Chapter 2
Scaffold Fabrication Protocols

Abstract Development of scaffolds in tissue engineering applications is growing in a fast pace. Scaffolds play a pivotal role in scaffold-based tissue engineering. The scaffolds must possess some important characteristics. Scaffolds should be biocompatible, should have appropriate porosity and porous microstructure and proper surface chemistry to allow cell attachment, proliferation and differentiation. Scaffolds should possess adequate mechanical properties and controlled biodegradability. There are many techniques available to fabricate scaffolds including freeze drying, electrospinning and rapid prototyping. Some of these techniques have gained much attention due to their versatility. This chapter points up the protocols for the fabrication and characterization of appropriate scaffolds for tissue engineering using biopolymers and composite biomaterials.

Keywords Fabrication · Freeze-drying · Electrospinning · Rapid prototyping

2.1 Techniques of Producing Scaffolds

There are many techniques used in making scaffolds and divided into two categories, non-designed manufacturing techniques and designed manufacturing techniques. Non-designed manufacturing techniques include freeze drying or emulsion freezing (Whang et al. 1995), solvent casting or particulate leaching, phase separation (Zhao et al. 2002; Liu and Ma 2004; Ma 2004), gas foaming or high pressure processing, melt moulding, electrospinning and combination of these techniques. Designed manufacturing technique includes rapid prototyping of solid free-form technologies.

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2.1.1 Electrospinning

To process solutions or melts of polymers into continuous fibers into continuous fibers with diameters ranging from nanometers to submicrometers, electrospinning is a highly versatile method. In this process, a polymer solution is contained in a syringe with a metal capillary connected to a high voltage power supply as an electrode. Subjected to an electric field, the polymer jet travels in the electric field which becomes thin fibers and deposits onto a conductive collector. The ultrafine fibers in the electrospun mats have high surface-to-volume ratios and porosity and mimic the natural extracellular matrix of body tissues. In order to regenerate various tissues including skin, blood vessel, cartilage, bone, muscle, ligament and nerve, electrospun fibers have been employed.

2.1.2 Solvent Casting and Particulate Leaching

To overcome the drawbacks associated with the fiber bonding technique, a solvent-casting and particulate-leaching technique was developed. Porous constructs of synthetic biodegradable polymers could be prepared with specific porosity, surface to volume ratio, pore size and crystallinity for different applications by appropriate thermal treatment. Though the technique was valid for PLLA and PLGA scaffolds, this could be applied to any other polymer that was soluble in a solvent such as chloroform or methylene chloride.

2.1.3 Polymer Phase Separation

Thermally induced phase separation (TIPS) of polymer solution was reported to be used in the field of drug delivery and to fabricate microspheres in order to incorporate biological and pharmaceutical agents (Ma 2004). In order to fabricate tissue engineering scaffolds, this process has become much popular. By altering the types of polymer and solvent, polymer concentration and phase separation temperature, different types of porous scaffolds with micro and macro-structured foams can be produced. In order to control pore morphology on a micrometer to nanometer level, TIPS process can be utilized (Ma 2004).

Depending on the thermodynamics and kinetic behaviour of the polymer solution under certain conditions, TIPS can be a complicated process. It was defined that if a system where the solvent crystallization temperature (freezing point) is higher than the liquid-liquid phase separation temperature, the system can separate by lowering the temperature, the process is called solid-liquid phase separation. After the removal of the solvent, the remaining pores have morphologies similar to

solvent crystallite geometries. On the other hand, when the solvent crystallization temperature is much lower than the phase separation temperature, if the temperature of polymer solution is decreased, a liquid-liquid phase separation takes place.

2.1.4 Rapid Prototyping

Rapid prototyping of solid free-form is a technique designed manufacturing technique that fabricates three-dimensional scaffolds with fully interconnected porous network (Lam et al. 2002). It includes three-dimensional printing, laser sintering and stereolithography. These techniques require a computer model of the desired scaffold architecture from computer-assisted design (CAD) or computed tomography (CT). The advantages of these techniques are their capability to fabricate scaffolds with complex architectures in micron scale μm (Lanza et al. 2007). There are some interesting and unique challenges in scaffold design (Lanza et al. 2007):

- Almost all bone defects are irregularly shaped; any proposed scaffold processing technique must be sufficiently versatile to allow the formation of porous polymer-based materials with irregular three-dimensional shape.
- The scaffold must have high strength to replace the structural function of bone temporarily until it is regenerated.

For many orthopedic applications, poly(α-hydroxyesters) were used in a solid form, but the compressive strength of foam scaffolds constructed of these materials rapidly decreased with increasing porosity. In order to formulate polymer/ceramic composites, an alternative method was proposed using a novel phase transition technique. Hydroxyapatite powder was added to a PLGA/dioxane solution according to this process. The mixture was then frozen for several hours to induce phase separation and then freeze dried to sublimate the solvent. The composite foams thus produced, exhibited interconnected irregular pore morphology with a polymer/hydroxyapatite skeleton. The compressive strength of these foams was significantly higher than that of foams made from pure PLGA. The porosity, pore size, and pore structure could be controlled by changing the polymer concentration, hydroxyapatite amount, solvent type and phase separation temperature. Composite foams with porosity of up to 95 % and pore size in the range of 30–100 μm were fabricated with this method.

2.1.5 Melt Molding

Another alternative method of constructing three-dimensional scaffolds is melt molding. By using this technique, PLGA scaffolds were produced by leaching PLGA/gelatin microsphere composites. According to this method, a fine PLGA

powder was mixed with previously sieved gelatin microspheres and poured into a Teflon mold, which was then heated above the glass transition temperature of the polymer. The PLGA/gelatin microsphere composite was then removed from the mold and placed in distilled-deionized water. The water soluble gelatin was leached out leaving a porous PLGA scaffold with the geometry identical to the shape of the mold. It was possible to construct PLGA scaffolds of any shape simply by changing the mold geometry by using this method. The porosity could be controlled by varying the amount of gelatin used to construct the composite material and the pore size of the scaffold could also be altered independently of the porosity by using different diameters of microspheres. Another advantage of this method was that it does not utilize organic solvents and is carried out at relatively low temperatures. For this reason, it had the potential for the incorporation and controlled delivery of bioactive molecules. This scaffold manufacturing technique could also be applied to other polymers such as PLLA and PGA. Many of the scaffold preparation design criteria were satisfied by this technique and offer an extremely versatile means of scaffold preparation. Alternative leachable components such as salt or other polymer microspheres could also be used other than gelatin microspheres.

2.1.6 Gas Foaming

In order to eliminate the need for organic solvent in the pore-making process, a new technique involving gas as a porogen was introduced. The process started with the formation of solid discs of PGA, PLLA or PLGA by using compression molding with a heated mold. The discs were placed in a chamber and exposed to high pressure CO_2 (5.5 MPa) for 3 days. At this time, pressure was rapidly decreased to atmospheric pressure. Up to 90 % porosities and pore sizes of up to 100 μm could be obtained using this technique. But the disadvantage was pores are largely unconnected, especially on the surface of the scaffold. Although the fabrication method required no leaching step and used no harsh chemical solvents, but the high temperature which was involved in the disc formation, prohibited the incorporation of cells or bioactive molecules. Also the unconnected pore structure made cell seeding and migration within the scaffold difficult. In order to produce an open pore morphology using this technique, both gas foaming and particulate leaching technique were developed. According to this, salt particles and PLGA pellets were mixed together and compressed to scaffold solid disks which were saturated with high pressure gas and the pressure was subsequently reduced. The salt particles were removed then by leaching. This combination guided to a porous polymer matrix with an open, interconnected morphology without the use of any organic solvents. This technique might have widespread use in cell transplantation applications of many types of cells, including hepatocytes, chondrocytes, and osteoblasts.

2.2 Electrospinning Protocol

The technique of using electrostatic forces to produce synthetic fiber has emerged since 100 years ago (Sill and von Recum 2008). In the early stage, electrospinning has not emerged as a feasible technique to produce small diameter of polymer fiber because of some technical difficulties. In the year 1934, Formhals patented a process and apparatus to spin fiber by using electrical charges (Formhals 1934). The apparatus use a moveable threat-collecting device to collect fiber. Aligned fibers can be collected by this apparatus. Formhals use acetone/alcohol solution as solvent to produce cellulose acetate fibers was a success by using this apparatus. However, it forms loose web structure due to the short distance between spinning and the collector. The solvent was not fully evaporated. Besides, incomplete evaporation of the solvent will also lead to the fiber stick on the collector making removal problematic.

In the second patent, Formhals detailed the apparatus by setting a bigger distance between the spinning and the collector in order to solve the problem faced which is incomplete evaporation of the solvent (Anton 1939). Formhals described the use of multiple nozzles. In 1940, Formhals patented a new process. In the process, composite fiber is formed by directly electrospun polymer solution onto a moving base thread (Formhals 1940). Taylor published his work in 1969 about Taylor cone (Taylor 1969). He found that when surface tension is balanced with electrostatic forces, the pendant droplet will form into a cone which is named by his name, Taylor cone. The fiber jet is emitted from the apex of the Taylor cone and this generates a smaller diameter of fiber produced which is smaller than the diameter of capillary tip. Taylor also determined the angle that is needed to balance the surface tension with electrostatic forces which is 49.3° with respect to the axis of the cone at cone apex or 98.6° of cone angle.

Besides, there are some parameters that can affect the structural properties of the electrospun fibers produced. The investigate of varying these parameters such as solution and processing parameters for example solution viscosity, applied voltage and flow rate is done by Baumgarten in 1971. The solution used by Baumgarten is polyacrylonitrile/dimethylformamide (PAN/DMF). In his investigation, he found out that higher viscosities will give larger fiber diameter. For electrical field, while continuously increasing the applied voltage, the fiber diameter will decrease initially until a minimum and then increase.

Approximately a decade after Baumgarten's work, there are other works began on electrospinning polymer melts. Larrondo and Mandley electrospun fibers from polyethylene and polypropylene melts and it was a success (Baumgarten 1971; Larrondo and St John Manley 1981). The difference between electrospun fiber produced from solution and melt is electrospun fiber from a melt has larger diameters. Larrondo and Mandley had discovered that melt temperature can inversely influence the fiber diameter.

Investigation of potential applications of electrospun fiber began after these findings. One of the applications is in tissue engineering field. Annis and Bornat

published their work on the application of electrospun polyurethane mats as vascular prosthesis in 1978 (Larrondo and St John Manley 1981). In 1985, long-term in vivo performance of electrospun arterial prosthesis was examined by Fisher and Annis (Annis et al. 1978; Fisher et al. 1984).

2.2.1 Electrospinning Process and Principle

There are three major components in electrospinning, high voltage power supply, spinneret/needle and collector which are normally metal screen and are grounded. DC voltage or AC voltage can be used. Figure 2.1 shows the schematic illustration of electrospinning. Electrospinning is a versatile and very simple process. It uses electrostatic force to produce fibers by electrospin with polymer solution or polymer melt. The diameter of the polymer fibers produced ranging from a few nanometers to micrometers.

Syringe pump is used to force the polymer solution through needle at a controlled rate (mL/h). A high voltage supply is connected to the needle to inject charge into polymer solution. Electrostatic force which is the repulsion of similar charges will be produced. When electrostatic force is balanced with surface tension, Taylor cone will be formed. By increasing the electric field, fiber jet will be ejected from the apex of Taylor cone when electrostatic force is larger than surface tension.

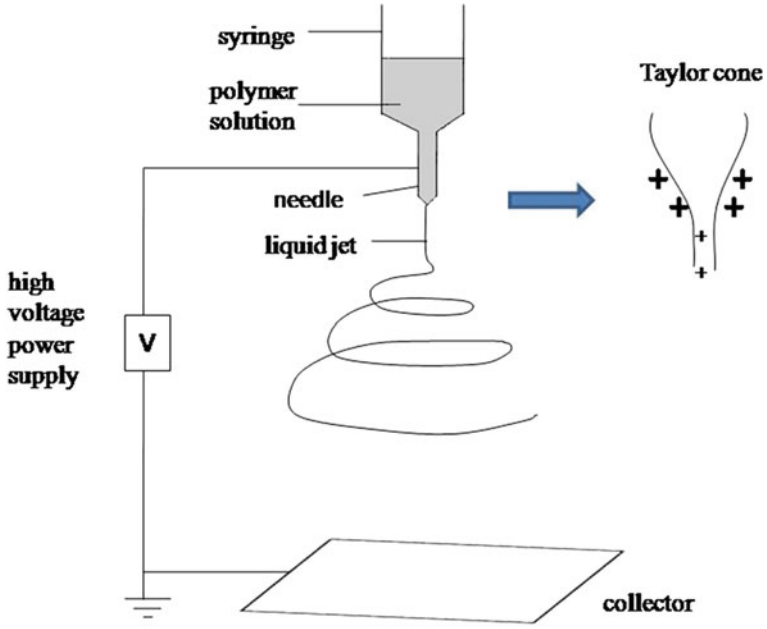

Fig. 2.1 Schematic illustration of electrospinning

During the ejection and elongation process, solvent is evaporated. The elongation and evaporation of the solvent reduces the diameter of the fiber from micrometer to nanometer. The electrified jet will undergo stretching and whipping process, long and thin thread will be formed. Lastly, the polymer fiber produced is attracted by grounded collector which is a metal screen (Doshi and Reneker 1995; Sill and von Recum 2008; Li and Xia 2004; Yu et al. 2009; Reneker and Chun 1996).

The polymer fibers produced by electrospinning process is called electrospun membrane or nanofiber. It has high porosity and similar to natural extracellular matrix (ECM). These fibers can enhance cell attachment, mass transfer and drug loading properties (Sill and von Recum 2008).

2.2.2 Nozzle Configuration

Nozzle Configuration can influence the electrospun fiber produced. There are a few nozzle configurations such as single, single with emulsion, side-by-side, and coaxial nozzles. Choosing of suitable nozzle configurations depends on the application and the product that want to be developed (Sill and von Recum 2008).

Single nozzle configuration technique is the most simple and common technique where charged polymer solution flows through single capillary. For spinning single polymer solution and polymers that is soluble in a common solvent, this configuration technique is suitable (Stitzel et al. 2006; Tan et al. 2005). For an example, poly(ethylene oxide) (PEO) was electrospun by this technique (Doshi and Reneker 1995).

Side-by-side nozzle configuration technique is used for the while desired polymer is not soluble in common solvent. In this configuration, two capillaries that located side-by-side contain two different polymer solutions. The ability of side-by-side configuration to form a single fiber jet is influenced by solution conductivity. Both polymer solutions have to have similar conductivities in order to form a single Taylor cone. Once the single Taylor cone is produced, by increasing the applied voltage, fiber jet that containing both polymers will be developed but the amount of every polymer will vary along the fiber. For an example, using of poly(vinyl chloride)/segmented polyurethane and poly(vinyl chlorine)/poly(vinylidiene fluoride) to electrospin biocomponent systems by this configuration (Gupta and Wilkes 2003).

Another potential configuration technique is coaxial configuration. In this configuration, two different polymers flow through two capillaries which are coaxial. A smaller capillary is inside the larger capillary. While applying an external voltage, Taylor cone is formed at the tip of the capillary. It will lead to the formation of the fiber where one polymer fiber is encapsulated by the other. This is known as core-shell morphology. The core polymer solution can either be or not be electrospinnable but the shell polymer solution has to be electrospinnable. It has the advantage that this technique is able to protect easily denatured biological agents effectively. It also can wrap all substances in the core regardless the interaction between the core

and the shell. It is a good technique to electrospin fibers containing drugs, genes, protein and growth factors (Huang et al. 2006; Li and Xia 2004; Loscertales et al. 2002). There are some researches on coaxial configuration technique in drug delivery application that successfully mitigated the initial burst release. The drugs are released in a controlled way and have longer sustained release. Zhang et al. encapsulated model protein, fluorescein isothiocyanate conjugated bovine serum albumin with poly(ethylene glycol) (PEG) in poly(e-caprolactone) (PCL) fibers (Huang et al. 2006). Huang et al. used PCL as the shell and medically pure drugs, Resveratrol and Gentamycin Sulfate as cores (Zhang et al. 2006).

2.2.3 Solution Versus Melt Electrospinning

Two forms of polymers can be used for electrospinning, solution and melt. A polymer can dissolve in suitable solvent or directly electrospinning from its melt. Both forms will produce different size of fibers. For solution form of polymer, the fiber produced has a greater range of size, microns to nanometer. However, for melt form of polymer, the fiber sizes produced are only in micron size (Larrondo and St. John Manley 1981).

Furthermore, there are some advantages and disadvantages of both solution and melt form of polymer. Melt electrospinning does not need any solvent but it has to be kept at high temperatures to be electrospun. However, solution electrospinning can be done at room temperature. For polymer in the form of solution where the solvent is very volatile, it will reduce the mass flow velocity (Reneker and Chun 1996). High temperature used for melt electrospinning will preclude the use of fiber in some applications such as tissue engineering field and also drug delivery system. Dalton et al. has discovered that the optimum melt temperature ranged between 60 and 90° for melt electrospinning of copolymers of poly(ethylene glycol) PEG and PCL (Dalton et al. 2006). Melt electrospinning will eliminate the problem of insufficient evaporation of the solvent during the ejection of fiber jet. However, the temperature needs to be able to be cooled before reaching the collector.

2.3 Parameters in Electrospinning

In recent years, the production of electrospun fibers has gained importance due to its versatility. However, there are some parameters that influence the structure and morphology of the electrospun fibers produced. The parameters are divided into two categories, processing parameters and solution parameters.

2.3.1 Processing Parameters

2.3.1.1 Applied Voltage

Applied voltage is the high voltage that applied to the needle. Increasing of applied voltage will lead to the formation of Taylor cone. While increasing the voltage again, it will result in fiber jet being ejected from the apex of the Taylor cone.

V. Sencadas examined the effect of applied voltage on electrospinning of poly (vinylidene fluoride–trifluoroethylene) (PVDF–TrFE) at 15/85 (15 % PVDF–-TrFE + 85 % solvent blend). The tip to collector distance is 20 cm, needle inner diameter is 0.5 mm, flow rate 0.5 ml/h and applied voltages of 15 and 35 kV. Travelling distance, needle inner diameter and flow rate are kept constant. In this experiment, there is small variations occurred. However, there is a trend that by increasing the applied voltage, fiber diameter is decreasing. It is due to variations of mass flow and jet dynamics (Sencadas et al. 2012).

2.3.1.2 Flow Rate

To investigate the influences of solution flow rate on fiber size and distribution, applied voltage and distance between capillary tip and collector need to be kept constant. Flow rate of solution brings impact on fiber size. It can also affect fiber porosity as well as fiber shape. Megelski et al. (2002) investigated polystyrene/tetrahydrofuran (THF) solution on this parameter. The result showed that increasing flow rate will increase fiber diameter and pore size. However, at high flow rate, bead defects will form due to insufficient evaporation of solvent. The fiber is not completely dry before reaching collector. The increase of flow rate increases the volume from the needle tip. It will lead to increase of evaporation time of the solvent and larger polymer crystallization time. Hence, a larger diameter of fiber and broader size distribution will be produced.

2.3.1.3 Capillary Tip to Collector Distance

During fiber jet ejection, evaporation of the solvent occurs. Fiber need to be completely dry before reaching the collector to avoid forming of bead defects where beads will form on fibers. Hence, the distance between capillary tip and grounded collector plays an important role to achieve a good fiber structure. A shorter fiber travelling distance will decrease the solvent evaporation time, results in insufficient evaporation. Fiber diameter decreases with increasing distance between capillary tip and collector. Megelski et al. showed the formation of beaded electrospun polystyrene fibers due to shortening the travelling distance which attributed to inadequate drying of polymer fiber prior reaching the collector (Sill and von Recum 2008).

2.3.2 Solution Parameters

2.3.2.1 Polymer Concentration

Surface tension and viscosity of solution depends on polymer concentration. Polymer concentration will affect the spinnability of the solution. The solution needs to have high polymer concentration for chain entanglements to occur but not too concentrated. If the solution is too concentrated, the fibers could not be formed because the viscosity of the solution is too high. However, if the solution is too dilute, the polymer fibers will be broken up into droplets before reaching the collector. It is because of the effects of surface tension. Moreover, within the optimal range of polymer concentration, increasing of polymer concentration will lead to increasing of fiber diameter (Sill and von Recum 2008).

2.3.2.2 Solvent Volatility

Selection of solvent is a very important task. A volatile solvent must be used in order for sufficient solvent evaporation to occur. Decreasing solvent volatility will increase the pore size with decreased pore depth. The pore density will be decreased. Megelski et al. (2002) investigated the structural polystyrene fibers properties by varying the solvent. Solvents used are dimethylformamide (DMF) and tetrahydrofuran (THF). THF is more volatile than DMF. Polymer solution with THF produces high density pores of fibers. The surface area increased. Polymer solution with DMF produced smooth fibers with almost complete loss of microtexture.

2.3.2.3 Solution Conductivity

Solution with higher conductivity has larger charge carrying capacity. The fiber jet of polymer solution which has higher conductivity will subject to greater tensile force. Zhang et al. (2005) has examined the effect of adding ions to PVA/water solution to increase the solution conductivity. They had added sodium chloride (NaCl) with increasing concentration to the PVA/water solution. In the result, the mean fiber diameter decreases. Hence, by increasing the concentration of NaCl ion increased the net charge density. It will then increase the electrical force of the jet. The fiber diameter will decrease (Table 2.1).

Table 2.1 Effects of electrospinning parameter on fiber morphology (Sill and von Recum 2008)

Parameter	Effect on fiber morphology
Applied voltage (increase)	Fiber diameter decreases initially then increases (not monotonic)
Flow rate (increase)	Fiber diameter increase (beaded morphologies occur if the flow rate is too high)
Distance between capillary tip and collector (increase)	Fiber diameter decreases (beaded morphologies occur if the distance between the capillary and collector is too short)
Polymer concentration (viscosity) (increase)	Fiber diameter increase (within optimal range)
Solution conductivity (increase)	Fiber diameter decreases (broad diameter distribution)
Solvent volatility (increase)	Fibers exhibit microtexture (pores on their surface, which increase surface area)

2.4 In Vitro Degradation of Scaffolds

Study of the hydrolytic degradation mechanism and rate is crucial factors for the application in biomedical and pharmaceutical applications. The degradation mechanism and rate of biodegradable polymeric scaffolds can be affected by numerous factors. The most common reasons for using absorbable polymer scaffolds are to accomplish time-varying mechanical properties and ensure complete dissolution of the implant, eliminating long-term biocompatibility concerns or avoiding secondary surgical operations. In order to release admixed materials such as antibiotics or growth factors, scaffold degradation may also be desired.

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