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Nano, Micro, and Macro Materials in Scaffolds for Biomedical Applications: A Review

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ABSTRACT

Nano, micro, and macro materials for bio-functional scaffolds have garnered more attention in the past few years owing to their ability to mimic the natural environment of the body tissue that needs a repair or replacement accordingly. Although micro structured materials were used in tissue engineering in different forms, the emergence of nanomaterials has enabled the development of nanostructured biomedical scaffolds. The nanostructured scaffolds show enhanced biological functions and properties than micro structured scaffolds. For example, nanostructured scaffolds have a higher surface area, thus allowing better cell adhesion than other conventional materials used in tissue engineering. In addition, the nanomaterials have a significant advantage of mimicking and resembling the natural Extra Cellular Matrix (ECM), which provides better protein absorption, thus stimulating improved tissue engineering. This review presents the different nano, micro, and macro biomaterials employed in developing nanostructured scaffolds and their fabrication techniques. In addition, different types of nanostructured scaffolds used in tissue engineering are elucidated.

Keywords: Nanomaterials; Nanostructured Scaffolds; Tissue Engineering; Bioceramics

Introduction

Tissue engineering is a branch of biomedical engineering that combines biomaterials and life sciences for clinical aspects in curing diseases [1]. This uses a mix of cells, technologies, materials, methods, and biochemical and physicochemical variables to restore, maintain, enhance, or replace a range of tissue. In the broadest sense of the word, tissue engineering includes three constituents: biomaterials, cells, and biological factors [2]. Biomaterials for tissue engineering should have controlled surface chemistry, porosity, and degradation and promote optimal cell adhesion, migration, and cell deposition of endogenous extracellular matrix materials [3]. In addition, the connection between the cells and the materials should be organized, depending on the strength of the adhesion between the cells and between the different cell types present in the tissue. Moreover, the tissues and structures integrated into the host's vascular system must ensure efficient nutrient delivery and waste removal [4].

Scaffolds can be fabricated in different shapes and forms based on the scale on which they are made. However, for any tissue engineering applications, it is necessary to mimic the native extracellular matrix (ECM) structures, which play a significant role by providing structural support and mechanical shielding for the cells, later help in the regulation of cell adhesion, migration,

proliferation, and differentiation [5]. The native ECM is dominated by fibrous collagen proteins, often forming a 3D nanofibrillar matrix. This is where scaffolds on a nanoscale range would be beneficial because this mimics the scale of nanofibers in the ECM. Hence Nanostructured scaffolds, specifically nanofiber scaffolds, show great promise in recapitulating the in vivo 3D environment that promotes cell growth and differentiation [6]. The preparation of nanostructured scaffolds involves nanotechnology, which concerns the manipulation, investigation, and interpretation of the materials at the nanoscale level [7]. The nanostructured scaffolds are essentially a combination of nanomaterials and different cues composed of supporting materials and cells, growth factors, and biomaterials used for implantation [8].

Materials at the nanoscale often have novel physicochemical properties and promising potential applications in tissue engineering [9]. Nanoscale materials can effectively deliver therapeutics into cells due to their smaller size and functional properties. Thus, we can achieve the controlled and targeted delivery of active pharmaceutical ingredients for better healthcare treatment [10]. The surface properties of nanomaterials decide where and how to deliver therapeutic substances to the body. For example, the selectivity and specificity of each nanomaterial are dependent on its surface properties, such as ligands, antibodies, and peptides. In addition, material surface properties mediate specific proteins (such as fibronectin, vitronectin, and laminin) adsorption and bioactivity before cells adhere to implants, further regulating cell behavior and dictating tissue regeneration [11]. The nanostructured materials with favorable cell surface properties promote more significant amounts of specific protein interactions to more efficiently stimulate new bone growth than conventional materials [12].

This is one of the underlying mechanisms why nanomaterials are superior to conventional materials for tissue growth [13]. Therefore, various nanophase ceramic, polymer, metal, and composite scaffolds have been designed for tissue engineering applications by controlling surface properties. Be it for any tissue engineering applications, the materials used should be exhibiting the same response to external loads and stresses as the native tissue itself align with making no compromises in the biocompatibility with the existing tissue [14]. The nanoporous scaffolds show an upper hand in this domain, especially for bone tissue engineering. These scaffolds provide a suitable microenvironment to ensure cell adhesion and proliferation while maintaining the secretory activities of the own extracellular matrix, thus helping the biodegradable scaffold [15]. Nanomaterials are classified into inorganic and organic nanoparticles based on their chemical nature. Organic nanoparticles are carbon-based nanomaterials and include polymer nanoparticles and nanofibers, micelles, liposomes, and dendrimers.

In contrast, inorganic nanoparticles include metallic, bimetallic, alloy nanoparticles, silica nanostructures, magnetic nanoparticles, conversion nanoparticles, and quantum dots [16]. The synthesis of nanoparticles occurs through either top-down or bottom-up approaches. In top-down approaches, bulk materials are the source materials, and continuous decreasing of size results formation of nanoparticles [16]. In contrast, in bottom-up approaches, the formation of the nanoparticles starts from the atomic or molecular level [17]. In addition, nanomaterials can also be grown or self-assembled into nanotubes or nanofibers, which can even more accurately simulate the dimensions of natural entities, such as collagen fibers [18]. Decreasing material size into the nanoscale, dramatically increased surface area, surface roughness, and surface area to volume ratios can be created to lead to superior physicochemical properties (i.e., mechanical, electrical, optical, catalytic, magnetic properties) [19]. In addition to the dimensional similarity to bone tissue, nanomaterials also exhibit unique surface properties, such as surface topography, surface chemistry, surface wettability, and surface energy, due to their increased surface area and roughness as opposed to their conventional counterparts.

Nanomaterials include nanoparticles, nanoclusters, nanocrystals, nanotubes, nanofibers, nanowires, nanorods, nanofilms, and so forth. In addition, numerous top-down and bottom-up nanofabrication technologies such as electrospinning, phase separation, self-assembly processes, thin film deposition, chemical vapor deposition, chemical etching, nano-imprinting, photolithography, and electron beam or nanosphere lithographies are available to synthesize nanomaterials with ordered or random nano topographies [20-22]. This review primarily focuses on the materials used in nanoceramics, nanoparticles, and crystals, and then nanocellulose, including some novel techniques for fabricating nanostructured scaffolds. These techniques, including freeze-drying, phase separation, gas foaming, solvent casting, and electrospinning, can all be used to fabricate nanofibers, with each method having its own set of strengths and biomaterials. Further, the various types of scaffolds prepared at the nanoscale are discussed. They include nanoporous, nanofibrous, polymer bioceramic composite, acellular, and hydrogel scaffolds at the nanoscale. Finally, a few critical applications of nanostructured scaffolds are categorized and discussed.

Materials Used in Scaffold

Nano Polymers

Polymers play an efficient role in the preparation of scaffolds for biomedical applications [23]. The polymers used require

some basic properties such as material chemistry, hydrophilicity, molecular weight, shape and structure, surface energy, water absorption, degradation, and erosion mechanism to be used for scaffold preparation. Nano structed polymers enhance the stability of scaffold which gives more advantage in natural process of the host system [24,25]. Moreover, it has wide recognition due to its individual properties like high surface to volume ratio, high porosity with small pore size, biodegradability and mechanical properties, higher degree of stiffness and strength with far less high-density material [26]. These are used to research the growing skin, bones, liver, heart valves, arteries, bladder, pancreas, and other soft tissues due to their versatility in chemistry, and other biological properties [27]. These polymers (synthetic or natural) can be either degradable or non-degradable. Both synthetic and natural polymers show different properties [28].

Natural polymers are materials that improve structural stability and bioactivity extracted from living organisms [29]. Natural polymers are of two types based on their origin. They can be of plant origin (obtained from agar, cellulose, rosin, starch, pectin, and Guar gum) or of animal origin (obtained from chitin, carrageenan, or psyllium) [30]. The shells from marine species are more compatible with the process since they are easily degradable [31]. Synthetic polymers are artificially made. These materials are fabricated through a chemical process for biomaterials to restore injured or diseased tissues [32]. These are extremely useful in biomedical field because of their porosity, degradation time, and mechanical characteristics in specific applications [33]. They also exhibit predictable and reproducible mechanical and physical properties and possess a suitable elastic modulus [34]. For both natural and synthetic polymers, polymeric nanoparticle drug delivery systems allow the polymer to be more target specific since the coating of the nanoparticles with polymers increases the amount of drug-loaded as well as tissue/cell-specific recognition proteins, which generates a more targeted and efficient nanoparticle.

Such nanoparticle systems in cancer treatment are ternary structures composed of a ligand or an antibody (targeting moiety), a polymer which acts as the carrier, and an active chemotherapeutic drug [35]. And there another type of polymer large used material is nanocellulose. Cellulose is known as one of the most abundant biodegradable materials in nature. Nanocellulose is a term referring to nano-structured cellulose, this material is also used in medical applications such as wound dressing, tissue engineering, controllable drug delivery system, blood purification, etc. This biomaterial helps in cell adhesion, which contributes to nanostructure to macroscale properties [36]. Thus, there are some applications in fundamental scientific research and biomedical engineering. These materials have vast differences in biochemical and biophysical environments. They will lead biomaterials and synthetic materials to advance in the frontier of scientific knowledge [37]. Nanocellulose has good reinforcement and high-water resistance ability that gives further more importance than cellulose, has unique physical, chemical, mechanical and biological properties that gives advantage to scaffolds [38] Nanocellulose biomaterials are used as artificial skin and wound dressings because of their tunable mechanical properties, high biocompatibility, versatility, and customizable surface structure in skin application [39].

In general, the nanocellulose are considered biocompatible are nontoxic, nonimmunogenic, noninflammatory, and facilitate cells are adhere, proliferated, migrate, and differentiate in composite with other materials [40]. It is also used in neural applications where cellulose scaffolds are suitable for 3D nerve cell proliferation and differentiation because of their adjustable surface chemistry and mechanical/physical properties compare to micro particle nano particle gives more advantage in the scaffold applications [41].

Nanobioceramics

Bioceramics help in the growth and regeneration of tissue and bone in the process of scaffold. This is an evolution in biomaterials used as biological substitutes to restore, maintain and improve damaged tissues [42]. But nano scale biomaterials used in bioceramics have many assistances in large surface area and good biocompatibility when compare to micro scale that gives more advantage to use in tissue and bone engineering to overcome the problems associated with natural reconstructive surgery [43,44]. Nano-bioceramics are practically lighter and stronger than micro forms so they can mostly use in drug and gene delivery. An in-depth study on bioceramics to understand has revealed their inorganic composition, high stiffness, hydrophilicity, biocompatibility, bioactivity, and Osteoconductivity [45]. Calcium phosphatase, ceramics, carbon-sulfur ceramics, and bioactive glasses are most common synthetic forms of both micro and nano-bioceramics [46]. Bioceramics with nano structured surface has significantly promote in cell attachment, proliferation and osteogenic. Which possess great potential in constructing vascularized tissue-engineered bone in medical applications [47]. They influence protein absorption and promote cell differentiation through cell-extracellular matrix interaction. They still have some critical problems that limit their clinical application [48]. There are several foaming techniques to develop micro/nano-bioceramics, such as incorporating an external gas by mechanical frothing, injection of a stream of gas, introducing an aerosol propellant, and the evolution of gas in situ. These decisive steps are the direct foaming methods which will induce stabilization by setting wet foams [49,50].

Nanocomposites

Nanocomposites are multiphase solid materials that contain two or more dimensional materials (< 100 nm in the nanoscale). There is much focus on nanocomposites' structural enhancements in Physiochemical properties and functionality [51,52]. It is also used in tissue engineering scaffolds by recreating the extracellular matrix found in vivo. Material has minerals for bone and tissue such as Calcium, Hydroxyapatite, Phosphatase, and combinations of materials like polymers such as poly (lactic acid), poly (-caprolactone), collagen, chitosan, and other different combinations [53,54]. Nanocomposites have specific growth hormones and adhesion sequences to attach the scaffold that are used in drug delivery in various kinds of tissue engineering applications [55]. Among these, there are two main type of nanocomposites such as polymer based and non-polymers based. Polymers are effective materials used in the neural system for regenerative reasons, which are further classified into ceramic, organic and inorganic polymer, polymer/layered silicate. Non-polymer are classified into metal, ceramic, ceramic-ceramic nanocomposites which has lower melting point, increased strength and hardness, improved magnetic properties and electrical resistivity [56,57]. The term tissue inducible biomaterial has been recently applied on the principle of biology and engineering to design nanocomposite scaffolds that restore, maintain, and improve the general damaged tissue [58]. These materials are used in many applications related to biomedical sciences. Compared to other materials, nanocomposites have advantage in tissue engineering applications.

Nanoparticles and Nanocrystals

Nanoparticles have good multimodal tools for scaffolds that help in tuning their mechanical power and their controlled supply over bioactive agents [59]. In addition, nanoparticles have low toxicity, contrasting agent properties, and control over enhancing scaffolds [60]. It is based on systems where tissue engineering scaffolds are used to deliver multiple growth factors to provide contrast in imaging and control the properties of the scaffolds. These particles are made of polymers, metals, and ceramics depending on the application [61]. Polymeric and inorganic nanoparticles has been used to develop scaffold properties for tissue engineering and regenerative medicine, these particles can be flexible for various size and shapes, demonstrate size depends on properties and functions. These particles should be over 10 to 1000 nm in size range for preparing the solid and colloidal forms and have an expansive area of applications in the production of the sensor, photovoltaic devices, and biomedical field drugs delivery and vaccine adjuvants [62,63]. In addition, these nanoparticle scaffolds were used in tissue engineering for regeneration applications. Compare to micro and macro particles, nanoparticles gives way more advantage in improving bioavailability by enhancing aqueous solubility, increasing resistance time in body, and targeting drug to particular spot [64]. Nanocrystal is a material with less than one dimension and smaller than 100nm, and it is also based on quantum dots and is composed of atoms that have single or poly-crystalline arrangements. These have advantages in physicochemical properties and chemical modifications in polysaccharide nanocrystals [65]. Nanocrystals differentiate them from larger crystals. These compounds have silicon on their base, and silicon nanocrystals can provide well-organized emission while bulk silicon is not in use; these also can be used as memory components [66].

Processes Involved in Scaffold Preparation

It is a conventional approach for merging different materials into one compound as a scaffold. For the scaffold preparation, some technical processes are easy ones, and others are problematic methods. They are also distinguished by the time taken and the process involved in the scaffold preparation. The major types of methods for scaffold preparation are given below:

Freeze Drying

Freeze drying is an industrial process used to ensure long-term stability to preserve the original properties of pharmaceutical and biological products. This is also known as lyophilization or cryodesiccation [67]. This method removes the lasting solvent from the materials by drying them into powder. This involves freezing the materials, lowering the pressure, and then the sublimation and desorption process. Materials are dissolved in a solvent and frozen in a dry-ice bath, and the solvent is removed by Vacuum, leaving a dry powder as given in the image below (Figure 1). During this process, the temperature is maintained sufficiently low for any remixing of the phase separation polymer solution. After the freezing phase it goes under primary drying where enough heat is supplied to material for the ice to sublime where pressure is controlled by vacuum, and also for accelerating drying process. And the secondary is removing unfrozen water molecules by desorption phase by nucleation temperature, its faster that the primary drying. There are many advantages to this process. It has a high-temperature capability, and the pore size is easily controlled by the freezing method. On the other hand, it has its own disadvantages. It is a long-term process with high energy consumption, and it gives an irregularity in the size of pores [68-74]. So when the polymer nanoparticles based scaffolds are prepared using the freeze drying method, in order to improve the physical and chemical stability of these systems water has to be removed. The most commonly used process which allows to convert solutions or suspensions into solids of sufficient stability for distribution and storage in the pharmaceutical field is freeze-drying [75].

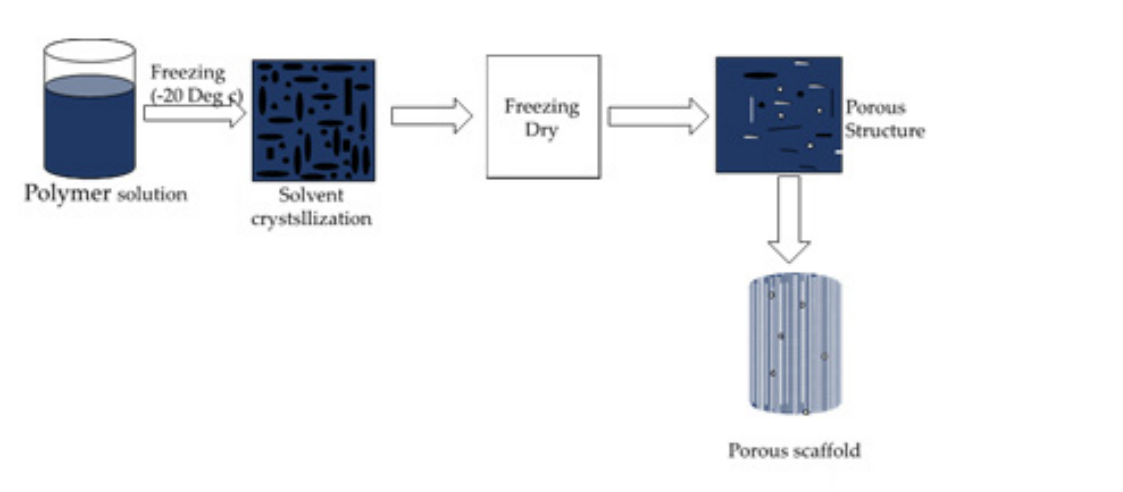

Figure 1: Process of the freeze-drying method.

Electrospinning

Electrospinning is a simple, rapid, and flexible technique for scaffold preparation. It is a prevalent method to process solutions, melt, or suspend into nano or microfibers with a high-voltage electric field [76]. This process essentially works on electrical discharge in the metal wires, which pass electric pulse around 104-106 A/mm2 for increased heat in materials. The rise in temperature converts the polymer solution into a polymer jet that solidifies through evaporation. The solvent is collected in the spinner. There are also other factors which help in the formation of taylor cone, jet and nanofiber deposit on collector, Some parameters like solution properties which affect electrospinning process are (conductivity, viscosity, surface tension, solvent volatility, solution phase transitions), environmental parameters (relative humidity, temperature), and solution feed-rate, applied potential, collector distance, voltage, velocity, and jet path are which come under process type parameters. It is the most helpful method for developing nanofibrous scaffolds, and the homogenous mixture is made of fibers with high tensile strength. The disadvantage is that the solvent can be toxic depending on its variables [77-81] (Figure 2).

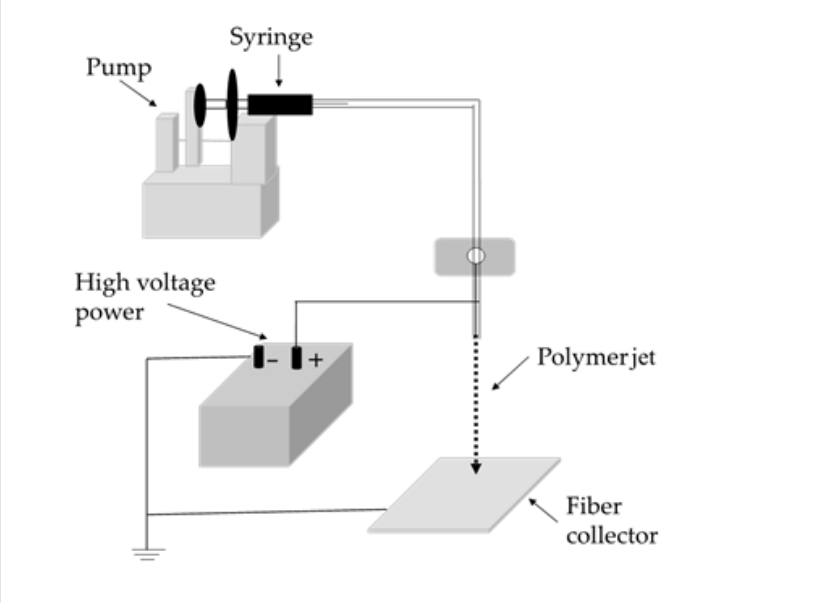

Figure 2: Process of electrospinning.

Solvent Casting and Particulate Leaching

Solvent casting is the method used to prepare film-type nanocomposite for scaffolds. These polymers are entirely soluble in the solvent and ensure uniform distribution of scaffold properties. This method can control the polymer surface structure, including surface heterogeneity and reorientation of the surface crystal [82,83]. This technique was frequently used to manufacture 2D structures and various 3D Structures in a short period. Both natural and synthetic nanomaterials of polymers get dissolved in a solvent. The principle of solvent casting begins with polymers dissolved in the solvent with uniform distribution of salt particles. Then, the solution is placed in the 3D model, which evaporates the liquid and leaves matrix deposited particles. These particles are dipped in water to get salt particles to leach out from the pores forming the desired nanoparticles, forming scaffolds [84-87]. This method has some advantages. The thin wall of 3D specimens has high porosity, and it is a low-cost technique. However, the disadvantages are that it is time-consuming for thin membranes and has widespread toxic solvents [88] (Figure 3).

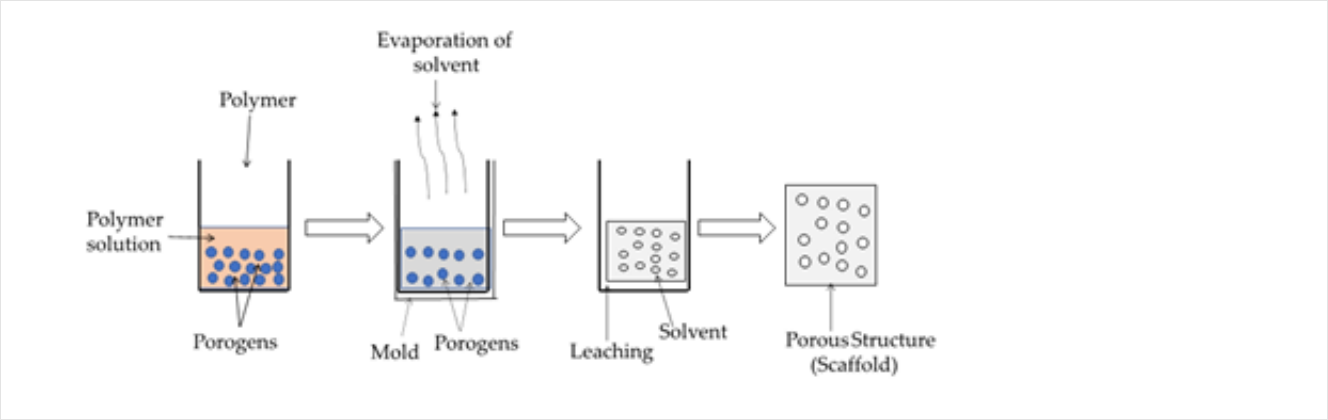

Figure 3: Process of Solvent casting and practical leaching.

Gas Foaming

Gas foaming is the most helpful method for preparing nanocomposite scaffold and biodegradable polymers, and this has originated for drug delivery applications. By using this method for preparing will help to reduce acid and glass nanoparticles present in nanocomposites. These applications take advantage of high pressure to produce the porous structure of the solvent, and also this method used with nanocomposite will enhance the scaffold in all aspect and increases the degradation and biocompatibility ability further [89,90]. The first step is to place polymers in the gas chamber containing CO2 and gradually increase pressure to the point where these gas-filled polymers are sufficiently soluble in the polymeric phase until it is saturated. The pressure releases that result in nucleation and growth. This results in the structure of a highly porous scaffold formation. Its porosity is up to 85%, and the scaffolds prepared by this method can support cellular functions, critical in tissue regeneration. This fabrication cannot be changed, which has a closed pore structure [91-94] (Figure 4).

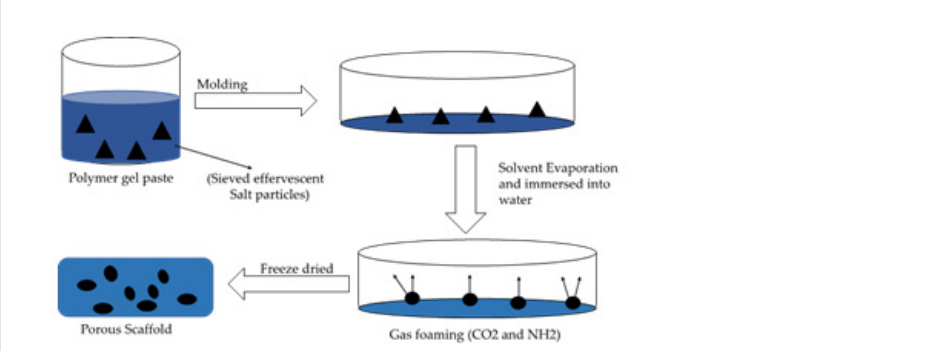

Figure 4: Process of Gas Foaming.

Phase Separation

Phase separation is a method based on a thermodynamic process known as thermal-induced phase separation (TIPS). Phase separation is mainly used to prepare nanofibers, and this method creates a biocompatible scaffold with nano polymers. By preparing nano scaffold by this method has great impact on high porosity, nano-diameter fibers and high surface area compare to other methods [95]. It is used to create a gel by adding a non-solvent to the polymer solution. The thermodynamic remixing of the homogenous polymer-solvent is separated into the polymer-rich and polymer lean phases [96]. This TIPS is going under two types, solid-Liquid and Liquid-Liquid phase separation, depending on the freezing point of the solvent used. Different in their temperature, in solid-liquid phase separation, the crystallization is at a higher temperature in a solvent when compared to the liquid-liquid phase. The crystallized solvent is removed by freeze-drying, where the quenched polymeric solution, which is below the solvent's freezing point, has been subsequently freeze-dried to be porous. The crystalline polymer scaffolds, which can integrate bioactive molecules at low temperatures are an added advantage. The porosity of fibers is more than 98% in this procedure [97-100] (Figure 5).

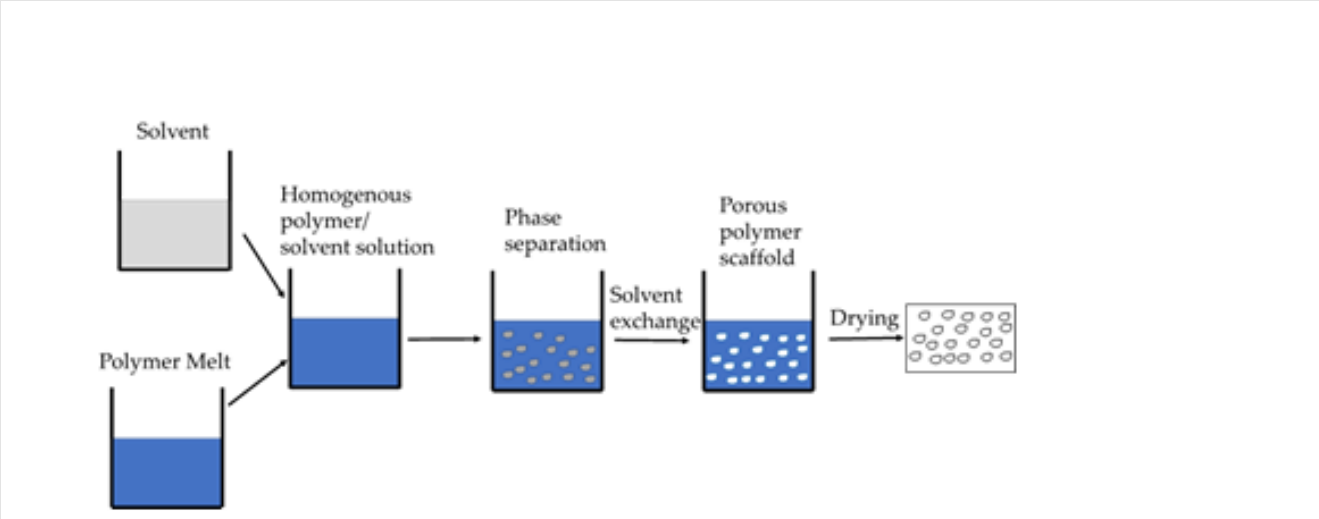

Figure 5: Process of Phase Separation.

Lithographic

Lithography is micro and nano fabrication method which enable the formation of specific and complicated 2D or 3D structures at small scale or nano scale. Scaffold fabricated by this technique has greater use in drug delivery, tissue engineering and disease-diagnostics [101]. The standard steps in lithography module are dehydration bake, HMDS prime, resist spin/spray, soft bake, alignment, exposure, post exposure bake, develop hard bake and descum. These techniques in micro-and nano materials are better in controlled in drug delivery system in the current methods, has divided in photolithography and soft lithography in biomedical field [102,103]. Photolithography is also known as optical lithography which mainly use light to transfer patterns, this technique is based on top-down approach. The nature of photoresists has different ranges of radiation which can be used such as electron beam, ion-beam, and X-ray [104]. The principle of photolithography lies on chemical alteration of the resist upon light exposure. The advantage of using photolithography is complex shaped pattern can be easily fabricated. with this technique, biocompatible and biodegradable materials can be fabricated in less than a minute [105]. Soft lithographic is an emulsified polymeric system which has polymer-based biomaterials, which utilizes elastomeric polydimethylsiloxane to generate micro and nanofabricated structures. Scaffold fabricated using both techniques were used to form multilayer structures by membrane lamination. It gives systems with better control, structure, scalability, reproducibility, composition, and high throughput [106,107].

Types of Scaffolds

Scaffold are specially prepared for preferable cellular interactions to provide the foundation in new functional areas and for the development of tissues in the medical field. There are different scaffold types for various purposes like tissue engineering, bone engineering, drug delivery, etc. These are the vital types of scaffolds.

Microsphere Scaffold

Microsphere scaffolds are usually used in tissue engineering applications such as tissue regeneration, gene therapy, and the treatment of infected bones. They have a spatial extension and temporal period that gives control and stiffness gradients to the connection in tissue engineering [108]. These microsphere scaffolds possess polymer matrix composite that are used in drug encapsulation. It also slows the prolonged period of polymer with a low molecular weight, which helps in developing a porous microsphere for rapid release in drugs. Due to their dense nature, the polymers with a high molecular weight in the microsphere have slow drug release. It also gives control to the drug delivery system [109,110]. Therefore, it is used in drug delivery and tissue engineering applications. Its benefits include physiochemical characteristics, easy fabrication, control over morphology, biocompatibility, and its versatility in controlling encapsulated factors' release kinetics [111]. There are many methods to prepare microspheres-based scaffolds like heal sintering, solvent vapor treatment, solvent/non-solvent sintering, and particle leaching. For example, the chitosan-based microsphere scaffold is fabricated in tissue engineering for cartilage and osteochondral tissues [112]. This microsphere matrix also shows the benefit of bone regeneration. The materials used to fabricate the microspheres scaffold are polymer ceramic matrices. The advantage of sintered microsphere is that it has a desirable 3D pore size and while using nanotechnology application, scaffold design shows the possibility of sustained release [113]. The microsphere matrix has been integrated with nanofibers to form hybrid scaffolds which can be used for bone tissue engineering. Here the composite ceramic/polymer microsphere scaffolds with synthetic ECM-mimetic networks which were nanofibers in their pore spaces. Using thermally induced phase separation, nanoscale fibres were deposited in the pore spaces of structurally sound microsphere-based scaffold with a density proportionate to the initial polymer concentration [114].

Nanofibrous Scaffolds

Fibrous scaffolds are extracellular matrices that give a natural environment for tissue growth compared to other scaffolds. It promotes cell adhesion, proliferation, and differentiation due to its high surface-volume ratio. Bioactive factors are incorporate in the fibrous scaffold. It also has biochemical and topographical cues with electrospinning methods [115,116]. The topography of fibrous and nanofibrous scaffolds has mostly resembled the natural biological environment. The fibrous scaffolds can be fabricated from linear biomaterials to possess the shape and mechanical characteristics. The fibrous scaffold has hydrophobicity and roughness that are largely dominated in scaffold fabrication [117]. Electrospinning is one of the most valuable methods for processing polymer into fibrous scaffolds. The materials used in fibrous scaffolds are silk, chitosan, collagen, and gelatin sponges [118].

There is a wide range of techniques to synthesize the nanofibrous such as self-assembly, electrospinning, freeze-drying, and phase separation. The growth factors can be added into the spinning solution or incorporated in the scaffolds by coaxial electrospinning, immobilization, and adsorption techniques [119]. The fibrous scaffolds have a high surface area to volume ratio and high porosity. They are used in tissue engineering, bone engineering, biomedicine, filtration, cell scaffolds interactions, etc. The fibrous scaffold used in tissue engineering has various applications like bone, cartilage, ligament, striated muscle, skin regeneration [120,121]. Compared to conventional scaffolds, nanofibrous scaffolds have better bioactivity to enhance cellular functions and more closely mimic the native structure of ECM. The cell dynamic process in bone tissue engineering includes attachment, proliferation, migration, and differentiation until the development of new bone tissue [122]. The nanofibrous scaffolds have been demonstrated to influence this entire process. In it has been investigated that the role of nanofibrous PCL scaffolds in human mesenchymal stem cell (hMSC) attachment and spreading. It is found that cells attached more efficiently on nanofibrous scaffolds than on microfibrous scaffolds [123].

Nanoporous Scaffold

Porous scaffolds are fabricated from natural and synthetic biomaterials are also known as 3D polymeric porous scaffolds. It has higher porosities and a homogeneous interconnected pores that are highly used in tissue engineering applications [124]. While nanoporous scaffold has a vast potential in enhancing the performance of biosensors and tissue engineering application compare to other scaffolds. This pore structure enhances cell seeding, cell penetration, and distribution in scaffolds. These help in tissue repairing and regeneration because of their high flexibility in various biological cargos, which can be delivered like antibiotics, anticancer drugs, proteins, and DNA [125,126]. These have advantages over synthetic biomaterials like biocompatibility, biodegradability, and remodeling. Likewise natural biomaterials have a natural source that includes polysaccharides, polynucleotides, and liquids [127].

Polymerization or condensation prepares these scaffolds for porogenic materials like chitosan hydroxyapatites, PLGA/ PCL, PDLLA/PEG, Etc. This nanoporous scaffold can be fabricated by lyophilization, particle leaching, gas foaming, electrospinning, and freeze-drying method. It helps in the preparation of scaffold with biocompatibility and other critical natural nuances that should be present. These scaffolds allow the cell to infiltrate and get attached to the scaffold that provides a high surface area to polymer ratio,

thus helping cells for interaction [128-130]. They have easy control over pore structure. The nanoporous scaffold plays a significant role in tissue engineering, bone tissue engineering, and drug delivery. The effects of surface chemistry, culture conditions, mechanical properties, and degradation also play a role in scaffold preparation depending on the fabrication methods and materials used [131-133].

Polymer-Bioceramic Composite Scaffold

These scaffolds are a combination of polymer and Bioceramic composite materials which are used in biomedical applications. It has good properties for being engineered to suit the mechanical and physiological demands of the host tissue by controlling the fraction, morphology, and reinforcing phase [134,135]. However, using the ceramics for the benefit like good compatibility, corrosion resistance, and high compression resistance also has some drawbacks like low fracture strength, difficulty to fabricate, low mechanical reliability, lack of resilience, and high density. Nevertheless, ceramics are used to treat various parts of the body, particularly bones [136]. These polymers re incorporated to prepare scaffolds along with natural and synthetic materials, thus combining polymer and ceramic composite materials for better mechanical properties, bioactive phases, bioresorbable, and scaffold degradation [137]. These scaffolds are made up of different materials like collagen, gelatin, chitosan, and hydroxyapatite for scaffold preparation. This polymer-bio ceramic composite scaffold supports uniform cell seeding, cell growth, tissue regeneration, and bone repairing. Moreover, it has an advantage in maintaining the scaffold's strength and stability while degrading and replacing natural host tissue [138,139].

Acellular Scaffold

The acellular scaffold has high mechanical properties. Its consist of organic components of extracellular matrix have carefully layered and consider as ideal represent of solid culture medium for tissue growth. These acellular scaffolds are made up of natural polymers, which are used to develop the acellular matrices for wound healing because of their biocompatibility and bioactivity and the biomechanical and biochemical activities of ECM [140,141]. The mechanisms of the host immune response to the acellular scaffold are derived from ECM [142]. Acellular scaffolds help cell transplants and construct bio-artificial skin to heal burn wounds up to 2 to 3-degree heat. The acellular scaffold supported cell growth and tissue regeneration, including the urethra and bladder [143]. The scaffold with polymer coating can improve mechanical stability and intensify the protein matrix's hemocompatibility [144]. This decellularization is takes place in the preparation of acellular extracellular matrix (ECM). Decellularization is defined as chemical or physically removing the cellular compartment of living tissue to creat an acellular ECM scaffold. They have a potential advantage in biological recognition [145]. Acellular scaffold play an essential role in transplants and tissue engineering and retain their anatomical structure even after cellularisation, have limited immune reaction, extended life span, and are cost-effective. It is also used in diseased lung treatment [146,147].

Biomedical Applications in Scaffolds

In the biomedical field, scaffolds play a significant role in healthcare science, which helps in the improvement of the human body cells and tissues. Their primary applications are discussed in the following sections.

Tissue Engineering

Tissue engineering is a branch of science used in biological sciences and engineering to develop artificial tissues. It primarily uses scaffolds for the treatment of tissues [148]. It aims to restore, maintain, and replace the tissue. The scaffolds used in tissue engineering are mostly made up of natural and synthetic materials [149]. Scaffold fabricated with nanoparticles have been serve various function and benefits in tissue engineering compared to other types of materials, such as enhancement of biological, electrical and mechanical properties, and patterning of cells, and facilitate the growth of various types of tissues to molecular detection in various applications. It also has high biocompatibility, biodegradability, and an excellent physiochemical state for human tissue cells [150,151]. There are some requirements for the use of tissue engineering, such as cytocompatibility, porosity, pore size, surface properties, and mechanical stability [152]. These scaffolds play a significant role in the tissue engineering process such as tissue repairing, tissue replacement, tissue regeneration, and wound healing and also play a role in tissue engineering services like matrices for cellular ingrowth, proliferation, tissue formation in 3D [153,154]. In addition, these scaffolds are used in tissue engineering for different applications like bone tissue engineering, skin tissue engineering, cartilage tissue engineering [155].

Bone Tissue Engineering

Bone tissue engineering is concerned with implantable bone substitutes for skeletal defects, which cannot be healed by themselves, and for treatments like bone loss due to trauma, infection, and tumor resection [156]. It also uses an artificial extracellular matrix, osteoblasts, and regulating factors for promoting cell attachment, differentiation, and mineralized bone formation [157]. These scaffolds also play a role in cell seeding, proliferation, and 3D tissue formation based on tissue engineering. The materials primarily used in replacing and repair damaged bone tissue are ceramics, polymers, and combination materials [158,159]. That have good flexibility, biodegradability,

biocompatibility, and good mechanical properties. The strategy for bone tissue engineering is based on composites with two or more elements [160]. The nanomaterials in bone tissue engineering have great effect because of their small size which enables to travel through highly compact microarchitecture of bone tissue and cross the blood-bone barrier. It plays a major role in enhancing the cellular adherence of the scaffold for improvement in regeneration of bone. This can be accomplished by several different methods, such as suspension of calcium phosphate with the polymer phase, which is an essential step for scaffolding [161]. The bone tissue engineering involves three main specs that includes isolated cells, tissue-inducing substances, and scaffolds. This process involves repairing damaged bone, regrow tissue, and replacing bone tissue with its biocompatible materials [162,163]. This involves collaboration between groups with engineering, clinician, cell biologists, biochemists, biomaterials science, and engineering. This method enhances the bone tissue cells, which leads to the repair and replacement of the bone tissues [164].

Skin Tissue Engineering

The intention of skin tissue engineering is the regeneration of normal anatomy and physiology of native skin, its aims is to reconstructing the structural and functional components of skin, by reducing scar formation, and improving the quality of wound healing [165]. The wounds can be divided into epidermal, superficial partial-thickness, deep partial-thickness, and full thickness are the different types which involves different application. This skin engineering scaffold has dual function of acting as a wound dressing physical barrier against external infection and provide support for dermal fibroblasts and keratinocytes for tissue regeneration [166,167]. These scaffolds can be fabricated by both synthetic and natural materials each has their physicochemical properties and functional groups for skin tissue engineering. By using nanoparticles in scaffold for skin tissue will accelerated the wound healing and improves the application like anti-inflammatory and antimicrobial activities, and also increases treating range and area, which is greater than other materials used in skin tissue engineering [168].

Cartilage Tissue Engineering

Cartilage tissue engineering is a method for therapeutic repair and regeneration of cartilage by using a combination of biocompatible scaffold material, cells, and growth factors to produce a cartilage like tissue which has similar biomechanical properties of native cartilage. Cartilage is a major component of body tissue which is soft and more flexible than bone it's a connective tissue of human bones [169,170]. Scaffold for cartilage regeneration can be made of synthetic or natural polymers or combination of both, natural biomaterials are the know scaffold for cartilage repair and regeneration because of their good biocompatibility for cell attachment and differentiation. Collagens are main protein components in natural cartilage, bone and other connective tissue and also of the extracellular matrix however it has some disadvantage so it moves on to micro and macro hybrid materials which involves synthetic and natural martials for preparation [171,172]. When is come to nanomaterials which in incorporation of nanoparticles into biomaterials has shows more advantage in cell attachments it leads to perfect construction of tissues, its has biocompatibility, porosity, bioresorbable and high mechanical properties [173,174].

Drug Delivery System

The scaffolds used in the drug delivery system are intelligent alternatives to standard formulations, allowing the control of active compounds' spatiotemporal releases [175]. The polymers blend for responsive targets in the drug delivery system. These drug delivery scaffolds are used in human health and various purposes, which are collaborated with natural and synthetic polymers and other few materials to fabricate scaffolds [176,177]. These materials are polymers, ceramics, nanocomposites, cellulose, etc. These scaffolds in drug delivery are developed for different applications like targeting controlled drug delivery in medical fields such as regenerative medicine and cancer therapy, including anti-inflammatory drugs and growth factors [178,179] The nanomaterials has good role in this application due to their small size and large surface area, it shows increase solubility and enhanced bioavailability, and also have ability to cross the blood brain barrier, pulmonary system , and absorbed through the closed junction of endothelial cells of the skin. It also has little disadvantage like the nanoparticles used to carry drugs may be toxic to the brain [180]. There are some methods for drug- encapsulation such as blend loading, soak loading, site-specific binding, and drug-polymer conjugation in a scaffold, which are used in drug delivery [181]. There are essentially some processes involved, like desorption, dissolution, and diffusion of drugs. This will reduce swelling, and there is also research on neural tissue engineering with drug delivery uses. They easily erode and degrade the matrix and maintain a biocompatible environment in drug delivery systems [182].

Conclusion

Nanotechnology and nanoscience play a tremendous role in health care applications in various streams, especially in biomedical applications. The nanomaterials are well organized as nanofibers that can accurately simulate the dimension of natural properties. Nanomaterials are proven to have potential benefits in regenerative medicine in neural systems. Cell response is affected at the cell-scaffold interface by mimicking the ECM and including nanoscale structural elements in tissue engineering scaffolds. Nano scaffolds facilitate the treatment of diseases and illnesses that

would otherwise lead to incapacitation or untimely death of the subject. Bone tissue engineering deals with the treatment of bones in trauma, infection, and tumor resection diseases. Drug delivery systems, where scaffolds are used as an implant or injecting cells, drugs, and genes into the body, require a collaboration of natural and Synthetic nanoparticles to prepare scaffolds. It is prominently used as regenerative medicine in cancer therapies. Researches on nano-based drug delivery systems show their broad affinity for neural tissue engineering, where nanotechnology plays a vital role in treatments.

Nanofibrous scaffolds are a synthetic replica of the naturally occurring ECM, which promote cell distribution and can promote new tissue formation. The addition of nanoscale crystals to a polymer scaffold mimics the deposition of materials onto the ECM and the multi-component composite structure of bone. Integration of nanoparticles into scaffolds enhances biological regulation of cell behavior for regeneration. The nanocomposites and nanoparticles are excellent multimodal tools containing multi-dimensional materials (<100 nm in size), focusing on the structural enhancement of physiochemical properties in a scaffold. These biodegradable synthetic and natural polymers are primarily used to fabricate nano scaffolds. The biocompatibility, biodegradation, in-vitro and in vivo stability, and mechanism of performance are the most critical parameters to understand before applying the nanomaterial for further advanced applications such as clinical studies. However, recent investigation and promising results giving hope for better healthcare in the future and can help design an artificial model. Scaffold with nanotechnology generation offers new space for primary scientific fields, including biology, physiology, HTS (high-throughput screening) for the pharmaceutical industry, pharmacokinetics, and others. Moreover, in the near future, its applications are more likely to spread swiftly in the service of humanity. Therefore, a balanced and keen optimization and evaluation of the various techniques discussed above, along with ethical considerations, is required to promote its potential clinical applications.

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