Available online at www.sciencedirect.com

ScienceDirect

Materials Today: Proceedings 24 (2020) 2318–2329

materialstoday: PROCEEDINGS

www.materialstoday.com/proceedings

ICMN-2K19

Composite scaffolds in tissue engineering

Safinsha.S[a], Mubarak Ali.M[b]*

[a]*B.Tech Student, Mechanical(Production) Engineering, T.K.M College of Engineering, Kollam, Kerala, India,691005*
[b]*Assistant Professor, Department of Mechanical Engineering, T.K.M College of Engineering, Kollam, Kerala, India,691005*

Abstract

Along with growth and development, the technology has also brought us accidents, ailments and diseases. Tissue loss is one of the problems resulting from these. The existing treatments like transplants, surgical repair etc. do not hold well as a permanent cure and they often require painful surgical procedures. Considering other alternatives like tissue engineering and regenerative medicine practices, they focus primarily on permanent cure. Current strategies of regenerative medicine are focused on the restoration of pathologically altered tissue architectures by transplantation of cells in combination with supportive scaffolds and biomolecules. In recent years, considerable interest has been given to biologically active scaffolds which are based on similar analogs of the extracellular matrix that have induced synthesis of tissues and organs. The application of different composites in the field of tissue engineering increased the scope and efficiency of tissue engineering field.

Selection and peer-review under responsibility of International Conference on Advances in Material Science & Nanotechnology, ICMN-2K19.

Keywords: composites; scaffolds; tissue engineering

1. Introduction

The field of tissue engineering has advanced dramatically in the last 10 years, offering the potential for regenerating almost every tissue and organ of the human body. The field aims to restore, maintain, or improve tissue functions that are defective or have been lost by different pathological conditions, either by developing biological substitutes or by reconstructing tissues [1].Several tissue engineered products have shown potential for clinical application over the past decade [2].Three approaches have been investigated singularly or in combination: cell-based therapies, tissue inducing factors and biocompatible scaffolds [3]. The last of these three is more frequently associated with the

* Corresponding author. Tel.: +91-9495748079.
E-mail address: safinshas@gmail.com

Selection and peer-review under responsibility of International Conference on Advances in Material Science & Nanotechnology, ICMN-2K19.

concept of tissue engineering, that is, the use of living cells seeded on a natural or synthetic extracellular substrate, called scaffolds, to create implantable pieces of the organism [1].

Developing scaffolds with the optimal characteristics, such as their strength, rate of degradation, porosity, and microstructure, as well as their shapes and sizes are more readily and reproducibly controlled in composite scaffolds. Scaffold design and fabrication are major areas of biomaterial research, and they are also important subjects for tissue engineering and regenerative medicine research. Here, we discuss about various scaffolds, their fabrication methods and importance of composite scaffolds.

2. Tissue Engineering

Tissue engineering is the use of combination of cells, engineering and materials, methods, and suitable biochemical and physicochemical factors to improve or replace biological tissues. Tissue engineering involves the use of a tissue scaffold for the formation of new viable tissue for a medical purpose. Treatment typically focuses on transplanting tissue from one site to another in the same patient (an auto-graft) or from one individual to another (a transplant or allograft). While these treatments have been revolutionary and lifesaving, major problems exist with both techniques [15].The aim of tissue engineering is to develop tissue and organ substitutes for maintaining, restoring or augmenting functions of their injured or diseased counterparts *in vivo* [2]. Tissue engineering cover a broad range of applications, in practice the term is closely associated with applications that repair or replace portions of or whole tissues (i.e., bone, cartilage, blood vessels, bladder, skin, muscle etc.).While it was once categorized as a sub-field of biomaterials, having grown in scope and importance it can be considered as a field in its own.

Different strategies are adopted to compensate for tissue loss such as implantation of isolated cells or cell substitutes, delivering of tissue inducing substances, placing cells on or within different matrices. Here, importance is given to the use of matrices or scaffolds, which can mimic the extra cellular matrix.

3. Scaffolding Process

In our body, cells are grouped together forming tissues. These cells are bound in tissues by extra cellular matrices. Using different methods we are trying to create scaffolds which can mimic the natural ECM of a host body. Scaffolds placed inside the host tissue should have properties similar to ECM's. Scaffold should possess adequate pore size such that attachment, proliferation, differentiation, migration etc. of cells occur smoothly [1].

When cell movement happens through the pores, the host cells itself secrete their own natural extracellular matrices. Hence, the scaffolds act only as supporting materials until the extra cellular matrix is formed. The scaffolding process is taking place such that the rate of formation of new ECM of the tissue should be equal to rate of degradation of the composite scaffold placed [2]. The concept of tissue engineering is shown in Fig.1 . Natural ECM's have its own binding sites; adhesive proteins are so added to increase the binding sites in scaffolds.

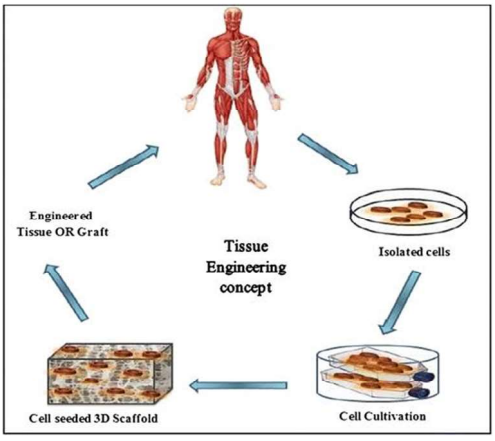

Fig.1. Concept of tissue engineering (Adapted from Anamika et.al. [17])

3.1. Scaffolding materials

Natural polymers like Collagen, Silk, Alginate, Chitosan and Hyaluronic acid are the most commonly preferred materials as they have good bio-degradation, cell attachment, proliferation etc. They have limitations such as low tenability on bio-degradation, degradation related inhibition of local cells etc. Synthetic polymer materials possess more load carrying capacity than natural ones [4]. Polymers are widely used materials in fabricating scaffolds; other materials include ceramics, metals etc.

In ceramics, bioactive ceramics are drawing more and more attention due to excellent biocompatibility, degradability and osteogenesis, hence used in bone-tissue engineering applications [5]. But, when used alone ceramic materials are hard, brittle and show varying degradation rates. Metals are very poor when considering their biodegradability, hence less suited for tissue engineering.

Another important material is Hydrogel. Hydrogels are physically or chemically cross-linked polymer networks that are able to absorb large amounts of water. Hydrogels can be used in injectable approaches to cell therapy and tissue engineering, which offers several advantages. This approach can replace multiple surgeries with minimally invasive injection procedures. However, the hydrogel-based biomaterials used in these studies have been limited by low-dimensional stability and limited nutrient and oxygen supply [16]. They can be classified into different categories depending on various parameters including the preparation method, the charge, and the mechanical and structural characteristics [6]. E.g. Chondroitin- Sulphate based hydrogel.

3.2. Desirable properties of scaffolds

For the successful application of scaffolds into a host body for tissue engineering application, scaffolds must possess some of the desired properties shown in “Table. I”.

Table 1. Desirable scaffold properties

Properties	**Definitions**
Bio-activity	Interaction and binding of scaffold material with host tissue.
Bio-degradability	Controlled scaffold degradation which can complement tissue in-growth whilst maintaining sufficient support
Scaffold architecture	Inter –connected pores allowing diffusion and cell migration and large surface area for cell-scaffold interaction
Mechanical properties	Compressive, elastic and fatigue strength comparable to host tissue
Bio-compatibility	Non-toxic and non-inflammatory scaffold components and break down products, avoiding immune rejection

3.3. Scaffold fabrication techniques

3.3.1. Particulate Leaching

Solvent casting/particulate leaching is a traditional method of scaffold manufacture that begins with dissolution of a polymer in an organic solvent. The technique uses porogens, substances that can be dispersed into a moulded structure and subsequently dissolved once the structure has set, resulting in the creation of pores [4]. Porogens are added to the polymer solution to create a polymer-porogen network. The polymer is subsequently hardened as the solvent evaporates, with water then used to dissolve the porogen which is often a salt such as sodium chloride. A hardened polymer scaffold with a porous network is left behind. The solvent casting, polymer leaching, and salt particulate leaching techniques were used to prepare Polycaprolactone scaffold.3D PCL scaffolds with highly porous and interconnected networks were prepared [7]. Although it is difficult to control pore shape and pore interconnectivity of scaffolds produced by this method.

3.3.2. Gas foaming

Gas foaming eliminates the use of solvents deployed in solvent casting/particulate leaching methods (Fig.2.). This technique creates a porous structure through the nucleation and growth of gas bubbles dispersed throughout a polymer. Compression moulding is first used to create solid discs of a scaffold material, such as poly(lactic-co-glycolic acid), within a heated mould. Following this, the discs are saturated with carbon dioxide by exposure to high pressure CO_2 gas (5.5 MPa) for 72 h at room temperature, before solubility of the gas in the polymer is rapidly decreased by reducing CO_2 pressure to atmospheric levels (P^0CO_2) [4]. This causes the CO_2 gas to clump together, creating pores. Porosities of up to 93% and pore sizes of up to 100 mm can be obtained using this technique. However, it is difficult to control pore connectivity and pore sizes by gas foaming.

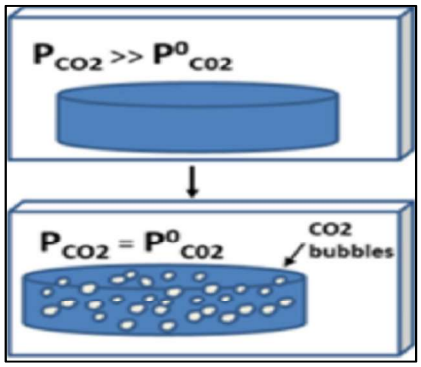

Fig.2. Gas foaming (Adopted from Gareth Turnbull et.al [4])

3.3.3. Electrospinning

Electro spinning is another popular scaffold fabrication technique with the ability to create nano-fibrous interconnected porous scaffolds (Fig.3.). This method uses an externally applied electric field to draw charged threads of polymer solutions or polymer melts as thin jets from a capillary tube towards a collector plate. Fibers in the micro- and nanometer range can be created and deposited sequentially to create a scaffold, with potential to include composite materials and biomolecules. An electrospun synthetic human elastin:collagen composite scaffold aimed at dermal tissue engineering was developed[8]. The panel of electrospun human tropoelastin and ovine type I collagen blends comprised 80% tropoelastin + 20% collagen, 60% tropoelastin + 40% collagen and 50% tropoelastin + 50% collagen. Electrospinning efficiency decreased with increasing collagen content under the conditions used [8].

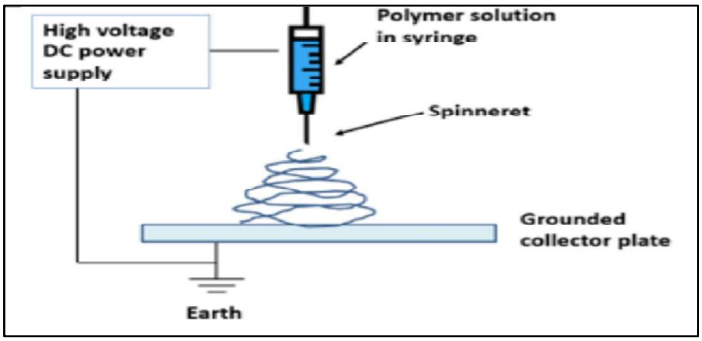

Fig.3.Electro-spinning (Adopted from Gareth Turnbull et.al [4]

3.3.4. Freeze drying

Freeze-drying begins with freezing of a polymer solution, resulting in the formation of solvent ice crystals surrounded by polymer aggregates (Fig. 4.). The surrounding pressure is then reduced via a vacuum, to a level lower than the equilibrium vapor pressure of the frozen solvent (P^0). The solvent is thus triggered to undergo sublimation directly into gas from the solid phase. When the solvent is completely sublimated, a dry polymer scaffold with an interconnected porous structure remains. Emulsification freeze drying can also be used as a primary scaffold fabrication method. PHBV and HA/PHBV scaffolds were fabricated using an emulsion freezing/freeze-drying technique which was originally developed for making pure polymer scaffolds [9].

The process begins by dissolving polymers/ceramics in a solvent and then mixing with water, to obtain an emulsion. The mixture is poured into a mould and frozen before the two phases can separate. The frozen emulsion is then freeze-dried to remove the solvent and dispersed water, creating pores in a solidified scaffold.

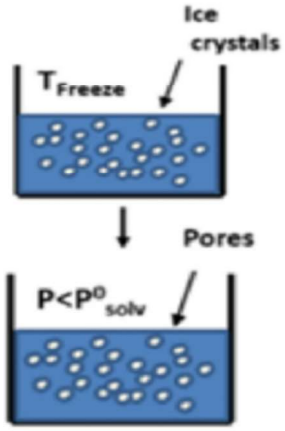

Fig.4. Freeze drying (Adopted from Gareth Turnbull et.al [4])

3.3.5. 3D Printing

The traditional methods of scaffold fabrication that have been discussed in brief so far generally offer limited control over pore size, geometry and interconnectivity. Overtime there has been an improvement in the ability to spatially

control scaffold micro architecture and spatial content as technologies such as 3D printing have emerged. In general, 3D printing fabricates objects via layer by- layer processing of powder, liquid or solid material substrates [4]. Starting from the bottom and building up, each newly formed layer is triggered to adhere to the previous layer, resulting in the creation of construct of gradually increasing size. The structure of a 3D printed object is dictated by a computer-aided design (CAD) model loaded onto a 3D printer. CAD models describe 3D objects in a series of cross-sectional layers, allowing 3D printers to physically reproduce models through an additive process. Complicated three-dimensional features such as internal voids, cantilevers, undercuts, and narrow tortuous paths are simply reduced to a stack of common two dimensional features such as circles, lines, and points. Fig.5. Shows the steriolithography process, which is an example of 3D printing. Exempted from tooling path restrictions, these additive technologies offer much higher levels in shape complexity [11]. Although these SFF (Solid free form fabrication) technologies were developed primarily for industrial applications, their flexibility in creating complex three-dimensional shapes make SFF technologies attractive candidates for biomedical engineering.

Rapid Prototyping (RP) methods like 3D printing have also been combined with conventional techniques to take advantages of both, for the creation of scaffolds [10]. RP has created designed global pores while conventional techniques make local pores necessary for providing potential space for tissue growth. Global pores serve the purpose of nutrient diffusion, fluid and blood flow, control of cell growth and tissue differentiation [10].Not all RP techniques are applicable for the processing of hydrogel materials, some more than others, the amount of RP technologies is further diluted. The fabrication of hydrogel scaffolds requires mild processing conditions. Some of the techniques are not able to meet those constraints due to the rather harsh processing conditions [12]. Different 3-D printing techniques include Selective laser sintering, Fusion deposition modeling, Stereo-lithography etc. A 3-D interconnected porosity controlled tricalcium phosphate (TCP, Ca_3 $(PO_4)_2$) – polypropylene (PP) composites was prepared [13] via fused deposition modeling (FDM) (Fig.6.), a commercially available RP technique and the PP-TCP polymer had a failure strength of 7.0 MPa.

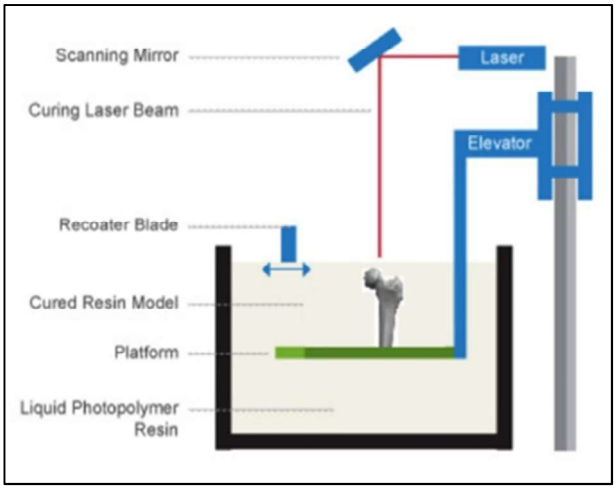

Fig.5. Stereo lithography (Adapted from Gareth Turnbull et.al

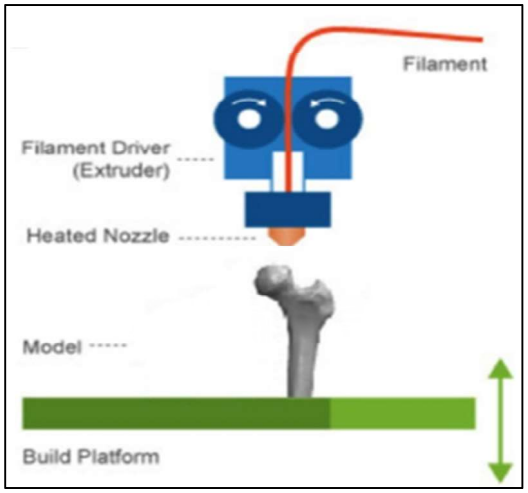

Fig.6. F.D.M process (Adapted from Gareth Turnbull et.al)

3.3.6. 3D Bio-printing

As an emerging technology, 3D bio printing offers a potential solution to help ease the burden of arthritis and other cause of bone defects within orthopaedics. Bio printing can be used to deposit living cells, extracellular matrices and other biomaterials in user defined patterns to build complex tissue constructs “from the bottom up.” The potential to create inherent vascular structures is also improved by bio printing, as internal channels containing vascular cells can be printed into constructs, fostering the in growth of blood vessels in vivo. By contrast, the conventional tissue engineering method of seeding cells onto a pre-fabricated scaffold does not allow for precise 3D placement of cells or biological content, limiting capacity to create complex hierarchical tissue

constructs. The process of bio printing (Fig.7.) typically begins with the selection of cells and biomaterials for inclusion in bio printed constructs.

A nozzle-deposition system also known as a direct-print tool was used to fabricate the 3-D polycaprolactone, polylactic acid (PLA), polyglycolic acid, chitosan scaffolds [14]. The machine consists of a dispensing system integrated with pumping technology to conformably deposit various types of materials. It uses a computer-aided-design/computer-aided-manufacturing (CAD/CAM) approach to build 3-D structures. The dispensing process is controlled by the motion control software and the CAD program, allowing flexible alteration of parameters such as speed of deposition, air pressure in the pneumatically actuated pump, dispensing height and 3-D geometry of the deposition pathways. The tool provides accuracy and reproducibility of the XYZ positioning of the dispensing nozzle with a resolution within few microns.

Cells for printing can be sourced from tissue biopsies, blood samples and from other sources, and expanded in number through culture to maximize cell density on bio-printing. The additional step of 3D cell culture may also be performed to creating aggregates of cells for printing. Cell aggregates or spheroids have superior Intercellular communication and extracellular matrix development when compared to cells grown in 2D culture, potentially accelerating the growth of printed constructs towards functional tissue after bio-printing.

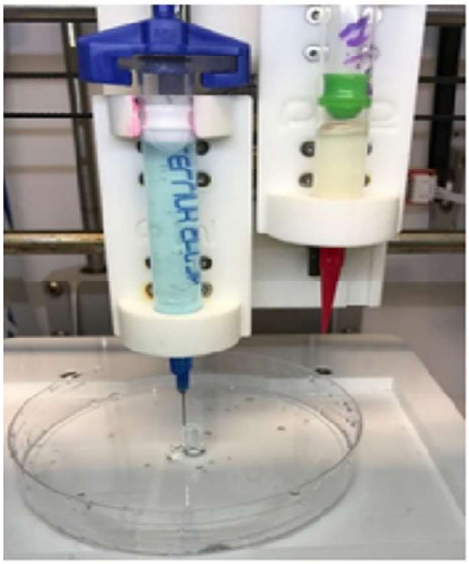

Fig.7. 3-D Bio printing (Adapted from Gareth Turnbull et.al)

4. Composite scaffolds in bone tissue engineering

To overcome the limitations of current treatment options like usage of auto grafts, allograft, and metalwork and bone substitutes etc., significant research in the field of bone tissue engineering (BTE) has been directed towards creating novel alternatives to traditional bone grafts [4]. Porous 3D scaffolds fabricated through a variety of methods and including a range of biomaterials have been utilized to aid and direct bone regeneration. Scaffolds are also used to deliver biomolecules that can facilitate bone tissue engineering. Biomolecules are integrated into scaffolds as proteins/growth factors. These growth factors control osteogenesis, bone tissue regeneration, and ECM formation via recruiting and differentiating osteoprogenitor cells to specific lineages [18].

However, the perfect scaffold material has yet to be encountered and clinical translation of 3D scaffolds has been limited as a result. Bone is a heterogeneous composite material with constituents including hydroxyapatite mineral (Ca_{10} $(PO_4)6(OH)_2$), a mixed organic component (type I collagen, lipids and non-collagenous proteins) and water [4]. During scaffold manufacture it would therefore seem logical to include a combination of materials to create a composite scaffold, potentially allowing greater scaffold bioactivity and structural biomimicry to be achieved. Amongst the natural polymers used in bone tissue engineering, collagen is perhaps the most frequently adapted into

scaffolds. Collagen composes 90% of the total weight of bone extracellular matrix proteins and is therefore a logical choice for inclusion in a composite BTE scaffold.

A collagen-HydroxyApatite (Col-HA) scaffold was developed (Villa et.al) [4] through a co-precipitation and freeze casting process. The scaffold created had a high degree of permeability suitable for cell infiltration, attachment and osteogenesis with 99% interconnectivity of pores. Mouse bone marrow derived mesenchymal stem cells (BMSCs) were seeded onto the scaffolds and implanted. After three weeks in vivo, near complete filling of the calvarial defects with bone on radiographic and mineralization analysis was found. After several weeks, host scaffold degradation occurring was seen. Comparison between Human Trabecular bone with Col-HA Scaffold can be seen in Fig.8. Compliant mechanical properties of the Col-HA scaffold were observed making it perhaps best suited for non-load bearing applications such as craniofacial repair.

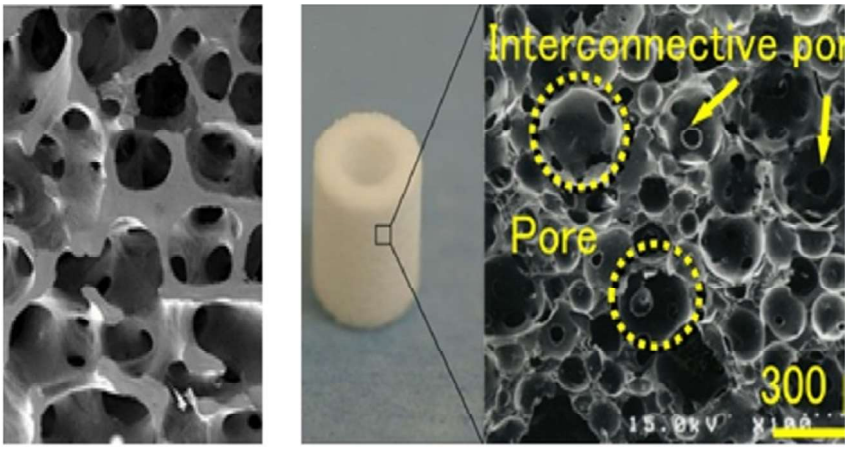

Fig.8. Comparison between Human Trabecular bone with Col-HA Scaffold (Adapted from Gareth Turnbull et.al)[4]

Silk fibroin (SF) is a natural protein-based polymer mainly produced by silkworms and spiders. SF possesses several characteristics desirable for use in bone tissue engineering, including biocompatibility, low immunogenicity, limited bacterial adhesion, tunable biodegradability, mechanical integrity and the ability to support the differentiation of mesenchymal stem cells along the osteogenic lineage [4].Blending silk with HA enhanced crystal formation of HA along the c-axis and the coordinative effect on the structure and properties between SF and HA was found during the composite film fabrication. The nucleation of HAp could enhance the molecular orientation and crystallinity of SF. alginate/HAp/SF composites as a bone replacement, was [19]. Four weeks after implantation, the rate of bone formation in the defected site was significantly higher using alginate/HAp/SF scaffold than alginate and control (unfilled defects) groups. Fig.9.Shows a SF-HA scaffold with its internal structure.

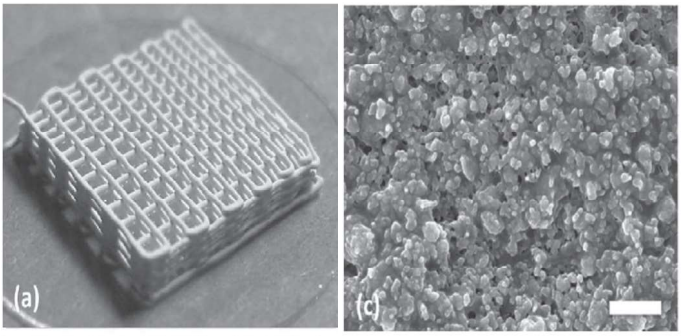

Fig.9.SF-HA scaffold with internal structure (Adapted from Lin Sun et.al [25])

From the study on using different alginate composites from scaffolding process [20], it was found that Alginate composition, molecular weight, purity and concentration used in the scaffolds play the biggest role in providing mechanical strength, biocompatibility, cell adhesion, proliferation and osteogenic differentiation so, It was found

better to use high molecular weight alginate for the purpose of hard tissue engineering. Better performance was observed with alginate hydrogels on cell viability, cell proliferation calcium content, alkaline phosphatase and osteocalcin level when compared to hyaluronicacid.

The effect of incorporating the HA mineral into porous silk scaffolds was investigated [21] for tissue engineered bone formation with hMSCs (Human mesenchymal cells). The HA mineral enhanced hMSCs osteogenic differentiation and provided a platform for bone-like structure formation when adequate HA content was incorporated. The HA mineral provided a platform for the formation of engineered bone by hMSCs, both through the osteoconductivity of the material and by providing nucleation sites for the newly produced mineral.

There are several issues to be addressed to develop a BTE scaffold based strategy. The starting point is the identification of the proper scaffold-based BTE therapy, including the choice of material's properties and manufacturing methods as well as of a multi- vs. single component treatment [22]. Around this nucleus revolve a series of important step elements: pre-clinical in vitro and in vivo investigations, clinical trial approval and conduction, scaffold commercialization and patient expectations.

5. Composite scaffolds in cartilage tissue engineering

Cartilage tissue lacks an intrinsic capacity for self-regeneration due to slow matrix turnover, a limited supply of mature chondrocytes and insufficient vasculature. Epidemiological studies have revealed that more than 70%ofadults between the ages of 55 and 78 experience disabilities due to osteoarthritis. Coupled with high disease prevalence, the limited capacity of adult cartilage to undergo self-regeneration has prompted the urgent development of functional cartilage tissue replacement therapy. Poor vascularization, slow matrix turnover, a limited number of progenitor cells and a scarcity of mature, on-dividing chondrocytes all contribute to the inability of cartilage lesions to heal, particular in the elderly.

Scaffolds of PHBV (poly (hydroxybutyrate-co-hydroxyvalerate) and its combination with CS (Chitosan) material for cartilage tissue engineering application were compared [24]. Conventional solvent casting-particulate leaching method was applied to prepare the PHBV and PHBV/CS composite scaffolds. It was found that composite scaffolds could better support chondrocytes to adhere on the scaffolds, penetrate into the scaffolds due to the better hydrophilicity of the composite scaffolds than that of pure PHBV scaffolds. Histological images (Fig.10.) show the difference in tissue growth of PHBV and PHBV/CS scaffolds for six and twelve weeks. In addition, in vivo results showed that the composite scaffolds could stimulate their generation of cartilage tissue as more GAG and collagen were expressed in the composite scaffolds than in the pure PHBV scaffolds. All of these results indicated that bioactive ceramic calcium silicate could also be applied in C.T.E (cartilage tissue engineering) to improve cell–material interactions and to stimulate regeneration of cartilage tissue. Both the scaffolds also had identical pore sizes (Fig.11)

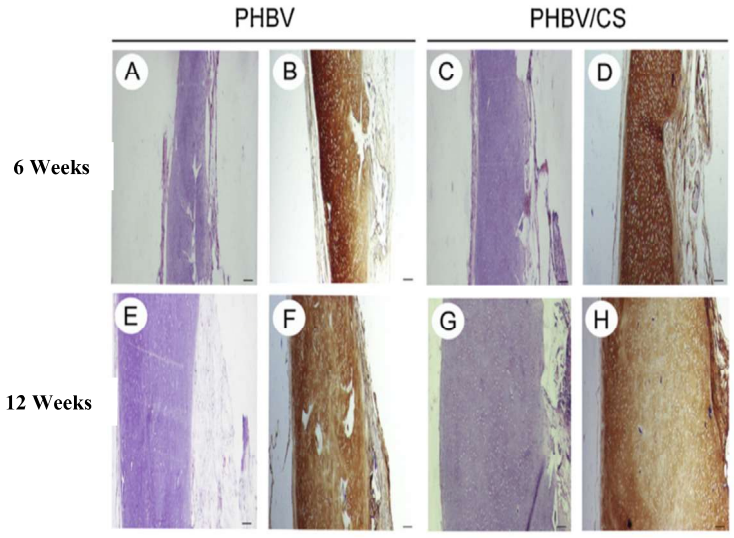

Fig.10.Histological images of in-vivo cartilage (Adapted from Jun Wu .et. al [24])

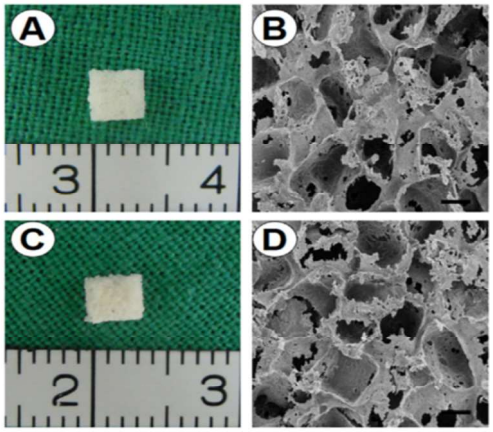

Fig.11. Optical and SEM micrographs of PHBV and PHBV/CS scaffolds (Adapted from Jun Wu et.al [24])

Based on a study conducted on Silk hydrogel composites for cartilage tissue repair, silk hydrogels reinforced with silk microfibers was found well suited for cartilage tissue engineering, providing mature chondrocytes with a structural and mechanical microenvironment that is highly supportive of cartilage matrix deposition [23]. Furthermore, the potential to surface modify the silk fibroin for enhanced cell attachment, or the opportunity to employ silk as a drug depot for local, controlled release of vascular or growth factors to the defect site significantly increases the utility of silk composite materials for cartilage tissue engineering.

3D cell-printed PCL–alginate scaffolds encapsulating chondrocytes and growth factors were developed by Additive Manufacturing techniques. Synthetic polymer (PCL) and the natural biopolymer (alginate hydrogel) were combined and chondrocytes were deposited onto it. The PCL polymer possesses superior mechanical properties; while the alginate hydrogels are widely accepted candidate materials for cell encapsulation [26].The composite scaffolds had well defined structure, showed higher ECM and GAG content in the engineered cartilage without an adverse tissue response etc.

Unlike using single, homogeneous biomaterials as scaffolds, there are proven results of getting advantages by usage of composite scaffolds. A 3-D woven fiber-reinforced composite scaffold that possesses initial mechanical properties that are nonlinear, anisotropic, and visco-elastic properties was developed [27], which provide advantages in forming cartilage construct capable of load-bearing without the need for extended *in vitro* cultivation. Such scaffolds, or other composite techniques, could provide biomimetic mechanical characteristics, while simultaneously providing an appropriate physiologic environment for embedded cells to sustain chondrogenesis. So, usage of composite materials in scaffolding can help in solving numerous problems associated with present cartilage tissue repair practices.

6. Composite scaffolds in cardiac tissue engineering

Cardiac tissue engineering is of great importance for therapeutic and pharmaceutical applications. So far, heart transplantation, cell therapy, and tissue engineering have been considered as promising strategies for the treatment of MI (Myocardial Infarction). Among them, cardiac tissue engineering offers a promising approach to repair damaged heart tissue thanks to the engineering of three-dimensional (3D) cellularized tissue constructs provided by 3D proper scaffolds [28].

Electro spinning fibrous materials is developing as practicable scaffolds for cardiac tissue engineering, and been widely studied in recent years. Electro spun scaffold design was integrated [29] to make the translation of electro spun-based engineered cardiac tissues for clinical applications more realistic and it was found that cardiac tissues formed on conductive electro spun scaffolds could potentially beat synchronously with the native myocardium by the stimulation of internal electrical signal after implantation.

A scaffold was developed which promote bundled orientation of cardio myocytes, increased mass transfer, enhanced neo vascularization, and integration with myocardial tissue. Then a biologically analogous scaffold was

fabricated with channel domains for cardio myocytes and spherical pore domains for mass transfer and invading vasculature [30]. The scaffold was a proangiogenic, bimodal scaffold for cardiac tissue engineering. Rod-like scaffold constructs could feasibly be implanted in infarcted human hearts using minimally invasive catheter introduction systems.

The scaffolds that can provide electrical conductivity and structural organization will be highly beneficial for cardiac tissue engineering. Such a scaffold was developed with electrical conductivity and porous structure composed of chitosan (CS) blending with graphene oxide (GO) for cardiac tissue engineering [28]. Properties like swelling, porosity, and conductive properties of GO/CS scaffolds could be modulated via adjusting the ratio of GO to CS. More importantly, GO/CS scaffolds had a swelling ratio ranging from 23.20 to 27.38 (1000%) and their conductivity (0.134 S/m) fell in the range of reported conductivities for native cardiac tissue.

The significance of mimicking the ECM in native myocardium have already been clarified in the design of scaffolds for engineering functional cardiac tissues, thus various materials have been fabricated and tested for their performance in cardiac tissue engineering [29] and incorporating composite scaffolds into this area beholds greater importance in future.

7. Conclusion

Many materials have been introduced so far in to tissue engineering practices. Each of them possesses its own advantages and limitations. As discussed above, combining different materials to make composite scaffold materials can replace conventional materials and induce many favourable properties to scaffolding practices in tissue engineering.

As technology developed, scaffolding process was made easier and versatile. Methods like 3D printing, Bioprinting etc. are some of the best techniques at present for scaffold fabrication. But, clinical introduction of these highly advanced regenerative medicine practices are still to achieve. Developing array of available bioactive materials, growth factors, functionalization techniques and biomimetic scaffold designs, the potential for creating complex scaffolds tailored to patient-specific applications in the future is vast. This also offers hope for the treatment of a variety of challenging conditions. With the increase in technology, the future of tissue engineering practices using composite scaffold materials looks promising to change the entire tissue repairing concept.

References

[1] B. Dhandayuthapani, Y.Yoshida, T.Maekawa and D.Sakthi Kumar, “Polymeric Scaffolds in Tissue Engineering Application: A Review” International Journal of Polymer Science, vol.2011,19pages,July 2011.
[2] A. Khademhosseini, R. Langer, “A Decade of Progress in Tissue engineering”, Nature Protocols-Perspective, vol.11, no.10, September 2016.
[3] A.Gloria, R. De Santis, L.Ambrosio, “Polymer-based composite scaffolds for Tissue engineering” Journal of applied Biomaterials& Biomechanics, vol.8, no.2, pp. 57-67, January 2010.
[4] G.Turnbull et.al, “3D bioactive composite scaffolds for Bone tissue engineering” Bioactive materials, vol.3, p.278-314,December 2017.
[5] C. Gao et.al, “Current progress in Bioactive Ceramic scaffolds for Bone repair and regeneration” International Journal of Molecular Sciences, p.4714-4732, March 2014.
[6] S. Van Vlierberghe, P. Dubruel, and E. Schacht, "Biopolymer-Based Hydrogels scaffolds for Tissue engineering Applications: A review” Bio macromolecules, March 2011.
[7] Thadavirul N, Pavasant P and Supaphol P, “Development of polycaprolactoneporous scaffolds by combiningsolvent casting, particulate leaching, and polymer leaching techniquesfor bone tissue engineering” J Biomed MaterRes Part A 2014:102A:3379–3392,October 2013.
[8] J. RnjakKovacina et.al, “Electro spun synthetic human elastin: collagen composite scaffolds for dermaltissue engineering” ActaBiomaterialia 8 p.3714–3722, June 2012.
[9] N.Sultana and E.Wang, “Fabrication of HA/PHBV composite scaffolds through theemulsion freezing/freeze-drying process and characterisation of the scaffolds” Mater Sci: Mater Med 19, p.2555–2561,August 2017.
[10] S. Kumar a, and J.-P. Kruth, “Composites by rapid prototyping technology” Materials and Design, p.850–856, August 2009.
[11] H.Chiaand B.Wu, “Recent advances in 3D printing of biomaterials” Journal of Biological Engineering 9:4, March 2015.
[12] T. Billiet, M. Vandenhaute, J. Schelfhout, S. Vlierberghe, P.Dubruel, “A review of trends and limitations in hydrogel-rapid prototyping for tissue engineering” Biomaterials 33, p. 6020-6041, June 2012.
[13] S.JyotiKalitaa,, S.Bosea, H. L. Hosickb, A.Bandyopadhyay “Development of controlled porosity polymer-ceramic composite scaffolds via fused deposition modelling” Materials Science and Engineering C 23, p. 611– 620, 2003.
[14] T. Serra, J.A. Planell, M. Navarro, “High-resolution PLA-based composite scaffolds via 3-D printing technology” Acta Biomaterialia 9, p. 5521–5530, November 2012.
[15] F. J. O’Brien, “Biomaterials and scaffolds for tissue engineering” Materials today, vol.14, no.3, p. 88-95, 2011.

[16] S. J. Lee and A.Atala, "Scaffold technologies for controlling cell behaviour in tissue engineering" Biomed. Mater. **8** 010201 (2pp)(editorial), 2013.
[17] A. R. Pandey&U.S. Singh &M.Momin and C.Bhavsar, "Chitosan: Application in tissue engineering and skin grafting, J Polymer Res, p.24-125, June 2017.
[18] S. Bose, M. Roy and A. Bandyopadhyay, "Recent advances in bone tissue engineering scaffolds" Trends in Biotechnology, vol. 30, no. 10, p.546-554 October 2012.
[19] M.Farokhi et.al, "Silk fibroin/hydroxyapatite composites for bone tissueengineering" Biotechnology Advances, (in press), October 2017.
[20] Jayachandran et.al, "Alginate composites for bone tissue engineering: A Review" International Journal of Biological Macromolecules, (in press), July 2014.
[21] S.Bhumiratana et.al, "Nucleation and growth of mineralized bone matrix on silk-hydroxyapatite composite scaffolds" Biomaterials 32, p.2812-2820, January 2011.
[22] L. Roseti et.al, "Scaffolds for Bone Tissue Engineering: State of the art and new perspectives" Materials Science and Engineering C 78, p.1246–1262, May 2017.
[23] S.Yodmuang et.al, "Silk microfiber-reinforced silk hydrogel composites for functional cartilage tissue repair" ActaBiomaterialia, September 2014.
[24] Jun Wu, Junying Sun, Jinbo Liu, "Evaluation of PHBV/calcium silicate composite scaffolds for cartilage tissue engineering" Applied Surface Science 317, p.278–283, August 2014.
[25] Lin Sun et.al, "Direct-Write Assembly of 3D Silk/Hydroxyapatite Scaffoldsfor Bone Co-Cultures" Adv. Healthcare Mater., 1,p.729–735, 2012.
[26] J. Kundu et.al, "An additive manufacturing-based PCL–alginate– Chondrocyte bio printed scaffold for cartilagetissue engineering" Journal of tissue engineering and regenerative medicine, J Tissue Engineering Med 2013, November 2013.
[27] Franklin T. Moutos and FarshidGuilak, "Composite scaffolds for cartilage tissue engineering" Bio rheology 45, p.501–512, 2008.
[28] Lili Jiang et.al, "Preparation of an Electrically Conductive Graphene Oxide/ Chitosan Scaffold for Cardiac Tissue Engineering" Applied Biochemistry and Biotechnology, February 2019.
[29] G. Zhao, X. Zhang, T. Jian Lu, and F. Xu, "Recent Advances In Electro spun Nano fibrous Scaffolds for Cardiac Tissue Engineering" Adv. Funct. Mater, 25, p.5726–5738, 2015.
[30] R. Madden et.al, "Proangiogenic scaffolds as functional template for cardiac tissue engineering" PNAS, vol. 107, no. 34, August 2010.