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Scaffolds Applied in Tissue Engineering: A Review on Previous Gains and Challenges

(Review Article)

Abstract

Tissue engineering is a modern and interdisciplinary science that examines the methods used in the structural and functional restoration of damaged tissues. One of the most important steps in tissue engineering is to prepare a suitable scaffold with characteristics compatible with the target tissue. In recent years, many scaffolds have been prepared, to repair different tissues. The present study examines recent research in the preparation of scaffolds in various tissue engineering. Many scaffolds including composites, nanofibers, hydrogels, synthetic or semi-synthetic polymers and ceramics have been prepared and used. Some scaffolds are also obtained during decellularization of natural tissues. Various methods, like electrospinning or 3D printing, have been used to prepare synthetic scaffolds. However, there is a need for more in-vivo studies to ensure the proper functioning of these scaffolds in in-body conditions.

Keywords: Tissue engineering, Regenerative medicine, Tissue scaffolds, Composite tissue allograft.

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Introduction

Tissue engineering is a multidisciplinary field that involves the development of biomaterials and techniques to create functional biological tissues to replace or repair damaged organs in the human body. The importance of tissue engineering lies in its potential to revolutionize regenerative medicine by providing alternatives to organ transplantation, promoting tissue repair and regeneration, and advancing drug testing and development(1).

Scaffold types in tissue engineering can be categorized into natural scaffolds (derived from biological sources like collagen or fibrin) and synthetic scaffolds (artificially created materials like polymeric nanofibers or hydrogels). These structures provide support for cell growth and tissue regeneration in biomedical applications(2).

However, this approach faces challenges such as providing suitable scaffolds. The scaffolds must not only mimic the structural, mechanical, and chemical properties of the tissue's natural extracellular matrix (ECM) but also possess adequate strength, biodegradability, biocompatibility, and the ability to deliver signals necessary for stem cell differentiation(3-8). In fact, the properties of the scaffold used play a crucial role in the success or failure of tissue repair in tissue engineering(9), a topic that has attracted considerable attention from researchers in recent years. Recently, due to technological advancements, a variety of scaffolds have been developed through different methods for use in tissue engineering(10,11). Although these developments have faced multiple challenges, they have also achieved significant successes. However, further studies are needed to address existing issues in previous research and achieve the most effective scaffolds. This study aims to review current research to highlight recent advancements in the design of tissue engineering scaffolds.

Newly Developed Scaffolds for Tissue Engineering Applications

In recent years, various scaffolds have been employed for engineering different tissues. Table 1 provides a summary of these scaffolds and the tissues they are designed to repair.

Biodegradable aliphatic polyesters

Biodegradable and biocompatible aliphatic polyesters with tunable physical, chemical, and biological properties are among the best scaffolds used in tissue engineering(30).

Polylactic acid (PLA)

This polyester is based on hydroxyalkanoic acids and derived from lactic acid monomers. Since it is obtained through sugar fermentation, it is considered environmentally friendly. Various methods are available for synthesizing this polymer, with the most important ones being ring-opening polymerization of cyclic dilactide monomers with a metal catalyst, melt deposition, and electrospinning.

Despite its favorable properties, PLA has some drawbacks, such as slow degradation, high crystallinity, and hydrophobicity, which can be addressed by combining it with other compounds like gelatin, graphene, and laponite(12-14,30)

Polyglycolic acid and poly lactic-co-glycolic acid

Polyglycolic acid (PLGA), being synthetic, has controllable properties and is capable of molding and tissue adaptability. Synthesis methods for this polymer include condensation and ring-opening polymerization, with copolymerization being the most common method for modifying its structure and function(30). For example, Abutalebi and colleagues enhanced the antibacterial properties of these scaffolds by adding zinc oxide for use in bone tissue engineering(15).

Polycaprolactone

Polycaprolactone (PCL) is a biocompatible polymer obtained through ring-opening polymerization of caprolactone.

Adding other compounds to it can enhance properties like cell viability, strength, and elasticity(30). For instance, combining this scaffold with keratin and carbon nanotubes increases porosity, adhesion, and cell viability(16). Additionally, crosslinking this polymer with polyethylene glycol and combining it with apatite creates a scaffold with suitable strength and mechanical properties for bone tissue engineering(17).

Polyhydroxyalkanoates

These polymers are produced and stored by many microorganisms as energy and carbon granules(30). For example, according to existing research, they can even be derived using activated sludge from urban wastewater treatment cultivated in reactors (with a cell retention time of 5 days and a hydraulic retention time of 10 hours). However, the internal conditions of the reactor, such as pH, feed composition, and gas ventilation, significantly impact the quality and quantity of the resulting polymer(31).

Table 1: Application of scaffolds from each material in the repair of various tissues.

Material	Tissue
Poly lactic acid(12)	Bone
Poly lactic acid/gelatin/graphene(13)	Bone
Poly lactic acid/ Laponite(14)	Bone
Poly lactic co glycolic acid(15)	Bone
Polycaprolactone/ Creatine /Carbon nano tube(16)	Bone
Poly ethylene glycol/Poly caprolactone/Apatite(17)	Bone
Apatite	Bone
Chitosan /Hyaluronic acid(18)	Wound
Poly caprolactone(19-21)	Vein/ Cartilage/ Nerve/ Adipose
Nano colinopetilolite/Gelatine/ β-TCP(22)	Jaw
Polyurethane/ Polyethylene tereftalat /Poly caprolactone(23)	Vein
Poly urethane(24,25)	Vein/Vagina
Collagen/Fibroine(26)	Cornea
Fibroin/ Titanium/ Flour(27)	.Bone
Katira(28)	Cartilage
Titanium/ Akremanit(29)	Bone

Nanostructured Apatite Scaffolds

Apatitic scaffolds, due to their high structural similarity to bone tissue, structural stability, mechanical strength, and biocompatibility, are influential factors in bone tissue engineering(31). Additionally, combining these scaffolds with materials such as ostrich eggshell, polycaprolactone, platelet-rich fibrin, carboxymethyl chitosan, and barium titanate improves the properties of the mentioned scaffolds(32-37). However, some studies indicate a greater impact of natural apatitic scaffolds derived from bone tissue compared to synthetic scaffolds(38).

Composite Scaffolds

Various composites with diverse compositions are used in tissue engineering for the repair of tissues such as bone. These scaffolds are constructed by combining biocompatible and bioactive materials like polycaprolactone, apatite, and gelatin to provide suitable mechanical properties while also enhancing biological characteristics. Additionally, the incorporation of antibiotics such as tetracycline can prevent infections(39-43).

Conductive Nanofibrous Scaffolds

Conductive scaffolds are used in the engineering of electroactive tissues such as heart, nerve, and bone. These scaffolds can be created by combining conductive organic materials with nanostructures. The nanostructures employed include a wide range of materials such as graphene, carbon nanotubes, and metal nanoparticles like gold.

Nano-structured apatite scaffolds

Apatite scaffolds are significant in bone tissue engineering due to their high structural similarity to bone tissue, structural stability, mechanical strength, and biocompatibility(32). The combination of these scaffolds with materials such as ostrich eggshell, polycaprolactone, platelet-rich fibrin, carboxymethyl chitosan, and barium titanate enhances their properties(33-38). However, some studies indicate that natural apatite scaffolds derived from bone tissue have a greater impact compared to synthetic scaffolds(39).

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Intrinsically conductive polymers

These polymers have found diverse applications in medicine due to their electrical conductivity, particularly in fields such as biosensors and implantable electronic devices. However, one major challenge in tissue engineering is the inherent non-degradability of these materials, which can be modified through combination with other substances.

Polypyrrole

Polypyrrole is one of the most well-known synthetic conductive polymers. This amorphous and opaque polymer is derived from water-soluble monomers. Due to features like ease of synthesis, modifiability, and stability, it is used in various applications, including biosensors and drug delivery(45).

Polyaniline

Polyaniline is a polymer produced by the redox polymerization of aniline under acidic conditions. It exhibits electrical conductivity and various colors in different oxidation states, making it of interest for use in tissue engineering for skin, nerve, and bone(46).

Polyethylene dioxythiophene (PEDOT)

This polymer is one of the most successful derivatives of thiophene, known for its high conductivity, thermal stability, and superior electrochemical properties. It has wide applications in electronic devices, bio-transistors, and bio-scaffolds for electrical stimulation.

Intrinsically conductive polymers

Carbon nanotubes

Due to their high electrical conductivity and stability, carbon nanotubes have found extensive applications in tissue engineering and nanotechnology. These nanomaterials can be used as substitutes or complements to intrinsically conductive polymers(47).

Graphene and graphene oxide

Graphene and its derivatives, such as graphene oxide, have attracted significant attention from researchers because of their electrical, thermal, and optical properties, which are very similar to those of carbon nanotubes. These materials are used in the design of conductive and smart scaffolds in tissue engineering(48).

Scaffolds based on neuroprotection of cerium oxide nanoparticles

In nerve tissue engineering, scaffolds made from allogenic tissues are favored due to their similarity to the natural environment and reduced immunogenicity.

One major challenge in nerve injury repair is the generation of free radicals, which can be managed using cerium oxide nanoparticles as antioxidants. These nanoparticles help neutralize reactive oxygen species due to their activity similar to that of superoxide dismutase and catalase(49).

Nanoclinoptilolite scaffold, gelatin and β-TCP

Composites made from biomaterials like gelatin and beta-tricalcium phosphate (β-TCP) are widely used in jaw tissue engineering. However, these composites have low strength, which significantly limits their extensive application(22).

Natural scaffolds

Natural biomaterial scaffolds are used in tissue engineering applications, such as cartilage, due to their favorable properties. These materials include chitosan, collagen/gelatin, alginate, fibrin, elastin, heparin, chondroitin sulfate, and hyaluronic acid. Despite their superior biological properties compared to synthetic types, they have limitations such as the risk of contamination, immunogenicity, limited production, and low mechanical strength. To address these challenges, synthetic scaffolds like polyglycolic acid (PGA), polyethylene oxide (PEO), polylactic acid (PLA), and polyethylene glycol (PEG) have gained attention(50-52).

Nanostructured scaffolds

Nanotechnology is a valuable tool for creating scaffolds that mimic the extracellular matrix in tissue engineering. Natural tissues, organs, and cells directly interact with nanostructured matrices. Nanofibers, including nanotubes, electrospun nanofibers, and nanoparticles, provide a promising nano-scale platform for applications in tissue engineering, such as cartilage(50).

Polyurethane based scaffolds

Polyurethane scaffolds are of great interest in tissue engineering, particularly for vascular and vaginal tissue regeneration(21,23,25). These scaffolds are prepared using nanotechnology techniques like electrospinning, and the nanometric fiber diameter allows for a strong resemblance to the natural matrix. Additionally, combining these scaffolds with polymers such as polycaprolactone and polyethylene terephthalate helps replicate the structure of vascular matrices(23,24).

Porous hybrid scaffolds based on PEPC

The research by Aghmioni and colleagues(52,53) indicates that the combination of polymers used in scaffold preparation plays a crucial role in providing the necessary microenvironment and substrate for tissue engineering. The study showed that PCP and PEPC scaffolds exhibited different biomechanical and biochemical behaviors, with the hybrid PCP scaffold being more suitable for soft tissue engineering.

Decellularized Scaffolds from Natural Matrices

One of the novel methods involves decellularizing natural scaffolds. In this approach, researchers use physical, chemical, or enzymatic methods to remove cells from the tissue without damaging the extracellular matrix (ECM), resulting in suitable scaffolds. For instance, in recent years, numerous scaffolds have been prepared through decellularization of tissues such as mouse testis, sciatic nerve, sheep bladder, and bovine trabecular bone tissue(54,57).

Hydrogels

Hydrogels are three-dimensional polymeric networks that are insoluble in water, cross-linked through chemical or physical methods. A key feature of hydrogels is their high capacity to absorb water or biological fluids(58). Structurally, hydrogels simulate the matrix differently compared to traditional three-dimensional scaffolds. They are derived from natural or synthetic polar monomers. Today, synthetic hydrogels have replaced natural ones due to their improved properties(59).

Fibrin scaffolds

Fibrin's significant properties, such as biocompatibility, physiological structure, ability to promote cell infiltration, and tissue regeneration through its degradation derivatives, have led to its widespread application in regenerative medicine, orthopedics, wound healing, and skin reconstruction(60).

Albumin-Based Scaffolds

Due to its abundance in the human body and unique structural characteristics, albumin is a biocompatible, biodegradable, and physiologically stable protein(61). These properties contribute to its various applications, such as being combined with other materials to create scaffolds or used as a coating for fabricated scaffolds(62).

Collagen/silk fibroin nanofiber scaffold

Zargar et al.(26) emonstrated that nanofiber scaffolds containing fibroin and collagen can aid in corneal epithelium repair. Additionally, the combination of fibroin with fluorinated titanium nanoparticles has shown suitable bioactivity for bone tissue engineering. Another study indicated that electrospun fibroin, even without additional modifications, has the potential to enhance the proliferation of mesenchymal stem cells(27-63).

Hardistonite

Calcium/silicate ceramics have a wide range of applications in tissue engineering due to their diverse properties. Hardystonite is one such ceramic. Sadeghzadeh et al.(64) were the first to produce bioactive hardystonite powder and scaffolds using mechanical alloying and pore-forming agents.

Katira hydrogel

In a study, a hydrogel was synthesized using katira gum containing tyramine, horseradish peroxidase enzyme, and hydrogen peroxide. The differentiation of mesenchymal stem cells into chondrocytes was confirmed through various assays(28).

Nano apatite/PLGA composite scaffold

Tabtar Ahangar(65) developed an apatite matrix similar to human trabecular bone by pyrolyzing bovine femur bone and enhancing its properties through the combination with PLGA and copper.

3D Gelatin-Laminin Scaffold

A study demonstrated the effectiveness of coating a three-dimensional gelatin scaffold with laminin to facilitate the differentiation of mouse adipose-derived mesenchymal stem cells into hepatocyte-like cells(66).

Polycaprolactone/keratin scaffold reinforced with COOH-MWCNT

In the research of Mirhaj et al.(67), the biocompatibility of polycaprolactone, polycaprolactone/ keratin, and polycaprolactone/ keratin scaffolds reinforced with carboxyl-functionalized multi-walled carbon nanotubes (COOH-MWCNT) was compared during electrospinning. The findings indicated that COOH-MWCNT provided effective reinforcement for the osteogenic differentiation of mesenchymal stem cells

Porous titanium scaffold covered with ackermanite

In a study(29), akermanite coating was prepared using the sol-gel method to enhance the properties of a porous titanium scaffold created with sodium chloride as a porogen. Bioactivity assessments (using simulated body fluid), scanning electron microscopy images, and X-ray diffraction analysis demonstrated the scaffold's suitability for bone tissue engineering.

Methods Used for Fabricating Tissue Engineering Scaffolds

Electrospinning (ES)

Electrospinning is one of the most efficient methods for fabricating nanostructured scaffolds, and it is widely used compared to other techniques. During ES, a polymer solution is processed into nanofibers (ranging from nanometer to micrometer in diameter) that have a high surface-to-volume ratio and are suitable for cell interactions. By controlling the voltage and solution properties, the characteristics of the resulting fibers can be adjusted. This versatility makes electrospinning highly popular among tissue engineers for nanofiber fabrication(68,69).

Despite its widespread use, ES has challenges, such as the random alignment of polymers affecting pore size. To address these issues, melt electrospinning (MES) is recommended(70,71).

In MES, polymers are melted by passing through a heater, and a jet initiation system is used to shape and collect the fibers(72).

Emulsion freeze drying

In this method, an emulsion is created by mixing a polymer solution with water. The emulsion is then rapidly cooled and frozen, resulting in a highly porous scaffold with pore sizes ranging from 20 to 200 micrometers and porosity up to 90%(71).

Thermally induced phase separation

This fabrication technique involves immersing a polymer solution in a temperature lower than the solvent's freezing point, causing the solution to separate into polymer-rich and polymer-poor phases, forming a porous scaffold. The scaffolds produced using this method have higher mechanical strength and smaller pores, although their properties are not easily controlled(71,73).

Melt molding

This technique involves mixing polymer powder and loading it into a mold. Upon heating, the mixture forms a scaffold with controlled characteristics.

Rapid prototyping (RP)

RP is noted for producing scaffolds with complete cross-linking. Unlike traditional methods, this technique allows precise control of scaffold architecture and pore size. In RP, a 3D computer model is created and digitally sliced into cross-sectional layers, which are then used to fabricate the scaffold layer by layer(74).

Natural 3D scaffolds

Biomaterials have extensive applications in scaffold design. For example, collagen is effective in creating bioactive scaffolds, providing an ideal environment for the adhesion and proliferation of osteoblast-like cells, which are essential for bone tissue engineering(75).

Suitable scaffolds with effective performance can also be created through the decellularization of natural matrices.

3D printed scaffolds

3D printing enables the fabrication of scaffolds with highly tunable properties using computer models. These scaffolds have predetermined structures with specific physical, chemical, and biological features, making them applicable for the repair of various soft and hard tissues(76).

Conclusion

The repair of damaged tissues is one of the major challenges in medicine, and tissue engineering has emerged as an effective solution. Designing scaffolds with suitable properties, such as biocompatibility and biodegradability, is crucial in this process. Techniques such as electrospinning, phase separation, and 3D printing have contributed to the development of various scaffolds for the repair of tissues like bone and cartilage.

However, further research is needed to evaluate the efficiency of these scaffolds under physiological conditions to identify the best scaffold for each type of tissue.

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