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Review

The Design of Scaffolds for Use in Tissue Engineering. Part I. Traditional Factors

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ABSTRACT

In tissue engineering, a highly porous artificial extracellular matrix or scaffold is required to accommodate mammalian cells and guide their growth and tissue regeneration in three dimensions. However, existing three-dimensional scaffolds for tissue engineering proved less than ideal for actual applications, not only because they lack mechanical strength, but they also do not guarantee interconnected channels. In this paper, the authors analyze the factors necessary to enhance the design and manufacture of scaffolds for use in tissue engineering in terms of materials, structure, and mechanical properties and review the traditional scaffold fabrication methods. Advantages and limitations of these traditional methods are also discussed.

INTRODUCTION

In the United States alone, approximately a quarter of patients in need of organ transplants die while waiting for a suitable donor.[1,2] The current demands for transplant organs and tissues is far outpacing the supply, and all manner of projections indicate that this gap will continue to widen.[1,3] Cell transplantation has recently been proposed as an alternative treatment to whole organ transplantation for failing or malfunctioning organs.[4–6] For the creation of an autologous implant, donor tissue is harvested and dissociated into individual cells, and the cells are attached and cultured onto a proper substrate that is ultimately implanted at the desired site of the functioning tissue. Because many isolated cell populations can be expanded *in vitro* using cell culture techniques, only a very small number of donor cells may be necessary to prepare such implants. However, it is believed that isolated cells cannot form new tissues by themselves. Most primary organ cells are believed to be anchorage-dependent and require specific environments that very often include the presence of a supporting material to act as a template for growth. The success of any cell transplantation therapy therefore relies on the development of suitable substrates for both *in vitro* and

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in vivo tissue culture. Currently, these substrates, mainly in the form of tissue engineering scaffolds, prove less than ideal for applications, not only because they lack mechanical strength, but they also suffer from a lack of interconnection channels.

FACTORS NECESSARY TO ENHANCE THE DESIGN OF SCAFFOLDS FOR USE IN TISSUE ENGINEERING

Tissue engineering (TE), an important emerging topic in biomedical engineering, has shown tremendous promise in creating biological alternatives for harvested tissues, implants, and prostheses.[7] The underlying concept of tissue engineering is the belief that cells can be isolated from a patient, and its population then expanded in a cell culture and seeded onto a carrier. The resulting tissue engineering construct is then grafted back into the same patient to function as the introduced replacement tissue. In this approach, a highly porous artificial extracellular matrix,[8] or scaffold, is thought to be needed to accommodate mammalian cells and guide their growth and tissues regeneration in three dimensions.

The creation of tissues for medical use is already used to a significant extend in hospitals. These groundbreaking applications involve fabricated skin,[9] liver,[10,11] pancreas, intestines, urothelium, esophagus,[12] nerves,[13] valve leaflet,[14] cartilage,[15] bone,[16–19] ligament, and tendon.[20] The first commercial application is a bioartificial skin product for burn treatment that was introduced in 1990.[21] Other applications that have reached the market include cartilage repair, hematopoietic progenitor cell isolation, and immunomodulatory therapy for cancer.[21] However, three-dimensional scaffolds for tissue engineering, to date, is found to be less than ideal for applications, not only because they lack mechanical strength,[22] which is thought to be an essential prerequisite for implantation, but they also lack interconnection channels that allow cell growth to penetrate such three-dimensional matrices.[23]

There are several requirements in the design of scaffolds for tissue engineering. Many of these requirements are complex and not yet fully understood. In addition to being biocompatible both in bulk and degraded form, these scaffolds should possess appropriate mechanical properties to provide the correct stress environment for the neotissues. Also, the scaffolds should be porous and permeable to permit the ingress of cells and nutrients, and should exhibit the appropriate surface structure and chemistry for cell attachment.

Materials

The first issue with regard to tissue engineering is the choice of suitable material. The desirable characteristics of these materials are biocompatibility (i.e., not to provoke any unwanted tissue response to the implant, and at the same time to possess the right surface chemistry to promote cell attachment and function) and biodegradability (i.e., degradable into nontoxic products, leaving the desired living tissue).[3]

Potential materials with these characteristics include natural polymers, synthetic polymers, ceramics, metals, and combinations of these materials.[24]

Metals. Over the past century, biocompatible materials such as metals, ceramics, and polymers have been used extensively for surgical implantations. Metals and ceramics have contributed to major advances in medicine, particularly in orthopedic tissue replacements. Typical implant metals are stainless steels, cobalt-based alloys, and titanium-based alloys,[25] and typical ceramics are alumina, zirconia, calcium phosphate, and bioglass.[26] Hip endoprosthesis is a typical device based on these materials that has remarkably improved the quality of life of many people. However, metals and ceramics have two major disadvantages for tissue engineering applications. First, they are not biodegradable (except biodegradable bioceramics such as α-tricalcium phosphate, β-tricalcium phosphate), and second, their processability is very limited. For these reasons, polymeric materials have received an increasing amount of attention from the scientific and medical communities.[27]

Polymers. Natural polymers, such as collagens, glycosaminoglycan, starch,[28] chitin, and chitosan, have been used to repair nerves, skin, cartilage, and bone. While naturally occurring biomaterials may most

closely simulate the native cellular milieu, large batch-to-batch variations upon isolation from biological tissues is the main limitation for their wide applications. Poor mechanical performances is also a drawback for transplantation scaffolds made from natural polymers, such as collagen and chitin, which cannot be easily melted with heat but require a special solvent.

Many synthetic resorbable polymers, such as poly(α-hydroxy ester)s, polyanhydrides, polyorthoesters, and polyphosphazens, have been developed to overcome the aforementioned problems associated with natural polymers. Most synthetic polymers are degraded via chemical hydrolysis and insensitive to enzymatic processes so that their degradation does not vary from patient to patient.

An important class of synthetic resorbable polymers includes poly(α-hydroxy ester)s and copolyesters of the lactic acid and glycolic acid. In the United States, polyglycolic acid, or polyglycolide (PGA), polylactic acid, or polylactide (PLA), polydioxanone, and copolymers thereof are the only synthetic, degradable polymers with an extensive U.S. Food and Drug Administration (FDA) approval history. They have been in use for over 20 years in surgical sutures, and have a long and favorable clinical record. By far, the family of PLA is the most commonly used synthetic biomaterial. A wide range of physical properties and degradation times can be achieved by varying the monomer ratios in lactide/glycolide copolymers (Fig. 1): poly-L-lactide (PLLA) and PGA exhibit a high degree of crystallinity and degrade relatively slowly, while copolymers of PLLA and PGA (i.e., PLGA) are amorphous and degrade rapidly.

The low-molecular-weight polymers of PLA and PGA can be prepared by direct condensation of lactic acid and glycolic acid. However, high-molecular-weight PLA and PGA are not possible to obtain by direct condensation of the related carboxylic acids because of the reversibility of the condensation reaction, backbiting reactions, and the high extent of reaction required.[27,29,30] Therefore, PGA and PLA are typically made by ring-opening polymerization of their respective cyclic diester dimers glycolide and lactide.[30,31] The monomers glycolide and lactide are prepared by first condensing glycolic or lactic acid into their respective low-molecular-weight condensation polymers. These low-molecular-weight polymers are then thermally cracked, preferentially forming the six-membered cyclic diesters. The crystalline cyclic diesters are highly purified by distillation, recrystallization, or both, and then polymerized by ring-opening, addition polymerization to form the high-molecular-weight polymers.[32] Properties of these polymers are summarized in Table 1.

1. *Polyglycolic acid*: All homopolymers of glycolide and substituted glycolides can be obtained as highly crystalline polymers, having glass transitions ranging from about 25°C to 65°C and melting temperatures from about 185°C to 225°C.[29,31,32] Almost all glycolide and substituted glycolide homopolymers can be melt-processed by extrusion or molding. As an absorbable material, its thermal stability is good and under dry extrusion or molding conditions, its melt characteristics are also good.[32] Relative to other biodegradable polymers, PGA is a highly crystalline polymer, with crystallinity typically reported in the

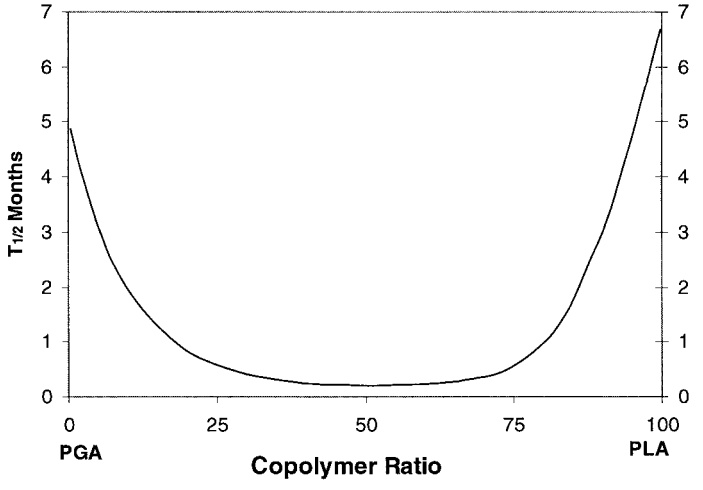

FIG. 1. Half-life of PLA and PGA homopolymers and copolymers implanted in rat tissue.[59]

range of 35–75%. Because of its high degree of crystallization, PGA is not soluble in most organic solvents; the exceptions are highly fluorinated organic solvents such as hexafluoroisopropanol (HFIP). Owing to its hydrophilic nature, PGA tends to lose its mechanical strength rapidly (50%) over a period of 2 weeks and is absorbed in about 4 weeks after implantation. It can be completely absorbed in 4–6 months.

2. *Polylactic acid*: Although structurally very similar to PGA, PLAs are quite different in chemical, physical, and mechanical properties because of the presence of a pendant methyl group on the alpha carbon. This structure causes chirality at the alpha carbon of PLA; and thus, L, D, and DL isomers are possible. Poly(L-lactide) (PLLA) is a semicrystalline and relatively hard materials with glass transition temperature at about 65°C and melting temperature of about 170–180°C. PLLA is generally less crystalline than PGA, with crystallinity reported in the range of 35%.[33] It can be melt-processed within a temperature range of about 200–250°C, depending on its molecular weight. Minimal residence time in the molten state is recommended. In contrast, a poly(D,L-lactide) (PDLLA) with a more or less random distribution of the stereosequences is an amorphous and transparent material with a glass transition temperature in the range of 50–60°C, depending on molecular weight. The degradation rate of PDLLA is consequently faster than that of PLLA, all other conditions being the same. Depending on the size and thickness of the specimen, hydrolysis of PDLLA may be completed within a period of 2–12 months. It must be pointed out that, although molecular weight, crystallinity, and copolymer composition are known to affect the degradation rate, some aspects of the *in vitro* and *in vivo* degradation of these resorbable polymers are still not yet fully understood. In melt-processing PLA, care must be taken to avoid excessive heating of the polymer to minimize the extent of monomer formation due to chain depolymerization.[27] Excessively high processing temperatures may result in monomer formation during the molding or extrusion process. The presence of excess monomer can act as a plasticizer, changing the material's mechanical properties, and can catalyze the hydrolysis of the polymer, thus altering degradation kinetics. Therefore, these materials should be processed at the lowest temperatures permissible.
3. *Poly(ϵ-caprolactone) (PCL)*: The ring-opening polymerization of ϵ-caprolactone yields a semicrystalline polymer with a melting point of 58–63°C and a glass transition temperature of −60°C. The repeating molecular structure of PCL homopolymer consists of five nonpolar methylene groups and a single relatively polar ester group. This structure gives PCL unique properties that are similar to polyolefin because of its high olefinic content, while the presence of hydrolytically unstable aliphatic-ester linkage causes the polymer to be biodegradable. This polymer has been regarded as tissue compatible and used as a biodegradable suture in Europe. Because the homopolymer has a degradation time in the order of 2 years, copolymers have been synthesized to accelerate the rate of bioabsorption.[31] For example, copolymers of ϵ-caprolactone with D,L-lactide have yielded materials with more rapid degradation rates.

Some limitations of these polymers should also be pointed out. For example all polyesters release acidic degradation products that can adversely affect biocompatibility. These polyesters tend to be relatively stiff materials. While this may be an advantage in load-bearing applications, it becomes a disadvantage when mechanical compliance with soft tissue or blood vessels is required. Finally, none of these polyesters provides a chemically reactive pendent chain for the easy attachment of drugs, crosslinkers, or biologically active moieties.[34] Thus, simple poly(α-hydroxy ester)s have performed well in establishing the foundation and feasibility of tissue engineering it may not be optimally suited for the construction of polymeric cell scaffolds serving a variety of applications. Tyrosine-derived polycarbonates and polyarylates,[34] lactide-based polydepsipeptide polymer,[35] polymerize poly(L-lactic acid-co-L-aspartic acid),[36] and lactide-based poly(ethylene glycol) polymer,[37] with functional side groups, are proposed as new biomaterials for tissue engineering. These materials are yet to be approved by FDA or available in the market so far.

Ceramics. Polymers by themselves are very ductile and not sufficiently rigid, whereas ceramics are deemed to be too stiff and brittle. By combining polymers with bioceramics, researchers hope to overcome the mismatch of mechanical properties that currently exists between bioceramics and natural load-bearing tissues.

Bioceramics such as hydroxyapatite, bioactive glasses, calcium phosphate ceramics, etc., exhibit bioactive, biocompatible behavior and have been used as filler material for bone defect repair and as artificial bone matrix. Bioceramics can be divided into the following three categories[38]:

1. Bioinert groups such as alumina and zirconia
2. Surface bioactive groups such as sintered HA (s-HA), Bioglass, alumina-wollastonite glass ceramic (AW-GC)
3. Bioresorbable groups such as neither calcined nor sintered HA (u-HA), α- or β-tricalcium phosphate (α-TCP, β-TCP), tetracalcium phosphate (TTCP), octacalcium phosphate (OCP)

For biodegradable purpose, the choice of bioceramics as strengthen phase should be category 3. Further choices should be according to the different biodegradation rate of the materials for different tissue applications. The rate of biodegradation is in the following order: OCP $>$ α-TCP $>$ β-TCP $>$ u-HA $>>$ s-HA, which are also affected by several others factors. For example, the rate of biodegradation[26,39] increases as (1) surface area increases, (2) crystallinity decreases, (3) crystal perfection decreases, (4) crystal or grain size decreases, and (5) ionic substitutions of carbonate ion (CO_3^{2-}), magnesium ion (Mg^{2+}), and strontium ion (Sr^{2+}) in HA take place. Factors that result in a decreasing rate of biodegradation include (1) fluorine ion (F^-) substitution in HA, (2) Mg^{2+} substitution in β-TCP, and (3) decreasing β-TCP/HA ratios in biphasic calcium phosphate.

Macro- and microstructure

The second issue to be addressed in tissue engineering is the macro- and microstructures of the materials. From materials engineering point of view, tissues are considered to be cellular composites representing multiphase systems. Cellular composites are then seen as consisting of three main structural components: (1) cells that are organized into functional units, (2) extracellular matrix, and (3) scaffold architecture. This architecture is increasingly believed to contribute significantly to the development of specific biological functions in tissues and thought to provide appropriate nutritional conditions and spatial organization for cell growth.

The regeneration of specific tissues aided by synthetic materials has been shown to be dependent on the porosity and pore size of the supporting three-dimensional structure.[11] A large surface area favors cell attachment and growth, whereas a large pore volume is required to accommodate and subsequently deliver a cell mass sufficient for tissue repair. Highly porous biomaterials are also desirable for the easy diffusion of nutrients to and waste products from the implant and for vascularization which are major requirements for the regeneration of highly metabolic organs such as liver and pancreas. The surface area/volume ratio of porous materials depends on the density and average diameter of the pores. Nevertheless, the diameter of cells in suspension dictates the minimum pore size, which varies from one cell type to another. Depending on the envisioned applications, pore size must be carefully controlled. The effect of implant pore size on tissue regeneration is emphasized by experiments demonstrating optimum pore size of 5 μm for neovascularization, 5–15 μm for fiberblast ingrowth, close to 20 μm for the ingrowth of hepatocytes, 20–125 μm for regeneration of adult mammalian skin, 40–100 μm for osteoid ingrowth,[24] and 100–350 μm for regeneration of bone[40] (See Table 2). Fibrovascular tissues appear to require pores sizes greater than 500 μm for rapid vascularization and for the survival of transplanted cells.[41]

Another important consideration is the continuity of the pores within a synthetic matrix. Materials trans-

Table 1. Properties of Biodegradable Polymers[27,29,31,32]

Polymer type	*Melting point (°C)*	*Glass trans. temp. (°C)*	*Degration time (months)*[a]	*Density (g/cm^3)*	*Tensile strength (MPa)*	*Elongation, %*	*Modulus (GPa)*
PLGA	Amorphous	45–55	Adjustable	1.27–1.34	41.4–55.2	3–10	1.4–2.8
DL-PLA	Amorphous	55–60	12–16	1.25	27.6–41.4	3–10	1.4–2.8
L-PLA	173–178	60–65	>24	1.24	55.2–82.7	5–10	2.8–4.2
PGA	225–230	35–40	6–12	1.53	>68.9	15–20	>6.9
PCL	58–63	−65	>24	1.11	20.7–34.5	300–500	0.21–0.34

[a]Time to complete mass loss. Time also depends on part geometry.

Table 2. Studies Defining Optimal Pore Size for Bone Regeneration[24]

Reference	*Scaffold pore size (μm)*	*Porosity*	*Mineralize tissue ingrowth/comments*
Klawitter et al.[40]	Type I: 2–6 μm	33.5%	No tissue ingrowth
	Type II: 15–40 μm	46.2%	No bone ingrowth, fibrous tissue ingrowth
	Type III: 30–100 μm 80% pores < 100 μm	46.9%	50 μm of bone ingrowth, osteoid and fibrous tissue ingrowth
	Type IV: 50–100 μm 63% pores < 100 μm	46.9%	20 μm of bone ingrowth by 11 weeks and 500 μm of ingrowth by 22 weeks, osteoid and fibrous tissue ingrowth
	Type V: 60–100 μm 37% < 100 μm	48.0%	600 μm of bone ingrowth by 11 weeks and 1,500 μm of ingrowth by 22 weeks, osteoid and fibrous tissue ingrowth
Whang et al.[24]	≤100 μm	35.3%	Not statistically different from untreated controls
	≤200 μm	51.0%	Not statistically different from untreated controls
	≤350 μm	73.9%	Statistically significant more bone than all other groups

port and cell migration will be inhibited if the pores are not interconnected even if the matrix porosity is high.[42] Mass transport is one of the most significant challenges in tissue engineering. Large-scale cell transplantation in open structures is presently limited by inadequate nutrient delivery. Cells more than approximately 200 μm from a blood supply are either metabolically inactive or necrotic due to low oxygen tension.[43] It is for this reason that cartilage, with its very low metabolic activity, has been one of the few cell types successfully engineered into large tissue structures. A further concern is the changes in the effective pore structure over time *in vivo*. If the matrices are biodegradable, as in the case with PLA and PGA matrices, the average pore size will increase and bottlenecks in the continuity of the pore structure will open.[44] If the matrix does not degrade, its effective pore size may be reduced by *in vivo* events such as the invasion of fibrous tissue into the pores and the nonspecific adsorption of proteins onto the material's surface.[8] Besides pore size and porosity, the shape and tortuosity can affect tissue ingrowth.[45] Strong cell adhesion and spreading often favor proliferation while rounded cell morphology is required for cell-specific function.[46] Thus, a polymer scaffold must act as a suitable substrate to maintain differentiated functions without hindering proliferation.[47]

Mechanical properties and processability

The scaffold should have the mechanical strength needed for the creation of a macroporous scaffold that will retain its structure after implantation, particularly in the reconstruction of hard, load-bearing tissues, such as bones and cartilages. The biostability of many implants depends on factors such as strength, elasticity, absorption at the material interface and chemical degradation. Mechanical properties of human tissue are found in Table 3.

Processability of the biomaterial is also required when the final shape of the repaired organ or regenerated tissue has a critical influence on its activity. The scaffold should be easily processed to acquire a variety of configurations. The reproducibility of scaffold or architecture is also vital in maintaining the dimensional stability of the scaffold.

The scaffold can also be formulated to contain additives or active agents for more rapid tissue growth or compatibility. For example, a bone implant may contain a form of calcium phosphate or a growth factor such as one of the bone morphogenetic proteins.

SCAFFOLD PROCESSING AND FABRICATION TECHNIQUES

Porous scaffolds or foams can be fabricated using a variety of methods. These methods include woven or nonwoven preparation from spun fibers, blown films using solvents or propellants, or sintered polymer

Table 3. Mechanical Properties of Human Tissues

	Tensile strength (MPa)	*Compressive strength (MPa)*	*Youngs' modulus (GPa)*	*Fracture toughness (MPa.m1/2)*
Cancellous bone[56]	N/a	4–12	0.02–0.5	N/a
Cortrial bone[56]	60–160	130–180	3–30	2–12
Cartilage[57]	3.7–10.5	N/a	0.7–15.3 (MPa)	N/a
Ligament[58]	13–46	N/a	0.065–0.541	N/a
Tendon[58]	24–112	N/a	0.143–2.31	N/a

particles. Polymers used in tissue engineering applications, as in most industrial applications, are often preformed and distributed in solid pellet form. This form is often not suitable to fit tissue engineering needs. The choice of the correct technique, however, is critical because the fabrication can significantly alter the properties of the implant and its degradation characteristics. Some of the published fabrication techniques are listed below.

Fiber felts or mesh

PGA fibers in the forms of tassels and felts were utilized as scaffolds to demonstrate the feasibility of organ regeneration.[48] Fiber meshes[49] consist of individual fibers either woven or knitted into three-dimensional patterns of variable pore size. The advantageous characteristic features of fiber meshes are a large surface area for cell attachment and a rapid diffusion of nutrients in favor of cell survival and growth. However, they lacked the structural stability necessary for *in vivo* use, which led to the development of a fiber bonding technique.[48]

Fiber bonding

Interconnected fiber networks have been prepared by Mikos et al., by the so-called fiber bonding technique.[47,48] Briefly, PGA fibers are aligned in the shape of the desired scaffold and then embedded in a PLLA/methylene chloride solution. After evaporation of the solvent, the PLLA-PGA composite is heated above the melting temperatures of both polymers. PLLA is removed by selective dissolution after cooling, leaving the PGA fibers physically joined at their cross-points. Obviously, this technique is not most appropriate for the fine control of porosity.[27] Choice of solvent, immiscibility of the two polymers, and their relative melting temperatures also restricts the general application of the technique to other polymers. Solvent residue in the scaffold may be harmful to the cell and organs.

Phase separation

The polymer is dissolved in a solvent such as molten phenol, naphthalene,[50] or dioxane[51] at a low temperature. Liquid-liquid or solid-liquid phase separation is induced by lowering the solution temperature. Subsequent removal of the solidified solvent-rich phase by sublimation leaves a porous polymer scaffold. One prominent advantage is to incorporate bioactive molecules into the matrices without decreasing the activity of the molecule due to harsh chemical or thermal environments. A slight change in the parameters, such as types of polymer, polymer concentration, solvent/nonsolvent ratio, and the most importantly, thermal quenching strategy, significantly affected the resultant porous scaffold morphology.[51]

Solvent casting and particulate leaching

This method consists of dispersing calibrated mineral[52,53] (e.g., sodium chloride, tartrate and citrate) or organic (e.g., saccharose) particles in a polymer solution. This dispersion is then processed either by casting or by freeze-drying in order to evaporate the solvent. The salt particles are eventually leached out by

selective dissolution to produce a porous polymer matrix. Highly porous scaffold with porosity up to 93% and median pore diameters up to 500 μm can be prepared using this technique.[52] A disadvantage of this method is that it can only be used to produce thin wafers or membranes up to 3-mm thick.

However, three-dimensional structure can be manufactured using the polymer membranes by laminating them together to form a three-dimensional matrix of the desired shape.[53]

Membrane lamination

This method is very similar to the laminated object manufacturing (LOM) in the rapid prototyping field. A contour plot of three-dimensional anatomical shape is first prepared.[53] Highly porous PLLA or PLGA membranes with the shapes of the contour were then manufactured using the solvent-casting and particulate-leaching technique. The adjacent membranes are bonded together by coating chloroform in their contacting surfaces. Three-dimensional structure can be manufactured using this method.

Melt molding

A mixture of fine PLGA powder and gelatin microspheres is loaded in a teflon mold and then heated above the glass-transition temperature of the polymer.[54] Subsequence dissolution of gelation from the PLGA-

Table 4. Polymer Scaffold Processing for Tissue Engineering

	Processing	*Advantage*	*Disadvantages*
1	Fiber felts	• Easy process • High porosity	• Lack structural stability
2	Fiber bonding	• High porosity	• Limit application to other polymers • Lack required mechanical strength for the load-bearing tissues • Solvent residue may be harmful
3	Phase separation	• Nondecreased activity of the molecule	• Difficult to control precisely scaffold morphology • Solvent residue may be harmful
4	Solvent casting and particulate leaching	• Controlled porosity, up to 93%, • Independent control of porosity and pore size • Crystallinity can be tailored	• Limit to membranes up to 3-mm thick • Lack required mechanical strength for the load-bearing tissues • Solvent residue may be harmful
5	Membrane lamination	• 3D matrix	• Lack required mechanical strength for the load-bearing tissues • Solvent residue may be harmful
6	Melt molding	• Independent control of porosity and pore size • Macro shape control	• High temperature required for nonamorphous polymer
7	Polymer/ceramic fiber composite foam	• Superior compressive strength • Independent control of porosity and pore size	• Solvent residue may be harmful
8	High-pressure processing	• No organic solvents	• Mostly a nonporous surface • Closed-pores structure inside the polymer matrix
9	Hydrocarbon templating	• No thickness limitation • Enhanced control over pore structure, porosity, etc.	• Solvent residue may be harmful

gelatin composite results into a porous PLGA matrice. The pore size is directly controlled by the microsphere diameter, and the general porosity changes with the polymer/gelatin ratio. Polymer scaffolds of various shapes can be constructed by simply changing the mold geometry. Substitution of L-PLA and PGA for PLGA is an alternative, although higher temperature is then required for melting the semicrystalline polymer.

Polymer/ceramic fiber composite foam

A solvent-casting technique is employed first in which hydroxyapatite short fibers and a porogen are dispersed in a PLGA/methylene chloride solution. After solvent evaporation, leaching of the porogen leaves open-cell porous composite foam of PLGA reinforced with hydroxyapatite short fibers. With a certain range of fiber content, these scaffolds have superior compressive strength compared to nonreinforced materials of the same porosity.

High-pressure processing

Solid disks of PLGA are exposed to high-pressure CO_2 to allow saturation of CO_2 in the polymer.[42] Thermodynamic instability is then created by reducing the CO_2 gas pressure to an ambient level, which results in nucleation and expansion of dissolved CO_2, generating macropores. The major advantage of this techniques is that it involves no organic solvents. The disadvantage is that it yields mostly a nonporous surface and closed-pore structure within the polymer matrix, which may be problematic for cell seeding.

Hydrocarbon templating

This process[55] is a combination of two distinct foam processes: (1) leaching of a fugitive phase with (2) polymer precipitation. It was achieved by using a non–water-soluble particulate hydrocarbon fugitive phase (porogen) derived from waxes, which allowed for the formation of pores with concomitant precipitation of the polymer phase. Unlike leaching of a water-soluble salt, in this process the porogen is actively extracted in an organic solvent. As a result, limitations on foam thickness are almost absent. The use of a hydrocarbon template allows for enhanced control over pore structure, porosity, and other structural and bulk characteristics of the polymer foam.

As remarked above, a variety of techniques have been used to produce two- or three-dimensional porous matrixes from synthetic polymers. However, from the summarized information listed in Table 4, it is obvious that the scaffolds fabricated by these processing techniques are either residual organic solvents or lack structural stability, mechanical strength and flexibility in control of microstructure.

CONCLUSION

The requirements of scaffolds for tissue engineering are complex and specific to the structure and function of the tissue of interest. The scaffold fabrication technique therefore needs to be developed appropriately to manufacture the scaffold with the desired characteristics such as the degradation rate, porosity, pore size, shape, distribution, and mechanical properties. Factors such as pore size, shape, and tortuosity can all affect tissue ingrowth but are thought to be difficult to control precisely using this processing techniques. New design and manufacture methodologies are required, and rapid prototyping tools are believed to be a good alternative.

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