Tissue reconstruction has an unmet need for soft active scaffolds that enable gentle loading with regeneration-directing bioactive components by soaking up but also provide macroscopic dimensional stability. Here microporous hydrogels capable of an inverse shape-memory effect (iSME) are described, which in contrast to classical shape-memory polymers (SMPs) recover their permanent shape upon cooling. These hydrogels are designed as covalently photo cross-linked polymer networks with oligoethylene glycol)-oligo(propylene glycol)-oligo(ethylene glycol) (OEG-OPG-OEG) segments. When heated after deformation, the OEG-OPG-OEG segments form micelles fixing the temporary shape. Upon cooling, the micelles dissociate again, the deformation is reversed and the permanent shape is obtained. Applicability of this iSME is demonstrated by the gentle loading of platelet-rich plasma (PRP) without causing any platelet activation during this process. PRP is highly bioactive and is widely acknowledged for its regenerative effects. Hence, the microporous inverse shape-memory hydrogel (iSMH) with a cooling induced pore-size effect represents a promising candidate scaffold for tissue regeneration for potential usage in minimally invasive surgery applications.

1. Introduction

Shape-memory polymers (SMPs) resemble a highly versatile class of active materials that can be used to create multifunctional devices.[1] In the classical, thermally induced shape-memory effect (SME) a polymer-based material is capable to reverse an elastic deformation starting from a temporary shape upon heating, which was set in a programming procedure before. First, the sample, which provides a polymer network structure (cross-linked oligo(propylene glycol)-oligo(ethylene glycol) dimethacrylates the classical SME functionality based on the $T_g$ of the poly(rac-lactide) segments could be combined with degradability.[2] In addition to the classical SME, materials with advanced functions such as triple- or multi-shape-effect were created.[3,4] Similarly to classical SME, in triple- or multi-shape-effect polymers the temporary shape is reversed by heating.

SME materials have great potential in biomedical application scenarios spanning from a SMP-based self-tightening suture for wound closure up to stents or aneurysm occlusion devices.[5] Of special interest are application scenarios for minimally invasive surgery based on their capability to change shape. So far SMP became elastic when heated. It was the aim of this study to design and fabricate a cell-compatible polymer-based network with a cooling-induced inverse SME (iSME) within a tissue-tolerated temperature range. In case of an iSME the temporary shape is stable until the material is cooled to $T_{sw}$. In analogy to the SME, the iSME is a one-time, one-way effect. Once the original shape is recovered, the material does not switch back. Even if heated again, the material remains in its permanent shape obtained during cooling. In this way iSME materials differ from soft artificial muscles (actuators)[6], who lose their shape obtained during cooling when heated. Potential applications for such a biomaterial system with an iSME are envisaged in soft tissue reconstruction where the device needs to be placed minimally invasively.

Soft tissue reconstruction faces various challenges. Current clinically established approaches are based on multiple surgical...
procedures, including autograft transplantation, often resulting in tissue necrosis, subsequent scarring, and therefore deformation. Hence, various types of scaffolds for tissue reconstruction are being explored as viable alternatives. Those are required to be histocompatible, while exhibiting good microporosity to facilitate cellular infiltration, vascularization, and thus a good histointegration.[7] Scaffolds purely based on biomacromolecules found in the extracellular matrix such as hyaluronic acid, collagen or its derivate gelatin can provide essential cues for the necessary interaction with cells and bioactive signals that promote tissue healing.[8] In such systems, the challenges to efficiently adjust elastic properties especially on the micro- and nanoscale as well as to control their degradation rate can be addressed by chemical modification. Such principles are often derived from synthetic polymers as building blocks for tissue reconstruction.[9] Those have finely adjustable mechanical and chemical properties, as well as degradation kinetics. Unfortunately, they often lack the required bioactivity to enable a suitable histointegration.

In order to address these challenges, we opted for the design of a synthetic polymer-based scaffold with well-defined properties and a thermosensitive pore size enlargement effect at physiological temperatures based on the iSME, which could allow the rapid and gentle loading of bioactive substances. Its capability to change the macroscopic shape upon cooling enables its application in a minimally invasive surgery scenario. Compared to classical shape-memory materials a potential harmful heating above 42 °C would be avoided. Furthermore, a potential increase of temperature, e.g., caused by inflammation would not result in softening of the implant. In particular, a microporous hydrogel scaffold with tissue-like properties was designed and prepared from the triblock copolymer oligo(ethylene glycol)-oligo(propylene glycol)-oligo(ethylene glycol) (OEG-OPG-OEG). It was shown previously that OEG-OPG-OEG-based materials can be prepared free of endotoxins, have very low protein absorption, do not induce any complement or immune cell activation, and, most importantly, are cyto- and histocompatible.[10] Thus, biomaterials based on this triblock copolymer are well suited as transplantation materials. In addition, the triblock copolymer forms micelles with increasing temperature.[11] We speculated that these micelles could act as potential physical temporary netpoints in a covalently cross-linked polymer network to enable fixation of the temporary shape. The permanent shape could be recovered by dissociation of micelles upon cooling thus enabling an isME. This thermosensitive material behavior was investigated for its ability to enable gentle loading of bioactive components.

2. Results and Discussion

2.1. Synthesis of OEG-OPG OEG-Based Microporous Hydrogel Scaffolds

Microporous hydrogel scaffolds composed of OEG-OPG-OEG triblock polymers were synthesized by emulsion templated polymerization from reactive OEG-OPG-OEG precursors (13k-OEG(70)diUEMA). In an inverse emulsion polymerization process microsized n-hexane droplets served as a template for the micropores during scaffold formation (Figure 1A,B). Since OPG has a higher hydrophobicity than OEG, OPG segments accumulated at the interface of the oil-in water emulsion and the OEG side segments protruded into the aqueous phase (Figure 1A,B). The scaffold structure was set by photopolymerization, which was performed under constant stirring with a stirring-bar in order to increase the probability of interconnected

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Synthesis of microporous hydrogel scaffolds based on oligo(ethylene glycol)-oligo(propylene glycol)-oligo(ethylene glycol) (OEG-OPG-OEG) triblock polymers. Sample nomenclature: cP(xx)yy represents cross-linked porous network formed from an emulsion of an aqueous solution of 13k-OEG(70)diUEMA (M, 13 kg mol⁻¹, hydrophilic ratio 70 w/w%) with a concentration of xx wt% and n-hexane, in which yy indicates the ratio between the aqueous solution and n-hexane in vol%. A) Schematic drawing of hydrogel synthesis on the macro and micro level. B) Structure formula of the copolymer UEMA-OEG-OPG-OEG-UEMA. C) Photographs of the hydrogel synthesis procedure. D) Scanning electron microscopy (SEM) images of the hydrogel scaffolds after freeze-drying (magnification 500×, scale bar 260 μm).
pores. Interconnection of pores was assumed to be beneficial to enable the efficient removal of the toxic template material and to support the efficient infiltration of cells into the scaffold structure. Stable hydrogels that exhibited a mechanical elasticity, allowing for a macroscopic change of shape, were obtained from aqueous solutions with 13K-OEG(70)diUEMA concentrations of 8, 10, and 12 wt% and water-to-oil ratios of 30:70, 40:60, and 50:50 v/v\% (Figure 1C). Interconnectivity and sizes of the pores were confirmed by scanning electron microscopy (SEM) (Figure 1D). Pore sizes in the microsize range were observed and were dependent on OEG-OPG-OEG concentrations as well as the water-to-oil ratio. The pore size decreased with increasing copolymer concentration or with increasing water-to-oil ratio (Figure 1D). In microcomputed X-ray tomography the average pore diameter ranged between 150 and 220 μm.

2.2. Influence of Thermosensitivity of the Polymer Network on Pore Size and Mechanical Properties of the Hydrogel Scaffold

The cross-linking density of the polymer network has a significant influence on the gel content and swelling behavior as well as mechanoelastic properties of the scaffolds. Since the cross-linking density is controlled by the permanent cross-links, to which the temporary cross-links caused by the formation of micellar aggregates contribute, increasing temperature would affect the physical properties of the OEG-OPG-OEG based microporous hydrogel scaffolds. Indeed, the swellability of the hydrogels decreased by up to 320% when measurements were conducted at 37 °C instead of 5 °C, indicating the formation of the additional temporary cross-links at higher temperature. This effect was most pronounced at a low initial polymer concentration and a small water-to-oil ratio thus in hydrogels with a lower gel content G (Figure 2A). Substitution of water by phosphate buffer solution changed swellability only slightly. Since a higher value of G indicates a higher density of polymer chain segments in a given volume (including micropores), the mobility of the polymer chain segments is decreased. This increased steric hindrance lowers the probability of temporary cross-link formation and thus caused a less prominent thermosensitivity of the polymer network. As netpoint density directly correlates with bulk elastic properties of a hydrogel, rheological measurements of the elastic G’ and viscous modulus G’' were conducted between 10 °C and 37 °C. Both moduli raised when temperature was increased indicating an enhanced toughness of the hydrogel (Figure 2B). Most importantly, changes in viscoelastic properties were reversible and went back to their original plateau upon cooling (Figure 2B).

Swelling of the hydrogel-based scaffold matrix will have an immense effect on pore size, but this is not reflected by the SEM in dry state (Figure 1). In order to investigate the influence of the thermosensitivity of the polymer network and swelling behavior on pore size, pores were also characterized

![Figure 2](https://example.com/figure2.png)

**Figure 2.** A) Sample composition, gel content G, and swelling properties Q of microporous hydrogel scaffolds based on 13K-OEG(70)diUEMA. a) Sample composition according to sample naming in caption of Figure 1. b) Gel content G determined from extraction with chloroform. c) Equilibrium degree of swelling in water. d) Difference of swelling between 5 °C and 37 °C. e) Swelling in PBS at 5 °C and 37 °C. B) Viscoelastic properties of hydrogel scaffolds as a function of temperature of cP(8), cP(10) and cP(12) series, light intensity cP(x)30, medium intensity cP(x)40, full intensity cP(x)50. Solid symbols: G', Void symbols G'".

Adv. Mater. Interfaces 2022, 9, 2101588 2101588 (3 of 9) © 2022 Helmholtz-Zentrum Hereon, Advanced Materials Interfaces published by Wiley-VCH GmbH
2.3. Investigation of the Inverse Shape-Memory Effect

The decrease of swelling and the increase in moduli of OEG-OPG-OEG-based microporous hydrogels at 37 °C indicated the formation of temporary cross-links. This process was reversible (Figure 2) indicating the material's suitability to exhibit an iSME. Contradictive to classical thermally induced SME in materials with an iSME capability, the shape is created by deformation and at lower temperature and temporarily fixed by raising the temperature, here in this case to body temperature.

To explore the iSME, bars cut from the hydrogel scaffolds were bent by 180° at 5 °C and were heated to 37 °C to fix the temporary shape. All samples were able to maintain the bent deformation by at least 16% as reflected by the shape fixity ratio $R_f$ as the ratio between the original straight and the bent shape. $R_f$ further increased with decreasing initial polymer concentration. This is not surprising since hydrogels with lower polymer content were shown to exhibit a higher thermosensitive effect (Figure 2), due to the higher polymer chain mobility, increasing the probability of forming micelles. After cooling the hydrogel scaffolds for 10 min the original shapes were completely regained in all conditions (Figure 4A).

In terms of application as a soft tissue substitute compression of a scaffold is a deformation of high relevance. Accordingly, the iSME was further evaluated in compression tests. iSM-Hydrogels were compressed by 30% at 10 °C and heated to 37 °C to fix the compressed shape. Compression fixity ratios $R_c$ of up to 80% were achieved. Noteworthy, during the compression experiment temporary netpoints formed throughout the whole hydrogel scaffold contributed to the fixation of the temporary shape. In contrast, in the bending experiment only temporary netpoints created at the bending site contributed to the shape fixation, explaining the higher fixity ratios in this comparison. Once cooled, the original shape was recovered with recovery ratios $R_r$ of at least up to 75% (Figure 4B). The observed incomplete recovery in some of the cases was believed to occur due to breaking of some of the hydrogel pores walls during the compression process. However, incomplete recovery could not be correlated to a certain hydrogel make-up and recovery ratios of up to 100% were achieved in various attempts.

2.4. Shape Fixation by Formation of Partial Micelles

Small-angle X-ray scattering (SAXS) was used to elucidate the underlying molecular mechanism for the iSME. The 2D pattern at 5 °C showed an amorphous halo whereas at 50 °C scattering attributed to the formation of nanostructured aggregates

![Figure 3. Thermosensitivity of hydrogel scaffolds. A) Relative change of pore size when heated from 6 °C to 37 °C. [Sample ID color coding according to sample IDs in Table B]. B) Macroscopic dimensional stability relative change in sample diameters, exemplarily shown for sample cP(12)40 in I) when heated from 5 °C to 37 °C.](image)
occurred (Figure 5 insert). The distance between aggregates could be estimated to be 17, 19, and 18 nm for cP(12)30, cP(12)40, and cP(12)50, respectively (Figure 5A). Since the size for micelles from solutions of 13kEG70% was reported to be approximately 10 nm, this larger distance between aggregates can be attributed to a lower degree of micelle formation caused by the incorporation in a covalently cross-linked polymer network. However, the aggregates were still capable to act as temporary netpoints in the hydrogel scaffold at higher temperatures to enable the fixation of the temporary shape (Figure 5B).

### 2.5. Thermosensitive Pore-Size Effect Enables Gentle Loading of Scaffolds with Bioactive Components

The studied hydrogel scaffolds showed excellent cytocompatibility (Supporting Information: “In vitro cytotoxicity testing,” Table S1 and Figure S1, Supporting Information) and exhibited mechanoeelastic properties comparable to soft tissue.[13] The iSME can be triggered in a physiologically tolerated temperature range with minimal macroscopic swelling. Furthermore, for nonporous films based on the same weight percentage of the reactive OEG-OPG-OEG precursors a very low thrombogenicity

| Sample ID \(^a^\) | \(R_f\) \(^b^\) \([\%]\) | \(R_r\) \(, 2\) \(min\) \(^c^\) \([\%]\) | \(R_r\) \(, 10\) \(min\) \(^d^\) \([\%]\) |
|------------------|------------------|------------------|------------------|
| cP(8)30          | 26 ± 1           | 100 ± 2          | 100 ± 2          |
| cP(8)40          | 27 ± 1           | 79 ± 1           | 100 ± 5          |
| cP(8)50          | 31 ± 1           | 95 ± 5           | 100 ± 4          |
| cP(10)30         | 19 ± 2           | 81 ± 4           | 100 ± 2          |
| cP(10)40         | 20 ± 3           | 77 ± 8           | 100 ± 8          |
| cP(10)50         | 20 ± 2           | 100 ± 10         | 100 ± 9          |
| cP(12)30         | 18 ± 1           | 98 ± 2           | 100 ± 2          |
| cP(12)40         | 18 ± 2           | 90 ± 9           | 100 ± 4          |
| cP(12)50         | 16 ± 1           | 100 ± 9          | 100 ± 8          |

### Figure 4. Quantification of the inverse shape-memory effect (SME). In A) bending and B) compression experiment. a) Sample ID according to sample naming in caption of Figure 1. b) Shape fixity ratio \(R_f\), determined from bending experiments, c) shape recovery ratio \(R_r\), determined from bending experiments after 2 min, d) \(R_r\), determined from bending experiments after 10 min, e) \(R_f\), determined from rheology, f) \(R_r\), determined from rheology after 10 min, g) \(R_r\), determined from rheology after 30 min.
Cool during the whole process (Figure 6A2–4). Thus, passive proteins) reached into the pores in materials that remained the scaffolds. In contrast, PRP (neither platelets nor plasma glutardialdehyde induced fluorescence, within the pores of plasma proteins and platelets (Figure 6A3–4, B3–4), visible by microscopy of cross-sections revealed a high accumulation of indicated a successful loading with PRP (Figure 6A2–B2).

Figure 5. A) Small-angle X-ray scattering (SAXS) measurement of the molecular structure in the formed hydrogels. B) Proposed molecular mechanism for inverse shape-memory effect (SME).

A major bottleneck of synthetic hydrogels is their lack of bioactivity, which is necessary to guide regeneration processes upon implantation.[14] Hence, various strategies exist to load scaffolds with cells or cellular products such as growth factors. These strategies however necessitate gentle methods, when bioactive factors are to be incorporated into the scaffolds during its synthesis. Alternatively, approaches that enable loading of scaffolds after synthesis would allow for a full range of manufacturing procedures and a spatial confinement of bioactive factors, e.g., into micropores. However, standard loading methods such as soaking of scaffolds that require in-migration of cells or passive diffusion of bioactive components led to inadequate and uneven loading.[15]

Here, the thermosensitive change of the pore sizes was used to gently load platelet-rich plasma (PRP) into the scaffolds. Platelets contain more than 300 biologically active components that are released upon activation and subsequently modulate the tissue healing and regeneration process.[16] Concentrated platelet products such as PRP have been recognized for their potential and are extensively clinically investigated for their augmentation of regeneration of bone, cartilage, and skin, among others.[17] The delivery strategy or its combination with scaffolds for tissue regeneration is thus critical for its immobility and efficacy.

Cooled (4 °C) or pre-warmed (37 °C) scaffolds (CP(8)50) were exposed to PRP exhibiting the same temperature and both samples were incubated for 30 min at 4 °C before scaffolds were retrieved for fixation (Figure 6A1,B1). A pronounced change in color to PRP-like dark-yellow of scaffolds that were cooled, indicated a successful loading with PRP (Figure 6A2–B2). Microscopy of cross-sections revealed a high accumulation of plasma proteins and platelets (Figure 6A3–4, B3–4), visible by glutardialdehyde induced fluorescence, within the pores of the scaffolds. In contrast, PRP (neither platelets nor plasma proteins) reached into the pores in materials that remained cool during the whole process (Figure 6A2–4). Thus, passive PRP-uptake was negligible and the PRP-loaded pores can be attributed to the shrinking of pores within the material while cooling. Noteworthy, no PRP was observed to leak into the wall of the scaffolds.

One major challenge during PRP loading into scaffolds is to not activate the platelets during this process or by the material surface. Platelets are very responsive and can be activated, e.g., by presence of small molecules, adhesion to various surfaces, induction of the coagulation cascade, prolonged cooling, and elevated shear forces (>50 N m⁻²).[18] Platelet activations then lead to a burst release of regenerative factors before transplantation, thus diminishing much of the therapeutic effect of PRP before application. To confirm that the loading process did not cause a pre-activation of the internalized platelets, cells were stained for CD42a (identification marker) and CD62b (P-Selectin, activation marker) (see Figure 6C). Exposed to the Thrombin Receptor Activator Peptide-6 (TRAP-6)—subsequent to the loading into the hydrogel scaffolds—platelets showed a markedly increased CD62P expression in comparison to those that were not post-treated with TRAP-6. These data provide evidence that neither the material surface itself nor the loading procedure led to an activation of the human blood platelets and that the functionality of the platelets was preserved during the entire processing (including blood sampling and preparation times). These observations might be associated with the very minor adsorption of proteins and activation of the view adhering platelets (see Supporting Information: “Blood and platelet rich plasma preparation”, and “Platelet rich plasma loading of hydrogel scaffolds”, and reference [10]). They also indicate that the shear forces, which occurred during the loading processes, were relatively low and beneath values that can lead to a shear-induced activation of platelets.

3. Conclusion

Microporous hydrogel scaffolds with an iSME were created, enabling a temporary shape fixation at body temperature and recovery upon cooling. In compression experiments the scaffolds were capable of shape fixation of higher than 82% and cooling-induced shape recovery of up to 100%. In addition to
the excellent histocompatibility of OPG-OEG-OPG triblock copolymers, the minimal volumetric swelling of the resulting microporous scaffolds renders them promising candidate materials for tissue substitution constructs as they do not soften, even when temperatures above 42 °C would be exceeded. Moreover, the gentle loading of bioactive components such as PRP into the microporous spaces is enabled by the thermally induced change of the pore size demonstrating its suitability for the iSM hydrogels as active biomaterial, which potentially can be used in a minimally invasive surgery application. However, more experimentation will be needed in future to pave the way toward a clinical application including, e.g., investigation of platelet stability over several days after recovery of the permanent shape. Last but not least, as the mechanism is applicable to other triblock copolymers, which are capable to generate micelles upon heating, a generic concept for the design of iSME polymers has been presented.

4. Experimental Section

Synthesis of 13K-OEG(70)diUEMA: 13K-OEG(70)diUEMA (Mn, 13 000 kg mol⁻¹, PDI = 1.14) was synthesized from the OEG-OPEG-OEG diol (Mn = 12 700 g mol⁻¹, PDI = 1.14, 70 w/w% OEG (13K-OEG(70)) and 2-isocyanato ethyl methacrylate catalyzed by dibutyltindilaurato (all Sigma-Aldrich, Steinheim, Germany) according to the procedure described elsewhere. Multidetector GPC measurements were performed at
a solvent flow rate of 1 mL min⁻¹ at 35 °C using chloroform as eluent and 0.2 wt% toluene as internal standard. The system was equipped with a precolumn, two 300 x 8.0 mm linear M columns (Polymer Standards Service GmbH, Mainz, Germany), an isocratic pump 2080, an automatic injector AS 2050 (both Jasco, Tokyo, Japan), a refractive index detector Shodex RI-101 (Showa Denko, München, Germany), and a dual detector T60A (Viscotek Corporation, Houston, USA). Molecular weight distributions were determined by the SEC software WINGPC 6.2 (PSS). Polystyrene samples were used for universal calibration to determine the hydrodynamic volume as function of elution volume.

Synthesis of Hydrogel Scaffolds: 13K-OEG(70)diUEMA was solubilized in distilled water in the appropriate concentrations of 8, 10, or 12 wt%. The solutions were degassed with N₂ and then pipetted into a vial equipped with a magnetic stirrer. n-hexane was then added according to the preferred W/O ratios (30:70, 40:60, or 50:50). The mixtures were thoroughly stirred for 5 min while cooled to 5 °C (2-hydroxy-1-[4-(2-hydroxyethoxy) phenyl]-2-methyl-1-propanone (Irgacure 2959, CIBA Chemicals, Basel, Switzerland) (0.3 wt% concentration relative to monomer in 70 v/v% ethanol was injected in the emulsions. Vials were covered with a quartz glass plate and irradiated for 5 min with UV-light from an excimer laser (Bluelight PS 30 P, Heraeus Noble Light, Hanau, Germany) under gentle stirring. Additional 5 min of irradiation was occasionally required for the most concentrated/viscous emulsions.

After cross-linking of the emulsion, the porous hydrogels were extracted in a 25 vol% ethanol/water solution (20 °C) and cut into discs (2–3 mm thickness and 2 cm diameter).

Gel content (G) and degree of swelling (Q) were determined gravimetrically according to Equations (1) and (2), where \( m_{\text{nat}} \) is the mass of the dry extracted gel, \( m_{\text{nest}} \) is the mass of the dry unextracted gel, and \( m_{\text{swT}} \) is the mass of the swollen sample at a determined temperature.

\[
G = \frac{m_{\text{nat}}}{m_{\text{nest}}} \times 100
\]

\[
Q_T = \frac{m_{\text{swT}}}{m_{\text{nest}}} \times 100
\]

Rheology measurements were performed in distilled water with parallel plate geometry on a Haake MARS II (Thermo Scientific, Karlsruhe, Germany) in controlled deformation mode. A constant force of 0.20 or 0.30 N was applied on the sample during all measurements (amplitude sweep, frequency sweep, and temperature ramp). Samples were protected from dehydration by a solvent trap.

**Macrosopic Experiments**: Inverse shape-memory experiments of porous hydrogels were performed in their equilibrium swollen state in distilled water. The samples are allowed to soften at 5 °C and then bent with an angle of 180° in case of bending experiments. Thus deformed, the sample was immersed in a 50 °C bath and the deformation maintained for 1 min. The bending force was released and the fixed shape determined. The recovery was obtained by immersion of the deformed sample in the cool bath at 5 °C.

Compression experiments were performed similarly but instead of an external water bath the thermochamber of the rheometer was used.

**Determination of Pore Size Change**: OEG-OPG-OEG-based hydrogel scaffolds were embedded in frozen section medium (Frozen Section Medium, Neg-50, Richard-Allan Scientific, Kalamazoo, MI, USA) for 10 min at −22 °C and cut into 40 μm slices with a cryostat HM560M (Microm, Thermodifischer Scientific, Walldorf, Germany). The specimens were moistened with Millipore water and placed in a microscope thermochamber (LT5350, Linkam Scientific Instruments, Surrey, UK).

The intended temperature (6 °C or 32 °C) was adjusted and images were recorded (AXIO Imager.A1m, Zeiss, Jena, Germany).

**Small Angle X-Ray Scattering**: SAXS was performed on a Nanostar diffractometer from Bruker AXS (Karlsruhe, Germany) with a Vantec-2000 detector operating at 40 kV and 35 mA on a copper anode giving a X-ray beam with a wavelength of 0.15418 nm (CuKα). The distance sample to detector was 1070 mm. Samples were placed into a sealed quartz cuvette (2 mm diameter) and exposed 3 h at temperatures of 5 °C and 50 °C to obtain a two-dimensional scattering pattern, which was corrected for spatial distortion and background subtraction. Isotropic scattering patterns were integrated to obtain one-dimensional scattering curves of scattered intensity versus scattering angle (θ versus 2θ). Furthermore, scattering angle was converted into scattering vector \( s \) being \( |s| = s = (2/\lambda) \sinθ \) and a Kratky-plot (Lorenz correction \( I^2 \) versus \( s^2 \)) was used to extract the long period \( L \) from the position of the peak maxima as \( L = r^2 \).

**Biological Experiments**: For description of biological experiments, please see Supporting Information. For PRP preparation, the protocol received an approval of the ethics committee of the Charité University Medicine Berlin (EA2/012/10) with informed consent from all participants.

**Supporting Information**

Supporting Information is available from the Wiley Online Library or from the author.

**Acknowledgements**

Dr. Ulrich Nöchel is acknowledged for SAXS measurement, Katrin Michel for performing cytotoxicity tests, Julia Görs for synthesis of hydrogels for biological experiments. This work was financially supported by the Helmholtz-Association through programme-oriented funding. A.B. thanks the Berlin-Brandenburg School for Regenerative Therapies (BSRT) for the postdoctoral fellowship (GSC 203).

Open access funding enabled and organized by Projekt DEAL.

**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords**

active scaffold, critical micellisation temperature, hydrogel, inverse shape-memory effect, platelet-rich plasma

Received: August 24, 2021
Revised: September 27, 2021
Published online: January 30, 2022

[1] a) A. Lendlein, S. Kelch, Angew. Chem., Int. Ed. 2002, 41, 2034; b) A. Lendlein, O. E. C. Gould, Nat. Rev. Mater. 2019, 4, 116; c) Q. Zhao, H. J. Qi, T. Xie, Prog. Polym. Sci. 2015, 49–50, 79; d) R. Reit, B. Lund, W. Voit, Adv. Polym. Sci. 2015, 267, 313; e) A. Lendlein, R. S. Trask, Multifunct. Mater. 2018, 1, 010201.

[2] a) C. Löwenberg, M. Balk, C. Wischke, M. Behl, A. Lendlein, Acc. Chem. Res. 2017, 50, 723; b) M. Balk, M. Behl, C. Wischke, J. Zottmann, A. Lendlein, Adv. Drug Delivery Rev. 2016, 107, 136.

[3] N. Y. Choi, S. Kelch, A. Lendlein, Adv. Eng. Mater. 2006, 8, 439.

[4] a) I. Bellin, S. Kelch, R. Langer, A. Lendlein, Proc. Natl. Acad. Sci. USA 2006, 103, 18043; b) T. Xie, Nature 2010, 464, 267; c) M. Behl, K. Kratz, J. Zottmann, U. Noechel, A. Lendlein, Adv. Mater. 2013, 25, 4466.

[5] a) A. Lendlein, R. Langer, Science 2002, 296, 1673; b) J. G. Hardy, M. Palma, S. J. Wind, M. J. Biggs, Adv. Mater. 2016,
28. 5717; c) S. L. Jessen, M. C. Friedemann, A.-M. Ginn-Hedman, L. M. Graul, S. Jokerst, C. B. Robinson, T. L. Landsman, F. J. Clubb, D. J. Maitland, ACS Biomater. Sci. Eng. 2020, 6, 2588; d) T. R. Yeazel, M. L. Becker, Biomacromolecules 2020, 21, 3957; e) J. Delaey, P. Dubruel, S. Van Vlierberghe, Adv. Funct. Mater. 2020, 30, 1909047; f) R. Liang, H. Yu, L. Wang, B. U. Amin, N. Wang, J. Fu, Y. Xing, D. Shen, Z. Ni, Chem. Mater. 2021, 33, 1190.
[6] a) M. Behl, K. Kratz, U. Noechel, T. Sauter, A. Lendlein, Proc. Natl. Acad. Sci. USA 2013, 110, 12555; b) Z. Deng, W. Wang, X. Xu, O. E. C. Gould, K. Kratz, N. Ma, A. Lendlein, Proc. Natl. Acad. Sci. USA 2020, 117, 1895.
[7] B. N. Brown, C. A. Barnes, R. T. Kasick, R. Michel, T. W. Gilbert, D. Beer-Stolz, D. G. Castner, B. D. Ratner, S. F. Badylak, Biomaterials 2010, 31, 428.
[8] a) Q. Lu, M. Li, Y. Zou, T. Cao, J. Controlled Release 2014, 174, 43; b) K.-H. Chang, H.-T. Liao, J.-P. Chen, Acta Biomater. 2013, 9, 9012.
[9] a) A. Sharma, S. Bhat, V. Nayak, A. Kumar, Mater. Sci. Eng., C 2015, 47, 298; b) A. Elampanthi, A. M. Punnoose, S. Kuruvilla, M. Ravi, S. Rao, S. F. D. Paul, Artif. Cells, Nanomed., Biotechnol. 2016, 44, 1318.
[10] a) J. Goers, T. Roch, L. Tartivel, M. Behl, N. Ma, A. Lendlein, Polym. Adv. Technol. 2015, 26, 1378; b) E. Russo, C. Villa, Pharmaceutics 2019, 11, 1378.
[11] a) P. Alexandridis, J. F. Holzwarth, T. A. Hatton, Macromolecules 1994, 27, 2414; b) P. Zarrintaj, J. D. Ramsey, A. Samadi, Z. Atoufi, M. K. Yazdi, M. R. Ganjali, L. M. Amirabad, E. Zangene, M. Farokhi, K. Formela, M. R. Saeb, M. Mozafari, S. Thomas, Acta Biomater. 2020, 110, 37.
[12] D. Wolfram, A. Backovic, R. Kaindl, H. Hussl, G. Wick, J. Plast. Reconstr. Aesthetic Surg. 2008, 61, 342.
[13] C. F. Guimarães, L. Gasperini, A. P. Marques, R. L. Reis, Nat. Rev. Mater. 2020, 5, 351.
[14] J. M. Zhu, Biomaterials 2010, 31, 4639.
[15] a) M. W. Tibbitt, K. S. Anseth, Biotechnol. Bioeng. 2009, 103, 655; b) R. M. Namba, A. A. Cole, K. B. Bjugstad, M. J. Mahoney, Acta Biomater. 2009, 5, 1884.
[16] E. M. Golebiewska, A. W. Poole, Blood Rev. 2015, 29, 153.
[17] a) T. E. Foster, B. L. Puskas, B. R. Mandelbaum, M. B. Gerhardt, S. A. Rodeo, Am. J. Sports Med. 2009, 37, 2259; b) F. Haubner, D. Muschter, N. Schuster, F. Pohl, N. Ahrens, L. Prantl, H. G. Gassner, Clin. Hemorheol. Microcirc. 2015, 61, 279.
[18] a) X. Chang, M. Gorbet, J. Biomater. Appl. 2012, 28, 407; b) K. S. Sakariassen, P. A. Holme, U. Orvim, R. M. Barstad, N. O. Solum, F. R. Brosstad, Thromb. Res. 1998, 92, 533; c) S. Braune, M. von Ruesten-Lange, C. Mrowietz, K. Lutzow, T. Roch, A. T. Neffe, A. Lendlein, F. Jung, Clin. Hemorheol. Microcirc. 2013, 54, 235.
[19] B. Jeong, Y. H. Bae, D. S. Lee, S. W. Kim, Nature 1997, 388, 860.
[20] L. Tartivel, M. Behl, M. Schroeter, A. Lendlein, J. Appl. Biomater. Funct. Mater. 2012, 10, 243.