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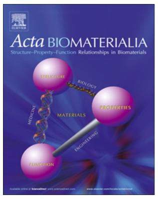

Fluorescent solute-partitioning characterization of layered soft contact lenses

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ABSTRACT

Partitioning of aqueous packaging, wetting, and care-solution agents into and out of soft contact lenses (SCLs) is important for improving wear comfort and also for characterizing lens physico-chemical properties. We illustrate both features of partitioning by application of fluorescent-solute partitioning into DAILIES TOTAL1® (delefilcon A) water-gradient SCLs, which exhibit a layered structure of a silicone–hydrogel (SiHy) core sandwiched between thin surface-gel layers. Two-photon fluorescence confocal laser-scanning microscopy and attenuated total-reflectance Fourier-transform infrared spectroscopy (ATR-FTIR) characterize the lens and assess uptake profiles of six prototypical fluorescent solutes. Comparison of solute uptake in a SiHy-core prototype lens (i.e., O_2OPTIX™) validates the core SiHy structure of DAILIES TOTAL1®. To establish surface-layer charge, partition coefficients and water contents are obtained for aqueous pH values of 4 and 7.4. Solute fluorescence-intensity profiles clearly confirm a layered structure for the DAILIES TOTAL1® lenses. In all cases, aqueous solute partition coefficients are greater in the surface layers than in the SiHy core, signifying higher water in the surface gels. ATR-FTIR confirms surface-layer mass water contents of 82 ± 3%. Water uptake and hydrophilic-solute uptake at pH 4 compared with that at pH 7.4 reveal that the surface-gel layers are anionic at physiologic pH 7.4, whereas both the SiHy core and O_2OPTIX™ (lotrafilcon B) are nonionic. We successfully confirm the layered structure of DAILIES TOTAL1®, consisting of an 80-μm-thick SiHy core surrounded by 10-μm-thick polyelectrolyte surface-gel layers of significantly greater water content and aqueous solute uptake compared with the core. Accordingly, fluorescent-solute partitioning in SCLs provides information on gel structure and composition, in addition to quantifying uptake and release amounts and rates.

1. Introduction

Partitioning of packaging, wetting, and care-solution agents in soft contact lenses (SCLs) is a well-explored avenue for improving and maintaining on-eye lens performance [1–6]. Similarly, partitioning of tear components in SCLs, such as proteins, salts and lipids, can affect lens behavior during wear [1,7–11]. Further, solute partitioning is critical for possible use of SCLs as a drug-delivery vehicle [12–15]. Thus, understanding how solutes partition and transport in hydrogels is an important challenge [13,16–20].

Although not as common, solute partitioning may be adopted to characterize hydrogel structure. Watkins et al. [21] used fluorescent-solute loading to visualize multi-laminated hydrogels. Furthermore, by employing non-interacting solutes of known shape and size, Walther et al. [22,23] ascertained the pore-size distribution (i.e. mesh-size distribution) of parent hydrogels. We apply this philosophy to understand the structure of DAILIES TOTAL1® lenses, which, according to trade and patent literature, consist of a 33% water-content SiHy core that transitions through an interpenetrating anchor region to outer surface-gel layers with water content >80% [24–28]. As daily disposables, DAILIES TOTAL1® lenses are designed for use without care solutions. Here, solute partitioning is used to ascertain the hydrogel structure. Because the reported surface-gel layers are of high water content, their mesh sizes are expected to be larger than those of the core region. Accordingly, larger aqueous solutes likely partition more favorably into the surface-gel region than into the core region [13,16,17]. Further, by comparing uptake of aqueous ionogenic solutes in their charged and neutral states, information can be obtained on the charge of the polymer strands in the surface and core gels. By comparing partitioning into a SiHy-core prototype lens (e.g. O_2OPTIX™ [29]), the core SiHy structure of DAILIES TOTAL1® can be validated. Finally, partitioning of oleophilic solutes from an oil solvent can be

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pursued to establish whether or not an aqueous-saturated surface gel can forestall low aqueous-soluble lipid penetration into the core SiHy region.

We measure uptake of six prototypical fluorescent solutes in DAILIES TOTAL1® SCLs. Two-photon fluorescence confocal laser-scanning microscopy (FCLSM) obtained profiles and partition coefficients of both hydrophilic (i.e. fluorescently labeled avidin and dextrans) and oleophilic (i.e. Nile Red and fluorescently labeled cholesterol) solutes. For the hydrophilic solutes in DAILIES TOTAL1®, FCLSM measurements confirmed consistently greater solute partitioning in the surface-gel layers and, therefore, a higher water content compared with that in the SiHy core. FCLSM confirmed both the layered structure and established the surface-gel-layer thickness. Higher surface-layer water content was validated using attenuated total-reflectance Fourier-transform infrared spectroscopy (ATR-FTIR). Penetration of two oleophilic solutes from silicone oil into the SiHy core was not prevented by the surface-gel layers. To establish a baseline, solute-uptake and water-content measurements were also performed on a single-water-content prototype SiHy SCL: O_2OPTIX™.

2. Materials and methods

2.1. Soft contact lenses

Two commercially available Alcon (Fort Worth, TX) SiHy SCLs were used in this study: DAILIES TOTAL1®(delefilcon A; composition unavailable) and O_2OPTIX™ (lotrafilcon B; containing *N*,*N*-dimethylacrylamide and methacryloxypropyl tris(trimethylsiloxy)silane [29]). The diameter, base curve, and were 14.1 and 14.2 mm, 8.5 and 8.6 mm, and −0.75 and −2.0, for DAILIES TOTAL1® and O_2OPTIX™, respectively. Prior to each measurement, lenses were extracted in excess pH 7.4 phosphate buffer saline solution (PBS) for at least 48 h to remove preservatives and surfactants from the packaging solutions. PBS was prepared as described previously [13,16,17]. For measurements at pH 4, extracted lenses were subsequently equilibrated for 24 h in excess pH-4 citrate buffer (1.2×10^{-2} M citric acid anhydrous, Cat. No. A940-500, Fisher Scientific; 8.2×10^{-3} M sodium citrate dihydrate, SX0445-1, EMD Chemicals; 0.15 M NaCl, S271-3, Fisher Scientific). All experiments were performed at ambient temperature.

2.2. ATR-FTIR

SCL surface water content was determined using ATR-FTIR [30–32]. IR spectra were obtained using a Nicolet 6700 FTIR spectrometer (Thermo Scientific, Madison, WI) equipped with a DTGS-KBr detector and a single-reflection Smart OMNI-Sampler ATR cell (No. 0028-899, Thermo Scientific). In all cases, ambient air was used as the reference spectrum. Prior to each water-content measurement, SCLs were removed from the extraction solution, lightly blotted with Fisherbrand® weighing paper (Fisher Scientific, Pittsburgh, PA), and forced onto the ATR crystal using the instrument supplied fixture or light weights to ensure intimate crystal contact. The applied force was low enough to ensure no gel collapse [33]. Subsequently, FTIR spectra were obtained in the range of wavenumber from 4000 to 650 cm^{-1} during 64 scans, with 2 cm^{-1} resolution. Each measurement was performed in triplicate.

Total internal reflectance probes surface properties through an exponentially decaying evanescent wave of penetration depth d_P, given by

$$d_P = \frac{\lambda}{2\pi n_1 \left[\sin^2\theta - (n_2/n_1)^2\right]^{1/2}} \quad (1)$$

where λ is the wavelength of light, θ is the angle of incidence (45°), and n_1 and n_2 are the refractive indices of the ATR crystal (Germanium: $n_1 = 4$) and either the surface-gel layer (approximated as water: $n_2 \approx 1.33$) or O_2OPTIX™ ($n_2 = 1.42$ [29]), respectively. Over the wavenumbers investigated, penetration depths into the lenses ranged from 0.1 to 1 μm, which are considerably smaller than the observed DAILIES TOTAL1® surface-layer thicknesses [27]. For O2OPTIX™, however, penetration depths are considerably greater than the 25-nm-thick plasma coating [29]. In this case, water contents measured by ATR-FTIR are averaged over the plasma-surface-coated region and the untreated bulk SiHy material.

Fig. 1 displays ATR-FTIR spectra for PBS solution, DAILIES TOTAL1®, and O_2OPTIX™ over the range of wavenumbers between 4000 and 2500 cm^{-1}, where water absorbs strongly. For clarity, the baseline was subtracted. In all cases, the O–H stretching band (3500–3000 cm^{-1} [34]) is clearly observed. Following Wilson et al. [30], the surface water content was calculated from the peak area between 3600 and 3000 cm^{-1}. To account for the contribution of lens polymer to the IR spectra (e.g. at 2950 cm^{-1}), overlapping peaks were deconvoluted using dry-lens spectra; thus, only peak areas corresponding to O–H stretching were used in the calculation. We neglected the O–H bending band, because the matrix polymer contributes significantly at these wavenumbers. ATR-FTIR-measured mass water contents were validated from in-house synthesized 2-hydroxyethyl methacrylate (HEMA)/methacrylic acid (MAA) copolymer hydrogels [13] of known bulk gravimeteric water content. Fig. 2 plots the ATR-FTIR-measured water content against known gravimetric water content for four HEMA/MAA hydrogels. Water content obtained by ATR-FTIR is in good agreement with that determined gravimetrically over the range of water contents studied.

2.3. Fluorescent solutes

PBS (pH 7.4) and citrate buffer (pH 4) solutions, prepared as described above, were solvents for the hydrophilic fluorescent solutes. Fluorescein isothiocyanate dextrans (FITC-dextran4, MW = 4000 g mol^{-1}; FITC-dextran20, MW = 20,000 g mol^{-1}; FITC-dextran70, MW = 70,000 g mol^{-1}) were obtained from TdBCons (Uppsala, Sweden). To remove free label (i.e. FITC), FITC-dextran solutions were extensively dialyzed in Slide-A-Lyzer Dialysis Cassettes (No. 66212, Thermo Scientific, cutoff MW = 2000 g mol^{-1}) for 1 week at 25 °C, with the surrounding dialyzing solution changed daily. Cationic FITC-conjugated avidin (FITC-avidin, MW = 68,000 g mol^{-1}) was acquired from Invitrogen (Eugene,

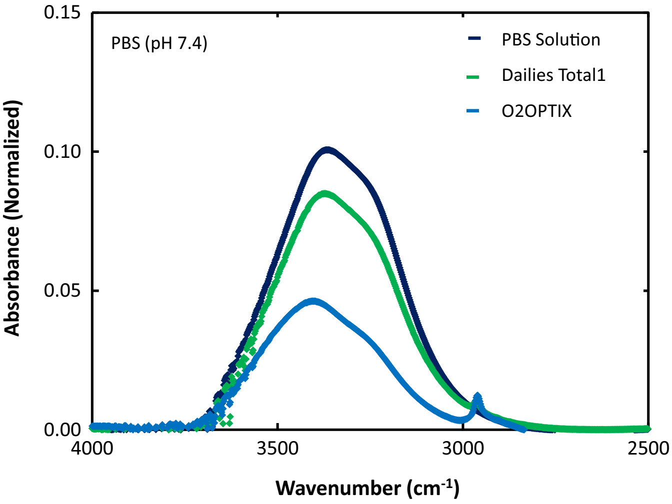

Fig. 1. Truncated ATR-FTIR spectra for PBS solution, DAILIES TOTAL1®, and O_2OPTIX™ over the range of wavenumbers between 4000 and 2500 cm^{-1}. The measured surface mass water content of DAILIES TOTAL1® and O_2OPTIX™ was 82 ± 3% and 43 ± 2%, respectively.