Chapter 7
Polymeric Nano-Composite Scaffolds for Bone Tissue Engineering: Review

Lokesh Kumar and Dheeraj Ahuja

Abstract Bone tissues have an amazing ability to repair and regenerate. However, complex bone fractures and defects still present a significant challenge to the researchers in biomedical field. Current treatments center on autograft-allograft and metal implant to substitute bone loss. While metal implant and allograft treatments are associated with several complications such as donor site morbidity and limited supply of material. Therefore, scaffolds can provide a new method to resolve such problems by restoring and improving tissue functions. An ideal scaffold should have biocompatible and biodegradable, as well as suitable 3D porous interconnected structure to facilitate cells and tissues in growth with proper circulation of bone mineralization. To date, various biomaterials are available for bone tissue engineering including ceramics, polymers and composites composed by calcium and phosphate bone minerals. Polymeric scaffolds can be modified to improve bioactivity and osseointegration mechanical strength in order to tailoring biological properties. In this chapter, strategies and techniques to engineer new kind of polymer surface to promote osteoconduction with host tissues will be discussed. Also, benefits and applications of polymeric composite scaffolds for orthopedic surgery will be discussed.

Keywords Tissue engineering · Polymer scaffold · Osteoconductive · Biodegradable

Abbreviations

HA Hydroxyapatite

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Visakh P. M. *Biodegradable and Environmental Applications of Bionanocomposites*, Advanced Structured Materials 177,
https://doi.org/10.1007/978-3-031-13343-5_7

TE	Tissue engineering
PLA	Polylactic acid
PU	Polyurethane
ECM	Extracellular matrix
PCL	Poly(caprolactone)
PGA	Poly(glycolic acid)
PMMA	Polymethylmethacrylate
PA	Polyamide
PLGA	Poly(L-lactic-*co*-glycolic acid)
TIPS	Thermally induced phase separation
PLA	Polylactide
TCP	Tri-calcium phosphate
TEA	Triethanolamine
DEA	Diethanolamine
PEG	Poly(ethyleneglycol)

7.1 Introduction

7.1.1 Scaffold for Bone Tissue Engineering

An extensive variety of clinical methods have been utilized for replacement or repair of bone or tissue damaged due to any disease or injury. Currently, the most widely utilized healing practice is based on three types of donor graft tissues: allograft, autograft and xenografts. The major limitation of utilizing these healing practices is less availability of donor and donor sites, higher morbidity rate, chances of disease transmission and rejection of grafts [1]. This limitation can be overcome by tissue engineering. Tissue engineering reproduces the damaged tissue by developing biological substitutes rather than restoring them with grafts. This helps in reviving and improving tissue function [2–4]. The first article on tissue replacement was published by Gaparo tagliacozzi in 1597 [5]. Tissue repair and regeneration are natural healing processes that take place after damage on patient's body. For example, liver is one of the organs of human body that can be regenerated after fractional noxiousness [6].

The tissues can be reproduced in two different ways. The first way includes isolation of cells from patient's body and growing them on three-dimensional scaffolds under controlled conditions. The tissues so cultured are then replaced with the defected tissue, and the scaffold is degraded over the time. Another way is directly growing tissue in vivo utilizing scaffold that instigates and targets growth of tissue. The in vivo method, i.e., direct growth of tissue in patient body, is beneficial over in vitro, i.e., growing tissue in culture and then replacing as for in vivo tissue grows in situ and patient's cells are not required. The combination of both in vivo and in vitro is known as tissue engineering triad and is shown in Fig. 7.1. This triad

generally works on three fundamentals, i.e., signaling mechanism, cells and extracellular matrix (ECM). ECM holds the cells and helps in regeneration and development of tissues [7]. The fundamental conception is to utilize inherent biological responses to tissue damage in conjunction with engineering fundamentals [8]. In tissue engineering, regeneration of bone tissue is widely studied area. As per bone tissue engineering fundamentals, bone tissue equivalents are developed by targeting osteogenic differentiation of multipotent mesenchymal stem cell of bone marrow [9]. It is being utilized for implant surgery, where the objective is to harvest the ideal tissue engineered bone construct [10, 11].

Tissue regeneration process is generally achieved by implying three steps that help in attainment of entire process. The first steps involve inoculation or transportation of grown cells to a damaged or injured site followed by transmission of tissue producing biomolecules to a targeted tissue. The final and third step involves growth and differentiation of a required cell type in 3D scaffolds. Among all these three steps or approach, tissue engineering based on scaffold is gaining attention as it has the possibility of assimilating chemical, physical and biological stimuli with scale variation for cell activity.

Therefore, in the last two decades research in the arena of scaffold-based tissue engineering has increased at a rapid rate [12, 13]. Among the varieties of scaffolds, research on biodegradable polymeric scaffolds for tissue engineering is gaining much attention as they cater sensual and structural surroundings for growth of cells and tissue [14–17]. Scaffold is central component that is utilized for delivering drugs, cells

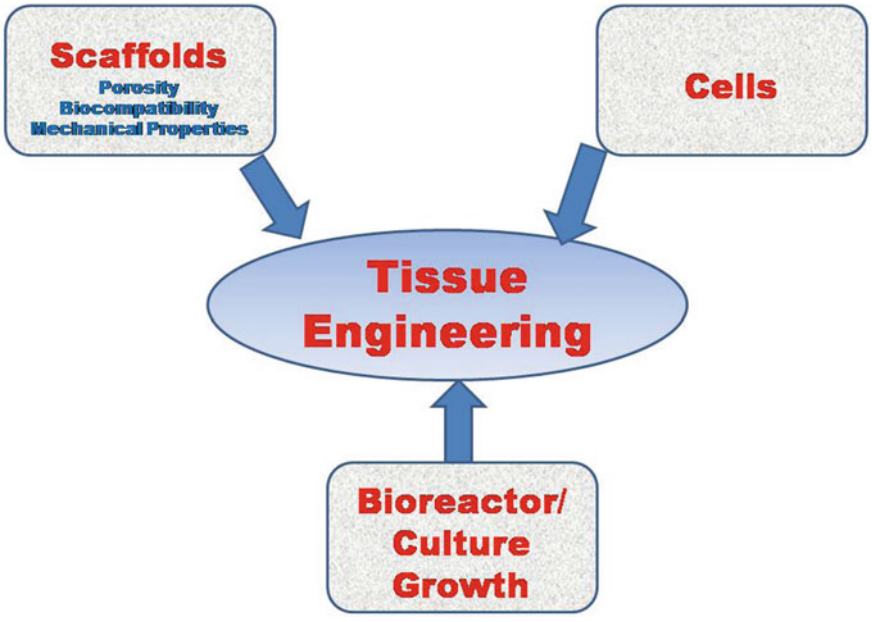

Fig. 7.1 Tissue engineering system (triad)

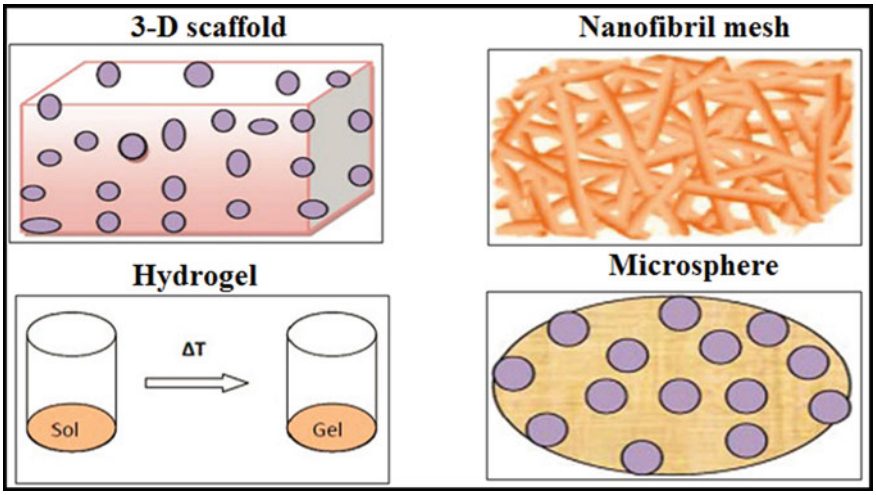

Fig. 7.2 Different types of polymeric scaffolds for cell and drug delivery

and genes into the patient's body. On the basis of this, scaffolds are classified as cell delivery scaffold and drug delivery scaffold. Implantation of cells into fabricated arrangement capable to support 3D tissue formation is referred as "cell delivery scaffolds," while fabricated arrangements capable of high drug loading efficiency and drug release for longer duration are known as "drug delivery scaffolds" [18, 19]. Polymeric scaffolds being utilized for cell or drug delivery application include 3D porous matrix, a nanofibrous matrix, a thermoresponsive sol–gel transition hydrogel and a porous microsphere as shown in Fig. 7.2 [20–23]. These all are being utilized for constant drug discharge formulations and have been practiced in tissue engineering for their possible usage as a cell delivery carrier or supportive matrix [24].

7.2 Properties of Scaffold

Scaffolds are three-dimensional structures formed by the implantation of cells that helps in cell formation. They also help in repositioning of contained structure and generating adequate mechanical settings for the proper healing of the organ by providing mechanical support. Also, they help in growth and attachment of cell, thereby leading to cell formation. Further, it also drops and absorbs cells and biomechanical factors, enables diffusion of vital cell nutrients and expressed products along with exerting specified mechanical and biological influences to change the performance of cell phase. Once the patient's body part or organs is healed, the extraneous part is required to be detached from human body together with clinical and biomechanical point of view. Hence, there are some of the key characteristics that must be considered while fabricating 3D scaffolds for tissue engineering. Generally, the

Table 7.1 Essential properties required for smooth functioning of cell delivery scaffolds and drug delivery scaffolds for tissue engineering

Cell delivery scaffolds	Drug delivery scaffolds
• Tolerable tensile properties to defense cells from tensile forces [32]	• Uniform distribution of drug all over the scaffold [33]
• Desired volume, mechanical strength and shape [34]	• Capability to deliver the drug at fixed interval of time [35]
• Admissible biocompatibility [14]	• Low drug abiding affinity so as to allow stable drug delivery during scaffold injection at a physiological temperature [36]
• Bioadsorption at fixed interval of time [37]	• Dimensionally, structurally and biologically balanced activity for longer duration [36]
• Biocompatible chemical combination with minimum allergic and immune responses [38]	
• An extremely porous and interrelated open pore architecture to concede high cell seeding density and tissue in growth [39, 40]	
• Physical architecture to hold cell adhesiveness and propagation [41]	

scaffold should be biocompatible and possibly biodegradable with desirable surface properties for cell adhesion, mitigation and normal functionality persuaded by the desired mechanical strength and porosity to be able to integrate with the surrounding tissue [17, 25, 26]. In addition, size of scaffold must be identical to the injured surface. Furthermore, biological signals from scaffolds such as small drug molecule, growth factors and cytokines in vitro and in vivo should be delivered in controlled manner as they are important parameters for foundation and enrichment of tissue morphogenesis, viability and functionalities [27–29]. Hence, fabrication should take into account the physico-chemical properties for the release of required biomolecules to direct and regulate biological responses of the cells into particular tissue.

As described in the above section that scaffolds for bone tissue engineering are classified as cell delivery scaffolds and drug delivery scaffolds. Some of the important properties that both types of scaffolds should possess for effective tissue engineering are mentioned in Table 7.1 [30, 31].

Apart from the abovementioned properties for cell delivery and drug delivery scaffolds, some of other important properties that should be considered for scaffold tissue engineering are discussed below:

7.2.1 Biocompatibility

It is referred as the ability of a material to meet the desired application without performing an allergic or harmful immune effect. The scaffold prepared to be seeded

should have admissible biocompatibility and toxicity profile [42]. Also, it must have sufficient surface chemistry for cellular attachment, differentiation and proliferation [43]. Further, it should adhere to the cells with minimal interruption of surrounding tissues. Variety of tissue responses are attained from seeding of scaffolds depending upon their composition [44]. When the scaffold seeded is nontoxic and degradable, new tissue is generated while the nontoxic and biologically effective scaffold assimilates with the neighboring tissues. In case the scaffold is biologically inactive, it may be enclosed with fibrous capsule, whereas it is rejected from the body resulting in the death of neighboring tissue when it is toxic [45–48]. Samandari and Samandari [49] studied the biocompatibility of prepared chitosan-graft-poly(acrylic acid-co-acrylamide)/hydroxyapatite nanocomposite scaffold using multistep model by MTT assays on HUGU cells. It was found that scaffold has good cytocompatibility and cell viability and proliferation enhanced with reinforcement of hydroxyapatite. Kumar and Ahuja [50] synthesized aliphatic polyurethane nanocomposite utilizing modified hydroxyapatite and performed cell culture and in vitro studies in simulated body fluid. It was observed that surface was partially hydrolyzed and prepared nanocomposite was suitable for bone tissue engineering.

7.2.2 Biodegradability

It is referred as the chemical disintegration of a biomaterial by bacteria or other biological molecules inclusive of hormones, acids and body fluids [51]. The developed scaffold shall be degradable. Products resulting from the degradation of scaffold control the response of immune system. Therefore, the degradation products of scaffolds shall be nontoxic and should be easily exterminated from the implanted spot of the body so as to get rid of further surgery to remove it. Further, the rate of degradation of scaffold shall be adjustable so that it can be balanced with the rate of tissue production so that it completely dissipates from the body after the tissue production. Hence, currently the scaffolds are developed from the familiar degradable polymers for scaffold tissue engineering. To impart the above-desired properties, the scaffold shall be able to tune mechanical properties, degradation kinetics and release kinetics for different purposes. The degradable polymers to be utilized for orthopedic injuries must fulfill series requirements like mechanical support during tissue growth, organized degradation to biocompatible breakdown products and controlled release of biomolecules and shall maintain osteoconductive and osteoinductive surroundings.

In the recent past, a great deal of attention is being focused on utilization of biodegradable polymers for the development of scaffolds. The reason for this is their well-acknowledged biocompatibility in vivo in addition to the two major reasons. Firstly, the scaffold prepared using degradable polymers can be tuned for their mechanical properties along with their controlled degradation. Secondly, with the passage of time after complete healing of the injury the architecture of scaffolds completely degrades eliminating the need of second surgery for the rehabilitation of the implant, thereby resulting in the fast recovery of the injured site. Among various

degradable polymeric scaffolds such as polyglycolic acid (PGA) [52], polylactic acid (PLA) [53], polyurethanes (PU) [54] and polycaprolactone (PCL) [55], polyurethane is best delivery scaffolds and offers several benefits in the design of injectable and biodegradable polymer composition [56–59].

7.2.3 Porosity

It is degree of material void space and is a part of void volume by absolute volume and is also referred as "*void fraction*" [60]. Competent porosity, pore size distribution and inter-pore connectivity support vascularization and cell growth [61, 62]. Mondal et al. in 2014 synthesized surface modified and aligned mesoporous anatase titania nanofibers-based mats for esterified cholesterol detection and found that around 61% enzyme molecules were loaded in the mat due to its high porosity of fibers [63].

7.2.4 Targetability

It is the capability of the formulation system to influence their prearranged spot and release their enclosed substances on the injured spot [64]. Formulation systems composed of nanofibers have magnificent capacity to transport their enclosed substances to the injured spot and escape from their side effects. This effective target ability results in the reduction of the dose and frequency of enclosed substances [65, 66]. Gong et al. encapsulated amphiphilic peptide developed by transformation of nanoparticles to nanofibers for growth of immune system after cancer treatment. It was observed that amphiphilic peptide had antitumor properties and low toxicity in mammalian cell indicating good biocompatibility in addition to antibacterial properties, to prevent from bacterial contamination [67].

7.2.5 Binding Affinity

As the name suggests, it is the capacity of the drug to bind the scaffold. It should be low enough to deliver the drug [68]. Varieties of scaffolds have been developed by different researchers utilizing various nanomaterials having binding affinity [69–71]. However, among them scaffold formulation of nanofibers has proved to be having adequate binding efficiency for continuous delivery of the enclosed substance for longer duration or accommodating of cells in their pore structure [72, 73].

7.2.6 Stability

Assessment of physical, chemical and biological activities of the developed scaffold at different environment condition is referred to as stability of the scaffold. The developed scaffolds must have chemical and biological stability along with dimensional stability for longer duration of time. Nanocomposites of scaffold exhibit magnificent stability at physiological temperatures, and their activity is sustained for prolonged period [74–76]. Polyvinylidene fluoride (PVDF)/poly(methylmethacrylate) (PMMA)/hydroxyapatite (HA)/titanium oxide (TiO_2) (PHHT) film scaffold nanocomposites with surface morphology nanowhiskers were developed by Arumugam et al. [77]. The prepared nanocomposites were explored for mechanical stability and in vitro studies for biomedical application. Results showed that nanocomposite scaffolds were mechanically stable and can be used for biomedical applications.

7.2.7 Loading Capability and Deliverance

It is the quantity of drug that can be immersed into the scaffold. The scaffold should possess high drug loading capability in order to deliver the drug for prolonged period after seeding of the scaffold in the body [78]. The drug from the scaffold should be delivered in controlled manner to allow the adequate amount of dose to be delivered to the cells over a given duration [79, 80].

7.2.8 Mechanical Properties

The assessment of developed scaffolds characteristics over different types of forces such as stress, strain, break, dent, stretch or scratch is referred as mechanical properties of the scaffolds [81]. These properties are influenced by the interior structure design of scaffold. Till date, plenty of porous scaffolds have been developed that have strength in the range of 10–30 Mpa. The strength can be altered by varying the porosity of the scaffold [82, 83]. So that during implantation, these properties of the scaffolds are competent with that of tissue at the seeding spot or they are able to protect the cells from ruining tensile and compressive forces and to sustain under physiological conditions [84]. Once the scaffold is implanted, it should impart minimal level of biomechanical function that should continuously recover till normal tissue function has been achieved [85].

7.2.9 *Scaffold Architecture*

Pore size and shape, pore tortuosity, degree of porosity and surface area constitute the architecture of scaffold [86]. Microstructure of scaffold is utilized to examine the movement of nutrients, waste and biological chemicals within scaffold and reciprocal action of cell on scaffold. Movement of cells within the scaffolds is adamant by degree of porosity and interconnectivity of pores [87, 88]. A scaffold with an undefended and interconnected pore arrangement and a high degree of porosity (>90%) is perfect to interconnect and assimilate with the host tissue [33, 89, 90].

7.3 2Dimesional (2D) Versus 3Dimensional (3D) Culture Scaffold

The scaffolds developed are seeded into two types of cultures, i.e., 2D and 3D culture. In the former culture, the cells are grown in a single layer on a glass or plastic over slip. They communicate only in two dimensions, i.e., x and y, while in case of 3D culture, cells are developed on a 3D porous matrix and are capable of connecting in multiple directions. 3D scaffold permits cells to regenerate and retain extracellular matrix (ECM) that is not possible in 2D [91]. In 2D, cells cannot clone the properties of nutrient gradients, signal propagation or the development of bulk mechanical properties [92]. 3D model gives more appropriate understanding of biochemical and biophysical signaling responses of the cells, especially of the outward response appearing in the ECM along with mechanical and chemical responses arising from both adjacent and distant cells. This approach leads to the generation of adequate cell-based assays for manufacturing of suitable biomaterials utilized to examine the cell material communication [93, 94]. The 2D and 3D scaffold with culture is shown in Fig. 7.3.

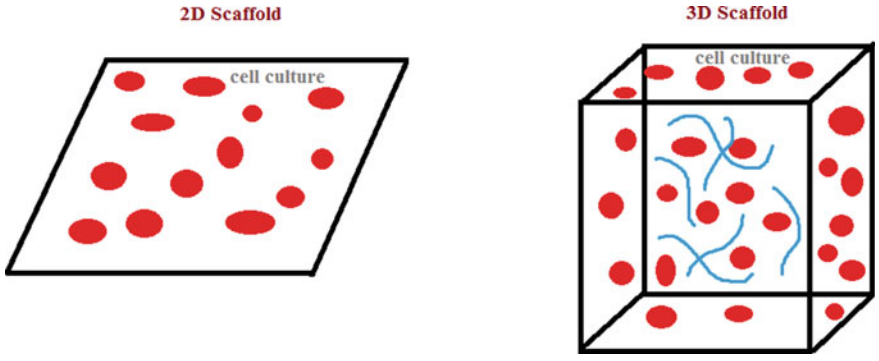

Fig. 7.3 2D versus 3D culture scaffold

7.4 Polymer Scaffold and Processing Techniques

An ideal scaffold for tissue engineering application should possess various important characteristics such as high porosity, surface area, structural strength and specific shapes (3D or 2D) [95, 96]. These characteristics depend on the manufacturing techniques of scaffolds. Till now, numerous manufacturing techniques have been utilized for development of natural and synthetic scaffolds for tissue engineering and regenerative medicines applications. The manufacturing techniques of scaffolds are generally divided into two categories, i.e., conventional manufacturing techniques and rapid prototyping. The former technique is also referred as "non-designed controlled fabrication" method and is used to synthesize scaffolds with irregular microporous structure [97], whereas the latter is also known as "designed controlled scaffold fabrication"; it facilitates fabrication of microporous structure scaffolds with controlled dimensions, location and geometry of pores [98, 99]. In the recent past, a new fabrication technique which is combination of conventional and modern manufacturing method has been used for the generation of porous scaffolds and is referred as combined manufacturing technique [100–103]. The above section summarizes the various fabrication techniques for the development of porous scaffolds (Fig. 7.4).

7.4.1 Conventional Techniques

Conventional techniques inclusive of particulate leaching and solvent extraction [104], emulsion and phase separation [105], gas foaming [106], electrospinning [107], freeze drying [108] or a combination of techniques [109] have been utilized for the fabrication of scaffolds for tissue engineering applications. These techniques

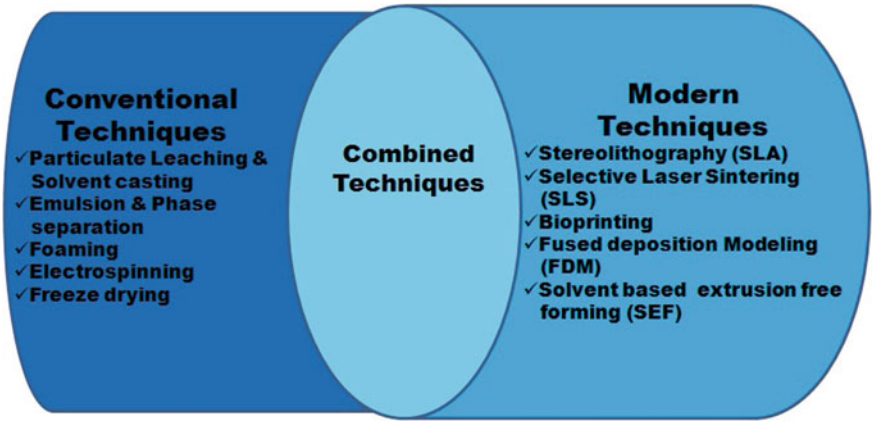

Fig. 7.4 Various manufacturing techniques of scaffold fabrication

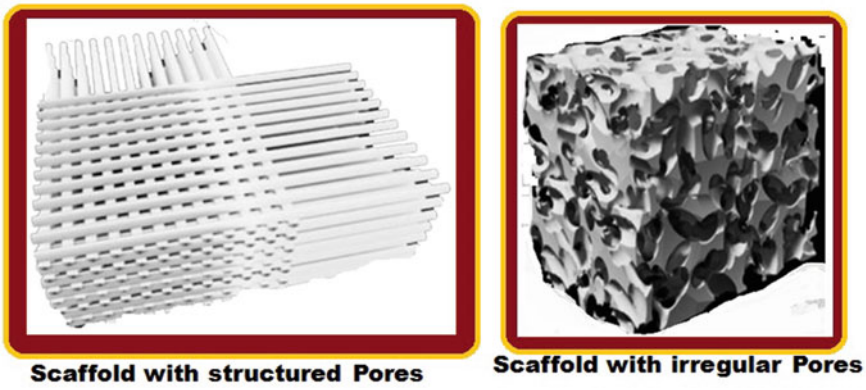

Fig. 7.5 Scaffolds with different pores arrangements

lead to the formation of porous scaffolds with irregular pores and structured pores as shown in Fig. 7.5.

7.4.1.1 Particulate Leaching and Solvent Casting

The technique particulate leaching can be used alone or in combination with solvent casting. Particulate leaching is widely utilized scaffold fabrication technique in bone tissue engineering and regenerative medicines. For this, initially the salt, sugar or wax of specified size is poured into the mold; thereafter, the polymer mixture is poured into the mold followed by hardening and crosslinking of polymer [110]. The scaffolds obtained have the pore size and shape identical to the dimensions of salt, sugar or wax [111, 112]. Gorna and Gogolewski [113] prepared 3D polyurethane scaffolds using salt leaching process for tissue repair and regeneration. In this, new elastomeric biodegradable polyurethanes having an enhanced affinity toward cells and tissues were synthesized using aliphatic diisocyanate, poly(caprolactone) diol and biologically active 1,4:3,6-dianhydro-d-sorbitol (isosorbide diol) as chain extender. The three-dimensional scaffolds showed poor water permeability. By loading the three-dimensional porous polyurethane scaffolds with calcium phosphate salts such as hydroxyapatite or tri-calcium phosphate, their osteoconductive properties can be additionally promoted, thus making them promising candidates for bone graft substitutes.

Solvent casting particulate leaching involves dissolution of polymer solution by homogeneously distributing salt, sugar or wax of specified size in combination with solvent. During the process, solvent evaporates leaving the matrix with salt particles. The matrix so obtained is then immersed in water where salt leaches out to develop a structure with high porosity [114, 115]. This method can be applied for thin membranes of thin wall three-dimensional samples, and under other conditions, the soluble particles are difficult to be separated from the polymer matrix. The major

benefits of this fabrication method are low cost and easy processing in addition to its high porosity with capability of controlling of pore size that make it an ideal technique for the development of 3D scaffolds [116–118]. However, the major limitation of this technique is that the scaffolds synthesized do not have any control on inter-pore connectivity and the pore structure. Moreover, it is time consuming as evaporation of solvent takes days or weeks [119, 120].

7.4.1.2 Emulsion and Phase Separation Method

Thermal-induced phase separation [121, 122] or liquid induced-phase separation [123–125] is other type of manufacturing method for development of scaffolds with interconnected irregular pores. A two-phase uniform mixture of polymer can be unsterilized thermally by changing the temperature leading to liquid/liquid or liquid–solid phase separation. For liquid phase separation, polymer is dissolved in solvent; thereafter, the solvent is separated by decreasing the temperature, resulting in the formation of porous polymer scaffold. This method is known as thermally induced phase separation (TIPS). The scaffolds prepared utilizing these methods have high porosity. Also, their pore size can be adjusted by variation in freezing temperature, type of solvents used, polymeric material and its concentration [126, 127]. Despite of its advantages, the major limitation is their small pore size that can be reproducibly obtained by this process. Furthermore, the technique utilizes organic solvents that may leach some residual after processing, and hence, complete monitoring of the process is required for the complete removal of solvents prior to biological analysis. In emulsion phase separation, polymer is dissolved in solvent and then freeze dried to induce crystallization of the solvent that acts as mold for the pores. These crystals are then removed by freeze drying to yield porous structure. Alteration in processing parameters induces different pore sizes and pore distribution. This technique generates relatively thick scaffolds with porosity greater than 90% and with medium and larger pore sizes [128].

Thermally induced phase separation method was utilized by Guan et al. [126] for preparation of polyurethane scaffolds. Effect of polymer concentration, melting temperature and monomer type effect on porosity and pore architecture were studied. The results showed that polyurethane scaffolds prepared with poly(ether ester urethane) urea monomer have better cell adhesion and growth. Cai et al. [129] developed biodegradable scaffold by blending polylactide (PLA) with natural dextran using phase separation method. The results showed that pore size of the films was around 5–10 mm.

7.4.1.3 Gas Foaming

Gas foaming technique is used to fabricate scaffold without using solvent. In this, gaseous porogens produced by chemical reaction or by release of gases such as

high-pressure carbon dioxide and ammonia are used to foam polymers. This technique results in the formation of scaffolds with sponge-like structure with a pore size of 100–500 μm and a porosity up to 93% that leads to the formation of porous structure. This large pore size and high porosity give expeditious production of fibrocartilaginous tissue and best in growth of mesenchymal tissue along with least inflammatory response [130–132]. Therefore, this method is best suited for the fabrication of polyurethane scaffolds for tissue engineering [58]. One of the major limitations with this method is that scaffolds so obtained may have closed pore structure or a solid polymeric skin [99, 132, 133]. However, combination with articulate leaching can lead to improvement in interconnectivity of pores. Porous nanohydroxyapatite/polyurethane composite scaffold was developed using foaming method by Dong et al. [134]. The prepared scaffolds were studied for biocompatibility and degradation along with morphology, strength and chemical structure. Results revealed that porosity and compressive strength of scaffolds are improved. Manavitehrani et al. [135] synthesized poly(propylene carbonate)-based porous scaffolds using gas foaming technique. Pore size was found to be within 100–500 μm, and biological studies showed biocompatibility and tissue infiltration in the scaffolds.

7.4.1.4 Freeze Drying

This manufacturing technique of scaffold fabrication is based on principle of sublimation. For this, polymers or ceramics are dissolved in water or organic solvents persuaded by emulsification in water phase. The solution containing polymers is dropped in the mold, and the solvent is evaporated by freeze drying to obtain a polymer scaffold with porous structure [136, 137]. Freeze drying is performed by freezing the material and thereafter reducing the surrounding pressure using vacuum and adding sufficient amount of heat to allow the frozen water in the material to sublime directly from solid phase to the gas phase. This technique can be applied to variety of polymers such as silk proteins, PEG, poly(L-lactic) acid (PLLA) and PLGA/poly(propylene fumarate) blends [138, 139].

7.4.1.5 Electrospinning

This method uses electricity for making fibers from a solution and is the most commonly utilized manufacturing method for preparation of nanofiber (NF) polymers and composite [140]. This technique can be used to generate small diameter fibers ranging from 5 μm to 50 nm with large surface area. For fabricating electrospinning fibers, polymer solution is charged using a capillary tip or needle with mechanical pressure through high voltage of around 10–30 kV. The polymer droplets coming out from the needle grow persuaded by evaporation of solvent, resulting in the generation of fine fibers which twin mat into porous scaffolds [141–143].

The diameter of fibers obtained using electrospinning can be varied by changing the different parameters of electrospinning inclusive of electric field voltage, space

among the capillary tip and solution parameters and feeding rates such concentration, solvent, surface tension, molecular weight and viscosity of polymers [144, 145]. In the recent past, this technique has been used to develop nanofiber meshes from a variety of polymers including poly(ethylene-co-vinylacetate) [146], poly(glycolic acid) [147], poly(D,L-lactide-coglycolide) [148], poly(D,L-lactic acid) [149], poly(ethylene oxide) [150], poly(L -lactic acid) [151], poly(ε-caprolactone) [152, 153] and silk [154]. Spider dragline silk protein and collagen-based composite fibers were fabricated by Bofan et al. using this technique [155]. The prepared composite was explored for mechanical properties and biomedical applications. The results showed that tensile strength of fiber improved with increase in silk percentage while a mall reduction was observed in its elasticity. Chitosan and polylactic acid-based blend nanofibers were synthesized to study the combined effect of natural and synthetic polymers [156, 157]. Karchin et al. [158] used melt electrospinning technique to prepare polyurethane scaffold. For this, the biodegradable segmented polyurethanes were synthesized using polycaprolactone diol, 1, 4-butane diisocyanate and 1,4-butanediol which were then melt electrospinned for the preparation of scaffold. The mechanical properties of the resulted scaffolds were similar to in vivo tissue and therefore can be used in bone tissue applications.

The major benefit of using this manufacturing method for scaffold fabrication is that scaffold developed is suitable for cell growth and tissue regeneration. Further, it generates superfine fibers with particular direction, high aspect ratio and surface area that favor the cell growth both in vivo and in vitro. Furthermore, this technique is simple and efficient and can produce both sheet and cylindrical shape [159–161]. Apart from this, there are some of limitations of using this method such as organic solvents used for electrospinning are sometimes toxic that is not good for cells and limited control over pore size [162, 163]. Hence, it is a big challenge to manufacture 3D scaffold with different pore geometry utilizing electrospinning method.

7.4.2 Rapid Prototyping Technique

Although conventional techniques are most widely used for the fabrication of scaffolds, due to their limitations these conventional techniques are being replaced by modern or rapid prototype technique inclusive of stereolithography, selective laser sintering, bioprinting, fused deposition modeling and solvent-based extrusion free forming because these techniques result in the development of 3D scaffolds through layer-by-layer assembly [164–168]. Also, pore size, porosity and shape of the manufactured scaffold can be altered that enhances the cell migration, proliferation and nutrient perfusion as compared to scaffold prepared utilizing conventional techniques [169].

Modern techniques or rapid prototyping methods are also referred as solid freeform fabrication and use computer-aided design (CAD) model to develop a 3D structure with controlled morphology, chemical composition and mechanical properties. The machine used in developing scaffolds using this technique generates the polymer

scaffold in layer-by-layer fashion. For this, the initial layer of the physical scaffold is developed persuaded by thickness of next layer. At last, the fabricated scaffold is detached from the base platform of the machine. CAD program containing scaffold structure design and modeling is used for controlling the layers in the manufacturing machine. For building CAD model of particular tissue regeneration, magnetic resonance imaging (MRI) scans and computed tomography (CT) data are utilized. These techniques are classified on the basis of printing fundamental or on the type of material used for printing [170].

Decreased starting time for producing prototype components, enhanced capability for anticipating part geometry due to its physical existence, prior exposure and contraction of design errors and elaborate calculation of assembling characteristics of components and assemblies are some of the major benefits of these techniques. However, resolution limit that inhibits the designing of scaffold with fine microstructure, use of toxic binders and low quality arrangement are the major drawbacks of these technologies [171, 172].

7.4.3 Combination of Techniques

The abovementioned technologies can be combined to fabricate specific polymer scaffold. For example, phase separation can be combined with particulate leaching [173], electrospinning with freeze drying [174], fused deposition in combination with gas foaming [109], etc. Song et al. [109] developed hierarchical bionanocomposite scaffolds with tunable micro/macroporosity structure utilizing fused deposition modeling in combination with gas foaming to control the pores. The above-prepared scaffold was explored for bone tissue engineering and found that they can be successfully used for bone tissue regeneration. PLA-based scaffolds for tissue engineering application were developed by Salerno et al. [173] utilizing phase separation technology in combination with porogen leaching and $scCO_2$ drying. Scaffolds prepared consisted of large pores and nanoscale pore walls.

Porous scaffolds with nanotopography can be fabricated by combining modern techniques with conventional technologies. In the recent past, progress in the development of tissue engineering scaffolds using combination of modern and conventional techniques was outlined by Giannitelli et al. [175]. The fabricated scaffolds on the basis of achieved level of integration were categorized as assembly, fabrication and technique level.

The various manufacturing technologies for scaffold with their advantages and disadvantages are shown in Fig. 7.6.

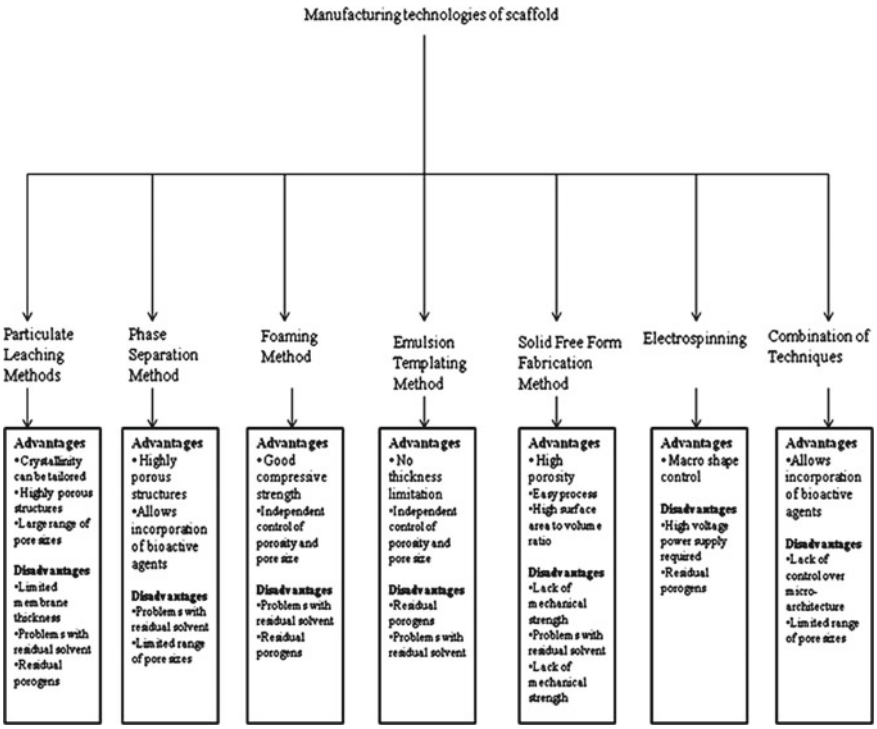

Fig. 7.6 Various Scaffold manufacturing techniques with advantages and disadvantages

7.5 Biomaterials for Tissue Engineering Polymeric Scaffold Manufacturing

A variety of biomaterials inclusive of ceramic, polymers (natural and synthetic) and composite material are used for the preparation of scaffolds for tissue engineering. As the scaffolds are aimed to use for healthcare applications, some of the important characteristics of biomaterials such as biocompatibility, biodegradability, cytotoxicity, adequate mechanical strength and mucoadhesive nature must be taken into consideration for their utilization. A variety of biomaterials like ceramics, natural and synthetic polymer and composites are widely utilized biomaterials for fabricating tissue engineering scaffolds.

7.5.1 Ceramics

Ceramics are inorganic biomaterials that can be categorized as bioinert and bioactive. Alumina and zirconia are bioinert materials while calcium phosphate [176],

bioglass and glass ceramics [177, 178] constitute bioactive materials. Bioceramics may either be osteoinductive (stimulate bone develop) or osteoconductive (support bone develop). All the bioceramics are osteoconductive as all help in bone formation but not osteoinductive. Some of the ceramic biomaterials most commonly used for scaffold fabrication include calcium phosphate-based bioglass and glass ceramics as their composition is alike mineral part of bone [179].

Two most widely used calcium phosphate bioceramics used in tissue engineering scaffolds are tri-calcium phosphate and hydroxyapatite (HA) [180, 181]. Tri-calcium phosphate is very frequently used as degradable scaffold material; on the other hand, HA is non-resorbable and osteoinductive used for coating biomedical implants. Osteoinductivity leads to bone regeneration, thus enabling the implant to assimilate with the surrounding tissue. Further, HA shows improved densification and improved sinterability because to their better surface area, that can expand fracture hardiness as well as other mechanical properties [182].

Henceforth, HA is most widely used bioceramics for scaffold fabrication. It can be prepared by using numerous technologies such as sol–gel processing, emulsion, batch hydrothermal process, mechano-chemical method, chemical vapor deposition, bio-mimetic techniques and ultrasonic spray pyrolysis [183, 184]. Among these techniques, sol–gel is generally used due to its low processing temperature, homogeneous molecular mixing and capability to produce bulk amorphous monolithic solids and nano-crystalline powders [185, 186].

7.5.2 Natural Polymers

Natural polymers represent a convenient alternative to synthetic polymeric material systems as their structure is similar to human bone matrix of tissues. Chitosan and alginate are two most commonly used polysaccharides that have wide application in tissue engineering scaffolds, which do not exist in the human body. But they exhibit good bioactivity and can approach to cell in growth. Alginate is water soluble and has simple gelatin chemistry with calcium ions, thus finding applications to synthesis of scaffolds for bone tissue engineering and liver disease treatment [187]. Chitosan is a derivative of chitin which naturally occurs in the exoskeletons of arthropods. Chitosan with composite scaffolds has been found suitable for skin and bone tissue engineering applications [188].

Fibrin is one of the most attractive natural proteins applied in tissue engineering arena. Fibrin can be used in the treatment of ordinary wound repair and has wide applications as an adhesive in ortho-surgery. It must be produced from human blood vessels, to utilize as an autologous scaffold. Fibrin is not degradable itself unless a protein inhibitor is used to control degradation. Fibrin hydrogels have been used to regenerate soft tissues with chondrocytes [189] Gelatin is the derivative of collagen that is produced by collagen molecules breaking it into single-phase molecule. Further, disadvantages of gelatin are poor mechanical strength and hence

are crosslinked with hyaluronic acid for skin tissue engineering and with alginate for wound healing applications [190, 191].

7.5.3 Synthetic Polymers

Synthetic polymers are preferred over natural properties as their physical, biological and mechanical properties can be adjusted. This can be done by altering the ratio of monomers units or by adding particular groups (e.g., RGD peptide (arginylglycylaspartic acid) that can be successfully recognized by human cells after the implantation in to human body. The products of degradation and degradation kinetics must also be controlled by adequate selection of the segment to form product that can either be released from the body by renal filtration system or can be metabolized into nontoxic products [192]. This can be done by utilizing biodegradable polymers such as polyglycolic acid (PGA), polylactic acid (PLA) and their copolymers like poly(DL-lactic-co-glycolic acid) (PLGA), approved by food and drug administration [193–195]. These synthetic polymers can be degraded hydrolytically and employed regularly due to their by-product degradation that can be easily expelled from the body as water and carbon dioxide. But, decreased pH in the localized area leads to inflammation during degradation. One of the other synthetic polymers, polycaprolactone (PCL), whose structure is analogous to PLA and PGA can also be degraded biologically at physiochemical condition and is generally being used for drug delivery applications as it degrades at a slower rate as compared to PGA and PLA [196–198]. Another most commonly used degradable synthetic polymer that is biocompatible, nontoxic and water-soluble polymer which is liquid at lower temperature and takes the form of elastic gel at body temperature (37 °C) is poly(ethyleneglycol) (PEG) [199]. The polymers based on PEG have been widely used as injectable scaffolds for tissue engineering applications [200]. The hydrophilicity and rate of degradation of PEG and PLA-based scaffolds can be controlled by tailoring the ratio of monomers.

Polyurethane (PU) is another synthetic polymer being utilized as scaffold for tissue engineering applications. The physical, chemical and mechanical properties of PU in addition to their biocompatibility and biodegradability can be altered in a controlled way by changing the composition of hard and soft segment [201]. Biodegradability of PU is generally achieved by integrating hydrolyzable moieties and labile soft segment or by combining with degradable polymers like poly(glycolic acid), poly(lactic-co-glycolic acid), polylactic acid, polycaprolactone, etc., for soft tissue engineering applications [202].

7.5.4 Composites

Scaffolds synthesized from single material show poor properties in terms of biocompatibility, mechanical strength and biodegradability. But composites scaffolds

Table 7.2 Different biomaterials for scaffold fabrication with their advantages and disadvantages

Sr. No	Scaffolds biomaterials	Advantages	Disadvantages
1	Bioceramics (hydroxyapatite)	• Biocompatible • Biodegradable	• Nonresorbable
2	Synthetic polymers (polylactic acid, polyglycolic acid and their copolymers)	• Biocompatible • Hydrophilic	• Degradation products are CO_2 and H_2O creating local acidic conditions
3	Natural polymers (collagen and alginate)	• Biocompatible • Good cell recognition • Simple gelation methods	• Poor mechanical properties
4	Composites (polymer-ceramics, polymer–polymer)	• Capability of altering mechanical and biological properties	• Compromise between "best" qualities of individual components with overall scaffold properties

including two or more bioactive materials enhance the biological properties in addition to mechanical properties of newly developed material. Polymer-hydroxyapatite (HA) (ceramics) composites, PLA/PLGA, PMMA/HA and hydroxyapatite (HA) reinforced with TiO_2 have been developed for application in tissue engineering [203–205]. In this approach, usually the composite matrix is prepared by biocompatible polymer and inclusions of bioceramic (HA, BG, tri-calcium phosphate) particles/fibers. Polymeric composites with ceramics, such as HA, can be used as coating on composites. Scaffolds represent an appropriate alternative of allograft or autograft and they combine the properties of polymers (degradability) and ceramics (bioactive) for tissue engineering application [30, 206, 207]. Advantages and disadvantages of various types of scaffolds are tabulated in Table 7.2.

7.6 Applications

Polymeric scaffold is most commonly used for cell delivery [208], drug delivery [209], genes delivery [179], wound healing and bone tissue engineering applications [210, 211]. For cell delivery application, cells are injected into the scaffolds and administered into the body, whereas for gene delivery application, polymeric scaffolds are used. Polymer scaffolds are architecture in such a way so as to deliver the genetic material as polyplexes, thereby transfecting to seeded cells and expressing the growth of cells to activate morphogenesis of particular cells to create the required tissue [212]. Drugs with low molecular weight that proliferate or differentiate the cells are fused into the scaffolds to activate cellular differentiation and cellular modeling [213]. In the recent past, dexamethasone (DEX) and green tea polyphenols (GTP) were delivered through electrospun polymer ultrafine fibers to attain a adequate balance between effective treatment of keloid and safety to skin [214]. Scaffolds have

shown excellent cell attachment, proliferation and penetration and thus are suitable for tissue engineering applications. The studies show that scaffolds can be used in blood vessels, bones, muscles, skins, neural tissue and other stem cells such as heart, cartilage, ligament and urinary tract [212, 215, 216]. Polymeric fibrous scaffolds due to high porosity, porous architecture, well interconnectivity and high surface area can be utilized for wound dressing. They not only heal the wound but also expel out the extra fluid from the wound area. Further, they also support rinsing of exogenous microorganism, thereby speeding the healing process [217–219]. Thus, all these make porous polymeric scaffolds an ideal biomaterial to be as tissue engineering and regenerative medicine biomaterial.

7.7 Conclusion and Future Prospective

In reviewing the published literature on polymeric composite scaffolds with bioactive properties, it was revealed that, in the recent past, new polymeric scaffold nanocomposite has been fabricated utilizing conventional, modern and combination of techniques. New materials and combination of composite scaffolds designs based on new fabrication method are being proposed continuously to advance bioactive and biocompatibility of composites. Combination of techniques methods is being widely used as it gives scaffold with required pore size and high porosity. Further, this review article highlights required properties of the scaffolds for bone tissue engineering and the numerous biomaterials being utilized for scaffold and its composite preparation. It is found that bioceramics, hydroxyapatite (HA), can be used as filler in polymer matrices to develop nanocomposite of scaffold. This has been found that HA is significantly associated to produce bionanocomposite scaffolds with similar structure and composition to human bones. It is well known that homogeneous dispersion of filler in polymer matrix plays a key role and mainly enhances osteoconductivity and mechanical properties. Moreover, nanoscale organized composites provide a better microenvironment for cell in growth in terms of cell adherence and proliferation. Hence, ceramics/polymer composites can be developed to enhance the mechanical and biological properties for biomedical applications. Overall, it was concluded that polymer scaffold composites can be used as tissue engineering scaffolds.

Despite of the well-known utilization of scaffolds, if we look into practicality and convenience, still there is a need to develop new degradable polymer composites that can meet all the needs of surgical implants, drug and cell delivery.

Acknowledgements Authors LK and DA are thankful to University grants commission for providing RGNF fellowship. Prof. AK is thankful to DST grant vide SEED/TIASN/008/2018 dated: 06/06/2018 and CSIR for Project Sanction no. 22(0798)/19/ EMR-II dated 24.7.2019. SM is thankful to DST for providing Inspire fellowship. All the authors are also grateful to TEQIP-III for providing financial assistance.

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