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Atropine and Roscovitine Release from Model Silicone Hydrogels

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ABSTRACT

Purpose. Drug delivery to the anterior eye has a low compliance and results in significant drug losses. In pediatric patients, eye diseases such as myopia and retinoblastoma can potentially be treated pharmacologically, but the risk associated with high drug concentrations coupled with the need for regular dosing limits their effectiveness. The current study examined the feasibility of atropine and roscovitine delivery from model silicone hydrogel materials which could potentially be used to treat myopia and retinoblastoma, respectively.

Methods. Model silicone hydrogel materials that comprised TRIS and DMA were prepared with the drug incorporated during synthesis. Various materials properties, with and without incorporated drug, were investigated including water uptake, water contact angle, and light transmission. Drug release was evaluated under sink conditions into phosphate buffered saline. Results. The results demonstrate that up to 2 wt% of the drugs can be incorporated into model silicone hydrogel materials without adversely affecting critical materials properties such as water uptake, light transmission, and surface hydrophilicity. Equilibrium water content ranged from 15 to 32% and transmission exceeded 89% for materials with at least 70% DMA. Extended release exceeding 14 days was possible with both drugs, with the total amount of drug released from the materials ranging from 16% to over 76%. Although a burst effect was noted, this was thought to be due to surface-bound drug, and therefore storage in an appropriate packaging solution could be used to overcome this if desired.

Conclusions. Silicone hydrogel materials have the potential to deliver drugs for over 2 weeks without compromising lens properties. This could potentially overcome the need for regular drop instillation and allow for the maintenance of drug concentration in the tear film over the period of wear. This represents a potential option for treating a host of ophthalmic disorders in children including myopia and retinoblastoma.

Key Words: silicone hydrogel, pediatric, drug delivery, myopia, retinoblastoma

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The treatment of ocular aliments is commonly achieved through topical eye drops, although many drugs delivered have less than a 5-minute residence time, and thus only 1 to 5% of the drug penetrates ocular tissue.1 The remainder of this drug is cleared from the eye and enters the systemic circulation, which can cause various side effects depending on the nature of the therapeutic. Eye drops also suffer from poor patient compliance, which is problematic in populations such as young children and for long-term treatments such as myopia and glaucoma.2 Therefore, controlled delivery systems that could improve the bioavailability of the therapeutics have been investigated.

Contact lenses have been investigated previously to deliver therapeutics, as they act as a slow, equilibrating reservoir and the prolonged corneal residence time improves bioavailability.2,3 The increased prevalence of silicone hydrogel extended wear lenses in 4 the market has created the option to use contact lenses for continuous drug delivery. While earlier studies focused on conventional daily wear lens materials, the utility of silicone-based materials for drug release has been evaluated in many cases recently, showing significant promise.2,5-23 With silicone-based materials, it is desired to create a drug-eluting contact lens that could be worn for extended periods of time where the release kinetics result in therapeutic concentrations for the wear period recommended by the lens manufacturer, without compromising the optical properties of the contact lens itself. Treatment of diseases in children with such materials would be particularly advantageous, overcoming the need for frequent drop instillation while taking advantage of the fact that younger patients are more likely to be willing adopters of lens technologies. The current study focuses on the use of lenses for the potential treatment of two specific childhood ocular conditions.

Retinoblastoma, an intraocular malignancy affecting about 1 in 20,000 children,24,25 appears as a yellow-white mass in the retina, often surrounded by dilated blood vessels. Mutations on the Rb gene, resulting in a compromised Rb protein, and additional mutations in other regulatory proteins are believed to contribute to the disease.24 CdK inhibitors, such as CYC202 (R-roscovitine), have shown to be potentially effective in preventing retinoblastoma, and treatment with these drugs could block tumor initiation in genetically susceptible populations.26 Treatment with lenses is appealing in this application, as penetration of the globe is prohibited due to fears of tumor seeding through the puncture site while minimizing systemic side effects.

Atropine has been studied since the 1970s as a pharmacologic means to arrest myopia, a much more common condition than retinoblastoma. It is believed that atropine has a biochemical effect on the retina or sclera that causes remodeling of the sclera associated with eye growth,27 thus allowing it to exude an effect on the overgrowth associated with myopia. Although this therapy shows some success, concentrations must be tightly controlled to reduce side effects28 and additional complications, such as growth upon treatment completion,29

limits its effectiveness. Both drugs show heat lability, making them amenable to delivery via a drug delivery system. Furthermore, because CYC202 and atropine, whose similarly sized structures are shown in Fig. 1, are required for use in young, developing children, it is desirable to create a delivery vehicle to reduce side effects by localizing drug delivery while ensuring patient compliance and minimizing invasiveness.

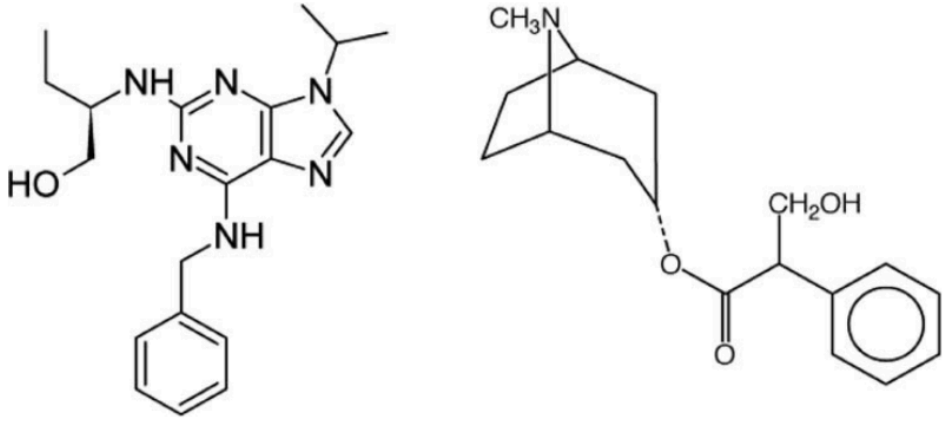

FIGURE 1.
Structure of molecules. CYC202 on left, atropine on right.

Therefore, the aim of this study was to evaluate silicone hydrogel materials as a potential drug delivery method for the delivery of CYC202 and atropine. Our laboratory has previously developed commercially similar model silicone lenses to facilitate the study of both direct drug loading and entrapment by soaking in drug solutions. In the current work, the release parameters of these drugs under various loading conditions were examined while ensuring the essential lens properties of the contact lens are maintained.

MATERIALS AND METHODS

Materials

N,N-Dimethylacrylamide (DMA), ethylene glycol dimethacrylate (EGDMA), and atropine were purchased from Sigma-Aldrich Chemicals (Oakville, ON). CYC202 was purchased from Selleck (Houston, TX). 3-Methacryloxypropyltris(trimethylsiloxy)silane (TRIS) and 3-(3-methacryloxy-2-hydroxypropoxy) propylbis(trimethylsiloxy) methylsilane (modified TRIS or TRIS-OH) were purchased from Gelest Inc. (Morrisville, PA). Irgacure 184 was generously supplied by BASF Corp. Plexiglas G-UVT for casting molds was supplied by Altuglas (Bristol, PA). All other reagents were purchased from Sigma-Aldrich unless otherwise stated.

Hydrogel Synthesis

Model hydrogel lenses used DMA and a silicone monomer, either TRIS or modified TRIS, in various ratios shown in Table 1 as previously described.30 All were initiated with Irgacure 184 (0.1 wt%) and crosslinked using EGDMA (3.3 wt%). Before use, all monomers were passed through inhibitor remover packed columns to ensure the removal of monomethyl ether

hydroquinone (MMEQ). The materials were prepared with or without CYC202 (0.5 wt%) and atropine (0.5 or 2 wt%) during synthesis. No degradation of the drugs due to UV exposure or heat treatment was found when examined using NMR and UV spectrometry. Using material 4 as an example, 0.5 wt% of atropine was dissolved in an 80:20 molar ratio of DMA/TRIS solution containing 3 mol% EGDMA and allowed to mix for at least 5 minutes. Irgacure 184 (0.1 wt%) was dissolved into the formulation then immediately syringed into a UV-transparent acrylic plate mold and polymerized in a 400 W UV chamber (Cure Zone 2 Con-trolcure, Chicago, IL) for 15 minutes. The mold included a 1 mm Teflon spacer. Individual discs were bored to 7.94 mm, except for materials 19 to 21 which required a short hydration period in a phosphate buffered saline (PBS) solution before being cut.

TABLE 1.
Hydrogel compositions evaluated

Material composition	DMA (mol%)	TRIS (mol%)	TRIS-OH (mol%)	Atropine (wt%)	CYC202 (wt%)
1 (80:20 control)	80	20			
2 (80:20-OH control)	80		20		
3 (80:10:10-OH control)	80	10	10		
4 (80:20 low atropine)	80	20		0.5	
5 (80:20-OH low atropine)	80		20	0.5	
6 (80:20 high atropine)	80	20		2	
7 (80:20-OH high atropine)	80		20	2	
8 (80:20 CYC202)	80	20			0.5
9 (80:20-OH CYC202)	80		20		0.5
10 (70:30 control)	70	30			
11 (70:30-OH control)	70		30		
12 (70:30 low atropine)	70	30		0.5	
13 (70:30-OH low atropine)	70		30	0.5	
14 (70:30 high atropine)	70	30		2	
15 (70:30-OH high atropine)	70		30	2	
16 (70:30 CYC202)	70	30		0.5	
17 (70:30-OH CYC202)	70		30	0.5	
18 (50:50 control)	50	50			
19 (50:50 low atropine)	50	50		0.5	
20 (50:50 high atropine)	50	50		2	
21 (50:50 CYC202)	50	50			0.5

Material Characterization

Equilibrium Water Content

The equilibrium water content (EWC) was determined using a mass balance method. The masses of the dry discs (MD) were obtained after drying in a 40 -C for at least 24 hours. These were compared to the hydrated masses (MH), as shown in Equation 1. The hydrated mass was obtained after soaking the discs in a PBS solution for 48 hours. Residual droplets were removed before the masses being examined.

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

Surface Wettability

Surface wettability was assessed using the advancing contact angle using a Kruss DSA Contact Angle Apparatus. Materials were swollen for at least 48 hours and placed flat on a slide. A single

drop of Milli-Q water was placed on the surface, allowing the contact angle to be measured under magnification.

Transmittance

Using light transmittance, as measured by UV-VIS spectrophotometry, the transparency of the hydrogels was assessed. Using a 96-well plate, 5.55 mm discs were hydrated in 100 KL of Milli-Q water for 24 hours and the transmittance was measured from 400 to 700 nm.

Drug Loading, Release, and Analysis

Atropine was directly loaded into the hydrogel materials as shown in Table 1. CYC202 was either directly loaded into the hydrogels or was loaded by soaking using control materials in a 2 mg/mL CYC202 solution, prepared in 50:50 water/methanol. This solvent composition was chosen to overcome the limited solubility of CYC202 in water. Briefly, 7.94 mm control disks were transferred to 1 mL of the uptake solution for 7 days. These were then dried at 40 -C for at least 24 hours before being used for any release experiments. Drug release experiments were completed in 1 mL of PBS (pH 7.4) at 37 -C; to ensure sink conditions, the discs were transferred to fresh PBS at regular intervals, initially at 1, 3, 6, 9, 12, 24, 48, 72, 96, and 120 hours, then at least 24 hours apart at later time points. The drug elution was measured by UV spectrophotometry at 292 nm for CYC202 and by HPLC at 254 nm for atropine. Percent drug release was then calculated as the average amount of drug released at that time point divided by the sum of the drug release at all time points for each material. Results were analyzed statistically using t test with a significance level of 95% or where multiple factors were examined simultaneously. ANOVA with post hoc testing using Tukey analysis was used.

RESULTS AND DISCUSSION

Material Characterization

Equilibrium Water Content

Because water content is often correlated to the on-eye comfort of contact lenses, the EWC of the model lenses were measured and shown in Table 2. All four material formulations were significantly different from each other (p G 0.05). Many of the materials achieved the 20 to 40% EWC range shown by most commercial contact lenses, and these were most closely examined for their drug release profiles.31 Swelling levels lower than 20% would be expected to lead to significant corneal discomfort and therefore not reasonable for the proposed application. Both the incorporation of the modified TRIS and greater DMA content resulted in higher water contents. This was expected, as these materials are more hydrophilic and thus are more likely to retain water in the hydrogel. Not surprisingly, DMA content appears to have a greater impact on the EWC than the modified TRIS material; this is likely due to its stronger hydrophilic character. The 50:50 DMA/TRIS materials exhibited very little swelling, as demonstrated by the low EWC. Although this material was quite stiff and not suitable as a contact lens, it was included to better understand the subsequent release kinetics for these materials and the effect of increased hydrophobic character on release of a hydrophobic drug such as CYC202. The EWC of the materials were not affected by the presence of the drugs. This is likely due to the small amounts of drugs added relative to the bulk composition of the lenses. Based on

these results, the 80:20 materials with both the regular and modified TRIS materials and the 70:30 materials with the modified TRIS were the most promising compositions for modeling the properties of contact lenses.

TABLE 2.
Equilibrium water content values and transmittance data at 600 nm for various material compositions (EWC: n = 3; transmittance: n = 5) (* indicates $p < 0.05$)

Material	Composition (mol%)	Average EWC	Transmittance
1	80:20 DMA/TRIS	27.2 ± 1.4%*	97.0 ± 0.4%
2	80:20 DMA/TRIS-OH	32.5 ± 1.1%	
4	80:20 DMA/TRIS low atropine	27.9 ± 1.5%	96.8 ± 3.4%
6	80:20 DMA/TRIS high atropine	29.2 ± 1.1%	98.0 ± 0.9%
8	80:20 DMA/TRIS CYC202	26.55 ± 0.5%	89.2 ± 7.2%
10	70:30 DMA/TRIS	15.8 ± 1.5%*	
11	70:30 DMA/TRIS-OH	22.1 ± 0.9%*	
18	50:50 DMA/TRIS	3.51 ± 1.1%*	92.9 ± 1.5%
19	50:50 DMA/TRIS low atropine	4.3 ± 1.1%	92.4 ± 2.0%
20	50:50 DMA/TRIS high atropine	4.5 ± 1.9%	97.3 ± 1.4%
21	50:50 DMA/TRIS CYC202	2.8 ± 0.6%	91.7 ± 5.6%

Transparency of Hydrogel

Because high optical transparency is an essential property of a contact lens, it was necessary to determine how the various material compositions and drug loadings affected the light transmittance. As shown in Table 2, all of the materials showed high transmittance at 600 nm, though the control materials with the greater DMA content, and thus the higher EWC, did show a slight improvement. Given the hydrophobic nature of the TRIS materials, it is expected that small, light scattering, silicone-rich domains form in the hydrogels. It is likely that these are smaller in the material that has less silicone. However, it is clear that in both a high silicone instance (50%) and a low silicone instance (20%), the domains are sufficiently small to give over 90% transmittance. Furthermore, the materials tested were approximately 1 mm in thickness. Because commercial contact lenses are much thinner than this, it is expected that these values would improve with a thinner sample, though this was limited by the molds used. Similar to the EWC, the incorporation of the drugs does not significantly affect the transmittance, particularly critical to the use of silicone hydrogel materials for drug release. Because the amount of drug is small and it is fully dissolved in the monomer solution before curing, it is not expected that the drug itself will alter the domain formation. Therefore, it is not expected that the drug incorporation by direct loading would have affected

Equilibrium water content values and transmittance data at 600 nm for various material compositions (EWC: n = 3; transmittance: n = 5) (* indicates p G 0.05)

the transparency.

Surface Wettability

To ensure comfort while blinking and maintain a stable tear film, a contact lens must be highly wettable. Table 3 compares the wettability of various materials, as measured by the advancing contact angle. Although silicones are known to have high contact angles, the incorporation of the DMA is able to decrease these substantially. The incorporation of atropine by direct loading, swelling, or imprinting does not affect the surface wettability. This is expected, as it did not have any impact on the bulk properties of the gel when entrapped during synthesis. This demonstrates that if any atropine is adsorbed to the material during the soaking, it does not have an appreciable influence on the surface wettability.

TABLE 3.

Advancing contact angles on material 1 discs (synthesized without atropine) and material 6 discs (synthesized with atropine), after soaking with 2 mg/mL atropine solution or PBS solution

Synthesis	Soaking	Average value (°)
Material 1	Without atropine (n = 3)	64.7 ± 3.0
	With atropine (n = 4)	69.2 ± 7.9
Material 6	Without atropine (n = 3)	59.8 ± 8.9
	With atropine (n = 4)	70.6 ± 11.6

Drug Release-Direct Loading

The drug release profiles from materials that incorporated the therapeutics during synthesis are shown in Figs. 2, 3, and 4, including the release of 2% atropine, 0.5% atropine, and 0.5% CYC202, respectively, from both the 70:30 and 80:20 DMA/TR IS or DMA/TRIS-OH materials. Although drug release studies were completed using the 50:50 material composition, given the low swelling of the material (less than 20%), these were determined to be less appropriate for a contact lens application and thus the profiles are not shown.

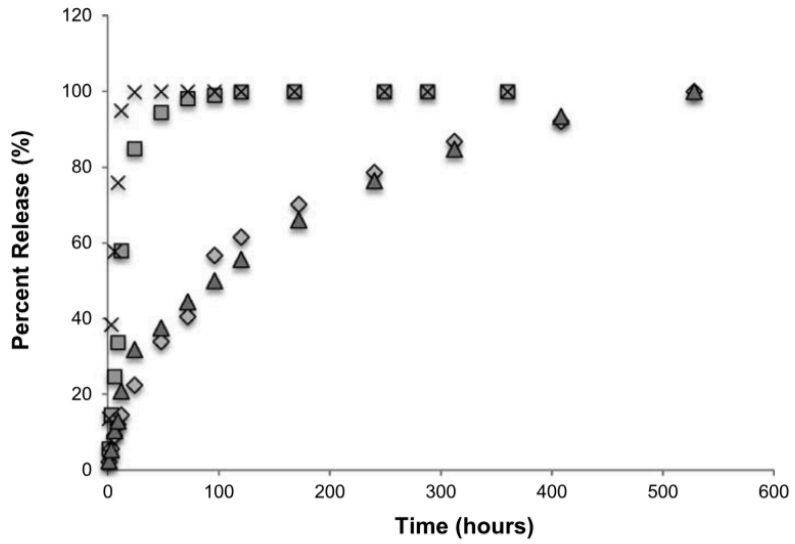

FIGURE 2.

Atropine release from various materials: square—material 4, X—material 5, diamond—material 12, triangle—material 13.

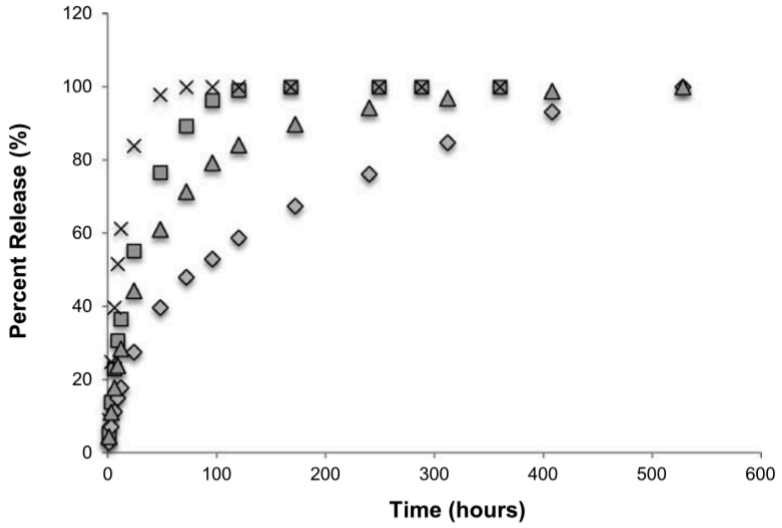

FIGURE 3.
Atropine release from various materials: square—material 6, X—material 7, diamond—material 14, triangle—material 15.

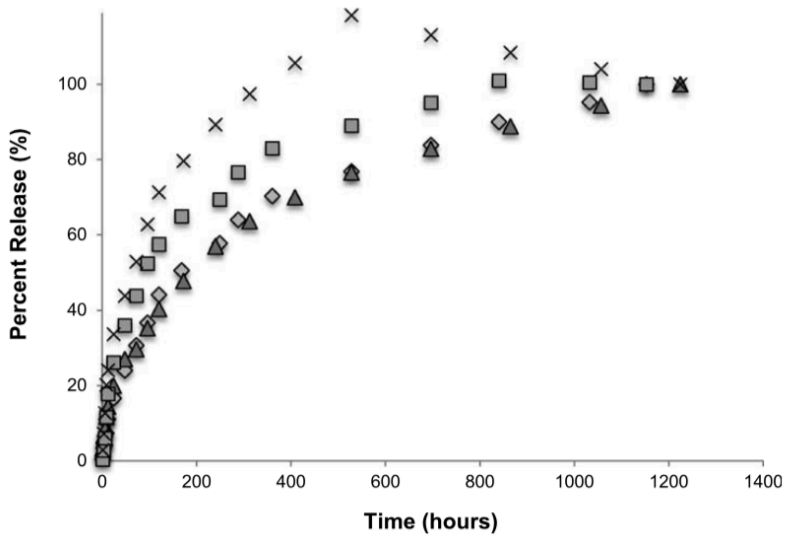

FIGURE 4.
CYC202 release from various materials: diamond—material 8, square—material 9, triangle—material 16, X—material 17.

With atropine, the materials with the greater DMA (80 mol%) released the atropine more quickly, regardless of the loading amounts. However, all materials with this high DMA composition show a large burst release, with most of the drug being released in the first 2 to 4 days depending on the amount initially loaded. However, because this is dependent on the loading, it is possible that this could be extended out slightly further with an even greater loading.

Furthermore, the material loading also has an effect on the cumulative amount of drug released, as expected. The greater the amount of drug loaded, the greater the amount of drug release. As shown in Table 4, most, if not all, of the drug is released from these materials with a reasonable water content. Due to the difficulty of measuring small amounts of drug, it is expected that the materials with higher than 100% of drug are a product of slightly higher drug

loading during initial incorporation. However, with the lower DMA content (50 mol%), it is clear that much of the drug remains in the material. This is expected, as atropine is likely trapped in the silicone domains of the materials formed during synthesis. Although these domains are small, they likely have limited swelling, and the drug is therefore required to diffuse through this domain, into the water channels in the other domains, and then out of the material. This is highly correlated to the swelling, as the materials that showed the least swelling also exhibited the greatest amount of residual drug in the matrix. For the materials with greater swelling, because atropine displays only moderately hydrophobic behavior and has some solubility in water, compounded with its lack of functional groups that interact with the silicone phase, it is likely that most of the drug will partition into the more hydrophilic phases in the presence of swelling.

TABLE 4.
Total amount of drug release from various materials based on anticipated loading (n = 4)

Material	Amount released
4	122%
5	95%
6	135%
7	102%
8	28%
9	24%
12	107%
13	117%
14	100%
15	121%
16	24%
17	16%
19	33%
20	33%
21	17%

Therefore, although increasing the loading amount would result in a more extended release profile, there would also be a greater amount of drug released, which could be problematic for atropine. Specifically, there are many side effects associated with atropine, such as light sensitivity from pupil dilation,28 and these would likely be worse from higher release amounts of atropine. It has also been shown that only a small amount of atropine is required to be effective for treatment in many instances, so lower release amounts are likely desirable.32 The incorporation of modified TRIS increased the release rate in the higher loading amount, most pronounced in the materials with the greater TRIS content, but showed no significant effect at lower loading. It is likely that at higher DMA compositions, this hydrophilic phase dictates the release profile, so the slightly more hydrophilic TRIS does not have a large impact. However, at the lower DMA levels, the TRIS component has a greater influence on the release parameters, and thus the release rate is greater with the modified TRIS. Because there is more drug present in this phase at the higher loading, it is likely able to exert a more appreciable change on the release rate.

To effectively treat ocular conditions, a controlled, sustained release of therapeutics is required from the contact lens material. Extended-wear lenses, such as silicone hydrogels, can be worn for up to 30 days continuously, although this depends on the manufacturer's recommendation.

It has been suggested that to improve patient compliance, regular intervals are required, such as changing the lenses every week or every 2 weeks. Considering the materials with the most appropriate EWC, sustained drug release is possible for 1 week at the lower loading and over 2 weeks at the higher loading for atropine, which is likely appropriate for use in children. However, materials 12 and 14 (70:30 with the modified TRIS) provided the best release profile with the appropriate material swelling, as the release is the most gradual and consistent over the duration of the release, although there was a still a burst release with both of these materials. This would mean that the amount of drug released in the first couple of days of wear would be greater than that at the end of the wear time, which is not desirable. It may be possible to modulate this during the packaging of the material, as it would likely experience some drug release during that time as it equilibrates with the packing solution.

Figure 4 shows the release for CYC202 from the various materials. Similar to atropine, the release is controlled by the rate diffusion of the drug. It appears that the material composition has less of an influence on the profile of the drug release here than with atropine, as the modified materials consistently released faster, but the profiles were quite similar between for a given TRIS monomer. This is likely due to the lower solubility of CYC202 in water and that many aromatic rings and few hydrophilic moieties are not likely to repel the silicone phase. Specifically, the modified TRIS materials have a higher water content, which likely exposes more drug to water channels. Given the limited solubility of the drug in water, it is likely that these internal water channels become quickly saturated, so the drug release is limited by the time to diffuse through these paths. Greater material water content facilitates greater drug diffusion. This is clear from the long release profiles seen with CYC202, and the amount of drug which remains in the matrix, as shown in Table 4. Similar to atropine, this appears to depend on the swelling of the material, though there is clearly a drug dependency, as more CYC202 is retained in the matrix than atropine for a given material composition.

Similar to atropine, only a small amount of CYC202 is expected to be required to exhibit its therapeutic effect.26 It is expected that the 30 to 55 Kg released from these 40 mg materials overall will be sufficient for this application, though in vivo models are required to confirm this. Therefore, a lower loading with a slow release profile is ideal. Unlike atropine, however, the treatment regime with CYC202 is expected to be short for retinoblastoma. Therefore, having a burst release, as seen by all of the materials examined, may be beneficial. Depending on the treatment time required, the most appropriate material composition could be selected. This is particularly important, as these materials showed release in excess of 30 days, which would be longer than any lens is recommended for wear. However, for both of these systems, it is important to note that these materials are thicker than commercial lenses. Therefore, thinner discs are expected to increase the release rate, as it is believed this is controlled by diffusion. However, other factors such as the release medium, mixing, and, most importantly, the release volume may also slow these release parameters relative to the experimental conditions. Therefore, this would require further testing in an in vivo system.

Drug Release-Soaked Loading

Control materials 1 to 3 were explored to determine the extent to which the drug release could be tailored based on the material composition, particularly when the materials are soaked in a drug solution to load. Although materials that incorporated the therapeutics during synthesis were able to load a greater amount of drug than those loaded by soaking, there may be manufacturing difficulties associated with a direct loading technique, particularly as these lens would likely require an extraction step to remove unreacted monomers. These materials were loaded in a methanol/water blend to increase the swelling of the material during loading and allow a greater loading concentration, as the solubility of CYC202 in water is quite limited. Although it was not possible to precisely measure the uptake of the materials, it is expected that more drug remains entrapped in the material when loading with a methanol blend than just water. This is likely due to the increased swelling of the silicone domains in methanol, where the drug to freely enters and becomes trapped after drying. Because these domains experience much less swelling in water alone, this drug is not able to access water channels to dissolve and be subsequently released.

Figure 5 shows that, using this loading technique, the release of CYC202 is possible for over 2 weeks. There is a similar trend with the soak-loaded release profiles. The incorporation of only 10 mol% modified TRIS does not appear to affect the uptake and subsequent release profile, whereas the incorporation of 20 mol% has a great impact. When the kinetics of the soaked release profile are examined over a month, they are very similar. However, their cumulative releases do show different total amounts of drug release. This could be due to differences in the uptake properties of the material during the soaking or the difference in the swelling of the material. Although it is unclear what concentrations would be required in the posterior of the eye to treat the diseased condition, this profile is likely tailorable based on the loading concentrations of the drugs.

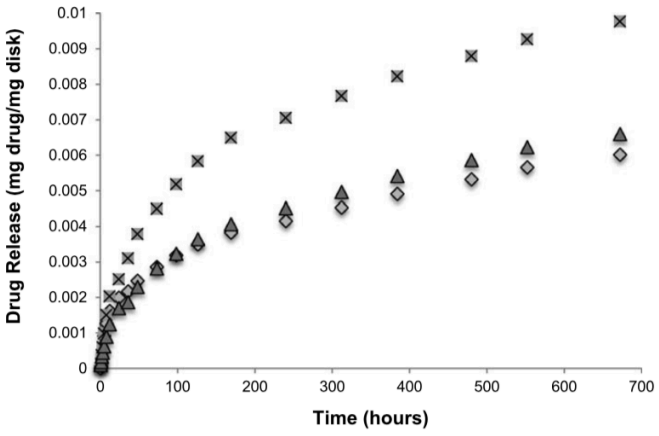

FIGURE 5.
CYC202 release from various materials soak loaded in 2 mg/mL 50:50 H_2O/methanol solution: diamond—material 1, square—material 2, triangle—material 3.

Of note, although the thickness of the materials is greater than that of typical contact lens materials, the overall fraction of drug released is not expected to be different than would be expected for thinner lens materials with similar loading. The surface area of edge is

substantially less than the surface area of the faces of the device meaning that edge effects can be neglected in both cases. However, the total amount of drug released is expected to be lower because the total amount of drug loaded is greater than would be the case with thinner materials.

CONCLUSIONS

To overcome compliance issues and minimize the need for frequent instillation of high concentrations of drug, model silicone hydrogel materials were examined for their potential to deliver atropine and CYC202. From these studies, it is clear that the drug releases can be altered based on both the monomer content and ratio of hydrophobic to hydrophilic components, meaning that the composition of the lens material will likely have to be tailored to some extent to obtain the desired release kinetics. However, the release was shown to also vary based on structure and nature of the therapeutic itself, as well as its loading concentration. Sufficient drug loading is possible from the initial manufacture of the lenses and can be varied to deliver an ideal cumulative release. It is also possible to load the drugs after manufacture by soaking and achieve sustained release profiles. These materials present a potential method to deliver both CYC202 and atropine that would be appropriate for use with children.

ACKNOWLEDGMENTS

The authors would like to acknowledge the financial support of the 20/20 NSERC Ophthalmic Materials Research Network.

Received April 9, 2015; accepted November 6, 2015.

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