WISELEAF SCIENTIFIC VENTURES

BIODEGRADABLE POLYMERS IN DRUG DELIVERY AND TISSUE ENGINEERING

CHAPTER-5

Scaffold Design and Biodegradable Polymers in Tissue Engineering: Recent Advances, Clinical Translation, and Future Perspectives

Sourabh Saklani[1], Ankur Goyal[2]

[1]School of Pharmacy and Emerging Sciences (SPES), Baddi University, Makhnumajra, Baddi, District Solan, Himachal Pradesh - 173205, India

[2]School of Pharmacy, Lingaya's Vidyapeeth (Deemed-to-be University) Faridabad, Haryana-121002, India

Abstract

Biodegradable polymers have emerged as one of the most promising classes of biomaterials for tissue engineering and regenerative medicine because of their excellent biocompatibility, controlled biodegradation, and ability to support cellular growth and tissue regeneration. These materials provide temporary structural support while gradually degrading into non-toxic by-products that are naturally eliminated from the body, thereby minimizing the need for secondary surgical interventions. Both natural polymers, including collagen, gelatin, chitosan, alginate, hyaluronic acid, and silk fibroin, and synthetic polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polyethylene glycol (PEG), and polyhydroxyalkanoates (PHAs) have been extensively investigated for scaffold fabrication and controlled drug delivery applications. This chapter comprehensively reviews the fundamental principles of tissue engineering, desirable scaffold characteristics, biodegradable polymer classifications, and major scaffold fabrication techniques, including electrospinning, freeze-drying, solvent casting, gas foaming, three-dimensional (3D) bioprinting, and emerging four-dimensional (4D) bioprinting technologies. Furthermore, the integration of biodegradable scaffolds with stem cells, growth factors, nanoparticles, extracellular vesicles, and controlled drug delivery systems is discussed in the context of enhancing tissue regeneration and clinical outcomes. Recent advances from 2024–2026, including smart biomaterials, AI-assisted scaffold design, nanotechnology-enabled regenerative platforms, personalized medicine, and sustainable biofabrication strategies, are critically highlighted. Finally, current challenges related to vascularization, immune compatibility, degradation control, large-scale manufacturing, regulatory approval, and clinical translation are examined, together with future research directions. Overall, biodegradable polymer-based scaffolds represent a rapidly evolving platform with significant potential to transform regenerative medicine and next-generation therapeutic interventions.

Keywords: Biodegradable Polymers , Tissue Engineering , Regenerative Medicine , Drug Delivery Systems , Scaffold Fabrication , 3D Bioprinting

1. Introduction

Tissue engineering has emerged as one of the most transformative disciplines in regenerative medicine, integrating biomaterials science, cell biology, pharmaceutical sciences, biomedical engineering, and clinical medicine to develop biological substitutes capable of restoring, maintaining, or enhancing the function of damaged tissues and organs[1]. Since the concept was formally introduced in the early 1990s, tissue engineering has evolved from experimental laboratory research into a clinically relevant field with applications in orthopaedics, cardiovascular medicine, dermatology, dentistry, ophthalmology, neural regeneration, and reconstructive surgery[2]. The increasing burden of chronic diseases, traumatic injuries, congenital abnormalities, cancer-related tissue loss, and age-associated degeneration has intensified the demand for regenerative therapies that overcome the limitations of conventional treatment modalities. Recent advances in biomaterials, additive manufacturing, stem cell biology, and controlled drug delivery have significantly accelerated the translation of tissue-engineered constructs from bench to bedside[3].

Traditional approaches such as autografts, allografts, xenografts, and organ transplantation remain the clinical standard for repairing extensive tissue defects. However, these strategies are constrained by limited donor availability[4], donor-site morbidity, immune rejection, disease transmission, high surgical costs, and lifelong immunosuppressive therapy. Consequently, researchers have increasingly focused on engineering biomimetic scaffolds capable of supporting cellular adhesion, proliferation, differentiation, and extracellular matrix (ECM) remodeling while gradually degrading as native tissue regenerates. Tissue engineering therefore represents a paradigm shift from tissue replacement toward functional tissue regeneration[5].

The classical tissue engineering strategy is based on the interaction of three fundamental components: **cells, scaffolds, and bioactive signaling molecules**. These three elements collectively recreate a microenvironment that resembles the natural extracellular matrix, thereby regulating cell migration, angiogenesis, mechanotransduction[6], and tissue maturation. Among these components, scaffolds play a central role because they determine not only the structural integrity of the engineered construct but also its biological performance through modulation of cell–material interactions. Modern scaffold design has therefore progressed beyond simple structural support toward multifunctional biomaterials capable of delivering drugs, genes, growth factors, extracellular vesicles, and stem cells in a spatially and temporally controlled manner[7].

Biodegradable polymers have become the cornerstone of scaffold fabrication because they provide temporary mechanical support without requiring surgical removal after tissue regeneration. Unlike permanent implants, biodegradable scaffolds gradually degrade into non-toxic metabolites that are metabolized or excreted by the body while newly synthesized extracellular matrix replaces the scaffold architecture. This synchronized process minimizes chronic foreign-body reactions and reduces long-term implant-associated complications[8]. Over the last decade, remarkable progress in polymer chemistry has enabled the development of

biodegradable materials with precisely controlled degradation kinetics, tunable mechanical strength, enhanced bioactivity, and programmable physicochemical characteristics[9].

Natural biodegradable polymers—including collagen, gelatin, fibrin, silk fibroin, alginate, chitosan, cellulose derivatives, and hyaluronic acid—closely mimic the biochemical composition of the native extracellular matrix and exhibit excellent cytocompatibility[10]. Nevertheless, their clinical application is frequently limited by inadequate mechanical stability, rapid enzymatic degradation, and batch-to-batch variability. Conversely, synthetic biodegradable polymers such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), polyethylene glycol (PEG), and polyhydroxyalkanoates (PHAs) provide superior reproducibility, adjustable degradation rates, ease of manufacturing, and enhanced mechanical performance[11]. Contemporary research increasingly focuses on hybrid scaffolds that combine natural and synthetic polymers to integrate the biological advantages of natural matrices with the structural robustness of engineered polymers[12].

Recent technological advances have profoundly transformed scaffold fabrication methodologies. Conventional techniques such as solvent casting, particulate leaching, freeze-drying, gas foaming, and phase separation are now complemented by sophisticated additive manufacturing technologies, including electrospinning, melt electrowriting, stereolithography, extrusion-based three-dimensional (3D) bioprinting, digital light processing, and microfluidic biofabrication[13]. These technologies permit precise control over pore geometry, fiber orientation, surface topography, mechanical gradients, and patient-specific architecture, thereby improving nutrient diffusion, vascularization, and cellular organization within engineered tissues. Particularly, 3D printing has emerged as a powerful platform for fabricating customized scaffolds with complex hierarchical microstructures that closely resemble native tissue architecture[14].

In parallel, nanotechnology has revolutionized scaffold engineering through the incorporation of nanofibers, nanoparticles, nanotubes, nanoclays, graphene derivatives, bioactive ceramics, and nanocomposite materials[15]. These nanoscale modifications enhance surface area, protein adsorption, antimicrobial activity, electrical conductivity, osteoinduction, angiogenesis, and controlled drug release. Electrospun nanofibrous scaffolds, in particular, closely resemble the fibrous architecture of natural extracellular matrix, making them highly suitable for skin, nerve, tendon, and cardiovascular tissue regeneration. Simultaneously, injectable hydrogels and stimuli-responsive "smart" polymers capable of responding to temperature, pH, enzymes, electrical stimulation, magnetic fields, or biochemical signals have opened new opportunities for minimally invasive regenerative therapies and precision medicine[16].

Another major milestone in regenerative medicine is the emergence of **4D bioprinting**, which extends conventional 3D bioprinting by enabling printed constructs to change shape or function over time in response to external or physiological stimuli[17]. Shape-memory polymers and dynamic hydrogels are now being investigated to fabricate adaptive scaffolds capable of mimicking tissue development and remodeling processes[18]. Moreover, artificial intelligence

(AI), machine learning, and computational modeling are increasingly being integrated into scaffold design to optimize biomaterial selection, predict degradation behaviour, personalize scaffold architecture, and accelerate biomaterial discovery. These computational approaches are expected to substantially shorten development timelines while improving reproducibility and clinical translation[19].

Despite these remarkable scientific advances, successful clinical translation of biodegradable polymer scaffolds continues to face significant challenges. Achieving rapid vascularization within large tissue constructs, balancing scaffold degradation with tissue regeneration, minimizing inflammatory responses, ensuring sterilization without compromising biomaterial integrity, scaling manufacturing under Good Manufacturing Practice (GMP) conditions, and satisfying increasingly stringent regulatory requirements remain major barriers[20]. Furthermore, translating promising laboratory findings into reproducible clinical outcomes requires multidisciplinary collaboration among material scientists, pharmacists, clinicians, biomedical engineers, regulatory agencies, and industry stakeholders[21].

Recognizing these developments, this chapter provides a comprehensive overview of scaffold design principles and biodegradable polymers in tissue engineering with a particular emphasis on recent advances published during the last few years. The chapter critically discusses scaffold design criteria, natural and synthetic biodegradable polymers, advanced fabrication technologies, drug- and cell-loaded scaffolds, biomedical applications across multiple organ systems, emerging smart biomaterials, nanotechnology-enabled regenerative strategies, clinical translation, regulatory considerations, current limitations, and future research directions. By integrating recent scientific evidence with established biomaterial principles, this chapter aims to provide researchers, academicians, postgraduate students, and healthcare professionals with a contemporary understanding of biodegradable scaffold technologies and their expanding role in regenerative medicine[22].

2. Fundamentals of Tissue Engineering and Principles of Scaffold Design

2.1 Fundamentals of Tissue Engineering

Tissue engineering is an interdisciplinary field that integrates principles from biomaterials science, pharmaceutical sciences, molecular biology, biomedical engineering, and regenerative medicine to develop biological substitutes capable of restoring, maintaining, or improving the function of damaged tissues and organs. Unlike conventional therapies that primarily alleviate symptoms or replace damaged tissues using prosthetic devices or donor grafts, tissue engineering focuses on regenerating functional tissues by recreating the native biological microenvironment[23]. This regenerative strategy has gained considerable attention due to the increasing prevalence of chronic diseases, traumatic injuries, congenital anomalies, and age-related degenerative disorders, all of which contribute substantially to the global healthcare burden. Recent advances in stem cell biology, biomaterials engineering, nanotechnology, additive manufacturing, and precision medicine have significantly accelerated the development of clinically translatable tissue-engineered products[24].

The concept of tissue engineering is primarily based on the interaction of three fundamental components, collectively known as the **Tissue Engineering Triad**: **cells, scaffolds, and bioactive molecules**. These components work synergistically to promote tissue regeneration by mimicking the physiological characteristics of the native extracellular matrix (ECM). Successful regeneration depends not only on the individual performance of these components but also on their coordinated interaction within the host environment[25].

Table 1. Comparison of Natural Biodegradable Polymers Used in Tissue Engineering

Polymer	Source	Advantages	Limitations	Major Applications
Collagen	Animal connective tissue	Excellent biocompatibility, cell adhesion	Low mechanical strength	Skin, Bone, Cartilage
Gelatin	Hydrolyzed collagen	Biodegradable, inexpensive	Rapid degradation	Wound healing
Chitosan	Crustacean shells	Antibacterial, biocompatible	Poor mechanical properties	Bone, Skin
Alginate	Brown algae	Injectable, hydrogel formation	Poor cell adhesion	Cartilage
Hyaluronic Acid	ECM	Cell migration, wound healing	Rapid degradation	Skin, Cartilage
Silk Fibroin	Silkworm	High mechanical strength	Slow degradation	Ligament, Bone

2.1.1 Cells: The Functional Component

Cells constitute the biological foundation of tissue engineering because they synthesize extracellular matrix proteins, secrete growth factors, respond to biochemical signals, and ultimately regenerate functional tissue. Depending on the target application, different cell sources are employed, including primary cells, mesenchymal stem cells (MSCs), induced pluripotent stem cells (iPSCs), embryonic stem cells (ESCs), adipose-derived stem cells (ADSCs), and tissue-specific progenitor cells[26].

Mesenchymal stem cells remain among the most widely investigated cell types owing to their multilineage differentiation potential, immunomodulatory properties, and relatively low ethical concerns. These cells can differentiate into osteoblasts, chondrocytes, adipocytes, myocytes, and fibroblasts under appropriate biochemical and mechanical stimuli. Recent investigations have also demonstrated that extracellular vesicles and exosomes secreted by MSCs contribute significantly to

tissue repair through paracrine signaling, angiogenesis, immune modulation, and inflammation control. Consequently, cell-free regenerative therapies based on stem-cell-derived exosomes have emerged as a promising alternative to conventional stem cell transplantation[27].

2.1.2 Bioactive Molecules

Bioactive molecules regulate cellular behavior by activating intracellular signaling pathways responsible for proliferation, migration, differentiation, angiogenesis, and extracellular matrix remodeling. These include growth factors, cytokines, chemokines, peptides, nucleic acids, and extracellular vesicles[28].

Among the most extensively investigated growth factors are vascular endothelial growth factor (VEGF), bone morphogenetic proteins (BMP-2 and BMP-7), transforming growth factor-beta (TGF-β), fibroblast growth factors (FGFs), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and epidermal growth factor (EGF). Controlled delivery of these molecules from biodegradable scaffolds enables localized therapy while minimizing systemic toxicity and maintaining therapeutic concentrations for prolonged periods[29].

Recent developments in pharmaceutical biomaterials have enabled the incorporation of gene therapy vectors, messenger RNA (mRNA), CRISPR-Cas systems, microRNAs, antimicrobial peptides, and immunomodulatory agents into scaffold matrices, thereby creating multifunctional platforms capable of simultaneously promoting tissue regeneration and preventing infection or inflammation[30].

2.1.3 Extracellular Matrix Mimicry

The extracellular matrix serves as the natural structural framework of tissues and provides both biochemical and mechanical cues regulating cell behavior. Native ECM consists primarily of collagen, elastin, laminin, fibronectin, proteoglycans, glycosaminoglycans, and various signaling proteins[31].

An ideal tissue-engineered scaffold should closely mimic the structural organization and biological functionality of the native extracellular matrix. Biomimetic scaffolds facilitate cell adhesion through integrin-mediated interactions, regulate mechanotransduction pathways, enhance nutrient diffusion, and promote tissue maturation[32]. Advances in decellularized extracellular matrix (dECM) technologies have enabled the development of highly biomimetic scaffolds retaining native tissue architecture and biochemical composition while minimizing immunogenicity[33].

2.2 Tissue Engineering Strategies

Modern tissue engineering generally follows three principal strategies.

Cell-Based Tissue Engineering

In this strategy, isolated cells are expanded in vitro before being seeded onto biodegradable scaffolds. Following implantation, these cells proliferate and regenerate functional tissue. This approach is widely used for cartilage regeneration, skin substitutes, bone repair, and vascular grafts[34].

Cell-Free Tissue Engineering

Cell-free approaches utilize acellular scaffolds containing bioactive molecules that recruit endogenous stem cells from surrounding tissues. This strategy simplifies manufacturing, reduces regulatory challenges, minimizes immunological risks, and lowers production costs. Recent evidence suggests that appropriately designed acellular scaffolds can achieve regenerative outcomes comparable to certain cell-based therapies[35].

In Situ Tissue Engineering

In situ tissue engineering combines advanced scaffold design with endogenous tissue regeneration. Instead of implanting cultured cells, biodegradable scaffolds are engineered to recruit host stem cells directly after implantation. Such approaches have gained increasing attention in cardiovascular, orthopedic, and dental tissue engineering because they eliminate the need for complex cell culture procedures[36].

2.3 Principles of Scaffold Design

Scaffolds represent the structural backbone of tissue engineering. They provide temporary mechanical support while regulating cell attachment, proliferation, differentiation, vascularization, and extracellular matrix deposition until complete tissue regeneration occurs[37].

Recent advances in biomaterials science have transformed scaffold design from passive supporting structures into intelligent multifunctional platforms capable of delivering cells, therapeutic agents, growth factors, nucleic acids, and biosensors[38].

An ideal scaffold should satisfy several biological, mechanical, and physicochemical requirements.

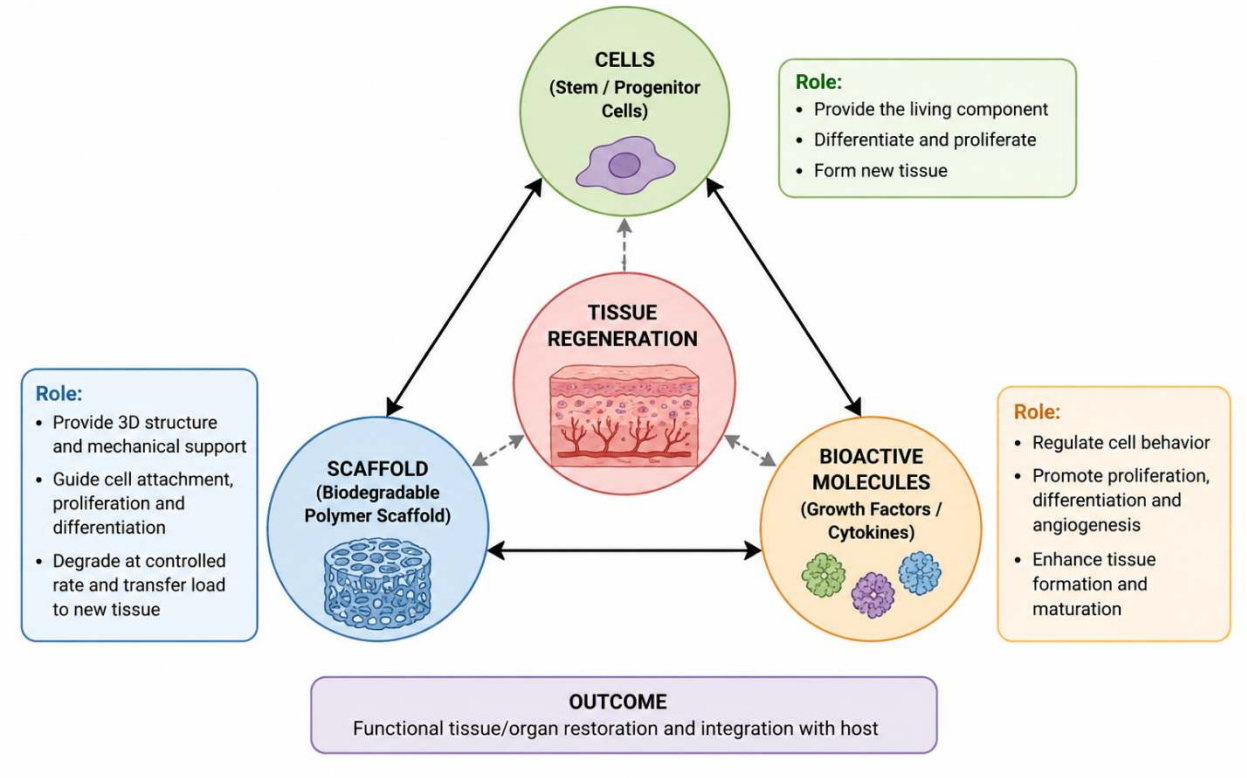

Figure 1: Schematic representation of the tissue engineering triad

2.3.1 Biocompatibility

Biocompatibility is the most critical characteristic of scaffold materials. A scaffold should neither induce cytotoxicity nor provoke excessive inflammatory or immune responses following implantation. Instead, it should support normal cellular activities while maintaining tissue homeostasis[39].

Modern biodegradable polymers are increasingly functionalized with bioactive peptides, extracellular matrix proteins, and cell-adhesion ligands such as RGD peptides to enhance cellular attachment and proliferation[40].

2.3.2 Controlled Biodegradation

The degradation profile of a scaffold should closely match the rate of new tissue formation. Premature degradation compromises mechanical stability, whereas delayed degradation may interfere with tissue remodeling and trigger chronic inflammation[41].

Current research focuses on programmable degradation using copolymerization, enzyme-responsive linkages, hydrolytically degradable polymers, and stimuli-responsive biomaterials capable of adjusting degradation according to physiological conditions[42].

2.3.3 Mechanical Properties

Mechanical properties must closely resemble those of the target tissue. Bone scaffolds require high compressive strength, whereas skin and neural scaffolds demand flexibility and elasticity. Inappropriate stiffness can alter mechanotransduction signaling pathways and impair tissue regeneration[43].

Advanced composite scaffolds combining biodegradable polymers with hydroxyapatite, bioactive glass, graphene oxide, carbon nanotubes, or ceramic nanoparticles have significantly improved mechanical performance while maintaining biocompatibility[44].

2.3.4 Porosity and Pore Interconnectivity

Highly interconnected porous structures facilitate oxygen transport, nutrient diffusion, waste removal, angiogenesis, and cellular infiltration. Pore size requirements vary depending on tissue type.

Generally, interconnected porosity exceeding 70% is considered beneficial for most tissue-engineering applications, although optimal pore dimensions differ between bone, cartilage, vascular, and neural tissues[45].

2.3.5 Surface Characteristics

Surface chemistry strongly influences protein adsorption, wettability, cellular adhesion, and differentiation. Surface modification techniques such as plasma treatment, peptide immobilization, polydopamine coating, and nanostructuring have significantly enhanced scaffold bioactivity[46].

Nanostructured surfaces better mimic native extracellular matrix topography and improve osteogenic, chondrogenic, and neurogenic differentiation[47].

2.3.6 Angiogenic Potential

Insufficient vascularization remains one of the major limitations preventing successful regeneration of thick tissues.

Modern scaffold designs therefore incorporate angiogenic growth factors, endothelial progenitor cells, oxygen-releasing biomaterials, and microchannel architectures to accelerate neovascularization after implantation[48].

2.3.7 Drug Delivery Capability

Contemporary scaffolds are increasingly designed as localized drug delivery systems capable of releasing antibiotics, anti-inflammatory drugs, anticancer agents, growth factors, nucleic acids, and stem-cell-derived exosomes in a controlled manner[49].

Such multifunctional scaffolds simultaneously provide structural support while improving therapeutic efficacy and reducing systemic adverse effects.

2.4 Emerging Concepts in Scaffold Design

Recent research (2024–2026) has expanded scaffold engineering beyond conventional biodegradable polymers toward **smart biomaterials** capable of responding to physiological stimuli. Shape-memory polymers, self-healing hydrogels, electroconductive scaffolds, magnetically responsive composites, and bioactive nanocomposites are now being investigated to enhance tissue regeneration. Furthermore, artificial intelligence (AI) and machine learning are increasingly being employed to optimize scaffold architecture, predict degradation kinetics, personalize implant design, and accelerate biomaterial discovery[50]. Coupled with **3D and 4D bioprinting**, these computational approaches enable the fabrication of patient-specific scaffolds with precise control over geometry, porosity, mechanical gradients, and bioactive molecule distribution. Such next-generation scaffold platforms are expected to play a central role in precision regenerative medicine and the clinical translation of tissue-engineered therapies over the coming decade[51].

3. Natural Biodegradable Polymers

3.1 Introduction

Natural biodegradable polymers are among the earliest biomaterials investigated for tissue engineering because of their excellent biocompatibility, biodegradability, low immunogenicity, and close resemblance to the native extracellular matrix (ECM)[52]. These polymers are derived from biological sources, including animals, plants, microorganisms, and marine organisms, and possess intrinsic biological cues that facilitate cell adhesion, proliferation, migration, and differentiation. Their structural similarity to ECM proteins enables effective communication between cells and biomaterials, making them highly suitable for regenerative medicine applications[53].

Unlike synthetic polymers, natural polymers contain bioactive motifs that promote integrin-mediated cell attachment and regulate cellular signaling pathways involved in tissue repair. However, they also exhibit limitations such as batch-to-batch variability, poor mechanical strength, rapid enzymatic degradation, and difficulties in large-scale manufacturing[54]. Consequently, recent research has increasingly focused on hybrid scaffold systems combining natural polymers with synthetic biodegradable polymers or inorganic nanomaterials to improve mechanical performance while preserving biological functionality[55].

The most extensively studied natural biodegradable polymers include collagen, gelatin, chitosan, alginate, hyaluronic acid, silk fibroin, fibrin, cellulose, and decellularized extracellular matrix (dECM). Each material possesses distinct physicochemical and biological characteristics that determine its suitability for specific tissue-engineering applications[56].

Table 2. Comparison of Synthetic Biodegradable Polymers

Polymer	Mechanical Strength	Degradation Rate	Advantages	Applications
PLA	High	Slow	Good strength	Bone
PGA	High	Fast	High biodegradability	Sutures
PLGA	Moderate	Adjustable	Drug delivery	Bone, Cartilage
PCL	Moderate	Very Slow	Flexible	Vascular, Bone
PEG	Low	Variable	Hydrophilic	Hydrogels
PHAs	Moderate	Moderate	Excellent biocompatibility	Tissue Engineering

3.2 Collagen

Collagen is the most abundant structural protein in mammals and represents nearly one-third of the total body protein. It is the primary constituent of the extracellular matrix in connective tissues, including skin, bone, cartilage, tendons, ligaments, blood vessels, and cornea. Owing to its excellent cytocompatibility and natural cell-recognition sequences, collagen remains one of the most widely used biomaterials in tissue engineering[57].

Collagen-based scaffolds support fibroblast proliferation, osteogenic differentiation, angiogenesis, and wound healing while exhibiting minimal inflammatory responses after implantation. Type I collagen is particularly preferred for bone, skin, tendon, and vascular tissue engineering because of its superior biological performance[58].

Despite these advantages, collagen possesses relatively poor mechanical strength and undergoes rapid enzymatic degradation in vivo. Therefore, chemical cross-linking agents, enzymatic stabilization, and nanocomposite reinforcement with hydroxyapatite, bioactive glass, graphene oxide, or synthetic polymers are frequently employed to improve structural stability and prolong degradation time[59].

Recent investigations have demonstrated that collagen-based bioinks used in three-dimensional bioprinting significantly enhance cell viability and tissue maturation, making collagen one of the leading biomaterials for personalized regenerative therapies[60].

3.3 Gelatin

Gelatin is a denatured derivative of collagen obtained through controlled hydrolysis. It retains many biologically active amino acid sequences responsible for cellular attachment while offering lower antigenicity, greater processability, and reduced production cost compared with native collagen.

Gelatin exhibits excellent biodegradability, hydrophilicity, and drug-loading capacity, making it particularly suitable for controlled drug delivery, wound dressings, injectable hydrogels, and tissue-engineered scaffolds[61].

Gelatin methacryloyl (GelMA) has recently emerged as one of the most promising bioinks for 3D bioprinting because of its photocrosslinkable properties, tunable stiffness, and high cytocompatibility. GelMA-based hydrogels have demonstrated encouraging outcomes in cartilage, skin, cardiac, and neural tissue engineering[62].

However, gelatin alone exhibits poor mechanical stability under physiological conditions. Consequently, it is frequently combined with alginate, chitosan, hyaluronic acid, PCL, or PLA to produce mechanically robust composite scaffolds.

3.4 Chitosan

Chitosan is a naturally occurring cationic polysaccharide produced by the deacetylation of chitin, which is abundantly found in crustacean shells, insects, and fungal cell walls. Owing to its biodegradability, antimicrobial activity, mucoadhesive properties, and excellent biocompatibility, chitosan has become one of the most extensively investigated polymers in pharmaceutical and biomedical research.

The positively charged amino groups of chitosan facilitate electrostatic interactions with negatively charged cellular membranes and extracellular matrix components, thereby promoting wound healing and tissue regeneration. Chitosan also exhibits intrinsic antibacterial activity against a broad spectrum of Gram-positive and Gram-negative bacteria, making it particularly valuable for chronic wound management[63].

Recent research has focused on chitosan-based nanocomposite scaffolds incorporating silver nanoparticles, zinc oxide nanoparticles, graphene oxide, and bioactive ceramics to improve antimicrobial efficacy, angiogenesis, and mechanical performance.

3.5 Alginate

Alginate is an anionic polysaccharide isolated primarily from brown seaweed. It consists of β-D-mannuronic acid and α-L-guluronic acid residues arranged in varying sequences that determine its mechanical properties and gel-forming ability[64].

Alginate readily forms hydrogels through ionic cross-linking with divalent cations such as calcium ions, enabling the encapsulation of living cells, proteins, and therapeutic molecules under mild processing conditions.

Because alginate lacks natural cell-adhesion motifs, surface modification using RGD peptides, collagen, gelatin, or fibronectin is commonly employed to enhance cellular attachment and proliferation[65].

Alginate hydrogels are widely investigated for cartilage regeneration, pancreatic islet transplantation, wound healing, and controlled drug delivery owing to their excellent biocompatibility and injectable nature.

3.6 Hyaluronic Acid

Hyaluronic acid is a naturally occurring glycosaminoglycan present in connective tissues, synovial fluid, skin, vitreous humor, and cartilage. It plays an essential role in cell migration, inflammation regulation, lubrication, angiogenesis, and extracellular matrix organization[66].

Owing to its high water-retention capacity and viscoelastic properties, hyaluronic acid is extensively utilized in injectable hydrogels, cartilage repair, ophthalmic biomaterials, and wound healing applications.

Chemically modified hyaluronic acid derivatives possessing photocrosslinkable or enzyme-responsive functionalities have significantly improved scaffold stability and enabled the fabrication of sophisticated bioinks suitable for three-dimensional bioprinting[67].

3.7 Silk Fibroin

Silk fibroin, primarily derived from *Bombyx mori*, possesses remarkable tensile strength, elasticity, biodegradability, and biocompatibility. Unlike many natural polymers, silk fibroin demonstrates excellent mechanical stability while supporting cellular proliferation and extracellular matrix deposition[68].

Silk-based scaffolds have shown promising outcomes in ligament, tendon, cartilage, vascular, bone, and nerve tissue engineering. Their slow degradation kinetics make them particularly suitable for tissues requiring prolonged mechanical support[69].

Recent studies have explored electrospun silk nanofibers, recombinant silk proteins, and silk-based bioinks for advanced regenerative medicine applications.

3.8 Cellulose and Bacterial Cellulose

Cellulose is one of the most abundant natural polymers and exhibits excellent mechanical properties, hydrophilicity, and chemical stability. Bacterial cellulose possesses an ultrafine nanofibrillar architecture resembling native extracellular matrix and demonstrates exceptional water-holding capacity[70].

Because mammalian tissues lack cellulase enzymes, cellulose degradation in vivo is limited; therefore, chemically modified cellulose derivatives are increasingly employed to improve biodegradability and biomedical performance[71].

Applications include wound dressings, vascular grafts, skin substitutes, cartilage regeneration, and drug delivery systems.

3.9 Decellularized Extracellular Matrix (dECM)

Decellularized extracellular matrix has emerged as a next-generation natural biomaterial that retains the biochemical composition, ultrastructure, and tissue-specific signaling molecules of native organs while removing immunogenic cellular components[72].

dECM-based scaffolds provide highly biomimetic microenvironments that regulate stem-cell differentiation and tissue-specific regeneration. Recent advances in decellularization protocols and dECM-derived bioinks have expanded their applications in liver, cardiac, lung, kidney, skeletal muscle, and pancreatic tissue engineering[73].

3.10 Advantages of Natural Biodegradable Polymers

Natural biodegradable polymers offer several advantages[74]:

- Excellent biocompatibility and cytocompatibility.
- Biomimetic extracellular matrix architecture.
- Intrinsic bioactivity promoting cell adhesion.
- Enzymatic biodegradation into non-toxic products.
- High water absorption and hydrogel-forming ability.
- Suitable for drug delivery and cell encapsulation.

3.11 Limitations

Despite their biological superiority, natural polymers present several limitations[75]:

- Poor mechanical strength.
- Rapid degradation under physiological conditions.
- Batch-to-batch variability.
- Potential pathogen transmission from animal-derived sources.
- Limited long-term structural stability.
- Difficulties in sterilization and large-scale manufacturing.

To overcome these challenges, contemporary research increasingly employs **hybrid composite scaffolds**, **nanocomposite reinforcement**, and **surface functionalization**, combining natural polymers with synthetic biodegradable polymers or bioactive nanoparticles to achieve improved mechanical integrity and controlled degradation.

4. Synthetic Biodegradable Polymers

4.1 Introduction

Synthetic biodegradable polymers have become indispensable biomaterials in modern tissue engineering because they provide superior mechanical strength, reproducible manufacturing, controlled degradation kinetics, and tunable physicochemical properties compared with many natural polymers. Unlike naturally derived biomaterials, synthetic polymers can be engineered with precise molecular weight, crystallinity, porosity, hydrophilicity[76], and degradation rates, enabling the fabrication of scaffolds tailored to the biological and mechanical requirements of specific tissues. These advantages have led to their widespread use in bone, cartilage, skin, vascular, neural, cardiac, and drug-delivery applications. Recent research has further expanded their utility through polymer blending, nanocomposite reinforcement, surface biofunctionalization, and advanced biofabrication techniques such as electrospinning and three-dimensional (3D) bioprinting[77].

Most synthetic biodegradable polymers used in tissue engineering belong to the family of **aliphatic polyesters**, which undergo hydrolytic degradation into biocompatible metabolites that are naturally metabolized or excreted. The degradation behaviour depends on polymer composition, crystallinity, molecular weight, porosity, and local physiological conditions. Current research focuses on matching scaffold degradation with tissue regeneration timelines to preserve structural integrity during healing while avoiding prolonged foreign-body responses[78].

4.2 Poly(Lactic Acid) (PLA)

Poly(lactic acid) (PLA) is one of the most extensively investigated biodegradable polymers because it is bio-based, biocompatible, biodegradable, and approved for numerous biomedical applications. It is synthesized through the ring-opening polymerization of lactide and degrades into lactic acid, which enters the tricarboxylic acid (TCA) cycle[89].

PLA exhibits:

- Excellent mechanical strength
- High tensile modulus
- Good processability
- Moderate degradation rate
- Low toxicity

These characteristics make PLA highly suitable for bone fixation devices, orthopedic implants, drug-delivery systems, tissue-engineering scaffolds, and biodegradable sutures.

Despite these advantages, PLA is relatively hydrophobic and brittle, limiting cellular attachment and flexibility. Consequently, researchers increasingly blend PLA with gelatin, collagen, polycaprolactone

(PCL), hydroxyapatite, graphene oxide, bioactive glass, and nanocellulose to improve biological performance and mechanical durability. Recent studies have also explored AI-assisted optimization of PLA scaffold architectures and 3D-printed patient-specific implants[80].

4.3 Poly(Glycolic Acid) (PGA)

Poly(glycolic acid) (PGA) was among the first biodegradable synthetic polymers introduced into clinical medicine, particularly as absorbable surgical sutures. PGA possesses high crystallinity, excellent tensile strength, and rapid hydrolytic degradation.

The degradation products are converted into glycolic acid, which is metabolized through normal physiological pathways[81].

PGA is commonly used for:

- Absorbable sutures
- Cartilage regeneration
- Bone tissue engineering
- Drug-delivery systems
- Temporary fixation devices

However, its rapid degradation may generate localized acidic environments capable of inducing inflammatory responses. Therefore, PGA is frequently copolymerized with PLA to produce PLGA, offering improved control over degradation kinetics.

4.4 Poly(Lactic-co-Glycolic Acid) (PLGA)

Poly(lactic-co-glycolic acid) (PLGA) is considered the gold standard biodegradable polymer for pharmaceutical and biomedical applications because its degradation profile can be precisely controlled by altering the lactic acid:glycolic acid ratio[82].

PLGA exhibits:

- Excellent biocompatibility
- Adjustable degradation
- Controlled drug release
- Ease of processing
- Regulatory acceptance for biomedical applications

PLGA has been extensively employed in:

- Controlled drug delivery

- Growth factor delivery
- Vaccine formulations
- Bone regeneration
- Cartilage repair
- Nerve conduits
- Injectable microspheres
- Tissue-engineering scaffolds

Recent investigations have demonstrated that PLGA coatings improve scaffold mechanical properties, osteointegration, and sustained therapeutic release, making PLGA a versatile platform for regenerative medicine.

4.5 Polycaprolactone (PCL)

Polycaprolactone (PCL) is a semicrystalline aliphatic polyester characterized by exceptional flexibility, excellent processability, and slow biodegradation. Unlike PLA and PGA, PCL maintains mechanical stability for prolonged periods, making it particularly suitable for tissues requiring extended regeneration[83].

Advantages include:

- Excellent flexibility
- High mechanical stability
- Easy electrospinning
- Excellent printability
- Low melting temperature
- Long-term structural support

Applications include:

- Bone regeneration
- Cartilage engineering
- Tendon repair
- Ligament reconstruction
- Skin substitutes
- Peripheral nerve regeneration
- Vascular grafts

Because PCL is hydrophobic and exhibits limited cell affinity, it is frequently combined with collagen, gelatin, chitosan, hydroxyapatite, graphene oxide, or bioactive glass. Recent reviews emphasize composite PCL scaffolds and AI-assisted scaffold optimization to enhance bioactivity and clinical translation.

4.6 Polyethylene Glycol (PEG)

Polyethylene glycol (PEG) is a hydrophilic synthetic polymer widely employed in hydrogel fabrication and drug-delivery systems[84].

PEG-based hydrogels provide:

- High water content
- Excellent biocompatibility
- Low protein adsorption
- Reduced immune recognition
- Tunable crosslinking

PEG itself lacks intrinsic cell-adhesion sites; therefore, it is commonly functionalized with collagen, gelatin, laminin, fibronectin, or RGD peptides to enhance cellular interactions.

Applications include injectable hydrogels, wound healing, cartilage engineering, ophthalmic biomaterials, and localized therapeutic delivery.

4.7 Polyhydroxyalkanoates (PHAs)

Polyhydroxyalkanoates are biodegradable polyesters synthesized naturally by microorganisms. Because of their renewable origin and excellent biocompatibility, PHAs have attracted increasing interest as sustainable scaffold materials[85].

Major advantages include:

- Excellent biodegradability
- Good mechanical properties
- Minimal inflammatory response
- Renewable production
- Controlled degradation

PHAs have demonstrated promising outcomes in cardiovascular tissue engineering, bone regeneration, peripheral nerve repair, wound healing, and biodegradable implant fabrication.

4.8 Emerging Synthetic Biodegradable Polymers

The latest generation of synthetic biomaterials extends beyond conventional PLA, PGA, and PCL.

Emerging polymers include[86]:

- Poly(glycerol sebacate) (PGS)
- Biodegradable polyurethanes
- Poly(trimethylene carbonate) (PTMC)
- Poly(propylene fumarate) (PPF)
- Shape-memory polymers
- Self-healing hydrogels
- Conductive biodegradable polymer composites

These materials are designed to provide enhanced elasticity, electrical conductivity, programmable degradation, and responsiveness to environmental stimuli, expanding their utility in cardiac, neural, and musculoskeletal tissue engineering. Functionalized conductive polymer composites are also being explored for electrically active tissues.

4.9 Comparative Advantages of Synthetic Polymers

Compared with natural polymers, synthetic biodegradable polymers offer[87]:

- Reproducible manufacturing
- Tunable degradation kinetics
- Superior mechanical strength
- Scalable industrial production
- Controlled porosity
- Excellent compatibility with electrospinning and 3D bioprinting
- Easier sterilization
- Better regulatory standardization

These advantages have made them the preferred platform for engineering patient-specific scaffolds and controlled drug-delivery systems.

4.10 Limitations

Despite their advantages, synthetic polymers present several limitations[88]:

- Hydrophobic surfaces reducing cell attachment
- Limited intrinsic bioactivity
- Acidic degradation products (particularly PLA and PGA)
- Delayed vascularization
- Potential foreign-body response
- Requirement for biofunctionalization

To overcome these challenges, contemporary research focuses on **hybrid scaffolds**, **polymer blends**, **nanocomposite reinforcement**, **surface modification**, and **AI-guided scaffold design** to improve biological performance while maintaining structural integrity.

5. Scaffold Fabrication Techniques

Scaffold fabrication techniques play a crucial role in determining the structural, mechanical, and biological properties of tissue-engineered scaffolds. An ideal fabrication technique should produce scaffolds with interconnected porosity, suitable mechanical strength, controlled biodegradation, and high biocompatibility to facilitate cell adhesion, proliferation, vascularization, and tissue regeneration. Over the past few decades, fabrication methods have evolved from conventional techniques to advanced biofabrication technologies that allow precise control over scaffold architecture[89].

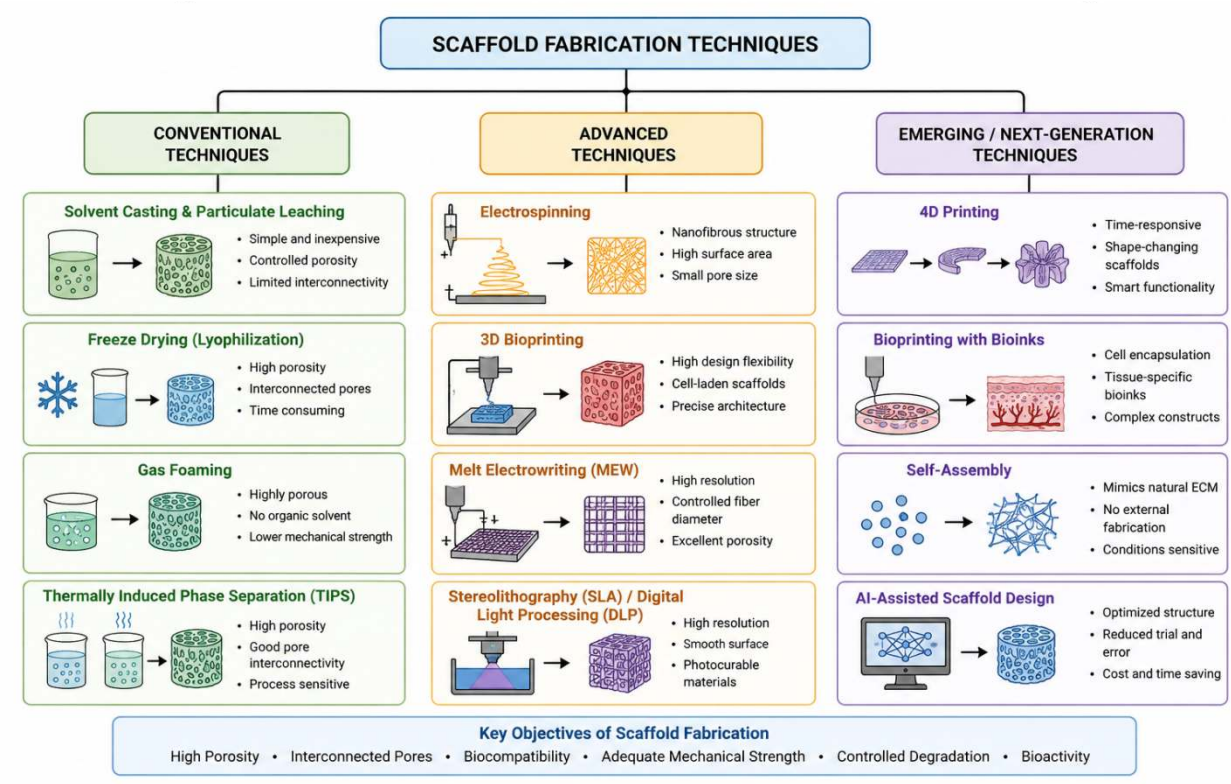

Figure 2. Overview of Conventional and Advanced Scaffold Fabrication Techniques

Solvent casting and particulate leaching (SCPL) is one of the earliest scaffold fabrication methods. In this technique, biodegradable polymers such as PLA or PLGA are dissolved in an organic solvent and mixed with porogens like sodium chloride. After solvent evaporation, the porogen is removed to create a porous scaffold. Although the method is simple and inexpensive, residual solvent toxicity and limited control over pore interconnectivity restrict its clinical application[90].

Freeze-drying (lyophilization) is widely used for fabricating highly porous scaffolds from natural polymers such as collagen, gelatin, chitosan, and alginate. Ice crystal formation followed by sublimation generates interconnected pores that support nutrient diffusion, cell infiltration, and extracellular matrix

deposition. However, freeze-dried scaffolds generally require crosslinking to improve their mechanical strength for load-bearing applications[91].

Gas foaming is a solvent-free method that employs compressed carbon dioxide to generate porous structures. The absence of organic solvents preserves the biological activity of incorporated drugs and growth factors, although pore interconnectivity remains relatively poor compared with other fabrication techniques. **Thermally induced phase separation (TIPS)** produces highly porous scaffolds with controlled microstructures by separating polymer-rich and polymer-poor phases during cooling. TIPS offers better control over pore morphology but requires specialized equipment and longer processing times[92].

Among advanced fabrication methods, **electrospinning** has become one of the most extensively investigated technologies because it produces nanofibrous scaffolds that closely mimic the architecture of the native extracellular matrix. Electrospun scaffolds possess high surface area, interconnected fibers, and excellent cell adhesion, making them suitable for skin, nerve, vascular, and musculoskeletal tissue engineering. Recent advances, including coaxial electrospinning and hybrid electrospinning–3D printing approaches, have further improved drug loading, mechanical performance, and cell infiltration[93].

Three-dimensional (3D) bioprinting has revolutionized scaffold fabrication by enabling layer-by-layer deposition of biodegradable polymers, bioinks, living cells, and bioactive molecules with high precision. This technology allows the fabrication of patient-specific scaffolds with controlled pore geometry and mechanical properties. More recently, **4D bioprinting** has emerged as an extension of 3D bioprinting, utilizing stimuli-responsive materials capable of changing shape or function after implantation, thereby improving tissue maturation and regenerative outcomes[94].

Overall, no single fabrication technique satisfies all the requirements of tissue engineering. Consequently, current research focuses on combining conventional and advanced fabrication methods to produce multifunctional scaffolds with optimized mechanical properties, controlled biodegradation, enhanced bioactivity, and improved clinical translation.

6. Drug Delivery and Growth Factors in Biodegradable Scaffolds

6.1 Introduction

The integration of drug delivery systems and bioactive growth factors into biodegradable scaffolds has transformed tissue engineering from a passive structural approach into an active therapeutic strategy. Traditional scaffolds primarily provided temporary mechanical support; however, modern scaffolds are designed as multifunctional platforms capable of delivering therapeutic agents, growth factors, stem cells, genes, and extracellular vesicles in a controlled and localized manner. This localized delivery enhances tissue regeneration while minimizing systemic toxicity and improving therapeutic efficacy. The combination of biodegradable polymers with controlled drug release technologies has become one

of the most significant advances in regenerative medicine, particularly for bone, cartilage, skin, cardiovascular, neural, and musculoskeletal tissue engineering[95].

6.2 Drug Delivery through Biodegradable Scaffolds

Biodegradable scaffolds serve as localized drug delivery systems by encapsulating therapeutic agents within the polymer matrix. As the scaffold gradually degrades, the incorporated drug is released in a controlled manner, maintaining an effective local concentration over an extended period. Compared with conventional systemic administration, scaffold-mediated drug delivery offers several advantages, including reduced dosing frequency, lower systemic adverse effects, enhanced patient compliance, and site-specific therapy[96].

A wide range of therapeutic agents can be incorporated into biodegradable scaffolds, including antibiotics, anti-inflammatory drugs, analgesics, anticancer agents, antioxidants, immunomodulators, peptides, nucleic acids, and nanoparticles. In orthopedic applications, antibiotic-loaded scaffolds help prevent implant-associated infections, whereas anti-inflammatory agents reduce excessive inflammatory responses and promote tissue healing. Similarly, anticancer drug-loaded biodegradable scaffolds have demonstrated promising outcomes in preventing local tumor recurrence following surgical resection[97].

Drug release from biodegradable scaffolds generally occurs through diffusion, polymer degradation, swelling, or a combination of these mechanisms. The release profile depends on polymer composition, molecular weight, porosity, cross-linking density, drug properties, and scaffold architecture. Contemporary research emphasizes sustained and stimuli-responsive drug delivery systems that release therapeutic molecules in response to physiological triggers such as pH, temperature, enzymes, or reactive oxygen species[98].

6.3 Growth Factors in Tissue Engineering

Growth factors are biologically active signaling proteins that regulate essential cellular processes, including proliferation, migration, differentiation, angiogenesis, extracellular matrix synthesis, and tissue remodeling. Their incorporation into biodegradable scaffolds significantly enhances regenerative outcomes by recreating the biochemical microenvironment of native tissues[99].

Among the most widely investigated growth factors are:

- **Bone Morphogenetic Proteins (BMP-2 and BMP-7):** Promote osteogenic differentiation and bone formation.
- **Vascular Endothelial Growth Factor (VEGF):** Stimulates angiogenesis and improves blood vessel formation.
- **Transforming Growth Factor-β (TGF-β):** Regulates cartilage formation, extracellular matrix deposition, and wound healing.

- **Platelet-Derived Growth Factor (PDGF):** Enhances fibroblast proliferation and tissue repair.
- **Fibroblast Growth Factors (FGFs):** Promote angiogenesis, cell proliferation, and tissue regeneration.
- **Insulin-Like Growth Factor (IGF):** Supports cartilage repair and musculoskeletal regeneration.
- **Epidermal Growth Factor (EGF):** Accelerates epithelialization and skin wound healing.

The therapeutic success of growth factors depends not only on their biological activity but also on maintaining appropriate concentrations at the target site. Therefore, biodegradable scaffolds provide an ideal platform for sustained and localized growth factor delivery[100].

Table 3. Major Growth Factors Used in Tissue Engineering

Growth Factor	Biological Function	Major Tissue Applications
BMP-2	Osteogenesis	Bone
VEGF	Angiogenesis	Skin, Bone
TGF-β	Chondrogenesis	Cartilage
PDGF	Cell proliferation	Skin
FGF	Cell growth	Blood vessels
EGF	Epithelial regeneration	Skin
IGF	Tissue regeneration	Cartilage

6.4 Controlled Release Strategies

Several strategies have been developed to achieve controlled release of drugs and growth factors from biodegradable scaffolds. Physical encapsulation is the simplest approach, where therapeutic molecules are entrapped within the polymer matrix during scaffold fabrication. Chemical conjugation involves covalent attachment of bioactive molecules to polymer chains, allowing more sustained release. Nanoparticle-mediated delivery, microsphere incorporation, hydrogel encapsulation, and multilayer scaffold systems have further improved release kinetics and therapeutic efficiency[101].

Recent research has also explored dual-delivery systems capable of releasing multiple bioactive molecules sequentially. For example, an initial release of VEGF promotes angiogenesis, followed by sustained BMP-2 release to stimulate bone regeneration. Such sequential delivery better mimics natural tissue healing processes.

6.5 Stem Cells and Extracellular Vesicles

Biodegradable scaffolds increasingly function as carriers for stem cells and stem-cell-derived extracellular vesicles (EVs). Mesenchymal stem cells (MSCs), adipose-derived stem cells, induced pluripotent stem cells, and dental pulp stem cells have demonstrated remarkable regenerative potential[102].

More recently, extracellular vesicles and exosomes have attracted considerable attention because they deliver proteins, lipids, messenger RNA, and microRNA without the risks associated with live-cell transplantation. EV-loaded scaffolds have shown promising outcomes in enhancing angiogenesis, modulating inflammation, promoting extracellular matrix synthesis, and accelerating tissue repair.

6.6 Gene Delivery and Emerging Therapeutic Approaches

Gene-activated scaffolds represent an emerging strategy in regenerative medicine. Instead of directly delivering proteins, these scaffolds deliver plasmid DNA, messenger RNA (mRNA), small interfering RNA (siRNA), or CRISPR-based systems that enable host cells to produce therapeutic proteins locally. This approach provides prolonged biological activity while reducing the need for repeated administration of recombinant growth factors[103].

Nanotechnology has further enhanced gene delivery efficiency through the incorporation of lipid nanoparticles, polymeric nanoparticles, and inorganic nanocarriers within biodegradable scaffolds.

6.7 Biomedical Applications

Drug- and growth-factor-loaded biodegradable scaffolds have demonstrated promising applications across multiple clinical specialties[104]:

- **Bone regeneration:** BMP-2, VEGF, and hydroxyapatite-loaded scaffolds enhance osteogenesis and vascularization.
- **Cartilage repair:** TGF-β and IGF promote chondrogenic differentiation and extracellular matrix formation.
- **Skin tissue engineering:** EGF, PDGF, antimicrobial agents, and silver nanoparticles accelerate wound healing and reduce infection.
- **Nerve regeneration:** Neurotrophic factors such as NGF and BDNF support axonal growth and functional recovery.
- **Cardiovascular tissue engineering:** VEGF and angiogenic peptides improve neovascularization and myocardial repair.
- **Cancer therapy:** Localized anticancer drug-loaded scaffolds minimize systemic toxicity and reduce postoperative tumor recurrence.

6.8 Recent Advances and Future Perspectives

Recent developments have shifted scaffold-based drug delivery toward smart and personalized therapeutic platforms. Stimuli-responsive biodegradable polymers, injectable hydrogels, 3D-bioprinted drug-loaded scaffolds, nanocomposite systems, and AI-assisted optimization of drug release kinetics are expected to play a central role in the next generation of regenerative medicine. Additionally, combination therapies integrating drugs, growth factors, stem cells, and extracellular vesicles within a single scaffold are increasingly being investigated to achieve synergistic regenerative effects[105].

Despite significant progress, challenges remain in maintaining long-term bioactivity of growth factors, preventing burst drug release, reducing manufacturing costs, and translating laboratory findings into routine clinical practice. Continued advances in biomaterials engineering, pharmaceutical sciences, nanotechnology, and computational modeling are expected to overcome these limitations and facilitate the development of highly effective scaffold-based regenerative therapies.

7. Recent Advances (2024–2026)

The period from **2024 to 2026** has witnessed remarkable progress in biodegradable polymer-based tissue engineering, driven by innovations in biomaterials science, additive manufacturing, nanotechnology, artificial intelligence (AI), and regenerative medicine. Current research has shifted scaffold development from passive structural matrices toward multifunctional, bioactive, and patient-specific platforms capable of simultaneously supporting tissue regeneration, controlled drug delivery, immunomodulation, and real-time biological interaction[106].

One of the most significant advances has been the development of **hybrid biodegradable scaffolds** that combine natural polymers (collagen, gelatin, chitosan, and hyaluronic acid) with synthetic polymers such as PLA, PLGA, and PCL. These hybrid systems integrate the excellent bioactivity of natural biomaterials with the superior mechanical strength and controlled degradation of synthetic polymers, resulting in improved cell adhesion, angiogenesis, and long-term structural stability[107].

Three-dimensional (3D) bioprinting has continued to evolve as a key fabrication technology, enabling the production of patient-specific scaffolds with precise control over pore size, geometry, and mechanical properties. Recent studies have focused on multi-material bioprinting, vascularized tissue constructs, and personalized implants that closely mimic native tissue architecture. Emerging **4D bioprinting** further extends this concept by using stimuli-responsive biomaterials capable of changing their shape or function after implantation in response to temperature, pH, moisture, or mechanical forces, thereby improving tissue maturation and functional integration[108].

Another important trend is the rapid expansion of **smart biodegradable biomaterials**. Shape-memory polymers, self-healing hydrogels, electrically conductive scaffolds, and enzyme-responsive materials are being designed to actively respond to the physiological environment. Such smart scaffolds can

release drugs on demand, promote cell differentiation, and dynamically adapt to tissue remodeling, making them highly attractive for neural, cardiac, and musculoskeletal tissue engineering[109].

Nanotechnology has further enhanced scaffold performance through the incorporation of nanoparticles, nanofibers, graphene derivatives, bioactive ceramics, and metallic nanomaterials. Nanoengineered scaffolds exhibit increased surface area, improved protein adsorption, enhanced osteogenesis, antimicrobial activity, and controlled release of therapeutic agents. Electrospun nanofibrous scaffolds continue to demonstrate exceptional promise because they closely mimic the nanoscale architecture of the extracellular matrix, thereby improving cellular attachment and tissue regeneration[110].

Recent investigations have also highlighted the growing importance of **extracellular vesicles (EVs) and exosome-loaded scaffolds** as cell-free regenerative therapies. Compared with stem-cell transplantation, exosome-based systems reduce immunological concerns while promoting angiogenesis, immunomodulation, extracellular matrix remodeling, and tissue repair. These platforms are increasingly being combined with biodegradable polymers to improve therapeutic efficacy and simplify clinical translation[111].

A major emerging direction is the application of **artificial intelligence (AI) and machine learning** in scaffold engineering. AI algorithms are being used to optimize scaffold architecture, predict degradation kinetics, identify optimal polymer combinations, and personalize scaffold design according to patient-specific anatomical and biomechanical requirements. Computational modeling has also accelerated biomaterial discovery while reducing experimental time and manufacturing costs[112].

Sustainability has become another research priority. Recent work has emphasized **green and solvent-free manufacturing technologies**, including supercritical CO_2 processing and melt electrowriting, to reduce residual solvent toxicity, improve scalability, and support environmentally responsible production of biodegradable scaffolds. These approaches are expected to facilitate industrial-scale manufacturing while maintaining scaffold quality and regulatory compliance[110].

The translation of biodegradable scaffolds into clinical practice has also advanced. Researchers are increasingly developing multifunctional scaffolds that integrate **drug delivery, growth factors, antimicrobial agents, and bioactive nanoparticles** into a single construct. Such systems provide structural support while simultaneously preventing infection, promoting vascularization, and accelerating tissue regeneration. Recent preclinical studies have demonstrated encouraging outcomes in bone, cartilage, skin, cardiovascular, and neural tissue engineering[113].

Overall, recent advances indicate that the future of tissue engineering will rely on **personalized, intelligent, multifunctional, and clinically translatable biodegradable scaffolds**. Continued integration of advanced biomaterials, AI-driven design, sustainable manufacturing, nanotechnology, and precision medicine is expected to overcome existing translational barriers and substantially improve regenerative therapies across a wide range of clinical applications.

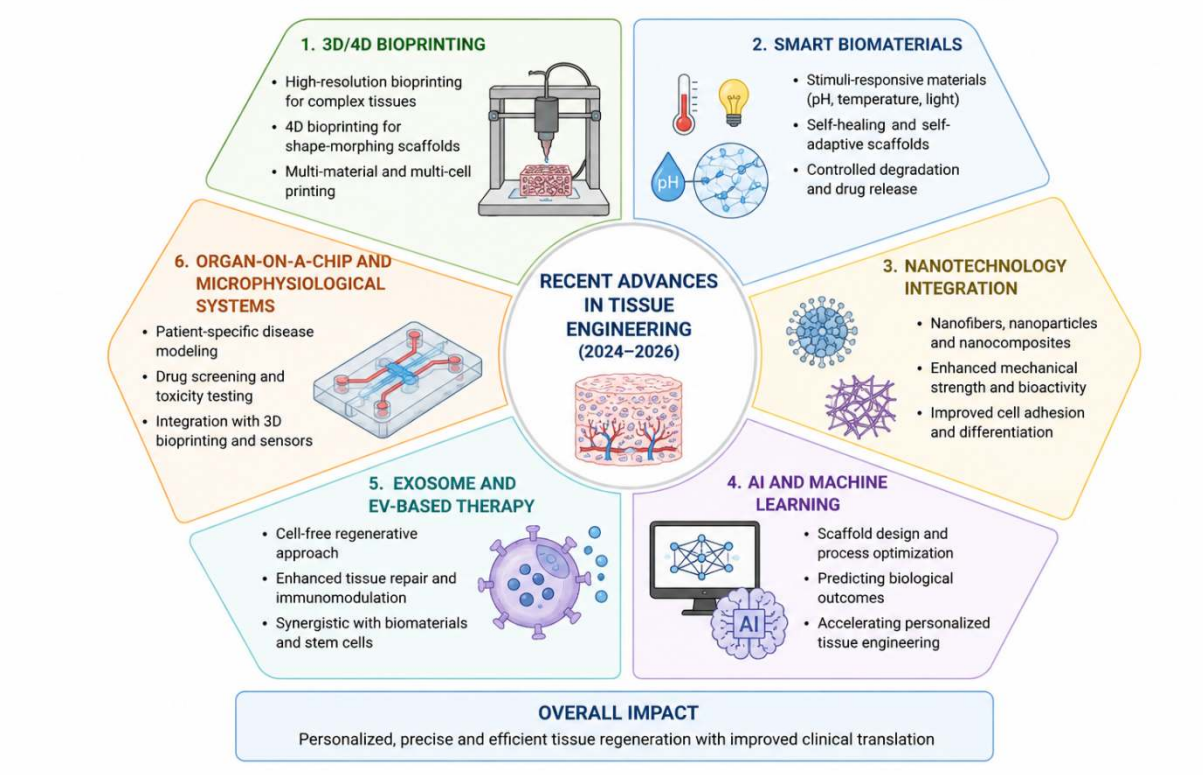

Figure 3. Recent Advances in Tissue Engineering (2024-2026)

8.1 Challenges

Despite remarkable advancements in biodegradable polymer-based scaffolds, several scientific, engineering, and clinical challenges continue to limit their widespread clinical translation. One of the most significant obstacles is achieving an optimal balance between scaffold degradation and tissue regeneration. Premature degradation may result in insufficient mechanical support, whereas prolonged persistence of scaffold materials can delay tissue remodeling and induce chronic inflammatory responses. Therefore, designing scaffolds with degradation kinetics that closely match the healing rate of specific tissues remains a major research priority[114].

Another critical challenge is the recreation of the complex native extracellular matrix (ECM). Although considerable progress has been made in biomimetic scaffold design, replicating the hierarchical architecture, biochemical composition, and mechanical properties of natural tissues remains difficult. Inadequate pore interconnectivity, non-uniform cell distribution, and poor nutrient diffusion often lead to reduced cell viability, particularly in large or highly vascularized tissues.

Insufficient vascularization is another major limitation in tissue engineering. Thick or highly metabolic tissues require rapid blood vessel formation to ensure adequate oxygen and nutrient supply. However,

delayed angiogenesis frequently results in cell death, impaired tissue integration, and reduced regenerative outcomes. Developing scaffolds that promote rapid neovascularization through angiogenic factors, bioactive materials, and vascular network engineering remains an active area of research[115].

Immune responses and biomaterial-associated inflammation also represent significant challenges. Although biodegradable polymers are generally biocompatible, degradation products, residual solvents, or manufacturing impurities may trigger inflammatory reactions that compromise scaffold performance and tissue healing. Therefore, improving material purity, surface biofunctionalization, and immunomodulatory properties is essential for long-term clinical success.

From a manufacturing perspective, producing scaffolds with consistent quality, reproducibility, and scalability under Good Manufacturing Practice (GMP) conditions remains difficult. Variations in polymer composition, fabrication techniques, sterilization methods, and storage conditions may influence scaffold performance. Furthermore, advanced technologies such as 3D bioprinting and nanofabrication require sophisticated equipment and specialized expertise, increasing production costs and limiting accessibility.

Regulatory approval presents another important challenge. Tissue-engineered products incorporating biodegradable polymers, living cells, growth factors, or gene therapy components require rigorous evaluation for safety, efficacy, quality control, and long-term biocompatibility. The absence of globally harmonized regulatory guidelines often delays commercialization and clinical implementation[116].

Finally, the high cost of biomaterials, fabrication technologies, preclinical evaluation, and clinical trials remains a significant barrier, particularly in low- and middle-income countries. Reducing manufacturing costs while maintaining scaffold quality and therapeutic performance is essential for expanding the clinical availability of regenerative therapies.

8.2 Future Perspectives

The future of tissue engineering is expected to be driven by the development of intelligent, multifunctional, and patient-specific biodegradable scaffolds. Emerging biomaterials capable of responding to physiological stimuli such as pH, temperature, enzymes, electrical signals, or mechanical forces are likely to enable dynamic regulation of drug release, cell behavior, and tissue regeneration. These smart biomaterials may significantly improve therapeutic precision and clinical outcomes.

Artificial intelligence (AI), machine learning, and computational modeling are anticipated to play an increasingly important role in scaffold design by optimizing material selection, predicting degradation behavior, personalizing scaffold architecture, and accelerating biomaterial discovery. The integration of AI with additive manufacturing technologies may facilitate rapid fabrication of customized scaffolds tailored to individual patient anatomy and disease conditions[117].

Advanced biofabrication technologies, including 3D and 4D bioprinting, are expected to revolutionize regenerative medicine by enabling the fabrication of highly organized tissue constructs with precise spatial distribution of cells, biomaterials, and bioactive molecules. Dynamic 4D scaffolds capable of adapting to physiological conditions may further enhance tissue maturation and long-term functionality.

Another promising direction involves the development of multifunctional scaffolds that simultaneously combine controlled drug delivery, stem cell therapy, extracellular vesicles, antimicrobial agents, growth factors, biosensors, and immunomodulatory molecules within a single biodegradable platform. Such integrated systems may promote more efficient tissue regeneration while reducing complications associated with infection and inflammation[118].

Sustainable biomaterial development is also gaining considerable attention. Environmentally friendly manufacturing processes, renewable polymer sources, and solvent-free fabrication technologies are expected to improve both environmental sustainability and industrial scalability. In addition, increasing collaboration among biomaterial scientists, biomedical engineers, clinicians, pharmaceutical researchers, and regulatory agencies will be essential for accelerating clinical translation.

Future research should also emphasize long-term clinical studies, standardized evaluation protocols, personalized regenerative therapies, and cost-effective manufacturing strategies to facilitate routine clinical application of biodegradable scaffold technologies.

8.3 Conclusion

Biodegradable polymeric scaffolds have emerged as a cornerstone of modern tissue engineering and regenerative medicine by providing temporary structural support while actively promoting cellular adhesion, proliferation, differentiation, extracellular matrix formation, and tissue remodeling. Both natural and synthetic biodegradable polymers possess unique advantages that can be strategically combined to fabricate biomimetic scaffolds with enhanced biological performance and mechanical stability.

Significant advances in scaffold fabrication technologies, nanotechnology, controlled drug delivery, growth factor incorporation, stem cell engineering, and additive manufacturing have substantially expanded the therapeutic potential of tissue-engineered constructs. Recent developments in smart biomaterials, hybrid polymer systems, AI-assisted scaffold design, and 3D/4D bioprinting are further transforming scaffold engineering toward personalized and precision regenerative medicine.

Despite these achievements, challenges related to vascularization, immune compatibility, degradation control, large-scale manufacturing, regulatory approval, and clinical translation remain. Addressing these limitations through multidisciplinary research and technological innovation will be critical for the successful commercialization of biodegradable scaffold-based therapies.

Overall, biodegradable polymers are expected to play an increasingly important role in the next generation of regenerative medicine. Continued advances in biomaterials science, pharmaceutical technology, biofabrication, nanotechnology, and computational design will facilitate the development of safer, more effective, and clinically translatable scaffold systems capable of improving patient outcomes across a broad spectrum of tissue engineering applications.

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