

Article

Photocrosslinkable Dexamethasone-Loaded GelMA Hydrogel for Peripheral Nerve Injury: Mechanical Behaviour and Anti-Adhesion Effect

Ji-Woo Park ¹, Jun-Kyu Kang ¹ , Chang Joo Lee ² , Kyoung Duck Seo ^{3,4,5}  and So-Jung Gwak ^{1,*}

¹ Department of Chemical Engineering, Wonkwang University, 460 Iksandae-ro, Iksan 54538, Republic of Korea; wldn0106@naver.com (J.-W.P.)

² Department of Food Science and Biotechnology, Wonkwang University, Iksan 54538, Republic of Korea; cjlee@wku.ac.kr

³ Division of Mechanical Engineering, Wonkwang University, 460 Iksandae-ro, Iksan 54538, Republic of Korea; kdseo85@wku.ac.kr

⁴ MECHABIOGroup, Wonkwang University, 460 Iksandae-ro, Iksan 54538, Republic of Korea

⁵ Advanced Bio-Convergence Research Center, Wonkwang University, 460 Iksandae-ro, Iksan 54538, Republic of Korea

* Correspondence: plus38317@wku.ac.kr

Abstract

Peripheral nerve adhesion after surgical injury severely hinders functional nerve regeneration, leading to pain and neurological dysfunction. In this study, we developed a photocrosslinkable methacrylated gelatin (GelMA)-based hydrogel membrane that locally releases dexamethasone to simultaneously prevent adhesion and suppress inflammation. GelMA, synthesized by reacting gelatin with methacrylic anhydride, formed a stable crosslinked network, as confirmed by FT-IR spectroscopy and rheological analysis. Cytocompatibility assays showed that both GelMA and Dexa-GelMA hydrogels were non-cytotoxic to neuronal and fibroblast cell lines. In a Sprague-Dawley (SD) rat sciatic nerve injury model, implantation of the Dexa-GelMA hydrogel significantly reduced perineural adhesion and inflammation compared with the untreated control. Western blot analysis showed an approximately 80% reduction in ED-1 expression, indicating suppression of macrophage activation. Overall, the Dexa-GelMA hydrogel provides a biocompatible, multifunctional platform that integrates physical barrier function with anti-inflammatory drug delivery, showing strong potential for preventing postoperative nerve adhesion and modulating early inflammatory responses in a peripheral nerve injury model.

Keywords: anti-adhesion; GelMA; dexamethasone; nerve regeneration; photo-crosslinking



Academic Editors: Hai-Feng (Frank) Ji and Rui F. Martins

Received: 22 January 2026

Revised: 20 February 2026

Accepted: 28 February 2026

Published: 3 March 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

1. Introduction

Peripheral nerves play a pivotal role in maintaining sensory and motor communication between peripheral tissues and the central nervous system. Damage to peripheral nerves caused by trauma, tumors, infections, or surgical interventions frequently results in considerable functional impairment and neuropathic pain [1,2]. In the setting of peripheral nerve surgery, postoperative perineural adhesion to adjacent tissues is widely recognized as a major obstacle to successful recovery [3,4]. Following neurolysis or traumatic injury, excessive activation and proliferation of fibroblasts and myofibroblasts promotes scar tissue formation with abundant extracellular matrix deposition, leading to dense perineural

fibrosis [5,6]. This fibrotic scar can compromise the regenerative microenvironment by restricting nerve gliding and mobility, increasing the likelihood of nerve tethering, compression, and persistent pain, and ultimately impeding functional restoration after repair [7]. It acts as a physical barrier, hindering axonal regeneration at the injury site, while the excessive accumulation of extracellular matrix (ECM) components restricts nerve mobility and promotes adhesion. Such adhesions prevent the nerve from moving freely during regeneration, thereby reducing its regenerative capacity and leading to complications such as pain and nerve compression [1,2]. Therefore, preventing perineural adhesion is an important therapeutic strategy for improving postoperative outcomes in peripheral nerve injuries [8].

To mitigate adhesion-related complications, various anti-adhesion barriers, including drug-based, film-based, and gel-based formulations, have been developed and evaluated in preclinical and clinical settings [9]. Despite these efforts, clinical translation remains limited. Many currently available barriers exhibit insufficient anti-adhesion performance at the injury site, inadequate mechanical properties to maintain barrier integrity, or overly rapid degradation that fails to cover the critical healing period [10–13]. In addition, fixation methods such as sutures or medical adhesives, often required to secure barriers in situ, may induce foreign-body reactions and local inflammation, thereby paradoxically promoting further adhesion formation [14,15]. These limitations highlight the ongoing need for anti-adhesion strategies that provide stable coverage, appropriate mechanical robustness, and favorable tissue compatibility without provoking inflammatory responses. Consequently, anti-adhesion barriers based on both synthetic polymers (e.g., polyethylene glycol and polylactic acid) and natural polymers (e.g., gelatin, chitosan, and hyaluronic acid) have been actively investigated [16–19]. In particular, natural polymers have attracted attention owing to their excellent biocompatibility and generally reduced immunogenicity, making them promising candidates for perineural barrier applications.

ECM-derived gelatin exhibits excellent biocompatibility and hydration properties [20–22]. It is non-immunogenic and effectively minimizes foreign body reactions [23]. However, despite these advantages, gelatin inherently degrades easily because of its low mechanical strength [24,25]. Accordingly, numerous studies have sought to enhance the stability and durability of gelatin through chemical crosslinking techniques that improve its mechanical properties while preserving biocompatibility [26]. For example, photocrosslinkable methacrylated gelatin (GelMA) is a photopolymerizable gelatin-based biomaterial produced by methacrylation of lysine residues in the gelatin backbone. This modification enhances the mechanical strength and stability of gelatin, while retaining its excellent biocompatibility and biodegradability, making GelMA a widely used material in tissue engineering and biomedical applications [27–31]. Accordingly, GelMA has been extensively investigated for its potential applications in tissue engineering and drug delivery, given its ability to maintain structural stability [27,28].

The regulation of early postoperative inflammation is critical for preventing perineural adhesion and supporting peripheral nerve repair [29]. Beyond acting as a physical barrier, an ideal anti-adhesion strategy should also modulate the inflammatory microenvironment, because excessive and prolonged inflammation after nerve injury aggravates secondary tissue damage and promotes fibroblast and myofibroblast activation, thereby accelerating fibrotic scar formation [5,6]. In this regard, pharmacological intervention offers a direct advantage by suppressing pro-inflammatory signaling cascades at the injury site, which can reduce downstream fibrosis and adhesion. Glucocorticoids have long been used to control detrimental inflammatory responses, and dexamethasone, a synthetic glucocorticoid, effectively inhibits pro-inflammatory pathways in activated macrophages and microglia, attenuating early inflammation and pain [30–32]. Furthermore, downregulation of cytokines such as IL-1, IL-6, IL-8, and TNF- α is associated with reduced inflammatory bur-

den and diminished fibrotic responses, which may translate into improved anti-adhesion outcomes [33,34]. Therefore, incorporating an anti-inflammatory drug component, particularly via localized delivery, can complement physical barrier function by targeting the biological drivers of adhesion formation while potentially minimizing systemic exposure.

In this study, we aimed to develop a hydrogel-based anti-inflammatory barrier that overcomes the rapid degradation and low mechanical stability of conventional anti-adhesion materials, thereby effectively preventing postoperative peripheral nerve adhesions. GelMA, a photocrosslinkable derivative of gelatin, was used to enhance the mechanical strength and stability of the barrier while maintaining excellent biocompatibility. To impart anti-inflammatory functionality, dexamethasone was incorporated into the GelMA matrix to suppress postoperative swelling and early inflammatory responses in nerve tissues. Consequently, a photo-crosslinked, drug-releasing membrane system, termed dexamethasone-loaded GelMA (Dexa-GelMA), was fabricated to simultaneously inhibit perineural adhesion and modulate neuroinflammation. The biocompatibility, anti-adhesion performance, and anti-inflammatory efficacy of the Dexa-GelMA hydrogel were systematically investigated *in vitro* and *in vivo* to validate its potential as an anti-adhesion and anti-inflammatory barrier and to determine whether it can create a microenvironment conducive to subsequent nerve repair.

2. Materials and Methods

2.1. Materials

Gelatin was obtained from Dae-Jung Co. (Siheung, Republic of Korea). Chemicals and reagents, including methacrylic anhydride (MA) and dexamethasone, were purchased from Sigma-Aldrich (St. Louis, MO, USA). Dialysis membranes with a molecular weight cutoff of 12–14 kDa were purchased from Spectrum Laboratories, Inc. (Rancho Dominguez, CA, USA). The B35, C6, and NIH-3T3 cell lines used in this study were purchased from the Korean Cell Line Bank (Seoul, Republic of Korea). Dulbecco's Modified Eagle's Medium (DMEM), Roswell Park Memorial Institute Medium 1640, fetal bovine serum (FBS), and penicillin–streptomycin (P/S) were obtained from Gibco Invitrogen (Grand Island, NY, USA).

2.2. Synthesis of Gelatin-Methacrylic Anhydride

Gelatin methacryloyl (GelMA) was synthesized according to a previously described method [35]. Briefly, gelatin (5 g) was dissolved in 100 mL distilled water at 35 °C for 3 h. Methacrylic anhydride (3.75 mL) was added dropwise to the gelatin solution, and the mixture was stirred continuously at 35 °C for 24 h. After stirring for 24 h, the reaction mixture was dialyzed using a dialysis membrane with a molecular weight cut-off of 12–14 kDa and lyophilized for 3 days to obtain purified GelMA powder.

2.3. Characterization of GelMA

The chemical structure of the lyophilized GelMA was characterized using Fourier transform infrared spectroscopy (FT-IR). To verify chemical modification, both gelatin and GelMA samples were ground with potassium bromide (KBr) and compressed into pellets. FT-IR spectra were recorded using a Spectrum Two LiTa spectrometer (PerkinElmer, Waltham, MA, USA) over a wavenumber range of 4000–400 cm^{-1} . All measurements were performed in quintuplicate to ensure reproducibility. The degree of GelMA methacrylation was determined using ^1H nuclear magnetic resonance (^1H NMR) spectroscopy. For analysis, 20 mg of GelMA powder was dissolved in 0.75 mL of D_2O , and the spectra were acquired at 500 MHz. The extent of substitution in the methacrylamide-modified gelatin was quantified by calculating the peak area ratio between the methacrylate vinyl protons

(C=C bond) and the methylene protons adjacent to the primary amines (–CH–NH bond). The degree of substitution was calculated using the following equation:

$$\text{Degree of substitution (DS)} = \frac{\text{Modified amino groups}}{\text{Primary amino groups}} \times 100\%$$

2.4. Preparation of GelMA or Dexa-GelMA Hydrogel

To prepare the GelMA hydrogel, 5 g of the GelMA powder was dissolved in 100 mL of distilled water. A dexamethasone stock solution was prepared by dissolving dexamethasone in sterile distilled water at a concentration of 1 mg/mL. Dexa-GelMA hydrogel was then obtained by incorporating dexamethasone into a 5% (*w/v*) GelMA solution to achieve a final concentration of 200 µg/mL. To prepare photocurable hydrogels, 0.1% (*w/v*) Irgacure 2959 (Sigma) as photoinitiator (PI) was added to 5% GelMA and 5% Dexa-GelMA solutions. The PI-containing GelMA and Dexa-GelMA prepolymer solutions were photocrosslinked using a UV spotlight source (Hamamatsu LIGHTNINGCURE, L9588-01; 365 nm, –01A type, Hamamatsu Photonics K.K., Hamamatsu, Japan) positioned 5 cm above the samples for 1 min. Crosslinking was performed without a plate lid, and the irradiation conditions were kept identical for all samples. In addition, the same type of plate and an identical sample arrangement were used across all groups to ensure a consistent irradiation environment.

2.5. Analysis of GelMA Hydrogels Loaded with Dexamethasone

For rheological analysis, 5% GelMA and 5% Dexa-GelMA hydrogels were prepared by dissolving dexamethasone (200 µg/mL) in a 5 wt% GelMA aqueous solution. The prepolymer solutions were mixed with 0.01% PI, cast into cylindrical molds ($1.5 \times 1.5 \times 0.15 \text{ mm}^3$), and subsequently photocrosslinked. Rheological measurements were performed using a Kinexus Prime lab+ rheometer (NETZSCH Korea Co., Ltd., Paju, Republic of Korea) equipped with a 1.5 mm parallel plate geometry and a 0.15 mm gap. Oscillatory frequency sweep tests were conducted over a range of 0.01–1 Hz at 25 °C to determine the storage modulus (G') and loss modulus (G'').

To examine the microstructural morphology, the crosslinked hydrogels were freeze-dried at –80 °C to obtain sponge-like structures. The dried samples were sectioned to expose their internal architecture, sputter-coated with gold, and examined under a scanning electron microscope (SEM; Hitachi S-4800, Tokyo, Japan).

2.6. Swelling Property

The swelling behavior of the hydrogels was evaluated by monitoring their weight changes in phosphate-buffered saline (PBS, pH 7.4) at 37 °C. The initial weight of the as-prepared hydrogels (W_0) was recorded, and the samples were immersed in PBS in sealed containers. At predetermined time intervals (1, 3, and 7 days), the hydrogels were removed from the solution, and their wet weight (W_t) was recorded after gently blotting excess surface water with filter paper. The swelling ratio was calculated using the following formula [36]:

$$\text{Swelling ratio (\%)} = \frac{W_t - W_0}{W_0} \times 100$$

2.7. Release Behavior of Dexamethasone from GelMA Hydrogel

To evaluate the in vitro release profile of dexamethasone, the dexamethasone-loaded hydrogels (100 µL volume, containing 200 µg/mL of dexamethasone) were incubated in 0.5 mL of phosphate-buffered saline (PBS; pH 7.4) at 37 °C with gentle shaking at 100 rpm for 6 days. At predetermined time points (1, 3, and 6 h; and 1, 2, 3, 4, 5, and 6 days), the

release medium (0.5 mL) was collected and immediately replaced with an equal volume of fresh PBS (pH 7.4) [36]. The collected samples were filtered through a 0.45 µm syringe filter (Whatman, Cytiva, Maidstone, UK) prior to analysis. Dexamethasone concentrations in PBS were quantified using high-performance liquid chromatography (HPLC; Jasco LC-4000, Tokyo, Japan). The mobile phase consisted of acetonitrile and water (70:30, *v/v*) at an isocratic flow rate of 1.0 mL/min. The injection volume was 20 µL, and the column temperature was maintained at 30 °C. Dexamethasone was detected at 239 nm using a C18 column (4.6 mm × 250 mm × 5 µm). The mass released at time *t* (M_t) was calculated using the following equation [37,38].

$$M_t = C_t V + \sum C_{t-1} V_s$$

where C_t is the concentration of drug in the release solution at time *t*, *V* is the total volume of release solution (0.5 mL) and V_s is the sample volume (0.5 mL).

2.8. Biocompatibility Assessment

B35, C6, and NIH-3T3 cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin (P/S) in a humidified incubator at 37 °C with 5% CO₂. The culture medium was refreshed every other day.

The cytotoxicity of 5% GelMA and 5% Dexa-GelMA hydrogels was evaluated using a CCK-8 assay. Briefly, cells were seeded at a density of 2×10^4 cells/well in 24-well plates and cultured overnight. The culture medium was replaced with fresh medium, and varying amounts of GelMA or Dexa-GelMA hydrogels (10 mg or 50 mg) were added to the wells containing medium supplemented with 10% FBS. The cells were incubated with hydrogels at 37 °C for 1 or 3 days. The medium was removed, and the cells were washed with PBS. Subsequently, fresh medium containing the CCK-8 solution was added, followed by incubation for 4 h at 37 °C. Absorbance was measured at 450 nm, and cell viability (%) was calculated using the following equation

$$\text{Cell viability (\%)} = \frac{\text{Absorbance of hydrogel sample}}{\text{Absorbance of control}} \times 100$$

2.9. In Vitro Anti-Adhesion Analysis

To assess cell proliferation and adhesion on hydrogels, 200 mg of 5% GelMA or 5% Dexa-GelMA hydrogel was dispensed onto the center of a confocal culture dish and photocrosslinked. After washing the crosslinked gels with PBS to remove residual impurities, B35, C6, and NIH-3T3 cells were seeded at a density of 5×10^4 cells/well. Three days after seeding, cell proliferation and adhesion were assessed by adding 200 µL of thiazolyl blue tetrazolium bromide (MTT; Sigma-Aldrich) solution (2 mg/mL in PBS) to each well.

2.10. Establishment of Sciatic Nerve Injury Model

Healthy 6-week-old male Sprague-Dawley (SD) rats (*n* = 27) were purchased from Samtaco (Korea). The rats were housed in pairs under controlled temperature (22 ± 2 °C), humidity ($50 \pm 10\%$), and a 12 h light/dark cycle, with free access to food and water. Animal care and experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Wonkwang University (approval no. WKU22-119). A compression injury of the sciatic nerve was induced using an 8 mm microclamp to evaluate peripheral nerve adhesions and inflammation. After exposure of the sciatic nerve through an incision of the biceps femoris muscle, a vascular clip exerting 60 g of force (Micro Serrafines; Fine Science Tools, North Vancouver, BC, Canada) was applied 10 mm proximal to

the trifurcation for 2 min. Rats were randomly assigned to three groups: Control, GelMA, and DEXA-GelMA. In the control group, the incision was closed by suturing after nerve compression. In the GelMA and DEXA-GelMA groups, after nerve compression, the UV-crosslinked GelMA or DEXA-GelMA hydrogel was wrapped around the nerve injury site and sutured. After injury, the muscles and skin were closed using a 3-0 silk suture (AILEE, Busan, Republic of Korea). Body temperature was maintained at 37 °C using a heating pad throughout the surgery and recovery periods. Postoperatively, cefazolin (25 mg/kg; Chong Kun Dang, Seoul, Republic of Korea) was administered twice daily for 5 days. The animals were sacrificed using a CO₂ chamber, and the sciatic nerves were harvested for dialysis.

2.11. Anti-Inflammatory Effects of DEXA-GelMA Hydrogel

For histological analysis, rats were sacrificed by CO₂ exposure one week after surgery. Nerve adhesions were evaluated seven days post-surgery. The degree of nerve adhesion was assessed according to the following grading system [6,39]: Grade 1 indicated no nerve adhesion or a condition in which separation could be achieved with minimal dissection; Grade 2 indicated cases requiring moderate dissection to separate the nerve from surrounding tissues; and Grade 3 indicated severe adhesion requiring sharp dissection using a scalpel and forceps to separate the nerve from the surrounding tissues. Adhesion scores were recorded and analyzed for each experimental group.

For immunofluorescence analysis, the peripheral nerve injury site was excised and fixed in 4% paraformaldehyde solution. The fixed tissues were embedded in O.C.T. compound, sectioned at a thickness of 10 µm, and mounted on positively charged glass slides.

Sections were stained using the primary anti-macrophage/monocyte antibody, clone ED-1 (1:200; Merck Millipore Ltd., Darmstadt, Germany), followed by 2d Alexa Fluor® 488-conjugated anti-mouse IgG (H + L) (1:200; Immunoresearch Laboratories, West Grove, PA, USA). Stained sections were then digitally imaged using an ECLIPSE Ti2-U fluorescence microscope (Nikon, Tokyo, Japan).

Western blotting was performed to assess inflammatory responses in peripheral nerves treated with GelMA and DEXA-GelMA (n = 3). Peripheral nerve tissue was lysed using RIPA lysis buffer and centrifuged at 13,000 × g for 5 min at 4 °C to remove tissue debris. Total protein concentration was determined using a BCA protein assay reagent kit (SMART BCA, iNtRON Biotechnology, Inc., Gyeonggi-do, Republic of Korea). Protein samples (30 µg/lane) were electrophoresed on a 10% sodium dodecyl sulfate–polyacrylamide gel and transferred onto polyvinylidene fluoride (PVDF) membranes. The membranes were blocked with 5% nonfat dry milk in PBS containing 0.1% Triton X-100 for 1 h at room temperature and then incubated overnight at 4 °C with a primary anti-macrophage/monocyte antibody (clone ED-1; 1:10,000; Merck Millipore Ltd.). After washing, the membranes were incubated for 2 h at room temperature with a horseradish-peroxidase-conjugated goat anti-mouse IgG (H + L) secondary antibody (1:10,000; Bioss, Woburn, MA, USA). Protein expression levels were normalized to β-actin using a monoclonal antibody (Invitrogen, Carlsbad, CA, USA). Finally, the membranes were incubated with an ECL solution (Westsave ECL, AbFrontier, Gyeonggi-do, Republic of Korea) and visualized using a chemiluminescence and fluorescence Western blot analyzer (FUSION SOLO 6X, Vilber Lourmat, Collégien, France).

2.12. Statistical Analysis

Comparisons among three or more groups were performed using a one-way ANOVA or the Kruskal–Wallis H test, as appropriate. In all analyses, statistical significance was defined as a *p*-value <0.05. All quantitative data are presented as mean ± standard deviation.

3. Results

3.1. Synthesis and Characterization of GelMA Hydrogel

Gelatin is a collagen-derived polypeptide bearing abundant reactive functional groups, including primary amine, hydroxyl, and carboxyl moieties, which enable chemical modification. GelMA is obtained by reacting gelatin with MA, thereby introducing methacryloyl substituents onto primary amines. Following photocrosslinking, GelMA hydrogels exhibit mechanical and physicochemical properties that can be tuned by adjusting the degree of methacrylation, polymer concentration, and curing conditions [40,41]. Figure 1 shows the FT-IR spectra of gelatin and GelMA, highlighting peaks corresponding to the characteristic functional groups. The broad associated with O-H and N-H stretching (Amide A) was located around 3426 cm^{-1} , while the C-H stretching peak appeared at 2928 cm^{-1} . These peaks were observed for both the pure gelatin and GelMA. The GelMA spectrum shows an amide II band (N-H modification) at 1547 cm^{-1} (nearly identical to the pure gelatin peak). Notably, GelMA exhibited a robust and dominant peak at 1658 cm^{-1} , shifted from the 1638 cm^{-1} (Amide I) peak in pure gelatin. This shift reflects the critical overlap of the Amide I (C=O) band with the C=C double bond from the methacryloyl group, thereby confirming the successful synthesis of GelMA. The chemical transformation from gelatin to GelMA was confirmed using $^1\text{H-NMR}$ (Figure 1B). In GelMA, increased signals at $\delta = 1.9\text{ ppm}$ and $\delta = 5.4\text{--}5.7\text{ ppm}$, corresponding to methyl and vinyl protons of the methacrylate group, were observed. The methylene proton signal of lysine at $\delta = 2.9\text{ ppm}$ decreased following methacrylation. The increase and decrease in peak intensities indicate the functionalization of gelatin by MA groups. To determine the extent of methacrylation, we compared the proton signals at $\delta = 2.9\text{ ppm}$ for gelatin and GelMA. The degree of methacrylation substitution was approximately 33%.

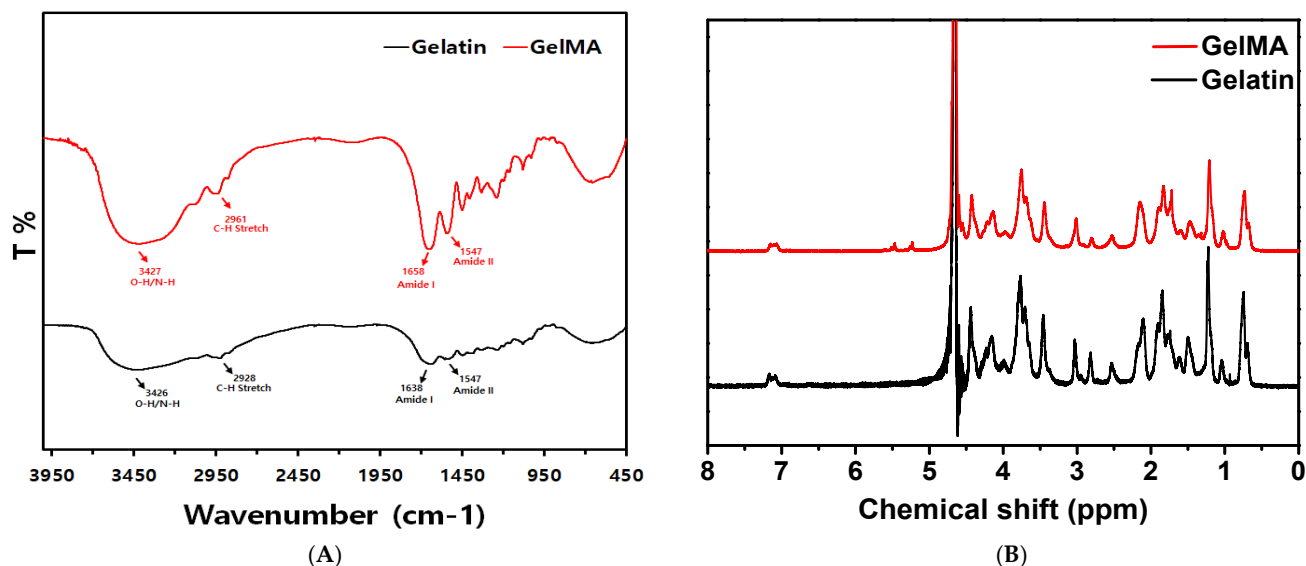


Figure 1. Characterization of GelMA synthesis. (A) FT-IR spectra and (B) H-NMR Spectroscopy.

3.2. Rheological Properties of Dexa-GelMA Hydrogel

GelMA hydrogels were formed via photochemical crosslinking of methacryloyl groups on the GelMA backbone in the presence of a photoinitiator (PI) (Figure 1A). Figure 2 demonstrates the photocrosslinking behavior of GelMA and Dexa-GelMA hydrogels under identical UV irradiation conditions (365 nm; Hamamatsu LIGHTNINGCURE L9588-01; 5 cm; 60 s; no lid; see Methods). In the absence of UV exposure (0 min), neither formulation exhibited gelation despite the presence of PI. In contrast, both prepolymer solutions rapidly formed stable hydrogels after 1 min of UV exposure, confirming successful

photocrosslinking. Notably, although the irradiation conditions were kept constant, the apparent gel stiffness differed depending on the hydrogel composition, suggesting that dexamethasone incorporation influences network formation and/or hydrogel structure.

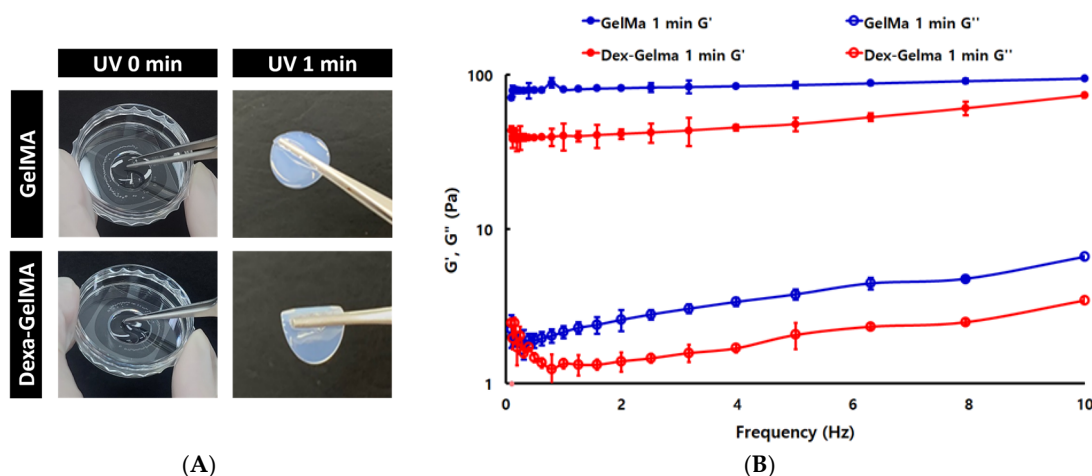


Figure 2. Photocrosslinking and rheological properties of GelMA and DEXA-GelMA hydrogels. (A) Photocrosslinking behavior of GelMA and DEXA-GelMA hydrogels before and after UV exposure (0 and 1 min). Photocrosslinking was performed using a 365 nm UV spotlight (Hamamatsu L9588-01) positioned 5 cm above the samples for 60 s at 25 °C. (B) Rheological analysis showing frequency-dependent changes in storage (G') and loss (G'') moduli of GelMA and DEXA-GelMA hydrogels, indicating the effect of dexamethasone incorporation on viscoelastic properties.

To quantitatively validate these findings, rheological analysis was performed, revealing distinct differences in the storage (G') and loss (G'') moduli between 5% GelMA and 5% DEXA-GelMA hydrogels (Figure 2B). These results indicate that the differences in gel strength induced by photocrosslinking influence the viscoelastic properties of hydrogels. The viscoelastic properties of the hydrogels are characterized by the storage modulus (G') and loss modulus (G''), which represent the elastic and viscous responses, respectively. A gel state is defined by a dominance of the storage modulus ($G' > G''$), whereas a sol state occurs when the loss modulus exceeds the storage modulus ($G' < G''$). Both 5% GelMA and 5% DEXA-GelMA hydrogels showed solid-like behavior after photocrosslinking, with storage moduli (G') exceeding loss moduli (G'') across the tested frequency range, indicating successful gel formation. However, DEXA-GelMA exhibited lower G' values than GelMA, suggesting reduced mechanical stiffness upon drug incorporation. The lower G' of DEXA-GelMA may be attributed to formulation-dependent changes in network formation, including a reduced effective crosslink density and increased hydration/plasticization of the matrix. Reduced crosslink density generally lowers the elastic response of hydrogel networks, while hydration can plasticize polymer matrices by weakening interpolymer interactions and enhancing chain mobility, leading to decreased stiffness. To evaluate the viscoelastic properties of the hydrogel under physiological (body-temperature) conditions, rheological measurements were additionally conducted at 25 °C and 37 °C (Figure S1). At representative frequencies (0.1, 1, and 5 Hz), DEXA-GelMA consistently exhibited higher storage moduli (G') than loss moduli (G'') at both temperatures, confirming a predominantly solid-like (gel) state. Notably, the G' values at 37 °C were maintained or slightly increased compared with those at 25 °C, indicating that the hydrogel preserves mechanical integrity at body temperature.

3.3. SEM Analysis of Hydrogel

The surface and internal morphologies of GelMA and Dexa-GelMA hydrogels were subsequently examined, as dexamethasone incorporation may influence the hydrogel microstructure. Figure 3A shows the surface morphology of Dexa-GelMA hydrogel and GelMA hydrogel. To evaluate the internal structure, cross-sections of the freeze-dried hydrogels were observed using SEM. Both Dexa-GelMA hydrogel and GelMA hydrogel exhibited overall similar porous architectures, with pores uniformly distributed and interconnected throughout the samples. The pore sizes were $24.7 \pm 4 \mu\text{m}$ for Dexa-GelMA hydrogel and $20.9 \pm 4 \mu\text{m}$ for GelMA hydrogel, and the difference between the groups was not statistically significant (Figure 3B). This interconnected porous network is expected to facilitate the diffusion of oxygen, nutrients, and drugs, thereby supporting the survival and functional maintenance of nerve cells.

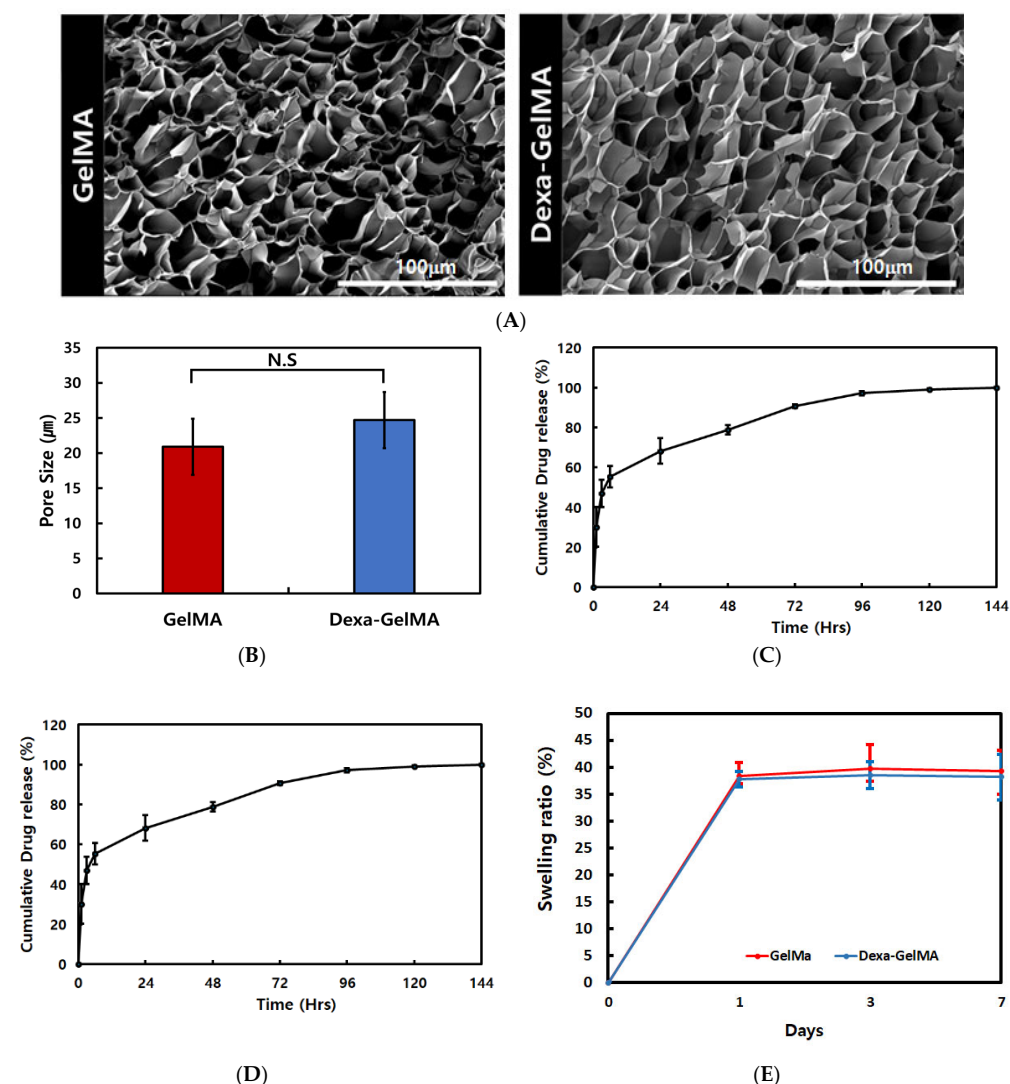


Figure 3. Surface morphology and drug release behavior of GelMA and Dexa-GelMA hydrogels. (A) Representative SEM images of the porous microstructure of photocrosslinked GelMA and Dexa-GelMA hydrogels (Scale bar: 100 μm). (B) Quantification of average pore size for GelMA and Dexa-GelMA hydrogels. Cumulative dexamethasone release profile from Dexa-GelMA hydrogel in PBS at 37 °C (C) 144 h and (D) the first 6 h. (E) Quantitative analysis of the swelling ratio of GelMA and Dexa-GelMA hydrogels over time ($n = 4$).

3.4. Swelling Kinetics and Drug Release Behavior of Dexa-GelMA Hydrogels

The drug release behavior of the hydrogels was further evaluated using dexamethasone as a model drug. Using dexamethasone as a model drug, the release study revealed that approximately 70% of the loaded drug was released within 24 h in PBS (pH 7.4) (Figure 3C,D) [42]. As shown in Figure 3E, the swelling ratio of the GelMA hydrogel (5%) was 0% on day 0, $38.31 \pm 2.57\%$ on day 1, $39.78 \pm 4.34\%$ on day 3, and $39.25 \pm 3.89\%$ on day 7. Also, Dexa-GelMA hydrogel was 0% on day 0, $37.77 \pm 1.43\%$ on day 1, $38.53 \pm 2.53\%$ on day 3, and $38.16 \pm 4.25\%$ on day 7. Both hydrogel groups exhibited rapid water uptake within the first 24 h and maintained a stable equilibrium swelling state up to 7 days. No significant difference was observed between the two groups, indicating that the low concentration of dexamethasone had no significant effect on the swelling behavior of the GelMA hydrogel (Figures 3E and S2). The swelling behavior of hydrogels is strongly governed by the physicochemical properties of encapsulated drugs. Hydrophilic and ionic compounds, such as cefazolin, increase swelling by enhancing water uptake through ion-dipole interactions and associated hydration effects [43]. In contrast, hydrophobic drugs, including dexamethasone, often reduce swelling by increasing the overall hydrophobicity of the polymer matrix and limiting water penetration. In the present study, however, the low dose of dexamethasone did not significantly alter the swelling behavior relative to the control group, indicating that the incorporated amount was insufficient to measurably affect the hydrophilic network structure of the GelMA hydrogels [36,43].

3.5. Biocompatibility of Dexa-Loaded GelMA Hydrogels

The biocompatibility of GelMA and Dexa-GelMA hydrogels was evaluated at two mass (10 mg and 50 mg) using B35, C6, and NIH 3T3 cells. On day 1, no significant differences in cell viability were observed among the control, GelMA, and Dexa-GelMA groups, nor between B35, C6 and NIH3T3 cells (Figure 4A,B). On day 3, the NIH/3T3 cells treated with 50 mg of hydrogel exhibited a slight reduction in viability compared with B35 and C6 cells (Figure 4C); however, this decrease was not statistically significant relative to the control. After 7 days of culture, the cell viability was 94% for B35, 95% for C6, and 94% for NIH 3T3 cells, which were comparable to those of the control group. These results indicate that there were no significant differences in cell viability between the GelMA and Dexa-GelMA hydrogels compared with the control group, demonstrating that both hydrogels possess excellent biocompatibility.

3.6. Anti-Adhesion Effect of Dexa-GelMA Hydrogel In Vitro

Figure 5 provides an overall view of initial cell attachment on GelMA-based hydrogels following cell culture and staining. In particular, Figure 5A shows the concentration-dependent attachment on GelMA hydrogels (5, 10, 15, and 20%, w/v). The control group (tissue culture polystyrene, TCPS) exhibited broad, intense purple staining, indicating a high level of cell attachment. In contrast, all GelMA hydrogel surfaces displayed markedly lower staining intensity, suggesting reduced cell attachment compared to the control. Notably, at the lowest concentration (5% GelMA), cell attachment was minimal. However, as the GelMA concentration increased to 10, 15, and 20% (w/v), the density of attached cells on the hydrogel surfaces progressively increased. These observations are consistent with previous reports showing that increasing GelMA concentration typically leads to higher crosslinking density and mechanical stiffness, thereby providing a microenvironment more conducive to cell adhesion and spreading [44].

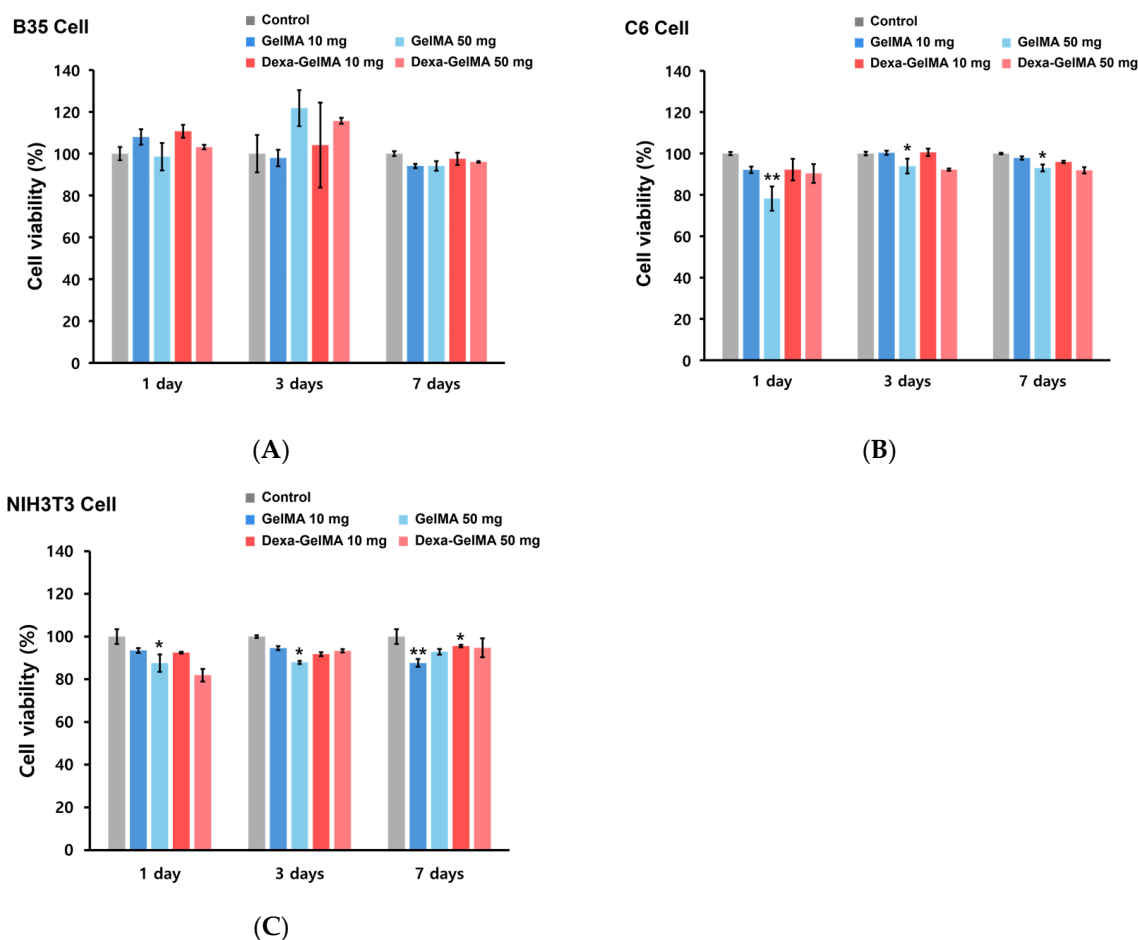


Figure 4. Biocompatibility of GelMA and Dexamethasone (Dexa)-GelMA hydrogels. Cell viability of (A) B35, (B) C6, and (C) NIH 3T3 cells cultured with GelMA or Dexamethasone (Dexa)-GelMA hydrogels for 1, 3, and 7 days. (* $p \leq 0.05$, ** $p \leq 0.01$, NS ≥ 0.05).

We evaluated the anti-adhesion performance of GelMA and Dexamethasone (Dexa)-GelMA hydrogels using B35, C6, and NIH/3T3 cell lines. The hydrogels were reproducibly positioned at the center of culture dishes, and cells were seeded onto the hydrogel-covered regions and incubated for 3 days prior to MTT staining. As shown in Figure 5, B35 cells (Figure 5B), C6 cells (Figure 5C), and NIH/3T3 cells (Figure 5D), all three cell lines displayed weaker staining on hydrogel-covered regions than on the uncovered TCPS regions within the same wells, indicating reduced cell attachment/coverage on the hydrogels. In these images, purple staining represents metabolically active cells remaining on the surface. Notably, Dexamethasone (Dexa)-GelMA consistently exhibited lower staining intensity than pristine GelMA, suggesting enhanced anti-adhesive performance upon dexamethasone loading. Collectively, these results indicate that GelMA-based hydrogels reduce cell attachment in vitro, and that dexamethasone incorporation further enhances this anti-adhesion effect.

3.7. Anti-Adhesion Effect of Dexamethasone (Dexa)-GelMA Hydrogel in Peripheral Nerve Injury

To evaluate perineural adhesion and inflammatory responses in surrounding tissues after peripheral nerve injury, a sciatic nerve compression model was established (Figure 6A). Animals were divided into three experimental groups: an untreated injury control group, a GelMA hydrogel-treated group, and a Dexamethasone (Dexa)-GelMA hydrogel-treated group. At 7 days post-injury, marked adhesions between the sciatic nerve and adjacent tissues were observed in the untreated injury control group (Figure 6B, left). In contrast, in the GelMA hydrogel-treated group, the extent of adhesion was visibly reduced com-

pared with the untreated group (Figure 6B, middle). Most notably, adhesions were minimal in the Dexa-GelMA hydrogel-treated group (Figure 6B, right), indicating the most pronounced reduction in adhesion formation among the groups. Figure 6C presents the semi-quantitative adhesion scores for each group. Perineural adhesion severity was graded on a 1–3 scale based on the ease of separating the sciatic nerve from surrounding tissues [6,45], adapting established protocols for rat sciatic nerve adhesion models: A score of 1 indicated no adhesion or mild adhesion separable by minimal blunt dissection; score 2 indicated moderate adhesion requiring vigorous blunt dissection; and score 3 indicated severe adhesion requiring sharp dissection for separation. Each condition was evaluated in three SD rats ($n = 5$). The untreated injury group exhibited the highest adhesion score (3.0). The GelMA hydrogel-treated group showed a lower score (2.3 ± 0.5). Notably, the Dexa-GelMA hydrogel-treated group presented the lowest adhesion score (1.3 ± 0.57), indicating significantly reduced adhesion formation compared with both the injury and GelMA hydrogel-treated groups.

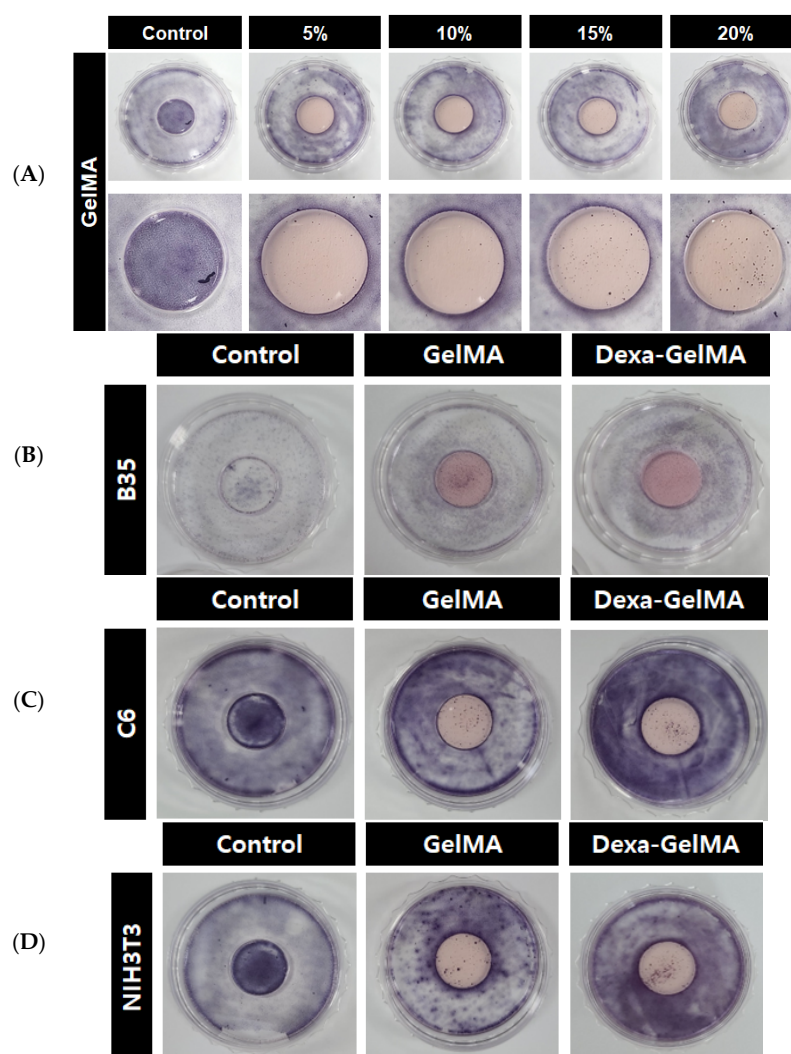


Figure 5. (A) NIH 3T3 cells cultured on GelMA hydrogels with different polymer concentrations (5, 10, 15, and 20%, *w/v*) for 3 days to evaluate concentration-dependent cell adhesion. Cell adhesion on GelMA and Dexa-GelMA hydrogels. (B) B35, (C) C6, and (D) NIH 3T3 cells cultured on control, GelMA, and Dexa-GelMA hydrogels for 3 days. Cell adhesion assessed by MTT staining showing reduced attachment to hydrogel-coated regions, with Dexa-GelMA hydrogel exhibiting stronger anti-adhesive effects than GelMA hydrogel.

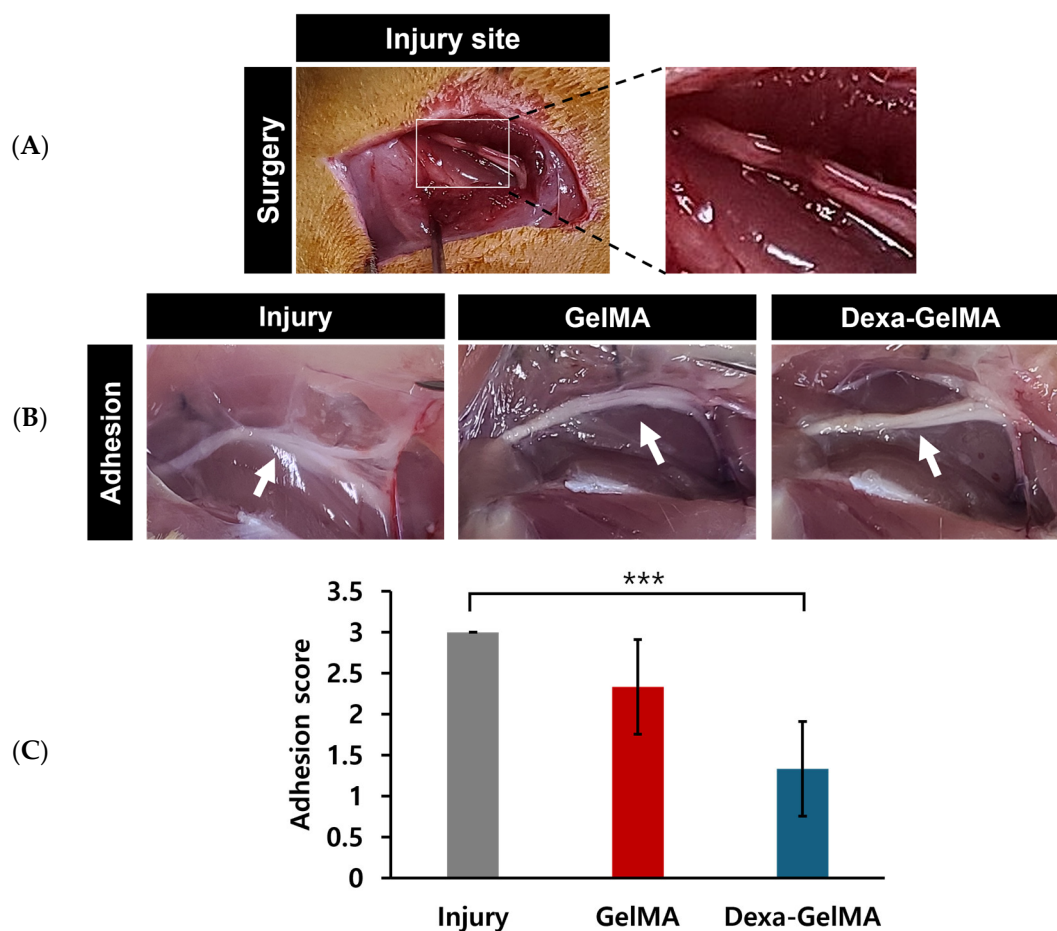


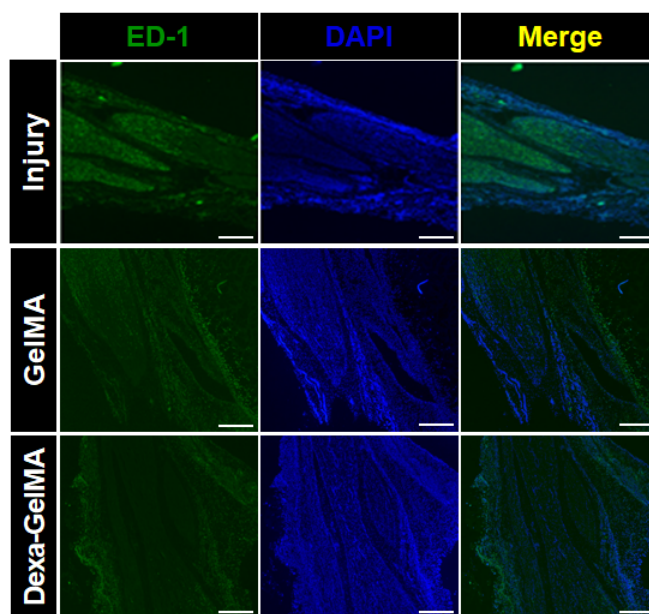
Figure 6. Effects of Dexa-GelMA hydrogel on anti-adhesion in a peripheral nerve injury model (A) Generation of a rat sciatic nerve injury model. (B) Representative gross images of tissue adhesion one week after hydrogel implantation in the sciatic nerve injury model. The arrows indicate the site of sciatic nerve injury site (C) Adhesion scoring of Nerve Tissues. *** $p \leq 0.001$.

3.8. Anti-Inflammatory Effect of Dexa-GelMA Hydrogel in Peripheral Nerve Injury

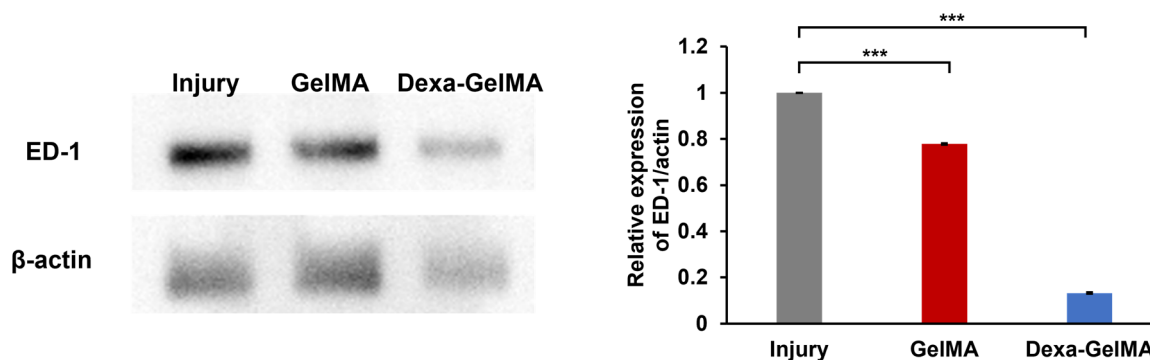
To evaluate the anti-inflammatory efficacy of the Dexa-GelMA hydrogel following peripheral nerve injury, nerve tissues were harvested 7 days post-surgery and subjected to immunofluorescence staining and Western blot analysis. Macrophage/monocyte infiltration was assessed using ED-1 immunostaining (Figure 7), and pro-inflammatory signaling was evaluated by quantifying TNF- α expression (Supplementary Figure S3). As depicted in Figure 7A and Supplementary Figure S3, the untreated injury control and GelMA-treated groups exhibited strong ED-1 immunoreactivity and elevated TNF- α levels, indicating pronounced inflammatory cell infiltration and activity within the injured region. In contrast, the Dexa-GelMA-treated group exhibited markedly fewer ED-1-positive cells and reduced TNF- α expression, suggesting attenuation of macrophage-associated inflammatory responses at the injury site. Collectively, these results support that local delivery of dexamethasone via the Dexa-GelMA hydrogel can mitigate early postoperative inflammation, which may contribute to its enhanced anti-adhesion performance.

Western blot analysis was performed to evaluate the anti-inflammatory effects of dexamethasone released from the Dexa-GelMA hydrogel, with β -actin used as a loading control for protein normalization (Figure 7B). ED-1 protein expression was highest in the untreated injury group, while only a modest reduction was observed in the GelMA-treated group. Notably, ED-1 expression was markedly decreased in the Dexa-GelMA-treated group. Quantitative densitometric analysis using ImageJ (v1.53t, National Institutes of

Health, Bethesda, MD, USA), with β -actin as the loading control, showed relative ED-1 expression levels of 0.78 and 0.13 in the GelMA- and Dexamethasone-GelMA-treated groups, respectively, compared with the injury group normalized to 1.0 (Figure 7C).



(A)



(B)

(C)

Figure 7. Effects of Dexamethasone-GelMA hydrogel on anti-inflammation in a peripheral nerve injury model (A) Immunofluorescence staining of ED-1 (green) and nuclei (DAPI, blue) in injured, GelMA-, and Dexamethasone-GelMA-treated nerves, showing reduced macrophage infiltration in the Dexamethasone-GelMA group. (B) Western blot analysis of ED-1 protein expression ($n = 3$). (C) Quantitative analysis of ED-1/ β -actin ratio. *** $p \leq 0.001$. Scale bar 400 μ m.

4. Discussion

Peripheral nerve adhesions remain a major obstacle to recovery after nerve injury and surgery, driven by rapid inflammation and fibrotic remodeling that lead to perineural scarring [4,5]. The pathogenesis of nerve adhesions involves macrophage recruitment, fibroblast activation, and collagen synthesis, processes that collectively impede axonal regeneration and functional nerve recovery [5–7]. Although currently available commercial anti-adhesion materials function primarily as passive physical separators, they often fail to adequately control the underlying inflammatory fibrotic cascade, especially during the

critical early postoperative period. Moreover, the clinical efficacy of these materials is frequently limited by practical drawbacks, including poor handling characteristics, short residence time due to rapid degradation, and the potential to elicit foreign-body reactions. Furthermore, their barrier function may be eventually compromised by fibroblast infiltration [14,15]. However, the application of active, drug-eluting hydrogel systems specifically designed for the demanding peripheral nerve microenvironment of peripheral nerves remains underexplored. In this study, we developed a photocurable, dexamethasone-eluting Dexa-GelMA hydrogel as an anti-adhesion barrier that combines conformal physical separation with early local immunomodulation. Specifically, the rapid initial release of dexamethasone from the hydrogel effectively attenuates early postoperative inflammation at the injury site. Because it enables photocrosslinking, Dexa-GelMA can be polymerized directly on moist, irregular nerve surfaces to form a conformal coating; this feature overcomes the handling limitations of preformed membranes while ensuring prolonged in situ retention during the critical window of adhesion initiation.

To achieve therapeutic efficacy, the structural characteristics of the carrier are crucial. Various drug delivery systems, including nanoparticles, liposomes, and hydrogels, have been developed to improve therapeutic outcomes [46,47]. Among these, hydrogels are widely regarded as promising biomaterials due to their high biocompatibility, adjustable physicochemical characteristics, and versatility in biomedical and tissue engineering applications. The microstructures of the GelMA hydrogel with and without dexamethasone are shown in Figure 3A. SEM analysis revealed a crosslinked three-dimensional network with a relatively uniform pore distribution. This porous architecture facilitates nutrient diffusion and provides pathways for the controlled transport of therapeutic molecules, validating the use of GelMA as a localized drug-delivery matrix. Moreover, this highly interconnected network enables the efficient incorporation and retention of bioactive agents, thereby allowing local modulation of the immune microenvironment and potentially supporting peripheral nerve repair and regeneration [48].

We evaluated the biological safety of the fabricated hydrogels using in vitro models. Both GelMA and Dexa-GelMA demonstrated excellent cytocompatibility across neuronal (C6, B35) and fibroblast (NIH 3T3) cell lines. Specifically, cells maintained normal morphology, and CCK-8 assays confirmed comparable viability trends across all groups, indicating no cytotoxic effects. In addition, minimal cellular attachment on the hydrogel surface (Figure 5) supports the interpretation that these materials can act not only as biocompatible matrices but also as low-adhesion interfaces that limit postoperative cellular colonization. Collectively, these data demonstrate that Dexa-GelMA preserves the intrinsic cytocompatibility of the GelMA platform while conferring functional properties mechanistically relevant to the mitigation of perineural adhesion. Consequently, both GelMA and Dexa-GelMA demonstrated excellent cytocompatibility, inducing no detectable cytotoxic effects. Beyond its biological safety, Dexa-GelMA served as a conformal and mechanically compliant physical barrier, ensuring stable coverage over moist and irregular nerve surfaces. This structural integrity contributes to the reduction of postoperative adhesions by impeding fibrous tissue overgrowth while permitting essential nutrient diffusion [49,50]. Notably, this nerve-specific design addresses critical limitations of conventional barriers, which frequently suffer from insufficient interfacial retention and mechanical mismatch under the continuous gliding and micromotion characteristic of the peripheral nerve microenvironment.

Dexamethasone is a potent anti-inflammatory agent that effectively suppresses inflammation-induced gene expression. It exerts anti-inflammatory and immunosuppressive effects through glucocorticoid receptors (GRs), which regulate gene transcription. Upon activation, GRs suppress inflammatory cell activity and inhibit the expres-

sion of pro-inflammatory cytokines (e.g., TNF and interleukins) and related genes, such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [51]. The release of dexamethasone from various delivery systems, including self-assembling peptide nanofiber gels and lipid-based carriers, has been shown to maintain its anti-inflammatory activity *in vitro* and substantially reduce inflammatory cell infiltration *in vivo*, indicating that continuous local delivery of dexamethasone effectively suppresses inflammation [48,52,53]. Dexamethasone inhibits the expression of lipopolysaccharide-induced genes by approximately 43–98% and markedly suppresses the expression of COX-2, IL-1 α , IL-1 β , and IFN- γ , primarily through the inhibition of p38 MAPK signaling [54]. Postoperative adhesions result from dysregulated inflammatory responses and fibrosis triggered by surgical injuries. The infiltration of inflammatory cells and fibrin deposition at the injury site activate fibroblasts and promote collagen accumulation, leading to the formation of abnormal intertissue connections (adhesions) between adjacent tissues [55]. In this study, the Dexa-GelMA hydrogel released approximately 65% of the incorporated dexamethasone within the first 24 h, followed by release up to 7 days. This initial burst was primarily attributed to the rapid diffusion of the drug loosely entrapped near the hydrogel surface and within easily accessible pores as the GelMA network swelled. This results in a high early local therapeutic concentration, which is strategic for suppressing acute inflammation and early fibroblast activation associated with the onset of perineural adhesion [56,57]. This release profile is particularly aligned with the temporal biology of perineural adhesion, in which the earliest postoperative phase is dominated by inflammatory cell recruitment and cytokine signaling that subsequently drives fibroblast expansion and collagen deposition.

The Dexa-GelMA hydrogel demonstrated significant efficacy in preventing postoperative perineural adhesion in a rat sciatic nerve injury model, with potential as an advanced anti-adhesion material for peripheral nerve repair. Notably, the hydrogel remained structurally intact at the implantation site for up to one week post-surgery, indicating sufficient *in vivo* stability during the critical adhesion-prone period. This sustained GelMA matrix enabled the continuous local release of dexamethasone, which effectively attenuated early inflammatory responses by suppressing macrophage infiltration (ED-1) and reducing pro-inflammatory cytokine (TNF- α) expression. Consequently, fibroblast proliferation and subsequent scar tissue formation around the injured nerve were effectively minimized (Figure 6). Despite the availability of several commercial anti-adhesion agents, their clinical effectiveness remains limited. Most currently used barriers, such as collagen membranes, hyaluronic acid films, and PEG-based hydrogels, primarily function as passive physical separators and do not actively modulate inflammatory or fibrotic responses. In addition, these materials often show inadequate mechanical stability and poor retention on irregular or moist tissue surfaces, which are able to compromise sustained postoperative protection. Some formulations may also degrade unpredictably *in vivo*, potentially increasing the risk of postoperative complications, whereas others fail to remain at the wound site long enough to provide prolonged anti-adhesion effects [14,15]. Liu et al. reported a Janus hydrogel adhesive with tissue-adhesive and anti-adhesive faces; however, the duration of its adhesive performance was not reported [58]. To address these limitations, Dexa-GelMA hydrogel represents a promising anti-adhesion material that combines anti-inflammatory drug delivery with conformal barrier function, thereby creating a more favorable microenvironment for peripheral nerve regeneration. In particular, the *in situ* photocrosslinked GelMA network enables tunable mechanical stiffness and elasticity, allowing the hydrogel to act as a soft, conformal sheath that minimizes mechanical irritation and stress concentration on the nerve while sustaining a continuous separation layer that resists displacement and fibroblast invasion during the adhesion-prone period. These findings are consistent with prior reports showing that conformal, mechanically compli-

ant hydrogel barriers with sustained local anti-inflammatory delivery reduce postoperative adhesion by limiting early inflammatory amplification and fibroblast-driven matrix deposition [59,60].

Importantly, while prior GelMA- or dexamethasone-based anti-adhesion strategies have been predominantly investigated in intraperitoneal/peritoneal settings, our work demonstrates an active, photocurable hydrogel barrier specifically tailored for peripheral nerves, where early inflammation is a critical upstream driver of fibroblast activation and perineural scarring. In an SD rat model of peripheral nerve injury, this study demonstrates that Dexa-GelMA exerts anti-inflammatory and anti-adhesion effects at an early postoperative time point, with the *in vivo* evaluation intentionally focused on short-term (1 week) outcomes capturing acute inflammation and initial perineural adhesion formation. Consistent with the temporal biology of adhesion formation, local dexamethasone delivery from Dexa-GelMA effectively mitigated early postoperative inflammation, thereby contributing to reduced fibrotic encapsulation and a more permissive microenvironment for peripheral nerve recovery. In future studies, we plan to investigate perform long-term *in vivo* experiments, including ISO-recommended cytotoxicity tests, axonal regeneration analyses, and sciatic functional index measurements, to systematically verify its efficacy for nerve regeneration. Collectively, these results suggest that the Dexa-GelMA hydrogel is a promising and biocompatible material for peripheral nerve regeneration and the prevention of postoperative adhesion.

5. Conclusions

In conclusion, the Dexa-GelMA hydrogel robustly attenuated early post-injury inflammation by reducing macrophage activation and infiltration at the injury site. The significantly decreased ED-1 expression further indicates that Dexa-GelMA provides enhanced local immunomodulation compared with GelMA. Moreover, considering that peripheral nerves undergo continuous gliding and micromotion, the conformal coverage and interfacial retention capability afforded by *in situ* photocrosslinking offer a significant translational advantage for maintaining barrier function during the adhesion-prone early healing phase. Collectively, these results suggest that Dexa-GelMA is a promising therapeutic platform for mitigating the early inflammatory cascade that precedes fibrotic remodeling, thereby minimizing perineural adhesion formation and creating a more favorable microenvironment for peripheral nerve regeneration.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/polym18050628/s1>, Figure S1: Frequency-dependent viscoelastic properties of the Dexa-GelMA hydrogel. Storage modulus (G') and loss modulus (G'') were measured at 25 °C and 37 °C during a frequency sweep (0.1, 1, and 5 Hz); Figure S2: Swelling characteristics of GelMA and Dexa-GelMA hydrogels. Representative optical images of pure 5% GelMA and Dexa-loaded 5% GelMA hydrogels before swelling (Day 0) and after incubation in PBS at 37 °C for 7 days; Figure S3: Anti-inflammatory effects of Dexa-GelMA in a peripheral nerve injury model. Representative immunofluorescence images of TNF- α (red) and nuclei (DAPI, blue) in injured nerves from the Injury, GelMA, and Dexa-GelMA-treated groups. Merged images are shown in the right column. TNF- α immunoreactivity was markedly reduced in the Dexa-GelMA group compared with the Injury and GelMA groups, indicating attenuated pro-inflammatory signaling at the injury site. Scale bars indicate 200 μ m.

Author Contributions: Conceptualization: S.-J.G., methodology: J.-W.P., Formal analysis: J.-W.P., C.J.L. and K.D.S., Validation and Investigation: J.-W.P. and J.-K.K. Resources: C.J.L. and K.D.S., Writing—original draft preparation: J.-W.P., Writing—review and editing: S.-J.G., Supervision: S.-J.G. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by the National Research Foundation of Korea (2022R1A2C2008149).

Institutional Review Board Statement: Animal care and experiment procedures were approved by the Chairperson of the Institutional Animal Care and Use Committee (IACUC) of Wonkwang University (Approval No. WKU22-119) with the approval granted on 1 December 2022.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in the study are included in the article; further inquiries can be directed at the corresponding author.

Acknowledgments: This study was supported by the Bio-Cluster Industry Capacity Enhancement Project of Jeonbuk Technopark (JBTP) by Jeonbuk State.

Conflicts of Interest: The authors declare no conflicts of interest.

References

- Menorca, R.M.; Fussell, T.S.; Elfar, J.C. Nerve physiology: Mechanisms of injury and recovery. *Hand Clin.* **2013**, *29*, 317–330. [[CrossRef](#)]
- Raza, C.; Riaz, H.A.; Anjum, R.; Shakeel, N.U.A. Repair strategies for injured peripheral nerve: Review. *Life Sci.* **2020**, *243*, 117308. [[CrossRef](#)]
- Meier Burgisser, G.; Buschmann, J. History and performance of implant materials applied as peritendinous antiadhesives. *J. Biomed. Mater. Res. B Appl. Biomater.* **2015**, *103*, 212–228. [[CrossRef](#)]
- Koninckx, P.R.; Gomel, V.; Ussia, A.; Adamyan, L. Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue. *Fertil. Steril.* **2016**, *106*, 998–1010. [[CrossRef](#)]
- Hellebrekers, B.W.; Kooistra, T. Pathogenesis of postoperative adhesion formation. *Br. J. Surg.* **2011**, *98*, 1503–1516. [[CrossRef](#)]
- Shintani, K.; Uemura, T.; Takamatsu, K.; Yokoi, T.; Onode, E.; Okada, M.; Nakamura, H. Protective effect of biodegradable nerve conduit against peripheral nerve adhesion after neurolysis. *J. Neurosurg.* **2018**, *129*, 815–824. [[CrossRef](#)]
- Ohsumi, H.; Hirata, H.; Nagakura, T.; Tsujii, M.; Sugimoto, T.; Miyamoto, K.; Horiuchi, T.; Nagao, M.; Nakashima, T.; Uchida, A. Enhancement of perineurial repair and inhibition of nerve adhesion by viscous injectable pure alginate sol. *Plast. Reconstr. Surg.* **2005**, *116*, 823–830. [[CrossRef](#)]
- Amadio, P.C. Interventions for recurrent/persistent carpal tunnel syndrome after carpal tunnel release. *J. Hand Surg. Am.* **2009**, *34*, 1320–1322. [[CrossRef](#)] [[PubMed](#)]
- Crosio, A.; Ronchi, G.; Fornasari, B.E.; Odella, S.; Raimondo, S.; Tos, P. Experimental Methods to Simulate and Evaluate Post-surgical Peripheral Nerve Scarring. *J. Clin. Med.* **2021**, *10*, 1613. [[CrossRef](#)] [[PubMed](#)]
- Soltani, A.M.; Allan, B.J.; Best, M.J.; Mir, H.S.; Panthaki, Z.J. A systematic review of the literature on the outcomes of treatment for recurrent and persistent carpal tunnel syndrome. *Plast. Reconstr. Surg.* **2013**, *132*, 114–121. [[CrossRef](#)] [[PubMed](#)]
- Xu, J.; Varitimidis, S.E.; Fisher, K.J.; Tomaino, M.M.; Sotereanos, D.G. The effect of wrapping scarred nerves with autogenous vein graft to treat recurrent chronic nerve compression. *J. Hand Surg. Am.* **2000**, *25*, 93–103. [[CrossRef](#)]
- Yang, Y.; Liu, X.; Li, Y.; Wang, Y.; Bao, C.; Chen, Y.; Lin, Q.; Zhu, L. A postoperative anti-adhesion barrier based on photoinduced imine-crosslinking hydrogel with tissue-adhesive ability. *Acta Biomater.* **2017**, *62*, 199–209. [[CrossRef](#)]
- Lee, Y.; Chung, H.J.; Yeo, S.; Ahn, C.H.; Lee, H.; Messersmith, P.B.; Park, T.G. Thermo-sensitive, injectable, and tissue adhesive sol-gel transition hyaluronic acid/pluronic composite hydrogels prepared from bio-inspired catechol-thiol reaction. *Soft Matter* **2010**, *6*, 977–983. [[CrossRef](#)]
- Perrin, B.R.; Dupeux, M.; Tozzi, P.; Delay, D.; Gersbach, P.; von Segesser, L.K. Surgical glues: Are they really adhesive? *Eur. J. Cardiothorac. Surg.* **2009**, *36*, 967–972. [[CrossRef](#)]
- Bakkum, E.A.; Dalmeijer, R.A.; Verdel, M.J.; Hermans, J.; van Blitterswijk, C.A.; Trimbos, J.B. Quantitative analysis of the inflammatory reaction surrounding sutures commonly used in operative procedures and the relation to postsurgical adhesion formation. *Biomaterials* **1995**, *16*, 1283–1289. [[CrossRef](#)]
- Ikeda, K.; Yamauchi, D.; Osamura, N.; Hagiwara, N.; Tomita, K. Hyaluronic acid prevents peripheral nerve adhesion. *Br. J. Plast. Surg.* **2003**, *56*, 342–347. [[CrossRef](#)] [[PubMed](#)]
- Li, Z.; Liu, L.; Chen, Y. Dual dynamically crosslinked thermosensitive hydrogel with self-fixing as a postoperative anti-adhesion barrier. *Acta Biomater.* **2020**, *110*, 119–128. [[CrossRef](#)] [[PubMed](#)]
- Jiang, S.; Yan, H.; Fan, D.; Song, J.; Fan, C. Multi-layer electrospun membrane mimicking tendon sheath for prevention of tendon adhesions. *Int. J. Mol. Sci.* **2015**, *16*, 6932–6944. [[CrossRef](#)] [[PubMed](#)]
- Amano, Y.; Qi, P.; Nakagawa, Y.; Kirita, K.; Ohta, S.; Ito, T. Prevention of Peritoneal Adhesions by Ferric Ion-Cross-Linked Hydrogels of Hyaluronic Acid Modified with Iminodiacetic Acids. *ACS Biomater. Sci. Eng.* **2018**, *4*, 3405–3412. [[CrossRef](#)]

20. Lukin, I.; Erezuma, I.; Maeso, L.; Zarate, J.; Desimone, M.F.; Al-Tel, T.H.; Dolatshahi-Pirouz, A.; Orive, G. Progress in Gelatin as Biomaterial for Tissue Engineering. *Pharmaceutics* **2022**, *14*, 1177. [\[CrossRef\]](#)
21. Ikada, Y.; Tabata, Y. Protein release from gelatin matrices. *Adv. Drug Deliv. Rev.* **1998**, *31*, 287–301. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Dallos Ortega, M.; Aveyard, J.; Ciupa, A.; Poole, R.J.; Whettnall, D.; Behnsen, J.G.; D'Sa, R.A. 3D printable gelatin/nisin biomaterial inks for antimicrobial tissue engineering applications. *Mater. Adv.* **2024**, *5*, 7729–7746. [\[CrossRef\]](#)
23. Kimura, A.; Yoshida, F.; Ueno, M.; Taguchi, M. Application of radiation crosslinking technique to development of gelatin scaffold for tissue engineering. *Radiat. Phys. Chem.* **2021**, *180*, 109287. [\[CrossRef\]](#)
24. Samadian, H.; Maleki, H.; Allahyari, Z.; Jaymand, M. Natural polymers-based light-induced hydrogels: Promising biomaterials for biomedical applications. *Coordin. Chem. Rev.* **2020**, *420*, 213432. [\[CrossRef\]](#)
25. Juncos Bombin, A.D.; Dunne, N.J.; McCarthy, H.O. Electrospinning of natural polymers for the production of nanofibres for wound healing applications. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2020**, *114*, 110994. [\[CrossRef\]](#) [\[PubMed\]](#)
26. Swilem, A.E.; Oyama, T.G.; Oyama, K.; Kimura, A.; Taguchi, M. Development of carboxymethyl cellulose/gelatin hybrid hydrogels via radiation-induced cross-linking as novel anti-adhesion barriers. *Polym. Degrad. Stabil.* **2022**, *197*, 109856. [\[CrossRef\]](#)
27. Ribeiro, J.S.; Bordini, E.A.F.; Ferreira, J.A.; Mei, L.; Dubey, N.; Fenno, J.C.; Piva, E.; Lund, R.G.; Schwendeman, A.; Bottino, M.C. Injectable MMP-Responsive Nanotube-Modified Gelatin Hydrogel for Dental Infection Ablation. *ACS Appl. Mater. Interfaces* **2020**, *12*, 16006–16017. [\[CrossRef\]](#)
28. Wang, J.; Wang, C.; Wang, Q.; Zhang, Z.; Wang, H.; Wang, S.; Chi, Z.; Shang, L.; Wang, W.; Shu, Y. Microfluidic Preparation of Gelatin Methacryloyl Microgels as Local Drug Delivery Vehicles for Hearing Loss Therapy. *ACS Appl. Mater. Interfaces* **2022**, *14*, 46212–46223. [\[CrossRef\]](#)
29. Li, Y.; Zhang, Z.; Xu, K.; Du, S.; Gu, X.; Cao, R.; Cui, S. Minocycline alleviates peripheral nerve adhesion by promoting regulatory macrophage polarization via the TAK1 and its downstream pathway. *Life Sci.* **2021**, *276*, 119422. [\[CrossRef\]](#)
30. Bordini, E.A.F.; Ferreira, J.A.; Dubey, N.; Ribeiro, J.S.; de Souza Costa, C.A.; Soares, D.G.; Bottino, M.C. Injectable Multifunctional Drug Delivery System for Hard Tissue Regeneration under Inflammatory Microenvironments. *ACS Appl. Bio Mater.* **2021**, *4*, 6993–7006. [\[CrossRef\]](#)
31. Jeong, D.U.; Bae, S.; Macks, C.; Whitaker, J.; Lynn, M.; Webb, K.; Lee, J.S. Hydrogel-mediated local delivery of dexamethasone reduces neuroinflammation after traumatic brain injury. *Biomed. Mater.* **2021**, *16*, 035002. [\[CrossRef\]](#)
32. Bianchini, M.; Micera, S.; Redolfi Riva, E. Recent Advances in Polymeric Drug Delivery Systems for Peripheral Nerve Regeneration. *Pharmaceutics* **2023**, *15*, 640. [\[CrossRef\]](#)
33. Fang, C.C.; Chou, T.H.; Huang, J.W.; Lee, C.C.; Chen, S.C. The Small Molecule Inhibitor QLT-0267 Decreases the Production of Fibrin-Induced Inflammatory Cytokines and Prevents Post-Surgical Peritoneal Adhesions. *Sci. Rep.* **2018**, *8*, 9481. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Patel, S.K.; Saikumar, G.; Rana, J.; Dhama, J.; Yatoo, M.I.; Tiwari, R.; Rodriguez-Morales, A.J.; Dhama, K. Dexamethasone: A boon for critically ill COVID-19 patients? *Travel. Med. Infect. Dis.* **2020**, *37*, 101844. [\[CrossRef\]](#)
35. Li, S.; Sun, J.; Yang, J.; Yang, Y.; Ding, H.; Yu, B.; Ma, K.; Chen, M. Gelatin methacryloyl (GelMA) loaded with concentrated hypoxic pretreated adipose-derived mesenchymal stem cells (ADSCs) conditioned medium promotes wound healing and vascular regeneration in aged skin. *Biomater. Res.* **2023**, *27*, 11. [\[CrossRef\]](#)
36. Annala, A.; Ilohonwu, B.C.; Wilbie, D.; Sadeghi, A.; Hennink, W.E.; Vermonden, T. Self-Healing Thermosensitive Hydrogel for Sustained Release of Dexamethasone for Ocular Therapy. *ACS Polym. Au* **2023**, *3*, 118–131. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Tu, J.X.; Cao, Z.; Jing, Y.H.; Fan, C.J.; Zhang, C.; Liao, L.Q.; Liu, L.J. Halloysite nanotube nanocomposite hydrogels with tunable mechanical properties and drug release behavior. *Compos. Sci. Technol.* **2013**, *85*, 126–130. [\[CrossRef\]](#)
38. Leach, J.B.; Schmidt, C.E. Characterization of protein release from photocrosslinkable hyaluronic acid-polyethylene glycol hydrogel tissue engineering scaffolds. *Biomaterials* **2005**, *26*, 125–135. [\[CrossRef\]](#)
39. Kikuchi, K.; Setoyama, K.; Takada, S.; Otsuka, S.; Nakanishi, K.; Norimatsu, K.; Tani, A.; Sakakima, H.; Kawahara, K.I.; Hosokawa, K.; et al. E8002 Inhibits Peripheral Nerve Adhesion by Enhancing Fibrinolysis of L-Ascorbic Acid in a Rat Sciatic Nerve Model. *Int. J. Mol. Sci.* **2020**, *21*, 3972. [\[CrossRef\]](#)
40. Pazhouhnia, Z.; Noori, A.; Farzin, A.; Khoshmaram, K.; Hoseinpour, M.; Ai, J.; Ebrahimi, M.; Lotfibakhshaiesh, N. 3D-bioprinted GelMA/gelatin/amniotic membrane extract (AME) scaffold loaded with keratinocytes, fibroblasts, and endothelial cells for skin tissue engineering. *Sci. Rep.* **2024**, *14*, 12670. [\[CrossRef\]](#)
41. Modaresifar, K.; Hadjizadeh, A.; Niknejad, H. Design and fabrication of GelMA/chitosan nanoparticles composite hydrogel for angiogenic growth factor delivery. *Artif. Cells Nanomed. Biotechnol.* **2018**, *46*, 1799–1808. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Wang, Q.S.; Xu, B.X.; Fan, K.J.; Fan, Y.S.; Teng, H.; Wang, T.Y. Dexamethasone-loaded thermo-sensitive hydrogel attenuates osteoarthritis by protecting cartilage and providing effective pain relief. *Ann. Transl. Med.* **2021**, *9*, 1120. [\[CrossRef\]](#)
43. Vigata, M.; Meinert, C.; Bock, N.; Dargaville, B.L.; Hutmacher, D.W. Deciphering the Molecular Mechanism of Water Interaction with Gelatin Methacryloyl Hydrogels: Role of Ionic Strength, pH, Drug Loading and Hydrogel Network Characteristics. *Biomedicines* **2021**, *9*, 574. [\[CrossRef\]](#)

44. Nichol, J.W.; Koshy, S.T.; Bae, H.; Hwang, C.M.; Yamanlar, S.; Khademhosseini, A. Cell-laden microengineered gelatin methacrylate hydrogels. *Biomaterials* **2010**, *31*, 5536–5544. [[CrossRef](#)]
45. Zhan, Y.; Zhou, Z.; Chen, M.; Gong, X. Photothermal Treatment of Polydopamine Nanoparticles@Hyaluronic Acid Methacryloyl Hydrogel Against Peripheral Nerve Adhesion in a Rat Model of Sciatic Nerve. *Int. J. Nanomed.* **2023**, *18*, 2777–2793. [[CrossRef](#)]
46. Sercombe, L.; Veerati, T.; Moheimani, F.; Wu, S.Y.; Sood, A.K.; Hua, S. Advances and Challenges of Liposome Assisted Drug Delivery. *Front. Pharmacol.* **2015**, *6*, 286. [[CrossRef](#)]
47. Li, J.; Mooney, D.J. Designing hydrogels for controlled drug delivery. *Nat. Rev. Mater.* **2016**, *1*, 16071. [[CrossRef](#)] [[PubMed](#)]
48. Wu, Q.; Wang, N.; He, T.; Shang, J.; Li, L.; Song, L.; Yang, X.; Li, X.; Luo, N.; Zhang, W.; et al. Thermosensitive hydrogel containing dexamethasone micelles for preventing postsurgical adhesion in a repeated-injury model. *Sci. Rep.* **2015**, *5*, 13553. [[CrossRef](#)]
49. Zhang, H.; Xu, J.; Saijilafu. The effects of GelMA hydrogel on nerve repair and regeneration in mice with spinal cord injury. *Ann. Transl. Med.* **2021**, *9*, 1147. [[CrossRef](#)]
50. Cai, J.; Zhang, H.; Hu, Y.; Huang, Z.; Wang, Y.; Xia, Y.; Chen, X.; Guo, J.; Cheng, H.; Xia, L.; et al. GelMA-MXene hydrogel nerve conduits with microgrooves for spinal cord injury repair. *J. Nanobiotechnol.* **2022**, *20*, 460. [[CrossRef](#)] [[PubMed](#)]
51. Weikum, E.R.; Knuesel, M.T.; Ortlund, E.A.; Yamamoto, K.R. Glucocorticoid receptor control of transcription: Precision and plasticity via allostery. *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 159–174. [[CrossRef](#)]
52. Webber, M.J.; Matson, J.B.; Tamboli, V.K.; Stupp, S.I. Controlled release of dexamethasone from peptide nanofiber gels to modulate inflammatory response. *Biomaterials* **2012**, *33*, 6823–6832. [[CrossRef](#)] [[PubMed](#)]
53. Rhen, T.; Cidlowski, J.A. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N. Engl. J. Med.* **2005**, *353*, 1711–1723. [[CrossRef](#)] [[PubMed](#)]
54. Abraham, S.M.; Lawrence, T.; Kleiman, A.; Warden, P.; Medghalchi, M.; Tuckermann, J.; Saklatvala, J.; Clark, A.R. Antiinflammatory effects of dexamethasone are partly dependent on induction of dual specificity phosphatase 1. *J. Exp. Med.* **2006**, *203*, 1883–1889. [[CrossRef](#)]
55. Fatehi Hassanabad, A.; Zarzycki, A.N.; Jeon, K.; Dundas, J.A.; Vasanthan, V.; Deniset, J.F.; Fedak, P.W.M. Prevention of Post-Operative Adhesions: A Comprehensive Review of Present and Emerging Strategies. *Biomolecules* **2021**, *11*, 1027. [[CrossRef](#)]
56. Yue, K.; Trujillo-de Santiago, G.; Alvarez, M.M.; Tamayol, A.; Annabi, N.; Khademhosseini, A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials* **2015**, *73*, 254–271. [[CrossRef](#)]
57. Vigata, M.; Meinert, C.; Pahoff, S.; Bock, N.; Huttmacher, D.W. Gelatin Methacryloyl Hydrogels Control the Localized Delivery of Albumin-Bound Paclitaxel. *Polymers* **2020**, *12*, 501. [[CrossRef](#)]
58. Cui, C.Y.; Wu, T.L.; Chen, X.Y.; Liu, Y.; Li, Y.; Xu, Z.Y.; Fan, C.C.; Liu, W.G. A Janus Hydrogel Wet Adhesive for Internal Tissue Repair and Anti-Postoperative Adhesion. *Adv. Funct. Mater.* **2020**, *30*, 2005689. [[CrossRef](#)]
59. Jiang, J.; Chen, L.; Zhang, Y.; Liu, Y. A mussel-like, biodegradable natural hydrogel can effectively prevent adhesion after cardiac surgery. *Nanoscale Adv.* **2025**, *7*, 4425–4435. [[CrossRef](#)]
60. Fan, C.; You, Q.; Li, L.; Shi, J.; Gui, X.Y.; Qin, Y.X.; Li, Y.; Su, X.Y.; Feng, P.; Yu, Q.; et al. Light curable peritoneal cavity anti-adhesive membrane via regulation of inflammatory microenvironment biofunctions. *Appl. Mater. Today* **2025**, *44*, 102758. [[CrossRef](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.