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Biodegradable and biocompatible synthetic polymers for applications in bone and muscle tissue engineering

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ABSTRACT

In medicine, tissue engineering has made significant advances. Using tissue engineering techniques, transplant treatments result in less donor site morbidity and need fewer surgeries overall. It is now possible to create cell-supporting scaffolds that degrade as new tissue grows on them, replacing them until complete body function is restored. Synthetic polymers have been a significant area of study for biodegradable scaffolds due to their ability to provide customizable biodegradable and mechanical features and a low immunogenic effect due to biocompatibility. The food and drug administration has given the biodegradable polymers widespread approval after they showed their reliability. In the context of tissue engineering, this paper aims to deliver an overview of the area of biodegradable and biocompatible synthetic polymers. We also discussed the frequently used synthetic biodegradable polymers in tissue scaffolding, scaffold specifications, polymer synthesis, degradation factors, and fabrication methods. Particular examples of synthetic polymer scaffolds are investigated to emphasize the many desired properties and corresponding needs for skeletal muscle and bone. Increased biocompatibility, functionality, and clinical applications will be made possible by further studies into a novel polymer and scaffold fabrication approaches.

Introduction

Since its development, synthetic polymer chemistry has advanced tremendously, thanks to decades of invention and advancement, leading to the variety of plastics people use daily. These polymers are suitable for various applications because of their highly functional characteristics, including toughness, stability, and durability. Degradation is one of the fascinating features of several polymers that has great significance in biomedicine and global waste management. Biodegradable polymers are crucial to developing

polymer chemistry because they are intrinsically susceptible to harsh conditions and environmental deterioration. Since biodegradability is highly valued in many sectors, medicine and tissue engineering have shown a particular interest in these polymers.

The dearth of donor sites in autologous grafts and the absence of the necessity for subsequent or repeated operations to eliminate non-degraded material are two advantages of tissue engineering over conventional grafting techniques [1]. The scaffold seeks to replicate the extracellular matrix (ECM), a structure surrounding the cells [2, 3]. A scaffold usually has various functions like monitor water and ion absorption, transport glucose and waste products, and protect cells from external strain pressures. As a therapy method, tissue engineering platforms can be transplanted into tissue defect locations or employed in vitro to create more accurate disease models [4]. The biodegradable scaffold will keep cells in place and then decay at a regulated pace so that the cells proliferate and produce their own ECM to substitute the scaffold, resulting in fully functioning regenerated tissue in the end [5]. Because fewer operations are needed to remove non-biodegradable scaffolds, and fewer long-term immunosuppressant medications are required, biodegradable polymers exhibit considerable benefits over the other substrates utilized as tissue scaffolds [6]. To achieve the ideal balance between functional qualities and biodegradation, biodegradable scaffolds must be adjusted.

Therefore, ideal tissue scaffolds should have high biocompatibility in both their scaffold and degraded forms. They should also have the necessary mechanical qualities to tolerate stress forces and supporting cells in vivo [7]. Additionally, scaffolds should have proper surface chemistry and be highly porous and permeable to allow cell adhesion and movement inside the scaffold while tolerating the required nutrition exchange [7]. These characteristics guarantee that tissue scaffolds perform at their peak levels, offering cells an environment to develop functional tissue-like structures [1]. In order to maintain acceptable structural characteristics during deterioration and finally be substituted by the regenerated tissues, the pace of degradation of scaffolds must also be configurable to their specific uses. Additionally, the precise mechanical and compositional characteristics and needs of a scaffold fluctuate greatly depending on the tissue type in a question and patient variations like age and gender [8]. Therefore, when evaluating certain biodegradable materials for the implant, a highly adaptable and flexible scaffold design is crucial.

Although natural polymers, like collagen, may be the most biocompatible and closely mimic the in vivo environment, they still have limits due to their poor mechanical characteristics and immunogenicity [7, 9]. Natural polymers, like fibrin and collagen, have the advantage of incorporating cell recognition and adhesion sites, like the arginine-glycine-aspartate (RGD) motif, which was first identified in natural polymers [10]. Therefore, the focus of this review will be on biodegradable synthetic polymer-based scaffolds, with an application-focused discussion of the advantages of composite materials with natural polymers. This review will first look into the processes of biodegradation and the unique physicochemical properties of biodegradable polymers, which enable and regulate this process. The usefulness of such materials in medical operations will next be highlighted through a study of production methods and examples of the implementation of specific biodegradable and biocompatible polymers in skeletal and bone tissue engineering.

Frequently used polymers

Numerous synthetic polymers, such as polyurethanes, polyacetals, and polyanhydrides, have the characteristics necessary for biodegradable scaffolds, as described above [6]. However, synthetic aliphatic polyesters, particularly poly (-caprolactone) (PCL), polylactic acid (PLA), which comes in two optically isomeric forms (D and L) and a racemic form (DL), and polyglycolic acid (PGA), as well as their copolymers, are the most frequently and widely utilized polymers for tissue engineering [6, 8, 11]. These polymeric materials are vulnerable to hydrolytic degradation through de-esterification, and the derived monomers are readily excreted from the body, making them extremely attractive as tissue scaffolds [12]. They also have good biocompatibility and sustainable production methods [6]. They have effectively been employed in clinical goods

because of their well-researched biodegradable and bioabsorbable qualities [5]. Pure versions of these polymers do, however, have some inherent drawbacks that must be considered. PLA's relatively poor cytocompatibility and biological inertness are two of the material's most significant flaws when used to create biodegradable tissue scaffolds [13]. Pure polymers frequently support decreased cellular contact and tissue regeneration. These polymers are commonly mixed in blocks with other polymers to tailor their degradability and mechanical characteristics to create better biomimetic and biocompatible scaffolds [5]. Numerous different chemical alterations, including the addition of hyaluronan [13], metallic nanoparticles [14], ceramics [15], or hydroxyapatite [16], have been demonstrated to increase the bioactivity of many polymers, enabling more efficient use in tissue engineering.

Blending synthetic polymers with substances like the aliphatic polyester group polyhydroxyalkanoates (PHA), which includes poly-3-hydroxybutyrate (PHB) and poly-3-hydroxyoctanoate (PHO), is another alteration [17]. Although these polymers may be synthesized, microbes often create them in purposefully imbalanced environments [18]. PHB may be synthesized from various monomers, such as BBL [19], propylene oxide, and carbon monoxide, to create syndiotactic PHB with lower crystallinity and a more significant transition melting temperature than its isotactic bacterial version [20]. polyorthoesters and polyanhydrides are surface-eroding biomaterials, in contrast to aliphatic polyesters, which are bulk-eroding. This enables them to deliver pharmacological payloads for an extended period at a controlled gradual rate while maintaining structural integrity. The only surface-eroding biomaterial that has received FDA approval is polyanhydrides. Yet, its complex manufacture and weak mechanical properties have prevented them from finding broader usage. Another more popular polymer is polyethylene glycol (PEG), a cross-linked hydrogel with soft gel-like properties that has potential in drug administration and wound healing. Based on its position in the body, PEG degrades in a different manner [21].

Many biodegradable synthetic polymers are used in tissue engineering as scaffold materials presenting unique properties, as shown in **Figure 1**. It is crucial to remember that compounds are frequently copolymerized or changed for a specific usage by changing various parameters. It would be too huge to be practical to create a complete library in tabular form that lists all the available polymers, together with copolymers, composites, and other types of modified polymers, along with their many production pro-

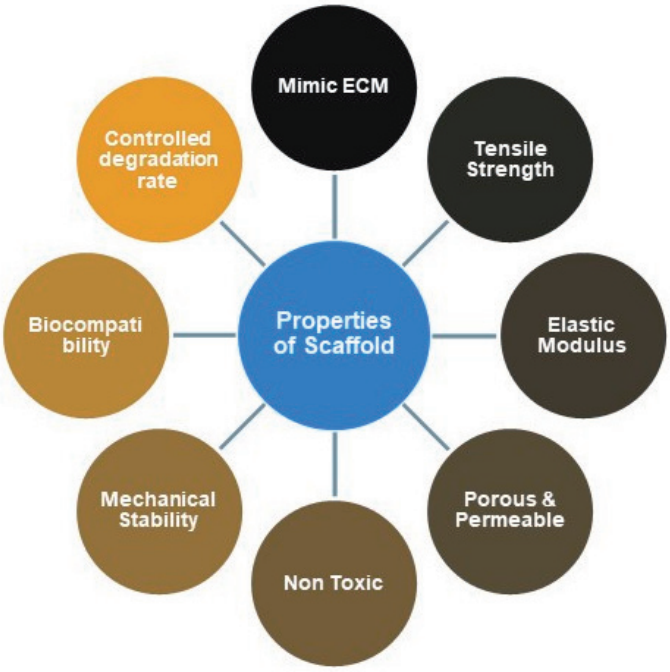

Figure 1. Properties of scaffolds used for application in tissue engineering

cesses, characteristics, and uses. However, compiling this data into a clear and concise database would help researchers and industrial players to comprehend the present state of the art for specific polymers and enable future research and industry to make decisions more quickly. This database may be connected to primary research publications and reviews like this one, allowing people to look deeper into the intricacies after choosing particular polymers or materials.

Mechanism of Degradation

Prior to describing how biodegradable polymers are utilized in tissue engineering, it's critical to talk about the degrading traits that make them desirable as biodegradable scaffolds. Oxidative biodegradation and hydrolytic biodegradation are the principal in vivo polymer degradation processes [11]. The former depends on reactive radical molecules created in vivo by phagocytic assault. Contrarily, hydrolytic degradation is a passive process that breaks down chemical bonds susceptible to interaction with water [11]. Passive hydrolysis stands out as the primary breakdown method in biological settings because of synthetic polymers' relatively reduced sensitivity to enzyme activity [22]. Due to hydrolytic breakdown, polymers can erode on their surface or in bulk. The macroscopic scale polymeric scaffold shrinks while keeping its structure at a uniform degradation rate because surface erosion only affects the polymer surface, as the name implies. Contrarily, bulk erosion occurs throughout the polymer, maintaining the polymer's size even when the degradation rate is not linear [22]. For tissue scaffolds and their intended uses, it is crucial to know whether the form of erosion is prevalent [15, 22]. The hydrophobic nature of scaffolds affects the diffusion of water into and across the polymeric scaffold, which in turn affects the pace of hydrolytic action. This is where polymeric scaffolds' pore size comes into play since bigger pore sizes allow for easier osmosis into the scaffold, which favors mass erosion.

Additionally, amorphous parts of polymers are destroyed first in biological settings because they are packed less densely and more favorable to diffusion. As a result, the crystalline areas remain intact for a more extended period [23]. It follows that a higher polymer crystallinity correlates with greater stiffness and strength as well as a slower rate of degradation. Another crucial factor is the polymer's glass transition temperature (Tg), particularly when considering the mechanical needs of scaffolds [23]. For instance, bone scaffolds often need long-lasting mechanical qualities; therefore, their Tg has to be higher than body temperature to guarantee an acceptable level of stiffness while still delaying early degradation [23].(**Figure 2**).

The molecular weight of the polymer has a substantial influence on the rate of degradation [24]. A rise in molecular weight causes more secondary bonds and entanglements to form between chains, which results in stronger bonding between polymer chains and a slower rate of disintegration [24]. A property of polymers that can store this data is dispersity, calculated as the ratio of weight average molecular weight and number average molecular weight (Mw/Mn).

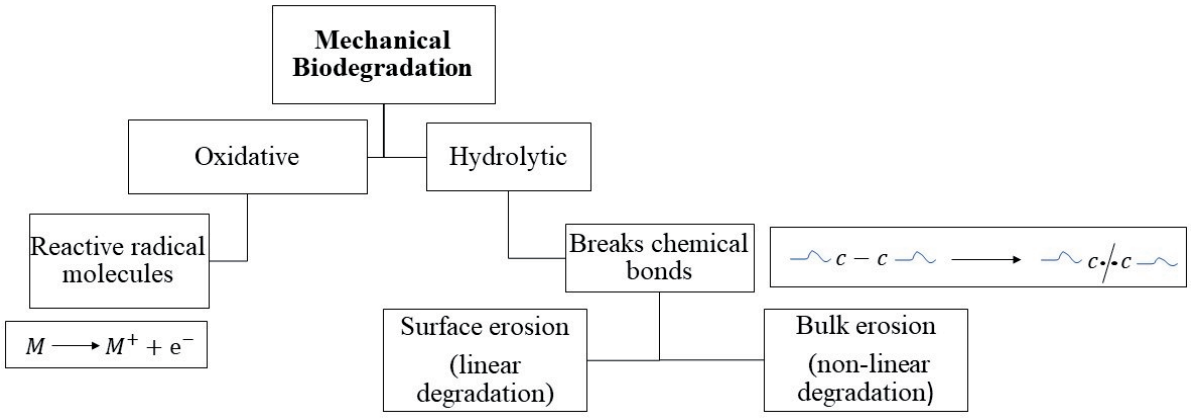

Figure 2. Schematic Diagram of mechanical degradation

Higher dispersity values highlight a smaller Mn because smaller molecules are easier to break down and may be broken down more quickly. Hence, biodegradable polymers need less dispersity, implying less variation in the chain length of the polymer, enabling better forecasts of the breakdown rate within shorter durations that consequently avoid problems like infection and inflammation [24, 25].

The versatility of synthetic polymers for tissue engineering applications makes it appealing to adjust the breakdown rate to fit specific needs. Copolymerization, in which the result consists of blocks of several degradable polymers, illustrates how to do this. Poly-L-lactide (PLLA), poly (-caprolactone) (PCL), and polyurethane, to mention a few, have all been fine-tuned using this approach [26–28]. Other strategies to control the degradation rate include blending, surface modification, and the inclusion of plasticizers [29]. By utilizing these methods on the wide variety of readily accessible polymers, polymer breakdown may be tailored to its role in tissue engineering.

Synthesis of Polymers

The polymers themselves must be produced before specialized 3D scaffolds can be created. There are two ways to make synthetic polymers: (i) step-growth polymerization of hydroxy-acid or combinations of diacid/diol monomers; or (ii) chain growth by ring-opening of cyclic monomer units [30]. The former is often quicker and generates more monomers with a greater molecular weight [31]. The second method is frequently preferred since, for aliphatic polyesters, that's not an issue [32]. The removal of severe reaction conditions, the elimination of undesirable byproducts, and more command of stereochemistry and molecular weights, which results in higher-quality polymers, are further advantages of chain-growth polymerization [33, 34]. In order to produce PCL, PGA, and PLA, it is therefore commonly employed [33]. Tin (II) bis (2-ethylhexanoate), often known as Sn (Oct) 2, is used in the manufacture of PLA in the vicinity of alcohol (ROH), although ring-opening needs catalyst-initiators. [30, 33]. There is no study to find metal-free catalysts that accomplish the same reaction rate [32, 35]. Adding heavy metal catalysts like Sn (Oct) 2 risks contamination during manufacturing, raising costs and potential toxicity of the finished product. Particularly, organocatalysts have increased their potential for ring-opening polymerization of racemic PLLA [19].

Other polymers, such as polyurethane (PU) and polyurethane urea (PEUU), are better suited for manufacture by step-growth polymerization because it is less expensive and more efficacious [31]. They are created mainly by processing hexamethylene-diisocyanate (HMDI) with a diol, then reacting with other polymers like PCL to generate a block polymer that can be broken down by de-esterification [36, 37].

Enzymatic polymerization is the third technique of polymer synthesis that is being increasingly researched as a more ecologically friendly substitute for both step and chain-growth processes [38]. Here, the immobilized enzymes, like ionic-liquid-coated lipases extracted from bacterial culture and deposited in a solvent solution, are combined with synthetic polymers like PCL [38]. Although reaction optimization and economic feasibility are still being investigated, this approach may create large molecular weights of polymers such as polyesters [39].

The production method frequently uses many monomers. Based on their combination ratio, block polymerization functions to integrate the qualities of its component homopolymer sections [40]. Contrarily, copolymerization of numerous monomers is frequently utilized to produce materials with unique features, perhaps with reduced stiffness, enhanced crystalline nature, or higher deterioration than any homopolymer. These manufacturing processes frequently result in straightforward pre-polymer forms, and their ultimate structure is usually achieved by the inclusion of extra blocks of polymer or side chains. These procedures enable atomic-level manipulation and control of polymer characteristics [40].

Fabrication of polymeric scaffolds

Once these polymers are created, they may be transformed into scaffolding structures to perform the desired tissue engineering functions. The method utilized to create the scaffold can significantly impact how it functions in vivo.

There are several techniques; the most popular ones include solvent casting, gas foaming, electrospinning, particle leaching, and additive manufacturing. Each produces a distinct structure and usefulness [9, 41]. These techniques' economic aspect is also crucial [42]. Particulate leaching refers to the addition of particles that are soluble in the polymer while it is still being formed. Later, the particles disintegrate in deionized water, leaving a web of porous holes behind [43]. Laminating layers of separately leached sheets can create a 3D scaffold [41]. Particulate leaching is a straightforward and inexpensive method, but it lacks precise structural control since pore interconnectivity depends only on the size and number of particles supplied [43, 44]. Since this ensures strong pore interconnectivity, it is suitable for scaffolding constructions with exceptionally high porosity leading to low load-bearing capacities, such as endothelial tissue [43].

One of the most extensively studied methods of scaffold production is electrospinning [43]. Mixing a biodegradable polymer, such as PCL, with a conductive polymer and injecting the mixture from needles under high voltage produces electrically active fibers. With the introduction of an external magnetic field, nanofibrous electrospun materials feature tuneable porosities, a high surface area-volume ratio, and adjustable porosities [45]. This method is quite effective, but it necessitates the optimization of several variables, including the applied voltage, solution concentration, and system humidity [43]. The fundamental issue is that the scaffold's need for a considerable amount of conductive polymer might change its mechanical characteristics [45] (**Figure 3**).

Innovative methods for producing scaffolds have also been made possible by advancements in additive manufacturing technology. Size, porosity, and shape may be finely controlled throughout the scaffold using fused-deposition modelling, selective laser sintering, and stereolithography [46]. Using a computer-aided design model, thermoplastic polymers like PCL and PLA are extruded in fused-deposition modelling to create layer-by-layer depositions. It makes it possible to create intricate porous scaffolds with precise dimensions [4, 48]. Optimization of additive manufacturing processes is highly desirable because of its accuracy and patient-specific potential, and this research topic is quite active [46, 49, 50]. 3D printing is among the promising technologies in tissue engineering and regenerative medicine to develop advanced scaffolds. This technique has been shown to successfully seed cells that lead to effective bone growth, and it may be utilized to generate tailored scaffolds

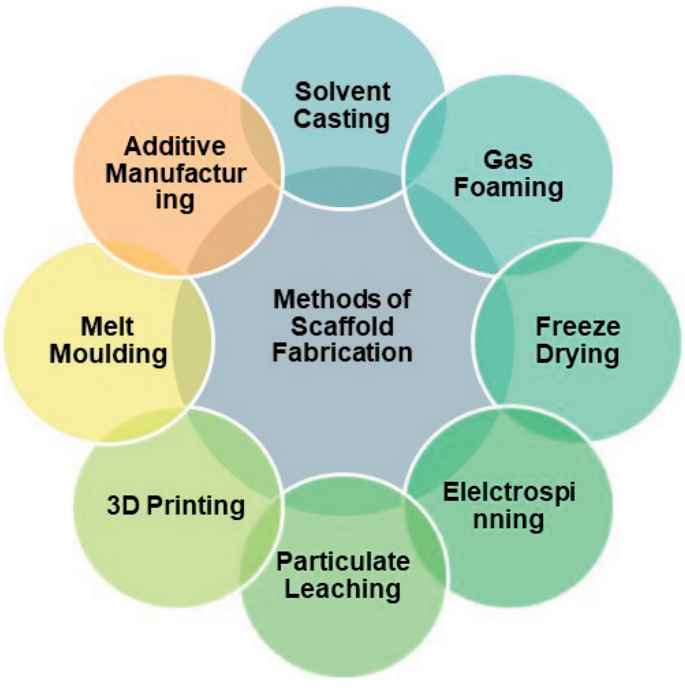

Figure 3. Various fabrication methods for scaffolds

using patient CT images [47]. Various materials are used for the 3D printing of scaffolds. Photosensitive resins, cross-linkable hydrogels, temperature sensitive polymers, thermoplastics, and ceramic paste are commonly used in scaffold 3D printing. It enables the creation of more precisely crafted biomimetic scaffolds with added bioactive ingredients to improve their functionality. Unprecedented potential for producing tissue structures from bone to skin has been demonstrated by 3D bioprinting stem cells. It allows for the delivery or mounting of cells and physicochemical factors essential for tissue regeneration, thus making 3D bioprinting a promising technology for future regenerative medicine.

Applications

The body has several different tissue types, each with unique structural characteristics and ECM compositions. When contemplating the sort of tissue that has to be replaced, the ability to customize the scaffold's qualities is quite helpful. The body is supported and protected by bones, which give more robust physical stability and a higher ECM: cell ratio primarily comprised of collagen [2]. In contrast, skin and muscles need to stretch rather than exert such mechanical strength, which causes the fraction of elastin in the ECM to grow [51]. Tendons and ligaments flexibly transmit stresses between muscles and bones, extending and recoiling to increase movement effectiveness. These require excellent tensile and mechanical strength, attained using plenty of aligned collagen structures [52, 53]. This summary clarifies that different tissue types have different scaffolding needs, which must be considered when choosing polymers and production techniques [5].

This section examines the particular needs and uses of synthetic biodegradable polymers in a couple of tissue types—skeletal muscle and bone-selected for their contrast. Studies on bone biomaterials have had a lot of success; there are currently clinical studies and various products on the market as a result [9, 54]. To the authors' knowledge, there isn't a clinically tested scaffold for skeletal muscle. These variations in patient accessibility have tissue complexity as their underlying cause. Still, they are also influenced by financial accessibility and the compatibility of existing authorized approved polymers to their needs [55, 56]. Here, we'll concentrate on the synthetic scaffolding methods utilized or investigated in these two subfields.

Scaffolding of Bone tissue

In order to enable regenerated bone to substitute the supports lost from the scaffold, the complicated interaction between mechanical support and time for degradation must be regulated due to the specific mechanical needs of bone-tissue scaffolds. For bone regeneration or osteoinductivity, a porosity of between 80 and 90 percent [57] and a pore size greater than 300 m are desirable [8, 58]. This might be improved by including osteoinductive, or growth, substances that can be released during disintegration [59]. Bone is a composite substance mostly made of the polymer collagen and the inorganic ceramic apatite [60]. Therefore, simulating this natural environment using composite scaffolds made of inorganic and polymeric phases may help in regeneration. Numerous polymers and polymer composites have been used to create clinical-grade scaffolds that successfully regenerate bone and have led to the development of commercial goods by including the optimum qualities for bone-tissue engineering scaffolds. Aliphatic polyesters like PGA, PCL, and PLA have been used quite often because they were given US FDA permission. The following will include specific scientific publications that accelerated commercial development, followed by illustrations of particular goods that are presently on the market.

In vitro osteogenic differentiation was demonstrated by [60] using a PLGA electrospun scaffolding with integrated silica nanoparticles, which led to increased bone nodule development and collagen secretion. A rat model used a different PLGA composite functionalized with a peptide similar to the osteoinductive bone morphogenetic protein 2 (BMP-2) to heal a critical-sized cranial lesion [61] successfully. The PLGA composite employed in this work is an appealing scaffold for bone tissue engineering applications due to its mechanical similarities and displaying that it may induce osteogenic differentiation as well as bone formation in vivo. For hip replacement surgery, PLA has been employed as a biodegradable bone graft with a metal core, demonstrating that it is

biocompatible and mechanically stable for effective bone regeneration [62].

Inorganic material has been added to scaffolds in several research areas to promote biomimicry and bone tissue regeneration. As early as 1986, a PLA/hydroxyapatite composite presented efficacy as a bone-filling scaffold in vivo [63]. Lately, a composite of PCL/hydroxyapatite helped bone marrow mesenchymal stem cells proliferate and differentiate [64]. Beyond biomimicry, adding hydroxyapatite to these investigations removes the drawbacks of pure hydroxyapatite's fragility and weak mechanical strength [65]. Recent research has demonstrated that it is possible to employ 3D printing to enhance hydroxyapatite content in a PLA composite without drastically changing the scaffold's mechanical characteristics. Investigation into hydroxyapatite-containing polymer composite is still underway [65]. The prior study found that this scaffold was beneficial both in vitro and in vivo; problems persisted with increased acidity levels during PLA breakdown that might cause inflammation. Even if the amount of hydroxyapatite has grown, further study is still needed before this scaffold is widely used in clinical settings.

Natural polymers could be added with synthetic polymeric scaffolds or utilized as coatings with the aim of promoting cell adhesion because of the advantage of possessing cell-binding RGD sites. Collagen coating was used to achieve this effect, which improved cellular adhesion and differentiation in PLGA [66] and PLLA [67]. In a different research, the persistent release of the BMP2-related peptide P28 was combined with a scaffold made of small intestine submucosa (SIS) and PLA to improve bone regeneration [68]. Collagen I and glycosaminoglycan-containing SIS were combined with PLA to create a highly biomimetic scaffold with tuneable bone-tissue development and breakdown. The specifics of several further experiments, including various polymer kinds, production processes, applications, and degradation timeframes, may be found in review papers [69, 70].

The studies cited above support the potential utility of specific polymers in bone regeneration. This has sparked numerous clinical investigations and the development of commercial goods. Zimmer Biomet produces a range of implants and screws called LactoSorb® that are made of PLA and are used in craniofacial procedures [71]. Narayanan et al. [69] provide a summary of several other commercially available PLA-based solutions, including RapidsorbTM and Biocryl®. Although several clinical investigations, such as using 3D-printed PCL scaffolding in dental surgery, are now underway, the economic success of other polymer kinds is less obvious.

Scaffolding of skeletal muscle tissue

To efficiently transfer force along the tissue, muscle has precise alignments and lengths of fibrils [72]. The skeletal muscle stem cells, or satellite cells [73], multiply, develop into multinucleated myoblasts, and subsequently merge into myotubes when forming new tissue [74]. Promoting satellite cellular migration into the scaffold is crucial because a skeletal muscle scaffold should be able to efficiently control cell migration and development to form these parallel, highly ordered fibers [72]. The architecture of skeletal muscle, mainly regulated mechanically, adds to the complexity of tissue scaffolding. A static scaffold cannot provide these physical development signals; therefore, the myotubes develop randomly [45].

Due to this, cultured skeletal muscle performs poorly when subjected to force in vivo [75] [76]. The scaffold must be exposed to a rhythmic mechanical or electrical component to simulate actual muscle usage in order to prevent this random direction of myoblast development [74]. Incorporating conductive polymers into the scaffold of skeletal muscle has been one of the main study areas [77]. Electrical stimulation has been found to cause muscle contractions and orient myoblasts parallel to the vectors of the electric field [78], suggesting that it may be a straightforward and affordable way to guarantee alignment and contractile capabilities. Electrospinning, which needs a highly conductive component to work, is well suited for the job since it can generate regulated alignment of polymer fibers. To create such an aligned polymer fiber scaffold, Chen et al. employed an electrospinning approach with a mixture of PCL and polyaniline (PANi) [45].

In vitro mouse myoblasts showed higher myotube fusion and cell proliferation than a non-aligned PCL/PANi combination. Similar outcomes were obtained by Jun et al. [79] using a mixture of poly(L-lactide-co-epsilon-capro-

lactone) (PLCL) and PANi, which combined the stiffness and brittleness of PANi with the highly elastic PLCL to produce a scaffold that was more suited than either pure polymer alone. A PANi-PLCL ratio of 3:7 was able to produce 170 percent strain, which is more than skeletal muscle can. However, PANi does not disintegrate despite being biocompatible [40, 45]; therefore, additional research into its polymer structure is necessary before it can provide the qualities that a biodegradable scaffold needs.

The usage of hydrogels is another method for scaffolding skeletal muscle. The FDA has cleared PEG, a highly biocompatible hydrogel for internal ingestion. Its cross-linking density, Mn, and water: polymer ratio may all be easily changed to change its qualities. After cells are suspended inside, its derivative, PEGDA, which is made by replacing its terminating hydroxyl groups with acrylate, may gelate from a liquid to a solid form when exposed to UV radiation. So, rather than relying on a premade scaffold form to specify the shape of the muscle tissue, the scaffold may be constructed after the myoblasts have matured into it. PEG, when mixed with a biological cell-adhesive foundation like fibrinogen, produces a scaffold with both tunable physical features and cell-signalling capabilities, facilitating blood vessels' formation and skeletal muscle regeneration in vitro [74]. Han et al. employed PEG in vivo as an injectable scaffolding cell-delivery method because it can be functionalized with maleimide groups, which makes it possible to store stem cells and adhere to patient tissue [18]. Dong et al. could combine the advantages of hydrogels with those of conductive polymers [40]. They mixed PEG with polyglycerol sebacate (PGS), a very hydrophilic polymer but also elastic [40]. Aniline pentamer (AP) side chains were added by esterification to the resultant polymer PEGS to increase conductivity. PEGS films possessed mechanical qualities that prevented mechanical fatigue and encouraged myoblast growth. Further investigation is warranted because this conductive, stretchy hydrogel can provide mechanical and electrical stimuli to control tissue development.

The combination of aliphatic polyesters and polyurethanes represents a relatively recent development in biodegradable skeletal muscle. Hydrophobic PCL and hydrophilic PEG copolymer soft segments and PU hard segments are combined to create thermoplastic PU and PEUU copolymers (TPUs) [37]. The facile customization of the synthetic process to adjust the soft and hard segment ratios to fit TPU for skeletal muscle scaffolding is made possible by the tunability of synthetic polymer manufacture. A 3D-printed scaffold made of oriented TPU filaments was described as "soft yet robust, sturdy, elastic, and hydrophilic" by Goyker et al. in 2021 [37]. They detected myoblast regeneration and capillary development to some extent at the implant site when assessed in vivo four weeks after implantation, with a recovery in the function of 86% [37].

Cartilage tissue engineering is a promising method for regenerating cartilage tissue damaged by disease or trauma. Articular cartilage has a limited capacity for healing and regeneration, making its restoration one of the biggest problems in musculoskeletal medicine. Cartilage tissue can be repaired when the polymer scaffold's mechanical strength and structural toughness are met with the requirements. The migration of metabolically active cells ECM components that are synthesized and turned over in large quantities is restricted. And hence, artificial cartilage to develop materials that can mimic natural cartilage is preferred. Self-assembly and biomineralization are crucial steps for cartilage repair because they mimic the natural ECM process. For biomineralization, a composite material resistant to high compressive loads can be formed by nucleation and alignment of hydroxyapatite crystals onto bundles of polymeric fibres. One potential process by which highly selective nucleation could occur is illustrated by a creating model that uses a co-polymer hydrogel system. It is believed that controlled nucleation may develop in bone by a similar approach [80].

Another approach to forming hybrid scaffolds for artificial biofunctionalization is combining synthetic polymers with short peptide sequences; scaffolds can be rationally designed with specified biofunctionality. Bioactive precursors with chemically reactive functional groups, such as amines, thiols, and carboxyls, or end-functionalized hydrophilic polymers, like PEG, which function as physical or chemical crosslinkers, can be used to create hybrid multifunctional networks. Of these multifunctional systems, the most adaptable and distinctive ones are based on PEG-peptide hydrogels. The peptides in this

system are made to be substrates vulnerable to proteases produced on the surfaces of migratory cells, such as plasmin and matrix metalloproteinase (MMPs). The field of cartilage reconstruction is expanding at a fast pace with many recent developments [81].

Conclusion

This field of study has particular difficulties because of the special biocompatible and biodegradable needs of tissue scaffolds and the intricacy of their interconnections within the human body. A scaffold must not only perform and decay correctly, but it should also do so for the proper tissue type, as each has specific mechanical and morphological needs. Even though a low level of dispersion is ideal, other parameters like crystallinity, Tg, and strain values are all influenced by the kind of tissue. Polymer breakdown kinetics must be managed to prevent gaps and inflammation throughout healing. In order to combine their properties into a scaffold that is much more appropriate for its function than either polymer in its pure state, well-researched polymers like PLA and PCL are frequently used in conjunction with other less biodegradable but more tissue-compatible polymers, either in block form or as a modification. The variety of fabrication processes that a polymer may be made to construct the 3D scaffolding the body demands, adjusting permeability and fiber arrangement to govern cell migration and proliferation, further enhances this control over the scaffold characteristics and mechanics. Bone, which has high porosity and stress requirements, has given rise to PLA-based scaffolds of bone that have been effectively used in clinical studies. Until now, PCL and PEG-based polymer scaffolds have been the sole in vitro success for muscle, which requires a conducting and elastic scaffold capable of experiencing mechanical loading. Clinical research has been restricted to a small number of biodegradable scaffolding polymers since only a few of them have received FDA and MHRA approval. Despite extensive study on their characteristics, these polymers aren't ideal for scaffolding in their pure forms. Even a perfect scaffold is still ten years away from being used in the general population since research into novel polymer architectures is now restricted to in vitro experiments, and rigorous testing is needed before clinical trials can be conducted. Synthetic polymers can be tuned in terms of both mechanical and biodegradable properties [56]. This review has just scratched the surface of the field's possible polymer and scaffold architectures because of the tunability, co- and block polymerization, and differences in the scaffolding approach. Establishing a list of known scaffold polymers accessible to the public and containing information on their characteristics, the impacts of various manufacturing methods, and the effects of copolymer additions would be the perfect next step for the discipline. Such a thorough evaluation of these polymers could guide and improve further research. Tissue engineering with biodegradable scaffolds is a relatively new area. Until this technology is used often in therapeutic settings, there are still numerous obstacles to be solved. But more research into the function of ECM in cell development, together with the evaluation of copolymers and cutting-edge production methods, will only expand the potential of this exciting area of study.

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