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Simultaneous interpenetrating network (SIN) hydrogels from poly(sarcosine) and poly(ethylene glycol) (PEG)

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Hydrogels are widely employed in biomedical applications such as drug delivery, tissue engineering, and wound healing due to their ability to mimic the properties of biological tissues. Here, the development of novel simultaneous interpenetrating network (SIN) hydrogels composed of polysarcosine (PSar) and poly(ethylene glycol) (PEG), crosslinked through orthogonal photochemical reactions is reported. The PSar single network was formed by free-radical polymerization of methacrylate-functionalized PSar, while the second network was generated simultaneously from cinnamic acid-modified PEG via [2 + 2] cyclo-addition. Comprehensive characterization revealed that the SIN hydrogels exhibit enhanced mechanical performance, including higher elongation at break, ultimate tensile strength, compressive strength, fracture strain, and Young's modulus, compared to the individual networks. Furthermore, rat mesenchymal stem cell assays confirmed superior cytocompatibility, with robust metabolic activity and proliferation on SIN hydrogels. Collectively, these findings demonstrate that PSar-based SIN hydrogels combine mechanical robustness with biocompatibility, highlighting their strong potential as functional materials for artificial tissue applications.

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Introduction

Hydrogels are three-dimensional, cross-linked polymeric networks capable of retaining large amounts of water.^{1–4} Owing to their high water content, tuneable permeability, and structural similarity to the extracellular matrix (ECM), hydrogels are preferred biomaterials for applications such as tissue engineering scaffolds.^{5–8} Natural polymers, for example hyaluronic acid, alginate, and gelatine, are commonly used in hydrogel fabrication due to their excellent biocompatibility and low immunogenicity.^{9–15} However, synthetic hydrophilic polymers like polyacrylamide (PAM), poly(vinyl alcohol) (PVA) and poly

(ethylene glycol) (PEG) offer greater chemical versatility, mechanical tunability, and consistent synthesis, making them an attractive choice for a broad range of bioengineering applications.^{16–22} PEG is particularly popular in these applications for its ability to minimize protein adsorption, and its compatibility with growth media.^{23–26} However, its widespread use has come under increasing scrutiny as growing evidence links PEGylated products to enhanced immune responses.^{27–29}

In recent years, polysarcosine (PSar) has emerged as a promising alternative to PEG in various biomedical applications, including drug delivery and tissue engineering, due to its excellent biocompatibility and non-immunogenicity.^{30–33} PSar is a hydrophilic polypeptide that can be synthesised via the ring-opening polymerisation of sarcosine *N*-carboxyanhydride (NCA), a *N*-substituted derivative of the natural amino acid glycine.^{34,35} The potential of PSar-based hydrogels in tissue repair has been demonstrated in a recent study.³⁶ It was shown that enhanced early-stage *in vivo* cartilage and bone regeneration can be achieved by modulating immune responses, mitigating foreign body reactions, and promoting ECM deposition. These advantages position PSar-based hydrogels as a highly promising platform for tissue engineering applications.

One challenge in the development of hydrogel materials for tissue applications is optimising their mechanical properties to improve cell interaction, structural stability, and long-term

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temperature. The Young's modulus, elongation at break, and ultimate strength were determined as averages of six independent drawing experiments performed under the same conditions.

Compression test. Compression tests were carried out using a Testometric M100-1CT equipped with a 50 N cell load (LC5) and CPS150 square compression platens. Hydrogels were prepared into cylinders with a diameter of 6 mm and height of 2 mm, and swell in water for 48 h before testing. A preload force of 0.1 N was set, and each test was carried out at a compression speed of 5 mm min⁻¹ at room temperature. Each gel was subject to a point-break test to determine the Young's modulus, stress at break and strain at break. All compression tests were repeated 6 times, and an average of data was taken.

Results and discussion

Polymer synthesis

Polysarcosine (PSar) was synthesised *via* ring-opening polymerisation (ROP) of sarcosine *N*-carboxyanhydride (Sar-NCA), using 1,6-hexanediamine as the difunctional initiator in dichloromethane (DCM) (Fig. 1A). Monomer conversion was monitored by FTIR spectroscopy (Fig. S1), where the disappearance of the NCA carbonyl stretching band at 1780 and 1850 cm⁻¹ confirmed complete NCA conversion. The degree of polymerisation (DP) was determined by ¹H NMR spectroscopy, based on the integration of four central methylene protons from 1,6-hexanediamine ($\delta = 1.24$ and 1.38 ppm) and the methylene protons of PSar ($\delta = 4.57$ –3.73 ppm), yielding a DP of 30, closely matching the theoretical DP of 28 (Fig. S2). Size

exclusion chromatography (SEC) analysis revealed a monomodal molecular weight distribution with a low dispersity ($D = 1.1$), indicative of a well-controlled polymerisation process (Fig. S2). To introduce photoreactive functionality, PSar was chain-end modified with 2-isocyanatoethyl methacrylate *via* urea bond formation to introduce methacrylate groups (PSar-MA). The modification efficiency (>95%) was confirmed by ¹H NMR through the emergence of methacrylate vinyl proton signals at $\delta = 5.67$ and 6.06 ppm (Fig. 1A). Additional confirmation was provided by diffusion-ordered spectroscopy (DOSY) NMR, which showed the same diffusion coefficients for the vinyl protons and PSar, consistent with successful incorporation of methacrylate groups into PSar (Fig. S2). FTIR spectra of PSar and PSar-MA further supported the modification, with the appearance of a characteristic peak at 1540 cm⁻¹ attributed to C=C stretching vibrations (Fig. S1). SEC analysis of PSar-MA demonstrated that the polymer maintained its monomodal distribution and low dispersity ($D = 1.1$) after functionalisation (Fig. S2).

4-Arm PEG-CA was synthesized from commercially available 4-arm poly(ethylene glycol) (4-arm PEG-OH; 2000 g mol⁻¹) which was end-functionalised with cinnamic acid (CA) *via* *N*, *N*'-dicyclohexylcarbodiimide (DCC)-mediated esterification to yield PEG-CA (Fig. 1B). Integration of the aromatic NMR proton signals of CA at $\delta = 7.38$, 7.53 ppm relative to the PEG methylene protons at $\delta = 3.62$ ppm (Fig. 1B and Fig. S3) confirmed successful end group modification exceeding 95%. DOSY NMR analysis further supported the conjugation, revealing a uniform shift in diffusion coefficients consistent with the formation of single-modified PEG species (Fig. S3). FTIR spectra of PEG and PEG-CA also confirmed successful func-



Fig. 1 Synthetic procedure for the synthesis of (A) PSar-MA and (B) 4 arm PEG-CA and their ¹H NMR spectra. Red and green boxes in the ¹H NMR spectra highlight reactive methacrylate (MA) and cinnamic acid (CA) end-groups. Full peak assignment available in Fig. S2 and S3.



nalisation, with characteristic signals (1700 cm^{-1}) corresponding to ester bond formation (Fig. S1). Size exclusion chromatography (SEC) analysis showed monomodal elution profiles with a low dispersity ($D = 1.1$), indicating a homogeneous distribution of molecular weights (Fig. S3).

Rheological and swelling studies

Resins were formulated using PSar-MA and PEG-CA, with phenylbis(2,4,6-trimethylbenzoyl)-phosphine oxide (BAPO, 4 wt%) as the radical photoinitiator and *N*-methyl-2-pyrrolidone (NMP) as the solvent to facilitate solubility of the photoinitiator. Initially curing experiments were carried out with the individual polymers to identify the required UV exposure time and inform the rheological investigation. While for PSar-MA gelation occurred within a few seconds, PEG-CA gelation was only observed after six hours (Fig. 2B and Fig. S4). The evolution of the viscoelastic properties of the hydrogels was then investigated through both time-dependent and frequency-dependent rheological measurements. Frequency sweep experiments were conducted at different curing times for a sample containing a one to one weight ratio of both polymers (SIN-1/1) to monitor the progressive formation of the dual-network structure (Fig. 2A). At 0 h, the storage modulus (G') and loss modulus (G'') were low and comparable at low frequencies, consistent with the typical behavior of liquid-like materials, indicating a weakly viscous liquid with limited chain interactions. After 0.5 h of curing, G' increased to 56 Pa, significantly higher than G'' across the frequency range, confirming the formation of the first network *via* radical cross-linking of PSar-MA. Upon extended curing (6 h), G' further

increased to approximately 274 Pa and exhibited reduced frequency dependence, signifying the establishment of the secondary PEG-CA network. This evolution from a weakly viscous liquid to a viscoelastic gel highlights the sequential and independent network formation of PSar-MA and PEG-CA, a characteristic of the SIN design.

The composition-dependent photoresponse of the SIN hydrogels was further examined through time-sweep rheology under UV irradiation (Fig. S5). The UV light source (405 nm) was switched on after 60 s to establish a time zero baseline. Upon irradiation, both SIN-1/1 (PSar-MA 15 wt%, PEG-CA 15 wt%) and SIN-2/1 (PSar-MA 20 wt%, PEG-CA 10 wt%) exhibited a sharp rise in G' , reaching the gel point almost simultaneously, indicating comparable photo-curing kinetics governed by the rapid polymerisation of PSar-MA. In contrast, SIN-1/2 (PSar-MA 10 wt%, PEG-CA 20 wt%) showed negligible change in G' throughout the measurement, confirming that an excess of PEG-CA significantly suppressed network formation within the observed irradiation period due to its low photo-reactivity. These results demonstrate that the SIN hydrogel system features tunable, time-dependent network formation, in which PSar-MA governs the rapid initial gelation, while PEG-CA contributes gradually to long-term network reinforcement.

Next, single network hydrogel as well as SIN hydrogel samples were prepared using PSar-MA and PEG-CA formulations at the same polymer ratios (0/1, 1/0, 1/1, 1/2 and 2/1). Films were cast by pouring the resin into rectangular molds (H 0.8 mm \times W 10 mm \times L 20 mm) and irradiated with 405 nm UV light (2 mW cm^{-2}) for 16 hours. As suggested by the rheological measurements, it was hypothesised that rapid cross-linking of PSar-MA would establish the primary network, followed by slower PEG-CA crosslinking to form a secondary network (Fig. 3). After curing, the films were first dried in a vacuum oven until their weight remained constant, then swollen in DI water for 24 h to remove residual NMP and uncrosslinked components.

Swelling tests of the films in DI water were carried out to evaluate the water absorption capacity and degree of swelling. The gel fraction and swelling ratio of the PSar-MA and PEG-CA single networks as well as their corresponding SIN hydrogels exhibited distinct trends, influenced by differences in network composition, photoreactivity, and crosslinking mechanisms



Fig. 2 (A) Frequency sweep showing the viscoelastic behavior of the SIN-1/1 hydrogel over a range of angular frequencies at constant strain, with curves measured at different UV (405 nm) exposure timepoints. Storage modulus (G' , filled symbols) and loss modulus (G'' , open symbols) (PSar-MA 15 wt%, PEG-CA 15 wt%, BAPO 4 wt%, NMP 70 wt%). (B) Gelation process of the PEG-CA hydrogel precursor solution over time (PEG-CA 15 wt%, BAPO 4 wt%, NMP 85 wt%).

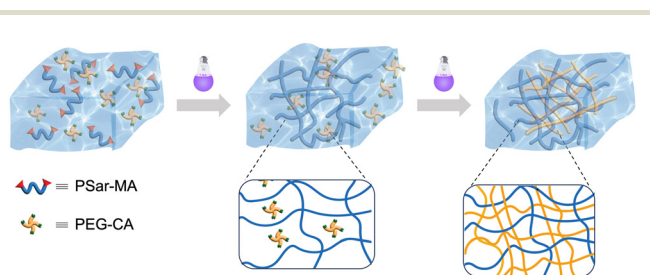


Fig. 3 Proposed SIN formation from PSar-MA and PEG-CA formulations.



(Table S1). Triplicate measurements of the gel fraction showed similar values across all samples, approximately 74%, indicating comparable crosslinking efficiency. Samples cured for only 10 min displayed a gel fraction of $59 \pm 4.9\%$ in agreement with crosslinking of predominantly the PSar-MA network. In contrast, the swelling ratios varied more substantially with composition. A lower swelling ratio was observed with increasing PEG-CA content. For instance, the swelling ratio of PSar-SN was 5.4 ± 0.04 , while that of PEG-SN was significantly lower at 1.8 ± 0.13 . Among the SIN hydrogels, SIN-2/1 exhibited a swelling ratio of 3.7 ± 0.08 , whereas the other SIN variants showed values in the range of 2.2–2.5. These lower swelling ratios at higher PEG-CA content suggest the formation of denser polymer networks. This is attributed to the tetrafunctional structure of PEG-CA and its 2 + 2 cycloaddition mechanism, which typically produces more uniform and tightly crosslinked networks compared to the free-radical polymerisation of the linear PSar-MA.^{57–59}

To assess mechanical performance of the films, tensile testing was conducted to measure Young's modulus, elongation at break, and ultimate tensile strength of the hydrogels. For the tensile tests, the PSar-MA exhibited a Young's modulus of about 159 ± 44 kPa and a strain at break of $62 \pm 15\%$ kPa (Fig. 4A and Table 1). The PEG-CA single-network hydrogel showed a comparable modulus (115 ± 16 kPa) but significantly lower strain at break (16%). This is likely a consequence of the higher cross-link density of the PEG-CA network due to its 4-arm structure.⁶⁰ In contrast, the SIN-1/1 hydrogel demonstrated enhanced mechanical performance, with a strain at break of $98 \pm 6\%$ and a Young's modulus of 307 ± 54 kPa. This improvement in flexibility and toughness is attributed to the interpenetrating network architecture, which facilitates energy

dissipation and more uniform stress distribution under load. When the ratio of the polymers was changed to 1/2 or 2/1 both tensile strength and elongation at break dropped suggesting optimal toughness and ductility for the SIN-1/1 (Fig. 4B and Table 1). These findings underline the importance of balanced network composition, with the 1/1 formulation providing the best synergy between the two polymer networks.

Compressive strength is critical for applications involving mechanical loading. As crosslinking density influences a hydrogel's resistance to deformation, compression tests were conducted to evaluate stiffness, stress at break, and energy dissipation across different network compositions. The compressive properties of PSar-MA, PEG-CA, and SIN hydrogels were assessed through stress–strain profiles and corresponding Young's moduli (Fig. 4C, D and Table 1). PSar-SN and PEG-SN exhibited moderate stiffness, with Young's moduli of 465 ± 20 kPa and 447 ± 66 kPa, respectively. However, their relatively low stress at break (184 ± 66 kPa for PSar-MA; 194 ± 49 kPa for PEG-CA) and limited strain at break (50%) suggest insufficient energy dissipation in single-network systems. In contrast, SIN hydrogels displayed markedly enhanced compressive properties. The interpenetrating architecture promoted effective load distribution and reduced localised failure, resulting in increased stiffness (Young's modulus up to >700 kPa) and stress at break exceeding 600 kPa. Further investigation into the role of network composition revealed a similar trend as for the tensile test with increased values for the SIN-1/1 (Fig. 4D and Table 1).

These results highlight the critical role of network composition in tuning the mechanical behaviour of the SIN hydrogels. The SIN-1/1 formulation consistently outperformed other ratios in both tensile and compressive tests, demonstrating a

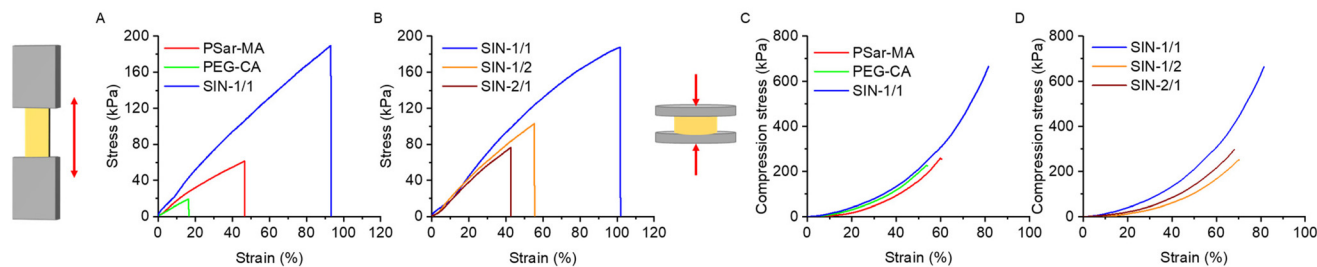


Fig. 4 (A) Stress–strain plot of PSar-MA, PEG-CA, and SIN; (B) stress–strain plot of SIN-1/1, SIN-1/2 and SIN-2/1; (C) compressive stress of PSar-MA, PEG-CA, SIN; (D) compressive stress of SIN-1/1, SIN-1/2, and SIN-2/1. Total polymers concentration 30 wt% in NMP, BAPO 4 wt%.

Table 1 Mechanical properties of single networks (SN) and simultaneous interpenetrating networks (SIN) (triplicate measurements)

Resin	Youngs modulus (tensile) (kPa)	Elongation at break (%)	Ultimate strength (kPa)	Youngs modulus (compression) (kPa)	Strain at break (%)	Ultimate compressive strength (kPa)
PSar-MA	159 ± 44	62 ± 15	63 ± 3	465 ± 20	51 ± 8	184 ± 66
PEG-CA	115 ± 16	16 ± 1	18 ± 1	447 ± 66	52 ± 5	194 ± 49
SIN-1/1	307 ± 54	98 ± 6	188 ± 3	728 ± 27	83 ± 1	648 ± 33
SIN-1/2	210 ± 22	53 ± 5	84 ± 17	403 ± 16	65 ± 8	212 ± 59
SIN-2/1	206 ± 15	43 ± 1	72 ± 4	735 ± 40	72 ± 5	340 ± 53



favourable balance of stiffness, strength, and extensibility. This study demonstrates the potential of compositionally optimised double-network PEG/PSar hydrogels for load-bearing biomedical applications, where precise mechanical performance is essential.

Cell compatibility

To evaluate the biological performance of the SIN hydrogels, we investigated their ability to support cell metabolic activity and proliferation of rat mesenchymal stem cells (rMSCs). rMSCs were seeded directly onto each hydrogel sample at 5×10^5 cells and incubated under standard culture conditions.⁶¹ Seeding efficiency, metabolic activity, and IPNA content were measured to assess the cell compatibility of PSar-MA and PEG-CA single hydrogels as well as the SIN-1/1 hydrogel. All experiments were carried out in triplicate.

When comparing the cell seeding efficiency, a crucial indicator for successful tissue development, only $18.6 \pm 1.3\%$ of the initially seeded cells remained on the PSar-MA single network after 24 hours of incubation. The PEG-CA single network exhibited a 2-fold higher efficiency of $42.2 \pm 1.0\%$ at the same time point (Fig. 5A). Remarkably, the SIN-1/1 hydrogel demonstrated the highest seeding efficiency of $71.9 \pm 1.3\%$, exceeding the PEG-CA by 1.7-fold and PSar-MA by 3.9-fold. Cell metabolic activity, as assessed on Day 1 (Fig. 5C), followed a similar trend: PEG-CA and SIN-1/1 hydrogels supported signifi-

cantly higher cell viability compared to PSar-MA. Over time, the SIN-1/1 hydrogel maintained consistent metabolic activity from day 1 to day 10, similar to the PEG-CA hydrogel. Interestingly, PSar-MA, despite its low initial cell viability, exhibited a steady increase in metabolic activity throughout the culture period. By day 10, no significant differences in cell viability were observed among the three hydrogel types, suggesting that all are non-toxic and capable of supporting sustained cell growth.

To assess long-term proliferation, total DNA content was quantified after ten days using the Quanti-iT PicoGreen assay (Fig. 5B). SIN hydrogels exhibited significantly higher DNA content than both single-network hydrogels, indicating superior support for cell proliferation. While the reasons for this need to be studied in more depth, it is possible that the balanced combination of network elasticity and hydrophilicity of the SIN-1/1 network creates a more favourable microenvironment for rMSC adhesion and proliferation, leading to higher DNA content.^{62,63} These results highlight the SIN hydrogel's enhanced ability to promote cell adhesion, viability, and expansion, supporting its potential in tissue engineering and regenerative medicine.

We further investigated the impact of SIN hydrogel composition on cell behaviour by comparing formulations with varying PSar-MA/PEG-CA ratios (1/1, 1/2, and 2/1). Seeding efficiency remained consistent across all variants (Fig. S6). All SIN compositions supported a gradual increase in cell metabolic activity over time, with no significant differences observed by Day 10 (Fig. S7). DNA quantification results mirrored this trend, with similar values across all formulations (Fig. S8).



Fig. 5 (A) Percentage of cell seeding efficacy at 24 h (rMSC). * represent statistical differences (at $p < 0.05$) between the various groups indicating that the SIN hydrogel has a highest seeding efficiency. (B) DNA concentration per hydrogel was determined after 10 days in cell culture. (C) Cellular metabolic activity per hydrogel determined at day 1, 3, 7, and 10 in cell culture. Data shown represent three individual MSC biological repeats ($n = 3$ per biological repeat).

Conclusions

PSar and PEG precursors were successfully synthesised and efficiently functionalised with methacrylate and cinnamic acid groups, respectively. Both were photo-crosslinked individually and simultaneously. Due to the markedly different cross-linking kinetics of the PSar-MA and PEG-CA, polymer blends afforded Simultaneously Interpenetrating Networks (SIN). Overall, it was found that the SIN hydrogels outperformed the single-network systems for all tested mechanical properties. Moreover, SINs promoted higher initial cell adhesion, sustained metabolic activity, and enhanced proliferation of rMSCs. These findings indicate that the synergistic combination of PSar-MA and PEG-CA within the SIN network provides a more favourable microenvironment for cell growth, suggesting their strong potential for applications in tissue engineering and regenerative medicine.

Conflicts of interest

There are no conflicts to declare.



Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: polymer ^1H NMR, FTIR, DOSY NMR spectra and SEC traces; table resin composition and swelling properties; cell data for SIN networks. See DOI: <https://doi.org/10.1039/d5py01018g>.

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