Structure–property relations in semi-crystalline combinatorial poly(urethane-isocyanurate)-type hydrogels

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Abstract

Within the fields of regenerative medicine and tissue engineering, the development of tough hydrogel biomaterials is a challenging topic that has received much attention over the past few years. Recently, a method was developed to synthesize tough combinatorial poly(urethane-isocyanurate) (PUI)-type hydrogels by the trimerization of mixtures of NCO-functionalized prepolymers. As this synthesis approach allows a large degree of freedom in terms of polymer network design with a high level of control over the polymer network structure, the resulting systems are ideally suited for studying structure–property relations in tough hydrogel systems. In this work, we aim to systematically investigate the influence of introducing a hydrophobic component into a PUI polymer network on the mechanical properties of the resulting PUI hydrogels. Additionally, the effect of (the degree of) crystallinity of the hydrophobic network component is investigated. For this, two series of combinatorial PUI hydrogels are synthesized, based on a hydrophilic poly(ethylene glycol) prepolymer and increasing amounts of either a crystallizable hydrophobic prepolymer (poly(ε-caprolactone)) or an amorphous hydrophobic prepolymer (poly(propylene glycol)). It is shown that the toughness of amorphous PUI hydrogels is hardly influenced by the hydrophobic content, whereas the toughness of semi-crystalline PUI hydrogels strongly increases with increasing hydrophobic content. Also, the toughness of the latter hydrogels increases further with increasing degree of crystallinity of the hydrogel. Finally, it is shown that the semi-crystalline PUI hydrogels are promising materials for biomedical adhesive and coating applications, as well as for load-bearing biomedical applications within the fields of tissue engineering and regenerative medicine.

Keywords: regenerative medicine; tough hydrogels; semi-crystalline hydrogels; structure–property relations; polyurethanes

INTRODUCTION

Over the past few decades, hydrogels have emerged as increasingly important (bio)materials in the field of regenerative medicine and tissue engineering, from both scientific and industrial points of view.1 In particular, high water content combined with good biocompatibility and physical properties resembling the natural extracellular matrix make hydrogels very attractive materials.2 However, the poor mechanical resilience typically associated with hydrogel materials (e.g. low elastic modulus, low ultimate tensile strength and/or poor toughness) still remains a drawback which has limited their application thus far, especially as load-bearing biomaterials. Therefore, the development of tough, mechanically resilient hydrogels has received much attention over the past few years.3–5 Various design strategies have been developed to increase the toughness of hydrogel materials. These include the use of (interpenetrating) double-polymer network structures,6 (dynamic) multivalent ionic crosslinking units,7, 8 nanoparticle fillers,9, 10 and physical (hydrophobic) interaction enhanced toughening mechanisms.11–15

Recently, we developed a method to synthesize tough polymer networks and hydrogels based on the trimerization of NCO-functionalized prepolymers.16 The resulting poly(urethane-isocyanurate) (PUI)-type networks typically demonstrate high mechanical resilience and toughness, both in the dry state and in the water-swollen state. Additionally, it was shown that combinatorial PUI-type networks can be synthesized by trimerizing mixtures of different types of NCO-functionalized prepolymers in solution.17 One of the advantages of this synthesis method over other synthesis methods typically used to produce tough hydrogels is that it allows a large degree of freedom in terms of polymer network design, while maintaining a high level of control over the polymer network structure.16 Consequently, this method is ideally suited for investigating the influence of variations in the polymer network structure on the material properties of the resulting hydrogels.

In this work, we aim to systematically investigate the influence of introducing a hydrophobic component into a PUI polymer...
network on the mechanical properties of the resulting PUI hydrogels. Specifically, the effect of increasing hydrophobic content on the ultimate tensile strength, elongation at break and toughness of the hydrogels is investigated, as these properties are typically the most difficult to target by design. For this, series of combinatorial PUI networks are synthesized containing increasing amounts of a hydrophobic prepolymer (see Scheme 1). Additionally, the effect of (the degree of) crystallinity of the hydrophobic network component is investigated by comparing PUI hydrogels in which the hydrophobic prepolymer is crystallizable in nature to PUI hydrogels in which the hydrophobic prepolymer is amorphous in nature. Since only the chemical structure of the hydrophobic network component is varied, the targeted structure–property relations are expected to be applicable to a wide range of hydrogel types, not limited to the PUI-type hydrogels specifically.

Poly(ethylene glycol) (PEG) or poly(caprolactone) (PCL) and poly(propylene glycol) (PPG) with number-average molecular weights (\(M_n\)) of 4 kg mol\(^{-1}\) are used as the polymeric diols. At the molecular weights used, PEG is a crystallizable hydrophilic polymer with a glass transition temperature (\(T_g\)) between −24 and −37 °C and a peak melting temperature (\(T_m\)) between 58 and 66 °C.\(^{18, 19}\) PCL is a crystallizable hydrophobic polymer with \(T_g\) between 24 and 37 °C, with a glass transition temperature (\(T_g\)) between 58 and 66 °C,\(^{18, 19}\) and PPG is an amorphous hydrophobic polymer with \(T_g\) of approximately −60 °C.\(^{21}\)

The resulting hydrogels are characterized for their thermal and mechanical properties, both in the dry state and in the water-swollen state. The heat of fusion, obtained from dynamic scanning calorimetry measurements, is used as a measure for the degree of crystallinity of the hydrogels and is correlated to the toughness of the hydrogel material in the hydrated state.

**EXPERIMENTAL DETAILS**

**Materials and methods**

Hexamethylene diisocyanate (HDI) and PPG (\(M_n\) 4 kg mol\(^{-1}\) were supplied by Covestro Deutschland AG. PCL (\(M_n\) 4 kg mol\(^{-1}\) was supplied by Perstorp Chemicals GmbH. All other chemicals were purchased from Sigma-Aldrich and used as received. The details of the characterization methods used have been reported previously.\(^{17}\)

**Synthesis of NCO-functionalized prepolymers and PUI networks**

The synthesis of NCO-functionalized prepolymers and combinatorial PUI networks was performed as reported previously.\(^{17}\) The resulting mixture was kept at 100 °C for 3 h in the case of PPG diols, a reaction temperature and time of 120 °C and 6 h were used, respectively. The mixture was then transferred to a short-path thin-film evaporator operated at 1 × 10\(^{-2}\) mbar and 140 °C. Reaction products were collected as clear, colorless, viscous resins, of which the PEG- and PCL-based resins crystallized upon cooling to room temperature. The resins were analyzed using size exclusion chromatography, gas chromatography and \(^1\)H NMR spectroscopy.

Next, a total of 4 g of prepolymer was dissolved in 4 g of propylene carbonate in the weight ratios provided in Table 1 (in the case of reaction mixtures containing functionalized PPG prepolymer, toluene was used as the solvent instead of propylene carbonate). After degassing, 60 mg of tin(II) 2-ethylhexanoate was added and the mixture was homogenized for 15 s in a DAC150FZ Hauschild Speedmixer. The homogeneous reaction mixture was then brought into a mold consisting of a 0.5 mm thick polycarbonate frame clamped between two siliconized glass plates and kept at 90 °C for 48 h. After demolding, samples were collected as flexible, macroscopically homogeneous, free-standing films. The films were subsequently extracted for 12–24 h using an excess of acetone, which was periodically refreshed. Next, the acetone was slowly exchanged for \(n\)-hexane over the course of 24 h. Finally, the films were vacuum-dried and characterized in the dry state using Fourier-transform infrared spectroscopy, differential scanning calorimetry, tensile testing and swelling experiments. Finally,

![Scheme 1. Synthesis of hydrophilic–hydrophobic combinatorial PUI hydrogels by the trimerization of mixtures of hydrophilic and hydrophobic NCO-functionalized prepolymers in various ratios.](image-url)
samples of each film were swollen in water for 24 h and characterized in the water-swollen state using differential scanning calorimetry and tensile testing.

RESULTS AND DISCUSSION

Synthesis of NCO-functionalized prepolymer s and PUI networks by selective trimerization of NCO-functionalized prepolymers

Polymeric diols were functionalized using HDI and subsequently trimerized as reported previously. It was confirmed that the functionalization of all polymeric diols with HDI succeeded selectively and quantitatively in all cases. The characteristics of all functionalized prepolymers have been reported previously.

Combinatorial PUI polymer networks were synthesized by the trimerization of a mixture of the NCO-functionalized prepolymers in solution. In this case, to prevent phase separation, toluene was used as the inert solvent for the PPG-containing prepolymer mixtures instead of propylene carbonate. All reaction mixtures were transparent and homogeneous throughout the trimerization reaction. The completion of the trimerization reaction was confirmed using attenuated total reflection Fourier transform infrared spectroscopy as reported previously.

| Table 1. Mechanical and thermal properties in the dry state of combinatorial PUI networks with increasing hydrophobic content (HC) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PEG–PCL | HC (wt%) | E\textsubscript{mod, dry} (MPa) | ⊞\textsubscript{b, dry} (MPa) | ε\textsubscript{b,dry} (%) | W\textsubscript{b,dry} (MJ m\textsuperscript{-3}) | T\textsubscript{g} (°C) | T\textsubscript{m} (°C) | ΔH\textsubscript{m} (J g\textsuperscript{-1}) |
| 0 | 208.9 (42.3) | 15.4 (3.1) | 403.8 (62.0) | −50.3 | 46.7 | 44.9 | 42.4 | 55.1 |
| 20 | 85.8 (26.2) | 7.5 (0.6) | 322.6 (41.9) | 19.5 (5.4) | 0.8 (0.6) | 32.0 (3.3) | 0.7 (0.5) | 4.2 (0.5) | 54.0 (7.7) | 0.7 (0.1) | 46.7 |
| 40 | 374.9 (9.4) | 7.8 (1.3) | 322.7 (68.3) | 15.0 (2.9) | 2.2 (0.5) | 4.0 (0.9) | 3.7 (0.3) | 4.2 (0.2) | 54.0 (7.7) | 0.7 (0.1) | 46.7 |
| 60 | 660.3 (3.5) | 11.4 (1.0) | 318.2 (22.2) | 23.0 (1.6) | 0.9 (0.2) | 33.4 (5.6) | 0.1 (0.0) | 4.2 (0.2) | 54.0 (7.7) | 0.7 (0.1) | 46.7 |
| 80 | 1111.1 (1.0) | 12.5 (1.6) | 222.4 (11.2) | 16.4 (1.4) | 0.7 (0.4) | 41.6 (2.0) | 0.0 (0.0) | 4.2 (0.2) | 54.0 (7.7) | 0.7 (0.1) | 46.7 |
| 100 | 1111.1 (1.0) | 12.5 (1.6) | 222.4 (11.2) | 16.4 (1.4) | 0.7 (0.4) | 41.6 (2.0) | 0.0 (0.0) | 4.2 (0.2) | 54.0 (7.7) | 0.7 (0.1) | 46.7 |

On the left, the hydrophobic component is crystallizable in nature (PEG–PCL); on the right, the hydrophobic component is amorphous in nature (PEG–PPG). Tensile data are provided as the average value of triplicate measurements, whereby the standard deviation is given in parentheses.

* Duplicate instead of triplicate measurement.

** Single instead of triplicate measurement.

* Not observed.

Figure 1. Tensile stress–strain diagrams of combinatorial PUI networks with increasing hydrophobic content (HC) in the dry state: (a) hydrophobic component is crystallizable in nature (PEG–PCL); (b) hydrophobic component is amorphous in nature (PEG–PPG).
Table 2. Mechanical properties in the water-swollen state of combinatorial PUI networks with an increasing hydrophobic content (HC)

| HC (wt%) | Water uptake (wt%) | \( E_{\text{mod, wet}} \) (MPa) | \( \sigma_b, \text{wet} \) (MPa) | \( \varepsilon_b, \text{wet} \) (%) | \( W_{b, \text{wet}} \) (MJ m\(^{-3}\)) | \( T_g \) (°C) | \( T_m \) (°C) | \( \Delta H_m \) (J g\(^{-1}\)) | PEG–PCL Swelling | Tensile | Thermal |
|----------|-------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| 0        | 380.5 (3.8)       | 1.1 (0.5)     | 0.4            | 34.6 (5.0)     | 0.08 (0.02)   | —              | —              | —              | 0              | 380.5 (3.8) | 1.1 (0.5) | 0.4 (0.05) |

| 20       | 220.8 (1.2)       | 2.5 (0.2)     | 0.7 (0.1)      | 63.6 (8.9)     | 0.29 (0.06)   | 40.9 (2)       | 0              | 34.6 (5.0)     | —              | —              | 313.4 (7.5) | 1.7 (0.4) | 0.2 (0.1) |

| 40       | 166.9 (1.2)       | 3.9 (0.1)     | 1.6 (0.6)      | 96.7 (66.9)    | 1.11 (0.76)   | 25.8 (2)       | —              | —              | 40             | 176.6 (2.9) | 2.0 (0.3) | 0.5 (0.0) |

| 60       | 151.3 (0.6)       | 12.0 (0.5)    | 3.7 (1.5)      | 158.2 (120.1)  | 4.86 (3.65)   | 41.2 (1)       | —              | 43             | 20             | 120.5 (1.9) | 2.5 (0.3) | 0.7 (0.1) |

| 80       | 16.3 (0.1)        | 54.7 (2.3)    | 10.9 (1.1)     | 35.4 (40.8)    | 23.84 (3.04)  | 45.3           | 19.3           | 80             | 39.6 (8.8)    | 1.8 (0.4) | 0.7 (0.04) |

| 100      | 0.9 (0.1)         | 103.6 (4.6)   | 6.6 (0.1)      | 77.9 (25.4)    | 4.74 (1.28)   | 44.8           | 25.5           | 100            | 1.8 (0.1)     | 2.3 (0.7) | 0.7 (0.03) |

On the left, the hydrophobic component is crystallizable in nature (PCL); on the right, the hydrophobic component is amorphous in nature (PPG). Tensile data are provided as the average value of triplicate measurements, whereby the standard deviation is given in parentheses.

- Not observed.
- Duplicate instead of triplicate measurement.
- Sample failed prematurely during measurement.
Material properties of combinatorial PUI networks in dry state

The thermal and tensile mechanical properties of the PUI networks in the dry state are reported in Table 1. The mechanical properties of the PUI networks varied based on the molecular weight and nature of the prepolymers present in the network. The tensile stress–strain diagrams of all PUI networks in the dry state are shown in Fig. 1. In the case of PEG–PCL combinatorial PUI networks, all networks were semi-crystalline in nature. These networks were generally tough materials, which is typical for semi-crystalline polymer networks. Since the PEG and PCL prepolymers used have peak melting temperatures in the same temperature range (58–66 °C), it could not be determined whether the crystalline domains observed in the dry state in combinatorial networks containing both PEG and PCL prepolymers consist of either PEG or PCL or both. In the case of PEG–PPG combinatorial networks, a melting peak was only observed in the dry state for the networks containing PEG. Since PPG is amorphous in nature, the crystalline domains are attributed to the PEG network components in these networks. A decreasing heat of fusion is observed for decreasing PEG content in these networks. The fact that crystalline domains are observed in the dry state for all combinatorial PUI networks containing at least one crystallizable prepolymer shows that these materials are phase-separated in nature and consist of segregated hydrophilic and hydrophobic domains.

Material properties of combinatorial PUI hydrogels in water-swollen state

The swelling properties of the combinatorial PUI networks and their thermal and tensile mechanical properties in the water-swollen state are reported in Table 2. The tensile stress–strain diagrams in the water-swollen state are shown in Fig. 2. For both the crystallizable and amorphous PUI hydrogels, the water uptake decreased with increasing hydrophobic content. The water uptake values ranged from 380 wt% for a completely hydrophilic PEG PUI network to <2 wt% for both completely hydrophobic PUI networks.

The tensile mechanical properties of the PUI hydrogels in the water-swollen state vary over a wide range, and strongly depend on the nature of the hydrophobic network component. The crystallizable PEG–PCL combinatorial hydrogels were generally tough and demonstrated ultimate tensile strengths and toughness values of up to 10.9 MPa and 23.8 MJ m⁻³, respectively. The amorphous PEG–PPG hydrogels on the other hand were mechanically very poor and demonstrated ultimate tensile strengths and toughness values <1 MPa and <0.3 MJ m⁻³, respectively.

As reported in Table 2, the PEG–PCL combinatorial hydrogels containing ≥60 wt% of PCL were semi-crystalline in the water-swollen state. This is in accordance with results reported previously. Furthermore, the PEG–PCL combinatorial hydrogels demonstrated increasing heat of fusion values for increasing PCL content, reaching up to approximately 25 J g⁻¹ for a neat PCL PUI network. Heat of fusion values were generally slightly lower than those we reported previously for comparable PEG–PCL combinatorial PUI hydrogels, which is attributed to batch-to-batch variation. All combinatorial PEG–PPG hydrogels were amorphous in the water-swollen state (i.e. no crystalline phase attributable to PEG domains was observed once these hydrogels were swollen in water).

For the amorphous PEG–PPG combinatorial hydrogels, no significant differences in mechanical properties are observed regardless of the hydrophobic content. This is illustrated by low ultimate tensile strengths <1 MPa and low toughness values <250 kJ m⁻³ observed for all PEG–PPG combinatorial hydrogels. This is an interesting result, as it shows that the presence of segregated hydrophobic domains within the hydrogel polymer network by itself is not enough to create a significant increase in toughness of the hydrogel, contrary to what is suggested in the literature.

For the PEG–PCL combinatorial hydrogels, on the other hand, things seem entirely different. In this case, the overall mechanical resilience and toughness of the hydrogels increase strongly with increasing hydrophobic content. This is illustrated by elastic modulus values of ≥12 MPa, ultimate tensile strength values of ≥3.7 MPa, elongation at break values ≥158% and, most notably, toughness values of ≥4.8 MJ m⁻³ observed for PEG–PCL combinatorial hydrogels with PCL contents of 60 wt% or higher. Since these are the only hydrogels in which a crystalline phase is observed in the water-swollen state, the increased toughness of these hydrogels can be attributed to the crystallinity of the hydrophobic domains. Also, the toughness of these hydrogels

![Graph](https://example.com/graph.png)

Figure 2. Tensile stress–strain diagrams of combinatorial PUI hydrogels with increasing hydrophobic content (HC) in the water-swollen state. The water uptake (WU) and, where applicable, heat of fusion (ΔHf) of each hydrogel are reported next to the respective curve: (a) hydrophobic component is crystallizable in nature (PEG–PCL); (b) hydrophobic component is amorphous in nature (PEG–PPG).
increases further with increasing degree of crystallinity of the hydrogel.

The results presented above show that the commonly adopted strategy for increasing hydrogel toughness by incorporating hydrophobic domains into the hydrogel polymer network is in fact highly dependent on the thermal properties of the hydrophobic network component used. As is the case for polymers in the dry state, semi-crystalline combinatorial PUI hydrogels are much tougher than their amorphous counterparts, whereby toughness increases further with increasing degree of crystallinity. This is considered an important structure–property relationship in the design of tough hydrogel materials. Since the only parameter that has been varied in this study is the chemical nature and relative content of the hydrophobic network component, it is expected that this relationship is applicable to most types of polymer hydrogels and is not limited to PUI-type hydrogels alone. Finally, it should be noted that the water uptake of the hydrogels decreases with increasing hydrophobic content, resulting in a trade-off between mechanical performance and water uptake. With the present synthesis method, however, the hydrophobic content, degree of crystallinity and water uptake of the hydrogel can easily be (fine-)tuned over a wide range of values, simply by selecting and mixing the desired hydrophilic and hydrophobic prepolymers in the desired ratios.

Considering that PUI hydrogels are typically biocompatible, relatively bioinert and show mechanical stability with respect to typical sterilization techniques, the combined mechanical and thermal properties of the combinatorial PUI hydrogels presented here are of interest for several biomedical applications. For example, the PEG–PCL combinatorial hydrogels with a relatively low PCL content of 20–40 wt% demonstrate mechanical properties suitable for application as biomedical adhesives or coatings (i.e. moderately high water uptake values in the range 100–300 wt%, high elastic moduli of ≥2.5 MPa and high toughness values of ≥250 kJ m⁻³). The PEG–PCL combinatorial hydrogels with a higher PCL content of 60–80 wt%, on the other hand, demonstrate mechanical properties suitable for (load-bearing) applications in regenerative medicine and/or tissue engineering (i.e. limited water uptake values in the range 10–100 wt%, high ultimate tensile strengths of ≥3 MPa and high toughness values of ≥4 MJ m⁻³). Examples may include the synthesis of artificial cartilage, artificial cardiovascular materials, artificial skin or artificial tendons and ligaments.

CONCLUSIONS

Two series of combinatorial PUI hydrogels based on a hydrophilic PEG prepolymer and increasing amounts of either a crystallizable hydrophobic prepolymer (PCL) or an amorphous hydrophobic prepolymer (PPG) were synthesized. In the combinatorial PUI hydrogels containing an amorphous hydrophobic prepolymer component, hardly any change in mechanical properties was observed upon variation of the relative hydrophobic content. This shows that introducing hydrophobic domains into the hydrogel polymer network by itself did not enhance the toughness of the hydrogel.

In the combinatorial PUI hydrogels containing a crystallizable hydrophobic prepolymer, on the other hand, a strong increase in mechanical resilience and toughness was observed with increasing hydrophobic content. This is illustrated by elastic modulus values ≥1.2 MPa, ultimate tensile strength values ≥3.7 MPa and toughness values ≥4.8 MJ m⁻³ observed for PEG–PCL combinatorial hydrogels with a PCL content ≥60 wt%. In these hydrogels, crystallinity was observed in the water-swollen state using dynamic scanning calorimetry measurements. As such, the enhanced toughness of the PEG–PCL hydrogels could be correlated to their crystallinity in the water-swollen state, whereby it was observed that toughness increased further with increasing degree of crystallinity. This correlation between toughness and crystallinity for hydrogels in the hydrated state is considered an important structure–property relationship in the design of tough hydrogel materials. It shows that the commonly adopted strategy for increasing hydrogel toughness by introducing hydrophobic domains into the hydrogel polymer network is in fact highly dependent on the thermal properties of the hydrophobic network component used.

Finally, it is shown that the PEG–PCL combinatorial hydrogels with a relatively low PCL content (20–40 wt%) are promising materials for biomedical adhesive and coating applications. The PEG–PCL combinatorial hydrogels containing higher PCL contents (60–80 wt%) are suitable for load-bearing biomedical applications within the fields of tissue engineering and regenerative medicine.

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