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Progressions and Challenges in Scaffold Fabrication for Bone Regeneration: A Review on Current Techniques

S. Suresh kannan*[1], Dr. Grace Rathnam[2], M. Selva Vignesh[1], S. Sathya Narayanan[1], V. Praveen kumar[1].

Student, Master of Pharmacy, Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Thoraipakkam, Tamil nadu, Chennai-600097, India. [2] Associate Professor, Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Thoraipakkam, Tamil Nadu, Chennai-600097, India.

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ABSTRACT

Bone tissue engineering (BTE) is an evolving field focused on developing scaffolds that support bone regeneration and repair. This review provides an overview of the advances in the fabrication techniques and materials used in bone tissue engineering scaffolds, with an emphasis on their role in enhancing bone regeneration. Various fabrication methods, including electrospinning, 3D printing, and freeze-drying, are examined, alongside the biomaterials commonly utilized, such as polymers, ceramics, and composites. We also discuss the challenges and gaps in current research, particularly the need for in vivo studies to better understand scaffold performance and biocompatibility. Despite significant progress, further exploration is required to optimize scaffold properties for effective bone healing. The review underscores the critical importance of continued research to innovate and improve scaffold designs for enhanced clinical applications in bone tissue engineering.

KEYWORDS:

Scaffold fabrication, Bone tissue engineering, Bone healing, Polymers, porosity, cells, 3D printing, Electrospinning, polymer.

INTRODUCTION:

Bone tissue exhibits remarkable self-healing abilities compared to other organs, as it can restore its original structure and strength without forming fibrotic scars.[1] However, when bone defects exceed the critical-size defect (CSD), they cannot heal autonomously and require clinical intervention.[2] Large bone defects caused by tumors, trauma, or infections often cannot be repaired through autogenous repair, potentially leading to serious disability without surgical intervention. While autogenous and allogeneic bone grafts are commonly used to promote healing, challenges such as infection, rejection, and limited donor availability remain significant in clinical practice.[3] Bone tissue engineering (BTE) addresses these challenges by utilizing scaffolds that provide a substrate for cell adhesion, proliferation, migration, and differentiation. These scaffolds regulate the behavior of bone-related cells, including osteoblasts, angioblasts, and immune cells, guiding their fate and ultimately determining the success of bone repair and regeneration.[4] Tissue engineering (TE) components are classified into three groups: (1) cells, including tissue-specific, stem, or embryonic cells (autologous or allogenic), (2) the matrix, which can be natural or synthetic and take forms like fibrous, foam, or hydrogel, and (3) in vitro culture systems, such as static, stirred, or dynamic flow conditions. Additionally, TE products can incorporate controlled drug delivery systems to release growth factors that enhance angiogenesis and support new tissue formation.[5] Tissue engineering integrates cells, growth factors, and scaffolds to act as an artificial extracellular matrix (ECM) for regenerating bone and generating new organs.[6] Developing cost-effective scaffolds for bone regeneration represents a significant alternative for improving patient recovery.[7] Scaffold is serving as structural guidance, and anchorage sites for cells, in order to develop engineered structure by a combination of scaffolds and living cells to restore, maintain or improve bone tissue function. [8]

Although a lot of recent research has been conducted on this topic, the selection of fabrication methodologies and different biomaterials for BTE is still grounded in hypothesis with no clear path forward. This review article explores various scaffold fabrication methods using biocompatible polymers for bone regeneration, discusses advancements in scaffold technology, and examines their properties and applications in the biomedical field and tissue engineering.

BONE TISSUE ENGINEERING:

Bone is a composite material made up of both organic and inorganic components. The organic phase primarily consists of collagen type I (COL-I), which accounts for about 30%, while the inorganic phase is mainly composed of calcium phosphates (around 70%), primarily in the form of hydroxyapatite (HA). [4] The mechanical strength and durability of bone are attributed to the nanoscale arrangement of these organic and inorganic phases. Collagen microfibrils, produced by osteoblasts, aggregate both laterally and longitudinally to form fibers, which are then called osteoid. During biomineralization, osteoblasts deposit HA crystals into the spaces between the collagen fibrils. The level of biomineralization plays a critical role in determining the mechanical properties of bone tissue: a higher degree of mineralization results in a stiffer structure, but also makes it more prone to fractures.

Before designing a scaffold for bone tissue engineering (BTE), understanding the basics of bone regeneration is essential, especially as it occurs following injury or trauma, such as after the implantation of a BTE scaffold. Bone formation, or osteogenesis, can occur through two main processes: endochondral ossification or intramembranous ossification. Both begin with the condensation of specialized mesenchymal stem cells (MSCs). [8]

The current understanding of critical-sized bone defects suggests they range from 2.5–3 cm or more, where the regenerative process cannot repair the bone without external assistance, typically in the form of an implanted bone substitute material. The key components of bone tissue engineering include scaffolds, biomaterials, stem cells, and growth factors.

Surgeons must carefully select the BTE approach that best addresses the patient's clinical needs, while also overcoming the limitations of conventional treatments. It is equally important to have a clear understanding of the desired outcome, whether it be the quality and functionality of the regenerated bone, and to consider potential side effects or complications associated with the proposed innovative treatment. [10]

Cells:

In addition to materials, cells have been used in BTE for seeding in bone scaffolds before implantation. Numerous cell sources, such as embryonic stem cells, bone marrow stromal cells, and muscle-derived stem cells, have been investigated in BTE. One of the most used cell sources is bone marrow stromal cells.

Growth factors in bone tissue engineering:

Osteoinductive growth factors (GFs), including bone morphogenetic proteins (BMPs), vascular endothelial growth factors (VEGFs), platelet-derived growth factors (PDGFs), insulin-like growth factors (IGFs), transforming growth factors (TGFs-β), and fibroblast growth factors (FGFs), are essential in stimulating bone and vascular development. These GFs regulate key cellular processes such as recruitment, migration, adhesion, proliferation, and differentiation. Osteogenic GFs have found extensive application in bone tissue engineering (BTE). Among them, BMPs are particularly well-known for their ability to promote MSC migration, osteogenic differentiation, and bone formation. [11]

In recent years, platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been increasingly used in bone augmentation treatments as natural sources of a variety of growth factors (e.g., INF-, TNF-, MCP-1, MIP-1α, RANTES, bFGF, PDGF, VEGF), cytokines (such as IL-1β, IL-1ra, IL-4, IL-6, IL-8, IL-12, IL-13, IL-17, IL-2, IL-5, IL-7, IL-9, IL-10, IL-15), and chemokines (like G-CSF, GM-CSF, Eotaxin, CXCL10 [IP-10], and MIP-1β), [12] which are thought to support bone regeneration. However, despite the significant role of growth factors in bone tissue regeneration, their use is also associated with various reported adverse effects. [13, 14]

VARIOUS COMPOSITION USED IN SCAFFOLD FABRICATION:

The majority of the scaffolds are made up of polymers, bioactive ceramics and hybrids. Depending on composition and intended use. [9]

Polymers can be categorized as either natural or synthetic. Naturally occurring polymers, such as fibrin, hyaluronic acid, chitosan, and collagen, offer excellent biocompatibility, osteoconductivity, and low immunogenicity. Synthetic polymers, including polyanhydride, polypropylene fumarate (PPF), polycaprolactone (PCL), polyphosphazene, polylactic acid (PLA), polyether ether ketone (PEEK), and poly(glycolic acid) (PGA), provide advantages such as controlled degradation rates, the ability to modify bone mechanical properties, the capacity to create complex shapes, improved cell attachment through negatively charged chemical groups, and the potential for delivering soluble molecules.[15]

A significant group of polymers used in bone tissue engineering (BTE) are hydrogels, which are hydrophilic polymer networks capable of absorbing water ranging from 10-20% to thousands of times their dry weight.[16] This property supports cell adhesion, proliferation, and differentiation. Both natural hydrogels (such as agarose, alginate, and gelatin) and synthetic ones (like polyvinyl alcohol based) can mimic the extracellular matrix (ECM) topography and deliver bioactive molecules.

Gelatin, derived from partially hydrolyzed collagen, is commonly used to create microparticles, which are widely employed as drug carriers due to their non-toxicity, stability, cost-effectiveness, and ease of preparation.

Bioactive ceramics, which can be natural or synthetic (e.g., coralline, hydroxyapatite [HA], tricalcium phosphate [TCP], sulfate, bioactive glass [BG], and calcium silicate), are chemically similar to bone. They offer high compressive strength and low ductility, providing significant resistance to deformation, but they also have inherent brittleness.

Natural polymers:

Natural polymers are highly biocompatible and can be easily modified and processed into various forms. [17] Some of the most researched natural polymers for bone regeneration include collagen, hyaluronic acid (HA), carboxymethyl cellulose (CMC), and chitosan. Collagen is a fibrous protein abundant in both animals and humans. Its properties vary depending on its fibrillar (e.g., type I, II, III, V, XI collagen) or non-fibrillar structure (e.g., type IV, VIII, IX, X, XII, XIV, XIX, XXI collagen) and it serves as a primary extracellular matrix (ECM) component in mammalian tissues.[18] In the context of bone regeneration, the degree of collagen crosslinking and the use of crosslinking agents are studied to enhance its mechanical properties. Hyaluronic acid (HA), a natural, hydrophilic, non-immunogenic, biodegradable, non-sulfated glycosaminoglycan, is commonly found in high concentrations during early bone fractures. [19] It supports bone growth effectively when combined with other osteoconductive molecules. However, due to its reduced viscoelastic properties, HA is less suitable for regenerating trabecular bone. Carboxymethyl cellulose (CMC), similar to chitosan in structure, is used in cellulose-based natural scaffolds for tissue regeneration. Sodium CMC, a water-soluble polymer, is frequently used because of its hydrophilic and viscoelastic properties, [20] which make it an ideal material for composite scaffolds aimed at addressing the challenges of osteoinductivity and osteoconductivity.[21] Chitosan, a polysaccharide composed of D-glucosamine and N-acetyl-D-glucosamine linked by (1,4) glycosidic bonds, has been extensively studied for tissue regeneration due to its promising qualities. [12]

Synthetic polymers:

Synthetic polymers are commonly utilized in bone tissue engineering (BTE) and include both biodegradable polymers (such as polylactic acid—PLA, polycaprolactone—PCL, and polylactic-co-glycolic acid—PLGA) and non-biodegradable polymers (such as polyethylene glycol—PEG, polyurethane—PU, polyvinyl alcohol—PVA, and poly 2-hydroxyethyl methacrylate—pHEMA) [22]. The fabrication of synthetic polymers is typically carried out through methods like salt-leaching, 3D printing, fused deposition modeling, and stereolithography.[23] Biodegradable synthetic polymers offer advantages such as biocompatibility, biodegradability, and controlled degradation rates. PLA is the most commonly used polymer in tissue engineering applications.[24] Both L and D forms of polylactide have high crystallinity and share the same melting temperature.[25] Poly(L-lactide) has a slow biodegradation rate, whereas poly(L/D-lactide), an amorphous material, degrades faster but has weaker mechanical properties. PCL has been extensively studied for BTE but suffers from poor cell adhesion and low mechanical strength. PLGA is often used as a biocompatible component in composite scaffolds that require appropriate mechanical stability. [26] While non-biodegradable polymers like PEG, PU, PVA, and pHEMA exhibit good biocompatibility and flexibility, their use in BTE is limited due to their low mechanical stability, poor cell attachment, and lack of biodegradability. [13]

MANUFACTURING TECHNOLOGIES:

3D fabrication available technologies can be divided into two main categories, Conventional and Rapid Prototyping (RP).

CONVENTIONAL TECHNOLOGIES:

Conventional techniques, include solvent casting and particle leaching, freeze-drying, Thermally Induced Phase Separation, gas foaming, powder-forming, sol-gel, and electrospinning

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Solvent casting:

Solvent casting, also known as particulate leaching, has proven effective in creating porous scaffolds at room temperature. Its primary benefit lies in the simplicity of preparation. In this technique, a polymer solution is mixed with uniformly distributed salt particles of a specific size. As the solvent evaporates, a matrix with embedded salt particles is formed. This matrix is then immersed in water, causing the salt to leach out and leave behind a highly porous structure. The pore size and porosity of the scaffolds can be adjusted by altering the size and shape of the salt crystals. After the salt is removed, the samples are dried in an incubator at 37ºC. [10]

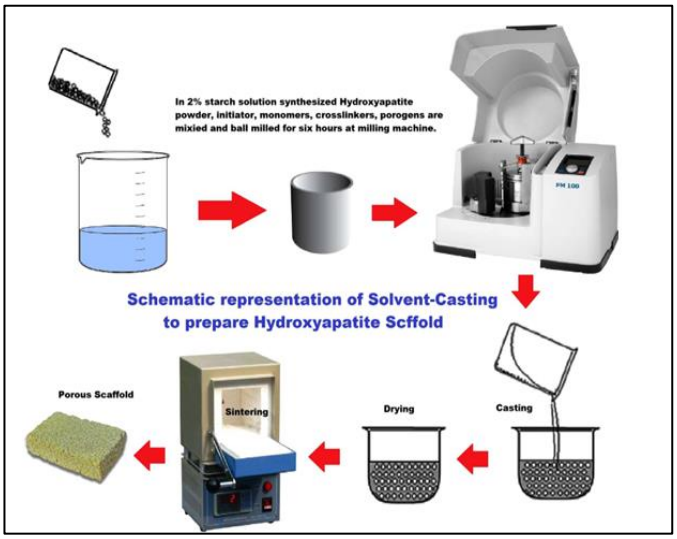

Figure 1 Images of solvent-casting technique [25]

Sudip Mondal and colleagues demonstrated the creation of natural hydroxyapatite scaffolds derived from fish scales using the solvent casting method. These scaffolds successfully replicated the structure, porosity, and mechanical strength of cancellous and cortical bone, exhibiting excellent bioactive properties. The key advantages of this method include high porosity and the ability to adjust pore size, potentially enabling better mimicry of bone-like tissue structures.[27]

Thermally Induced Phase Separation (TIPS):

Thermally induced phase separation (TIPS), also known as freeze-drying, was developed in the early1980s [28] TIPS allows the creation of a variety of porous structures by modifying the process parameters. The initial step in preparing the scaffold is to create a uniform and homogeneous polymer solution.[29] The solvent system typically consists of a blend of dioxane and water. The polymer is dissolved in the solvent by heating the mixture to 60ºC for a specified duration. Components like hydroxyapatite can be dispersed in the solution using ultrasonication.[30] In the next stage, the homogeneous solution is heated to 15°C above its cloud point temperature, causing the polymer solution to become cloudy. The solution is then gradually cooled to the desired quenching temperature using a controlled temperature profile. The final step involves removing the solvent to achieve the desired porous structure. Solvent removal can be done through either freeze-drying or freeze-extraction. However, freeze-drying has some drawbacks, including being time- and energy-intensive and causing surface skin issues.[31]

TIPS is a low-temperature process in which a polymer solution is quenched, leading to liquid-liquid phase separation that forms two distinct phases: one rich in polymer and the other poor in polymer. The polymer-rich phase solidifies, while the polymer-poor phase is removed, resulting in a highly porous, nanoscale fibrous network.[33] The use of low temperatures helps facilitate the incorporation of bioactive molecules. The prepared scaffolds were then stored in a desiccator. [34] Yanfang Yang et.al, fabricated porous poly(L-lactide-co-glycolide) (PLGA) scaffolds by com bining thermally induced phase separation and porogen leaching. Big pores with about 75–400 lm diameters in the obtained scaffolds were generated by the porogen, The compressive modulus and strength were significantly lowered by increasing the scaffold porosity, that is, by increasing porogen fraction, or de creasing the polymer concentration, or reducing the freezing temperature Results showed that the size of small pores decreased by decreasing the polymer concentration and reducing the freezing temperature, whereas the interconnectivity of the scaffolds was improved by increasing the porogen fraction. [32]

Gas Foaming:

The gas foaming technique was developed to eliminate the use of organic, cytotoxic solvents. This process involves using relatively inert gases, such as carbon dioxide or nitrogen, to pressurize molded biodegradable polymers along with water or fluoroform until they become saturated with gas bubbles. The result is typically sponge-like structures with pore sizes ranging from 30 to 700 µm and a porosity of up to 85%. However, gas foaming has some drawbacks, including the need for excessive heat during compression molding, the creation of small, non-interconnected pores, and a non-porous skin layer on the scaffold's surface. Recently, gas foaming (GF) has gained attention for its ability to create 3D porous scaffolds with well-controlled porosity and pore size distribution using various biocompatible and biodegradable materials. However, GF alone may not achieve high pore interconnectivity, so it is often combined with other techniques, such as reverse templating, to enhance the final structure.

A.Salerno et.al they designed poly(e-caprolactone) (PCL) scaffolds characterized by well controlled pore structures obtained by gas foaming of multi-phase blends of PCL and thermoplastic gelatin (TG). It was prepared by melt mixing and, subsequently gas foamed in an auto clave to induce the formation of the porous network. A mixture of N2 and CO2 was used as blowing agent and the foaming process performed at temperature higher than PCL melting, in the range 70–110 C. The foams were finally soaked in water at 37ºC to selectively extract the TG and achieve the final pore structure.[35]

M. Oliviero et.al, designed porous scaffolds with controlled porosity and pore size distribution from blends of poly(e-caprolactone) (PCL) and thermoplastic gelatin (TG), a thermoplastic natural material obtained by de novo thermos plasticization of gelatin. Preparation of co-continuous blends of poly(e-caprolactone) (PCL) and thermoplastic gelatin (TG) with the ultimate goal to design PCL scaffolds characterized by multi-scaled porosity distribution by the combination of gas foaming (GF) and selective polymer extraction (PE) processes. [36]

Sol-gel technique:

The sol–gel technique involves the inorganic polymerization of metal alkoxides. A sol is created by adding a surfactant, followed by condensation and gelation reactions. This process enables the production of ceramic or glass materials in forms such as ultra-fine or spherical powders, thin-film coatings, ceramic fibers, microporous inorganic membranes, monolithic ceramics and glasses, as well as highly porous aerogels. In short, the sol–gel process consists of two stages: the solution stage, where a colloidal suspension of solid particles (sol) is formed, and the gelation stage, where a network of interconnected solid particles (gel) is created. Tetraethyl orthosilicate (TEOS) is commonly used as a precursor in the sol–gel method for bone tissue engineering. [37]

Kebing Chen et.al, prepared two types of organic–inorganic composite scaffolds (F-A-T0/T3/T5 and F-B-T5-P0/P0.5/P1.5/P2.5) using chitosan nanofibers (CSNF) prepared by the beating-homogenization method, combined with the sol–gel method, and further introduced polyvinyl alcohol (PVA). The F-A-T3 and F-B-T5-P1.5 exhibited interconnected pore and surface nanofibers structures, high porosity (>70%), outstanding swelling properties, and a controllable degradation rate.[37]

M. M. Pereira et.al, fabricated resorbable 3D macroporous bioactive scaffolds by foaming sol–gel derived bioactive glasses with the aid of a surfactant. The foams exhibit a hierarchical structure, with interconnected macropores (10–600 mm) and mesopores (2–50 nm). The effects of processing variables on the structure and properties of the obtained bioactive glass foams are discussed in the present paper. The method is then applied to produce bioactive glass–polymer (polyvinyl alcohol) hybrid scaffolds with improved mechanical properties. [38]

Electrospinning:

Electrospinning is a well-established method for producing nanofibers. The resulting membrane fibers have a small diameter and a large specific surface area, closely resembling the natural extracellular matrix (ECM) in both morphology and structure. This similarity promotes cell adhesion, proliferation, and activity. Additionally, the high specific surface area of the nanofibers aids in the adsorption and release of active cells and growth factors, enhancing the biological properties of composite materials. Furthermore, the process for creating nanofiber structures is simple, and the fiber structure can be easily adjusted. [39]

Electrospinning technology operates through an electrohydrodynamic process, where electrical charges are used to draw fine fibers, down to the nanometer scale, from a syringe pump and create a nanofibrous structure on a collector. This process results in a network of fibers with large surface areas capable of adsorbing proteins and providing binding sites for cell membrane receptors. A typical electrospinning system consists of four main components: a spinner with a metallic needle, a syringe pump, a high-voltage power supply, and a grounded collector. The electric field generated by the system overcomes the surface tension of the droplet, creating a charged liquid jet that is stretched and whipped by electrostatic repulsion until it is deposited on the grounded collector. As the solvent evaporates, the jet solidifies into a nonwoven fibrous membrane. Electrospinning is a versatile method that can process a

wide variety of materials to produce scaffolds with the desired morphology and porosity, including fibers ranging from a few microns to the nanometer scale. Various electrospinning techniques used to fabricate nanofibrous structures include solution electrospinning, melt electrospinning, multi-axial electrospinning, modified collector electrospinning, nozzle-free electrospinning, and multi-nozzle electrospinning.

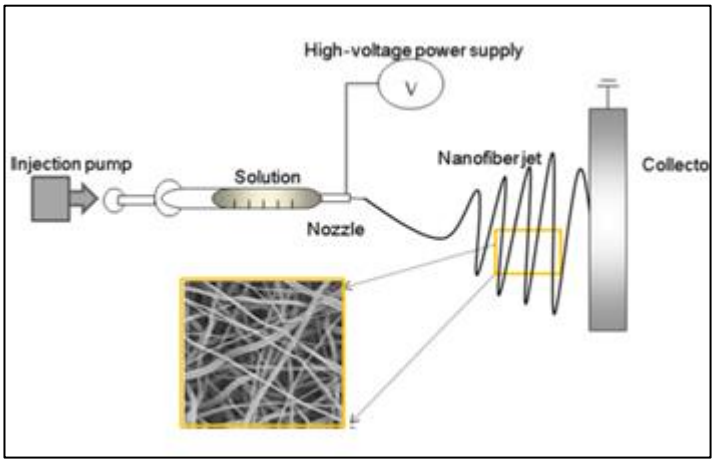

Figure 2 Image of Electrospinning method [49]

Jihang Yao et,al. fabricated silk fibroin (SF)/poly(lactide-co-glycolide) (PLGA) nanofiber scaffolds containing recombinant human bone morphogenetic protein 2 (rhBMP2) and dexamethasone (DXM) via coaxial electrospinning the controlled release of two bioactive factors (rhBMP2 and DXM) was achieved by using an SF/PLGA core-shell through coax ial electrospinning. The core-shell structure of the nanofiber was analyzed by different characterization methods. In vitro drug release studies were carried out to study the potential of nanofiber scaffolds as drug delivery vectors. Osteogenic differentiation and osteogenesis of this scaffold were evalu ated by measuring the adhesion, proliferation, and osteo genic differentiation of rBMSCs including ALP activity and extracellular matrix calcium content. [39]

Particulate leaching:

Particulate leaching is a straightforward method for creating a 3D porous scaffold, involving the uniform mixing of a polymer solution with salt or sucrose particles of a specific size. As the solvent evaporates, the polymer matrix retains the embedded particles. When the composite is immersed in water, the particles dissolve, resulting in the formation of a porous structure. [54] In particulate leaching-based methods, porosity and pore size can be independently controlled by adjusting the quantity of leachable particles for porosity and their size for pore size. However, the resulting scaffold often exhibits limited interconnectivity, which can negatively impact cell seeding and ingrowth.[55]

Hamid Mirzadeh et al. developed PUU-based scaffolds with interconnected pores and controlled porosity, ranging from 77% to 87%. These scaffolds were fabricated using a mixture of PEG and salt particles through a double porogen particulate leaching method. The cells were able to penetrate the pores of the scaffold, indicating the successful formation of proper morphology. This new approach allows for the creation of highly porous scaffolds with a uniform distribution of interconnected pores and well-defined pore structure by maintaining the correct ratio of porogens. [55]

RAPID PROTOTYPING:

The main RP technologies developed within the last years are: Stereolithography (SL), Fused Deposition Modeling (FDM), Selective Laser Sintering (SLS), 3D Printing (3DP) and Bioprinting, also defined as 3D plotting or Direct-Writing.

Stereolithography:

The term "Stereolithography" (SL) was introduced by Charles Hull, who invented the technique and described it in his 1986 U.S. Patent. He developed a method and apparatus for creating solid objects by successively printing thin layers of ultraviolet (UV)-curable material on top of one another. This approach addressed some of the limitations of traditional subtractive methods, such as eliminating waste from unused raw materials and reducing the wear caused by milling tools. In a typical SL system, there is a tank of photo-sensitive liquid resin, a movable build platform, a UV laser for resin irradiation, and a dynamic mirror system. The process

begins with the UV laser applying a layer of photo-sensitive resin onto the platform. After the layer solidifies, the platform is lowered, and another layer is added on top of the first. This process is repeated until the full 3D scaffold is created. Once complete, uncured resin is washed away, and the scaffold is post-cured under UV light to fully harden. In a study by Castro and colleagues, an osteoconductive nanocrystalline hydroxyapatite (HA) material was produced using SL. Stereolithography (SLA) is a promising manufacturing technology that addresses the limitations of commercially available particulate biomaterials for intra-oral bone regeneration. SLA is particularly suitable for processing custom-made bone substitute scaffolds, overcoming these challenges. Light-based SLA is one of the most advanced rapid prototyping techniques, relying on ultraviolet light to induce photopolymerization of photocurable resins.[40]

Stereolithography holds significant potential for creating porous bioceramics with bone-like structures and favourable mass transport properties. It is considered one of the most precise additive manufacturing technologies for processing ceramic components. Stereolithography (SLA) consists of three primary systems: a computer system, an optics system, and a machine system. Using a customized hydroxyapatite (HA) suspension, scaffolds with varying pore sizes were successfully fabricated through stereolithography. [41]

Chuanzhen Huang et.,al. fabricated scaffold , a minimal pore with a diameter size of 500μm can be fabricated, and it has a high dimension precision up to about 60μm. The compression test showed that the scaffolds had an effective elastic modulus ranging from 2.4GPa to 5.9GPa, which could match with the cancellous bone well. The result also shows that this scaffold with intricate pore shape, fabricated by stereolithography, has a high dimension precision up to about 60 μm. [41]

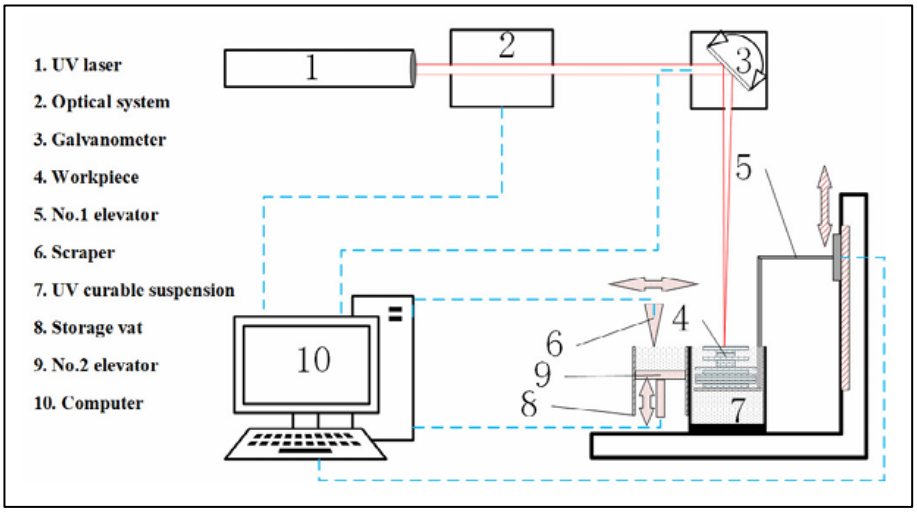

Figure 3 Image of stereolithography [41]

Fused Deposition Modeling:

In the FDM process, molten thermoplastic materials are extruded through a nozzle and deposited onto a base platform according to a path determined by CAD and CAM software. Once a layer is completed in the xy plane, the platform is lowered along the z-axis, and the process is repeated. By adjusting the amount of material deposited, the spacing between deposition paths, and the height interval (z-axis), 3D scaffolds with customizable pore size and porosity can be created. Key benefits include high material porosity, excellent mechanical strength, no need for toxic solvents, and flexibility in material handling and processing.

A key challenge of the FDM technique is the need for pre-formed fibers with consistent size and material properties to be fed through the rollers and nozzle. Additionally, its use with biodegradable polymers, except for PCL, may be limited. The FDM method creates three-dimensional objects from computer-generated solid or surface models, similar to traditional RP processes. These models can also be derived from computer tomography scans, magnetic resonance imaging scans, or data from 3D object digitizing systems. FDM utilizes a small, temperature-controlled extruder to push a thermoplastic filament material, depositing semi-molten polymer onto a platform in layers. The monofilament, driven by two rollers, acts like a piston to push the semi-molten material. After each layer is completed, the base platform is lowered, and the next layer is added. The object is built as a three-dimensional part through the precise layering of extrudate. The deposition path and parameters for each layer are determined based on the material, fabrication conditions, the intended use of the part, and the designer's preferences. [42]

The processing parameters for filling each layer are determined by the inputs provided to the slicing software, which include the FDM head speed, roller speed, slice interval, and deposition direction for each layer. Each layer consists of "roads" deposited along the X and Y axes, arranged in a raster, contour, or a combination of both. The deposition direction, referred to as the "raster angle," can be set between 0° and 180° relative to the X-axis for each layer. The road width (RW) is regulated by the flow parameters at a temperature above the melting point of the thermoplastic material, as well as by the nozzle tip's fine size. [42]

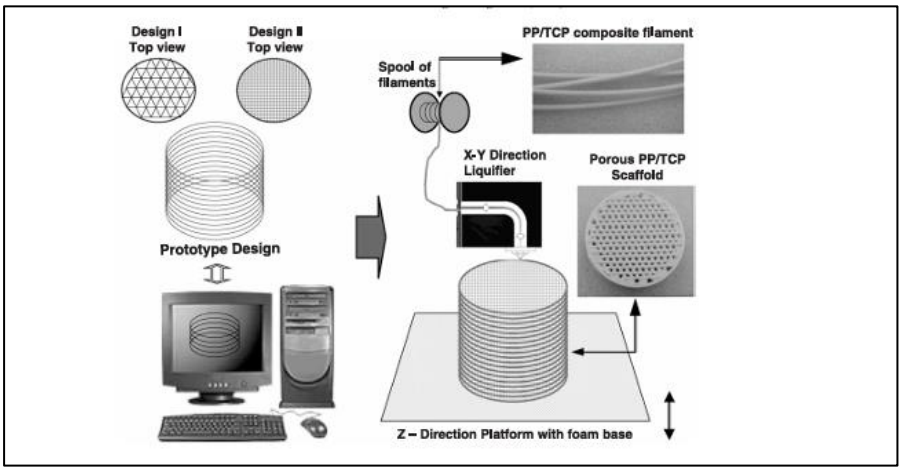

Figure 4 Image of Fused deposition machine [42]

A key advantage of the FDM process is its ability to control the shape, size, and internal structure of porous materials. The main FDM processing parameters that influence the shape, size, and pore volume of any prototype include the road or raster width, road gap, slice thickness, and the angle between consecutive layers of roads.

Samar Jyoti Kalita et.al, developed Controlled porosity scaffolds via the fused deposition process, one of the commercially available rapid prototyping (RP) techniques with Particulate-reinforced polymer-ceramic composites were developed by high shear mixing of polypropylene (PP) polymer and tricalcium phosphate (TCP) ceramic. Processing aids were used to improve plasticity and processibility to the composites. Results showed that these samples were non-toxic with excellent cell growth during the first two weeks of in vitro testing. [20] W. Hutmacher et.al, fabricated PCL scaffolds in fused deposition modelling with a range of channel size 160–700mm, filament diameter 260–370mm and porosity 48–77%, and regular geometrical honeycomb pores, depending on the processing parameters. The compressive stiffness ranged from 4 to 77MPa, yield strength from 0.4 to 3.6MPa and yield strain from 4% to 28%. Analysis of the measured data shows a high correlation between the scaffold porosity and the compressive properties based on a power–law relationship. [43]

Selective Laser Sintering:

Selective Laser Sintering (SLS), developed by the University of Texas in Austin in 1986, uses a high-power laser, such as a carbon dioxide laser, to fuse powder particles in thin layers. Each new layer binds to the previous one, following the cross-sectional data from pre-defined CAD files. Since the powders are kept at low compaction forces after sintering, the resulting structures have an internally porous texture, making them suitable for bone scaffolds. Scaffolds produced by SLS, primarily using PCL and a mix of PEEK and HA, feature anatomically shaped outer structures and a porous inner design that is ideal for load-bearing applications requiring high fracture toughness and mechanical strength.

SLS is a type of Rapid Prototyping (RP) technology that uses powdered materials, radiant heaters, a CO2 laser, and a computer control system. To begin, the CAD files must be uploaded to the computer. The scaffolds are then built layer-by-layer in specific regions, with each powder layer being fused to the one below it. This method allows the creation of highly complex scaffolds without the need for organic solvents. These scaffolds can have large surface areas and be designed to match the shape of a specific bone tissue defect. SLS technology has been extensively studied by various research teams. [44]

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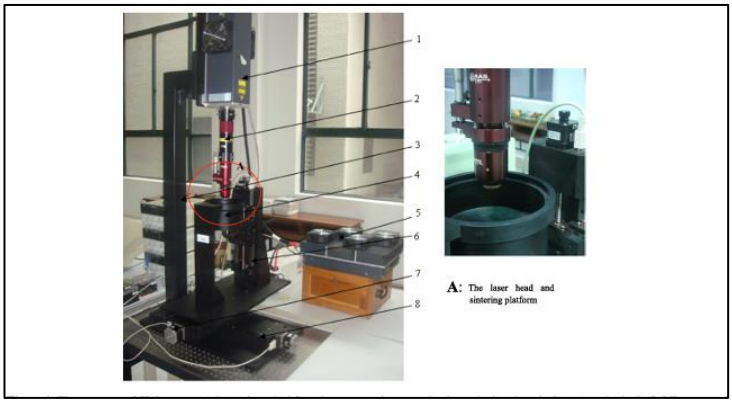

Figure 5 Image of SLS technique [45]

SLS technology has been employed to enhance process performance and produce porous bone scaffolds made entirely from n-HAP material. The technology is utilized to optimize the fabrication of artificial bone scaffolds with a nanoporous structure, taking advantage of the laser's benefits, including concentrated energy, rapid heating and cooling, and precise controllability. [45]

Yan Xia et. al., goals were to fabricate nano-HA/PCL bone scaffolds using SLS and examine their physical characteristics, biocompatibility, and bioactivity using in vitro experiments, and to confirm their ability to promote bone defect healing in an animal model. In this study, we used SLS to successfully fabricate nano-HA/PCL scaffolds with 70%–75% porosity, well-ordered macropores, and irregular micropores. The interconnected macropores and micropores facilitated blood vessel migration, cellular nutrient diffusion, and waste exchange.

Cijun Shuai et.al, SLS system was developed which was able to implement the arbitrary movements and shape of the artificial bone scaffolds based on the non-uniform rational B-Spline (NURBS) theory. Results suggest that the newly developed SLS system can be used for preparation of complete-HAP scaffolds in bone tissue engineering. [45]

Three Dimensional Printing:

The 3DP technique was initially used for creating engineering prototypes, but recent advancements have led to the development of printers capable of producing products that rival those made through traditional manufacturing methods. A large number of commercially available files now contain detailed information about the objects to be printed, such as color, texture, and layer thickness. This technology offers several advantages in terms of cost, time, and setup, enabling mass customization on a large scale and increasing competitiveness in smaller production runs. Additionally, a high degree of customization is possible, as the cost remains the same for both the first and last items. Direct 3DP provides precise control over both micro- and macro-architecture. However, limitations include the restricted pore size and the dissolving effect of organic solvents on most print heads. To address this, stencils may be used, but this limits the ability to create highly complex shapes or small features.

In the indirect technique, molds are printed using commercially available plaster powder, and biodegradable polymers are cast into these printed molds. Indirect 3DP involves creating a simple 3D sacrificial template that serves as a mold for a secondary structure. This template is then removed through physical, chemical, or thermal methods, resulting in the desired 3D scaffold. This approach overcomes several limitations of the direct method: aqueous binders eliminate the need for stencils, the size of the porogen is not restricted since it is introduced into the mold after printing, and it does not affect the printing resolution or layer interconnectivity. However, challenges include high-density packing of the porogen in complex features (such as intricate internal undercuts or intersecting channels) and design restrictions due to difficulty in demolding.

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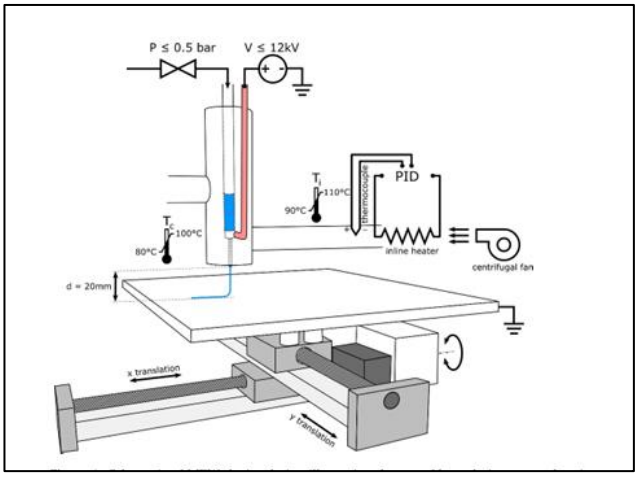

Figure 6 Image of 3D printing machine [48]

The ability to process 3DP technology at room temperature allows for the use of a wide variety of powder materials and the incorporation of various pharmaceutical and biological agents, such as peptides, proteins (e.g., fibrinogen, collagen), polysaccharides (e.g., hyaluronan, alginate), DNA plasmids, and cells, all of which can enhance bone formation. One significant application of 3DP is the fabrication of customized, anatomically shaped constructs based on CT medical data. 3DP also enables the creation of multilayered scaffolds for regenerating hybrid tissue systems. Recently, 3D-printed scaffolds have garnered significant attention due to their ability to support bone cell tissue regeneration and be customized in shape. Among the many challenges, the material composition and geometric structure are critical factors influencing scaffold performance. [46]

Yong Chen et.al, current 3D printing methods can only achieve the fabrication of HA/TCP scaffolds with certain range of microporous structure. To overcome this challenge, we developed a slurry-based microscale mask image projection stereolithography, allowing us to form a HA/TCP-based photocurable suspension with complex geometry including biomimetic features and hierarchical porosity. We determined that a 30 wt% HA/TCP scaffold with biomimetic hierarchical structure exhibited superior mechanical properties and porosity. Cell proliferation was investigated in vitro, and the surgery was conducted in a mouse in vivo model of long bone with cranial neural crest cells and bone marrow mesenchymal stem cells. The results showed our 3D-printed HA/TCP scaffold with biomimetic hierarchical structure is biocompatible and has sufficient mechani cal strength for surgery. [46]

Yuan Pang et.al, proposed a 3D-printed scaffold with a sequential delivery platform loaded with nanotubes and micro spheres to realize the coupling regeneration of blood vessels and bones. Deferoxamine was loaded onto halloysite nanotubes by electrostatic interaction to promote the pre-vascularization of the defect area, which can provide a better blood supply for the subsequent regeneration of bone tissue. BMP2 was encapsulated into the microspheres to achieve continuous long-term osteogenic induction. The PLGA/ TCP solution mixed with microspheres and halloysite nanotubes was shaped into a scaffold by 3D low temperature deposition printing to ensure drug inactivation did not occur. [47]

Electron Beam Melting:

EBM is an additive manufacturing process that uses a high-energy electron beam to melt metal powder layer by layer. This process occurs in a vacuum environment, which helps maintain the material's chemical composition and is ideal for reactive materials like titanium alloys. The powerful electron beam ensures even temperature distribution, allowing the metal powder to melt completely and resulting in materials with high strength. The vacuum and high-temperature conditions in EBM reduce thermal shrinkage and promote a consistent quality of the unmelted powder. [50]

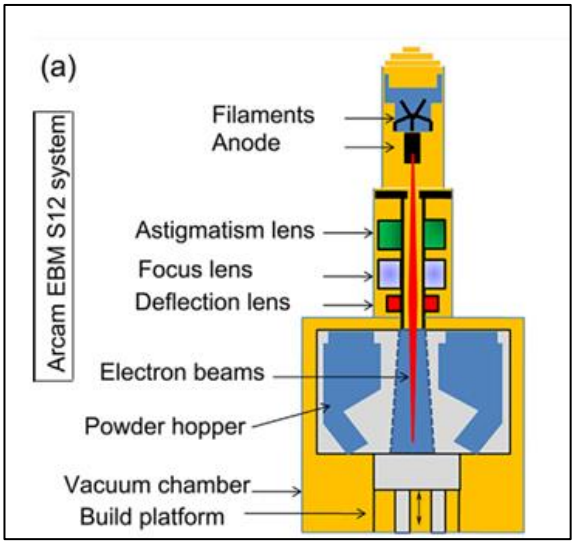

Figure 7 Image of Electron beam melting [52]

The EBM Build Assembler was utilized to import STL files, generate volume supports, slice the STL files into 2D compressed layer files, view the layer files, assign and assemble them into Arcam Build files, and export the final Arcam Build files. Due to their ability to meet high dimensional accuracy standards and the required performance characteristics of the fabricated materials, SLM and EBM demonstrate considerable potential for producing customized metallic implants with cellular structures for orthopedic applications.[51] EBM could conveniently produce scaffolds with tunable porosity and shapes and complex structures based on the popular "bottom-up" concept.[52] EBM is one of the emerging powder-based additive manufacturing (AM) techniques known as the process of "joining materials to make objects from three-dimensional (3D) CAD data, usually layer upon layer. [53]

Hong Cai et al, successfully created two types of Ti6Al4V scaffolds with different pore sizes using the advanced EBM technique. While both scaffold types supported the attachment and proliferation of hMSCs with minimal inflammatory cytokine secretion during the experimental period, the scaffolds with smaller pores were found to be more compatible and better at promoting osteogenesis, likely due to their larger specific surface area. With their biocompatible surface properties, the EBM-fabricated porous Ti6Al4V scaffolds effectively supported cell attachment, proliferation, and osteogenic differentiation while minimizing the secretion of inflammatory cytokines. [52]

Rongzeng Yan et al. showed that the morphological characteristics of the grafted mandible closely resembled those of a normal native mandible, indicating successful recovery. These findings suggest that titanium scaffold meshes produced by EBM are effective in repairing mandibular defects. The EBM process reduced production time compared to traditional manufacturing methods. Additionally, the titanium scaffold meshes produced by EBM demonstrated excellent biocompatibility. The ability to design custom implants allows surgeons to perform procedures more efficiently, ultimately reducing the time required for surgery. [56]

CONCLUSION:

In conclusion, this review has highlighted the significant advances and current trends in bone tissue engineering scaffolds. We have discussed key findings related to various fabrication techniques and materials used in scaffolds for bone regeneration, demonstrating both progress and critical areas of development. However, certain gaps remain in our understanding of scaffolds, and further research is needed to address these issues. Future studies should focus on in vivo research, which could enhance our knowledge and improve bone healing outcomes. Overall, the insights from this review underscore the importance of continued exploration in this field to drive innovation and improve the efficacy of scaffolds in promoting bone regeneration.

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