

Bioactive nanofibers covered stent with matched mechanics and durable gemcitabine release for treating esophageal cancer

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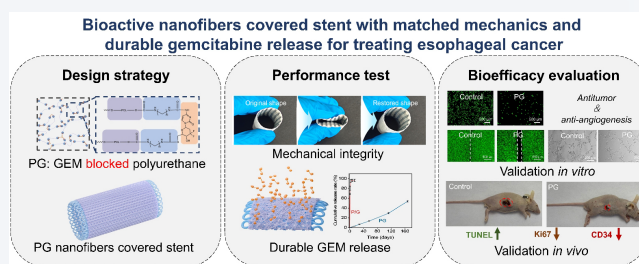
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ABSTRACT: Developing a drug-eluting esophageal stent (DEES), which provides both mechanical support and local chemotherapy, represents a preferred treatment option for patients with advanced esophageal cancer. However, existing DEES have limitations such as drug loading via surface micro/nano-structures or physical blending of drugs into polymer covering, often lead to issues like initial burst release, short-lasting therapeutic effects, or compromised mechanical properties. To address the above challenges, we synthesized gemcitabine (GEM) blocked biodegradable polyurethane (PG) and then covered it around the surface of nickel-titanium (NiTi) stent via electrospinning to form nanofibers covered stent. This electrospun PG nanofibers achieved firm adhesion without compromising the original mechanical integrity of NiTi stent. *In vitro* data demonstrated that the PG fibers presented prominent antitumor therapy effect and antiangiogenesis ability, as well as enabled degradation-associated drug release, resulting in less than 1% initial burst release within 24 h and sustained release over 24 weeks. *In vivo* assessments indicated that the PG fibers could continuously inhibit tumor growth by inducing tumor cell apoptosis and suppressing tumor angiogenesis. This study demonstrates the bioactive nanofibers covered stent with matched mechanics and durable efficacious antitumor, which could offer a potential strategy for treating esophageal cancer via local chemotherapy.

KEYWORDS: esophageal cancer, gemcitabine, durable release, nanofibers covered stent, local chemotherapy



1 Introduction

Esophageal tumors threaten the lives of approximately 600,000 people worldwide every year, and their hidden early symptoms result in about 70% of patients being diagnosed with advanced disease [1, 2]. Advanced patients with poor physical conditions do not support surgical resection, radiotherapy and chemotherapy, so esophageal stenting is often used clinically as a palliative treatment to relieve patients with dysphagia and maintain nutritional intake [3]. However, this regimen cannot inhibit tumor development, and it is difficult to significantly extend the survival of patients [4].

Therefore, the development of drug-eluting esophageal stent (DEES) is of great significance.

The surface of esophageal stent is loaded with antitumor drugs to dilate esophageal stenosis and treat esophageal tumors locally. Compared with esophageal stenting plus intravenous/oral drugs, DEES have the advantage of increasing local drug accumulation and reducing systemic toxicity [5]. However, the development of DEES has been slow, and traditional development strategies have focused on constructing micro-/nano structures on the stent strut or using the stent covering as a drug carrier. Among them, the micro-/nano structures on the stent strut are often constructed by deposition, etching, anodic oxidation, and other schemes, which undoubtedly affect the mechanical properties of the stent, and the drug load is limited and the drug release duration is short [6–10]. The specific strategy of stent covering as a drug carrier is to physically dope the drug into the polymer covering, and the drug loading capacity is greatly increased. However, in order to avoid

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drug burst release and prolong the drug release period, the membrane thickness needs to be increased or composite multi-layer drug membrane, which also has an adverse impact on the mechanical integrity of the stent [11–14]. More importantly, because the drugs are only physically dispersed within the polymer matrix, these systems often suffer from rapid initial burst release and insufficient long-term release stability. Therefore, it is urgent to develop a novel DEES with mechanical integrity and long-term stable release of drugs.

Traditionally, gemcitabine (GEM) is a commonly used chemotherapy drug that is effective against a variety of malignant tumors, including esophageal cancer [15]. However, its poor oral availability and severe systemic toxicity caused by frequent high dose administration seriously limit its application [16]. To address these issues, researchers have attempted to encapsulate GEM into nanocarriers such as polymeric nanoparticles, lipid-based nanoparticles, metal nanoparticles, and micelles, with the aim of prolonging its *in vivo* circulation time [17–20]. Nevertheless, these strategies did not demonstrate significant improvement in efficacy compared to conventional injectable formulations [21]. In a study by Wang et al., GEM was encapsulated in a poly(lactic-co-glycolic acid)-poly(ethylene glycol)-poly(lactic-co-glycolic acid) (PLGA-PEG-PLGA) thermosensitive hydrogel and administered via local injection into the tumor site [22]. Although promising local efficacy was observed, over 20% of GEM leaked within 24 h, and the overall treatment duration was less than 18 days. Similarly, Babu et al. developed a GEM-eluting biliary stent for local drug delivery [23]. However, this system exhibited an initial burst release of nearly 10% within 24 h, increasing the risk of systemic toxicity. These studies indicate that conventional physically loaded GEM delivery systems still face substantial challenges in achieving long-term stable release with minimal burst effect. Furthermore, as a representative broad-spectrum antitumor drug, GEM is suitable as a proof-of-concept model for validating long-term localized drug-delivery strategies.

The poly(ester-urethane)urea (PEUU) series of polymer elastomers designed in our previous research exhibits excellent mechanical properties, long-term drug release capability, and a flexibly designable drug unit structure [24, 25]. Based on this characteristic, the drug molecules can be incorporated into the polymer backbone during polymer synthesis rather than being simply physically encapsulated. This strategy is fundamentally different from conventional physically loaded DEES and is expected to establish a degradation-associated sustained drug-release mechanism with extremely low burst release. Therefore, applying this material series to the covering of drug-eluting esophageal stents, which can integrate the mechanical integrity and long-term localized chemotherapy, holds significant potential. In addition, this platform strategy may potentially be extended to other therapeutic agents or treatment modalities in the future. However, exploration in this area remains limited.

To solve the above challenges, this study developed a blocked biodegradable polyurethane (PG) using GEM as chain extender. An electrospun covering was applied to the surface of a knitted NiTi stent to construct fibers covered stent. The PG not only retains the inherent excellent elasticity and mechanical stability of polyurethane, ensuring that the mechanical integrity of the stent remains uncompromised after covering and allows long-term stable attachment, but also demonstrates an extremely low initial burst release of GEM and sustained GEM release during degradation.

2 Experimental

2.1 Materials

Polycaprolactone diol (PCL diol), $M_n = 2000$, hexamethylene diisocyanate (HDI), dimethylolbutanoic acid (DMBA), and hexafluoroisopropanol (HFIP) were purchased from Shanghai Titan Scientific Co., Ltd. (Shanghai, China). GEM and protease K were acquired from Shanghai Yuanye Bio-Technology Co., Ltd. (Shanghai, China). NiTi wires (diameter 0.20 mm) were provided by Ushare Medical Technology Co., Ltd. (Zhuhai, China). All raw materials and reagents were used as received without purification unless otherwise specified.

2.2 Synthesis of GEM blocked polyurethane

GEM blocked PG was synthesized by a two-step method. First, PCL diol was used as the soft segment and HDI as the hard segment. The product polyurethane pre-polymer (Pre-PU) was obtained by reaction under nitrogen protection at 80 °C for 3 h after mixing and drying of PCL diol and HDI. When the reaction temperature dropped to 40 °C, GEM was subsequently added as a chain extender and the reaction was continued for 18 h (the reaction termination was determined by Fourier transform infrared (FTIR) spectroscopy at the first time and control the experimental condition in subsequent reaction). The synthetic product was collected and soaked in deionized water for 3 days to purifying. Finally, PG was obtained after freeze-drying for 48 h in sealed storage for subsequent characterization and testing. The molar ratios of PCL diol, HDI, and GEM were 1:2:1, 1:2:0.5, and 1:2:0.33, as well as synthesized polymers namely PG1, PG0.5, and PG0.33, respectively. In addition, we also synthesized a control polyurethane namely PEUU as the control group, in which GEM was replaced with DMBA during the synthesis process, and the other processes were consistent.

2.3 Preparation of nanofibers and stents

1 g of the PG product was dissolved in 4 mL HFIP, and stirred until completely dissolved as electrospinning solution. Then, the above solution was transferred into a 10 mL syringe, followed by the setting of electrospinning parameters as follows: syringe pump flow rate of 1 mL/h, electrospinning voltage of 11 kV, and collector distance of 25 cm. Upon completion of electrospinning, the collected PG electrospun fibers were placed in a vacuum drying oven and dried at 25 °C for 48 h to ensure the complete evaporation of the solvent. 1 g of polyurethane (PU) product and 0.034 g of GEM were dissolved in 4 mL of HFIP, and stirred until completely dissolved to obtain the electrospinning solution. The electrospinning parameters are the same as above mentioned, and the resulting electrospun fibers are named physically blended GEM/polyurethane (P/G).

A NiTi alloy wire was used as raw material to prepare a knitted tubular fabric using a small-diameter weft knitting mechanism independently developed by Donghua University. The tubular fabric was then placed on a 20 mm diameter mandrel and heating at 550 °C for 15 min to obtain a knitted esophageal bare stent. Using the bare stent as an electrospinning receiver, and the covered esophageal stent was obtained by rotating the bare stent so that the fibers were uniformly deposited on its surface.

2.4 Characterization and testing of synthetic polyurethane

The chemical structures of PCL diol, HDI, GEM, Pre-PU, and PG

were determined by FTIR spectroscopy. FTIR experiments were conducted using a Nicolet 6700 Fourier transform infrared spectrometer (Thermo Fisher, USA) over the range of 5400–4000 cm^{-1} , with 32 scans per experiment. The chemical structure of the polymer was tested by nuclear magnetic resonance (NMR) spectrometer (Bruker, Germany) with DMSO- d_6 as the nuclear magnetic solvent. The surface elements of PG were analyzed by X-ray photoelectron spectroscopy (XPS) (Thermo Fisher, USA), with a C 1s peak of 284.8 eV as the calibration peak. The number-average molecular weight of Pre-PU and PG was measured by PL-GPC50 gel chromatograph (Agilent, USA) with the sample solution concentration of 4 mg/mL, DMSO as the mobile phase, flow rate set to 1 mL/min, and measured at room temperature. The X-ray diffraction pattern of the material was measured by the Bruker D8 ADVANCE X-ray diffractometer (Bruker, Germany). In the experiment, the tube voltage was 40 kV, the scanning speed was 6°/min and the diffraction angle was 5°–60°.

The TG209 F1 Libra thermal gravimetric analyzer (NETZSCH, Germany) was used to take about 5 mg of samples, and the samples were scanned from room temperature to 800 °C at a heating rate of 10 °C/min under the protection of nitrogen gas at a flow rate of 20 mL/min. The thermogravimetric (TG) and derivative thermogravimetric (DTG) curves were recorded during the scanning process, and the thermal stability of the experimental samples were analyzed respectively. The crystallization temperature of PG was determined by DSC 8500 differential scanning calorimeter (PerkinElmer, USA). The mass of the sample is 5 mg, and it is heated from room temperature to 100 °C at 10 °C/min for 10 min to eliminate the thermal history, then cooled to –20 °C at –10 °C/min for 10 min and heated again at 10 °C/min to 10 °C to read the crystallization temperature on the map.

2.5 Characterization and testing of fibers and stents

The morphologies of the samples were examined by using a field emission scanning electron microscope (FE-SEM) (Hitachi, Japan). Prior to imaging, the samples underwent a gold coating process at a current of 15 mA for 60 s (MC1000; Hitachi, Japan). Imaging was performed at an accelerating voltage of 5 kV. The mean diameter of the fibers was determined using ImageJ software (National Institutes of Health) by measuring the diameter of a minimum of 100 fibers. Tensile strength tester (Wenzhou Darong Textile Instrument Co., Ltd., China) was used to test the tensile strength of PG. The sample size was 5 mm $\times$ 40 mm, the clamping distance was 20 mm, and the tensile speed was 10 mm/min. The tensile stress-strain curve was recorded. Then the maximum strain was set to 30%, cyclic fatigue test was performed for 20 times, and the elastic recovery rate of the fibers was recorded. In the course of the experiment, three sets of parallel experiments were conducted and recorded.

In this study, local compression method was used to test the radial compression performance of esophageal stent [26]. The test instrument was YG061 radial compression instrument (Laizhou Electronic Instrument Co., Ltd., China), the diameter of the presser foot was 20 mm, the compression distance was 10 mm, and the compression speed was 20 mm/min. A total of 3 samples were selected for each group of stents, and the test area of each sample was the middle of the stent. Radial compression strength and quick elastic recovery rate after compression were used to characterize the radial compression performance of the stent.

The macromorphology of the covered stents was observed after

repeated compression for 100 times to characterize the bonding fastness of the PG fibers and the stents.

In this study, the cantilever beam method was used to test the bending performance of the stents [27]: A section of stent with a length of 5 cm is taken, the left end of which was 2 cm was fixed by a fixture, and the other free end was pressed under the presser foot to bend the stent. The compression speed was 20 mm/min, and the force value F when the stent was bent at 20° was recorded. The bending stiffness (EI) of the stent is calculated according to the following equation (Eq. (1))

$$EI = \frac{F \cdot L^3}{3S} \quad (1)$$

where F is the force when the stent is bent at 20°; L is the length of the stent, and S is the bending deformation of the stent. In this study, $L = 20$ mm, $S = 7.3$ mm.

In this study, the anti-migration performance of stents was tested *in vitro* to predict their performance *in vivo* [28]. The upper end of the stent was evenly fixed with yarn and placed into the simulated esophagus (inner diameter 19 mm), the lower end of the simulated esophagus was fixed, and the upper yarn was stretched upward with the tensile strength tester (Wenzhou Darong Textile Instrument Co., Ltd., China), and the esophageal stent was dragged to slide in the simulated esophagus. The drawing speed is 200 mm/min. The average value of the stable sliding force of the esophageal stent was taken as the anti-migration force of the stent.

In order to test whether the retrievability performance of the knitted bare stent is affected by the fibers covering, the retrieval force of the stent was tested in this study. The lower end of the stent was fixed and the upper end was disassembled into a wire. The head end of the wire was stretched upward using tensile strength tester. The drawing speed is 200 mm/min, and the average force of the dismantled yarn 60 mm length is used as the retrieval force of the stent.

A commercially available esophageal stent (Boston Scientific Ultraflex) was used as a reference for comparing the mechanical properties of the self-fabricated bare stent.

2.6 Degradation and GEM release testing *in vitro*

The degradation experiments *in vitro* to analyze the degradation behavior of PG fibers was carried out. The 40 mg PG fibers was immersed in 4 mL phosphate-buffered saline (PBS) containing 0.2% protease K and placed in a 37 °C shaker. Proteinase K was employed as a standardized degradation medium, considering that implanted esophageal stents are exposed to protease-containing biological environments. The degradation solution was changed every 3 days to ensure enzyme activity. Samples were taken after 1, 2, 4, 8, and 16 weeks respectively, washed repeatedly with deionized water and vacuum dried before weighing. The weight remaining rate is calculated according to the following equation (Eq. (2))

$$\text{Weight remaining rate (\%)} = \frac{w_0 - w_1}{w_0} \times 100\% \quad (2)$$

where w_0 and w_1 are the weight of the fibers before and after degradation, respectively.

At the same time, SEM (HITACHI, Japan) was used to observe the morphology changes of the fibers. Tensile strength tester is used to test the mechanical properties of the degraded samples.

A certain mass of GEM was dissolved in PBS and its maximum absorption wavelength was measured by ultraviolet spectrophotometer (Beijing Puxi General Instrument Co., Ltd.,

China). A series of GEM solutions with different concentrations were configured, their OD values at the maximum absorption wavelength were tested, and a standard concentration curve for calculating the GEM concentration was drawn.

A certain amount of PG fibers or P/G fibers was added to 10 mL PBS (with and without 0.2% protease K) and placed in a 37 °C shaker. 2 mL of supernatant from the specified time was taken to test its absorbance and the corresponding GEM concentration according to the standard curve was calculated. 2 mL fresh PBS buffer was added. The cumulative release rate of GEM is calculated as follows (Eq. (3))

$$\text{Cumulative release rate (\%)} = \frac{10 \times C_n + 2 \times \sum_{x=1}^{n-1} C_x}{m_0} \times 100 \quad (3)$$

where C_n and C_x represent the GEM concentration in the supernatant taken from time n and x , and m_0 represents initial total amount GEM.

2.7 Cell experiment *in vitro*

Preparation of the extract solution: 100 mg sterilized samples (P/G fibers and PG fibers) were immersed in 10 mL base medium and incubated in a 0.5% carbon dioxide incubator at 37 °C. At day 7, the extract solution was taken out and designated as short-term extracts of P/G fibers and PG fibers (P/G_s, PG_s), respectively. Fresh culture medium was then replenished, and after 14 days, the medium was collected again and designated as long-term extracts of P/G fibers and PG fibers (P/G_L, PG_L). Furthermore, GEM was dissolved in base medium at concentrations of 0.1, 1, 10, and 100 µg/mL to evaluate the sensitivity of TE-1 cells to GEM. All the extracted media were stored in a 4 °C refrigerator for later use.

In order to verify the inhibitory effect of PG fibers on tumor cells, esophageal tumor cells TE-1 were inoculated into 24-well plates, 1 mL of the above extract was added after cell adhesion, and the liquid was changed every 2 days. Cell viability was assessed by cell counting kit-8 (CCK-8) after 1, 3, and 5 days of culture (Eq. (4)):

$$\text{Cell viability (\%)} = \frac{OD_s - OD_b}{OD_c - OD_b} \times 100 \quad (4)$$

where OD_c and OD_s represent the optical density (OD) values of control and sample, while OD_b is the absorbance of the blank group.

Calcein-AM/propidium iodide (PI) indicator staining was used at days 1, 3, and 5, and observed under fluorescence microscope.

To evaluate the effect of PG fibers on angiogenesis in tumor tissue, we performed scratch and tube-forming experiments on human umbilical vein endothelial cells (HUVECs). The endothelial cells were implanted in a 6-well plate, and a blank trace was drawn in the center of the plate when the cells fused. 1 mL of extract solution was added to each well for further culture, and Calcein-AM was added for staining at 0, 12, and 24 h, respectively. Finally, the solutions were observed and photographed under fluorescence microscope. Relative migration rate is calculated as follows (Eq. (5)):

$$\text{Relative migration rate (\%)} = \frac{D_n - D_0}{D_0} \times 100 \quad (5)$$

where D_0 and D_n represent the scratch distance after 0 and n h of culture.

Further, tube formation assay was performed to assess the effect of PG fibers on angiogenesis. Briefly, 100 µL of Matrix-Gel is added to a 48-well plate and incubated at 37 °C until gelatinized. The HUVECs were diluted to 3×10^4 cells/well with the extract solution and seeded into the 48-well plate. After 4 h, the tube formation was observed by microscope. The software Image J was used to count the number of junctions and the total branching length.

2.8 Test of antitumor effect of fibers *in vivo*

2.8.1 Tumor model establishment

All animal studies were approved by the Institutional Animal Care and Use Committee. BALB/c nude mice aged 4–6 weeks were purchased from Shanghai Bikai Keyi Biotechnology Co., Ltd. All animal experiments were reviewed and approved by the Experimental Animal Welfare and Animal Experiment Ethics Committee of Shanghai Pudong Hospital (No. 20241216-001). Animal experimental procedures strictly adhered to animal experimentation guidelines. KYSE-150 cells in the logarithmic growth phase were digested with trypsin, resuspended in PBS, and adjusted to a density of 1×10^7 cells/mL. A 100 µL cell suspension was subcutaneously inoculated into the dorsal region of nude mice. Tumor formation was monitored daily.

2.8.2 Sample implantation

When the average tumor volume reached 100 mm³, mice were randomly divided into three groups ($n = 3$): PU group, P/G group, and PG group. PU, P/G, and PG fibers were surgically implanted adjacent to the tumors. Body weight was recorded every 2 days. Tumor short diameter (a) and long diameter (b) were measured every 2 days, and tumor volume was calculated using the equation (Eq. (6)):

$$V = \frac{1}{2} \times a^2 \times b \quad (6)$$

Mice were euthanized 14 days post-implantation. Tumors were completely excised, weighed, photographed, and fixed in 4% paraformaldehyde. Major organs (heart, liver, spleen, lung, and kidney) were also harvested and fixed.

2.8.3 Histological analysis

Paraffin-embedded sections were subjected to antigen retrieval. Immunohistochemical staining was performed using antibodies against Ki-67, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), and CD34. Stained sections were observed under a microscope to evaluate tumor cell proliferation, apoptosis, and vascularization. Hematoxylin and eosin (H&E) staining was performed on major organ sections to assess pathological changes.

2.9 Statistical analysis

Statistical analysis was conducted using Origin Pro software. The data were expressed as the mean $\pm$ standard deviation (SD). The statistical analysis method was the Student's t -test or one-way analysis of variance (ANOVA). The statistical significance was considered as "ns" for no significant difference, $*P < 0.05$, $*P < 0.01$, and $**P < 0.001$.

3 Results and discussion

Herein, we designed and fabricated a DEES for treating esophageal cancer via local chemotherapy with durable GEM release.

Specifically, we synthesized a PG using the chemotherapeutic drug GEM as a chain extender (Fig. 1(a)). This material was designed to achieve GEM segmented on the molecular backbone while retaining the inherent excellent mechanical properties of PG. Subsequently, we uniformly covered the knitted NiTi alloy esophageal stent with PG fibers via electrospinning (Fig. 1(b)). It is expected that the covering will adhere firmly to the stent without compromising its mechanical integrity, and that GEM will be sustainably released from the stent covering until the material is fully degraded. This DEES is expected to achieve long-term suppression of tumor progression by killing tumor cells and inhibiting angiogenesis in the tumor region (Fig. 1(c)).

3.1 Synthesis and performance evaluation of PG and PG fibers

Over the past few decades, many different types of polyurethanes with different properties have been used for covered stents. Most of these polyurethanes lack durable bioactivity and can only be functionally modified through blending or chemical grafting, which results in the rapid release and inactivation of the functional components in polyurethanes matrix. In this research, PCL diol reacted with HDI to generate the Pre-PU. Subsequently, the

chemotherapeutic drug GEM was blocked as a chain extender, ultimately yielding the target GEM blocked polyurethane (Fig. 2(a)).

Proton NMR spectra, as shown in Fig. 2(b) and Fig. S1(a) in the Electronic Supplementary Material (ESM), verified the chemical structure of PG. Proton signals from the Pre-PU backbone (1.0–4.0 ppm) were fully retained, indicating its skeleton remained intact during chain extension. Simultaneously, the appearance of aromatic proton peaks of GEM (6.13 and 7.8 ppm) demonstrated the successful blocking of GEM into the PG network. Gel permeation chromatography (GPC) (Fig. 2(c)) analysis showed that the molecular weights (M_n) of Pre-PU and PG were 21,945 and 50,637, respectively. The significant increase in molecular weight indicated successful chain extension. FTIR analysis (Fig. 2(d) and Fig. S1(b) in the ESM) showed that characteristic peaks of PCL diol ($-\text{CH}_2$: 2862 cm^{-1} ; $-\text{CH}_2$: 2943 cm^{-1}) and the vibration peak of the C=C bond in GEM (1652 cm^{-1}) were retained in the PG elastomer. Furthermore, the disappearance of the isocyanate group ($-\text{NCO}$, 2280 cm^{-1}) in HDI indicated complete polymerization. Moreover, the characteristic element F signal in GEM was clearly visible in XPS (Fig. 2(e)).

The crystallization behavior and thermal properties of PG were further analyzed. X-Ray diffraction (XRD) (Fig. 2(f)) showed that

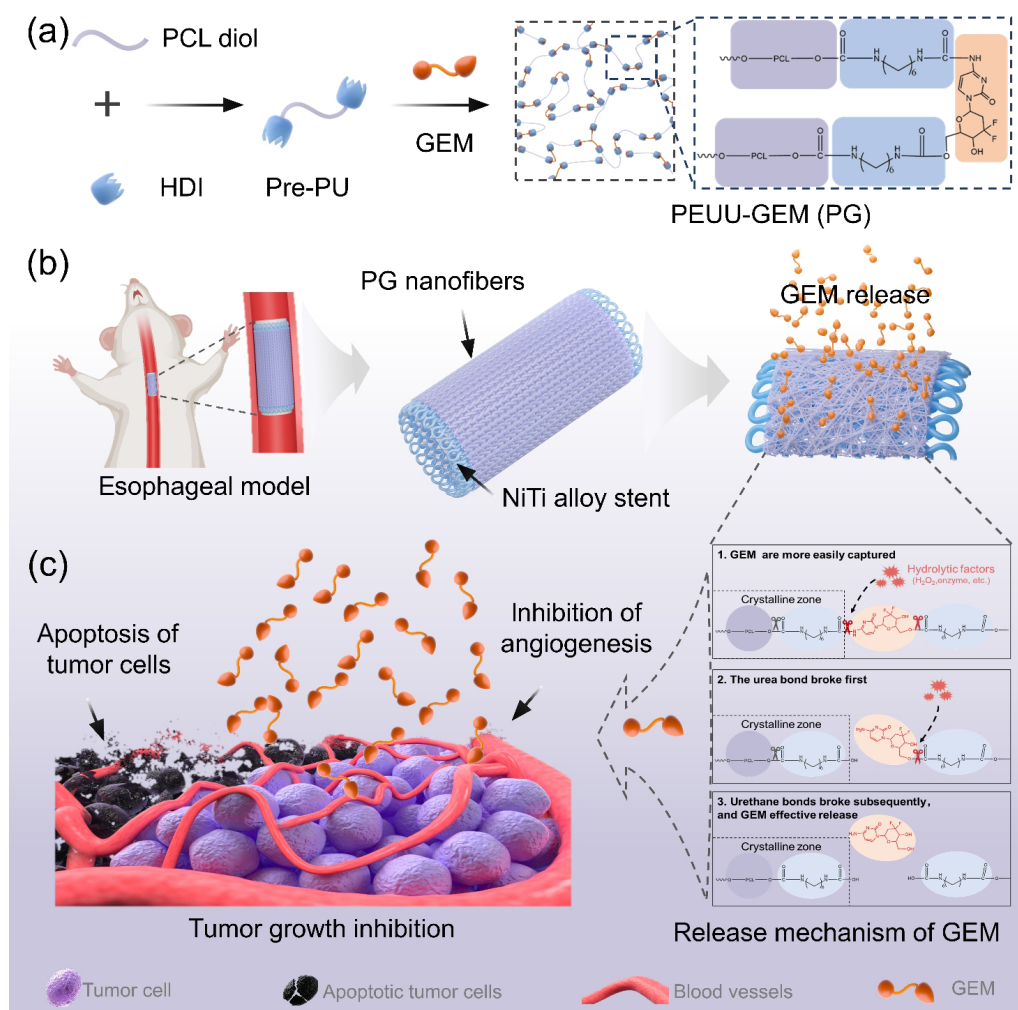


Figure 1 Schematic illustration for the design and application of PG nanofibers covered NiTi alloy stent. (a) Schematic illustration for synthesis of GEM blocked biodegradable polyurethane. (b) Schematic diagram of PG nanofibers covered NiTi alloy stent as a durable local drug delivery platform. (c) Mechanism of durable GEM release and tumor inhibition.

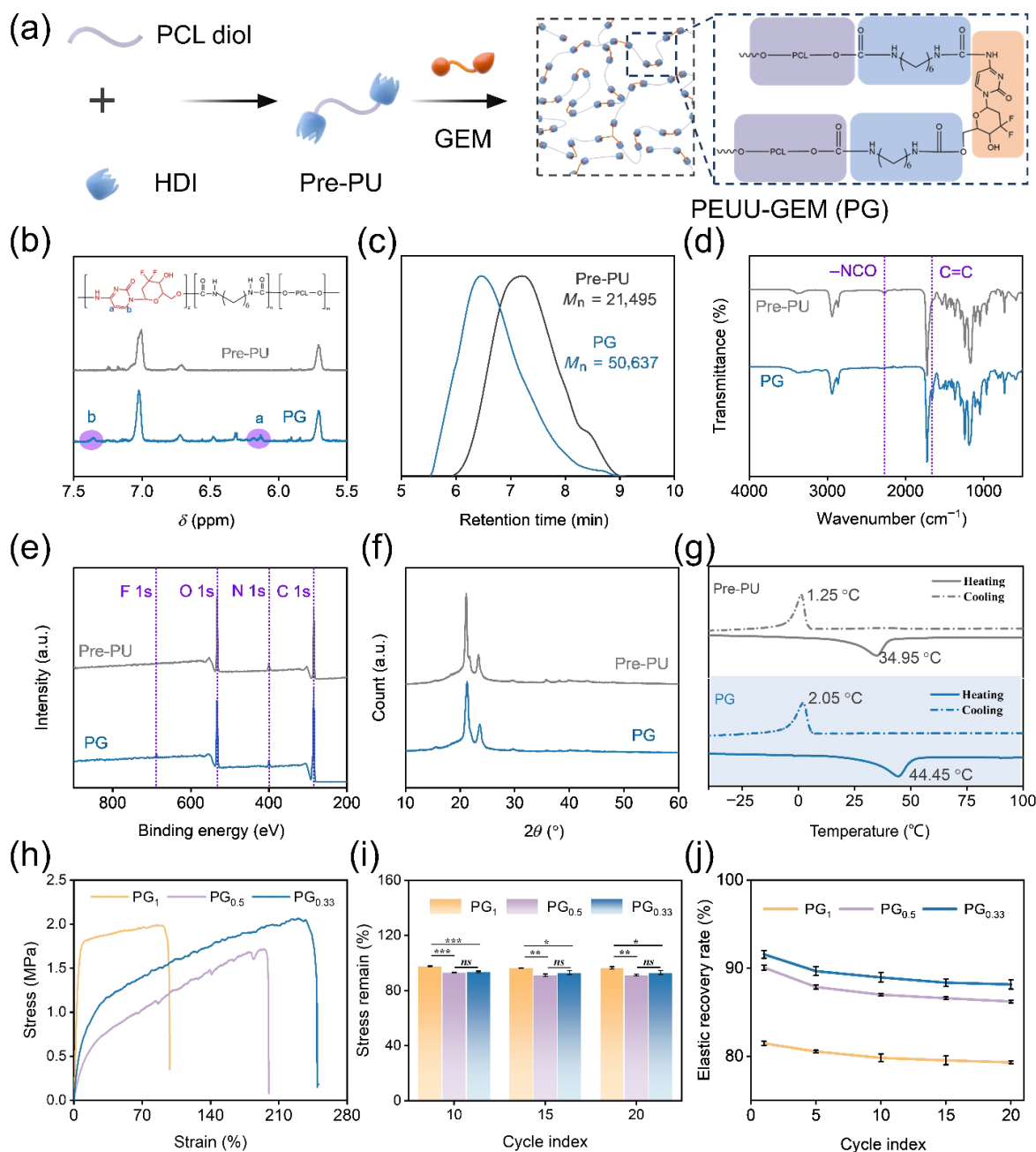


Figure 2 Synthesis and characterization of PG and PG fibers. (a) Schematic illustration for synthesis of GEM blocked biodegradable polyurethane. (b) ¹H NMR spectra, (c) GPC curves, (d) FTIR spectra, (e) XPS spectra, (f) XRD curves, (g) DSC curve of Pre-PU and PG, (h) tensile stress-strain curves, (i) cyclic stress retention rates, and (j) strain recovery rates of PG₁, PG_{0.5}, and PG_{0.33} fibers ($n = 3$, ns: non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

both Pre-PU and PG exhibited diffraction peaks at $2\theta = 21^\circ$ and 24° corresponding to the (110) and (200) crystal planes of the PCL soft segment. However, compared to Pre-PU, the crystallinity of PG significantly decreased, attributed to the introduction of the rigid GEM hard segment exacerbating microphase separation. The independent phase domains formed by the hard segments restricted the ordered arrangement of the PCL soft segments. DSC results showed that the melting peak temperature of PG ($\sim 44^\circ\text{C}$) is higher than body temperature, ensuring its stability in physiological environments (Fig. 2(g)). TG/DTG analysis demonstrated that PG exhibits excellent thermal stability, with an initial degradation temperature reaching 250°C (Figs. S1(c) and S1(d) in the ESM).

After clarifying the chemical structure of PG, a series of polymers—PG₁, PG_{0.5}, and PG_{0.33}—were synthesized by adjusting the molar ratios of PCL diol, HDI, and GEM to 1:2:1, 1:2:0.5, and 1:2:0.33, respectively. As shown in Fig. S2 in the ESM, three polymers exhibited significantly different molecular weights, which may be attributed to differences in the reaction rates of the hydroxyl and amino groups in the amino alcohol chain extender GEM. When the GEM ratio increases, more reactive amine groups rapidly consume a large number of -NCO groups, causing the subsequent hydroxyl chain extension reaction to terminate prematurely due to insufficient -NCO, thereby limiting chain growth [29]. Electrospinning was then performed using these three polymers,

and the fibers were analyzed for their microstructure using SEM (Fig. S3(a) in the ESM). The results showed that the PG₁ fibers exhibited significant adhesion between fibers and a broad diameter distribution of $2.76 \pm 0.86 \mu\text{m}$ (Fig. S3(b) in the ESM). In contrast, PG_{0.5} and PG_{0.33} polymers formed intact, mutually independent fibrous networks. The origin of this morphological difference can be traced back to the effect of polymer molecular weight. Low molecular weight resulted in excessively low viscosity of the PG₁ spinning solution, making it difficult to form a stable Taylor cone during electric field stretching. This led to rapid deposition of the solution as a jet stream and secondary fusion between fibers during solvent evaporation. In contrast, the increased molecular weight of PG_{0.5} and PG_{0.33} significantly enhanced chain entanglement, effectively suppressing fiber adhesion [30].

The chain extender ratio modifies the molecular weight of the polymer and the morphology of the fibers, thereby influencing their mechanical properties. Tensile fracture test results for the three electrospun fibers are shown in Fig. 2(h) and Figs. S4(a)–S4(c) in the ESM. PG₁ formed a rigid network due to fiber adhesion, exhibiting the highest initial modulus among the three groups, but the lowest elongation at break. This indicates that although adhesion between fibers increased the stress at break, they severely restricted elastic deformation induced by molecular chain slippage. In contrast, PG_{0.5} and PG_{0.33} exhibited typical elastomeric characteristics: their initial modulus decreased, while their elongation at break significantly increased. The formation of a microphase-separated structure is the key mechanism for enhanced elasticity—the synergistic effect between hydrogen bond crosslinking points among hard segments and the mobility of soft segments allows the material to dissipate energy through reversible hydrogen bond breakage/reformation and chain slippage under stress. Particularly, PG_{0.33}, due to its higher molecular weight and thicker fiber structure, outperformed PG_{0.5} in both stress and elongation at break.

As an esophageal stent covering, the material must withstand periodic mechanical stimuli from swallowing movements, making fatigue resistance crucial. Repeated tensile tests (20 cycles) were performed on the three groups of electrospun fibers. Results in Fig. S4(d) in the ESM showed stress retention rates more than 90% for all three fibers (Fig. 2(i)). However, significant differences were observed in elastic recovery rates (Fig. 2(j)). PG₁ exhibited the lowest elastic recovery rate, possibly due to the fracture of adhesion points during stretching. In contrast, the elastic recovery rates of PG_{0.5} and PG_{0.33} remained above 85% even after 20 fatigue cycles, and the more elastic PG_{0.33} had a higher recovery rate, indicating its optimal long-term service reliability. This excellent fatigue resistance likely stems from its dynamic physical crosslinked network resulting from microphase separation.

Based on the above mechanical property analysis, PG_{0.33} possesses the best tensile fracture properties and optimal fatigue resistance, meeting the core requirements for an esophageal stent covering. Therefore, it was selected as the optimized system for subsequent biological evaluation.

3.2 Mechanical properties of covered stents

Using a knitted bare stent as the substrate, whose mechanical properties were comparable to those of a commercially available esophageal stent (Fig. S5 in the ESM), the PG_{0.33} solution was electrospun onto its surface to fabricate a fiber-covered esophageal stent (Fig. 3(a)). After covering, the stent surface was uniformly

covered with a PG fiber layer (Fig. 3(b)). To evaluate the interfacial bonding between the covering and the stent substrate, 100 compression cycles were performed (Fig. 3(c)). After testing, no significant changes were observed in the surface morphology of the covering. The PG covering remained intact without any peeling or damage. Microstructural analysis revealed only slight bending deformation of the fibers, with no fiber fracture detected. Further observation of the compression-recovery process (Fig. 3(d)) demonstrated that the covering maintained tight adhesion to the stent substrate surface throughout, with no interfacial detachment even at the maximum compression stage. These results confirm a stable and robust interfacial bond between the PG covering and the stent substrate, indicating that the covered stent can meet the long-term mechanical demands imposed by dynamic esophageal contraction during physiological peristaltic movements. This performance can be attributed to the excellent elasticity and fatigue resistance of the PG fibers.

Subsequently, systematic mechanical tests were conducted on the stents before and after covering. First, the radial compression performance, a critical parameter for esophageal stents, was evaluated. After covering, the radial compression strength of the stent increased (bare stent: $130.44 \pm 0.55 \text{ N}$; covered stent: $146.61 \pm 0.485 \text{ N}$), while the elastic recovery rate remained above 98% (Figs. 3(e1) and 3(e2)). This ensures that the stent can effectively dilate the stenosed esophagus and rapidly rebound during swallowing. However, due to the fixation effect of the PG covering on the stent interlacing points, the bending stiffness of the covered stent increased (Figs. 3(f1) and 3(f2)). Although the covered stent exhibits higher bending stiffness than the bare stent, its bending stiffness ($573.42 \pm 66.63 \text{ N}\cdot\text{mm}^2$) remained within the reported range of commercially available esophageal stents (160.74 – $986.38 \text{ N}\cdot\text{mm}^2$) [27], indicating that the increase did not compromise its flexibility for esophageal stent applications. Furthermore, the anti-migration force of the covered stent increased by 180.16% compared to the bare stent. This is attributed to the micron-scale rough surface of the PG fiber increasing the friction coefficient and contact area at the stent-esophageal wall interface (Figs. 3(g1) and 3(g2)). This characteristic can effectively reduce the risk of stent migration after implantation. Additionally, the retrievability of the knitted stent was retained. Although the covering slightly increased the stent retrieval force (bare stent: $0.30 \pm 0.08 \text{ N}$, covered stent: $0.62 \pm 0.17 \text{ N}$), both retrieval forces were less than 1 N, facilitating clinical retrieval operations (Figs. 3(h1) and 3(h2)).

3.3 Degradation and GEM release from PG fibers

The controlled drug release characteristics of the PG fibers are key to long-term inhibiting tumor growth. In this design, GEM is chemically bonded into the polymer segments to achieve degradation-associated sustained GEM release. To verify this design, PG fibers were immersed in a simulated physiological environment and monitored for 24 weeks, systematically analyzing their degradation and drug release behavior.

Morphological changes of the PG fibers during degradation are shown in Fig. 4(a). No significant changes were observed in the PG fibers within the initial 2 weeks. Microcracks first appeared at 4 weeks, gradually expanded by 8 weeks, formed larger pores by 16 weeks, and the fiber structure was nearly fractured by 24 weeks. Synchronous weight remaining analysis (Fig. 4(b)) showed minimal weight loss in the first 4 weeks (weight remaining rate $97.49\% \pm$

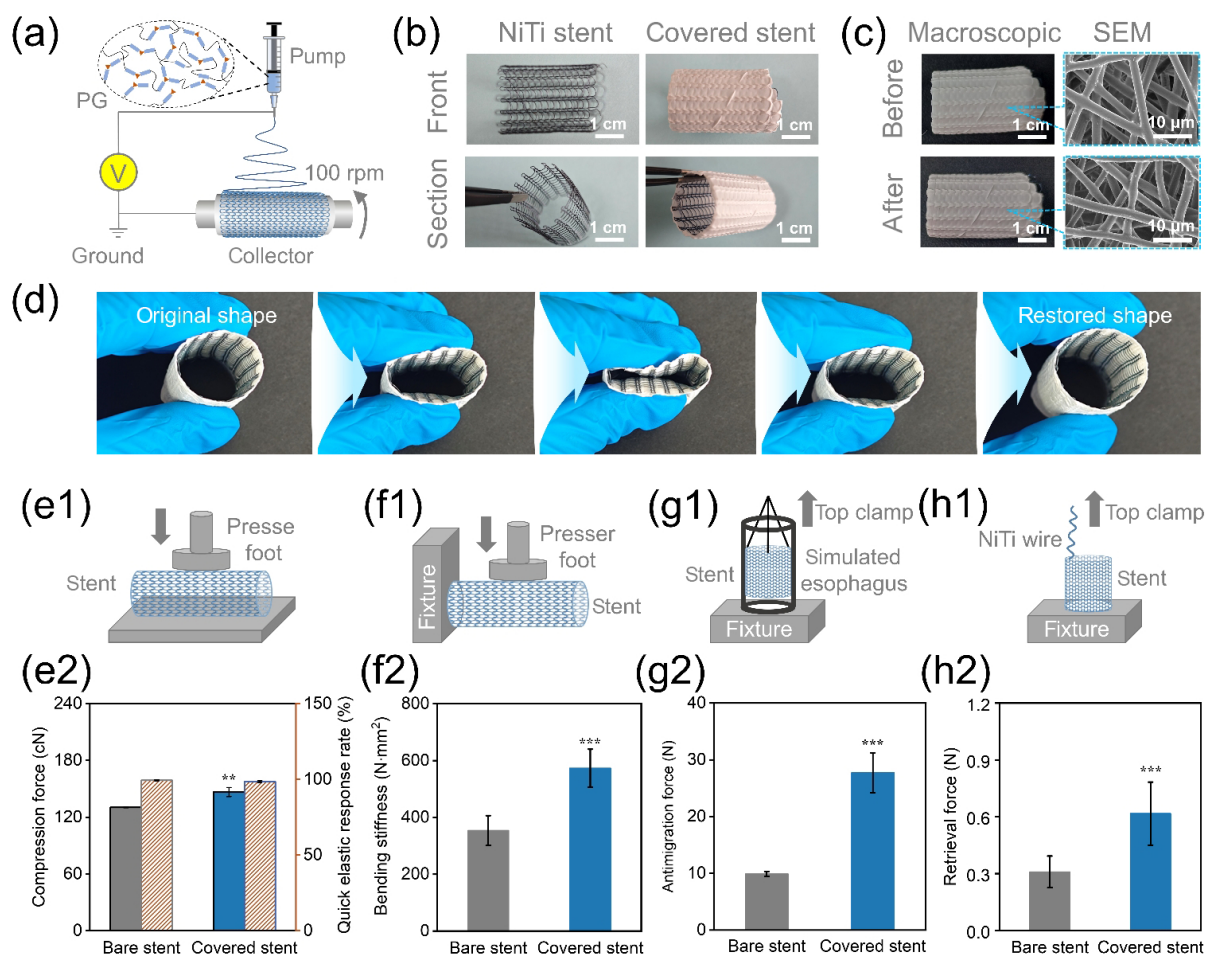


Figure 3 Mechanical properties. (a) Schematic illustration of the preparation of PG nanofibers covered NiTi alloy stent. (b) Macroscopic morphology of the stent before and after covering. (c) Macroscopic and SEM images of the covered stent after repeated compression for 100 times. (d) Images of bonding condition between the stent and the PG fibers covering during the compression process and elastic deformation of stent that, following radial compression and expansion, can regain their original shape. (e1) Compression performance test and (e2) compression force-quick elastic response rate, (f1) bending performance test and (f2) bending stiffness, (g1) antimigration performance test and (g2) antimigration force, (h1) retrieval performance test and (h2) retrieval force of bare stent (NiTi alloy stent) and covered stent (PG nanofibers covered NiTi alloy stent), respectively ($n = 3$, $^*P < 0.01$, $^{**}P < 0.001$).

0.52%). After 8 weeks, weight decreased more rapidly with crack propagation (weight remaining rate $95.52\% \pm 0.63\%$). Subsequently, weight decreased rapidly, with the weight remaining rate dropping to $73.79\% \pm 1.71\%$ at 24th week. The trend in weight remaining rate was highly consistent with the structural collapse observed via SEM images. The degradation of the polymer and the release of GEM are inevitably accompanied by a decrease in the molecular weight of the polymer. Figure 4(c) shows the trend in number-average molecular weight (M_n) during degradation. Consistent with the weight remaining rate, M_n decreased minimally in the first 4 weeks and accelerated its decline after 8 weeks. Notably, even at 24 weeks, M_n decreased to 2.82×10^4 , which was still higher than that of the pre-polymer (2.19×10^4), indicating that PG fiber had not yet been completely degraded.

GEM release behavior (Figs. 4(d) and 4(e)) exhibited significant synergy with the degradation stages. The cumulative release rate within 0–4 weeks was less than 5%. The release rate gradually increased between 8–16 weeks, reaching a cumulative release rate of $53.71\% \pm 1.26\%$ at 24th week. This sustained release pattern contrasts sharply with the control sample, P/G fibers (GEM/PU blend), which exhibited burst release of over 80% within 1 day and approached complete release ($96.36\% \pm 4.78\%$) by 7 days. This fully

confirms the superiority of the chemical bonding strategy for sustained and stable GEM release. As shown in Fig. S6 in the ESM, by comparing the long-term treatment studies of esophageal cancer in recent years, we found that the PG fibers prepared in this study have significant advantages in terms of burst release within 24 h, release duration, and release half-life [31–33]. It should be noted that the studies included in Fig. S6 in the ESM were conducted under similar but not identical experimental conditions. Therefore, the comparison is primarily intended to illustrate overall trends in release duration and burst-release behavior. Pearson correlation coefficients (PCCs) analysis (Fig. S7 in the ESM) confirmed a highly linear correlation (PCCs = 0.993) between the weight of released GEM and weight loss of PG fibers, clearly indicating that GEM release is strongly associated with fiber degradation. To further quantitatively elucidate the release mechanism, the cumulative GEM release data were fitted using zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models (Fig. S8 in the ESM). Among these models, the Korsmeyer–Peppas model exhibited the highest correlation coefficient ($R^2 = 0.995$), indicating the best fit to the experimental release profile. The release exponent (n) was more than 0.89 and corresponds to a Super Case II transport mechanism, suggesting that polymer relaxation and erosion processes dominate

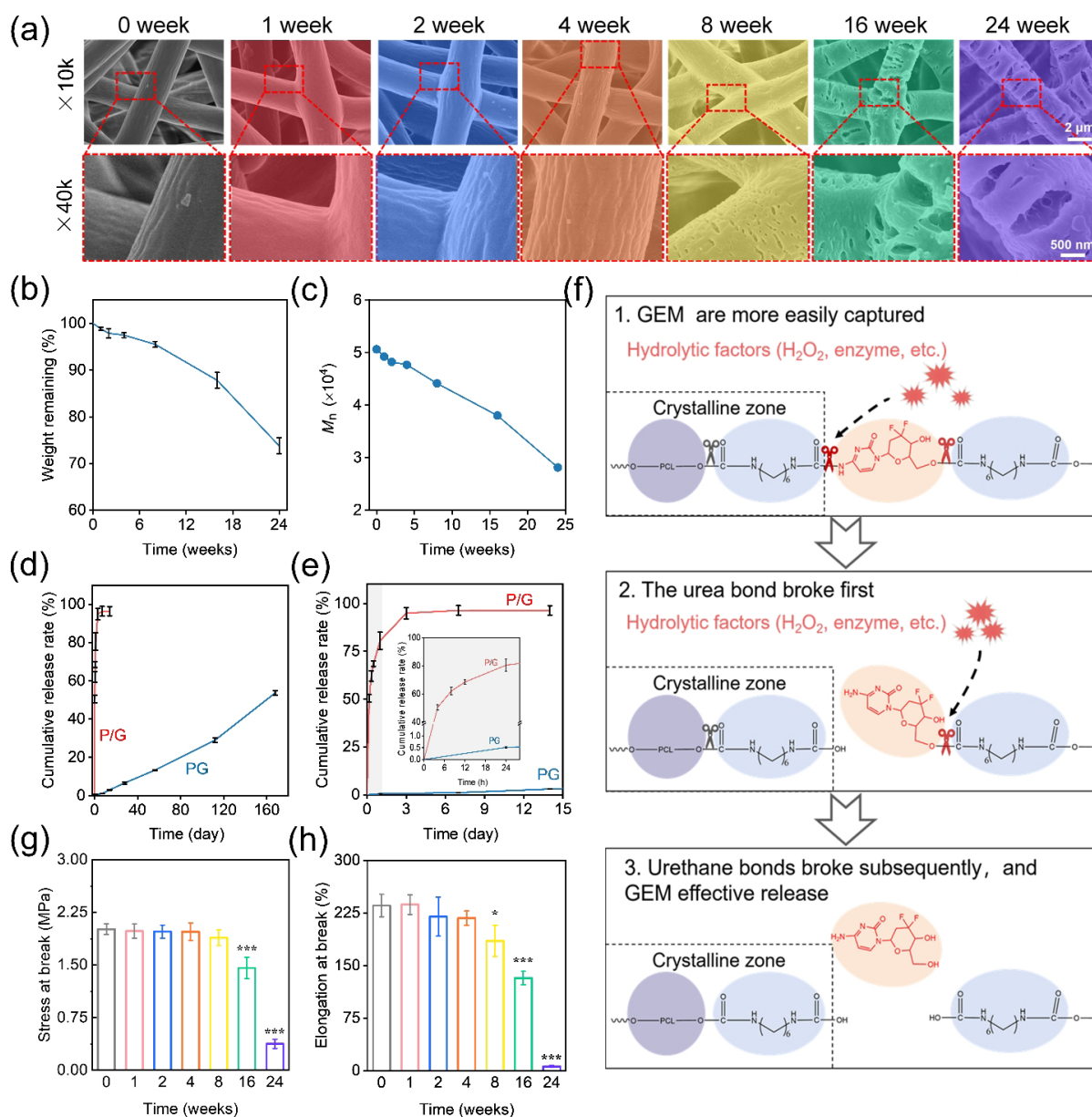


Figure 4 Evaluation of degradation and GEM release behaviors of PG fibers. (a) SEM images of PG fibers during the GEM release-degradation process. (b) Weight remaining of PG fibers during degradation. (c) Changes in number-average molecular weight of PG fibers during degradation. (d) and (e) Release behaviors of GEM from P/G fibers and PG fibers. (f) The release mechanism of GEM in PG. (g) Stress at break and (h) elongation at break of PG fibers during degradation ($n = 3$, $^*P < 0.05$, $^{***}P < 0.001$).

the release behavior. Therefore, the kinetic analysis further supports that GEM release is predominantly governed by degradation/erosion of the PG matrix rather than simple Fickian diffusion.

Further analysis based on material microdomain characteristics reveals the microscopic degradation process. GEM resides in the non-crystalline regions of the polymer, where molecular chain arrangement is loose and regularity is low, allowing water molecules or enzyme to easily penetrate and initiate degradation [34]. Thus, GEM can be released early in the degradation process. The specific degradation-GEM release process is illustrated in Fig. 4(f). Urea bonds in the amorphous regions undergo hydrolytic cleavage first, exposing GEM fragments. Subsequently, the urethane bonds connecting GEM to the main chain gradually hydrolyze, ultimately releasing free GEM molecules [24, 25]. In conventional physical

blending systems, where drugs are freely dispersed within the matrix, the absence of chemical anchoring leads to rapid diffusion-based release. In contrast, the degradation-associated release mechanism designed in this study predominantly regulates drug release through the hydrolysis of key chemical bonds, while localized diffusion or preferential release from amorphous domains may also occur during degradation. This fundamental difference in the release mechanism is key to achieving significantly low burst release and sustained release.

A comparison of degradation and GEM release behavior under enzymatic and enzyme-free conditions is shown in Fig. S9 in the ESM. No significant differences in weight remaining rate or GEM release rate were observed between the two groups within 0–4 weeks, indicating that urea bond hydrolysis dominated this

stage and was unaffected by protease. After 4 weeks, the degradation rate and GEM release rate were significantly accelerated in the enzyme group, proving that the urea bonds had been sufficiently hydrolyzed. The presence of protease accelerated the cleavage of urethane bonds within the GEM fragments, thereby accelerating material degradation and promoting GEM release.

The mechanical behavior of the PG fibers during degradation was also continuously tracked. The variations in stress and strain are shown in Figs. 4(g) and 4(h). Stress and elongation at break remained relatively stable within 0–4 weeks, indicating that early surface microcracks had no significant impact on the overall mechanics of the fibers. After 8 weeks, mechanical properties decayed as chemical bond breakage intensified. After 16 and 24 weeks, stress and elongation at break decreased significantly, closely related to the enlargement of surface pores and the sharp drop in polymer molecular weight.

In conclusion, the degradation-associated sustained GEM release system designed in this study was successfully constructed, achieving extremely low initial burst release and a sustained GEM release cycle exceeding 24 weeks, providing a novel long-term strategy for local chemotherapy of esophageal cancer.

Clinically, esophageal stents are primarily applied in patients with advanced unresectable esophageal cancer. Recent studies have reported that median survival after stent implantation is approximately 6–9 months [35]. Therefore, the 24-week sustained-release period (~5.5 months) of GEM in the present study is within the expected survival duration of many patients. Besides, tumor ingrowth and overgrowth are the main causes of recurrent dysphagia and stent failure, typically occurring several months after implantation, with a median occurrence time of around 170 days [36]. Notably, this overlaps well with 24 weeks release period observed here, indicating that the sustained local drug release may effectively provide antitumor activity during the clinically relevant high-risk period for restenosis.

3.4 Evaluation of antitumor activity *in vitro*

The long-term anti-tumor potential of the PG fibers-covered esophageal stent was verified at the cellular level through *in vitro* experiments. Short-term (0–7 days, P/G_s, PG_s) and long-term (7–14 days, P/G_l, PG_l) extracts were prepared (Fig. 5(a)) to investigate the differences in the long-term inhibitory effects of P/G fibers and PG fibers on esophageal cancer cells TE-1.

As shown in Fig. 5(b), at day 1, the cell viabilities for P/G_s fibers and PG_s fibers were 95.62% and 97.90%, respectively, showing no significant inhibition. The limited inhibitory effect observed at day 1 may reflect the time-dependent nature of GEM cytotoxicity. Previous studies have demonstrated that GEM first induces S-phase arrest, whereas substantial apoptosis and cell loss often become more evident after prolonged exposure (48–96 h) [37–40]. By day 3, TE-1 cell viability in the P/G_s fibers and PG_s fibers extracts significantly decreased, further dropping to 14.34% and 16.56% by day 5, indicating that short-term extracts can provide sufficient GEM to induce tumor cell apoptosis. However, the CCK-8 test results of the long-term extract solution showed different results, as shown in Fig. 5(c). At day 1, neither showed significant inhibition. At day 3, cell viability of the P/G fibers group was comparable to the control ($***P < 0.001$), and at day 5, cell viability was about 89.90% of the control, lacking the ability to significantly inhibit tumor growth. In contrast, cell viability in the PG fibers group significantly decreased by day 3, and by day 5, the survival rate was only 20.16%, effectively inhibiting tumor cell growth.

Subsequently, live/dead cell staining (Fig. 5(d)) visually verified this result: in the short-term, live cells (green fluorescence) decreased significantly in the P/G_s fibers and PG_s fibers groups at day 3, and the number of live cells was reduced at day 5, although the fluorescence images did not show an obvious increase in attached dead cells, possibly because some apoptotic cells detached during the staining and washing procedures. These results indicate that both P/G fibers and PG fibers short-term extracts have significant anti-tumor effects. And in the long term, the number of live cells of the P/G fibers group remained similar to the control, with almost no dead cells. In the PG group, live cells significantly decreased, with a large number of dead cells observed at day 3, and at day 5, only a small number of living cells remained. These results indicate that both P/G fibers and PG fibers short-term extracts have significant anti-tumor effects, but only PG fibers have the ability to inhibit tumor growth in the long term.

These results can be explained by the cumulative release profile shown in Fig. 4(d). P/G fibers were almost completely released within 7 days, very little releasable GEM remained during the 7–14 days extraction period, and the corresponding long-term extract (P/G_l) contained negligible GEM, explaining its lack of biological activity. In contrast, PG fibers continued to release GEM during this period, and the estimated GEM concentration in the PG_l extract (~4.17 µg/mL according to Fig. 4(d)) falls within the concentration range that remained cytotoxic to TE-1 cells in the free-GEM control experiment (Fig. S10 in the ESM). This concentration is also of the same order of magnitude as plasma concentrations reported following standard clinical GEM infusion, while being maintained locally for an extended period. These findings demonstrate that the stable and sustained release behavior of PG fibers can maintain therapeutically effective GEM concentrations over time, thereby providing both immediate antitumor activity and prolonged growth inhibition. In contrast, the physically blended P/G fibers rapidly lose efficacy due to burst release. Collectively, these results highlight the advantage of the blocked strategy in achieving sustained drug release and long-term antitumor efficacy.

3.5 Evaluation of anti-angiogenesis ability *in vitro*

Tumor blood vessels are the foundation for tumor growth and metastasis, making the inhibition of tumor angiogenesis highly significant for tumor therapy [41]. This study first used a scratch assay to evaluate the potential of PG fibers to inhibit HUVECs migration, a prerequisite for inhibiting tube formation.

Initially, after creating the scratch, extracts were applied for 12 and 24 h incubation. Fluorescence staining images (Fig. 6(a)) revealed that, compared to the control group where cells rapidly migrated and healed the scratch, both short-term extract groups (P/G_s fibers and PG_s fibers) showed larger scratch areas and slower cell migration after 12 and 24 h incubation. In contrast, the P/G_l fibers group exhibited rapid cell migration from both sides toward the center, with the scratch nearly invisible after 24 h, similar to the control group. However, the PG_l group still displayed a distinct scratch at 24 h. Quantitative analysis of the fluorescence images demonstrated that, in the short term, both P/G_s fibers and PG_s fibers significantly inhibited HUVECs migration at 12 and 24 h (Fig. 6(b)). In the long term, at 24 h, the relative migration rate of the P/G_l fibers group was $98.98\% \pm 0.56\%$, while that of the PG_l group was only $54.77\% \pm 8.06\%$ (Fig. 6(c)). These results indicate that P/G_l fibers lack the ability to inhibit HUVECs migration,

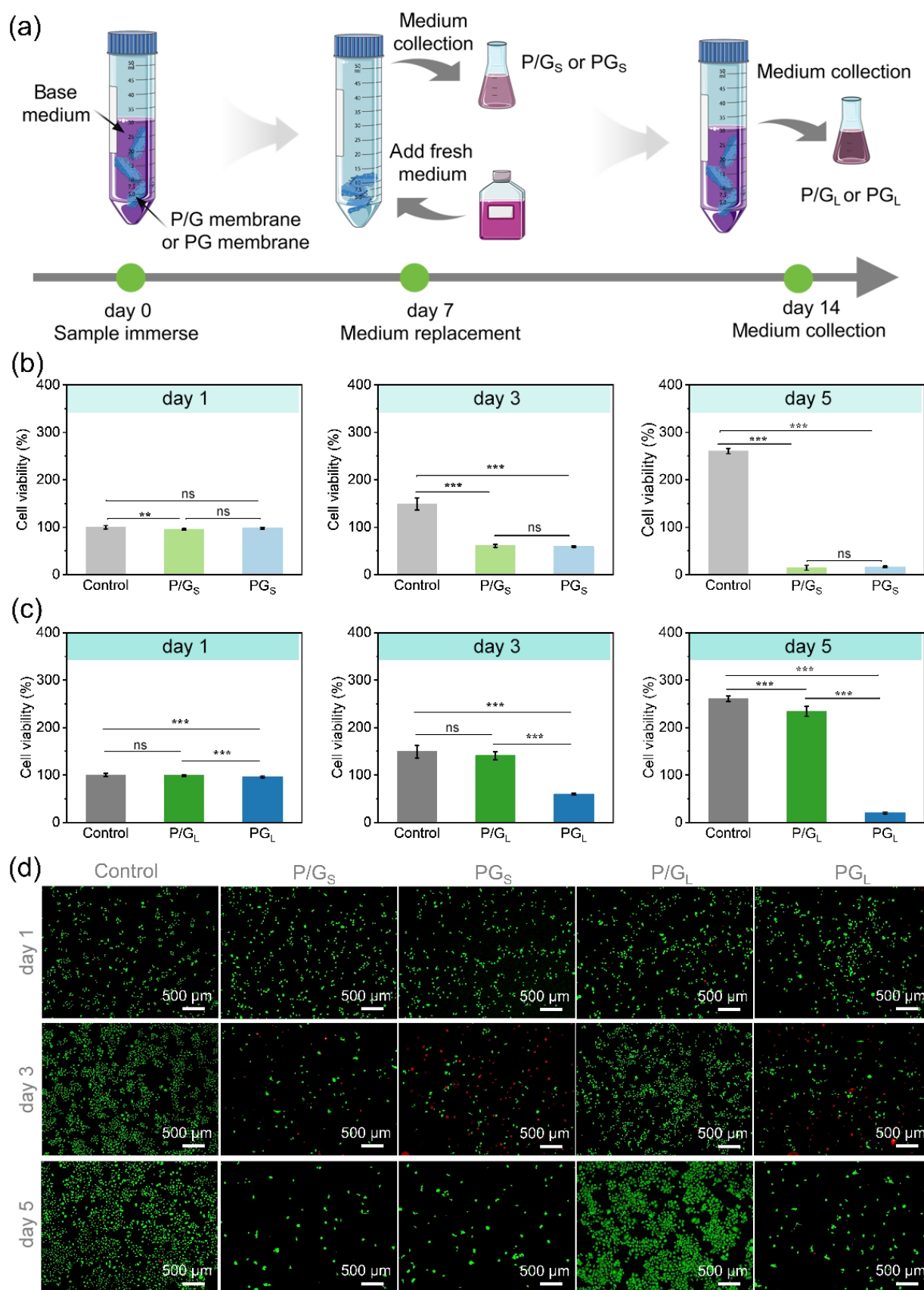


Figure 5 *In vitro* anti-tumor therapy effect evaluation. (a) Schematic of extract preparation from P/G fibers and PG fibers. TE-1 cells viabilities of TE-1 cells after incubation with (b) short-term extracts and (c) long-term extracts. (d) Live-dead cell staining of TE-1 cells after incubation with different extracts ($n = 3$, ns: non-significant, ** $P < 0.01$, *** $P < 0.001$).

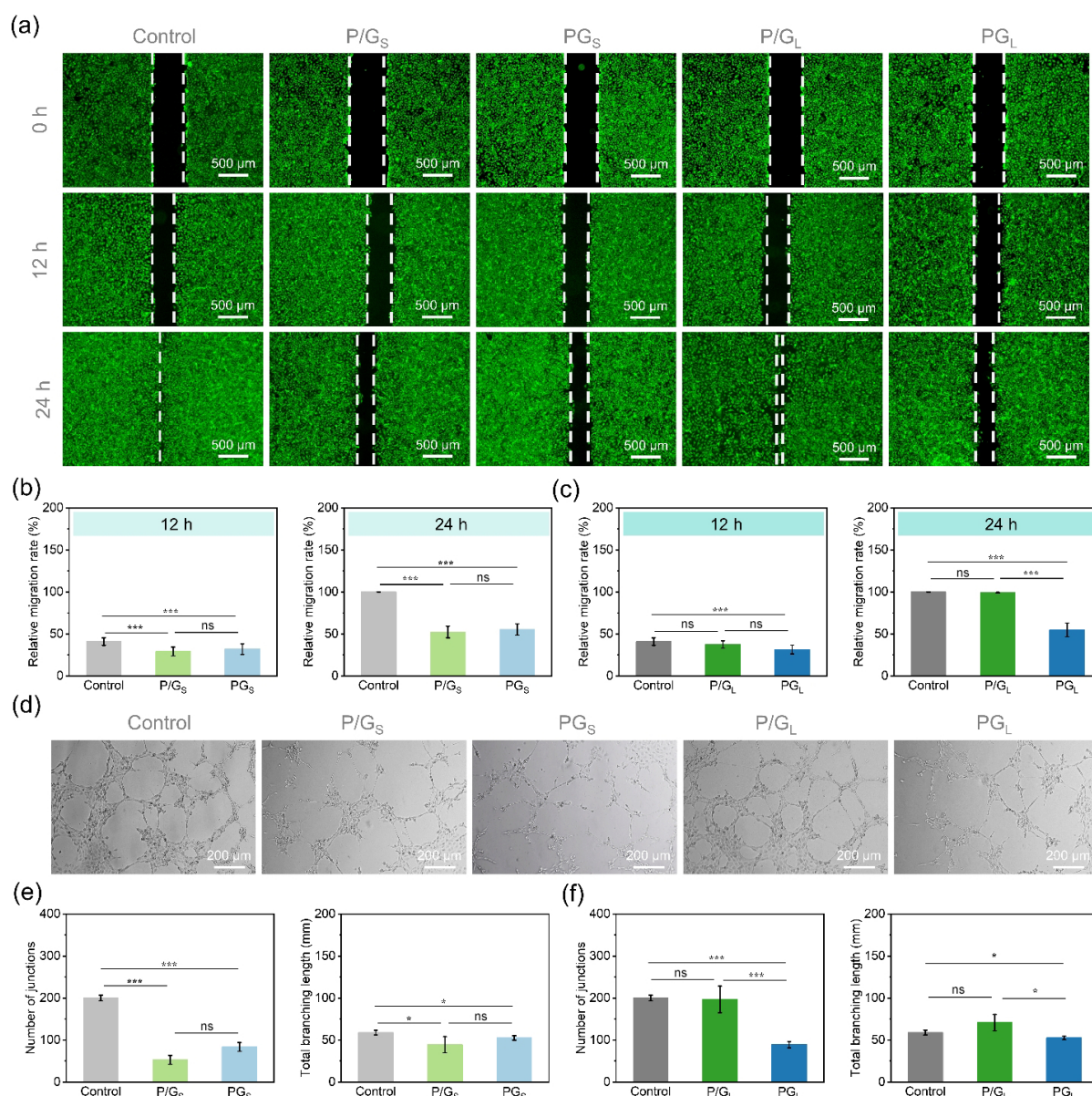


Figure 6 Evaluation of anti-angiogenesis ability *in vitro*. (a) Representative images of HUVECs migration after incubation with different extracts. Quantitative analysis of HUVECs migration after incubation with (b) short-term extracts and (c) long-term extracts from P/G and PG fibers for 12 and 24 h. (d) Representative images of angiogenesis after incubation with different extracts. Quantitative analysis of angiogenesis after incubation with (e) short-term extracts and (f) long-term extracts from P/G and PG fibers ($n = 3$, ns: non-significant, * $P < 0.05$, *** $P < 0.001$).

whereas PG_L fibers show significant inhibitory effects. In conclusion, thanks to the sustained release of the GEM, PG exhibits long-term capability to inhibit HUVECs migration.

To further evaluate the long-term potential of PG fibers to inhibit angiogenesis, an *in vitro* tube formation assay was conducted. Figure 6(d) shows representative images of tube formation after incubation with short-term and long-term extracts. Only the control and P/G_L fibers groups formed continuous, intact closed lumens, while other groups only showed elongated cell pseudopods but struggled to form lumens. Quantitative analysis of the images (Figs. 6(e) and 6(f)) revealed that the number of vascular junctions and the total branching length in the P/G_L group showed no significant difference from the control. In contrast, the P/G_S fibers, PG_S fibers, and PG_L fibers groups showed significantly reduced numbers of vascular junctions and total branching lengths,

further indicating that the anti-angiogenic effect of P/G fibers fails long-term, while PG fibers possess the ability to continuously inhibit angiogenesis.

In conclusion, the inhibitory effect of P/G fibers on tumor-associated angiogenesis lasted only about one week, whereas PG fibers exhibited excellent anti-angiogenic efficacy over two weeks. Although a positive control was not included, the difference between P/G and PG fibers was significant. This is attributed to the sustained release of GEM enabled by the blocking approach, achieving long-term blockade of nutrient supply to the tumor region, thereby helping to inhibit tumor growth and spread.

3.6 Evaluation of antitumor effect *in vivo*

A nude mouse xenograft model was established by subcutaneously injecting esophageal cancer cells. Once tumor volume reached

approximately 100 mm³, tumor-bearing mice were randomly divided into three groups: implanted with either GEM-free fibers (control), blended-GEM fibers (P/G fibers), or PG fibers (Fig. 7(a)). On day 14 post-implantation, tumors in the control group had nearly reached the ethically permissible maximum size, so this time point was set as the experimental endpoint. After 14 days of treatment, as shown in Fig. 7(b), the tumors in the P/G fibers group were slightly smaller than those in the control group, while the tumors in the PG fibers group were significantly smaller than those in the other groups, demonstrating the optimal tumor suppression effect. Analyzing the dynamic changes in tumor volume during treatment (Fig. 7(c)) revealed no significant differences among groups in the first 4 days post-implantation, possibly due to lag

effects from release, cellular uptake, and metabolic activation of GEM. By day 6, tumor growth rates significantly slowed in the P/G fibers and PG fibers groups, confirming the inhibition of esophageal cancer cell proliferation. Notably, in the later treatment phase (8–14 days), the inhibitory effect in the P/G fibers group attenuated, and tumor volume rapidly increased to a level similar to the control group. This observation was consistent with the cumulative release profile (Fig. 5(d)) showing that most GEM had already been released from the P/G fibers during the early stage. In contrast, the PG fibers group maintained sustained GEM release through slow degradation, and tumor volume remained significantly smaller than the control group (** $P < 0.01$) throughout. At the treatment endpoint, tumors were excised,

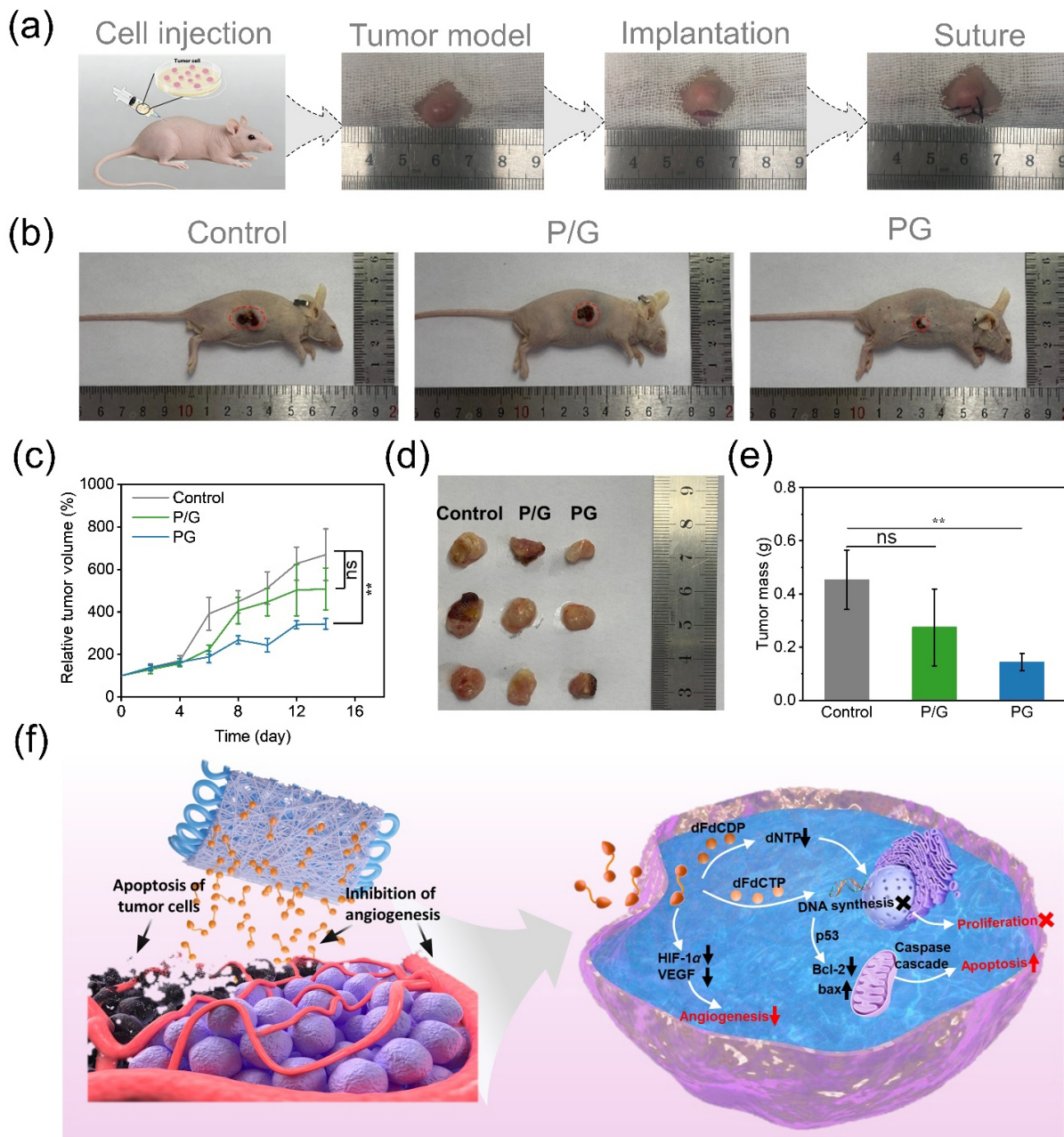


Figure 7 *In vivo* antitumor therapy. (a) Animal model establishment and treatment regimen. (b) Photographs of nude mice at the end of treatment. (c) Relative tumor volume curve during treatment. (d) Photographs and (e) mass of excised tumor tissues at the end of treatment. (f) Schematic diagram of the therapeutic mechanism ($n = 3$, ns: non-significant, ** $P < 0.01$).

photographed, and weighed (Figs. 7(d) and 7(e)). Tumor volume and mass in the P/G group were comparable to the control group, while the PG group had significantly lower tumor volume and mass ($**P < 0.01$), consistent with the tumor volume change results.

Based on previous *in vitro* experiments and current analysis of the antitumor mechanisms in this study, we propose that as the PG fibers gradually degrade, GEM is released from the DEES and subsequently taken up by tumor cells. Although intracellular GEM metabolites were not directly measured in this study, the phosphorylation-dependent activation pathway of gemcitabine has been extensively validated in previous reports [42, 43]. As illustrated in Fig. 7(f), GEM undergoes phosphorylation within the cell to form its active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). The former inhibits the synthesis of deoxy-ribonucleoside triphosphate (dNTP), while the latter is directly incorporated into the DNA strand, collectively blocking DNA replication and thereby suppressing cell proliferation [44]. Additionally, the DNA damage induced by GEM activates the p53 signaling pathway [45]. This leads to an upregulation of Bax and downregulation of Bcl-2, disrupting mitochondrial balance and

triggering the caspase cascade, ultimately inducing apoptosis [46]. Furthermore, GEM treatment can inhibit the function of the HIF-1 α /VEGF signaling pathway, reducing tumor angiogenesis, cutting off the nutrient supply to the tumor, and synergistically inhibiting tumor growth [47].

To further elucidate the tumor growth inhibition mechanism, excised tumor tissues were subjected to TUNEL apoptosis staining, Ki67 proliferation marker staining, and CD34 angiogenesis immunohistochemical analysis (Figs. 8(a) and 8(b)). Quantitative analysis revealed that the proportion of TUNEL-positive cells (green fluorescence) within the PG fibers group tumor tissue was significantly higher than other experimental groups (Fig. 8(c)). Simultaneously, the Ki67-positive cell rate (brown) was the lowest (Fig. 8(d)), indicating that the PG fibers inhibit tumor growth by inducing tumor cell apoptosis and suppressing cell proliferation activity. Furthermore, CD34 staining revealed that both the fluorescence intensity and number of microvessel (red fluorescence) in the PG fibers group were significantly lower than in the control and P/G fibers groups (Figs. 8(e) and 8(f)), suggesting that the PG fibers further block tumor nutrient supply by inhibiting

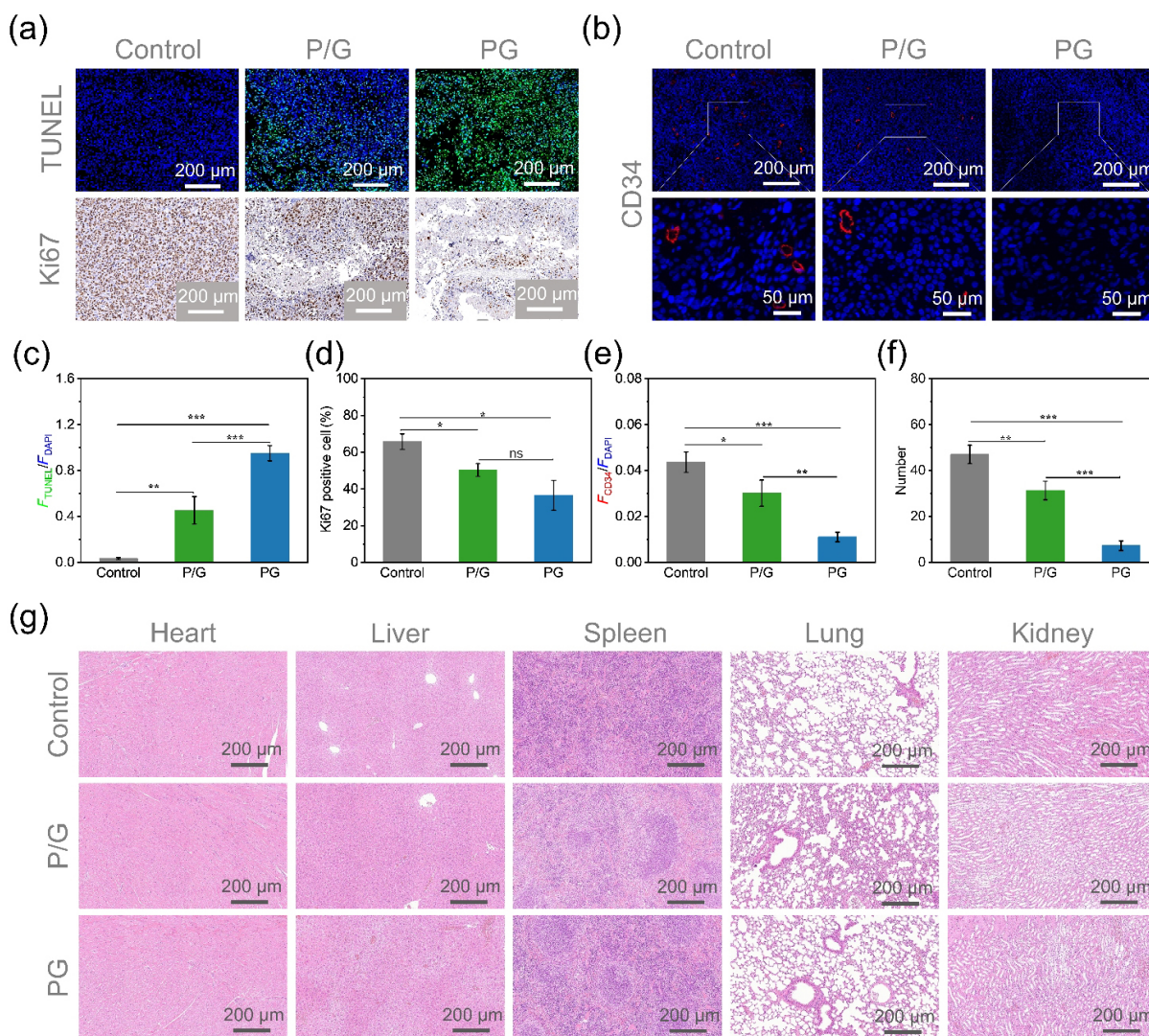


Figure 8 Histological assessment of the tumor and major organs. Representative images of (a) TUNEL, Ki67, and (b) CD34 staining of tumor tissue. Quantitative analysis of (c) TUNEL, (d) Ki67, and (e) and (f) CD34 staining of tumor tissue. (g) H&E-stained images of major organs (heart, liver, spleen, lung, and kidney) were collected from the mice ($n = 3$, ns: non-significant, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$).

angiogenesis. These results are highly consistent with the previously observed inhibitory effect of the PG fibers on HUVECs migration *in vitro* (Fig. 6), and further validate our proposed mechanism: the sustained anti-tumor efficacy of the PG fibers stems from its sustained-release GEM system regulating the apoptosis-proliferation balance in tumor cells and blocking tumor angiogenesis.

Additionally, no significant fluctuations in body weight occurred in any group during treatment (Fig. S11 in the ESM), and the heart, liver, spleen, lungs, and kidneys showed no visible damage (Fig. 8(g)), suggesting that none of the implanted materials caused significant systemic toxicity.

Several limitations of this study should be acknowledged. Due to time and ethical constraints, the sample size was limited and a free-GEM bolus control was not included. Moreover, the *in vivo* observation period (14 days) was shorter than the designed 24 weeks release duration, primarily because the tumor volume in the control group reached the humane endpoint. Local tissue responses at the implantation site (e.g., fibrosis, inflammation) were also not evaluated. Nevertheless, consistent and statistically significant differences across multiple endpoints (tumor volume, weight, Ki67, TUNEL, CD34) provide strong preliminary evidence for the efficacy of PG fibers. Future studies with larger cohorts, longer observation periods, appropriate free-drug controls, and comprehensive local biocompatibility assessments—particularly in orthotopic esophageal models—are warranted to further validate these findings.

4 Conclusions

In this study, we successfully developed a novel DEES using a GEM-synthesized degradable PG elastomer. By incorporating the chemotherapeutic agent GEM as a chain extender during polymer synthesis, we achieved a material that synergistically combines excellent mechanical properties with sustained and degradation-associated drug release capability. The optimized PG_{0.33} formulation exhibited superior elasticity, fatigue resistance, and was uniformly covered onto a knitted stent via electrospinning. This covering demonstrated firm adhesion without compromising the stent's essential mechanical properties, including radial compression strength, elastic recovery, and anti-migration force. Crucially, the PG fibers demonstrated a remarkably low initial burst release (< 1% within 24 h) and sustained GEM release over 24 weeks, a release profile governed by the polymer's degradation kinetics. Comprehensive *in vitro* studies confirmed the potent and long-term anti-tumor efficacy of the PG system, inducing apoptosis in esophageal cancer cells and effectively inhibiting angiogenesis, outperforming conventional physically blended drug fibers (P/G). These findings were further validated in an *in vivo* nude mouse xenograft model, where the PG fibers provided sustained inhibition of tumor growth, promoted apoptosis, suppressed proliferation, and reduced tumor microvessel density, all without inducing significant systemic toxicity. In conclusion, this work presents a transformative strategy for the design of DEES that seamlessly integrate mechanical robustness with long-term, localized chemotherapy. It addresses the critical limitations of current systems, such as burst release and short duration, offering a highly promising treatment option for patients with advanced esophageal cancer, although further long-term biocompatibility and implantation-site safety evaluations are still required.

Beyond esophageal cancer treatment, this nanofiber-covered stent design may potentially be adaptable to other luminal tumor therapies requiring local stent implantation, such as biliary or airway tumors. By integrating mechanical support with sustained local drug delivery, this strategy may help suppress tumor ingrowth and reduce restenosis while minimizing systemic toxicity. Moreover, the blocking strategy may provide a versatile platform for integrating various therapeutic modalities according to different clinical needs. Nevertheless, different luminal organs possess distinct physiological and mechanical environments, and therefore further optimization of material properties and structural design would be required for specific clinical applications.

Electronic Supplementary Material: Supplementary material (polymer characterization, fiber and stent mechanical testing, degradation-release profiles, kinetic analysis, and *in vitro* cytotoxicity assays) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94908970>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and/or the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

H. T.: Conceptualization, data curation, formal analysis, project administration, validation, visualization, writing – original draft, writing – review & editing. C. J. L.: formal analysis, methodology, project administration, supervision. J. L.: Conceptualization, formal analysis, project administration, resources, supervision, writing – review & editing. T. H. Z.: Conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, visualization, writing – original draft, writing – review & editing. L. W.: Conceptualization, funding acquisition, project administration, resources, supervision, writing – review & editing.

Informed consent

Not applicable.

Ethics statement

All animal experiments were reviewed and approved by the Experimental Animal Welfare and Animal Experiment Ethics Committee of Shanghai Pudong Hospital (No. 20241216-001). Animal experimental procedures strictly adhered to animal experimentation guidelines.

Use of AI statement

None.

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