Postprint: Shape Memory Polymers in Tissue Engineering Applications

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Abstract

Shape memory polymers constitute a class of intelligent polymeric materials comprising a fixed phase and a reversible phase, which exhibit the characteristic of inducing shape changes under external stimuli. Compared with conventional shape memory alloys and ceramics, they possess specific biodegradability, enhanced tunability of mechanical properties, superior shape recovery capability, and improved biocompatibility. Capitalizing on these material attributes, research on the application of shape memory polymers in tissue engineering has gained increasing momentum in recent years, encompassing vascular tissue, skeletal muscle tissue, neural tissue, and bone tissue, among other areas. This article provides a comprehensive review of recent experimental innovations, technological breakthroughs, and application expansions of shape memory polymers across multiple tissue engineering domains, exemplified by their utilization as novel porous vascular scaffolds, skeletal muscle repair scaffolds, nerve repair conduits, and bone defect fillers. It is anticipated that with the continuous advancement of technology and materials, the application of shape memory polymers in tissue engineering will achieve greater maturity.

Full Text

Application of Shape Memory Polymers in Tissue Engineering

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Abstract

Shape memory polymers (SMPs) are intelligent polymeric materials composed of a stationary phase and a reversible phase that can induce shape changes under external stimuli. Compared with traditional shape memory alloys and ceramics, SMPs offer specific biodegradability, greater tunability of mechanical properties, superior deformation recovery capability, and enhanced biocompatibility. Leveraging these material characteristics, recent research on SMP applications in tissue engineering has expanded rapidly across vascular, skeletal muscle, neural, and bone tissues. This review examines recent experimental innovations, technological breakthroughs, and application developments of SMPs in various tissue engineering fields, including their use as novel porous vascular scaffolds, skeletal muscle repair scaffolds, nerve repair conduits, and bone defect fillers. With continuous advancements in technology and materials, SMP applications in tissue engineering are expected to mature further.

Keywords: shape memory polymers, tissue engineering, 3D scaffolds

Introduction

Shape memory polymers (SMPs) are smart materials that can be designed and processed into a permanent shape, programmed into a temporary fixation, and then induced to recover their original shape through specific external stimuli [1-3]. SMPs consist of polymer networks where rigid segments serve as the stationary phase and soft segments function as the reversible phase. The reversible phase possesses high elasticity, enabling deformation and fixation during the shape memory cycle, while the stationary phase reduces its stiffness under stimulus to trigger shape recovery—a phenomenon known as the shape memory effect (SME) [4-6]. Researchers classify SMPs based on various criteria including crosslinking methods [7], stimulus types required for deformation [8], polymer motion forms [9], and differences in polymer transition structures [10].

Shape memory alloys, shape memory ceramics, and SMPs all belong to the category of shape memory materials [11]. However, compared with conventional shape memory alloys and ceramics, SMPs exhibit superior performance characteristics, including higher mechanical tunability and deformation recovery capabilities. Certain SMPs also possess biocompatibility and biodegradability, enabling their widespread use in medical [12], textile [13], aerospace [14], packaging [15], and industrial [16] applications. For medical applications, however, SMPs must meet more stringent requirements regarding polymer safety, degradation behavior, mechanical properties, biocompatibility, and the stimulus methods needed for in vivo shape transformation. Current medical applications of SMPs primarily include scaffolds [17], drug delivery carriers [18], wound closure devices [19], embolization devices [20], and tissue engineering [21].

SMPs can be combined with other compounds to achieve functionalization [22], making them highly adaptable for tissue engineering applications such as vascular and neural construction and the repair of damaged muscle and bone. Unlike traditional tissue engineering approaches that construct organs in vitro before implantation [23], current methods increasingly employ electrospinning [24] or 3D printing [25-26] to fabricate tissue scaffolds that are implanted through minimally invasive surgery and then expanded in vivo. This approach leverages the unique advantages of SMPs and minimally invasive techniques, significantly reducing patient suffering while achieving ideal therapeutic outcomes, making SMPs highly promising for human tissue engineering applications.

1. Applications in Vascular Tissue Engineering

Various vascular diseases such as atherosclerosis, aneurysms, and thromboembolism represent major causes of human mortality [27]. The most effective treatment currently involves finding vascular substitutes, which are categorized as biological or artificial vessels. Biological vessels are often harvested from humans or other organisms but face limitations including scarce availability and disease transmission risks [28]. Consequently, developing artificial blood vessels has become a research focus, with significant progress achieved through experimentation with various biosynthetic materials [29]. However, synthetic vessels still suffer from issues such as low biocompatibility, thrombosis formation, and difficulty in fabricating small-diameter grafts [30-31]. SMPs can be designed as elastic conduits or tubular porous scaffolds for endothelial cell culture, serving as effective vascular substitutes that address thrombosis and oversized lumen diameters.

Zhao Qilong et al. [33] designed a 2D bilayer scaffold as a vascular substitute. The inner layer consisted of a shape memory polymer, poly(lactide-trimethylene carbonate), serving as the deformation layer, while the outer layer was a nanofibrous membrane obtained through electrospinning of poly(-caprolactone) and gelatin methacrylate, functioning as the functional layer. Chitosan was used as an adhesive to create the bilayer scaffold. Human umbilical vein endothelial cells were seeded on the functional layer and cultured at 37°C. Under temperature-induced stimulation, the temporary planar structure of the deformation layer transformed, enabling the 2D bilayer scaffold to recover into a permanent 3D tubular structure. This morphological change facilitated uniform distribution of endothelial cells throughout the scaffold lumen. Cell culture studies demonstrated excellent biocompatibility and adhesion, promoting rapid endothelialization. This scaffold shows promise as a vascular substitute with an endothelial monolayer or as a biomimetic endothelial model for drug screening.

Liu Dian et al. [34] constructed a shape memory vascular scaffold with micropatterned surfaces based on crosslinked six-arm poly(ethylene glycol)-poly(-caprolactone) (PEG-PCL) polymer films that were rolled into multilayered tubular scaffolds. The inner and outer surfaces featured distinct topological structures: the inner surface had square patterns to enhance endothelial cell adhesion

and migration, preventing cell washout by blood flow and accelerating endothelialization; the outer multilayers featured rectangular patterns to induce circumferential alignment of vascular smooth muscle cells. When implanted into rabbit carotid arteries, no platelet aggregation or thrombosis was observed after 7 days, indicating that the scaffold material and surface patterns were inert to platelet activity. Doppler ultrasound examination at 15 days revealed a scaffold inner diameter of only 1.5 mm. By day 30, the inner surface was completely endothelialized, and the outer multilayers were also covered with endothelial cells. After 120 days, the vascular scaffold had fully degraded, with the neovessel showing excellent patency, mature vascular smooth muscle cell layers, and compressive strength reaching 260 ± 57 kPa. This artificial vascular scaffold therefore holds promise for vascular tissue replacement and damaged vessel repair.

2. Applications in Skeletal Muscle Tissue Engineering

Human skeletal muscle possesses strong repair and regeneration capabilities but cannot effectively address volumetric muscle loss (VML) exceeding 20% of muscle volume [35]. Current treatments for such injuries primarily include prosthetic support devices [36], functional free muscle transplantation [37], and cell therapy [38]. However, support devices face volume and weight limitations and are expensive, while muscle transplantation involves complex surgical techniques with success heavily dependent on the surgical team' s skill level. Therefore, current research on severe muscle injuries focuses on regenerative medicine approaches such as cell therapy, which involves implanting scaffolds at the injury site to promote skeletal muscle regeneration. These scaffolds can be categorized as biomaterial-based or cell-matrix-based, though cell-matrix scaffolds suffer from low mechanical strength and limited functionalization [39], giving biomaterials like SMPs significant advantages.

Deng Zexing et al. [40] synthesized a shape memory copolymer based on poly(-caprolactone) (PCL) and aniline trimer with amino end groups (AT). The biodegradable and biocompatible PCL served as the reversible phase, while AT, a conductive polymer, functioned as the stationary phase. The electroactive stationary phase effectively regulated cell adhesion, proliferation, and differentiation, while AT incorporation significantly reduced the copolymer's crystallinity, achieving an elongation at break of up to 1331%—far exceeding that of PCL alone and demonstrating excellent elasticity. When fabricated into films for culturing mouse C2C12 myoblasts, the copolymer clearly promoted cell proliferation and myogenic differentiation, as well as subsequent myotube formation and expression of myogenic differentiation genes.

Wang Lin et al. [41] designed an alginate-based shape memory porous scaffold implanted into mice with severely damaged tibialis anterior muscles through minimally invasive surgery, combined with injections of myoblasts, insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF). Comparative studies demonstrated that alginate scaffold implantation increased contractile force in healed muscle tissue and reduced fibrosis. The addition of IGF-1

and VEGF stimulated blood vessel formation and muscle tissue structure recovery while attenuating inflammatory responses and scar formation—critical factors for inducing skeletal muscle regeneration. Final results showed that control mice without treatment exhibited no spontaneous healing within 5-6 weeks, whereas scaffold-implanted mice showed good tibialis anterior muscle recovery by the sixth week.

3. Applications in Neural Tissue Engineering

Traumatic injuries to the human peripheral nervous system present persistent clinical challenges for neural tissue repair and regeneration [42]. Traditional treatments include direct suturing between nerve ends and autologous nerve grafting [43]. However, end-to-end connection is only suitable for short-gap injuries, while autologous grafts are limited in availability and cause donor site functional loss [44]. Recent advances in neural tissue engineering have employed biomaterials to fabricate artificial nerve conduits for nerve repair. Early materials suffered from non-degradability and limited extensibility, requiring nerve traction devices [45] or multiple surgeries with suboptimal outcomes. With material and medical advancements, researchers have begun exploring SMPs for nerve repair applications.

Chen Cheng et al. [46] synthesized three shape memory networks through physical crosslinking of poly(lactide-glycolide) at different ratios, fabricating a three-stage intelligent nerve conduit with 0.3 mm thickness and 2 mm inner diameter via electrospinning. The three polymer networks exhibited different glass transition temperatures, enabling stepwise elongation recovery under deformation stimuli. The conduit' s shape recovery was induced by 36°C aqueous solution, allowing safer and more practical use in the human body. To test biocompatibility, Schwann cells were cultured on the polymer networks, showing excellent adhesion and proliferation, indicating significant potential for future nerve repair and regeneration applications.

Kai Dan et al. [47] synthesized a shape memory polyurethane composed of polydimethylsiloxane (PDMS) and poly(-caprolactone) (PCL) segments. By adding small amounts of carbon black, a series of nanofibers were prepared through electrospinning. PC12 cell culture on these nanofibers revealed that appropriate low concentrations of carbon black did not affect biocompatibility but imparted electrical conductivity, effectively increasing neurite length and neuronal differentiation to promote nerve regeneration. The polymer also exhibited ultra-fast response, achieving shape recovery within 2 seconds under thermal stimulation. These features make the shape memory nanofibers promising for minimally invasive injectable nerve conduit applications.

4. Applications in Bone Tissue Engineering

Traditional bone scaffold materials for repairing bone defects, such as porous ceramics [48], metals [49], and glasses [50], have various disadvantages for clinical

use. Ideal bone fixators or implants must possess degradability, biocompatibility, excellent mechanical properties, and avoid stress shielding [51]. SMPs not only meet these requirements but also effectively fill 3D bone defect spaces while integrating regenerated bone with surrounding tissue, making them ideal bone scaffold materials.

Xie Ruiqi et al. [52] fabricated shape memory composite foams using poly(-caprolactone)-hydroxyapatite (HA) polymer through gas foaming for treating load-bearing bone defects. The shape memory foams were implanted into rabbit femoral defects and triggered with 40°C saline solution. The SMP foam' s temporarily fixed compact shape rapidly expanded within 60 seconds to adapt to the bone defect, and upon cooling to body temperature, the polymer' s crystalline domains recrystallized to provide sufficient mechanical support. At 12 weeks post-surgery, the control group without foam scaffolds showed only 24% bone repair, while the experimental group achieved 46% bone repair. The SMP foam also exhibited clear bone mineralization, neovascularization, and increased osteoblast proportions on bone surfaces, demonstrating significant advantages for bone scaffold applications in treating bone defects.

Yu Juhong et al. [53] synthesized a water-responsive shape memory polyurethane based on poly(-caprolactone)-polylactic acid (PCL-PLA), incorporating superparamagnetic iron oxide nanoparticles (SPIO NPs) to enhance osteogenic induction of human bone marrow mesenchymal stem cells. Polyethylene oxide (PEO) or gelatin was added to modify the material, followed by 3D printing. For shape memory performance, PEO-added 3D-printed scaffolds exhibited superior characteristics with both shape fixation and recovery rates reaching 100%. For biocompatibility, gelatin-modified scaffolds showed better cell viability. SPIO NP incorporation enhanced crystallinity of PCL and PLA segments in the polyurethane, increasing shape fixation rate. During bone formation, nanoparticle release from the scaffolds promoted osteogenic gene expression and collagen and calcium secretion and deposition, all beneficial for bone regeneration and repair.

SMPs applied in tissue engineering exhibit excellent deformability, biocompatibility, biodegradability, and adequate mechanical properties. The 2D or 3D scaffolds prepared from these materials typically feature porous structures suitable for transplanting appropriate human cells, and the polymers can be modified to incorporate other organic or inorganic materials that promote cell growth or tissue repair, making SMPs ideal materials for human tissue engineering. Related research has achieved considerable progress, though SMPs still present certain limitations, such as inadequate control over scaffold degradation timing. Since human tissues vary in structure and characteristics, degradation rates that are too long or too short can hinder tissue repair and regeneration. Additionally, scaffold degradation may cause sudden mechanical property deterioration and produce unwanted byproducts. Currently, most SMP research in tissue engineering remains at the stage of culturing tissue cells in scaffolds or applying them in animal models, not yet reaching human clinical application. However,

with continuous technological and material advancements, SMP applications and research in tissue engineering will undoubtedly mature further.

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