

Poly(ethylene glycol)-based poly(urethane isocyanurate) hydrogels for contact lens applications

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Abstract

Over the past few decades, the global use and market of contact lenses have expanded steadily. Due to the many demands on material properties (e.g. mechanical, optical and biological), the development of novel contact lens materials is challenging. Specifically, the ideal combination of high equilibrium water content, high toughness in the hydrated state and low protein adsorption is difficult to realize. In this work, poly(ethylene glycol)-based poly(urethane isocyanurate) (PEG PUI) type hydrogels that combine the above important properties are presented as a new class of materials for contact lens applications. It is shown that these PEG PUI hydrogels demonstrate high toughness values in the hydrated state ranging from 98 to 226 kJ m⁻³ and elastic moduli ranging from 0.8 to 17.2 MPa for networks with equilibrium water contents ranging from 76.3 to 16.1 wt%. These hydrogels also demonstrate transmittance values >90% across the visible spectrum, clarities close to 100% in most cases and refractive indices ranging from 1.48 to 1.36. Importantly, these hydrogels are non-cytotoxic and demonstrate lower bovine serum albumin adsorption values than several commercial contact lenses of 0.24 to 0.65 mg g⁻¹ compared to 0.55 to 1.38 mg g⁻¹ after 24 h, respectively. This combination of high equilibrium water content, high toughness in the hydrated state and low protein adsorption is exceptional. These properties can be attributed to the PEG PUI network structure: the use of a PEG polymeric backbone provides hydrophilicity and chemical inertness while the PUI-type crosslinking units provide high toughness in the hydrated state.

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Keywords: PEG-based poly(urethane isocyanurate); soft contact lenses (SCL); tough hydrogels; structure–property relations

INTRODUCTION

Since the introduction of soft contact lenses in the 1960s, the development of contact lens materials has received much attention over the years and is still an actively discussed topic today.^{1,2} At present, the market for soft contact lenses is estimated to exceed \$8.5 billion globally, with an estimated 150 million users of contact lenses worldwide in 2019.^{3,4} Historically, the market for soft contact lenses has been dominated by two main classes of materials: organic (polymer) hydrogels (e.g. based on poly(2-hydroxyethyl methacrylate) (pHEMA)) on the one hand and silicone-containing hydrogels on the other hand.¹ An overview of common contact lens materials and literature data regarding their general physical properties are presented in Table 1.²

Despite the long history of the field, novel (classes of) soft contact lens materials are still actively sought after and reported on today.⁵ The development of new contact lens materials is considered a challenging field though. This is easily appreciated when looking at the impressive list of typical requirements a material has to fulfil before being considered for contact lens applications (Table 2).^{2,5,10}

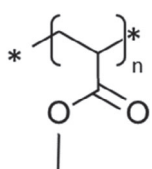
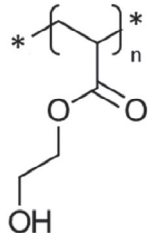
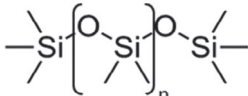
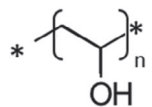
Typically, modification of the various material characteristics is not complementary and improving one property often negatively affects another. A specifically challenging combination of contradictory material properties for organic (polymer) hydrogels is high hydrophilicity, high toughness and low biofouling.^{11,12} One of the reasons for this is that the hydrophilicity of contact lens materials is generally realized by the introduction of hydrogen-bonding moieties (e.g. -OH, -NH₂ or -COOH groups) into the polymeric backbone. However, the presence of such hydrogen-bonding moieties has been shown to play a key role in the biofouling process of hydrogel materials.¹³ By facilitating biofouling, contact lenses can hold microbes in prolonged contact with the cornea of the eye, leading to ocular infections and

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Table 1. General properties of some common contact lens materials

Material	EWC (%)	E_{mod} (MPa)	O_2 -perm ^a (Dk)	Wear time ^b (days)	Polymer structure
PMMA	0	1000	0	<1	
PMMA–silicone	0	– ^c	15	– ^c	
Silicone–HEMA (rigid)	0	10	10–100	– ^c	
pHEMA hydrogel	30–80	0.2–2	10–50	1–7	
Silicone (PDMS) hydrogel	20–55	0.2–2	60–200	ca 7–28	
PVA	60–70	– ^c	10–30	<1	

Adapted from Musgrave *et al.*²
^a Oxygen permeability, typically reported in Dk units (mL O₂ mL⁻¹ mmHg⁻¹).
^b Recommended maximum wear time before lens disposal.
^c Data not reported.

complications.¹² In fact, even with good contact lens care practice, up to 80% of contact lenses and contact lens cases were found to harbour disease-causing microbes.¹⁴ This shows that there is still a need for a low-biofouling hydrophilic hydrogel material for contact lens applications.^{10,12,15–17}

In this context, poly(ethylene glycol) (PEG) is considered a promising material.^{2,5} Specifically the combination of high hydrophilicity with chemical inertness is attractive. The main drawback associated with PEG hydrogel materials, however, is their poor mechanical performance (i.e. poor toughness) in the hydrated state that is typically associated with crosslinked PEG hydrogels.^{18–20} Consequently, the use of PEG has thus far been limited to surface modification procedures of existing contact lens materials.^{12,15,21} Hydrogels based on crosslinked PEG have not been reported in this context.

In the work reported here, we investigated the use of a recently developed new class of PEG-based poly(urethane isocyanurate) (PUI) type polymer networks for contact lens applications.²² The synthesis of these networks is based on the functionalization and subsequent trimerization of PEG polymeric diols using hexamethylene diisocyanate (HDI), as shown in Scheme 1. The resulting PEG PUI networks were shown to exhibit high water uptakes of up to 508 wt% combined with high toughness in the hydrated state.²² Since both PEG- and PUI-type polymer networks are also known for their excellent optical properties,^{23,24} high refractive indices^{25–27} and biocompatibility,^{28,29} we hypothesize that these types of PEG PUI hydrogels would be a promising class of materials for contact lens applications. PEG PUI hydrogels of

varying crosslinking density were synthesized and characterized for properties relevant to contact lens applications (Table 2) and compared to commercially available contact lenses.

EXPERIMENTAL

Materials and methods

Materials

PEGs ($\bar{M}_n = 0.4, 0.6, 1, 2, 4$ and 10 kg mol^{-1}), stannous octoate (Sn(II)Oct₂) and resazurin sodium salt were purchased from Sigma-Aldrich. HDI was supplied by Covestro Deutschland AG. A human retinal pigment epithelium cell line (Arpe-19) and Dulbecco's modified Eagle medium/nutrient mixture F-12 (DMEM/f12) with 10% foetal bovine serum (FBS) cell culture medium were purchased from ATCC. Commercial contact lenses (Midafilcon A day lenses manufactured by Menicon, and Riofilcon A day lenses, Comfilcon A month lenses and Somofilcon A month lenses manufactured by Cooper Vision) were kindly supplied by a local optometrist. A DC Protein Assay kit was purchased from Bio-Rad. All other chemicals were purchased from Sigma-Aldrich. Unless stated otherwise, all chemicals were used as received.

Hydrogel synthesis and characterization

All chemical reactions were conducted under a nitrogen atmosphere using standard Schlenck-line techniques. NMR spectra were collected with a Bruker Avance III-700 in C₆D₆. SEC was performed according to DIN 55672–1:2016–2103, with four PSS SDV Analytical columns ($2 \times 100 \text{ \AA}$, 5 \mu m ; $2 \times 1000 \text{ \AA}$, 5 \mu m) using an

Table 2. List of typical requirements for organic (polymer) contact lens materials

Material property	Requirement/comment
<i>Physical and chemical</i>	
Hydrophilicity	As high as possible. Typically indicated by the EWC
Oxygen permeability	As high as possible
Mechanical properties in the hydrated state	Need to be suitable. Most notably, a suitable elastic modulus and high toughness
Chemical stability	Sufficient. With respect to both shelf-life and common sterilization techniques such as UV exposure or autoclaving
<i>Optical</i>	
Transmittance	As high as possible across the visible spectrum
Clarity	As high as possible. Clarity is typically considered a measure for the see-through quality of the material
Refractive index	Needs to be suitable ^a
<i>Biological</i>	
Biocompatibility	Required. Typically indicated by non-cytotoxicity
Biofouling	As low as possible. Specifically, low protein adsorption

^a The literature regarding the preferred value of the refractive index of contact lens materials is inconsistent. On the one hand, it is reported that the refractive index value of a contact lens material should preferably be as high as possible, in order to allow the manufacture of the thinnest possible contact lenses.^{6,7} On the other hand, it is also reported that the refractive index of a contact lens material should preferably match that of the human cornea as closely as possible, values ideally lying between 1.372 and 1.381.^{5,8} Typical values reported in the literature for commercial and novel scientific contact lens materials range from approximately 1.38 to 1.45.^{6,7,9}

Agilent 1100 Series pump and an Agilent 1200 Series UV detector (230 nm) with tetrahydrofuran as the elution solvent at 40 °C and 1.00 mL min⁻¹. Residual monomeric diisocyanate contents were determined using gas chromatography (GC) according to DIN EN ISO 10283 with an Agilent Technologies 6890 N system using a 15.0 m DB17 column and tetradecane as an internal standard. Attenuated total reflection Fourier transformed infrared (ATR-FTIR) spectra were recorded using a Bruker FTIR Tensor II spectrometer with a platinum ATR unit with diamond crystal.

Physical properties

DSC measurements were performed under nitrogen with samples of on ca 10 mg using a PerkinElmer DSC-7 calorimeter in two heating runs from -100 to +150 °C with a heating rate of 20 K min⁻¹ and a cooling rate of 20 K min⁻¹. The glass transition temperature (T_g) and peak melting temperature ($T_{m,p}$) were determined based on the second heating run. Tensile tests were performed in triplicate at room temperature using a Zwick Z0.5 tensile tester equipped with a 500 N load cell at 200 mm min⁻¹, with a grip-to-grip separation of 35 mm on strips of ca 60 mm × 4 mm × 0.5 mm cut from a cured film. Elastic moduli and strain values were derived from the initial grip-to-grip separation and are indicative. The toughness values of the materials were calculated from the

work at break value, normalized for the dimensions of the specimen.

For swelling measurements, three samples measuring approximately 10 mm × 20 mm × 0.5 mm were cut from a cured film and weighed in the dry state (values denoted m_d). Each sample was then swollen in excess deionized water for at least 24 h, blotted dry and weighed again in the hydrated state (values denoted m_w). The water uptake of the material was then estimated as:

$$\text{Water uptake} = \frac{m_w - m_d}{m_d} \times 100\% \quad (1)$$

The equilibrium water content (EWC) was estimated as:

$$\text{EWC} = \frac{m_w - m_d}{m_w} \times 100\% \quad (2)$$

Oxygen permeabilities were estimated according to the model proposed by Morgan and Efron³⁰ using the equation

$$Dk = 1.67e^{0.0397\text{EWC}} \quad (3)$$

where Dk is the oxygen permeability of the material in Dk units (mL O₂ mL⁻¹ mmHg⁻¹).

Optical properties

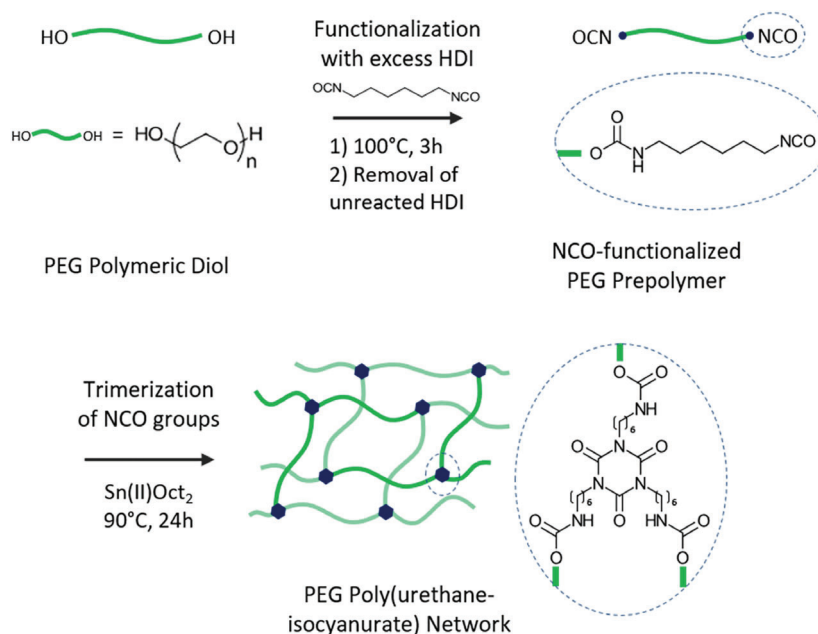
Wavelength-dependent transmission experiments were performed using a Konica Minolta CM-5 spectrophotometer. Scattering experiments were performed using a BYK-Gardner Haze-Gard Plus haze meter according to ASTM D 1003_11. Scattering characteristics are divided into three parameters: transmittance (T), haze (H) and clarity (C). Of these, transmittance is defined as the ratio of transmitted light compared to incident light. Haze indicates the amount of light diffused under wide-angle (>2.5°) scattering. Clarity indicates the amount of light diffused under narrow-angle (<2.5°) scattering. Refractive index measurements were performed at 20.0 °C using a Rudolph Research J357 automatic refractometer equipped with a temperature-controlled sample presser for gels. Six independent measurements were taken for each sample, of which the average value is reported.

Biological properties

Sterilization by UV exposure was performed for 1 h under four 9 W UV lamps at 365 nm and ca 6 mW cm⁻². Sterilization by autoclaving was performed for 20 min at 120 °C with a PBI International pressure cooker from Salm and Kipp BV. Fluorescence measurements were performed with a PerkinElmer Wallac Victor3 spectrophotometer.

Synthesis and characterization of NCO-functionalized PEG prepolymers

All polymeric diols were dried prior to use by azeotropic distillation in toluene, which was subsequently removed under reduced pressure. In a typical experiment, 0.25 g of dibutylphosphate was added to 100 g of dried polymeric diol (where necessary, kept in the melt using a heat gun). This mixture was added dropwise to HDI at 100 °C, using a molar ratio of NCO:OH of 15:1, and subsequently kept at 100 °C for 3 h. The resulting mixture was then transferred dropwise into a short-path thin-film evaporator, which was operated at a reduced pressure of 1 × 10⁻² mbar and 140 °C. Products were collected as transparent, colourless, viscous resins, of which the PEG-1k-, PEG-2k-, PEG-4k- and PEG-10k-based resins



Scheme 1. Schematic of synthesis of PEG PUI polymer network. First, a PEG polymeric diol is functionalized using HDI; next the PUI network is formed by the selective trimerization of the NCO-functionalized PEG prepolymer.

crystallized upon cooling to room temperature. Products were analysed using SEC, GC and ¹H NMR (700 MHz, C₆D₆, representative data for PEG-4k: δ = 4.60 (2H, brs), 4.26 (4H, t), 3.50 (410H, m), 2.97 (4H, q), 2.56 (4H, t), 1.12 (4H, t), 1.02 (4H, t), 0.88 (8H, m) ppm).

Synthesis and characterization of PEG PUI polymer networks by selective trimerization of NCO-functionalized PEG prepolymers

PUI polymer networks were synthesized in analogy to a previously reported procedure, with slight modifications.²² In a typical experiment, 8 g of NCO-functionalized prepolymer was weighed into a polypropylene cup, heated to 90 °C and subsequently degassed by gently applying reduced pressure until no more gas formation was observed. Next, *ca* 60 mg of Sn(II)Oct₂ (corresponding to *ca* 0.75 wt% relative to the prepolymer) was added at 90 °C. After mixing for 15 s in a Hauschild Speedmixer DAC150FVZ, the reaction mixture was transferred to a mould consisting of a 0.5 mm thick polycarbonate frame clamped between two silanized glass plates measuring approximately 20 cm × 10 cm and kept at 90 °C for 24 h. Products were collected as flexible transparent homogeneous films, of which the films based on PEG-4k and PEG-10k prepolymers slowly turned opaque upon cooling to room temperature. The films were analysed in the dry state using ATR-FTIR spectroscopy, water swelling measurements, tensile testing and DSC experiments and subsequently swollen in excess water for at least 24 h. Finally, the films were analysed in the hydrated state for physical properties (tensile testing and mass loss after sterilization by UV exposure or autoclaving), optical experiments (transmittance, scattering and refractive index) and biological experiments (cytotoxicity and protein adsorption, described below).

Indirect cytotoxicity measurements of PEG PUI hydrogels and commercial contact lenses

Cytotoxicity measurements were performed on the PEG PUI hydrogels and several commercial contact lenses as described previously, with minor modifications.³¹ In short, PEG PUI hydrogels

were swollen in MilliQ water, cut into discs with a diameter of 12 mm (*n* = 3), blotted dry and weighed. Next the hydrogels were transferred to a phosphate-buffered saline (PBS) solution and autoclaved for 20 min at 120 °C in a pressure cooker. The PEG PUI hydrogels and the commercial contact lenses (*n* = 3) were then incubated in DMEM/f12 with 10% FBS (0.1 g mL⁻¹) at 37 °C in a humidified incubator containing 5% CO₂. Meanwhile, Arpe-19 cells were seeded on a polystyrene tissue culture well plate with a concentration of 12.5 × 10⁴ cells mL⁻¹ and left for 24 h at 37 °C in a humidified incubator containing 5% CO₂. After 24 h, the medium was removed from the Arpe-19 cells and replaced with conditioned medium from the PEG PUI hydrogels or commercial contact lenses, respectively. A control cell culture was kept in which the medium was replaced with fresh medium that had not been in contact with hydrogel materials. After 48 h the cell viability was measured using an Alamar blue solution (440 μmol L⁻¹ resazurin sodium salt in PBS) and normalized with respect to the control cell culture. To measure the cell viability, a 10:1 (v/v) mixture of cell medium and Alamar blue solution was added to the cells. After incubating for 2 h at 37 °C, the fluorescence emission of the solution at 590 nm was measured using an excitation wavelength of 560 nm.

Protein adsorption measurements of PEG PUI hydrogels and commercial contact lenses

Protein adsorption measurements were performed on the PEG PUI hydrogel films and several commercial contact lenses as described previously, with minor modifications.¹⁰ In short, the PEG PUI hydrogels were swollen in MilliQ water and cut into discs with a diameter of 12 mm (*n* = 3). Commercial contact lenses were used as supplied. All samples were incubated for 24 h in 2 mL of PBS, containing 1.5 mg of bovine serum albumin (BSA) per millilitre of PBS, under gentle shaking at 37 °C. Afterwards, the samples were extracted three times with neat PBS for at least 1.5 h per extraction step and subsequently dried. The dry samples were then swollen in PBS containing 1% (v/v) sodium dodecylsulfate and kept at 37 °C

under gentle shaking for three days. The concentration of BSA in the supernatant was then determined using a Bio-Rad DC Protein Assay kit according to the supplier's instructions.

RESULTS AND DISCUSSION

Synthesis of NCO-functionalized PEG prepolymers and PEG PUI polymer networks by selective trimerization of NCO-functionalized PEG prepolymers

PEG polymeric diols were functionalized using HDI and subsequently trimerized as reported previously.²² Using ¹H NMR, SEC and GC, it was confirmed that the functionalization of all PEG polymeric diols with HDI succeeded selectively and quantitatively. The characteristics of all functionalized PEG prepolymers are reported in the supporting information in Table S1. Next, the NCO-functionalized prepolymers were crosslinked by the selective trimerization of the terminal NCO groups. This resulted in the formation of PEG PUI type polymer networks. The completion of the trimerization reaction was confirmed using ATR-FTIR spectroscopy (supporting information, Fig. S1).

Physical properties of PEG PUI networks and hydrogels: EWC, oxygen permeability, mechanical properties and stability

Water uptake, EWC and oxygen permeability

Due to the hydrophilicity of PEG, the water uptake and resulting EWC of the PEG PUI networks were generally high. The shortest-chain PEG PUI network, synthesized from a 0.4 kg mol⁻¹ PEG prepolymer, demonstrated a water uptake of 19.2 wt%. This corresponds to an EWC of 16.1 wt% in the hydrated state. The longest-chain PEG PUI hydrogel on the other hand, synthesized from a 10 kg mol⁻¹ PEG prepolymer, demonstrated a water uptake of 321.6 wt%, corresponding to an EWC of 76.3 wt%. All water uptakes and EWCs are reported in Table 3. Owing to the well-defined network structure on which we reported previously, the water uptakes and EWCs of the hydrogels could easily be controlled over a wide range.²² Notably, the range of EWCs measured for the PEG PUI hydrogels encompasses almost the entire range of EWCs typically reported for contact lens hydrogels (i.e. ca 20 to 80 wt%; Table 1).² This includes both soft and rigid contact lens hydrogels.

From the EWCs, the oxygen permeabilities of the PEG PUI hydrogels were approximated using the model proposed by Morgan and Efron (Eqn (3)) and are reported in Table 3.³⁰ This semi-empirical model correlates oxygen permeability (the product of oxygen diffusivity and solubility, typically referred to as 'Dk' in contact lens literature) to EWC and is used for conventional, non-silicone hydrogels.³² The model assumes that oxygen transport only takes place through the water phase of the hydrogel while no oxygen transport takes place through the solid phase of the hydrogel. Consequently, the oxygen permeability values estimated using this model should be considered as minimal values rather than the actual oxygen permeability values. The difference between the predicted and actual oxygen permeability values evidently depends on the specific oxygen transport properties of the hydrogel's solid phase. In this respect, it is worthwhile noting that PEG polymer networks have been shown to exhibit a non-zero oxygen permeability in the dry state and actually demonstrate a certain level of oxygen affinity.³³ Therefore, we expect the PEG PUI hydrogels to have higher actual oxygen permeability values than the approximated values reported in Table 3. However, an experimental assessment will be needed to determine the exact oxygen permeabilities of the PEG PUI hydrogels.

Mechanical properties in dry and hydrated states

The mechanical properties of all polymer networks were assessed both in the dry state and in the hydrated state and are reported in Table 3. It was found that the dry polymer networks were generally tough materials, with varying mechanical properties dependent on network density and crystallinity. In the dry state, the elastic moduli ($E_{\text{mod,dry}}$) of the networks ranged from 6.6 to 309.2 MPa, while the stress at break ($\sigma_{\text{b,dry}}$) and elongation at break ($\epsilon_{\text{b,dry}}$) values ranged from 1.4 to 26.4 MPa and from 11.5 to 517.0%, respectively. The PUI networks synthesized from PEG prepolymers with a molecular weight of 2 kg mol⁻¹ and higher were semi-crystalline in nature in the dry state, displaying melting peaks in the range 20–60 °C.

Table 3 also presents the mechanical properties of the hydrogels in the hydrated state, which are important for their application as contact lenses. The PEG PUI hydrogels were generally tough in the hydrated state, covering a wide range of material properties. In the hydrated state, the elastic moduli of the materials ($E_{\text{mod,wet}}$) ranged from 0.8 to 17.2 MPa, the stress at break ($\sigma_{\text{b,wet}}$) values ranged from 0.4 to 2.0 MPa and the elongation at break ($\epsilon_{\text{b,wet}}$) values ranged from 9.4 to 88.9%. The hydrogels demonstrated toughness ($W_{\text{b,wet}}$) values in the hydrated state ranging from 98 to 226 kJ m⁻³.

The tensile stress–strain diagrams of the PUI hydrogels in the hydrated state are shown in Fig. 1(a), illustrating the high toughness of the gels. Importantly, the stress at break values were >400 kPa for all hydrogels and the toughness values were approximately 100 kJ m⁻³ or more. This illustrates the high mechanical resilience of these hydrogels in the water-swollen state. In practice, it was observed that in the water-swollen state, all hydrogels could easily be handled without fracture or rupture. It should be noted that this is non-trivial for crosslinked PEG hydrogels. As far as we know, these PEG PUI hydrogels are the toughest crosslinked PEG hydrogels reported in the literature, clearly outperforming other typical crosslinked PEG hydrogels.^{18–20} As a result, hydrogels with a relatively high EWC and low modulus can be synthesized that still exhibit sufficient toughness for handling and production. This is exceptional and attractive for contact lens applications. The beneficial combination of high EWC, low modulus and high toughness is best illustrated by the PEG-10k-based PUI hydrogel, which combines an EWC of 76% with a modulus of 0.8 MPa and a toughness value of 226 kJ m⁻³. These values match those of the best-performing organic polymer contact lens materials reported in the literature.² The high toughness of the PEG PUI type hydrogels can likely be attributed to the PUI-type network structure on which we reported previously.²²

To illustrate the wide range of mechanical properties accessible using the synthesis method employed, the tensile elastic moduli of the hydrogels are plotted together with the EWCs in Fig. 1(b). The measured range of elastic moduli covers most of the range of elastic moduli typically reported for soft contact lens materials (0.2–2 MPa) and also includes typical values reported for rigid contact lens materials (ca 10 MPa) (Table 1).² It should be noted that the current span of elastic moduli is obtained simply by varying the density of the polymer networks using PEG prepolymers of different molecular weights. Other strategies typically used to manipulate the mechanical properties of hydrogel materials may also be considered, such as the incorporation of monofunctional prepolymers and/or prepolymers with a different chemical nature.

Hydrogel stability during sterilization

A first assessment of the stability of the PEG PUI hydrogels was done by exposing the hydrogels to two common sterilization

Table 3. Physical properties of PEG PUI networks and hydrogels in the dry state and in the hydrated state. Numbers in parentheses are standard deviations

PEG PUI hydrogel prepolymer	Water uptake (%)	EWC (%)	T_g (°C)	$T_{m,p}$ (°C)	$E_{mod,dry}$ (MPa)	$\sigma_{b,dry}$ (MPa)	$\epsilon_{b,dry}$ (%)	$E_{mod,wet}$ (MPa)	$\sigma_{b,wet}$ (MPa)	$\epsilon_{b,wet}$ (%)	$W_{b,wet}$ (kJ m ⁻³)	O_2^- perm. ^a (Dk)
PEG-0.4k-diNCO	19.2 (0.1)	16.1 (0.1)	-20.2	- ^c	17.1 (2.4)	2.7 (0.8)	13.9 (2.6)	17.0 (0.8)	2.0 (0.4)	9.8 (2.3)	110 (40)	3.2
PEG-0.6k-diNCO	26.1 (0.3)	20.7 (0.2)	-23.2	- ^c	18.7 (1.3)	2.8 (0.4)	13.6 (1.6)	17.2 (0.5)	2.0 (0.3)	9.4 (1.6)	99 (27)	3.8
PEG-1k-diNCO	87.1 (0.6)	46.5 (0.2)	-47.2	- ^c	10.9 (0.6)	1.4 (0.2)	11.5 (2.1)	9.6 (0.3)	1.6 (0.8)	14.1 (8.5)	142 (123)	10.6
PEG-2k-diNCO	150.6 (0.7)	60.1 (0.1)	-42.9	21.6	6.6 (1.1)	1.6 (0.4)	25.1 (10.1)	5.9 (0.4)	1.1 (0.1)	17.0 (2.8)	98 (20)	18.2
PEG-4k-diNCO	222.6 (0.7)	69.0 (0.1)	-49.5	39.3	171.5 (6.1)	19.3 (0.5)	250.7 (26.2)	4.0 (0.2) ^b	0.8 (0.1) ^b	21.7 (1.0) ^b	104 (5) ^b	25.9
PEG-10k-diNCO	321.6 (4.2)	76.3 (0.2)	-49.4	53.8	309.2 (30.0)	26.4 (2.7)	517.0 (40.9)	0.8 (0.3)	0.4 (0.1)	88.9 (23.8)	226 (94)	34.5

^a Approximated value calculated from the EWC assuming zero transport of oxygen through the solid phase of the hydrogel. Reported in Dk units (mL O₂ mL⁻¹ · mmHg⁻¹).

^b n = 2.

^c Not observed.

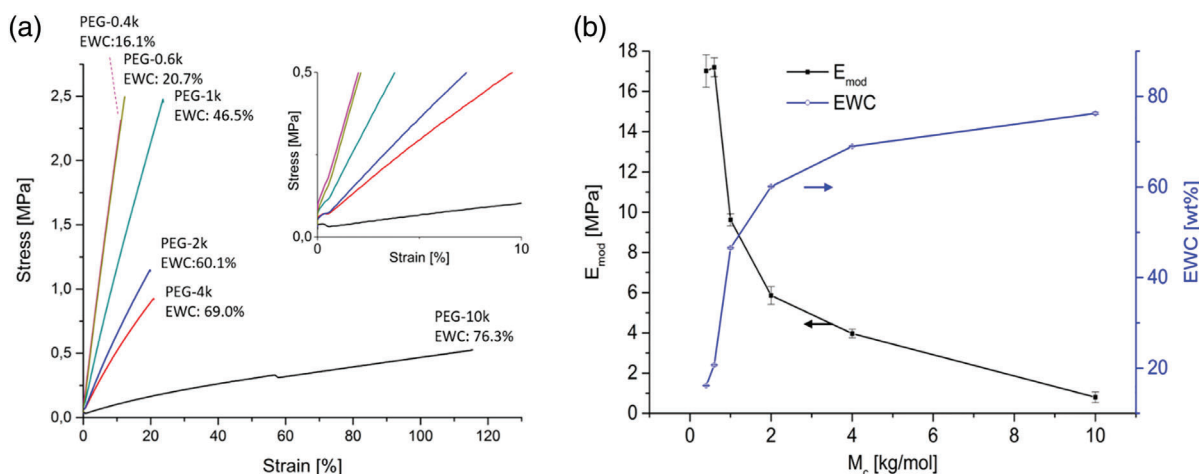


Figure 1. Mechanical properties of PEG PUI hydrogels in water-swollen state. (a) Tensile stress–strain diagrams of PEG PUI hydrogels in the hydrated state. The molecular weights of the respective prepolymers as well as the EWCs are reported next to the curves. (b) Tensile elastic moduli (E_{mod} ; black squares; approximated as the tangent of the linear regime of the tensile stress–strain dependence) and EWC (blue circles) of PEG PUI hydrogels as a function of the number-average molecular weight between crosslinks M_c of the polymer network, approximated by the number-average molecular weight of the respective prepolymer M_n .

procedures. The hydrogels were analysed gravimetrically to detect any changes in mass and visually by inspecting each sample for changes in colour, size and/or opacity.

No mass loss was determined for any of the hydrogels after 1 h of UV exposure and none after autoclaving at 120 °C for 20 min. Also, no changes in colour, size or opacity of the hydrogels were observed. Although changes in other material properties, such as mechanical properties, degree of swelling or optical properties, have not been investigated, these results indicate that the PEG PUI hydrogels are stable under the sterilization procedures used.

Optical properties of PEG PUI hydrogels: transmittance, haze, clarity and refractive index

Transmittance, haze and clarity

The transparency of the PEG PUI hydrogels was investigated using two methods. Firstly, the transmittance of the hydrogels was determined as a function of wavelength. The transmission spectra of all hydrogels are shown in Fig. 2(a). Typically, an average transmittance of 90% is considered a minimum requirement for contact lens applications,^{2,34} although minimum values of 95% are also reported.⁵ As seen in the spectra, the transmittance of the hydrogels was generally >90% throughout the visible spectrum

and on average around 95% for most hydrogels. It should be noted that these measurements were performed on hydrogel films with a thickness of 0.5–1 mm, whereas the typical centre-point thickness of a contact lens is around 50–250 μm.³⁵ In other words, even in non-optimized form the PEG PUI hydrogels already meet the general transmittance requirements for contact lens applications.

Secondly, the scattering characteristics of the transmitted light were investigated (Table 4). All hydrogels demonstrated high transmittance values of >90%, with the PEG-1k, PEG-2k and PEG-4k hydrogels demonstrating transmittance values of around 95%. This is consistent with the wavelength-dependent measurements discussed previously. More importantly, the PEG PUI hydrogels generally showed very high clarities, in most cases with values close to 100%. Clarity is also referred to as the ‘see-through quality’ of a material and describes how well fine details and sharp images can be perceived when looking through the material.³⁶ Finally, the haze values, considered as a measure for the loss of contrast,³⁶ were in most cases generally low and in the range 1–4% with the exception of the PEG-10k PUI hydrogel. Considering that this hydrogel has the highest EWC and is the most crystalline in the dry state, the reduced optical performance of this hydrogel is likely

Table 4. Scattering characteristics (transmittance, haze and clarity) and refractive indices (n_{D20}) of PEG PUI hydrogels

PEG PUI hydrogel prepolymer	Transmittance (%)	Haze (%)	Clarity (%)	Refractive index, n_{D20}
PEG-0.4k-diNCO	93.1	3.4	96.2	1.4796
PEG-0.6k-diNCO	93.1	1.8	99.5	1.4707
PEG-1k-diNCO	95.2	1.9	99.4	1.4010
PEG-2k-diNCO	95.1	3.0	99.4	1.3768
PEG-4k-diNCO	95.7	2.2	98.7	1.3611
PEG-10k-diNCO	90.5	22.8	86.3	1.3562

attributable to slight dehydration of the surface during the optical measurements.

Refractive index

The refractive indices of the PEG PUI hydrogels in the hydrated state are reported in Table 4 and plotted in Fig. 2(b) together with their EWCs. The refractive indices ranged from *ca* 1.48 for the shortest-chain (PEG-0.4k) hydrogel to *ca* 1.36 for the longest-chain (PEG-10k) hydrogel. As indicated by the trends shown in Fig. 2(b), the refractive index seems to be mostly dependent on the EWC of the hydrogel. This is consistent with what is reported in the literature.⁹

The PEG PUI hydrogels span a wide range of refractive index values, encompassing all values mentioned in the literature. In this regard, it is safe to say that the range of refractive index values of the PEG PUI hydrogels is suitable for contact lens applications. The intrinsically high refractive indices of the materials comprising the solid state of the hydrogel networks are considered beneficial in this context. For example, a refractive index value of 1.48 is reported for a pure HDI polyisocyanurate network²⁶ and a value of 1.47 is provided by the manufacturer for a liquid PEG-0.6k polymeric diol. Furthermore, the refractive index of PEG polymeric diols has been shown to increase for increasing PEG molecular weight.²⁵ This allows for hydrogel formulations with a higher EWC and/or thinner contact lenses (both of which are associated with improved wearing comfort) whilst still retaining a sufficiently high overall refractive index of the hydrogel.⁶ Also, the broad range of and easy control over the refractive index of the PEG PUI hydrogel materials are considered beneficial for further optimization.

Biological properties of PEG PUI hydrogels: biocompatibility and protein adsorption

Biocompatibility

The biocompatibility of the prepared and extracted PEG PUI hydrogels was investigated in an indirect cytotoxicity study in analogy to a procedure reported previously.³¹ A human retinal pigment epithelium cell line (Arpe-19) was used as a model cell line for this. The viabilities of the cells after 48 h are reported in Table 5. As is evident, all PEG PUI hydrogels were non-cytotoxic under these conditions, indicating good biocompatibility. This is in line with our expectations, considering that all the chemical moieties present in the hydrogel network are known to be biocompatible.^{28,29} In most cases, PEG PUI hydrogels had a slight stimulating effect on cell growth, indicated by cell viabilities >100% compared to the control cell culture.

Protein adsorption

To investigate the biofouling properties of the PEG PUI hydrogels, a protein adsorption study was performed in analogy to a procedure reported previously.¹⁰ BSA was used as a model protein. The amounts of adsorbed BSA after 24 h, normalized for the dry weight of the hydrogel, are reported in Table 5 for all PEG PUI hydrogels and several commercial contact lenses. The PEG PUI hydrogels demonstrated BSA adsorption values ranging from 0.24 to 0.65 mg g⁻¹. These values are significantly lower than those of the commercial contact lenses tested, which ranged from 0.55 to 1.38 mg g⁻¹. Especially, the disposable contact lenses intended for single-day use demonstrated high BSA adsorption values of 0.85 and 1.38 mg g⁻¹. This indicates that PEG PUI hydrogels are suitable for the production of contact lenses with a wear time of ≥ 1 month, at least as far as biofouling properties are concerned.

The low biofouling of the PEG PUI hydrogels can likely be attributed to the inert chemical structure of the PEG PUI hydrogel networks. The new PEG PUI hydrogels are unique in this context, in the sense that they are hydrophilic but do not contain any free -OH, -NH₂, -COOH or charged moieties. This results in the desirable combination of high-EWC hydrogels with low biofouling propensity, which is challenging to achieve using the currently used contact lens materials. This is considered a significant improvement, since biofouling is at present one of the main issues associated with contact lens materials.^{10,12,15–17} In combination with the high toughness in the hydrated state discussed previously, this makes

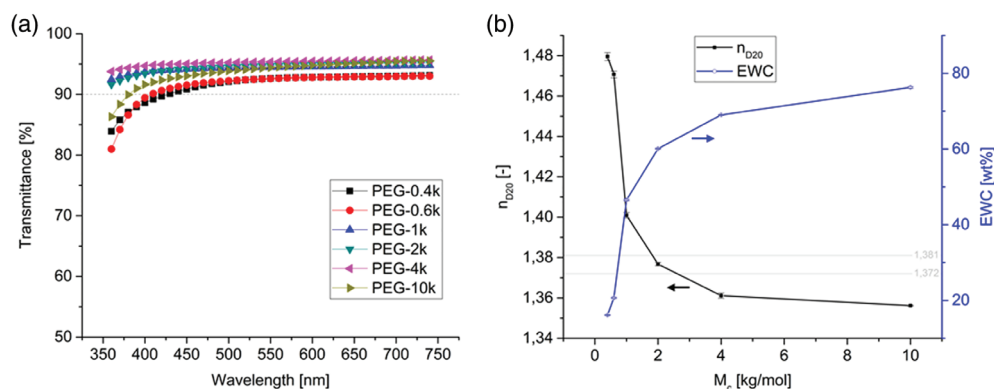


Figure 2. Optical properties of PEG PUI hydrogels. (a) Wavelength-dependent transmission spectra of the PEG PUI hydrogels in the UV-visible region. A dotted grey line is included at the 90% transmittance threshold as a guide for the eye. (b) Refractive indices (n_{D20}) and EWCs of the PEG PUI hydrogels as a function of the molecular weight between crosslinks of the PEG PUI networks. Marked by grey lines is the range of refractive indices described by Caló *et al.* as 'ideal hydrogels should have a refractive index value matching the range 1.372–1.381'.⁵

Table 5. Biological properties of PEG PUI hydrogels and a selection of commercial contact lenses. Numbers in parentheses are standard deviations

PEG PUI hydrogel prepolymer	EWC (%)	Cell viability after 48 h (%)	Adsorbed BSA after 24 h ^a (mg g ⁻¹)	Contact lens material (manufacturer, wear time)	EWC (%)	Cell viability after 48 h (%)	Adsorbed BSA after 24 h ^a (mg g ⁻¹)
PEG-0.4k-diNCO	16.1 (0.1)	111 (3)	0.24 (0.09) ^b	Midafilcon A (Menicon, day)	56 ^c	99 (4)	0.85 (0.07) ^b
PEG-0.6k-diNCO	20.7 (0.2)	110 (3)	0.45 (0.05)	Riofilcon A (Cooper Vision, day)	58 ^c	92 (3)	1.38 (0.33)
PEG-1k-diNCO	46.5 (0.2)	109 (2)	0.39 (0.18)	Comfilcon A (Cooper Vision, month)	48 ^c	- ^d	0.55 (-) ^e
PEG-2k-diNCO	60.1 (0.1)	106 (1)	0.64 (0.19)	Somofilcon A (Cooper Vision, month)	- ^f	- ^d	0.71 (-) ^e
PEG-4k-diNCO	69.0 (0.1)	102 (1)	0.65 (0.08)				
PEG-10k-diNCO	76.3 (0.2)	104 (3)	0.64 (0.14)				

^a Quantified as the total mass of adsorbed BSA in 24 h, normalized for the dry weight of the hydrogel sample.

^b $n = 2$.

^c As provided by the manufacturer.

^d Not determined.

^e $n = 1$.

^f Not provided.

PEG PUI hydrogels an attractive new class of materials for contact lens applications.

CONCLUSIONS

PEG PUI hydrogels comprise an attractive novel class of hydrogel materials for contact lens applications, meeting all requirements for material properties reported for the application (Table 2). Owing to the specific PEG PUI network structure, a desirable combination of high EWC, high toughness in the hydrated state, excellent optical properties, good biocompatibility and low bio-fouling propensity is achieved. Also the oxygen permeability and the chemical stability with respect to common sterilization techniques of the PEG PUI hydrogels are suitable for the application in mind.

This particular combination of properties can be attributed to the PEG PUI polymer network structure comprising the hydrogel networks. The use of a PEG polymeric backbone provides the unusual combination of hydrophilicity and chemical inertness. As a result, high-EWC hydrogels that demonstrate a low protein adsorption are obtained. The PUI-type crosslinking units provide the high toughness needed for contact lens applications, which conventional crosslinked PEG hydrogels typically lack.

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SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

REFERENCES

- Nicolson PC and Vogt J, *Biomaterials* **22**:3273–3283 (2001).
- Musgrave CSA and Fang F, *Material (Basel)* **12**:261 (2019).
- Nichols JJ and Fischer D, *Contact Lens Spectr* **34**:18–23 (2019).
- Moreddu R, Vigolo D and Yetisen AK, *Adv Healthc Mater* **8**:1900368 (2019). <https://doi.org/10.1002/adhm.201900368>.
- Caló E and Khutoryanskiy VV, *Eur Polym J* **65**:252–267 (2015).
- Childs A, Li H, Lewittes DM, Dong B, Liu W, Shu X et al., *Sci Rep* **6**:34905 (2016).
- Varikooty J, Keir N, Woods CA and Fonn D, *Eye Contact Lens Sci Clin Pract* **36**:2–5 (2010).
- Patel S, Marshall J and Fitzke FW, *J Refract Surg* **11**:100–105 (1995).
- Gonzalez-Mejome JM, Lira M, López-Alemayn A, Almeida JB, Parafita MA and Refojo MF, *Ophthalmic Physiol Optics* **26**:57–64 (2006).
- Zhang W, Li G, Lin Y, Wang L and Wu S, *J Biomater Sci Polym Ed* **28**:1935–1949 (2017).
- Annabi N, Tamayol A, Uquillas JA, Akbari M, Bertassoni LE, Cha C et al., *Adv Mater* **26**:85–124 (2014).
- Xiao A, Dhand C, Leung CM, Beuerman RW, Ramakrishna S and Lakshminarayanan R, *J Mater Chem B* **6**:2171–2186 (2018).
- Elder MJ, Stapleton F, Evans E and Dart JKG, *Eye* **9**:102–109 (1995).
- Dart J, *Contact Lens Anterior Eye* **20**:113–118 (1997).
- Thissen H, Gengenbach T, du Toit R, Sweeney DF, Kingshott P, Griesser HJ et al., *Biomaterials* **31**:5510–5519 (2010).
- Lord MS, Stenzel MH, Simmons A and Milthorpe BK, *Biomaterials* **27**:567–575 (2006).
- Korogiannaki M, Samsom M, Schmidt TA and Sheardown H, *ACS Appl Mater Interfaces* **10**:30125–30136 (2018).
- Zant E, Bosman MJ and Grijpma DW, *J Appl Biomater Funct Mater* **10**:197–202 (2012).
- Gong JP, *Soft Matter* **6**:2583–2590 (2010).
- Sakai T, Matsunaga T, Yamamoto Y, Ito C, Yoshida R, Suzuki S et al., *Macromolecules* **41**:5379–5384 (2008).
- Moser T, Celma C, Lebert A, Charrault E, Brooke R, Murphy PJ et al., *ACS Appl Mater Interfaces* **8**:974–982 (2016). <https://doi.org/10.1021/acsami.5b10831>.
- Driest PJ, Dijkstra DJ, Stamatialis D and Grijpma DW, *Macromol Rapid Commun* **40**:1800867 (2019).
- Meier-Westhues U, Danielmeier K, Kruppa P and Squiller EP, *Polyurethanes: Coatings, Adhesives and Sealants*. Vincentz-Network, Hanover (2019).
- Driest PJ, Lenzi V, Marques LSA, Ramos MMD, Dijkstra DJ, Richter FU et al., *Polym Adv Technol* **28**:1299–1304 (2017).
- Kolská Z, Valha P, Slepíčka P and Švorčík V, *Arab J Chem* (2016). <https://doi.org/10.1016/J.ARABJC.2016.11.006>.
- Flipsen TAC, Steendam R, Pennings AJ and Hadziioannou G, *Adv Mater* **8**:45–48 (1996).

- 27 Fabbri P, Mohammad Poor S, Ferrari L, Rovati L, Borsacchi S, Geppi M *et al.*, *Polymer (Guildf)* **55**:488–494 (2014).
- 28 Liu G, Li Y, Yang L, Wei Y, Wang X, Wang Z *et al.*, *RSC Adv* **7**:18252–18259 (2017).
- 29 Burel F, Poussard L, Tabrizian M, Merhi Y and Bunel C, *J Biomater Sci Polym Ed* **19**:525–540 (2008).
- 30 Morgan PB and Efron N, *Contact Lens Anterior Eye* **21**:2–6 (1998).
- 31 Ulu A, Balcioglu S, Birhanli E, Sarimeseli A, Keskin R, Koytepe S *et al.*, *J Appl Polym Sci* **135**:46575 (2018).
- 32 Seitz ME, Wiseman ME, Hilker I, Loos J, Tian M, Li J *et al.*, *Polymer (Guildf)* **118**:150–162 (2017).
- 33 Lin H and Freeman BD, *Macromolecules* **39**:3568–3580 (2006).
- 34 Tummala GK, Rojas R and Mihranyan A, *J Phys Chem B* **120**:13094–13101 (2016).
- 35 Lira M, Pereira C, Real Oliveira MECD and Castanheira EMS, *Contact Lens Anterior Eye* **38**:120–126 (2015).
- 36 *Optical Properties of Transparent Materials: Transmission – Haze – Clarity*. BYK-Gardner Catalogue (2010/2011).