on the water content ($p > 0.05$). Interestingly, increasing the MW of HA did not lead to an increase in the water uptake of the silicone hydrogels as might be expected. Apparently, due to the limited solubility of HA in the monomer solution, the degree of dispersion within the hydrogel matrix plays a more significant role in case of

direct entrapment of HA than the length of the polymer chain, since lower MWs of HA exhibited better dispersion in the silicone hydrogels during synthesis. It is likely that the higher MW HA exhibited significant phase separation and therefore did not contribute to increased water uptake. Hence, better distribution of the HA chains throughout the matrix in combination of higher chain mobility (due to lower MW) may play a greater role in determining hydrogel structure. The water content of PVP-containing materials was similar to those of HA-containing silicone hydrogels for both formulations. Incorporation of 10 wt% PVP (10 kDa) in the p(HEMA-co-TRIS) hydrogel materials (H/T material 15) resulted in the greatest increase in the EWC ($p < 0.00001$), suggesting that the presence of PVP within the matrix reinforced the hydrophilic domains, and thus higher difference in osmotic pressure led to higher water uptake. In the case of p(HEMA-co-TRIS) materials, the presence of both high drug concentration and wetting agent acted had a synergistic effect increasing the water content of the developed silicone hydrogels (H/T materials 11–15, $p < 0.001$).

These results suggest that the presence of low concentrations of the releasable wetting agent had a minimal impact on the hydrophilic domains of the silicone hydrogel matrix as no significant changes in the water uptake of the materials were observed. Overall, the EWC of p(HEMA-co-TRIS) and especially that of p(DMA-co-TRIS) hydrogels was within an acceptable range and similar to commercially available contact lenses.⁶⁸

Optical transparency study

Optical transparency is critical for contact lens application and provides insight into material morphology. Phase separation between hydrophilic and the hydrophobic domains reduces visible light transmission, causing substantial image distortion. Contact lenses must have a morphology that allows at least 80%, and more preferably greater than 90% of visible light to be transmitted.⁶⁹ Therefore, the impact of wetting and/or therapeutic agent presence on the light transmittance of the model silicone hydrogels was examined. The results, showing transmittance (%) at 600nm as representative wavelengths, are summarized in Table 1.

According to Table 1, the p(HEMA-co-TRIS) materials were characterized mainly by similar or lower optical transparency compared to the p(DMAco-TRIS) ($p < 0.005$) with the exception of the PVP containing materials. A possible explanation for the decreased optical clarity of the p(HEMA-co-TRIS) materials is that phase separation occurs between the hydrophilic (HEMA) and hydrophobic (TRIS) monomers. This phase separation is the result of the immiscibility of the silane-based monomer TRIS in the hydrophilic HEMA, when cohesive interactions between chemically identical or similar molecules are stronger than the adhesive interactions between chemically different molecules.⁷⁰ Hence, these results suggest that the size of the hydrophilic–hydrophobic domains in the p(HEMA-co-TRIS) materials is larger than those in p(DMA-co-TRIS).

For non wetting agent-containing samples, the addition of drug during synthesis did not affect significantly the optical transparency of the p(HEMA-co-TRIS) materials ($p > 0.5$); whereas a decrease in the optical clarity was observed for the TM-loaded p(DMA-co-TRIS) samples ($p < 0.0002$) although their light transmittance remained greater than 85%. In contrast, a decrease in the transparency of both model silicone hydrogel materials was observed when HA was physically embedded during synthesis ($p < 0.002$). Contrary to the effect of the MW, increasing the concentration of HA led to a further decrease in transparency ($p < 0.0001$), suggesting an inverse correlation between concentration and the respective transparency of model lens, similar to that previously observed by Guidi et al.⁶³ Due to the low miscibility of the long hydrophilic chains of HA within the monomers of the prepolymerization mixture, the dispersed HA polymer chains were trapped within the polymer matrix leading to light refraction. Of note, there was a small increase in the transparency of the HA-containing materials following release, demonstrating that only a small fraction of the loaded wetting agent was released (data not shown). Furthermore, the incorporation of up to 0.5wt% of releasable PVP within p(HEMA-co-TRIS) materials did not affect the optical properties of the model silicone hydrogels (H/T materials 6, 7 and 13, 14; $p > 0.8$). Even at concentrations of 10 wt% PVP, there was good compatibility and no significant precipitation within the prepolymer mixture, unlike with HA, however a small reduction in the optical acuity compared to the control samples was observed ($p < 0.02$). This thought to happen due to the presence of the drug and not due to the wetting agent as the p(HEMA-co-TRIS) hydrogels that contained only 10 wt% PVP and not drug had a light transmittance of 86.6% \pm 3.7 (data not shown). This further demonstrates that wetting agent miscibility within the prepolymer matrix is critical for generating transparent materials. Contrary to p(HEMA-co-TRIS), the p(DMA-co-TRIS) materials were significantly less clear when loaded with PVP even at low concentrations (0.1wt%, D/T material 13; $p < 0.0003$), suggesting a microphase separation during synthesis due to the incompatibility between pDMA and PVP.⁷¹ The importance of marrying the properties of the matrix and the wetting agent is hence demonstrated. Further analysis of these materials is required to better understand the impact of wetting agent on their bulk structure.

It is important to mention that the samples examined herein were significantly thicker (1 mm) than commercial contact lenses (approximately 100 μ m) and based on previous results, thicker materials exhibited lower light transmission.^{63,72} It is expected that preparation of materials with thicknesses more representative of contact lens materials would have improved optical properties and a less profound drop in the light transparency due to the presence of the wetting agent. However, limitations in our polymerization setup meant that it was not possible to prepare thinner materials.

Surface wettability

Surface wettability is another critical parameter for contact lens applications, since sufficiently wettable surfaces may maintain the tear film stability upon lens insertion,

allowing for higher degree of compatibility and comfort.⁷³ For the analysis of the surface wettability, static contact angles were measured using the captive bubble technique, since this method gives results more representative of an eye wear. Lower contact angles between the air bubble and the solid surface are indicative of more wettable surfaces.⁷⁴

The impact of the wetting agent and TM on surface wettability is presented in Figures 1 and 2. In all cases, p(DMA-co-TRIS) materials exhibited lower contact angles ($p < 0.03$), thus better surface wettability than p(HEMA-co-TRIS) samples, probably due to the presence of the more hydrophilic DMA ($\log P_{\text{DMA}} 1/4 0.14$ vs. $\log P_{\text{HEMA}} 1/4 0.3^{67}$). The combination of lower contact angles of p(DMA-co-TRIS) samples and higher transparency, even though they have more TRIS in their matrix, suggests that the (DMA-co-TRIS) materials are characterized by better phase distribution than p(HEMA-co-TRIS).

For both p(DMA-co-TRIS) and p(HEMA-co-TRIS) hydrogels, the presence of both hydrophilic TM as well as wetting agent, particularly HA, led to materials with lower contact angles when compared to the control samples ($p < 0.03$ and $p < 0.02$, respectively) (Figures 1 and 2). Direct entrapment of lower MW of HA in p(DMA-co-TRIS) resulted in lower contact angles ($p < 0.03$) (Figure 1) and thus enhanced surface wettability, suggesting that the higher mobility of short HA chains due to lower MW, in combination with the higher degree of dispersion of the polymer within the silicone hydrogel matrix may allow HA to migrate and accumulate more evenly on the surface, leading to improved surface characteristics. On the other hand, in drug-loaded p(HEMA-co-TRIS) materials, the presence of the releasable wetting agent, regardless of its nature and MW, did not exhibit any significant changes in the surface wettability ($p > 0.1$) (Figure 2). These results are in agreement with previous studies where HA was used as a functional additive for molecular imprinting,⁶³ whereas when HA was used as internal wetting agent improved surface wettability of the same silicone hydrogels examined in the current study.⁵⁸⁻⁶¹ Based on the HA release profile from the p(HEMA-co-TRIS) materials, as discussed below, most of the HA release was found to occur within 24h from these materials, whereas the contact angles were not measured until 48 h, at which time there was presumably not sufficient HA left to affect the surface characteristics. However, the surface wettability of the TM-containing p(HEMA-co-TRIS) materials was significantly improved with the entrapment of 10 wt% of PVP within the hydrogel, which led to a 30% decrease in the examined contact angles (H/T material 15, $p < 0.0005$) (Figure 2). It is interesting to note that the presence of TM in the 10 wt% PVP-containing materials caused a significant 1.5-fold increase in the contact angle compared to those materials loaded only with PVP 10wt% ($p < 0.0006$). This result could possibly be attributed to the different degree of hydrophilicity between the therapeutic and the wetting agent. Based on the above results, it is reasonable to assume that during drug release, the wetting agent (HA or PVP) migrates to the surface and attracts water molecules due to its high hydrophilicity, generating a surface with improved wettability

due to the presence of a ‘‘layer’’ of wetting agent on the surface. In addition, based on previous results, lower MW releasable HA was also found to interact with lysozyme, hindering protein sorption, only on the surface of model p(HEMA-co-TRIS) hydrogel discs and not on p(DMA-co-TRIS) hydrogel surfaces.⁶⁵ Hence, different parameters affect the surface characteristics of the examined model silicone hydrogels when either HA or PVP is noncovalently entrapped within the polymer matrix, presumably due to differences in polymer structure. Clearly further experimentation is necessary to understand the relationship between surface structure and bulk composition.

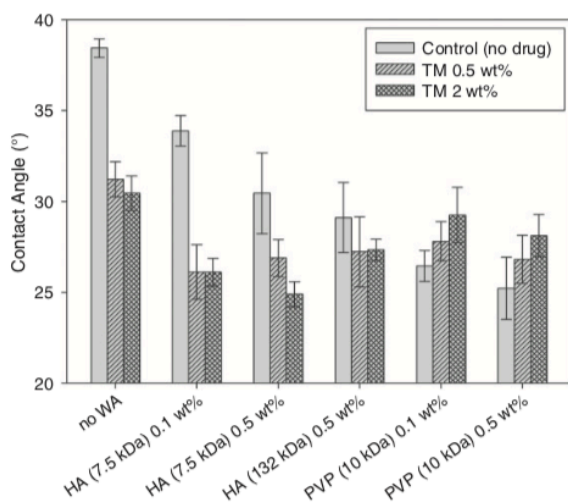


Figure 1. The impact of the drug and the wetting agent (WA) on the surface wettability of swollen timolol maleate (TM)-loaded p(DMA-co-TRIS) materials was determined by the mean contact angle (\pm SD), using captive bubble technique ($n = 4$).

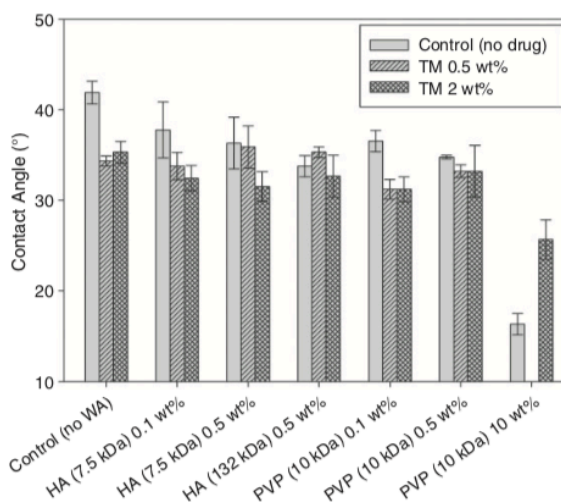


Figure 2. The impact of the drug and the wetting agent (WA) on the surface wettability of swollen timolol maleate (TM)-loaded p(HEMA-co-TRIS) materials was determined by the mean contact angle (\pm SD), using captive bubble technique ($n = 4$).

In vitro drug release study from model p(DMA-coTRIS) and p(HEMA-co-TRIS) hydrogels

The drug-loaded p(DMA-co-TRIS) and p(HEMA-co-TRIS) hydrogels used in the current study were initially in a dry state prior being immersed in the PBS release medium. Therefore, our system is considered as a monolithic device that is initially a ‘‘swelling controlled’’ system, whereas after reaching the EWC, the system becomes a ‘‘diffusion-controlled’’ system. While this does not represent the case of a contact lens, which would be swollen and presumably in equilibrium with a drug solution prior insertion, it provides a preliminary evaluation of the drug release mechanism from a wetting agent-containing system. The effect of the therapeutic and wetting agent loading concentration on TM release profile was determined. To observe the drug release kinetics of the examined systems, the mass of the TM released divided by the total amount of drug released was plotted as a function of time.

In p(DMA-co-TRIS) materials, the release of TM at a loading of 0.5 wt% lasted for four days, with 90% of the drug being released within 60 h (2.5 days), followed by a lower rate of release (Figure 3). A further increase in the loading TM concentration did not alter either the release duration as expected, or the release kinetics, suggesting that the amount of drug loaded is below the percolation threshold. On the other hand, the release of TM from p(HEMA-co-TRIS) hydrogels lasted for 14 days, with 90% of the drug being released within the first eight to nine days, depending on the drug concentration. In contrast with the p(DMAco-TRIS) hydrogels, the release profile and kinetics of TM from p(HEMA-co-TRIS) were found to be drug concentration dependent, while the release duration remained the same. A fourfold increase in the TM concentration led to a slightly higher release rate of the hydrophilic TM in a less controlled manner (Figure 3), which is in accordance with previous results,⁷⁵ suggesting that upon insertion in PBS, the volume initially occupied by the solid drug particles was replaced by its solution of higher concentration over time, and thus a greater concentration gradient between the matrix and the aqueous environment led to faster transport of TM from these materials. In all cases, an initial burst release was observed, followed by a period of extended TM release.

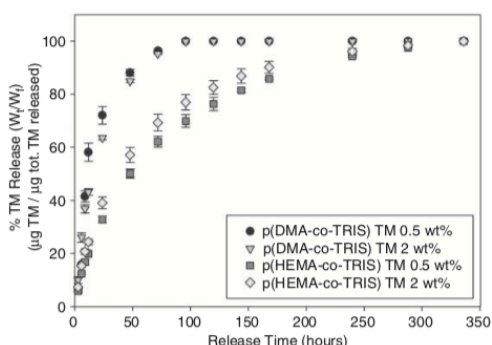


Figure 3. Plot of the percentage TM cumulative release by p(DMA-co-TRIS) and p(HEMA-co-TRIS) discs in PBS. Drug release (Wt) divided by the total amount released (Wt) is plotted as a function of time. Data are shown as $M \pm SD$ ($n = 4$).

Similar release results were obtained in the case of wetting agent-containing materials as reported below. This initial burst release is attributed to the dissolution of the drug exposed to the surface of the silicone hydrogel upon insertion in the release medium, due to polymer relaxation during hydration⁷⁶ and an increased concentration gradient between the bulk of the silicone hydrogel and the aqueous environment. Subsequently upon water imbibition into the matrix, drug release occurs via dissolution of the hydrophilic therapeutic agent through the macromolecular mesh of water-filled pores in the silicone hydrogel and diffusion into the bulk. Consequently, the changes in the dimensions due to water uptake and swelling of the polymer matrix may lead to time-dependent diffusion coefficients resulting in a complex kinetic process.^{77,78} The longer release duration of TM from p(HEMA-co-TRIS) hydrogels compared to p(DMAco-TRIS) was attributed to the lower water content of p(HEMA-co-TRIS) materials in combination with the greater affinity of the drug for the HEMA domains.³²

In vitro drug release study from HA and PVP-containing p(DMA-co-TRIS) hydrogels

The physical entrapment of releasable HA into p(DMA-co-TRIS) hydrogels led to reduced TM release rates when compared to those samples that contained solely drug and not wetting agent (0.5wt% TM: $p < 4 \times 10^{-7}$; 2wt% TM: $p < 0.0003$) (Figure 4(a) and (b)), governed by similar release kinetics for the same release duration.

Under the release conditions (pH=7.4), HA is deprotonated ($pK_a=3$), while TM is protonated ($pK_a=9.2$); therefore, it would be reasonable to assume that an electrostatic interaction would occur between HA and TM. In addition, due to the significantly higher MW of HA compared to that of TM, the wetting agent should diffuse through the silicone hydrogel at a much slower rate than the drug. Therefore, the slower rate of HA diffusion in combination with the electrostatic interactions between HA and TM, presumably enabled the drug release to be controlled by TM binding and subsequent interaction with HA. The similarity in the release kinetics between the therapeutic and the wetting agent (Figure 5) further supports this speculation. It is hence suggested that electrostatic interactions between the TM and the HA determined the drug release with HA diffusion being the limiting step in the drug release mechanism. The interactions between the silicone hydrogel matrix and the therapeutic or the wetting agent played a secondary role in the drug release profile. The released HA/TM complex formed, will presumably dissociate in the presence of ions in the tears, although retention of this complex in the tear film may be enhanced compared with drug alone due to the mucoadhesive nature of HA.⁵⁷ A further increase in the concentration of HA (7.5kDa) resulted in lower drug release rates, while the examined MWs of HA did not have a significant impact on the TM release profile (Figure 4(a) and (b)). The latter observation is somewhat surprising since higher MW HA would be expected to release for longer periods of time. However, it is believed that the release duration was not altered due to the lower degree of miscibility of higher MW of HA in the prepolymer mixture, which led to a lower amount of HA available for release through the hydrophilic domains. Moreover, the interactions between HA and TM were found to be weaker when the drug concentration was increased, according to the changes observed in the drug release profile (Figure 4(b)). As the TM:HA ratio was increased, it is reasonable to hypothesize that there were fewer HA binding sites for the TM, and thus the drug release could be mainly controlled by the diffusion of TM through the hydrophilic domains of the silicone hydrogel matrix.

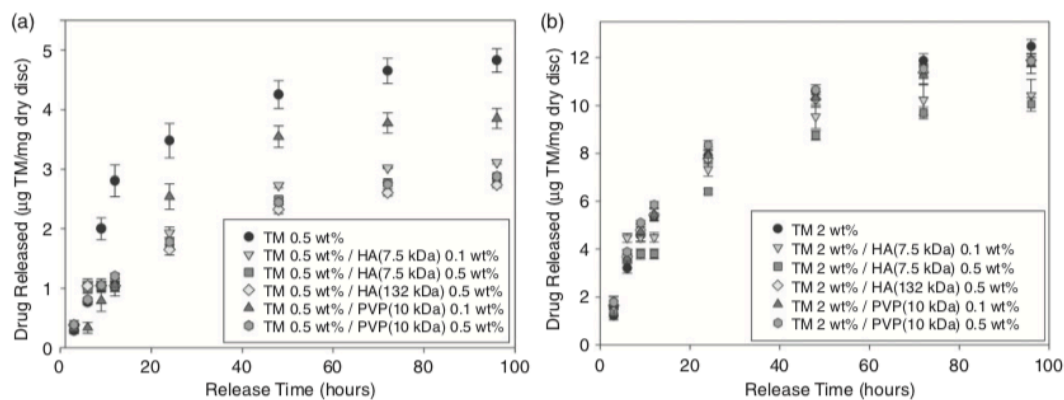


Figure 4. Cumulative release profiles of timolol maleate (TM) loaded at (a) 0.5 wt% and (b) 2 wt% from wetting agent-loaded p(DMA-co-TRIS) materials. Data are shown as $M \pm SD$ ($n = 4$).

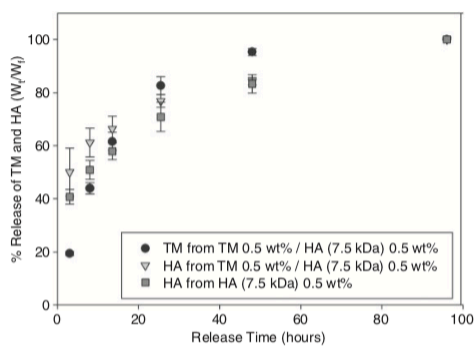


Figure 5. Fractional release profile of both HA and TM from p(DMA-co-TRIS) hydrogels. The TM or HA release (Wt) divided by the total amount released (Wt), respectively, is plotted as a function of time. Data are shown as $M \pm SD$ ($n = 4$).

Finally, the physical entrapment of PVP into the p(DMA-co-TRIS) network was also found to impede the release of TM, leading to lower than the control release rates (0.5wt% TM: $p < 4 \times 10^{-3}$, 2wt% TM: $p < 0.004$) (Figure 4(a) and (b)). As with HA, the TM release profiles were controlled by the concentrations of TM and PVP without any change in release duration and release kinetics. Based on the chemistry of TM and PVP, the only interaction that may possibly affect the TM release would be hydrogen bonding between the carbonyl groups (C=O) groups in PVP and the hydroxyl groups (–OH) of TM.⁷⁹ Additionally, due to the incompatibility between the wetting agent and the hydrophilic monomer, it is speculated that the presence of interfaces in the silicone hydrogel matrix may affect the release mechanism. This hypothesis could be further supported by the observed reduction in the TM release rate ($p < 6 \times 10^{-4}$) when the PVP concentration was increased (Figure 4(a)), since a further increase in the concentration of PVP would be expected to improve the diffusivity of the hydrophilic TM by reinforcing the hydrophilicity of the silicone hydrogel domains of the polymer matrix. Based on previously reported results, incorporation of PVP in pDMA hydrogels during synthesis led to materials with significantly decreased pore size compared to the pDMA alone.⁷¹ Alteration of the porosity and thus the tortuosity of the p(DMA-co-TRIS) hydrogels

could cause an entanglement of the long chains of PVP in the silicone hydrogel mesh, hindering the movement of PVP⁸⁰ and consequently that of TM through the silicone hydrogel network. Thus, increasing further the PVP concentration would lead to further obstruction of the TM diffusion. Interactions between PVP and the silicone hydrogel matrix, due to the amphiphilic nature of the wetting agent⁸¹ could also contribute to the latter observation. Hence, it would be useful to determine the PVP release profile. On the other hand, the impact of PVP on the release rate of TM was significantly decreased with a fourfold increase in the concentration of TM, leading to drug release profiles that were similar to that of the control discs (Figure 4(b)), providing evidence that it is indeed an interaction between the PVP and the TM that is controlling the drug release at low loading concentrations (0.5wt%). As observed with the HA-containing samples, it can be assumed here as well that with increased amounts of TM relative to wetting agent, the drug release becomes controlled by diffusion of the TM and not of the wetting agent through the matrix. In general, there was not an identifiable trend that could suggest a specific release mechanism of TM from PVP-containing p(DMA-co-TRIS) materials. In addition, when the impact of PVP was compared to that of HA, all samples exhibited similar release kinetics independent of the TM and wetting agent concentration.

In vitro drug release study from HA and PVP-containing p(HEMA-co-TRIS) hydrogels

In contrast to p(DMA-co-TRIS) silicone hydrogels, the impact of HA on the release profile of low drug concentration-loaded p(HEMA-co-TRIS) materials was found to be MW dependent. More specifically, as shown in Figure 6(a), only those silicone hydrogel discs loaded with high MW of HA (132 kDa) exhibited slightly lower release rates when compared to the control samples, without though altering either the release kinetics or duration ($p < 0.00015$). A further increase in the loading concentration of TM (from 0.5wt% to 2 wt%), while maintaining the same as above HA concentration, led to similar release drug release profiles (Figure 6(b)). Moreover, different amounts of HA within the p(HEMA-co-TRIS) silicone hydrogel matrix did not play a role in the TM release profiles ($p > 0.05$), independent of the TM-loaded concentration. It was thus speculated that interactions between the HA and TM could potentially affect the drug release profile, but were not the controlling step for TM release, as in the case of p(DMA-co-TRIS) silicone hydrogels.

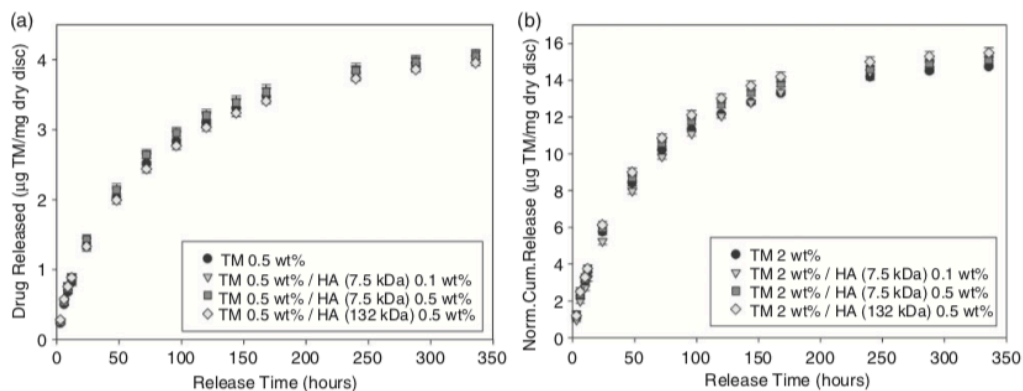


Figure 6. Cumulative release profiles of timolol maleate (TM) loaded at (a) 0.5 wt% and (b) 2 wt% from HA-containing p(HEMA-co-TRIS) materials. The effect of HA loading amount and MW was studied for different drug loadings. Data are shown as $M \pm SD$ ($n = 4$).

In order to further support this idea, the release kinetics of HA (7.5 kDa) was examined and compared to that of TM (Figure 7). According to the results, HA was released significantly faster (within 24 h) than TM through the p(HEMA-co-TRIS) discs, suggesting that the intramolecular binding interactions between the amino, ether, and hydroxyl groups of TM and the hydroxyl groups of HEMA are the predominant factors for drug diffusion in these domains, while the presence of the wetting agent may play a secondary role. Further investigation of the release profile of higher than 7.5 kDa MW of HA would be useful to better understand the release mechanism. However, due to low degree of miscibility and thus low amount of wetting agent released, it was thought that detection of higher MWs of HA from the studied materials would be hard to accomplish.

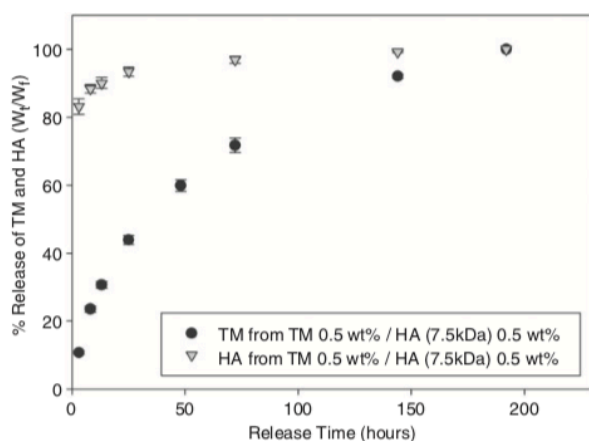


Figure 7. Fractional release profile of both HA and TM from p(HEMA-co-TRIS) hydrogels. The TM or HA release (W_t) divided by the total amount released (W_f), respectively, is plotted as a function of time. Data are shown as $M \pm SD$ ($n = 4$).

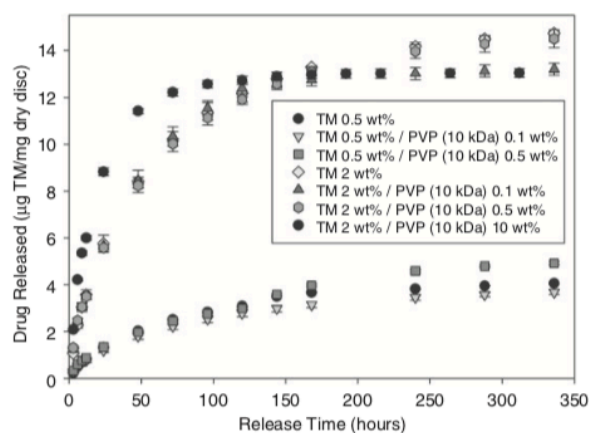


Figure 8. Cumulative release profile of different timolol maleate (TM) loadings from PVP-containing p(HEMA-co-TRIS) materials. Data are shown as $M \pm SD$ ($n = 4$).

Physical entrapment of PVP during synthesis of the p(HEMA-co-TRIS) silicone hydrogels, resulted in TM release rates and kinetics that were dependent on the loading

PVP concentration (Figure 8). In the case of 0.5 wt% TM-loaded discs, an increase in the amount of PVP from 0.1 wt% to 0.5 wt% caused controlled and higher release rates of TM (H/T material 7, $p < 0.0002$) for the same as the control release duration. The observed increase in the TM release rate could be attributed to the reinforcement of the hydrophilic domains through which the drug release occurs, due to the presence of higher amounts of PVP. In addition, PVP may also release faster than the drug, similarly to HA, and thus changes in the porosity and tortuosity of the material upon PVP release may possibly lead to faster diffusion of the drug through the pores of the silicone hydrogel. Therefore, it would be useful to also determine the release profile of PVP from these samples as well. In order to further support the above explanation for the release mechanism, the amount of PVP was increased significantly (20 times to 10 wt%), loaded in concentrations similar to those used in commercial contact lenses. As it would be expected, an initial burst release was observed, with 90% of the drug being released within the first three days compared to seven days for PVP 0.5 wt%, with the remaining TM getting released over the next four days (Figure 8). The burst release observed was attributed to the improved hydrophilicity of the HEMA domains due to the high concentration of PVP, as evidenced also by the increase in the EWC. The physically entrapped wetting agent (PVP) has the potential to act as an osmotic agent, causing a greater gradient of osmotic pressure between the matrix core and the release medium that leads to higher water uptake and thus accelerated drug transport through the silicone hydrogel network.

Overall, it is worth noting that despite the prolonged release duration observed in the examined model hydrogels, the thickness of the discs used is an important parameter in the case of diffusion. The results presented herein are derived from materials that are thicker than commercial contact lenses (1mm vs. 100mm). Considering that in this study the hypothesized release mechanism is diffusion, reducing the thickness of the materials and thus increasing the surface area to volume ratio, would lead to significantly faster release rates. However, other parameters such as the release medium and its volume as well as mixing conditions, the presence of lipids, proteins, and various other components of the tear film as well may have an impact on the drug release profile of such a system. Therefore, it is believed that this system is not necessarily representative of the results that would be obtained from an on-eye contact lens study but provide insight into drug release mechanism. Ultimately, cytotoxicity studies would be necessary to assess the compatibility of the developed materials under in vivo conditions.

Total amount of drug released from p(DMA-co-TRIS) and p(HEMA-co-TRIS) hydrogels with or without wetting agent

Despite mimicking sink conditions for the in vitro release study, by regularly changing the release medium (PBS), the direct entrapment of the wetting agent as well as higher drug loading concentrations during synthesis affected the total amount of drug released. It is important to clarify that the percentage of the total amount of drug release mentioned

herein, refers to the amount of drug released during the monomer extraction procedure and the studied release period in correlation to the drug loading concentration during synthesis. For low drug concentrations (0.5 wt%), 90% of the TM initially added to the model silicone hydrogel controls during synthesis was released from the matrix. However, the amount of nonreleasable drug was found to be a function of initial drug loading as shown in Figure 9.

Contrary to what would be expected, increasing the concentration of the drug added to the silicone hydrogels during synthesis was found to decrease significantly the percentage of the total amount of TM released for both materials ($p < 0.00015$). Overall, p(HEMA-coTRIS) hydrogels released more drug in total than p(DMA-co-TRIS) ($p < 0.002$). The two main differences between these materials are the different degree of hydrophilicity between HEMA and DMA phases as well as the higher TRIS concentration in the case of p(DMA-co-TRIS) hydrogels. Since the materials with the lower TRIS content released more TM, it could be speculated that the unreleased hydrophilic drug is irreversibly trapped into the polymer phase in areas that are not permeated by PBS, such as the hydrophobic crosslinked TRIS domains. This might suggest that there could be a threshold in the drug loading amount in the studied materials above which no further TM could be released, explaining the similarities in the release durations between low and high TM loadings and also supporting the hypothesis that drug release is controlled by the diffusion of TM through the hydrophilic domains of the hydrated material.

Furthermore, for the wetting agent-containing silicone hydrogels examined in this study, the total amount of drug released was found to be directly correlated to the drug release profiles since the release duration remained the same in all cases. As shown in Figure 9, a decrease in the total TM amount released of up to 42% was observed for HA-containing p(DMA-coTRIS) discs (material D/T 4, $p < 0.0002$). The impact of HA was significantly lower in the case of p(HEMAco-TRIS) hydrogels ($p < 0.005$) since more than 74% of the drug initially loaded was released. Since HA was mainly dispersed in the silicone hydrogel matrix due to its low miscibility in the prepolymer mixture, it was thought that the HA concentration was below the percolation threshold and thus some of the HA/TM complex was likely trapped irreversibly in the crosslinked network during synthesis due to physical entrapment in tightly bound regions⁴⁰ and only a small number of the hydrophilic particles were close to pores accessible to PBS, thereby allowing for release. Significantly low concentrations of HA released were previously reported when the wetting agent was physically entrapped solely during synthesis in these materials, with only 4–5% of the HA initially loaded being released.⁸² Additionally, the porosity and the tortuosity of the material would also play a significant role in the HA release as it could be speculated that a high degree of crosslinking could be a reason for hindering the reptation of the long HA polymer chains through the silicone hydrogel matrix. This also explains why the transparency of the HA-loaded materials was slightly improved at the end of the release (data not shown).

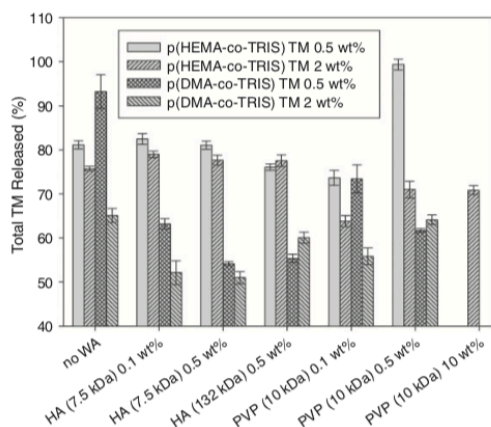


Figure 9. Total amount of TM released from both silicone hydrogel materials, based on the initial concentration loaded, when different amounts and MW of wetting agent (WA) were physically entrapped during silicone hydrogel synthesis. Data are shown as $M \pm SD$ ($n = 4$).

Similar to HA but to a lesser extent, the incorporation of PVP within the hydrogel matrix also reduced the total amount of PVP released ($p < 0.0002$), with the exception of the p(HEMA-co-TRIS) materials loaded with 0.5 wt% TM and 0.5 wt% PVP, where the presence of higher PVP concentrations allowed higher amounts of TM to be released when compared to the control samples ($p < 0.0002$). It is of interest to mention that even though the release rate of TM from p(HEMA-co-TRIS) containing PVP (10 kDa, 10 wt%) was increased significantly, the overall amount of drug released was not increased, but was actually found to be lower than that of the control ($p < 0.005$). In general, the impact of PVP was less significant than that of HA possibly due to the higher degree of solubility of PVP in the hydrophilic monomers of the prepolymer mixture. Decrease in the amount of drug available for release undermines the potential efficacy of contact lenses as drug delivery systems. However, the amount of unreleased drug in the case of direct entrapment in silicone hydrogel materials is still significantly fewer than the amount of drug wastage associated with the instillation of topical formulations – eye drops.

Conclusions

In this work, novel wetting agent-containing model p(DMA-co-TRIS) and p(HEMA-co-TRIS) hydrogels were used to investigate the effect of releasable wetting agents, HA and PVP, on the *in vitro* release of TM in order to evaluate their potential as contact lens-based ocular drug delivery devices. The direct entrapment of low amounts of wetting agent (up to 0.5wt%) led to minimal changes in the water content, with the degree of dispersion and concentration of the wetting agent having a greater impact on the water uptake than its MW. Due to the low degree of miscibility of HA in the monomer mixture, only low concentrations of HA could be incorporated into the model lenses without negatively impacting the transparency. Overall, the developed silicone hydrogels had acceptable properties for contact lens-based applications. Depending on the wetting agent

concentration and the MW, the surface wettability of both examined materials was increased with the incorporation of low MW HA and PVP due to greater chain mobility.

In vitro release studies with TM-containing silicone hydrogels, showed a sustained release profile for extended periods (4–14 days) depending on the composition of the material, with diffusion of the drug through the hydrophilic silicone hydrogel domains and the water-filled pores being the main mechanism of both therapeutic and wetting agent release. The release duration and kinetics of TM were presumably controlled by the water content of the silicone hydrogel, the drug concentration as well as the interactions between the drug and the material's hydrophilic domains. For wetting agent-loaded silicone hydrogels, based on the above results, it is likely that a complex combination of factors including affinity of the drug for the wetting agent, the partitioning of wetting agents within the hydrophilic and hydrophobic phases, the water content of the materials, as well as the MW and concentration of the wetting agent played a significant role in determining the release mechanism and the total amount of drug released. Understanding these interactions, however, is complex and warrants further investigation, but it would give valuable insights into the mechanisms behind controlled drug release from materials such as those studied herein; and it could potentially be used to design systems with appropriate release parameters. Embedding wetting agents into silicone hydrogels may be useful for controlling the release of the desired ocular drug, in particular when it is possible to take advantage of the electrostatic interactions between the therapeutic and the wetting agent. Concluding, the studied novel materials can be used for the design of contact lens-based drug delivery devices for sustained drug release to the anterior segment of the eye while also possibly providing comfort during wear.

Acknowledgements

Funding support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and the 20/20 NSERC Ophthalmic Materials Research Network is gratefully acknowledged.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by Natural Sciences and Engineering Research Council of Canada (NSERC); and the 20/20 NSERC Ophthalmic Materials Research Network.

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