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Nanoparticle-loaded UV-blocking contact lenses

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ABSTRACT: We have developed a novel approach of incorporating UV-blocking features into contact lenses by dispersing nanoparticles into the lenses. The nanoparticles are prepared by controlling polymerization dynamics using chain terminating and chain transfer agents. A theoretical model is developed to predict the effect of various formulation parameters on the particle size. This approach can produce UV-blocking nanoparticles of controlled size below 10 nm in diameter with close to 10% conversion. The model predictions for the mean size are in reasonable agreement with the experimental data. The nanoparticles are cleaned and loaded in silicone hydrogel contact lenses by soaking the lenses in a solution of particles in ethanol and acetone. Lenses loaded with about 6% particles w/w in the hydrated lens block sufficient UV light to be classified as Class 1 blockers. The nanoparticles are retained in the lens during soaking in phosphate buffered saline (PBS) and are stable to sterilization by autoclaving. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42495.

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INTRODUCTION

Exposure to ultraviolet radiation from the sun is known to have the potential to cause significant damage to the body, including skin irritation and burning to more serious diseases such as skin cancer. Environmental damage to the ozone layer has further exacerbated the damaging potential of exposure to the sun and thus it has become common practice to use UV-blocking lotions and creams to minimize the damage from sun exposure. While the general population is well aware of the potential for damage to the skin from UV radiation, there is less awareness of the possibility of damage to other organs, particularly to the eyes. UV radiation can cause mild irritation and a foreign body sensation in the eyes, and regular exposure can cause far more serious problems such as snow blindness, cataracts (which is the leading cause of blindness in the world), photokeratitis, erythema of the eyelid, solar retinopathy, retinal damage, and rarely cancer of the cornea or conjunctiva.[1–4] Damage from UV radiation is likely due to the creation of free radicals that can cause protein modification and lipid peroxidation.[5] The intraocular lens (IOL) in an adult eye filters out a majority of the UV light, but the lens of an infant's eye transmits nearly all of the UV light. The UV transmittance decreases with age and by the age of 25, the lens absorbs UV light almost completely.[5] The accumulated exposure to UV light before the age of 25 could cause significant retinal damage.[5] The potential for retinal damage due to UV exposure is even higher in Aphakic patients, i.e., patients who have lost their natural IOL.

Exposure of the ocular tissue to UV radiation can be minimized by wearing glasses that block UV light. The extent of blocking, however, depends on the type and design of the lenses. Most styles of sunglasses do not offer complete protection from UV radiation because UV light can reach the eyes through the top, bottom, and sides of the glasses. The limitations of sun glasses could be overcome by wearing UV-blocking contact lenses as contact lenses cover the entire cornea and thus can provide protection from light at all angles.[5–7]

Currently, the U.S. Food and Drug administration (FDA) has established standards for UV-blocking contact lenses based on those set by the American National Standards Institute (ANSI). Based on these standards, UV-blocking contact lenses have been classified into two categories (Class 1 and Class 2) depending on the extent of the protection. Class 1 lenses must block more than 90% of UVA (316–380 nm) and 99% of UVB (280–315 nm) radiation. The lenses in the Class 2 category must block more than 70% of UVA and 95% of UVB radiation. The health benefits of UV-blocking contact lenses has been well recognized, yet the only contact lenses classified as Class 1 blocking lenses are ACUVUE® brand lenses.[8,9]

UV-blocking features are typically incorporated into contact lenses by adding a UV-absorbing molecule to the lens composition. The absorption spectrum of a molecule depends on the molecular structure and a large number of molecules are known in literature to absorb UV radiation.[10,11] Also, a number of patents have been filed and issued for UV-blocking contact

lenses.[12–17] These patents focus on novel UV absorbers or methods of producing a contact lens containing the absorbers. In all applications, the UV-absorbing molecules are copolymerized with the polymer(s) used to manufacture the lens to eliminate any possibility of leaching of the UV-blocking agent either during processing steps after polymerization or during lens wear. The major challenges in preparing a contact lens loaded with the UV blocker are: (i) contact lenses are typically polymerized in molds by UV light, which gets absorbed by the UV-blocking agent making the process of lens curing longer or requiring increased light intensity. Even with increased duration or light intensity, the properties of the final lens might be significantly compromised; (ii) the presence of the UV-blocking agent could also impact the kinetics of polymerization particularly if the molecule is loaded in appreciable amounts. Furthermore, the requirement of copolymerization of the UV-blocking agent with the lens matrix limits the choice of molecules, and molecules that have the copolymerization feature may not be the most efficient UV absorbers.

We have developed a unique approach for incorporating UV-blocking feature into the contact lenses which minimizes or eliminates some of the problems of the current state of the art approaches. Our approach is based on incorporating UV-blocking molecules in nanoparticles and dispersing the nanoparticles into contact lenses. The particles can be loaded into the lenses in a medium that significantly swells the lens to increase the pore size, allowing the particles to diffuse into the lenses. After particle loading, the lenses can be soaked in PBS to extract the loading medium and collapse the pores in the lens matrix trapping the particles. The nanoparticles are not chemically linked to the lens, but instead are trapped due to having a larger diameter than the pore size of the lens which prevents diffusion of the particles. This approach of loading the UV blockers post lens curing eliminates the problems associated with curing lens compositions containing the UV blockers.

We used a mixture of two UV-blocking molecules in our formulations, 1,3-diphenylpropane-1,3-dione (dibenzoyl methane; DBM) and 2-(4-Benzoyl-3-hydroxyphenoxy)ethyl acrylate (BHPEA), to maximize the blocking of both UVA and UVB radiation. The structures of DBM and BHPEA are shown in Figure 1(a) and 1(b), respectively. DBM is the precursor of an FDA-approved ingredient of sunscreens, while BHPEA is a polymerizable derivative of oxybenzone [Figure 1(c)], which is also approved by the FDA, and widely used in sunscreen applications. The UV-blocking particles are prepared by free radical polymerization of the mixture of the two UV-blocking molecules with a crosslinker and a chain transfer agent (CTA). The presence of the CTA and DBM, which acts as a chain termination agent, facilitates production of sub 10 nm size particles. Commercial contact lenses loaded with the nanoparticles are shown to be Class 1 blockers.

MATERIALS AND METHODS

Materials

The crosslinker propoxylated glyceryl triacrylate (PGT) was obtained from Sartomer (Exton, PA). The CTA isooctyl 3-mercaptopropionate (IMP), the UV blockers dibenzoylmethane (DBM) and BHPEA, and the free radical initiator benzoyl peroxide (BP) were purchased from Sigma-Aldrich (St. Louis, MO). The solvents ethanol and acetone were supplied by Fisher Scientific (Pittsburgh, PA). The O_2 Optix commercial lenses were gifted by Alcon, Ciba Vision (Des Plaines, IL).

Absorption Spectra of DBM and BHPEA

The UV-blocking potential of DBM and BHPEA was characterized by measuring the absorbance spectra in a UV–Vis spectrophotometer. Both molecules have limited solubility in water, so the absorbance spectra was first measured in ethanol at a concentration of 0.02 mg/mL and then in water at a low concentration of 0.001 mg/mL. The absorbance spectra [$A(\lambda)$] was used to calculate the molar absorptivity (ε) in both mediums using the Beer Lambert law, i.e.,

$$A = \varepsilon c l \quad (1)$$

where $l = 1$ cm is the path length and c is the concentration in solution.

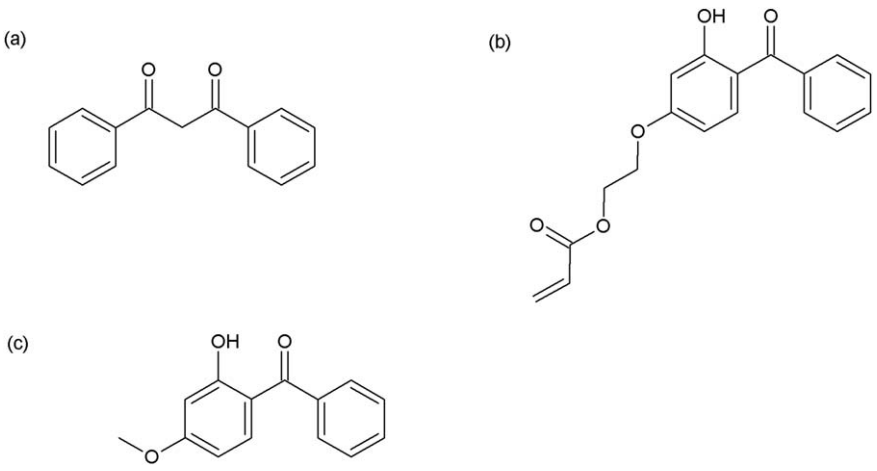

Figure 1. Structure of the UV-blocking molecules: (a) 1,3-diphenylpropane-1,3-dione also known as dibenzoyl methane, (b) 2-(4-Benzoyl-3-hydroxyphenoxy)ethyl acrylate also known as 2-Hydroxy-4-acryloylethoxy benzophenone, and (c) oxybenzone.

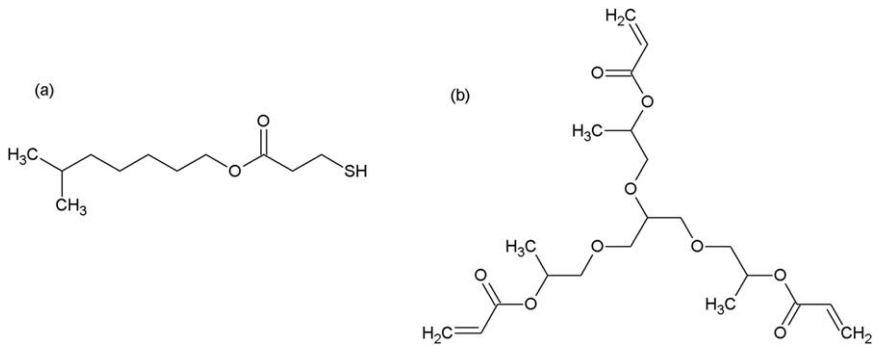

Figure 2. Structures of (a) the chain transfer agent isooctyl 3-mercaptopropionate and (b) the try vinyl monomer propoxylated glyceryl triacrylate.

Preparation of UV-Blocking Nanoparticles

Particle Formation by Thermal Polymerization. The nanoparticles were prepared by bulk polymerization of a mixture of BHPEA and DBM with a tri-vinyl monomer PGT. To prevent macrogelation and achieve small particle size, a CTA IMP was also included in the polymerization mixture. The structures of PGT and CTA are shown in Figure 2. The particles were prepared by thermal polymerization of the mixture using 0.1% by weight BP as the initiator. As an example, a mixture of 40% PGT, 40% CTA, 10% BHPEA, and 10% DBM was mixed, followed by the addition of 0.1% initiator BP. Nitrogen was then bubbled through the mixture for 15 min to remove any dissolved oxygen followed by heating to 80°C for 4 h.

Dialysis of the Polymerized Solution to Remove the Unreacted Components. The polymerized solution contains nanoparticles as well as unreacted components and small polymer chains. Incorporation of the unreacted components and the small chains into the contact lenses is undesirable due to the potential for elution during wear and so two stages of dialysis were used to remove the undesired components from the solution. In the first dialysis step, the polymerized solution was placed inside a dialysis bag with 12,000 Da cutoff, and the bag was submerged in a mixture of 75% ethanol and 25% acetone for a period of 16 h. After the 16 h, the solution inside the bag was withdrawn and placed into a fresh dialysis bag for the second stage. In each stage, the volume of the outer solution was 20 times the volume of the liquid inside the bag.

Determining Particle Size. After dialysis, particle diameters were determined using Dynamic Light Scattering (Malvern Zetasizer Nano). Solutions were diluted in ethanol by a factor of 10 and volume distributions were used. Particles solutions were also examined by transmission electron microscopy (TEM) analysis to verify these particle sizes. After the dialysis step, 2 μL of the particle solutions in 75% ethanol and 25% acetone were placed on formvar carbon films on 200 mesh nickel grids. After drying, the particles were stained with osmium tetroxide so as to be visible during TEM analysis. TEM analysis was performed on the stained particles using a Hitachi H-7000 TEM. Particle diameters were estimated from the images using the ImageJ software.

Determining the Conversion of the Particles. At the end of the 16 h duration in the second stage of the dialysis, the absorbance spectra of the outer solution (A_o) and the solution in the bag (A_i) were measured to determine the composition of the particles and the overall conversion by following the process described below.

The absorbance spectra can be expressed as a sum of the absorbance from various components in the solution, i.e.,

$$A(\lambda)=(\sum \varepsilon_i c_i)l \tag{2}$$

where ε_i and c_i are the molar absorptivity and concentration of the ith component, respectively, l is the path length, and the sum is carried over all the components in the solution. Due to the very high absorbance from BHPEA and DBM, we can neglect the absorbance contributions from all other components. Since the molar absorptivity of both BHPEA and DBM are measured a priori (Figure 3) and l is fixed at 1 cm, the absorbance spectra depend only on the concentrations of BHPEA and DBM, i.e.,

$$A(\lambda)=(\varepsilon_{DBM}c_{DBM}+\varepsilon_{BHPEA}c_{BHPEA})l \tag{3}$$

We determine the unknown concentrations by a least square fit between the measured absorbance and the absorbance based on the above equation for wavelengths ranging from 250 to 350 nm. The concentration of both BHPEA and DBM were determined in the solution from the dialysis bag and that from the dialysate, i.e., the outer solution. The dialysis bag retains most of the nanoparticles but allows the concentration of the unreacted components to equilibrate in the inner and outer solutions. Thus the concentrations of DBM and BHPEA are higher in the solution in the bag, and the difference between the inside and the outside concentrations represents the nanoparticle-incorporated concentration of the components. The concentrations of the nanoparticle-incorporated DBM and BHPEA were then used to determine the conversion of both components. The solution from inside the bag was also used for measuring the particle size distribution by dynamic light scattering.

Determining Composition of the Particles. Composition of the nanoparticles was determined by taking 2 mL of select particle formulations that had been dialyzed and measuring the concentration of UV-blocking components in the solution using UV–Vis spectrophotometry as discussed above. The ethanol and acetone were then evaporated and the pure particle mass was measured. Using the concentration and volume measurements

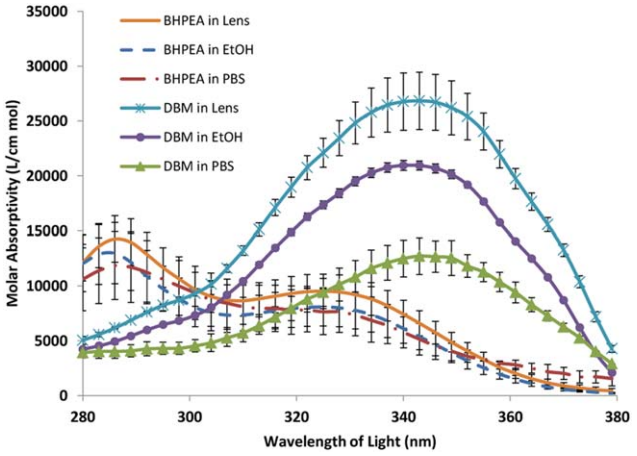

Figure 3. Molar absorptivities of DBM and BHPEA in different environments. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

gives the total mass of UV-blocking components which can be used with the total mass to determine the fraction of these components in the nanoparticles.

Loading UV-Blocking Nanoparticles into Preformed Contact Lenses

After the second dialysis stage, the nanoparticle solution was evaporated to obtain the nanoparticles which were then dispersed in a 75 : 25 mix of ethanol and acetone at various loadings ranging from about 0.5 to 3% (w/v) of the UV-blocking material. The exact com positions of the solutions used in the lens loading are listed in Table II. Previous groups have shown that soaking a contact lens in ethanol or acetone swells the lens to from 1.5 to 2 times its original size.[18] To load the nanoparticles, O_2 Optix contact lenses with a −3.00 diopter power were soaked in 1.5 mL solution of 75 : 25 ethanol and acetone-containing particles for a period of 5 min, which was determined to be sufficient for complete swelling of the lens in the solution. After the 5 min soak, the lenses were withdrawn, rinsed in pure acetone for very short time to remove any surface deposited particles, and then submerged in DI water for further use.

Characterization of Contact Lenses Containing UV-Blocking Nanoparticles

Measuring the UV-Blocking Properties of the Lens. The transmittance of the nanoparticle-laden lenses was measured using a UV–Vis spectrophotometer (Thermospectronic Genesys 10 UV). The lenses were hydrated and then mounted on the outer surface of a quartz cuvette. The cuvette was placed in the spectrophotometer and the transmittance was measured from 280 nm wavelength to 380 nm. Since the transmittance of the lens depends on the thickness, the thickness profile was measured along the radius. For all transmittance measurements, the lenses were positioned in the cuvette such that the light beam passed through the lens at a radial location half way in between the center and the periphery, where the thickness was measured to be 130 μm. Previous work has shown that the thickness of the lens through which the beam travels can affect the UV-blocking properties of the lens.[19] Therefore, every effort was made to ensure that the contact lenses were measured at the same point for every run. The transmittance spectrum was used to calculate average blocking in UVA and UVB range. For the UVA range, average blocking was determined from the range 316–380 nm and the average blocking for UVB was determined from the range 280–316 nm.

Determining the Concentration of DBM and BHPEA Loaded in the Lens. The transmittance spectra was converted to the absorbance spectra

$$A = -\log_{10}\left(\frac{T}{100}\right) \tag{4}$$

and the spectra was then fitted to eq. (3) by a least square fit to determine the concentration of DBM and BHPEA in the lens. The molar absorptivity of a component is sensitive to the environment, so it may change on loading of the molecules in the lens. To obtain the molar absorptivity of DBM in the lens, a contact lens was soaked in a solution of DBM in ethanol at a concentration of 0.2 mg/mL. The absorption spectrum of the lens was measured before and after soaking and the lens was then soaked in ethanol to extract the loaded DBM. By measuring the concentration of DBM in the ethanol, we calculated the mass of DBM extracted, and that was used for calculating the concentration of DBM in the lens. By using the measured absorbance and the calculated concentration, we determined the molar absorptivity of DBM in the lens by using the Beer Lambert law with a path length of 130 μm. The molar absorptivity of BHPEA in the lens was measured by the same approach. By using the molar absorptivities and fitting the absorbance from the particle-loaded lenses to eq. (3), we determined the concentration of BHPEA and DBM loaded in the lens. To validate this result, the particle-loaded lenses were soaked in ethanol to extract the UV-blocking molecules, and the concentration of DBM and BHPEA was determined in ethanol by measuring the absorbance spectra. The calculated concentration in ethanol was then used to calculate the concentration in the lens.

Release of the UV-Blocking Molecules in PBS from the Particle-Loaded Lenses

The nanoparticles were dialyzed to minimize the concentration of monomeric DBM and BHPEA to avoid toxic effects from diffusion of these components into the eyes. To test if there is significant release of residual monomeric UV-blocking molecules in the loaded lenses, the lenses were soaked in 3 mL of PBS for 24 h. The concentrations of the UV blockers in PBS were determined using UV–Vis spectrophotometry. Also, the release medium was tested for presence of particles by DLS.

Effect of Sterilization and UV Exposure

Contact lenses are sterilized by autoclaving, which could potentially impact the UV absorbance of the nanoparticles. To test the effect of this sterilization on UV blocking, the particle-loaded lenses were placed in DI water and allowed to equilibrate with the solution for 24 h. The samples were then autoclaved with a 25 min sterilization time followed by a slow exhaust. The UV absorbance of the lenses was measured before and after the exposure to determine any changes in the absorbance.

In addition, it is important that the UV-blocking capabilities of the contact lenses remain after exposure to UV light. In order to ensure this, nanoparticle-loaded lenses were exposed placed in DI water and exposed to UV light for 12 h using a UVB

Transilluminator (UVB-10, ULTRA·LUM, INC, Carson, CA, USA). The intensity of light was measured using a light meter (Sper Scientific light meter, Scottsdale, AZ) and compared to intensity measurements of direct sunlight at noon on a clear day in Florida. The transilluminator had an intensity of 16.50 mW/cm^2 with a sharp peak at 310 nm, while the sunlight showed an intensity of 13–14 mW/cm^2 in the range of 280–400 nm. The intensity of the direct sunlight decreased significantly to 1 mW/cm^2 when in the shade or under cloudy conditions. These values are consistent with those published in the literature.[20,21] The UV transmittance was measured before and after to determine the effect this exposure had on the UV-blocking properties. Formulation F1 was used for both the sterilization and the UV exposure studies.

RESULTS AND DISCUSSION

Molar Absorptivity of the UV-Blocking Molecules

Figure 3 shows the molar absorptivities of DBM and BHPEA in PBS, ethanol, and in the hydrated contact lenses. The peak absorption of DBM is in the UVA range while that of BHPEA is in the UVB range, thereby allowing broadband protection from the mixture. The absorbance spectra of BHPEA is relatively similar in PBS, ethanol, and in the lens, but the DBM spectra changes significantly with an increased absorptivity in the lens compared to both PBS and ethanol. Overall, DBM is a much better UV blocker compared to BHPEA and additionally its absorptivity increases on loading in the lens, so a much lower concentration of DBM is required in the lenses compared to the concentration of BHPEA. DBM is very hydrophobic and it could potentially partition in the silicon-rich phase of the contact lenses, leading to an increased molar absorptivity.

Particle Formation Process

Mechanisms. Nano or micron sized polymeric particles (nanogels or microgels) can be produced by solution or bulk polymerization of a monomer and avoiding bulk gelation can be achieved by using dilute monomer solutions.[22–25] Additionally, macrogelation can be prevented by including CTAs into the formulation.[26–30] In the presence of a CTA, free radical polymerization progresses normally, except that a growing chain can be capped by the train transfer agent followed by the release of a free radical leaving group, which can then initiate a new chain.

Our formulation for the polymerization includes BHPEA and PGT as the monomers, IMP as the CTA, and BP as the thermal initiator. Additionally, DBM was included in the formulation because it can also reduce the particle size by acting as a chain terminating agent. DBM has the added benefit of being an effective UVA absorber. The thermal initiation creates free radicals that initiate polymer chains by reacting with the vinyl groups in BHPEA and PGT. Since PGT has three vinyl groups, the growing chains are crosslinked leading to formation of nanogels as opposed to long-chain polymers. The CTA can also react with the active ends of chains to terminate the reaction and in turn produce a leaving group that can initiate another chain. The mechanism of the reaction of IMP (CTA) with an active vinyl group involving the chain termination and initiation of another chain is shown in Figure 4(a). DBM also caps the growing chains as shown in Figure 4(b), but the activity of the leaving group is much smaller compared to that of other active molecules, and thus DBM acts more as a chain termination agent. The leaving group of DBM [Figure 4(b)] is the UV-absorbing group, so the only mechanism for incorporation of the UV blocking from the DBM is the initiation of another chain by the leaving group. Due to the low activity of the leaving group of DBM, only a small fraction is incorporated into the particles. The reaction of the active groups on the surface of a nanogel with BHPEA or PGT leads to growth but the reaction with either CTA or DBM leads to termination. After a majority of the active groups on the surface of a particle are capped, the nanogels stop growing. Thus, the particle size can essentially be controlled by the changing the fraction of chain transfer or termination agents in the formulation.

Particle Size Distribution. We prepared several polymerization mixtures by varying the fractions of DBM, CTA, and PGT while keeping BHPEA fractions fixed at 10%. The formulations were polymerized by thermal polymerization and the particle size distributions in the polymerized solutions were measured by dynamic light scattering. The size distributions are plotted in Figure. Each of the three figures shows the distributions for a fixed fraction of DBM and varying fractions of the CTA. Figure 5 shows the profiles for CTA concentrations ranging from 10 to 40% with a DBM concentration of 10%. The size distributions are broad for CTA fractions of 10–30% and shift to smaller sizes with an increasing concentration of CTA. On increasing the CTA fraction to 40%, the distribution becomes narrower with a mean size of about 3 nm. The results in Figure 5(b) also show that for DBM concentration of 5%, increasing the concentration of CTA again decreases the particle size. Also, increasing the CTA concentration to above 25% results in a relatively narrow distribution. Finally, for 1% DBM, the distribution is broad with a mean size >10 nm for CTA concentration of 40%. The data in Figure 5 proves that increasing the concentration of the CTA decreases the particle size and narrows the size distribution, and additionally, inclusion of DBM also decreases the particle size.

TEM Imaging of Particles. TEM images were collected to verify the size results obtained from DLS measurements and to verify the formation of particles. Formulation F3 was used for the analysis. These images are shown in Figure 6. The average particle diameter from these images is 4.57 ± 1.13 nm, which compares well to the particle diameters determined by DLS for the sample which averaged 4.09 ± 0.16 nm for the sample used for the TEM analysis. Figure 7 shows the comparison for the distribution of particle sizes. The image indicates that the DLS measurements tend to underestimate the size of the nanoparticles, but this effect is not significant and the DLS measurements should give a good estimate for the particle size distributions of the particle formulations.

Conversion. For a few selected compositions, the polymerized solution was dialyzed twice to determine the concentrations of polymerized DBM and BHPEA. These compositions are listed in Table I along with the mean particle size and the conversion of BHPEA and DBM in the reaction. As discussed earlier, the mechanisms of DBM incorporation are based on the reaction of

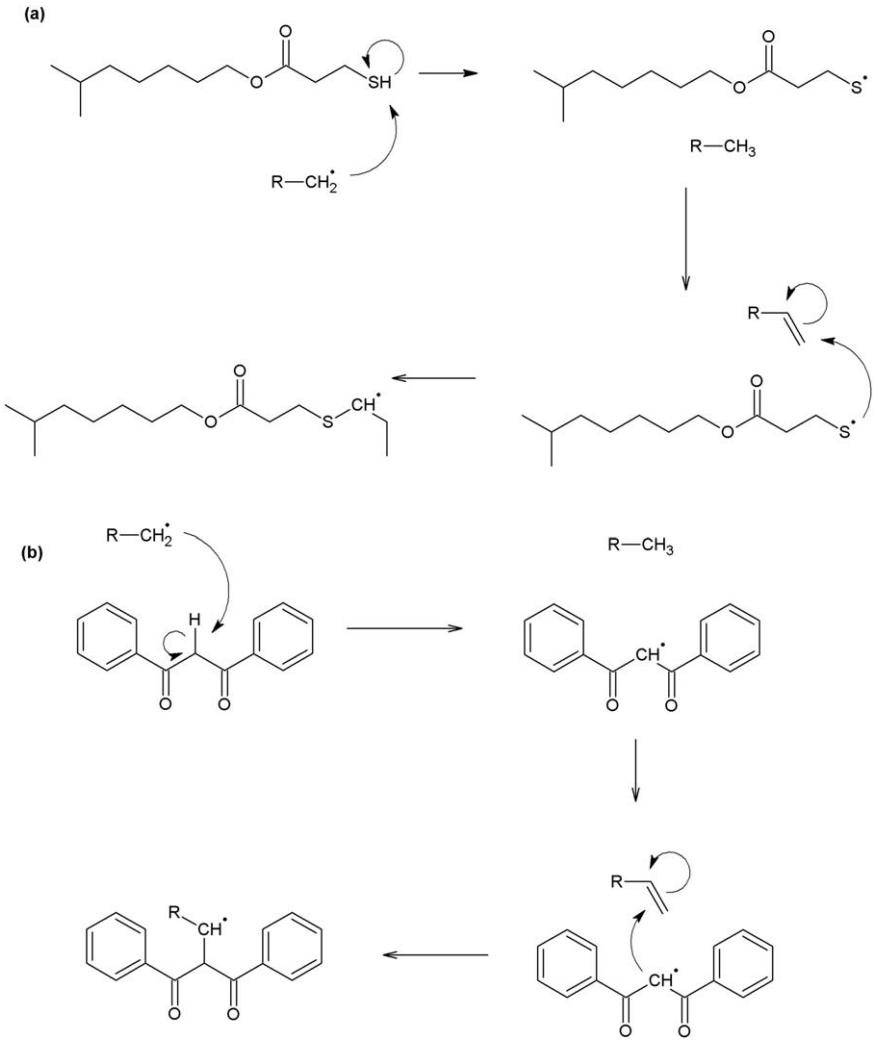

Figure 4. Proposed reaction mechanisms for (a) the chain transfer agent isooctyl 3-mercaptopropionate and (b) dibenzoyl methane DBM.

the leaving group after the DBM caps an active site on a growing particle. Since the reactivity of the leaving group is low for DBM, a low conversion was expected, in agreement with the conversions listed in Table I. The DBM conversion is about 0.1% for the starting DBM fraction of 10%, i.e., only 0.1% of the DBM in the initial formulation is incorporated into the nanoparticles. The conversion increases with a decrease in the initial fraction of the DBM to a value of 0.3% for the DBM fraction of 1%. The conversion of BHPEA is relatively similar for all compositions in Table I ranging from 5.7 to 9.2%. The conversion of BHPEA is higher than that for DBM because of the differences in the mechanisms of incorporation. The conversion of the BHPEA is also low (<10%), suggesting that the polymerization is far from complete in the 4 h reaction time. A longer time was explored in some cases but no change in conversion occurred, so the reaction time was kept at 4 h. Even though the conversion of DBM is an order of magnitude lower than that for BHPEA, it is critical to include DBM because its absorptivity in UVA range is at least an order of magnitude higher than that for BHPEA. Additionally, DBM is also required for reducing the particle sizes, which is critical to ensure loading of particles in the polymerized lenses.

Nanoparticle Composition. The fraction of BHPEA in the nanoparticles was examined for a few particle formulations. These values are listed in Table I for a few formulations. The data shows a range of the percent of BHPEA in the particles from 3 to 6%, which is lower than the fraction of BHPEA in the monomer mixture initially. This is indicative of a lower rate of reaction of BHPEA compared to PGT, resulting in a larger fraction of PGT in the particles than merely the ratio of the two monomers. The lower fraction of BHPEA in the particles will result in a higher necessary loading of the particles in the lenses to ensure adequate UV blocking.

Quantitative Model for Particle Growth. Based on the mechanism of particle formation described above, we have developed a model to predict the average size of particles formed based on the loading of DBM and CTA. To model the particle growth, we assume the particle to be a sphere of radius $R(t)$. The surface of a growing particle has a number of active sites ($N(t)$)

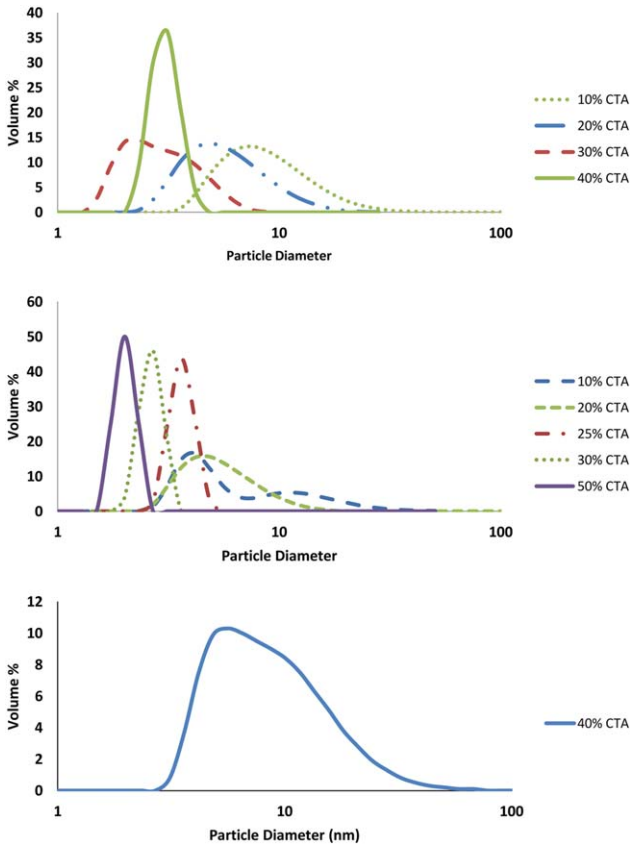

Figure 5. Size distributions of nanoparticles for formulations with 10% BHPEA and variable fractions of the other components. The DBM fractions are (a) 10%, (b) 5%, and (c) 1% DBM, and the CTA concentrations are indicated in the figure legends. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

which can react with monomers, crosslinkers, or chain transfer/chain termination agents. Reaction with a monomer will preserve the activity, while that with a CTA will end the growth. Reaction with the crosslinker preserves the growth and provides additional vinyl bonds that can be activated by free radicals from the initiator or from the fragmented parts of the CTA. The probability of an active end reacting with any of the three types of molecules (monomer, crosslinker, or CTA) is proportional to the product of the fraction of those compounds in the solution (f) and their reactivity (r). We further assume that due to relatively low conversions the fractions of the various components do not change significantly during the polymerization process. The reaction of the active sites on the particle surface grows the particle by a radius roughly equal to the length of a monomer unit (l_m), which we assume is comparable for all types of molecules. This growth will be accompanied by a reduction in the number of active sites due to reaction with the chain transfer or chain termination agents. The fraction of groups that remain active can be approximated as $N-N(f_{CTA}r_{CTA}+f_{CTX}r_{CTX})$, where CTX represents the chain terminating agent. Thus, for every cycle of growth by a distance l m, the number of active sites decrease by the ratio $1-(f_{CTA}r_{CTA}+f_{CTX}r_{CTX})$. In this model, the reactivity of all monomers is considered to be comparable and ri represents the relative activity of the CTA and CTX with respect to the monomer. We assume that the growth of the particle is terminated when about 99% of the active groups on the surface are terminated. Based on our model, the number of growth cycles before termination can be approximated by the relationship

$$\left(1-f_{CTA}r_{CTA}+f_{CTX}r_{CTX}\right)^{n}=0.01 \tag{5}$$

which yields

$$n=\frac{-2}{\log\left(1-f_{CTA}r_{CTA}-f_{CTX}r_{CTX}\right)} \tag{6}$$

The size of the particle after these n steps of growth can be estimated to be $n^{*}l_m$. Thus, we get the following expression for the mean particle size of the nanoparticles formed in our process:

$$\bar{R}=\frac{-2l_m}{\log\left(1-f_{CTA}r_{CTA}-f_{CTX}r_{CTX}\right)} \tag{7}$$

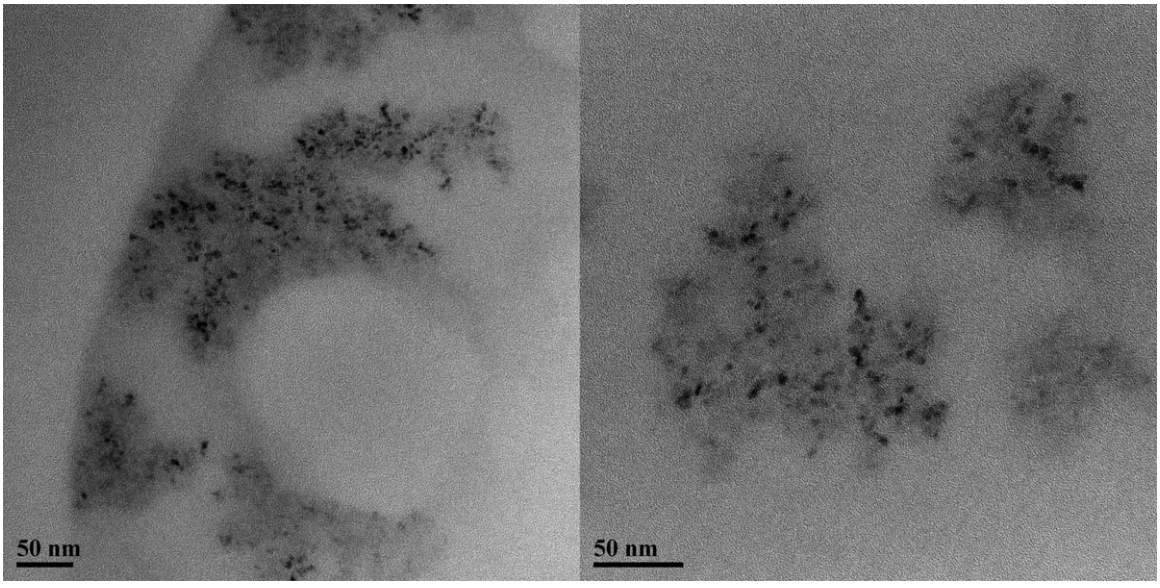

Figure 6. TEM images of formulation F3.

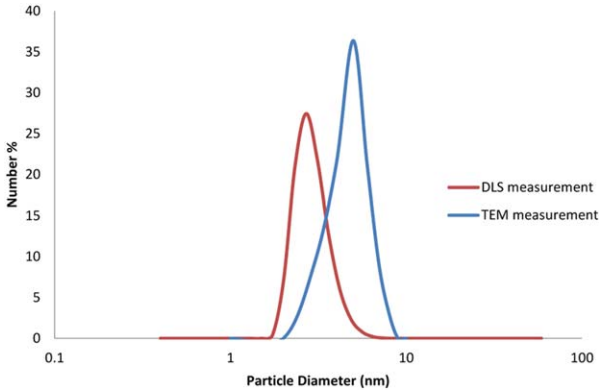

Figure 7. Particle diameter comparison between TEM images and DLS measurements. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The above expression can be represented as

$$1-f_{CTA}r_{CTA}-f_{CTX}r_{CTX}=10^{-\frac{2l_m}{R}} \quad (8)$$

To test the validity of this simple model we plot $10^{-\frac{2l_m}{R}}$ as a function of the fraction of the CTA in the polymerization mixture in Figure 8 using a value of 1 nm for l_m. The two curves represent two sets of experiments with the concentration of DBM (CTX) kept constant in each set. The above equation predicts that the plot should be linear with a negative slope equaling the relative reactivity of the CTA, which is supported by the data in the Figure 8. The model predictions are also included in the figure for relative reactivity values of 1.5 and 2 for CTA and DBM (chain terminating agent), respectively. The predictions are in good agreement with the data despite the simplicity of the model.

The model proposed above does not explicitly account for the rates of reactions and thus cannot predict the evolution of the polymerization with time. Another model limitation is that it neglects the initial phase of the particle formation in which a few growing chains join together to form the nucleus that eventually grows into a particle. Due to these limitations, the model cannot predict the number of particles in the system, except toward the end of the reaction when the number of particles can be predicted by an overall mass balance. Also the model predicts only the mean size without any information about the size distribution. Several researchers have used stochastic simulations to model free radical polymerization to predict the dynamics of systems with complex polymer structure such as branching, cyclization, etc.[31–38] The detailed simulations can provide substantial more information about the polymerization dynamics compared to our model. However, the mean size is frequently the most critical parameter and so the simple relationship between the composition and the particle size that our model predicts makes it very valuable, particularly for experimentalists interested in preparing particles of a desired size.

Incorporation of Particles into the Contact Lenses

Transmittance Spectra of Particle-Loaded Contact Lenses. Based on the particle size distributions, the formulation with 10% DBM, 40% CTA, 10% BHPEA, and 40% PGT (Formulation 1 in Table I) was considered to be the most suitable for incorporation into the contact lenses, and thus all experiments described below used the particles prepared by polymerizing this formulation. The formulation was polymerized thermally for 4 h and then subjected to two dialysis steps to separate the unreacted components. The solution was then evaporated completely, and then dispersed in a 75 : 25 mix of ethanol and acetone at various particle loadings varying from about 1–3% w/v of BHPEA (Table II). Although the same composition was used for preparing particles for each of the cases in Table II, the compositions in Table II represent separate batches of particles prepared with the same formulation, and thus the compositions are slightly different from those expected by serial dilutions of different extents. The contact lenses were loaded with the particles by soaking in the solution for 5 min, which was determined to be sufficient for complete swelling of the lens. A few experiments were conducted with 24 h loading duration and the particle uptake after 24 h was comparable to that after 5 min, indicating that the uptake is self-limiting. After the 5 min loading step, the lenses were withdrawn and quickly rinsed with acetone to remove surface deposits. The lenses were then soaked in water to return the lens to its pre-swelled size, physically trapping the nanoparticles in the lens. The nanoparticles are trapped due to their size being larger than the size of the pores

Table I. Formulations Used for Particle Preparation

Formulation	F1	F2	F3	F4	F5
% BHPEA	10	10	10	10	10
% DBM	10	5	5	5	1
% IMP	40	20	30	40	40
% PGT	39.9	64.9	54.9	44.9	48.9
% Initiator	0.1	0.1	0.1	0.1	0.1
Particle size (nm)	3.1	4.7	3.4	5.0	18.6
% Conversion BHPEA	6.5	8.2	6.7	5.7	9.2
% Conversion DBM	0.1	0.3	0.2	0.2	1.4
% BHPEA in particles	5.6		3.4	4.9	

All fractions are based on w/w basis.
BHPEA—2-(4 benzoyl-3-hydroxyphenoxy)ethyl acrylate, DBM—dibenzoyl methane, IMP—isooctyl 3-mercaptopropionate, PGT—propoxylated glyceryl triacrylate.

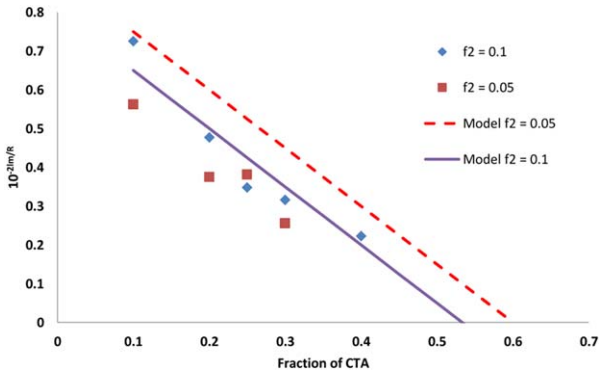

Figure 8. Comparison of measured nanoparticle sizes with model predictions. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of the lens which prevents them from diffusing out of the lens. This is different from currently available technologies where the UV-blocking components are chemically linked to the contact lens, whereas the nanoparticles loaded here are not chemically linked to the lenses.

The loaded lenses were visually all clear and blocked a large fraction of the UV light as evident from the transmission spectra shown for a few representative cases in Figure 9. The spectra were used to calculate the average transmittance in the UVA and UVB range, as summarized in Table III. A Class 1 lens must block more than 99% UVB and more than 90% UVA radiation. Based on the average transmittance listed in Table III, three of the lenses can be categorized as Class 1 blockers, while the others are Class 2 blockers. It should be noted though that the Class 1 classification is based on the average transmittance across the entire lens, while the measured spectra and the values in Table III correspond to a thickness of 130 μm. Below we determine the concentration of the UV blockers in the lens and then use that to calculate the average transmittance across the entire lens.

Determining the Concentrations of DBM and BHPEA in the Contact Lenses. The spectra in Figure 9 were fitted to eq. (3) with the a priori measured absorptivity values (Figure 3) to determine the concentrations of DBM and BHPEA in the lenses after the loading (Table III). Additionally to further validate this approach, the lenses were soaked in ethanol to extract out the UV-blocking molecules and the concentration of the molecules in ethanol was used to estimate the original concentrations in the lenses. The results from both approaches were comparable. The concentrations in Table III are the total concentrations of DBM and BHPEA, and thus include both the fraction encapsulated in the particles and the free monomeric form. Comparing this data with the fraction of BHPEA in the particles from Table I can give an estimate for the particle loading required for Class 1 UV-blocking lenses. Based on sample #3 which has the lowest loading of UV blockers while maintaining Class 1 UV blocking, the concentration of particles in the lens is calculated to be 62.5 mg/mL or 6.25% particles in the lens.

The concentration in the contact lenses for several different loadings of the F1 formulation is plotted against the concentration in the loading solution in Figure 10 for BHPEA and Figure 11 for DBM. These plots show a linear relationship between loading solution concentration and lens concentration indicating that the lenses are reaching equilibrium with the loading solution. The slopes of the lines represent the partition coefficients of the two components for absorption into a contact lens from a 25 : 75 acetone–ethanol solution. The partition coefficients are 1.37 for DBM and 0.24 for BHPEA. The lens swells almost 100% in the 25 : 75 acetone–ethanol solution and the free concentration of any solute in the liquid phase is expected to equal that in the solution, which would suggest that the partition coefficients should be larger than one, even if the solute does not adsorb on the polymer. A majority of the BHPEA is covalently attached to the particles (Table II) and certain regions of the lens matrix may be inaccessible to the particles, either due to repulsive interactions or size limitations (steric hindrance) of the particles, which results in a low partition coefficient. On the contrary, a majority of DBM is unreacted (Table II), thus it can diffuse into all the regions of the lens leading to a partition coefficient value larger than one.

Estimating Average Lens Transmittance. A Class 1 lens is required to block an average of 99% of UVB and 90% of UVA light. Since the UV transmittance values reported in Table III were measured at only location, the data cannot be directly utilized to determine whether the lens achieved the Class 1

Table II. Composition of Solutions into Which the Lenses were Soaked for Loading the Particles

Sample#	1	2	3	4	5
Formulation used	F1	F1	F1	F1	F1
Total BHPEA (mg/mL)	8.30	7.01	11.74	25.87	27.61
Reacted BHPEA (mg/mL)	7.60	6.46	11.03	22.79	24.79
Unreacted BHPEA (mg/mL)	0.70	0.55	0.71	3.08	2.82
Ratio reacted/unreacted BHPEA	10.89	11.64	15.56	7.40	8.79
Total DBM (mg/mL)	0.61	0.48	0.77	2.83	3.83
Reacted DBM (mg/mL)	0.15	0.15	0.25	0.26	1.40
Unreacted DBM (mg/mL)	0.46	0.33	0.52	2.57	2.43
Ratio reacted/unreacted DBM	0.32	0.45	0.47	0.10	0.58

BHPEA—2-(4 benzoyl-3-hydroxyphenoxy)ethyl acrylate, DBM—dibenzoyl methane.

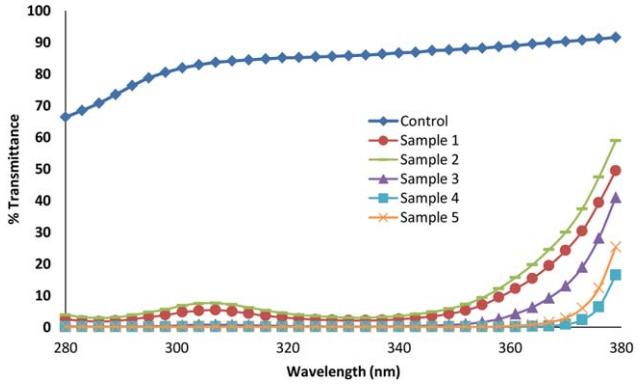

Figure 9. UV transmittance spectra of particle-loaded lenses. The compositions of the solutions used for loading the lenses are indicated in Table II and the concentrations of the UV blockers in the lenses are indicated in Table III. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

blocking. It is however possible to calculate the average transmittance if the thickness profile of the lens is known. We measured the lens thickness at various locations and additionally calculated the profile by using the following approximation proposed by Cambell for the thickness variation of a lens based on the distance from the center of the lens:

$$t = t_c - \frac{d^2 P * 10^{-3}}{2(n-1)} \tag{9}$$

Here, t is the thickness in mm, t_c is the center thickness in mm, d is the distance from the center of the lens in mm, P is the power in diopters, and n is the index of refraction.[39] The measured thickness profiles were in good agreement with the predictions from eq. (9). Since the absorbance of the lens is proportional to the path length, it is possible to get the absorbance spectra for every point on the contact lens surface and determine the average transmittance over the entire lens by evaluating the following integral

$$\text{Avg}\%T = \frac{\int \%T dA}{\int dA} \tag{10}$$

The shape of the contact lens is complex and involves multiple base curves. The majority of the region, however, can be approximated as a sphere with fixed radius but variable thickness given by eq. (10). Based on this shape, the average transmittance can be computed by using the spherical coordinate system and utilizing the symmetry in the θ direction. Substituting in the equations for % transmittance and differential area,

$$\text{Avg}\%T = \frac{\int_0^{\phi} 10^{-\varepsilon c t(\phi)} 2\pi r^2 \sin(\phi) d\phi}{\int_0^{\phi} 2\pi r^2 \sin(\phi) d\phi} \tag{11}$$

Here, ϕ and r are the azimuthal angel and the radius and t is the thickness of the lens, which is a function of ϕ.

$$\text{Avg}\%T = \frac{2\pi r^2 \int_0^{\phi} 10^{-\varepsilon c\left(t_c - \frac{d^2 P}{2(n-1)}\right)} \sin(\phi) d\phi}{2\pi r^2 (1-\cos(\phi))} \tag{12}$$

The distance from the center of the lens, d, is equal to $r^*\sin(\phi)$

$$\text{Avg}\%T = \frac{\int_0^{\phi} 10^{-\varepsilon c\left(t_c - \frac{r^2 \sin^2(\phi) P}{2(n-1)}\right)} \sin(\phi) d\phi}{1-\cos(\phi)} \tag{13}$$

This integration can be evaluated analytically for a positive power lens but must be done numerically for a negative power lens as used in this study. Since there are two UV-blocking molecules in the lens, the term εc in the above equation is the sum of εc for the two components. The absorptivity for both components is shown in Figure 3 and the concentration in the lenses is reported in Table III. The above method is only valid for the central region of the lens that can be described by the spherical base curve. The peripheral region includes other base curves as well and thus the integration in the above equation was limited to a distance of 5 mm from the center of the lens, while the lens periphery is about 7 mm from the center. Since the lens thickness in the peripheral region is larger than that in the central region, our calculated values shown in Table III are likely underestimates of the average transmittance. Based on these results, lenses 3–5 can be classified as Class 1 UV-blocking lenses.

Table III. Concentration and % Transmittance of the Nanoparticle-Loaded Lenses

Sample #	1	2	3	4	5
UV transmittance measured at 130 μm thickness					
UVA transmittance (%)	10.4	13.2	5.2	1.0	1.8
UVB transmittance (%)	3.6	5.3	0.5	0.1	0.1
Concentration of UV blockers in lens					
BHPEA (mg/mL)	2.4	1.9	3.5	7.1	5.3
DBM (mg/mL)	1.2	1.1	1.8	6.1	4.0
Calculated average transmittance					
UVA transmittance (%)	11.4	14.3	5.8	1.2	2.2
UVB transmittance (%)	4.5	6.3	0.8	0.2	0.2
Class 1			Yes	Yes	Yes

BHPEA—2-(4 benzoyl-3-hydroxyphenoxy)ethyl acrylate, DBM—dibenzoyl methane.

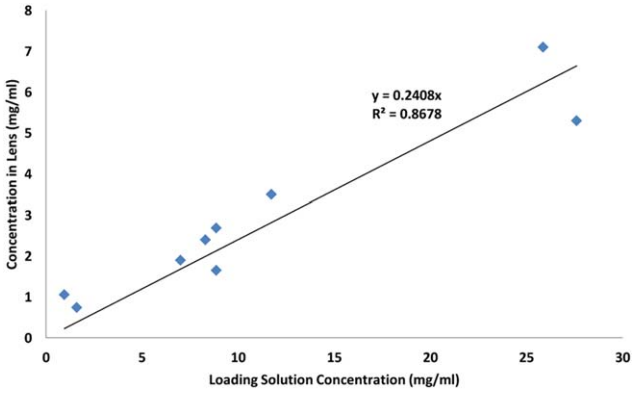

Figure 10. Relationship between the total concentration of BHPEA in the lens and that in the loading solution. The slope of the linear fit is the partition coefficient for BHPEA absorption into the lens from the 75 : 25 ethanol–acetone solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

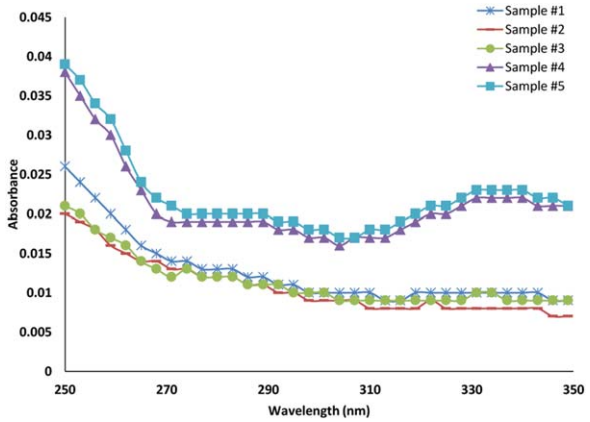

Figure 12. The absorbance spectra of PBS after soaking of the particle-loaded contact lenses in 3 mL of the solution for 24 h. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Leaching of UV-Blocking Components from Lenses

DBM is precursor for the FDA-approved sunscreen component avobenzone and BHPEA is a polymerizable derivative of oxybenzone, which is also an approved ingredient for sunscreens. Additionally, DBM is considered to have anticancer properties as it has been reported to inhibit tumor growth in several animal models of tumor.[40] It is not currently known whether the leaching of these materials into the eyes would raise toxicity concerns, so it would be preferable to prevent any leaching of these materials into the tear film. To measure the potential for release of DBM and BHPEA, the UV-blocking lenses were soaked in PBS for 24 h. The absorbance spectra of the PBS after the 24-h soaking are shown in Figure 12 for a few representative cases. The figure shows that very little material is released from the lens, indicating that most of the material in the lens is chemically linked in the particles. Also the unreacted DBM will likely have a very low solubility in PBS, further limiting the potential for release. Since the particles cannot elute from the lenses in PBS because of the smaller pore sizes, the released components are likely the monomeric UV-blocking molecules.

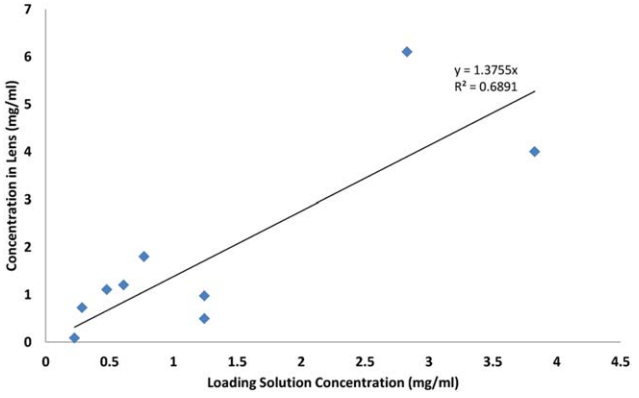

Figure 11. Relationship between the total concentration of DBM in the lens and that in the loading solution. The slope of the linear fit is the partition coefficient for DBM absorption into the lens from the 75 : 25 ethanol–acetone solution. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The absence of particles in the PBS was confirmed by dynamic light scattering, therefore the material that released into the PBS solution should only be unreacted components. Production of these particles for commercial use would require additional cleanup of the nanoparticles to ensure none of this material is present in the lens to prevent any toxicity concerns.

Effect of Autoclaving and UV Exposure on UV Blocking

Contact lenses are sterilized by autoclaving, so it is necessary to determine the effect of autoclaving on the UV-blocking efficiency of the particle-loaded lenses. Lenses containing the UV-blocking particles were loaded into DI water and allowed to equilibrate with the solution for 24 h. The samples were then autoclaved with a sterilization time of 25 min. Testing before and after autoclaving showed only a small change in the transmittance of UV light through the lens as shown in Figure 13. The sterilization procedure does not reduce the UV blocking, suggesting that the UV-absorbing nanoparticles are stable and also do not elute out even during soaking at high temperatures.

In addition to requiring stability to the sterilization process, it is important that these lenses retain their UV-blocking properties after exposure to UV light in order to ensure that wearers are protected throughout the day. To test this, lenses were

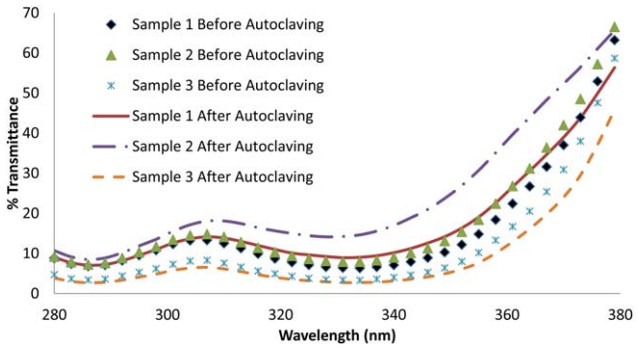

Figure 13. Effect of autoclaving the particle-loaded lenses on the UV-blocking properties of the lens. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

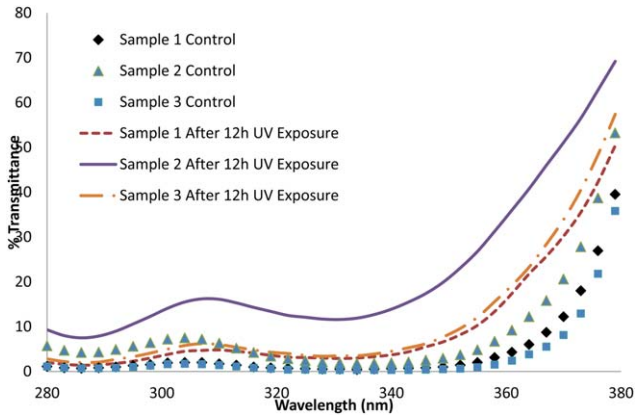

Figure 14. Effect of 12 h of UV exposure on UV-blocking properties of particle-loaded lenses. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

placed in a water solution and irradiated with a UVB Transilluminator for 12 h. The transmittance of the lenses was measured before and after the irradiation, and the results are shown in Figure 14. There was some degradation of the UV components on exposure to the UV light with approximately 15–30% of the UV blocker losing its efficacy, indicating that this will not be a major issue for daily disposable contact lenses as the particle loading can easily be increased by 15% to compensate for this deterioration. However, the eyes are protected somewhat from solar exposure due to their position deep in the socket and due to coverage from eyelids. In addition, the intensity of light in the transilluminator used for this study is close to the maximum intensity of sunlight during the day and so it would not be exposed to this intensity throughout the entirety of the day. The reduction in degradation due to these factors may allow for use of these particles in extended wear contact lenses, but this needs to be tested through in vivo studies.

CONCLUSION

Ultraviolet radiation can damage ocular tissues leading to moderate to severe problems. Contact lenses can be more effective than glasses at reducing UV exposure due to better protection against peripheral radiation. While the importance of UV blocking in contact lenses has been recognized, there are only a few commercial contact lenses that provide Class 1 UV protection. We have developed a novel approach of incorporating UV blocking into pre-fabricated commercial contact lenses by incorporation of nanoparticles that contain a UV-blocking compound. Our approach is based on the preparation of sub 10 nm diameter UV-blocking particles and soaking the lenses in a solution of the particles in a suitable solvent that swells the lenses to increase the pore size. We prepared the sub 10 nm size UV-blocking particles by polymerizing a mixture of UV-blocking monomer BHPEA and a crosslinker PGT in the presence of a CTA. Additionally, DBM is also included to incorporate UVA blocking and to reduce the particle size through chain termination. By polymerizing a formulation with 40% CTA, 10% BHPEA, 10% DBM, 39.9% PGT, and 0.1% initiator, we successfully prepared nanoparticles with a narrow size distribution and a mean size of about 3 nm. The conversion of BHPEA was about 10% while that for DBM was less than 1%. A stochastic-based model was also developed and validated to predict the effect of various formulation parameters on the particle size.

The pore sizes of the lenses are much larger in ethanol and acetone compared to PBS, so the particles are loaded into the lenses by soaking the lens in a solution of particles dispersed in ethanol–acetone. The particles that diffuse into the lenses during soaking stay trapped in the lenses after the organic liquids are extracted and the lenses are hydrated in PBS. This differs from the current state of the art in that the UV-blocking component is not chemically linked to the lens, but trapped in the lenses due to stearic constraints. Lenses loaded with about 6% particles reached sufficient UV absorbance to be categorized as a Class 1 blocker. The loaded particles do not diffuse out into the PBS and the UV blocking is also stable under high temperature exposure. The approach developed here can be integrated into any commercial contact lens and also possibly into other biomedical devices. While these results are encouraging, further studies on impact of particle incorporation on critical lens properties such as ion and oxygen permeabilities as well as cytotoxicity studies of the nanoparticles are required. Additionally, the polymerization process should be optimized to increase the yield and the fraction of reacted DBM.

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