

Review Article Scaffold Techniques and Designs in Tissue Engineering Functions and Purposes: A Review

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In this review paper, the definition of the tissue engineering (TE) was comprehensively explored towards scaffold fabrication techniques and applications. Scaffold properties and features in TE, biological aspects, scaffold material composition, scaffold structural requirements, and old and current manufacturing technologies were reported and discussed. In almost all the reviewed reports, the TE definition denotes renewal, development, and repairs of damaged tissues caused by various factors such as disease, injury, or congenital disabilities. TE is multidisciplinary that combines biology, biochemistry, clinical medicine, and materials science whose application in cellular systems such as organ transplantation serves as a delivery vehicle for cells and drug. According to the previous literature and this review, the scaffold fabrication techniques can be classified into two main categories: conventional and modern techniques. These TE fabrication techniques are applied in the scaffold building which later on are used in tissue and organ structure. The benefits and drawbacks of each of the fabrication techniques have been described in conjunction with current areas of research devoted to deal with some of the challenges. To figure out, the highlighted aspects aimed to define the advancements and challenges that should be addressed in the scaffold design for tissue engineering. Additionally, this study provides an excellent review of original numerical approaches focused on mechanical characteristics that can be helpful in the scaffold design assessment in the analysis of scaffold parameters in tissue engineering.

1. Introduction

The term "tissue engineering" (TE) was initially introduced by Professor Robert Nerem in 1988 at UCLA Symposia on Molecular and Cellular Biology [1], where a comprehensive definition of TE was given as the application of life sciences and engineering to develop a basic understanding of the functional and structural relationships of natural and pathologic mammalian tissues and the development of biosubstitutes that can be utilized to restore, maintain, or improve tissues damaged or lost by various disease conditions [2]. In summary, TE refers to restoration, improvement, and maintenance of damaged tissues caused by various factors such as disease, injury, or congenital disabilities [3].

The conventional method of tissue regeneration and healing is the auto graft method and is mainly dependent on the availability of donor tissues, coupled with other additional effects such as pain and risks to patients such as donor tissue morbidity and infectious diseases [4]. Currently, artificial scaffolds have been applied and used as a supporting structure for cell cultures and domination of cell growth in repair of impaired tissues or organs. During the cell regeneration, the scaffold temporarily help in cell regeneration and gradually biodegrades either in the course of the healing process or after, and a new tissue with a desired shape and properties is produced [5]. This degradability property of the scaffold obviates the need to remove the material later and thus, eliminates the side effects resulted from foreign materials left in the body [4]. Hence, the utilized scaffold should meet specific chemical, mechanical, and physical requirements to achieve cell diffusion and 3D tissues formation.

In scaffold fabrication, the extracellular matrix (ECM) has always received considerable attention among researchers because of its high biological compatibility, biological degradability, and the possibility of rapid remodeling in vivo [6]. Theses ECM mainly consist of proteins, including collagen, fibrin, fibrinogen, gelatin, elastin, etc., and polysaccharides, especially alginates, hyaluronic acid, cellulose, chitosan, etc., [6]. This complex mixture offers mechanical and biochemical support to surrounding cells and controls their performance in regeneration. Most of these polymers are selected because their chemical properties can be modified by introducing various chemical moieties that produce derivatives possessing enhanced adhesion, crosslinking, and biodegradability properties [6]. Therefore, creating biologically mimetic and functionalized scaffolds such as biologically active ECM is necessary in creating an in vivo-like microenvironment mimicking biological entities and stimulating cell-specific responses to lead to tissue regeneration and repair [4, 5]. Figure 1 presents the assembly of a 3D printer and fabrication steps of a scaffold.

Additionally, Figure 1 also presents the laser-aided gelling (LAG) process in scaffold fabrication: (a) driving the servo motor to keep the feeding area at a fixed distance; (b) evenly paving the slurry in the feeding area on the surface of the working platform using a scraping plate and then returning the scraping plate to its original position after evenly paving the slurry in the forming area; (c) using the CO_2 laser as the thermal energy source scanning the shape for moulding with the laser scanner until the moisture of the slurry evaporates and the shape sets; and (d) the scaffold is finished. Step (a) through step (c) are repeated until the scaffold is finished [7].

Even though there exist several methodologies for scaffold fabrication, however, most methods are characterized by low efficiency because of the challenges involved in the making a scaffold that promotes 3D healing and forming a blood vessel within the scaffold [8, 9]. This paper presents a discussion on some of the most promising scaffold fabrication methods and materials that are widely used in tissue engineering applications.

2. Significance of Tissue Engineering

TE is an interdisciplinary field based on a broad range of areas, where the life sciences and engineering principles are applied to the development of biosubstitutes to restore, maintain, or improve the function of tissue or organ. Thus, TE is a multidisciplinary study combining biology, biochemistry, clinical medicine, and materials science along with materials science to achieve clinical applications [10]. Recently, TE or regenerative medicine has become a promising technique for repairing damaged tissues to overcome the complications associated with conventional organ donation techniques. TE has become an alternative due to increasing demand for organ transplant in clinical medicine [11].

Scaffolds can serve as cellular systems or as delivery vehicles for cells and drug in cell and tissue regeneration; thus, the cellular material must be capable of adequately colonizing the host cell to meet the needs of regeneration and repair. The other alternative is to have the scaffolds combined with various types of cells that can improve the formation of tissues in vivo by osteogenic lineage or release specific soluble molecules for lineage. These cells may be selectively expanded ex vivo before implanting into the

target site [11]. The fabricated scaffold properties depend on the type of tissues that needs repair, whether they are hard tissues, such as bones, or they are soft such as neural tissues; for example, in the engineering of hard tissues, biological scaffolds are used to fill bone defects and should be able to withstand loads, in addition to leading in the development of new bone. The healing of bone depends on scaffold properties, such as size, shape, wall thickness, interconnectivity, and wall surface of scaffold pore as well as resorption kinetics, porosity, surface morphology, surface chemistry, degradation rate, and mechanical stability [10, 12]. These scaffold properties should be designed for a specific application, depending on factors, such as anatomical location, patient age, trauma severity, and other pathological conditions. The mechanical aspects of the scaffold, such as strength, must be resistant to physiological stress and reduce stress shielding. For example, in bone TE, TE is intended for recovery and regeneration of damaged neural tissues.

In cell regeneration, different types of cells (expanded or nonexpanded) extracted from a donor or a patient are included in the scaffold. Adult stem cells, such as bone marrow, fatty tissue, teeth, blood cells, embryonic stem cells, induced pluripotent stem cells (iPS cells), peripheral bloodderived stem, and genetically engineered cells, are the source of extended cells, while bone marrow aspirate-derived platelet-rich plasma cells are the main source for nonexpended cells [11]. These cells are created in different forms in vocal or in molecular molecules, hence, the importance of scaffold with specific properties. For example, hydrogels have been utilized for stimulating regeneration of spinal cord tissue because hydrogels can adapt to the mechanical aspects of spongy soft and viscoelastic neural tissue [3, 12]. Furthermore, gross mismatch between tissues and implant leads to death of façade tissues [3].

3. Scaffold Features for Tissue Engineering

Even though several studies have reported on numerous discoveries in TE, commercialization of these newly discovered functions have significantly increased due to the medical applicability of these findings. Thus, to improve the acceptance of clinical applications of such technologies, it is essential to incorporate specific biological, clinical, and mechanical aspects, which are not only theoretical but can play a role in practical implementation. An appropriate scaffold must be capable to repair body tissues with minimum requirements, for cell growth, vascularization, proliferation, and host integration, and finally, materials should be degraded naturally during or after the healing process [11]. However, a scaffold has specific characteristics related to the biological aspect, structure, and chemical composition [11].

4. Biological Characteristics

The biological aspects of scaffolds include their biocompatibility and nontoxicity properties. Cells grown in scaffolds must be able to reproduce and discriminate freely without interference to produce a new matrix [2, 13]. Therefore, a scaffold is considered an ideal scaffold for TE





FIGURE 1: 3D printer assembly and fabrication of the scaffold: (a) servo motor driving: (1) CO₂ laser, (2) laser scanner, (3) working platform, (4) scraper, and (5) feeder; (b) paving material; (c) start of 3D printing; (d) end of 3D printing [7].

applications if it can mimic the properties of ECM of tissues for perfect and complete regeneration. However, as already mentioned, the function of the supporting cell relies on parameters, such as the selected cell line, the underlying material, the surface properties, and the scaffolding structure [2].

Biocompatibility allows simultaneous formation of new tissue along with the degradation of the matrix. The matrix should not be toxic so that the system can dispose of it without disturbing other members [11]. The biological properties of a scaffold are a significant modulating problem as it affects the interaction of scaffolds with tissues and organs. Due to the low capacity of the biological material to cross-talk with the environment, efforts have been made to incorporate the bioactive scaffolds to promote proper cellular interaction, migration or differentiation, tissue information, and incorporation into the host and to use bioactive scaffolds to avoid undesirable processes such as scarring. Furthermore, it is necessary that the scaffold avoid host immune responses. Recently, the immune-inert biomaterials concept has been implemented, and its immune modulatory regulates the immune system (i.e., decreased NK cell activity and T and B cells mediated immunity) [11].

5. Structural Characteristics

Biological tissue is an incredibly complex 3D structure with complex mechanical functions associated with mass transport characteristics. Therefore, the critical objective of TE is to abridge this structural complexity and function using biological scaffolds that provide cells, proteins, and genes for tissue reconstruction. It is clear that the biological materials and structures cannot replicate complex tissue environments, including numerous cell types that interact with a variety of cytokines to produce extracellular matrices within cells with hierarchical properties that show mechanical function that exhibits high nonlinearity and two-phase [2]. The development of vascularized engineering scaffolds is one of the leading challenges due to the lack of vascular insufficiency leading to the inefficient incorporation of osseo specifying that material selection affects the final physical features of the scaffold [9, 11]. It is often desirable that the porosity of the scaffold must improve its mechanical properties to support cell growth. Additionally, the scaffold with appropriate pore size improves cell migration and water absorption [14] as well as promotes the high mass transfer of oxygen throughout the scaffold [15].

6. Chemical Composition

Typically, most scaffolds consist of polymers, bioceramics, and hybrid materials, whether natural or human-made [14]. Based on the source of materials utilized for fabricating the scaffold, there are concerns related to biocompatibility, composition, and decomposition products of such matrices. Even though a wide range of materials have been evaluated for a scaffold, it has been reported that some materials do not support cell growth within scaffolds [2].

Polymers are of two types, natural polymers or synthetic polymers. Natural polymers, like hyaluronic acid, fibrin, chitosan, and collagen, have good biological compatibility, low immunogenicity, and osteoconductivity. However, they suffer from free degradation rates and low mechanical stability [11]. Synthetic polymers, like polypropylene fumarate (PPF), polyanhydride, polycaprolactone (PCL), polyphosphazene, polyether ether ketone (PEEK), polylactic acid (PLA), and poly (glycolic acid) (PGA), exhibit controlled degradation rates. Additionally, they possess the ability to be fabricated into complex shapes and have improved cell attachment (negatively-charged chemical groups) and the capability to deliver soluble molecules [11]. Furthermore, synthetic polymers can be produced at low cost, in large quantities and have a longer shelf life [11].

Some in vitro studies have reported that the material itself can destroy the results of ex vivo tissue formation compared to natural tissue matrices. Also, in in vivo situation, impaired regeneration can be strongly affected by material immunogenicity, unexpected degradation time, and side effects stemmed from degradation products. Depending on these considerations, the matrices closest to the natural extracellular matrix are the most promising in TE. Therefore, the recently developed approaches in the process of extracorporeal tissue engineering are to prevent nonbiodegradable scaffolds that are reabsorbed at time rate different from skeletal tissue regeneration. Hence, new methods have been developed to overcome these problems by abandoning scaffolds.

7. Current Scaffold Manufacturing and Fabrication Technologies

At the in vivo level, a tissue consists of 3D units repeated with a scale ranging from 100 to $1000 \,\mu\text{m}$ (e.g., nephron, islet). The 3D structure of these repetitive tissue units is the basis for the coordination of multicellular processes, developing of mechanical properties, and incorporation with different organ systems via microcirculation. Thus, the scaffolds are designed to achieve this evolution in 3D cells by providing mechanical support during tissue repair [16]. The local cellular environment is another significant component of tissue at the in vivo level. The microbiological environment (~10 μ m) is responsible for biochemical, cellular, and physical catalysts signaling pathways included in cellular fate processes such as differentiation, proliferation, migration, and death. Thus, successful fabrication of entirely functional scaffolds should be addressed in two levels: (a) microscale level should contain an environment suitable for cell survival and function and (b) macroscale tissue construction should permit the coordination of multicellular processes, provide adequate transport of nutrients, and possess mechanical properties.

In practice, the techniques of the fabrication of 3D scaffolds are subdivided into a conventional or rapid prototyping (RP) method (Table 1), each producing different scaffolds with different characteristics [11]. Conventional techniques of scaffolding fabrication include the construction of porous polymer structures such as substrates for cell adhesion, but it is difficult to obtain complex structures with tunable microscale and macroscale using conventional methods [16]. The RP scaffold fabrication technique provides a plethora of potential opportunities for tissue engineering. Firstly, the independent control of macroscale and microscale features allows the fabrication of multicellular structures needed for complex tissue functions. Secondly, three-dimensional vascular beds fabrication will allow support of massive tissue formation that otherwise would have been possible. Thirdly, combining clinical imaging data and 3D fabrication techniques can provide the possibility of production of customized scaffolds as well as mass production of the scaffold designs [15, 17].

7.1. Conventional Fabrication Techniques. A significant number of scaffolds have been developed conventionally for drug delivery, but they have subsequently been used in 3D cell culture in the context of TE [18]. The traditional techniques of scaffold fabrication like solvent casting/ particulate leaching are intended to define the scaffold shape and pore size but are mostly limited to the prior the scaffold internal design or connectivity of the void space [16, 18].

7.2. Solvent Casting and Particle Leaching. In this technique, a solvent combined with uniformly distributed salt particles of a certain size is used to dissolve the polymer solution. The solvent evaporates leaving a matrix containing salt particles. The matrix is then submerged in water, and the salt leaches away to form a structure with high porosity. The solvent casting with particle leaching only fits thin membranes of thin wall three-dimensional specimens; otherwise, the soluble particles cannot be separated from within the polymer matrix [19]. Scaffolds developed by this method have a porosity between 50% and 90% [13]. This technique is relatively easy and low cost. One of the main benefits of this technique is that the produced scaffold is of high porosity and with the capability of tuning the pore size, which makes it appropriate for the development and growth of the 3D cell [10].

| Fabrication technique | | Advantages | Disadvantages |
|---|--|---|---|
| Conventional fabrication techniques | 1. Freeze-drying | Use in a variety of purposes Capability of obviating high temperatures The pore size is manageable to be controlled by changing the freezing method [20] | High energy consumption Long-term timescale The use of cytotoxic solvents The generation of small Irregular size pores (usually in the |
| | 2. Solvent casting and practical leaching | Fits thin membranes of thin wall three-dimensional specimens High porosity (50–90%) Lost cost technique | range of 15 to 35 μ m) 1. Time consuming since thin membranes are only used 2. The widespread use of very toxic solvents 1. If the fobrication process did not |
| | 3. Gas foaming | 1. Porosity up to 85% | change, the product obtained might have a closed pore structure or a solid polymeric skin |
| | 4. Electrospinning | Essential technique for developing nanofibrous scaffolds for the TE Homogeneous mixture made of fibers with high tensile strength | Used solvents can be toxic Problematic to obtain 3D structures as well as sufficient size of pores needed for biomedical applications Process depends on many variables |
| | 5. Thermal-induced phase separation | Construction of the thermoplastic crystalline polymer scaffold Low temperature can be utilized for the integration of bioactive molecules The porosity of fibers is more than 98% a higher surface-to-volume ratio than those constructed | Only used for thermoplastic |
| Rapid prototyping (RP) | 1. Stereolithography (SLA) | Enables to overcome the challenges related to wastage in subtractive fabrication methods High resolution Uniformity in pores interconnectivity | Has limitations in the process of photopolymerization Requiring massive amounts of monomers and postpolymerization treatment to improve monomer conversion |
| | 2. Selective laser sintering (SLS) | Using ultrahigh-molecular-weight polyethylene Provides user excellent control over the microstructures of the produced scaffold by an adapting SLS process parameters Utilized to obtain the preferred properties of the created scaffold | Steps after processing the spin of the phase are required to remove injected powder High operating temperature |
| | 3. Solvent-based extrusion freeforming (SEF) | It can be utilized to make ceramic, metal, and metal/ceramic composite part It can directly or indirectly function in printing the actual part or a mould It is a new fabrication method for tissue engineering that can be utilized for precise control of scaffold structure at the micron level Success involves the ability to strictly follow the structure of the natural tissue and the mechanical characteristics of the scaffold Low costs | 1. Temperature extrusion. Their design includes a change to the factors affecting extrusion pressure, including nozzle length-to-diameter ratio, a paste formulation, and the extrusion velocity |
| | 4. Bioprinting 5. Fused deposition modeling (FDM) | 2. Higher accuracy and greater shape complexity 3. The high speed of printing with the capability of supporting parallel high cell viability (80/90%) 1. Useful in the scaffold design under the different aspect of scaffold fabrication. Low-temperature deposition | Depends on existence of cells Has limitations in its application to biodegradable polymers [13] |

TABLE 1: Classification of the scaffold fabrication technologies.

Thanh et al. [21] suggested PLA/MD-HAP/PEO porous nanocomposite for application in bone engineering from polylactic acid (PLA), which was combined with different NH₄HCO₃ contents with different progenies by solvent casting with particle leaching technique. Other researchers have also applied this technique in the scaffold fabrication for different purposes, such as the combination of natural polymers [22, 23] or the integration of bioactive compounds into the scaffold [24, 25].

One of the drawbacks of this fabrication technique is its time consumption since it only uses thin membranes. Layers of porous sheets allow only a defined number of pore networks between them and may, therefore, limit its suitability to use because of the limited porous size [24]. This technique applies various toxic solvents which take a lot of time to evaporate (days or weeks).

7.3. Freeze-Drying. The process of freeze-drying is also known as lyophilization; it involves the use of a synthetic polymer that is first dissolved in an appropriate solvent. After dissolution, the polymer solution is cooled under the freezing point, resulting in a solid solvent that is evaporated by sublimation to leave a solid scaffold with numerous interconnected pores [11]. In this technique, when the solution is cooled to freezing point, the solutes can be separated in the ice phase resulting in a small porous structure characterized by a "fence" of matter surrounding the ice. The scaffolds are achieved after consequent drying; by simple dissolving and freeze-drying, the macro porosity corresponds to the empty area initially occupied by ice crystals. The benefit of this technique is the capability of obviating high temperatures that could decrease the activity of integrated biological factors. Also, the pore size is manageable by controlled and changing the freezing method [26]. This method has been utilized in the fabrication of BG-collagenphosphatidylserine scaffold with corresponding interrelated pore measuring about $300 \,\mu\text{m}$. It has been shown that it is capable of forming complexes with calcium and phosphate and nucleate HA formation. Many researchers reported that the method is thriving in the scaffold fabrication for use in a variety of purposes [9]. Min and Lee [27] applied this technique for a three-dimensional scaffold fabrication using chitosan nanoparticles. Additionally, Jayachandran et al. [20] reported on the production of chitosan-alginate biocomposites involving fucoidan for a bone tissue by lyophilization. Their scaffold has promising properties on porosity and water absorption. Additionally, Aranaz et al. [26] also reported a similar strategy. Although this technique is widely utilized in the fabrication of scaffolds, it still has several disadvantages such as high energy consumption, long-term timescale, the use of cytotoxic solvents, and the generation of small and irregular size pores (usually in the range of 15 to $35\,\mu\text{m}$) [28]. To overcome these problems, Géraldine et al. [29] suggested varying the freezing temperature (-10°C to-70°C) and the introduction of an additional annealing step to increase the growth rate of the ice crystal.

Freeze-drying technique is a more suitable method in biomedical application because of the use of water and ice crystals instead of an organic solvent during scaffold fabrication; however, this methodology is challenged in the fabrication of hierarchical structured scaffolds such as vascular systems in biomedicine [30]. Additionally, this method also uses cytotoxic solvents for mixing the polymer; hence, the fabricated scaffold needs to be washed repeatedly to remove the solvent and to minimize cell death.

7.4. Thermal-Induced Phase Separation (TIPS). TIPS is a low-temperature method designed to force phase separation via the temperature alternate related to setting the homogeneous polymer solution with a high temperature in a

decrease temperature environment to induce phase separation so that a polymer-rich phase, as well as a poor polymer phase, is achieved [13, 15]. A porous scaffold structure can be achieved when the solvent is eliminated with the aid of freeze-drying leaving a relatively porous, nanoscale fibrous network. This method can be utilized for the construction of the thermoplastic crystalline polymer scaffold. Low temperature can be utilized for the integration of bioactive molecules within the fibrous scaffold material. Blaker et al. [31] proposed a new fabrication approach via the use of TIPS to obtain microspheres for TE and drug delivery; this technique made it practical to adjust the pore sizes to allow inclusion of fillers and drugs. The inclusion of proteins within the pore areas was proven to be homogeneously disbursed together with more suitable exposure time when exposed to solvent/water interphase. Smith et al. [32] introduced a comparable approach for the construction of nanofibrous scaffolds which have been integrated with different components accomplishing pore sizes between 50 and 500 nm, thus making them as close to mimic the tissue structure. The main drawback of this technique is that limited materials can be used in fabrication and inadequate resolution.

Phase separation holds great potential in fabrication of 3D nanofibrous scaffolds with uniform pore structures through dual or multiple phase separation processes compared to electrospinning [30]. Additionally, Phase separation technique can be used together with other fabrication techniques such as solid free-form (SFF) in TE.

7.5. Gas Foaming. Gas foaming technique is a technique that has been evolved to cope with using high temperature and organic cytotoxic solvents. This technique uses relatively inert gas foaming agents such as carbon dioxide or nitrogen to pressurize modeled biologically degradable polymer with water or fluoroform until they are saturated or full of gas bubbles. This technique usually produces structures like a sponge with a pore size of 30 to 700 μ m and a porosity up to 85% [15]. The drawback of this technique is that at times, the product obtained might have a closed pore structure or a solid polymeric skin. To solve this problem, Harris et al. [33] improved the process to achieve a very porous product with improved porous connectivity. In vitro studies on material have shown that seeded cells would adhere to the matrix and continue to take on 3D tissues.

7.6. *Electrospinning*. Electrospinning is known as a technique for making fibers from a solution by using electricity. This technique is vital for developing nanofibrous scaffolds in TE. Electrospinning is a very complicated technique in which charging liquid under high voltage leads to the interaction between the surface tension and electrostatic repulsion that causes droplets on spinneret to erupt and stretch. A standard electrospinning system consists of four main components: a spinner with a syringe pump, a metallic needle, a high-voltage power supply, and a grounded collector, as shown in Figure 2. The strength of the electric field exceeds the surface tension of the droplet to produce a liquid jet that is then extended and



FIGURE 2: Electrospinning device.

whipped continuously by electrostatic repulsion until it is deposited on the grounded collector. The solvent evaporates in the process, and the jet is solidified to form into a nonwoven fibrous membrane [13, 15].

Bofan et al. [34] applied electrospinning to make composite fibers consisting of spider dragline silk protein and collagen. The study reported to create a homogeneous mixture made of fibers with high tensile strength. In vitro, other studies have stated that the fabricated matrix can support the spread of human choroid decidua parietalis placental stem cells (hdpPSCs). Sarhan et al. [35] applied the same method by integration of antimicrobial agent in the fabrication of a nanofibre of wound dressing materials. Thus, the fabricated scaffolds showed to have active antimicrobial agents against Staphylococcus aureus, Escherichia coli, methicillin-resistant S. aureus (MRSA), and multidrugresistant Pseudomonas aeruginosa. In order to combine the benefits of both synthetic and natural polymers, chitosan-based blend nanofibers have been fabricated via electrospinning using chitosan and synthetic biodegradable polymers such as poly lactic acid (PLA) [36, 37].

Even though electrospinning is a simple and quick method in fabrication of nanofibrous scaffolds, there still exists a challenge in fabrication of scaffolds with complex structures such as homogeneous distribution of pores, hence limited applications in biomedicine [30].

7.7. Rapid Prototyping (RP). Rapid prototyping (RP) technologies, also known as solid free-from fabrication (SFF), are a set of manufacturing processes that can generate direct forms directly from computer-aided design (CAD) models of an object without needing specific tooling or knowledge. The RP systems combine powder, liquid, and sheet materials to make parts compared to machining methods (e.g., milling and drilling). Layer by layer, rapid prototyping machine can produce wood, ceramic, plastic and metal objects using thin horizontal cross sections from a computergenerated model [23]. RP scaffold fabrication technique enables manufacturing of designs with precise spatial control over polymer structure to deal with some of the challenges in traditional production methods [17]. The main benefit of these techniques is that they enable the production of customized and patient-specific scaffolds suitable for tissues and organs in question [15]. The basic RP techniques include 3D printing (3DP), fused deposition modeling (FDM), selective laser sintering (SLS), and stereolithography [13, 15].

7.8. Stereolithography. Stereolithography method is basically used to creating solid, three-dimensional objects by consecutively printing a thin layer of ultraviolet (UV) curable material layer-by-layer. A stereolithography system (Figure 3) has four main components, namely, a tank with a photosensitive liquid resin, a transferable built platform, a UV laser for radiating resin, and a dynamic mirror system. The process begins with a UV laser by depositing a layer of photosensitive liquid resin on the platform. After the solidification of the initial layer, the platform is lowered vertically. A second layer is then placed on the first layer; the process is repeated until a 3D scaffold is created. Finally, the uncured resin is cleaned off, and the scaffold is postcured under UV light. Therefore, this method overcomes the challenges related to wastage in subtractive fabrication methods. Melchels et al. [38] applied stereolithographic method in the construction of scaffold structures of sophisticated design at high resolution. The designs were made using poly (D, L-lactate) or poly (D, L-lactide-co-e-Caprolactone) based resin. The study reported that when the mechanical evolution of the scaffolds was carried out, the scaffold conformed to finite element predictions. Similarly, Robert et al. [39] applied an equivalent method in the design of 3D scaffolds using gelatin methacrylate to obtain a specially designed scaffold with precise mechanical properties as needed. The scaffold that they created showed uniformity in pores interconnectivity within in vitro studies reporting that it supported the distribution and proliferation of the human umbilical vein endothelial cells (HUVECs) making it suitable for TE use. Although many types of research showed the success of stereolithography in



FIGURE 3: Stereolithography (SLA).

scaffold design, the method also has limitations in the process of photopolymerization, requiring massive amounts of monomers and postpolymerization treatment to improve monomer conversion [40].

Studies have reported that stereolithography technique has the potential to fabricate different types of cellular machines that could have applications in a broad spectrum of disciplines, such as biosensing, environmental remediation, drug discovery, and energy harvesting, making it a powerful biofabrication technology. However, the feature size of a scaffold that can be fabricated is limited to the beam width of the laser [41].

7.9. Fused Deposition Modeling (FDM). In FDM technique, a solid polymer is cast into a hot extrusion nozzle to be melted and extruded on the surface of 3D object using a computercontrolled extrusion and deposition processes; the scaffold is made from multiple layers of adjacent microfilaments. FDM has been utilized to process thermoplastic biopolymers, Hutmacher et al. [42] used biologically degradable polyesters to create nonwoven scaffolds to help the cells grow in TE. Additionally, Zein et al. [43] demonstrated the versatility of modeling new scaffold structures with controlled mechanical properties using this FDM; the study reported to produce a polymer bioresorbable poly (e-caprolactone) (PCL), a primer material that is used to produce porous scaffolds. Generally, form several studies, FDM is useful in the scaffold design under different aspects of scaffold fabrication [44]. The main setback in FDM is the need for preformed consistent-sized fibers to feed through rollers and nozzle; it also has limitations in its application to biodegradable polymers [15]; to overcome these drawbacks, many modified FDM processes have been proposed. Xiong et al. [45] confirmed the use of lowtemperature deposition manufacturing use in fabricating composite scaffold for the engineering of bone tissue. Additionally, the study reported that the scaffold showed excellent biocompatibility, suitable biodegradation, and bone conductivity properties for bone repair.

7.10. Selective Laser Sintering (SLS). SLS was developed in 1986 by Texas University of Austin. This technique uses laser as the power source to sinter powdered material defined by a

3D model in thin layers. Due to the use of a laser, this technique has been utilized to make various materials, such as polymers, metals, or ceramics [46]. The efficiency of this technique has been shown in the fabrication of scaffold using ultrahigh-molecular-weight polyethylene [47] and in fabricating of bionanocomposite microspheres composing of that PLLA that can efficiently produce microspheres carbonated hydroxyapatite (CHAP) nanospheres within a poly (L-lactide) (PLLA) matrix, in order to build TE scaffold [48]. The SLS is an advantageous technique since it provides excellent user control over the microstructures of the produced scaffold by adapting various SLS process parameters such as percentage compositions of physically mixed polymer/composite powder blends to be utilized to obtain the preferred scaffold properties [47]. One of the main drawbacks of SLS is that additional procedure is required to remove injected powder at high operating temperature after processing the spin of the phase [47].

7.11. Three-Dimensional Printing (3DP). 3DP is a process of creating tools and functional prototype features directly from the computer models, as described in Figure 4. 3DP technique is performed by applying the powdered material in layers and the selective fusion of the powder by "inkjet," where the adhesive is printed. After continuous deposition of the layers, the unbound powder is taken out, yielding a complex 3D object. This process can be utilized to make ceramic, metal, and metal/ceramic composite part. The 3DP process can directly or indirectly function in printing the actual part or a mould [49]. 3DP is a new fabrication method for TE that can be utilized for precise control of scaffold structure at the micron level. Although its success involves the ability to strictly follow the structure of the natural tissue and the mechanical characteristics of the scaffold, the scaffolds produced by 3DP technique have limited emulating of the nanoscale extracellular matrix properties of the tissue they aim to replace [50].

Studies have demonstrated the design of poly (dopamine) coatings for 3DP poly (lactic acid) scaffolds for bone tissue engineering [50]. In addition to promoting osteogenesis, coatings were shown to improve cell adhesion as well as proliferation. Modified 3DP technology has been developed to improve the produced scaffold to mimic the



FIGURE 4: Three-dimensional printing (3DP).

specific tissue [15]. Kao et al. [51] confirmed the utilization of cold atmospheric plasma (CAP) as an effective and quick way to change some properties of 3D printed scaffold surface, such as nanoscale roughness and chemical composition. The technique showed high effectiveness in producing superior scaffolds with better nanoscale roughness and the ratio of oxygen to carbon as well as maintained water contact angle after CAP-based treatment compared to untreated 3D PLA scaffolds. Zhong et al. [52] introduced the modified 3DP technology designed for printing high-quality ceramic scaffolds under low-temperature extrusion. Their design includes a change to the factors affecting extrusion pressure, including nozzle length-to-diameter ratio, a paste formulation, and the extrusion velocity. Results presented in the study showed that low-temperature extrusion 3D printed scaffold had uniformity of its microstructure after printing parameter optimization. Yang and Vaezi developed a lowcost production technology to 3D print scaffolds and compression moulds of bioactive PEEK/HA composites for bone tissue engineering [52, 53, 54]. Table 2 depicts the process and methods of the technique as it is applied to create a bioactive PEEK/HA composite for bone tissue engineering scaffolds [52].

7.12. Bioprinting. Bioprinting is a 3DP technique, defined as "using material transfer processes for developing a biological pattern and assembly of relevant materials, cells, molecules, tissues, and biodegradable biomaterials with a prescribed structure to achieve some biological functions" [55]. The introduction of solvent-free, aqueous-based systems allows the direct printing of biomaterials on three-dimensional scaffolds for transplantation with/ without seeded cells [55]. In general, bioprinting enables personalized medicine by using the technical form of cell growth (illustrated in Figure 5). Currently, the technologies of 3D bioprinting can be classified into two types, namely, acellular and cellular constructs. Using acellular bioprinting, the scaffold and biomaterial can be produced without a cell during the printing process. In comparison with cellular bioprinting, acellular bioprinting can deliver a higher accuracy and greater shape complexity because it has less restrictive fabrication conditions than methods requiring the cell viability maintenance. Cellular

bioprinting integrates cells and other bioagents with the material during the production process to fabricate living tissue constructs. Therefore, the conditions and optimization of parameters in the construction of these constructs vary depending on existence or inexistence of living cells as well as biological substances.

There are numerous different ways of 3D bioprinting, among which autonomous self-assembly, biomimicry, and minitissue building block are based on [55]. Currently, microextrusion, laser-assisted, and inkjet printing are the most widely used methods for the deposition and patterning of biological materials [15, 55]. Inkjet bioprinting is known as a noncontact technique that uses picolitre bioink droplets to construct 2D or 3D structures layered onto a substrate. Thermal ink jetting, acoustic wave jetting, and electro-hydrodynamic jetting are typical examples of material jetting techniques. These techniques have several advantages, such as low costs because of its similarity to the structures of a commercial printer, high speed of printing with the capability of supporting parallel work mode, and high cell viability (80/90%). However, the major challenges are that the method includes the narrow material selectivity, the frequent print head clogging [15], and keeping the biological material in liquid form for droplet formation [55].

In contrast, microextrusion bioprinting includes a temperature-managed material handling and dispensing system and stage, with either one or both being able to move along the *x*, *y*, and *z*-axes. The fiber-optic-based light source could be used to eliminate the deposition area for photoinitiator activation and photographers' activity and as a piezoelectric humidifier and a video camera to command and control for x-y-z. Some systems use more than one print heads to make the serial dispensing of several materials easy without retooling. Microextrusion printers are controlled by removing robot-controlled extrusion of material deposited on a substrate using a microextrusion head. Microextrusion generates continuous material beads instead of liquid droplets. Small beads of material are deposited in 2D. Based on CAD-CAM software, the microextrusion head is moved alongside z-axis, and the deposited layer is the basis for the subsequent layer. Many materials correspond to microextrusion printers, among which are biodegradable copolymers hydrogels and cell spheroids [55].

| Step | Process | Diagram | Method |
|------|--|---|--|
| 1 | Preparation of ceramic paste | Bioceramic (binder) PEG (plasticizer) | Adhesive binder polyvinyl butyral (PVB) and plasticizer polyethyleneglycol (PEG) are fully dissolved in propan-2-ol solvent with the ratio of 75% (w/v) PVB and 25% (w/v) PEG. HA ceramic powder is then added to the solution (with 60% (v/v) of ceramic based on the dried paste) and stirred for 2 hours to achieve a well- dispersed solution |
| 2 | Solvent evaporation | Solvent Blowing hot air evaporation Well-dispersed solution | Excess solvent is evaporated by fast stirring and blowing hot air (such as using hair dryer) until a viscous ceramic paste is achieved |
| 3 | 3D printing | | Ceramic paste is loaded into a syringe for 3D printing. The extrusion process forms lattice-shaped 3D scaffolds by incrementing regularly arranged 2D layers in the vertical axis |
| 4 | Drying, debinding, and sintering of the scaffold | Image: second | The scaffold is left at room temperature for 24 hours to allow evaporation of excess solvent and subsequently to place the scaffold in an oven for debinding and sintering. Different heating procedures can be applied depending on the type of ceramic, such as the maximum sintering temperature for HA is 1300°C with a dwelling time of two hours. The bioceramic scaffold is then obtained |
| 5 | Compression moulding of PEEK powder into the HA scaffold | Heating element Mould PEEK powder compression moulding Using both static and dynamic loads to produce a PEEK/HA composite | Static loading: the mould is heated up to 250°C and then load is applied until the temperature reaches 400°C, maintained for a further 20 minutes (dwelling time) and then heating is stopped, and the mould is left to cool under pressure. Dynamic loading: the mould is heated up to 400°C and maintained for 20 minutes. Load is applied for 5 seconds before heating is stopped and then the mould is left to cool under pressure, whereby the PEEK matrix crystallized and solidified |
| 6 | Obtaining bioactive PEEK/HA composite | PEEK/bioceramic composite with interconnected bioactive phase | Composites are removed from the mould when the temperature has fallen to just below the glass transition temperature (143°C), followed by cooling to room temperature, thus mitigating thermal stress and cracking |

TABLE 2: The method for fabricating bioactive PEEK/HA bone scaffolds.

Laser-assisted bioprinting is a technique based on laserinduced forward transfer. A typical system includes a pulsed laser beam coupled with a focusing system; a "ribbon" with donor transport support covered with a layer of gold or titanium able to absorb laser energy and a celland-hydrogel-containing layer of biological material; and a receiving substrate facing the ribbon. The laser-assisted bioprinter directs laser pulses on the laser-absorbing gold layer of the ribbon leading high-pressure bubble, which in turn drives the cell-containing materials to the collector substrate. One of the benefits of this method is that it has nothing to do with the problem of nozzle clogging with cells or material because it is nozzle free. Moreover, it shows compatibility with some biomaterial's viscosities (1–300 mPa/s). It has been first applied to print a nano-HA scaffold in mice calvarial defects, using a workstation specified to the high throughput biological laser. Before laser printing experiments, it was shown, by MRI, the nonexistence of inflammation due to laser irradiation on mice dura matter. Preliminary results indicated that in vivo bioprinting is feasible and can be utilized for future medical robots and computer-assisted interventions [55, 56]. Even though this method has shown some advantages, the high-resolution LAB entailed rapid gelation



FIGURE 5: Schematic illustration of the bone tissue engineering paradigm.

kinetics to accomplish high shape fidelity, resulting in a relatively low flow rate.

8. Conclusions and Perspectives

Tissue engineering is an interdisciplinary field constructed on a broad range of areas, so the development of this field has been obtained by numerous biomedical 3D scaffold fabrication techniques comprising conventional and current scaffold manufacturing technologies. The conventional methods are solvent casting and particle leaching, freeze-drying, TIPS, gas foaming, and electrospinning, while the modern methods (rapid prototyping) have included stereolithography, fused deposition modeling (FDM), selective laser sintering, and three-dimensional printing. Based on the previous literature and this review, the TE technique is a modern technique in the construction of scaffolds to be used in tissue and organ structure. Both benefits and drawbacks of each of the fabrication techniques mentioned above have been described in conjunction with current areas of research devoted to deal with some of the challenges.

To sum up, the highlighted aspect is aimed to define the advancements and challenges that should be addressed in the scaffold design for tissue engineering. This study provides an excellent review of original numerical approaches focused on individual characteristics of the fabrication techniques that can be helpful in the choosing the suitable scaffold design method for assessment and analysis of scaffold parameters in tissue engineering. According to all mentioned information in this text, we found that the prototyping techniques represented the modern aspect of fabrication of scaffolds for different applications. In addition, nonstop growing of technology and synthesizing materials will help in appearance of other new methods. And among prototyping techniques, 3D printing will play an important role in large applications that concern the scaffold-based field.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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