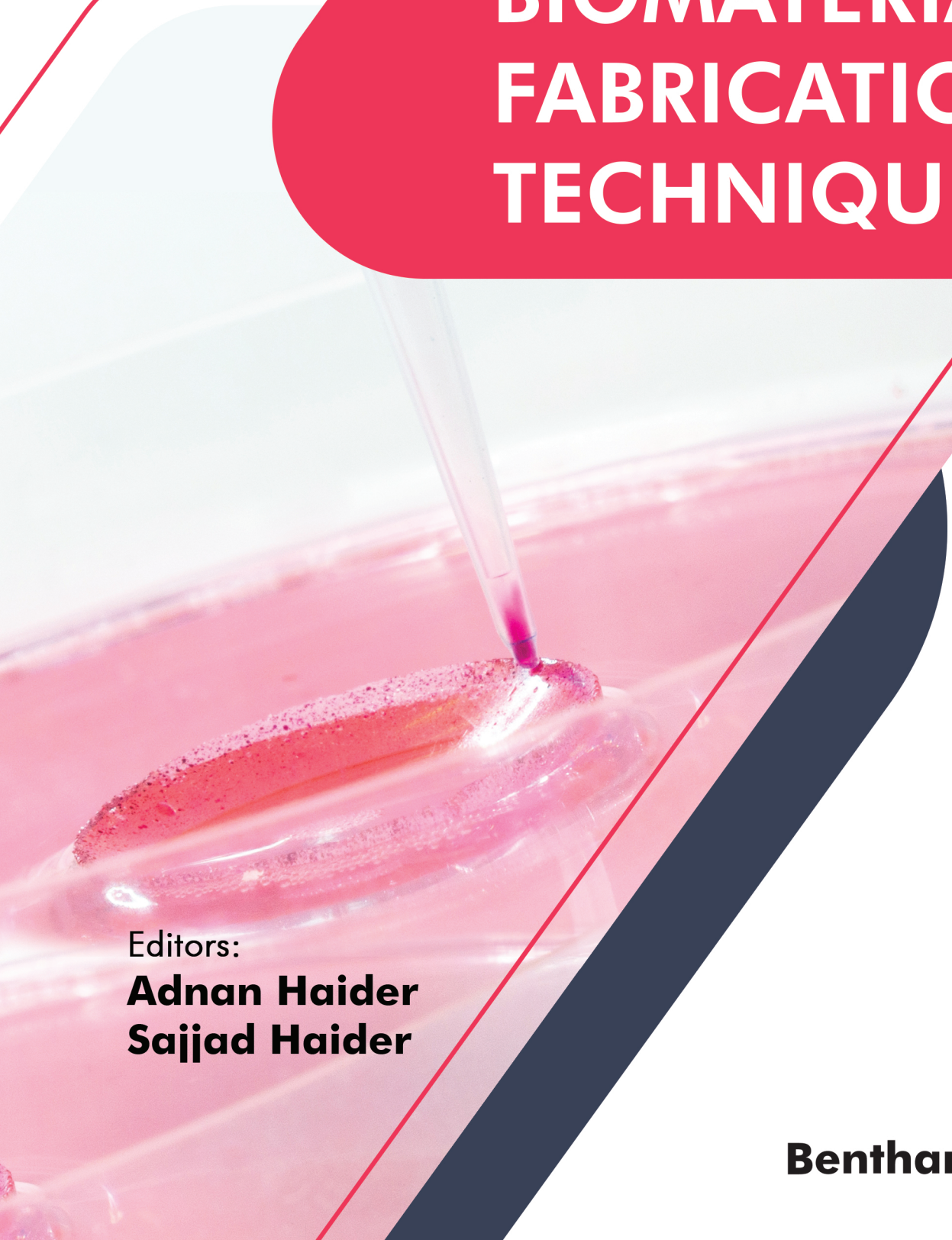
BIOMATERIAL FABRICATION TECHNIQUES



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Biomaterial Fabrication Techniques

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FOREWORD

This book provides an up-to-date, comprehensive, and authoritative overview of advancements in scaffold manufacture and uses in tissue engineering, combining the foundations for a wide understanding of scaffolds for tissue growth and development. The chapters cover a wide range of issues, including innovative materials and methodologies for scaffold preparation, difficulties, and future prospects. The chapters include topics such as novel materials and techniques for scaffold preparation, challenges, future prospects, and much more. The authors have carefully analyzed and summarized recent research findings in the aforementioned areas, providing an in-depth understanding of scaffold that maintains a balance among a variety of topics related to tissue engineering, including biology, chemistry, material science, and engineering, among others, while prioritizing study topics that are likely to be useful in the future.

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PREFACE

This book is a collection of research and review articles from various parts of the world, highlighting the pivotal importance of biomaterials and their potential biomedical application. The articles link new findings and critically review the fundamental concepts and principles that are making the base of innovation. The book comprises ten chapters; the first two chapters deal with vital information about biomaterials and the strategies used for their fabrication. The rest of the chapters highlight the most widely used technique, their principle and their application in detail. The book contains up-to-date knowledge of biomaterials, their fabrication technique and their potential application, which is beneficial both for the experience as well as new researchers.

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CHAPTER 1

Introduction to Biomaterials and Scaffolds for Tissue Engineering

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Abstract: Biomaterials are essential elements in various fields, especially medicine. They can help restore biological functions and speed up the healing process after injury or disease. Natural or synthetic biomaterials are used in clinical applications to provide support, replace damaged tissue, or restore biological function. The study of such types of biomaterials is an active area of research, particularly in the field of tissue engineering (TE). In general, the term TE describes the regeneration, growth, and repair of damaged tissue due to disease or injury. TE is a modern science that combines biology, biochemistry, clinical medicine and biomaterials, which led to the research and development of various applications. For example, in the field of regenerative medicine, biomaterials can serve as a support (scaffold) to promote cell growth and differentiation, which ultimately facilitates the healing process of tissues. This chapter describes the various properties of biomaterials, a detailed discussion of scaffolds in terms of design, properties and production techniques, and future directions for TE.

Keywords: Biomaterials, Scaffold, Tissue engineering.

INTRODUCTION

The U.S. National Institute of Health defines biomaterials as "any substance or combination of substances, other than drugs, of synthetic or natural origin, that can be used for any period of time, partially or completely augments or replaces a tissue, organ, or function of the body to maintain or improve the quality of life of the individual" [1]. Interestingly, the use of biomaterials dates back to ancient times, when the Romans and Egyptians used plant fibres to suture skin wounds and made prosthetic limbs from wood [2]. Since then, the use of biomaterials has gone through different phases. In the industrial era, biomaterials have changed dramatically, leading to the synthesis of novel biomaterials for various applic-

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ations, especially in regenerative medicine and tissue engineering strategies. In general, biomaterials can be divided into three groups: Ceramics, synthetic polymers and natural polymers. However, each group has advantages and disadvantages [3]. In humans, the extracellular matrix (ECM) is considered a natural template biomaterial that provides support, spatial organisation, and maintenance of a biologically active microenvironment. The matrix is composed of different proteins that serve different functions, *e.g.*, structural support proteins such as collagen and elastin, adhesion proteins such as fibronectin and laminin, and swellable proteins that contain polysaccharides such as glycosaminoglycans (GAGs) and proteoglycans [4]. The restructuring and remodelling of the ECM support tissue regeneration, cell survival, proliferation, and other functions [5]. Based on the functions of ECM, researchers are working to synthesise biomaterials that can mimic the role of ECM, which is currently not possible. Therefore, the most typical approach in the field of biomaterials is to understand the ECM mechanisms at the cellular level [6]. The approach has led to the emergence of a new field called tissue engineering (TE), which enables the formation of functional tissues. However, the equation is not simple, as the host response to biomaterials is complex and can trigger a proinflammatory response [7, 8]. TE is a multifaceted field that connects many disciplines, as shown in Fig. (**1**). Interestingly, in recent studies, macrophages play a crucial positive role in remodelling by secreting cytokines and/or scaffold degradation products [9 - 12].

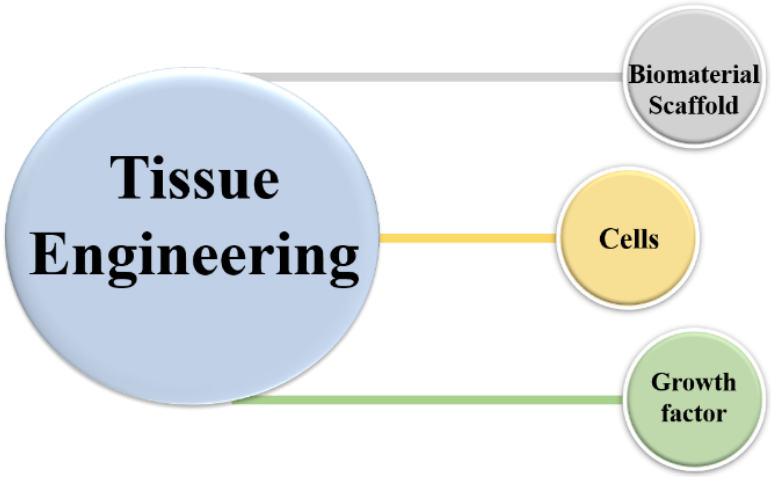

Fig. (1). Basic components in TE: Biomaterial scaffold serving as a template for tissue formation. Cells for regeneration, and signal either chemically from growth factors or physically from bioreceptor.

BIOMATERIALS FOR SCAFFOLD FABRICATION

As mentioned earlier, biomaterials play an important role in tissue replacement and regeneration. So far, various types of materials have been synthesised and used as scaffolds in TE. In the following section, these biomaterials are described in detail.

Ceramics

Ceramic-based biomaterials are inorganic compounds of natural or synthetic origin that can be doped or un-doped with metals. Ceramics are an ideal choice as biomaterials because they have excellent properties, such as biocompatibility and osteoinductivity. This type of material has a similar chemical composition to natural human bone and hardly triggers any immune response. They also help in cell migration and facilitate osteogenic differentiation. Therefore, these types of biomaterials are popular to rebuild injured body parts, especially in bone regeneration. However, ceramics have some disadvantages that limit their use in scaffold fabrication, such as fragility and slow degradation [13 - 15]. There are three types of ceramic biomaterials: (I) inert to the biological environment; (II) resorbable: subject to *in vivo* degradation by phagocytosis; and (III) bioactive by chemically bonding with the cell surface [16]. Commonly used ceramic biomaterials include (a) calcium phosphate (CaP) biomaterials such as hydroxyapatite (HA), beta-tricalcium phosphate (BTP), a mixture of HA and BTP, (b) bioactive glass, (c) alumina, and (d) zirconia.

Natural HA is derived from a certain type of bovine ribbon phosphate and contains minute amounts of magnesium, sodium, carbon trioxide and fluorine. Synthetic HA, on the other hand, is prepared by various methods, including chemical deposition, biomimetic deposition and wet chemical precipitation [17]. Several reports have been published on synthetic HA. For example, Ray and colleagues reported synthetic HA with biocompatible and biomimetic properties. The prepared material was used for bone tissue engineering and iliac wings of dogs [18]. Similarly, Calabrese prepared a bilayer type 1 collagen HA /Mg scaffold and used it for osteochondral regeneration *in vitro* and *in vivo* [19 - 21]. Bioglass is composed of different elements with different weight percentages in the following order: SiO_2, CaO, Na_2O, and P_2O_5 with weight percentages of 45, 24.5, 24.5, and 6.0, respectively. It was first described by Hench and named 45S5 Bioglass, which has been used in biomedical applications [22]. Since then, various methods for the synthesis of bioglass have been reported, such as polymer foam replication, thermal bonding, and sol-gel. Bioglass and HA have similar properties, such as higher Ca to P content, making them ideal for bone grafts. The role of Bioglass in bone regeneration is outlined in Fig. (**2**). Moreover, bioglass

CHAPTER 2

Biocomposites for Tissue Engineering

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Abstract: The goal of tissue engineering is to restore damaged tissue by combining cells with biomimetic material to initiate the growth of new tissue. Biomimetic material plays a crucial role in tissue engineering as it serves as a template and is responsible for providing a suitable environment for tissue development, which includes adhesion of cells, their proliferation and deposition of extracellular matrix. Biocomposites are composite materials, consisting of one or more multiphase materials of biological origin. In this chapter, the biocomposites used for tissue engineering are described in detail. The chapter also highlights the scaffolds and their mechanical properties. This chapter also includes various materials used for scaffold fabrication.

Keywords: Biocomposites, Ceramics, Polymers, Scaffold, Tissue Engineering.

INTRODUCTION

Biocomposites are composite materials composed of single- or multiphase material derived from natural sources, such as plant fibers, flax, cotton, or fibers from wood, waste paper, or food crop byproducts [1 - 5]. The criteria for selecting suitable fibers are determined by the required values of tensile strength, stiffness, elongation at break, adhesion of fiber and matrix, thermal stability, dynamic and long-term behavior of a composite, and processing cost [6]. Composite materials can be classified into (1) Particle reinforced composites, (2) Fiber reinforced composites, and (3) Structural composites. These materials have been used as scaffolds for tissue engineering. The aim of tissue engineering is to restore damaged tissue based on the combination of cells with biomimetic material. The biomimetic material should serve as a template for tissue regeneration and provide a suitable environment for tissue growth [7]. According to the National Science Foundation (1988), tissue engineering was defined as "the understanding of the relationship between structure and function of mammalian tissues under physiological and pathological conditions and their restoration, maintenance, or

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improvement of function through the development of biological substitutes based on fundamental principles and procedures of engineering and biological sciences" [8]. Langer and Vacanti defined tissue engineering as "an interdisciplinary field involving the application of principles of engineering and biological sciences to the development of biological substitutes for the restoration, maintenance, and improvement of the function of a tissue" [9]. The basis of tissue engineering is the use of biomimetic material that provides a suitable environment for the development of tissues and serves as a template for cell adhesion, their proliferation and the development of an extracellular matrix until the complete restoration of tissues. Tissue engineering is based on various scientific principles, such as clinical medicine, material science, mechanical engineering and biological sciences [10 - 14]. The combination of scaffold, cells and growth factors (signaling molecules) forms the basis for tissue engineering [15]. Fig. (**1**) shows a schematic representation of the role of the scaffold in bone tissue regeneration.

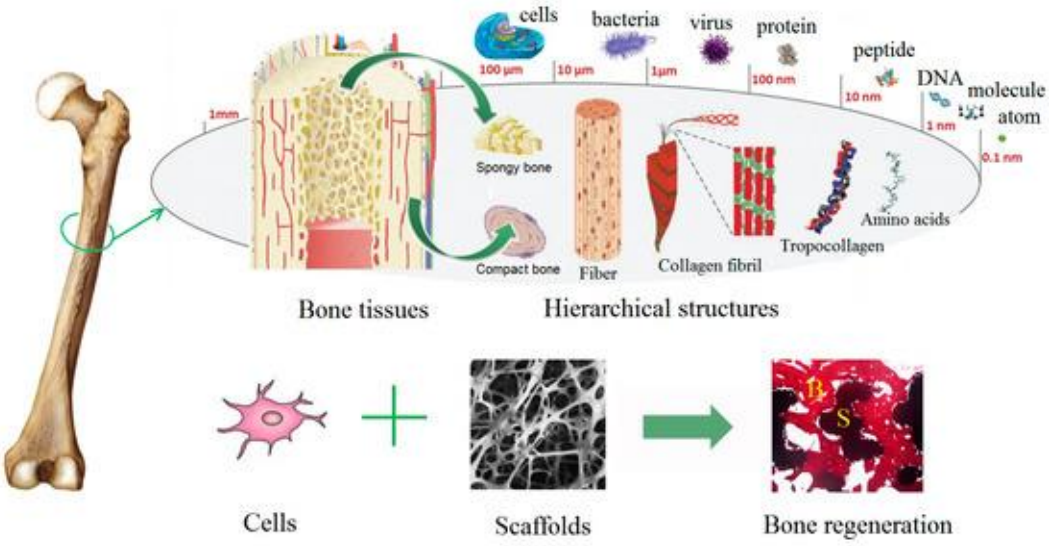

Fig. (1). Schematic presentation of the role of the scaffold in bone tissue regeneration [16].

BIOMATERIALS FOR TISSUE ENGINEERING

Biomaterials are "natural or synthetic substances (not drugs by nature) or their combination that can be used as part of a biological system to treat, support, or replace a tissue or organ" [17]. Since ancient times, natural materials of both animal and plant origin have been sought in nature for wound healing and maintenance and restoration of bodily functions. Plant fibers were used by the Egyptians and Romans to suture skin wounds and were capable of sculpting wooden prosthetic limbs [18]. Over time, various synthetic materials, including

metallic and polymeric materials, were used to make medical devices. These materials had need-based properties and were suitable for use in medical devices. In the modern era, regenerative medicine and tissue engineering are based on biomaterials derived from both natural and synthetic sources. Biomaterials of different types such as polymers (natural and synthetic), ceramics, metal, composites, and hydrogels, have been used to fabricate scaffolds that are used in tissue engineering [19]. To be suitable for scaffold fabrication, any material should have basic properties such as biocompatibility, bioactivity and biodegradability.

Biocompatibility is the basic requirement for any biomaterial to be used for scaffold fabrication, and its compatibility with the biological system [20]. Any biomaterial to be used for tissue engineering should not induce an immune response or inflammatory reaction that may lead to rejection or interfere with wound healing after implantation into the living system. Rather, it should promote cell adhesion, cell proliferation and surface migration [21, 22]. The next is bioactivity, which is the ability of a biomaterial to interact with tissue and ensure that cell adhesion, proliferation, and differentiation occur [23]. The bioactivity of a biomaterial is high when the composition of the biomaterial is similar to the target tissue and capable of inducing the cellular responses required for tissue growth. Bioactivity can be increased by surface modification of the biomaterial by adding macromolecules from the extracellular matrix such as collagens, fibronectins and laminins. These macromolecules create an environment similar to the host tissue that modulates the cellular response [24]. The other important property is biodegradability, which is the breakdown of biomaterials by the living system into non-toxic products that can be easily excreted from the body without adverse effects on other body tissues. This is one of the fundamental properties of biomaterials used in tissue engineering, as the scaffolds only serve to support tissue repair and growth and should not remain in the body forever [25]. The *in vivo* degradation kinetics of any biomaterial should be accurately determined as it controls the rate of its elimination from the body. If the biodegradation rate of a biomaterial is high, the scaffold will not be able to support cell growth for a sufficient period of time. In the case of slow biodegradation, the scaffold remains in the body longer and may cause inflammation and necrosis [26].

SCAFFOLDS FOR TISSUE ENGINEERING

Scaffolds are intended to be implanted in an anatomical location in the body, and their structure should be suitable for the intended site of implantation. Scaffolds should have mechanical strength suitable for the anatomical site and be strong enough to withstand surgical manipulations during the implantation process [27]. The structural properties of a scaffold include macrostructural properties and

CHAPTER 3

Freeze Drying: A Versatile Technique for Fabrication of Porous Biomaterials

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Abstract: The freeze-drying process involves solvent sublimation under vacuum from pre-frozen solution resulting in porous materials. Pore volume, pore size, and density depend on several variables, including freezing temperature, solute and solvent type, solution concentration, and freezing direction. Researchers have investigated aqueous and organic solutions, supercritical CO_2 solutions, and colloidal solutions to produce various porous structures. A more recent process involves freeze-drying of emulsions, which leads to controlled pore volume and pore morphology, and porous organic nanomaterials. Directional and spray freezing are used to produce aligned porous materials and porous particles. In this chapter, we describe the basic principles of the freeze-drying process, the factors affecting the porosity of freeze-dried biomaterials, and their biomedical applications. The freeze-dried porous biomaterials are discussed in detail based on their morphology: porous structures, micro- nanowires, and micro-nanoparticles. We have summarised the current status and given some directions for future research in this field.

Keywords: Freeze drying, directional freezing, biomaterials, porous structure, microwires, nanowires, microparticles, nanoparticles.

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INTRODUCTION

In recent decades, researchers have shown great interest in the fabrication of three-dimensional (3D) scaffolds for various biomedical applications, including tissue engineering.Various fabrication methods are based on the transformation of liquid precursors (mainly polymers and their composites) to solid-state, including 3D printing, gas foaming, electrospinning, solvent casting/porogen leaching, and freeze-drying (FD) [1 - 8]. The FD method can produce 3D scaffolds with a porosity of 90% and a pore diameter in the range of 20 - 400 μm. The FD method was first used by Shackell in 1909 for freeze-drying biological materials. The first patent for FD was filed by Tival in 1927, while Flosdorf patented the use of a modern FD method to prevent degeneration of blood serum [9 - 13]. However, its application for 3D porous scaffolds started only recently. Nowadays, FD technologies are widely used in various industries, including food industry, pharmaceutical industry, nanotechnology, biomaterial development, *etc*. [14]. It is the method of choice for high-value materials or heat-sensitive products, or has special applications due to the direct sublimation of the solvent from ice to vapors at low pressure and temperature.Therefore, sensitive materials, including biological samples and drugs, are neither vaporized nor decomposed. Accordingly, only the solvent is removed from the freeze-dried final product, and the properties of the ingredient are retained. In addition to 3D scaffolds, the FD method has also been developed for the preparation of various other biological materials. For example, nanoparticles and porous materials have been obtained by combining emulsion and freezing techniques, nanofibers and microwires by controlled freezing of polymer solutions, and colloidal suspensions and microparticles by spray freeze-drying.

In this chapter, we ought to explain the basics of the freeze-drying process and then introduce the biomaterials obtained through this process, including porous scaffolds, nano/microwires, nanoparticles, and microparticles. Due to the significant amount of research on porous structures, we have discussed them based on the solution system applied for fabrication; aqueous solutions, organic solutions, emulsions, and colloidal suspensions. Although the conventional method involves the immersion of liquid samples in liquid nitrogen, recent strategies involve directional freezing to fabricate porous materials with layered or aligned pores. Herein, we have introduced the conventional porous materials and then compared them to the materials obtained by directional freezing in each preparation process.

THE FREEZE-DRYING PROCESS

A typical freeze dryer contains refrigeration, vacuum and control systems, a product chamber, and a condenser. The freeze-drying process involves four basic steps: (1) formulation or pretreatment, (2) freezing, (3) primary drying, and (4) secondary drying [14]. In the first step, the precursor is prepared for the process, which may involve mixing or functionalization, leading to better stability in the FD process, such as increased resistance to the low pressure or enhanced 3D porosity. The freezing step involves the precursor loading into specific molds placed in freeze dryer shells by freezing using mechanical refrigeration, liquid nitrogen, or dry ice in aqueous methanol. The main objective is to obtain the temperature lower than the solvent triple point, which is the lowest temperature at which all three solvent phases coexist. Sublimation will occur at temperatures lower than the solvent triple point rather than melting during drying (Fig. **1**) [14 - 17]. It is worth mentioning that larger solvent crystals sublimate easily. Large and more uniform ice crystals are obtained through sluggish freezing or annealing. However, large ice crystals usually lead to non-uniform 3D porosity and weak mechanical properties. Therefore, the solution is rapidly frozen to a temperature lower than the eutectic point, which usually lies between -40 to -80 ºC to avoid the formation of giant crystals. However, amorphous materials do not have a eutectic point, so their critical point is considered for the freeze-drying process. In any case, it is necessary to prevent the starting materials from melting or collapsing during the freeze-drying process. Almost 95% of solvent (mostly water) in the frozen samples is sublimated in the primary drying step. It is a prolonged step and usually takes several hours or days to avoid temperature-induced physical damage. The secondary drying involves the evaporation of solvent molecules that remained unfrozen during the freezing process. For efficient desorption of surface solvent molecules, the temperature is raised to 0 ºC, and the pressure is dropped further. After complete drying, the vacuum is broken by an inert gas [1, 18, 19].

CONTROLLED FREEZING

The freezing step determines the morphology of the porous materials produced. During this step, the frozen solvent crystals grow, excluding the solute particles, until the sample is completely frozen. Freezing conditions, such as solute and solvent, solution concentration, freezing temperature, and direction determine the pore structure and pore density of the prepared material. For example, freezing aqueous solutions in liquid nitrogen results in rapid freezing and smaller ice crystals. However, freezing at -20 ºC results in large ice crystals due to slow nucleation leading to porous materials with large pores after freeze-drying.

CHAPTER 4

Centrifugal and Solution Blow Spinning Techniques in Tissue Engineering

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Abstract: Nanofibers are a necessary source for fibrous materials and other useful applications such as tissue engineering, filtration, safety fabrics, batteries for the production of nanofibers so far. However, due to its low production rate, the wide commercial use of electrospinning is minimal. Almost all nanofiber fabrication techniques (*e.g.*, melt blowing, two-component processes, phase splitting, template synthesis, and self-assembly, *etc*.) are used to produce nanofibers from a limited number of polymeric materials. Centrifugal spinning (CS) and solution blow spinning (SBS) are advanced replacement processes to fabricate nanofibers with full performance from various low-cost raw materials. This chapter focuses on a comprehensive overview of CS and SBS as well as various other aspects of the fabrication of nanofibers.

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Keywords: Centrifugal spinning, Nanofibers, Solution blow spinning, Tissue engineering.

INTRODUCTION

Electrospinning is a well-known technique for the production of nanofibers to prepare scaffolds for tissue engineering. Various polymers, including synthetic and natural polymers [1, 2], can be used to develop scaffolds for tissue engineering using different techniques. The specific surface area, porosity, biomimetic structure of the extracellular matrix (ECM), and improved biocompatibility are all advantages of scaffolds fabricated by electrospinning for tissue engineering. The ECM can associate, release and trigger signalling molecules and stimulate cell response [3, 4]. Scaffold nanofibers can be filled with various bioactive compounds such as proteins, peptides and small molecule drugs to functionalize the scaffolds and promote cell adherence, differentiation and proliferation. As a result, electrospun scaffolds offer significant advantages in biomimetic ECM processes and packaging of bioactive materials. Electrospun scaffolds are also used for drug delivery. In recent years, interest in submicron fibre mats for tissue engineering applications has increased. They provide a good surface area for cell adhesion and mimic the fibrillar structure of native ECM. The porosity of the mat favours the diffusion of nutrients, leading to rapid cell proliferation [5, 6]. The presence of fibres in the form of implants often makes them easy to handle during surgery. Submicron fibres for tissue engineering applications are currently being developed primarily using electrospinning technology, but the process has several limitations. Limitations of the process include low efficiency, limited protective features, and poor alignment and reproducibility of fibre morphology. In addition, the electrospinning process is an environmentally sensitive fibre production technique where even a small change in humidity affects fibre production and consistency. For tissue engineering applications, a new method that can overcome the above limitations is highly desirable [7].

Due to their high rate and easy production of fibres with different morphologies, fibres produced by centrifugal force have attracted the attention of scientists in recent years [8]. Polymer concentration, solvent selection and evaporation rate, spinneret rotation speed and collector unit distance from the spinneret are important parameters that contribute to the improvement of fibre quality [9]. By changing the spinneret configuration and the type of fibre collection, fibres with different morphologies can be produced. An aligned fibre mat can be easily obtained to develop biomaterials for biomedicine [10].

Micro/nanofibers are widely used in both nature and industry due to their

exceptional properties and utility. These fibres are now being used in tissue bandages. These tissue bandages have high filtration efficiency, optical sensor, large surface area, rough surface and intense interfacial interaction [11]. Various techniques can be used to develop continuous microfibers, such as melt spinning, wet spinning, coaxial spinning, electrospinning and blow spinning. The biomaterial based on these fibre fabrication techniques has certain limitations and suffers from non-uniformity of shape and size [12]. Various hardware issues, dynamic configurations and low throughput are industrial obstacles. Consequently, it is a major limitation to fabricate continuous submicron/nanofibers with tunable and uniform morphology [13]. It is true that electrospinning is widely used in biomedical, energy, environmental, catalysis, *etc*. But as mentioned earlier, the process has its limitations when it comes to the use of high static voltages, safety and equipment [14] and the conductivity of the polymer solution. This limits the spinnability of the non-conductive polymers [15]. At the same time, the most important argument is that the nanofibers produced by electrospinning have poor yield. It is difficult to produce large quantities, which significantly hinders commercial production. CS and SBS have been proposed to overcome these limitations and eliminate the safety concerns associated with the electrospinning process. Therefore, there is a need to develop a new solution for nanofiber development that overcomes the limitations of the above approaches [16]. In this chapter, alternative methods using centrifugal spinning and solution blow spinning are discussed to economically fabricate nanofibers from various materials with maximum production. CS and SBS prevent high voltage as a simple and scalable method to fabricate nanofibers for various biomedical applications.

CONVENTIONAL FABRICATION TECHNIQUES

The fibrous material can be produced by a number of conventional techniques. In the late 19th century, Lord Rayleigh produced nanofibers through a technique known as electrospinning. This technique has the ability and potential to produce nanofibers with specific properties. Spun nanofibers have numerous advantages, including an extremely high surface-to-volume ratio, adjustable porosity, formability, pore size and shape, and the ability to control the morphology and size of the nanofiber to achieve desired properties. Nanofibers have unique advantages as they are used as basic structural building blocks in living organisms [17]. In addition to their use in tissue engineering, nanofibers prepared from biopolymers and synthetic polymers are also widely used in drug discovery [18, 19]. In the following, we will discuss some of the known conventional techniques (Fig. **1**) for the fabrication of nanofibers.

CHAPTER 5

Electrospun Nanofibers Scaffolds: Fabrication, Characterization and Biomedical Applications

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Abstract: The electrospinning (ES) technique in the fabrication of biomaterials-based electrospun nanofibers (ESNFs) has risen to prominence because of its accessibility, cost-effectiveness, high production rate and diverse biomedical applications. The ESNFs have unique characteristics, such as stability and mechanical performance, high permeability, porosity, high surface area to volume ratio, and ease of functionalization. The characteristics of ESNFs can be controlled by varying either process variables or biomaterial solution properties. The active pharmaceutical agents can be introduced into ESNFs by blending, surface modification, or emulsion formation. In this chapter, in the first part, we briefly discuss the fundamental aspects of the fabrication, commonly used materials, process parameters, and characterization of ESNFs. In the second part, we discuss in detail the biomedical applications of ESNFs in drug delivery, tissue engineering, and wound healings, cancer therapy, dentistry, medical filtration, biosensing and imaging of disease.

Keywords: Biomedical Applications, Electrospinning, Electrospun Nanofibers.

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Adnan Haider & Sajjad Haider (Eds.)

INTRODUCTION

Nanotechnology deals with the fabrication of materials ranging from 1 nm to about 1000 nm (nanomaterials) and represents one of the newest approaches in medicine and science. Due to their unique physicochemical properties and biocompatibility, nanomaterials have increasingly been used in a variety of biological applications, including drug delivery, wound healing, and tissue engineering [1]. Electrospun nanofibers (ESNFs) are an example of nanomaterials that are mostly fabricated *via* the electrospinning technique [2]. Rayleigh introduced electrospinning in 1897. This is a flexible process in which ESNFs are produced from polymer solutions using an electric field [3]. It is worth mentioning that the ESNFs can be produced using either natural polymers, such as chitosan, alginates, collagen, and gelatin or synthetic polymers, such as poly (lactic-co-glycolic acid) (PLGA), poly(ethylene-co-vinyl acetate) (PEVA), poly(lactic acid) (PLA) polyvinyl alcohol (PVA) and polycaprolactone (PCL) [4, 5].

ESNFs are used in various fields, such as air and water filtration [6], semiconductors and sensors [7], sound absorptions [8], chemical resistance [9, 10], and clean energy [11]. However, the most pivotal applications of ESNFs lie in the biomedical fields, which include cancer therapy, drug delivery, dentistry, wound dressing, tissue engineering and diagnosis of disease [12]. The versatile biomedical application of ESNFs is attributed to their unique properties, such as large surface area and variable porosity. Moreover, the unique chemical composition and physicochemical characteristics of ESNFs usually facilitate the incorporation of hydrophilic and hydrophobic drugs [4]. The usefulness of ESNFs using polymers (biocompatible and biodegradable/non biodegradable) and other compounds can be predicted from the fact that research and review articles are published regularly. This book chapter highlights the aforementioned promising biomedical advances of ESNFs reported in literature.

Fundamental Aspects of Electrospinning

Electrospinning is a simple and versatile nanofiber fabrication process that uses a strong electric field to transform a viscoelastic fluid (*e.g.*, a polymer solution) into continuous nanosized fibers. The polymer solution is pushed from a syringe towards the tip of a metallic needle. The fiber jets are generated from the Taylor cone (formed at the tip of the metallic needle) when high electrostatic forces overcome the cohesive forces [13].

The instrument used in electrospinning consists of a syringe pump and a syringe with a metallic needle, a high voltage power supply as a power source, and a collector plate (grounded metal plate) (Fig. **1**). To operate the instrument, the

syringe is filled with the polymer solution and the orifice of the needle is connected to one terminal of the high voltage power supply, and the other terminal of the power supply is connected to the collector [2, 10]. The main function of the syringe is to pump the polymer solution at a constant flow rate (mL/h) to produce continuous ESNFs. The electrostatic forces overcome the surface tension and form fibrous jets (the Taylor cone formed at the tip of the needle), which are collected at the collector. The electric voltage range is from about 10 to 50 kV approximately [10].

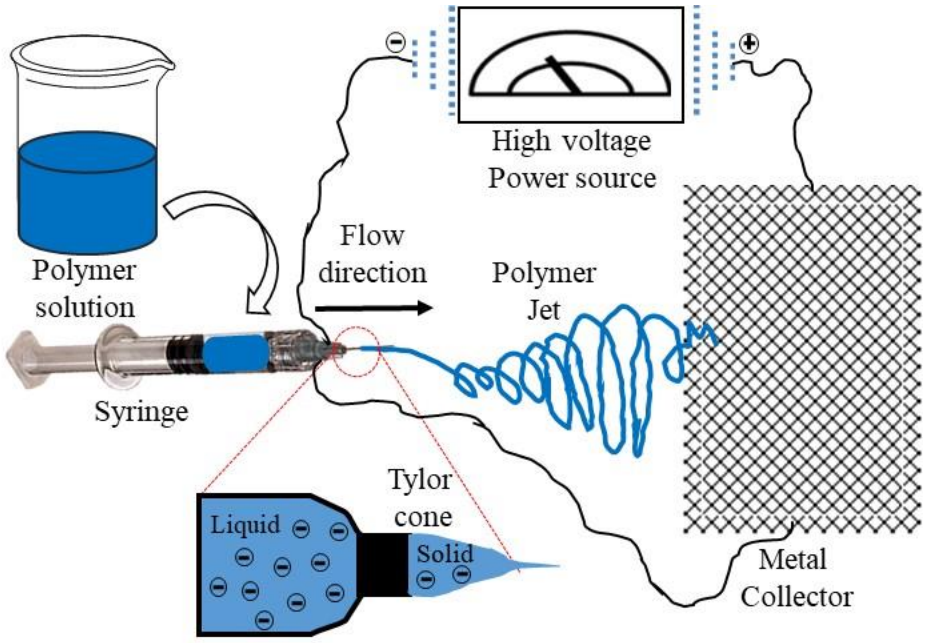

Fig. (1). Schematic diagram representing the fabrication of ESNFs.

Electrospinning Techniques for ESNFs Fabrication

Blending Electrospinning

In the blending approach, the drug is dissolved or distributed in a polymeric solution which is then subjected to the process of electrospinning. The relationship between the mechanical and physicochemical properties of the obtained ESNFs can be enhanced mainly by using the polymer blend. The polymeric blend is an effective means to control the release rate of the drug from the ESNFs [14, 15].

CHAPTER 6

3D Printed Biomaterials and their Scaffolds for Biomedical Engineering

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Abstract: Over the past decade, three-dimensional printing (3DP) has gained popularity among the public and the scientific community in a variety of disciplines, including engineering, medicine, manufacturing arts, and, more recently, education. The advantage of this technology is that it is capable of designing and printing almost any object shape using various materials such as ceramics, polymers, metals and bio-inks. This has further favored the use of this technology for biomedical applications in both clinical and research settings. In biomedicine, there has been a remarkable development of a variety of biomaterials, which in turn has accelerated the significant role of this technology as synthetic scaffolds in various forms such as scaffolds, constructs or matrices. In this chapter, we would like to review the trailblazing literature on the application of 3DP technology in biomedical engineering. This chapter focuses on various 3DP techniques and biomaterials for tissue engineering applications (TE). 3DP technology has a variety of applications in biomedicine and TE (B- TE). Customized structures for B- TE applications using 3DP have several advantages, *e.g.*, they are easy to fabricate and are inexpensive. On the other hand, conventional technologies, which are costly, time-consuming, and labor intensive, are generally not compatible with 3DP. Therefore, the capabilities of 3DP, which is a novel fabrication technology, need to be explored for many other potential applications. Here, we provide a comprehensive overview of the different types of 3DP technologies and how they can potentially be used.

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Keywords: Three-Dimensional Printing (3DP), Scaffolds, Biomedical Engineering, Tissue Engineering.

INTRODUCTION

Tissue engineering (TE) has greatly changed the need to design complicated 3D biomedical devices. Reconstruction of 3D anatomical defects, scaffolds for stem cell differentiation, and reconstruction of complicated organs with sophisticated 3D microarchitecture (*e.g*., lymphoid, liver organs) are some of the applications for 3D biomedical devices. For example, anatomical defects in the craniomaxillo facial complex as a result of cancer, trauma, or congenital defects require functional restoration of important elements of our body systems, such as nerves, vessels, muscles, ligaments, cartilage, bones, and lymph nodes, to name a few.

In recent years, several new approaches have been explored that rely on TE principles to restore and reanimate functional tissues that are highly important in maxillofacial tissue regeneration. In the field of TE, scaffolds are important for a variety of functions, including providing structural support for cell infiltration and proliferation, providing space for extracellular matrix regeneration and remodeling, controlling cell behavior by extending biochemical cues, and reinforcing physical connections for destroyed tissue. Scaffold fabrication requires design at the macro, micro and nano levels of architecture, which in turn are important for cell structural integrity, nutrient transfer and cell-matrix interactions [1, 2, 3]. The macroarchitecture dictates the overall structure of the device, which can be complex considering the various anatomical features as well as patient specificity and organ specificity. The architecture of the tissue with features such as pore size, porosity, shape, spatial distribution and interconnectivity, is replicated at the micro-architectural level. Finally, the nanoarchitecture reflects changes at the surface level, such as the attachment of a biomolecule to ensure cell adhesion, proliferation, and differentiation. Traditional manufacturing uses formative (molding) and subtractive (machine) techniques. These techniques are a multi-step process and require an inefficient infrastructure that makes it impossible to make changes to the final product in a timely manner [4]. Moreover, these conventional techniques limit the scope for fabrication of highly complicated patterns and geometries which are more commonly required in biomedical engineering applications [1].

Over the last four decades, 3D printing or additive manufacturing (AM) has emerged as a robust tool to reconstruct geometrically complicated objects in a short time and in an economical manner [4, 5, 6]. 3D printing, developed in the 1980s, uses a computer-aided model to deposit material layer by layer in a 3D space [7]. This breakthrough paved the way for the adoption and reproduction of

complex 3D structures that would have been impossible to achieve using traditional manufacturing methods. Various industries have adopted this technology due to the creation of complex designs and the far-reaching impact of 3D printing technology on healthcare [4]. Due to its direct application in drug delivery [8, 9, 10], surgical planning [11], implant design [12], and tissue engineering [13, 14, 15], 3D printing's function in healthcare is increasingly becoming critical.

Another rapidly expanding application of additive manufacturing is bioprinting, which allows cells to be seeded in a 3D space while taking into account spatial organization [16]. Bioprinting enables the fabrication of replicates *in vitro* for drug screening, disease modeling, and biofabrication of implantable tissues such as skin [17], bone [18] or cartilage [19]. In this review, we aim to highlight AM fabrication methods, printing materials used in biomedicine and their use in health-related applications. The main focus of this review is on the advanced 3D printing technologies currently used to build scaffolds, with emphasis on their ability to align cells and a wide range of materials along intricate 3D gradients. Most of these technologies have been used to date as surgical templates for formulating patient-specific models, preoperative planning, and prosthesis fabrication. Some of the aforementioned technologies have also received FDA approval for implantable device fabrication. In this chapter, we will mainly highlight the work done in the last five years to show the recent progress the field has made [20].

Three-Dimensional Printing (3DP) Technologies

3DP technology and its applications have made several advances, focusing on the suitability of material processing. Different states such as solid, liquid and powder form the basis for different classes of 3DP technology. The materials used for printing are primarily differentiated by the specific technology used in 3DP. However, all 3DP techniques have one thing in common: the combination of a device with 3D modeling software. The processes involved are [21]:

- CAD sketch is obtained, and interpretation is made by the 3DP device of the data retrieved from the CAD file.
- A layer upon layer structure is built *via* plastic, paper sheet, liquid or powder filaments, all of which make up the printing materials.

Widely used 3DP technologies such as material jetting, photopolymerization, binder jetting, powder bed fusion and material extrusion are shown in Fig. (**1a**) [22]. Photo-polymerization uses ultraviolet (UV) light to stiffen each layer of

CHAPTER 7

Fabrication of Photosensitive Polymers-based Biomaterials through Multiphoton Lithography

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Abstract: The use of polymers in the development of biomaterials for various biomedical applications has become increasingly important in recent decades. To match the innate properties of biological tissues, the polymer-based tissue scaffolds must have the desired structural and functional properties. However, the polymer-based hydrogels prepared by conventional methods are often delicate and fragile and require pre-stabilisation. This necessitates the exploration of bio-friendly cross-linkers that promote kinetic or reversible crosslinking in the polymer network of hydrogels and must be nontoxic to cells and tissues. The light initiators with well-organized multiphoton cross sections that are reactive at specific wavelengths could be ideal candidates. This chapter reviews the fabrication of solid or viscoelastic biological scaffolds by multiphoton lithography (MPL) of liquids. It describes the similarities and differences between conventional and MPL photo polymerization of biological scaffolds in terms of synthesis chemistry, properties, and their relevance to biological applications. These photosensitive scaffolds could be useful biomaterials for their biomedical applications.

Keywords: Biomaterials, Biomedical Applications, Cross-Linkers, Hydrogels, Multiphoton Lithography, Photosensitive Polymers.

INTRODUCTION

The emergence of the polymer industry in the early 1950s led to the synthesis of several new products for everyday use [1 - 3]. Currently, the use of various polymers is attracting much attention in the biomedical field, where they are used in the development of drug delivery systems [4 - 6], tissue engineering scaffolds

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[4, 7 - 9], synthetic organs [10], medical implants [11 - 14], and medical equipment such as biosensors [15 - 17]. The use of various polymers for their biomedical applications requires the development of specialized materials for specific applications by controlling their synthesis process. To this end, advances in photophysics and synthetic chemistry are leading to the synthesis of polymers in a controlled environment, *e.g*., the initiation and propagation of the polymerization reaction in the presence of light [18, 19].

The use of light as a catalyst during the polymerization reaction allows unique control of the reaction as well as the freedom to perform the experiment at different times and places. Photo polymerization is a reaction carried out in the presence of light that, under suitable conditions, converts the low molecular weight prepolymer solution or monomers into high molecular weight materials. The conventional photo polymerization reaction for material synthesis is usually carried out by the light-induced radical polymerization [20], which requires a suitable light source and at least one precursor solution consisting of a multifunctional monomer and a photo initiator. The light is used to irradiate the precursor solution and produce the photopolymerizable material. The photomask dictates the shape, while the light dose and intensity control the degree and rate of the polymerization reaction [21]. *In vivo* or *in situ* photo polymerization can also be performed by introducing the precursor solution into the body and then initiating the photo polymerization reaction [22]. In this way, a biomaterial corresponding to the desired tissue shape can be rapidly produced. On the other hand, interfacial photo polymerization can be performed by adsorbing or attaching a light initiator to the surface of a polymerizable material that can produce brushes. These photo polymerization approaches are useful for achieving consistent coatings, casting compounds, and *in vivo* implantation of grafts. However, they are limited to planar patterns only and cannot take advantage of the full 3D and spatial resolution offered by light initiation [18].

Over the last couple of decades, photo polymerization has played a crucial role in the establishment, growth, and expansion of several modern industries, such as integrated circuits, coatings and adhesives, and optical devices, due to its unique properties [23, 24]. Even the ancient Egyptians explored photo polymerization by using sunlight to crosslink oily linen to form an environmental barrier during the mummification process [25]. Nowadays, photo polymerization uses monomers and terminal functional polymers to develop functionalized and biocompatible scaffolds and hydrogels [26].

In the field of biomaterials, the photo polymerization process has been used to overcome the limitations of functional design, such as achieving defined shapes,

e.g., in bone implants and skin tissues [13, 27 - 29] and sol-gel transitions after application, *e.g*., in hydrogels developed *in situ* [30 - 32]. The photo polymerized biomaterials are effectively used as cell [33] and drug delivery systems [34], membrane barriers [35, 36], tissue-engineered scaffolds [37, 38], and as coating materials for medicines [26]. These biomedical applications of biomaterials require the development of biocompatible networks or hydrogels, which are related to the crosslinked polymers but differ in their physical state. The former are crosslinked polymers in an undissolved state, while the latter contains a lot of water and are in a swollen state. The high degree of swelling of hydrogels mimics the mechanical properties of biological tissue *in vivo* and facilitates the exchange of nutrients, waste products, and signaling molecules, making them ideal candidates for various biomedical applications [39]. In both cases, the three-dimensional (3D) and sequential control during polymer synthesis enabled by photo polymerization can produce highly structured materials with predetermined shapes and *in situ* polymerization capabilities [40].

With the increasing demand and applications of biomaterials, the old-fashioned monolithic photo polymerization technique cannot meet the desired standards of material production in various disciplines and for various applications. For example, the extracellular matrix (ECM) is a natural environment that supports and controls cellular functions. However, its time-varying structural design at the nanoscale and microscale is very complex [41, 42], and thus cannot be fabricated using conventional techniques. Similarly, many applications require high functional resolution of polymers through 3D objects. Among various material synthesis techniques, photolithography and stereo lithography are widely used for the fabrication of functional biomaterials at micro and nano scales. At the same time, multiphoton lithography (MPL) technology has been applied to photo polymerization to make these necessary tools widely available in the biomedical field [43]. The development of integrated circuits using photolithographic techniques can significantly improve the spatial resolution in the microelectronics industry [44]. The irradiated areas are photo polymerized into non-resolvable blocks, while the non-polymerized areas are eroded after the fabrication process is complete. Then, users create planar structures in the micrometer range and obtain 3D structures by building them layer by layer [45]. The lithographic technique requires high-resolution photo coverage for each shape. It is limited by diffraction and can only produce 3D structures. The photo polymerization technique can also be used for soft lithography [46, 47]. At this time, the main mold is made from the elastomer material, such as polydimethylsiloxane, with a predefined shape. The mold is filled with a precursor solution that photo polymerizes to restore the desired properties. This method has proven successful in the fabrication of pharmaceutical microbial materials [48], tissue engineering scaffolds [49], and microfluidic biosensing [50]. Recent advances in multiphoton technology have

CHAPTER 8

Particulate Leaching (Salt Leaching) Technique for Fabrication of Biomaterials

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Abstract: The most important characteristic of a scaffold used in tissue engineering is the possession of appropriate physical and mechanical properties to support or restore the biological function of damaged or degenerated tissue. Pore size, porosity, pore interconnectivity, and mechanical strength are all physical and mechanical properties that must be considered. Various fabrication techniques have been investigated to create a scaffold suitable for tissue engineering. One example is the particulate leaching (salt leaching) technique. The type of polymers and salts used, the particle size of the salt, and the fabrication technique all affect the desired physical and mechanical properties of salt leaching scaffolds. Over the past decade, there have been numerous studies on the fabrication of scaffolds for tissue engineering. This chapter reviews the different types of materials used, the basic salt leaching process, and its new modifications. It also discusses the advantages and disadvantages of the salt leaching technique and its future prospects.

Keywords: Interconnectivity, Mechanical strength, Polymers, Porosity, Salt leaching, Scaffold, Tissue engineering.

INTRODUCTION

Tissue engineering is a discipline of biomedical engineering that aims to facilitate cell ingrowth or replace damaged or diseased tissue with a combination of bioactive molecules, biomaterials, and cells or engineered cells [1]. To achieve these goals, scaffolds are commonly used in tissue engineering. Various biomaterials, from biopolymers to bioceramics to biodegradable metals, have been shown to be useful in the fabrication process [2].

The most important characteristics of a scaffold for tissue engineering are sufficient mechanical strength to support biological function by promoting cell

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adhesion, differentiation, and proliferation [3, 4]. Various techniques have been investigated to fabricate such scaffolds, including particle leaching (salt leaching), freeze-drying, solvent casting, self-assembly, phase separation, electrospinning, rapid prototyping, melt molding, gas foaming, and membrane lamination [5]. This chapter deals exclusively with the fabrication of a framework by particle leaching (salt leaching).

Particulate leaching (salt leaching/porogen leaching) is one of the most common, long-established conventional techniques for preparing porous biomaterials for tissue engineering. It involves dispersion of salts/porogens in a polymeric or monomeric solution, followed by gelation or fixation in the template and removal of salts/porogens to form an interconnecting porous architecture. The method has several advantages and disadvantages, which are also discussed in this chapter.

The main goal of preparing biomaterials for tissue engineering is to create a well-designed three-dimensional (3D) scaffold. The scaffold is an important tool to facilitate tissue formation both *in vitro* and *in vivo*. To regenerate tissue, tissue engineering uses biodegradable or non-biodegradable polymers, with or without the inclusion of molecules or biological cells. Many scaffolds for tissue engineering have been fabricated using the particle leaching technique (salt leaching). However, different tissues require different scaffold properties. For example, scaffolds for bone engineering may have different desirable properties than scaffolds for skin substitutes or retinal neural progenitor cells. Therefore, selecting the right polymers, salts, and salt leaching techniques (simple or modified) is critical, especially if the scaffold is designed to allow the target cells to function in the manner required for tissue regeneration. In this chapter, particle/salt leaching is presented for the preparation of biomaterials for tissue engineering applications. The materials and methods used and their new modifications are compared. Recent studies on scaffold materials fabricated using these techniques are summarized and discussed.

PARTICULATE LEACHING (SALT LEACHING) TECHNIQUE

The technique of particle leaching (salt leaching) involves the use of polymers or a combination of polymers and salt particles of a specific size to produce a suitable scaffold for tissue engineering. The desired physical and mechanical properties of the scaffold depend largely on the choice of the type of polymer and salt, the size of the salt particles, and the fabrication techniques. The types of polymers and salt typically used in the salt leaching technique, as well as the step-by-step approach to the basic salt leaching technique and its modifications, have been discussed in this section.

Polymers

Natural or synthetic biodegradable polymeric materials are widely used for the production of biomaterials because their properties offer greater advantages compared to other materials, such as metal or ceramics. Apart from the fact that biodegradable polymers are naturally absorbed by the human body, some of them are also suitable for tissue regeneration, which is basically helpful in injuries and reconstruction of damaged or aging tissues. Another advantage of polymers as biodegradable drug carriers is their low cost and ability to adapt to target organs or tissues. In laboratory processing, the particle leaching (or salt leaching) technique is often used in the development phase to produce biodegradable or non-biodegradable polymeric scaffolds with sufficient porosity for use in tissue engineering. The fabrication technique of this polymer can be easily extended to a larger quantity through industrial production [6].

Polymers are available with different mechanical and physical properties. Therefore, the basic properties of scaffolds, such as biocompatibility with the human body, sterilizability, and a suitable degradation profile, must be considered before fabrication. The processing of polymers into scaffolds for tissue engineering with specific properties for each application is highly dependent on the type of polymer chosen. The most commonly used biodegradable polymers for salt leaching techniques are aliphatic polyesters, such as poly(lactic acid) (PLA), polyglycolic acid (PGA), polycaprolactone (PCL) and their copolymers. However, there are also some other polymers, such as silk fibroin (SF), nylon and many others that are used to produce biomaterials for tissue engineering. Table **1** summarizes the properties of the polymers used in the production of biomaterials using the salt leaching technique.

Table 1. The properties of the polymer used in the preparation of biomaterial with the salt leaching technique.

Materials		Density (g/cm^3)	*E* (GPa)	σ (MPa)	ε (%)	References
Biodegradable Polymers	Non-biodegradable Polymers or Other Material					
Poly (glycolic acid)	-	1.53	>6.9	>68.9	15-20	[7]
Poly (L-lactic acid)	-	1.210–1.430	2.4-4.2	55.2-82.7	5-10	[8]
Poly (L-lactic-co-glycolic acid)	-	1.3	1.4-2.08	41.4-55.2	3-10	[9]
Polycaprolactone	-	1.14	0.21-0.34	20.7-34.5	300-700	[8, 10]
Chitosan	-	0.15–0.3	-	30	-	[11]
Starch	-	1.5	116.42–294.98	4.48–8.14	35.41–100.34	[12]
Poly(3-hydroxybutyrate-co-3-hydroxyvalerate)	-	1.17–1.2	0.7–3.5	20–60	6–8	[10]
polymethyl methacrylate	-	1.17-1.20	1.8–3.1	48-76	2-10	[10]
Cellulose nanofiber	-	0.96–1.02	138	10	-	[13]
Silk fibroin	-	1.40	9.860	513	23.4	[10, 14]

CHAPTER 9

Principles of Supra Molecular Self Assembly and Use of Fiber mesh Scaffolds in the Fabrication of Biomaterials

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Abstract: Tissue engineering techniques aim to create a natural tissue architecture using biomaterials that have all the histological and physiological properties of human cells to replace or regenerate damaged tissue or organs. Nanotechnology is on the rise and expanding to all fields of science, including engineering, medicine, diagnostics and therapeutics. Nanostructures (biomaterials) specifically designed to mimic the physiological signals of the cellular/extracellular environment may prove to be indispensable tools in regenerative medicine and tissue engineering. In this chapter, we have discussed biomaterial design from two different perspectives. Supramolecular self-assembly is the bottom-up approach to biomaterials design that takes advantage of all the forces and interactions present in biomolecules and are responsible for their functional organization. This approach has the potential for one of the greatest breakthroughs in tissue engineering technology because it mimics the natural, complex process of coiling and folding biomolecules. In contrast, a fiber mesh scaffold is a top-down approach in which cells are seeded. The scaffolds form the cellular scaffold while the cells produce and release the desired chemical messengers to support the regeneration process. Therefore, both techniques, if efficiently explored, may lead to the development of ideal biomaterials produced by self-assembly or by the fabrication of optimal scaffolds with long shelf life and minimal adverse reactions.

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INTRODUCTION TO SELF ASSEMBLY

In the recent past, nanotechnology has emerged as a potential area for the development of advanced, innovative techniques in various fields, including tissue engineering and regenerative medicine. Recent studies in nanomedicine have focused on its application in the production of biomaterials. To this end, nanotech-based biomaterials are being developed and intensively studied for their safety, efficacy, and long- and short-term effects on the human body. Nanofibers and nanotubes have been described in many studies as vehicles for drug delivery. Nanostructures specifically designed to mimic the physiological signals of the natural cellular and extracellular environment may prove to be indispensable tools in regenerative medicine.

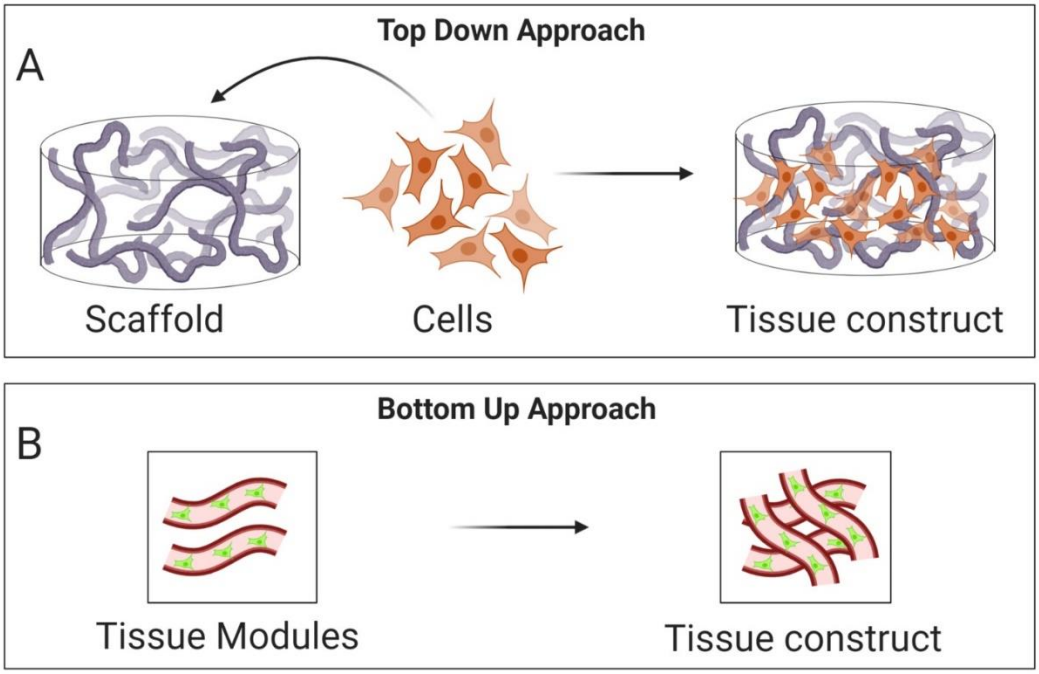

Fig. (1). Approaches for tissue engineering in regenerative medicine **A.** Traditional scaffold-based top-down approach where cells are seeded into fully formed porous scaffolds **B.** Recent bottom-up approach which involves cellular seeding in self-assembling tissue modules, capable of forming a complex three-dimensional network.

Traditionally, regenerative tissue engineering has used the top-down approach, in which the desired cells are incorporated into a scaffold in which they proliferate and differentiate into the desired tissue/organ while supported by the scaffold material (Fig. **1**). This method has some weaknesses, such as the difficulty in constructing complex vital organs with intricate architecture, such as liver and kidneys. To overcome these drawbacks, tissue engineering scientists have explored the relevance and feasibility of other approaches. One of the mechanisms used to produce such biomaterials is the bottom-up approach of self-assembly (Fig. **1B**). In this approach, cells are incorporated into modules that can spontaneously fold and form complex scaffolds. The tendency toward self-assembly is driven by the need for molecules/modules to achieve thermodynamic stability [1, 2]. The design of complex nanostructures by supramolecular self-assembly of simple biological/synthetic building blocks is one of the attractive mechanisms for the fabrication of biomaterials for various applications in biomedical sciences [3 - 5].

Self-assembly is a natural phenomenon that leads to the formation of complex macromolecules. Understanding the principles of self-assembly of natural molecules has greatly helped us in the synthesis of biomaterials using the same bottom-up approach. Molecular and supramolecular self-assembly is a spontaneous process driven by various interactions of chemical entities (charge, size, orientation, bonds) that are in close proximity to each other. The forces underlying the phenomena of self-assembly are weak (non-covalent) forces that come into play when the distance between molecules is reduced. These forces include hydrophobic interactions, weak Van der Waals forces, electrostatic interactions between dipoles, ion-dipole interactions, and hydrogen bonding (Fig. **2**). Although these forces are weak individual forces, they are collectively responsible for the formation of the unique, intricate three-dimensional biological structures with varying complexity and multiple levels of 2-organisation (Fig. **3**) [6 - 8].

Molecular Forces Responsible for Self-Assembly

Electrostatic Forces

Most macromolecules carry functional groups with charged moieties (polar groups in side chains of amino acids). The interaction between such charged groups of a macromolecule generates electrostatic attraction/repulsion, which leads to the folding of the macromolecule into supramolecular structures (ion-ion interaction, ion-dipole interaction, and dipole-dipole interaction). The self-assembly triggered by such interactions is found in polypeptides and lipids [9, 10].

CHAPTER 10

Solvent Casting and Melt Molding Techniques for Fabrication of Biomaterials

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Abstract: Biomaterials are receiving tremendous attention, especially in the biomedical field, due to their impressive structural, physiological, and biological properties, such as nontoxicity, biocompatibility, and biodegradability. Numerous biomaterials have been used to fabricate scaffolds for applications in tissue engineering and regenerative medicine, where they are used as wound dressings, grafts, organs, and substitutes. To date, a number of techniques have been developed for the fabrication of scaffolds from biomaterials. This chapter focuses on the fabrication of scaffolds by solvent casting and melt-casting techniques. It examines the solvent casting and melt-casting techniques in terms of their application in the fabrication of biological scaffolds with tailored micro- and nanostructures for their use in tissue engineering. The merits and limitations of these techniques in fabricating biological scaffolds for desired biomedical applications are also discussed. Finally, various challenges faced by solvent and melt casting techniques are described, and solutions are proposed for future research to develop biomaterials for advanced biomedical applications.

Keywords: Biocompatibility, Biomaterials, Fabrication techniques, Scaffolds, Structural features.

INTRODUCTION

Tissue engineering provides an innovative platform focused on developing scaffolds with biological and mechanical properties to overcome serious medical problems, such as tissue loss or damage and organ failure. It is highly dependent

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on the biocompatibility, biodegradability, and bioresorbability of scaffolds, which limits access to available materials and viable techniques [1, 2]. Microstructural properties, such as porosity and pore connectivity, as well as the required mechanical strength of the scaffold, pose a major challenge for biomaterials to meet the desired properties of the target tissue or organ [3, 4]. In addition, the cost, reproducibility, and simplicity of the techniques without compromising the biocompatibility of the material are other obstacles to the fabrication method [5]. The conventional fabrication technologies, such as solvent casting and melt casting techniques, have numerous limitations; nevertheless, their simple protocols have promoted their use. These techniques are inexpensive, straightforward, and easily scalable compared to their counterparts [6 - 8]. In recent years, solvent casting technology has evolved into a high-precision technique used in the fabrication of optical and medical films, opening up potential applications in bioelectronics [9]. Melt casting techniques such as additive extrusion or injection molding techniques are widely used in the development of solid implants such as plates, rods, and screws, and are also used in dentistry. These techniques are often combined with other technologies to obtain a framework with the desired properties.

Biomaterials

Biomaterials are non-toxic substances composed of either natural or synthetic components, that do not induce immunogenic and inflammatory reactions, and are frequently used in medical applications [10, 11]. A biomaterial interacts with the biological system and supplements or replaces a natural function. Generally, biomaterials are classified into two broad categories, namely natural and synthetic biomaterials. Natural biomaterials are mostly composed of natural polymers, including proteins such as collagen [12], fibrin [13], and silk [14], and polysaccharides such as cellulose [15 - 17], chitosan [18], alginate [19, 20], and hyaluronan [21, 22]. Synthetic biomaterials include three categories with polymers such as peptides and ceramic-based biomaterials [23, 24]. Examples of commonly used synthetic polymers in the development of biomaterials include poly (lactic-co-glycolic acid) (PLGA) [25], poly (ε-caprolactone) (PCL) [26], poly (ethylene glycol) (PEG) [27], poly (vinyl alcohol) (PVA) [28, 29], and others. Peptide-based materials include amino acids and peptides [29], ceramic-based biomaterials include hydroxyapatite (HAp) [30], and ceramic-based biomaterials include hydroxyapatite (HAp) [31] and bioactive glass [32]. Biomaterials are used together with cells and bioactive substances to synthesize new tissues using tissue engineering techniques [33]. Recently, biological scaffolds have become an important medical substitute for synthetic implants and tissue grafts [34]. A well-designed three-dimensional (3D) scaffold should have certain important properties to allow the cells to regenerate the tissues and organs

in the desired shape and size. They should be biocompatible with the host tissue and have the required porosity and mechanical strength. Their surface should have adhesive properties that allow cell attachment, growth, migration and differentiation. Controlled biodegradability and safe implantation, as well as suitable mechanical properties, are other structural and chemical requirements for the successful development of biological scaffolds [18, 22, 35, 36, 37].

FABRICATION TECHNIQUES

Living tissue comprises different cell types and extracellular matrix organized into a complex architecture performing cellular and mechanical functions. Designing of scaffolds requires a strategical analysis of the microcellular structure of native tissue and its functioning at the cellular level enabling the proliferation and migration of cells. The engineering of scaffolds requires techniques to deliver scaffolds with the best regenerative performance with respect to the native tissue requirements. There are several methods for the fabrication of scaffolds, such as solvent casting, melt molding, phase separation, freeze-drying, gas foaming, phase separation, and membrane lamination, to name a few. In this section, the main techniques for solvent casting and melt molding are discussed in detail.

Solvent Casting

Solvent casting is a simple and inexpensive technique that requires a mold and a polymer dissolved in an organic solution to produce scaffolds. The polymer is dissolved in an organic solvent, and the scaffold is obtained by simply evaporating the solvent. The desired scaffold is obtained either by immersing the mold in the polymeric solvent or by adding the polymeric solution to the mold. In the first method, the mold is immersed in the solution and then dried to form a mold from the polymer membrane. In the second method, the solution is added to the mold, and the solution is allowed sufficient time to dry so that a layer of the polymer membrane forms on the mold [38]. Fig. (**1**) shows a generalized diagram depicting the technique of solvent casting with particle leaching to develop scaffolds.

Solvent casting is a widely used technique because it allows uniform distribution of polymer throughout the framework and provides changeable reaction conditions [39]. The role of the solvent is a critical factor in the preparation of the polymer surface. The heterogeneity of the surface, the swelling behavior, and the deformation rates of the scaffold affect its application [40]. The main advantages of the solvent casting technique are its simplicity, convenience, and easy fabrication of scaffolds. The degeneration of the scaffold does not affect the regeneration rate of the native tissue. However, the long drying time of the molds, the toxicity of the organic solvents used in the fabrication of the scaffolds, and the

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