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Revisão

FEATURES AND STRATEGIES FOR SCAFFOLD DESIGN AND PRODUCTION FOR TISSUE ENGINEERING

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Failure or loss of human tissues and organs due to illness or injury requires the partial or even total transplantation. Although transplantation is a successful intervention, donor availability and immune rejections represent still the main drawbacks. In addition, the fast and proper recovery of the patient is nowadays more than necessary to prevent infection, chronic inflammation, and other complications during the tissue/organ healing process. There is still a tremendous interest of alternatives to transplantation, such as scaffold-based tissue engineering, that may contribute to practical outcomes for the worldwide health concern related to severe tissue injuries. Herein, we explore the features, benefits and scaffold designs applied for biotechnological sciences, particularly for tissue engineering. The great potential to transform biocompatible polymers in three-dimensional matrix, assimilating the extracellular matrix (ECM), makes them attractive for cells adhesion and proliferation. On the basic of relevant results recently reported in the literature, along with the pioneering works, we discuss specific issues and challenges such as matrix-cell interactions, strategies to design scaffolds with homogeneous nano/microscales using different techniques, e.g., hydrogels, electrospinning, and rotary jet spinning, as well as the combination of some of these techniques.

Keywords: tissue engineering; scaffolds; biomaterials; polymers; manufacturing techniques.

INTRODUCTION

WHO Global Observatory on Donation and Transplantation (GODT) provides data that evidence a critical problem about organs donates worldwide; even if the number of solid organ transplants performed achieves over 130,000, it supports only less than ten percent of the global require.[1] According to the Brazilian Association of Organ Transplants (ABTO), thousands of patients suffer, per year, from failure or loss of tissues or organs due to disease or accidents. Although the latest survey by the Brazilian Government reveals that the number of organ transplants broke the record, about 27,000 in 2017, there were still more than 32,700 patients waiting for transplantation.[2] Despite of being, in general, a successful intervention, the major obstacles of transplantation are the high occurrence of immunological rejections and the limited number of donors.[3]

Tissue engineering appears as a revolutionary option for tissue repair and artificial organs production.[3] The term was first defined, in 1987, by the *United States National Science Foundation*, which addressed future perspectives and relative ethical questions. This technology aims to "apply the principles and methods of engineering and life sciences to the fundamental understanding of the structure-function relationship in normal and pathological tissues of mammals and the development of biological substitutes for the repair or regeneration of tissue or organ function".[4,5]

Organs and tissues can be constructed from the growth of *in vitro* cell culture on a scaffold, acting as a three-dimensional support that mimics the extracellular matrix of native *in vivo* tissues.[4,6] Three-dimensional cell culture supports have been proposed, and built by different manufacturing techniques, to stimulate cell adhesion, differentiation, migration and proliferation.[7] Among the most usual materials used for scaffolds, biomaterials have noteworthy combined advantages,[3,8–10] such as biocompatibility, biodegradability and eventual bioresorbility, for a minimal immunological reaction.[8,11]

Several challenges must be overcome for scaffold manufacturing to create a 3D cell culture environment for tissue engineering application. The main concept of the present review is to highlight the recent advances in the field of tissue engineering and how new biomaterials and scaffold building techniques may improve the three-dimensional environments for sustainable cells growth.

BIOMATERIALS FOR SCAFFOLD FABRICATION

According to Owen and Shoichet,[12] the scaffolds are directly responsible for cellular behavior. This fact served as motivation for the cultivation of cells in three dimensions in detriment of the 2D culture. The three-dimensional culture simulates the physical and biochemical properties of the natural microenvironment of cells, tissues and organs, more faithfully than two-dimensional cell culture.[13]

For the scaffold design, some requirements must be fulfilled such as water permeability,[14,15] porosity,[14,15] protein affinity,[16,17] biocompatibility,[18–20] biodegradability,[18,21,22] availability of reactive functional groups for direct reactions with living tissue and for chemical modifications,[16,23–25] and ease of preparation.[26–28] All these parameters have been widely defined and their influence on cell behavior intensively investigated.[4,5,11,13,29] The biodegradation of the material may provoke an immediate cellular response, such as an inflammatory process from the release of acidic substances or residual catalysts. The porosity of the scaffold should reproduce the natural environment of the cells, presenting micro and nanostructures, which allow the cells phenotype modulation and activity.[30–32] Besides, the porosity is critical to promote an appropriate mass transfer through the scaffold, in order to allow gas exchange as oxygen supply and medium culture supply for cultivated tissue.[32,33] Obviously, the scaffold porosity should be optimized for the target tissue and associated cell types. The cells adhesion and migration, for their

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proliferation through the 3D matrix depend not only on the pore size[15,34] and interconnection,[15,34] but also their morphology,[35,36] surface chemistry[37,38] and mechanical properties.[39,40] It is worth mention also the bioresorbility, which evokes the *in vivo* degradation of the biomaterial by metabolic pathways followed its reabsorption, with the subsequent elimination of its by-products from the organism.[18,30,41]

The cells adhesion at the scaffolds surface occurs mainly through absorbed proteins mediation. Such interactions depend tightly on the scaffold surface hydrophilic/hydrophobic balance, that may affect both an eventual prior surface functionalization by cell-adhesive proteins and the absorption of such proteins when the scaffold is immersed in serum or body fluid. For instance, hydrophobic surfaces tend to keep the proteins in an inactive conformation.[6] The extension of cells infiltration and proliferation through the 3D-matrix is clearly dependent on the micro-architecture of the porous structure, i.e. pore size and distribution, surface roughness, degree of heterogeneity and inter-connectivity of the pores within the scaffolds.[29,30] To favor cell attachment, scaffolds must have a large, accessible surface area and high internal surface area to volume ratios, capable of allowing sufficient cell growth to replace the damaged tissue or organ.[42]

In addition to these features, a key feature for the use a biomaterial in scaffold production is the availability of chemically and biologically active molecular groups and suitable linkers which may be recognized by the cells, allowing the cell-scaffolds interaction to occur. Such characteristics can be achieved by appropriated selected synthetic and natural polymers,[30,43] as an example, we can mention natural polymers, such as collagen, which have as ligands the amino acid sequence Arg-Gly-Asp, known as RGB, which allows cell adhesion. In synthetic polymers, these groups must be incorporated for this interaction to occur.[44] Another example is chitosan, the presence of the protonable amino group along D-glucosamine residues provides chitosan properties as biocompatible and hemostatic.[45,46] Chitosan positive charges interact with the negative part of cells membrane, providing a cellular adhesion enhancing property.[45,47]

In both cases, the scaffolds characteristics can be altered through surface modifications and immobilization of biomolecules in order to optimize their biocompatibility and biological properties.[42] Because they have bioactive properties, polymers of natural origin have the best cell-scaffold interactions and, consequently, better performance of cells in the *in vivo* environment.[42]

The presence of reactive groups at scaffolds surface is critical to improve from hydrophilicity to cell adhesion, methods as alkaline hydrolysis,[48–50] laser[51] and plasma treatment have been used to create chemical reactive groups as carboxyl, amino or hydroxyl in the scaffolds surface.[48,52] Another way to add biological active groups on the scaffolds is by adsorption or covalent bonds of bioactive molecules such as protein,[53,54] enzymes,[55,56] antibody,[57,58] and ECM components.[52,54,59]

There have been countless efforts over the past decades to establish a convenient definition of "Biomaterial", since the first one given, in 1987, by the *Consensus Conference on Definitions in Biomaterials of the European Society for Biomaterials*,[43] as "a non-viable material used in a medical device intended to interact with biological systems". Consecutive definitions have been proposed among which, according to Williams,[43] the most accurate is "a substance which has been manipulated to take a form which, either alone or as part of a complex system, is used to direct, by the control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure in humans or veterinary medicine. ''

Biomaterials can be divided into two main categories, bioinert and biodegradable. Bioinert materials do not change their structure in the period of implantation;[60,61] on the contrary, biodegradable materials decompose when in contact with biological fluids during the gradual recovery of the tissue,[60,62] inducing byproducts that can be easily absorbed and eliminated by the body metabolism.[60]

Another class of biomaterial is the active biomaterials or bioactive materials.[63] The choice between active or inert biomaterials depends exclusively on its application. Currently, biologically active scaffolds are attracting attention, due to the fact that they can be used to stimulate a series of biophysical and biochemical responses at the implant / tissue interface.[64] For example, in bone tissue regeneration, a first approach is to improve the bioactivity of the scaffold, using hydroxyapatite or other calcium phosphates, as they are similar to bone mineral and are biocompatible, bioactive and osteoconductive (which are a juxtaposition of bone tissue on its surface). The second approach incorporates growth factors and other biological portions into the scaffold, promoting and accelerating the bone formation.[65]

Another material that has also been used in bone regeneration is silica-based bioactive glasses, since these materials bind to bone tissue through the formation of a phase similar to apatite on its surface when in contact with physiological fluids. A third material used is bioactive ceramics that provide resistance to moderate fracture and chemical corrosion or wear after implantation.[66]

Biologically active materials can also be used with the aim of modulating the immune response and healing that the body will have when it is in contact with the implant. The interaction of biomaterials with blood is what triggers the body's immune response. Thus, bioactive biomaterials can be used with the objective of inducing the response in the host, adding peptides, carbohydrates and proteins on the surface of the biomaterial.[67–70]

In 1997, the term "biomimetics" emerged, which is nothing more than a way of observing and understanding nature, using its model to imitate its forms, processes, systems and strategies, to solve human problems in a more sustainable way.[71] However, a major challenge is to understand the fundamentals and physical and chemical mechanisms that define the structural organization of biological systems at the molecular, cellular, tissue and organismal levels. For this reason, research in this area needs to include three different strands. The first step is to understand the structure-function relationships of biological materials. Second, it is to understand the physical-chemical concepts of this structure-function relationship, through theoretical and experimental studies, with the objective that they can be used in materials science and engineering. And, third, it is to make the manufacture of biomimetic materials possible, following physical-chemical principles, but also taking into account available resources, both scientifically and economically.[72]

For the development of biomimetic materials, there are three different approaches. The first is the insertion and release of bioactive molecules. The second is the use of extracellular matrix bioadhesive macromolecules or specific binding moieties to modify the surface of biomaterials and, finally, the nanoscale standardization of materials.[69]

An example of this is what some authors did, where they used the 3D printing technique to manufacture biomimetic materials inspired by the lotus plant root. Using raw materials such as ceramic, metal and polymer, they manufactured biomimetic materials that looked like lotus root (packaging pattern, porosity, specific surface area, mechanical property and structure) that had better cell fixation and proliferation *in vitro*, in addition to enabling osteogenesis *in vivo*, signaling its potential application for cell delivery and bone regeneration.[73]

One of the first attempt to analyze the biological tissue tolerance to different materials was performed by J. Levert, in 1829, highlighting the fact that platinum was the best tolerated material by the organism.[74] Thereafter, in the earlier 20th century, after trying different materials for implants, Lambotte recommended the use of noble metals, for

corrosion resistance enhancement. It was, in 1924, when attempting to evaluate the biocompatibility of metals, that A. Zierold marked the beginning of the modern science of biomaterials, although the term "biocompatibility" itself had not yet been defined.[74] Jergesen and Leventhal reported, in 1951, the use of pure titanium for the manufacture of screws and plates, giving rise to the production of such orthopedic accessories, in the United States and England.[75]

In the case of biodegradable materials, remarkable advances have been reached in the development of implantable devices, between 1940 and 1980.[30] During the World War II, the biocompatibility of PMMA poly (methyl methacrylate) has been fortuitously discovered, by observing that shards from artillery towers involuntarily implanted in aviators' eyes provoked only a slight foreign body reaction.[76,77] In the late 1950s, Dacron fabrics (Polyethylene terephthalate) was well-established for clinical use and commercially available to surgeons as synthetic grafts for arterial prostheses.[78]

CELL CULTURES AND TISSUE ENGINEERING

Scientific and technological researches in tissue engineering deal with the conception, design and development of new materials and devices capable of promoting specific interactions with biological systems, serving as support and architecture for cells adhesion and growth, for a given tissue to be implanted.[79]

Among the bottlenecks to be solved are the *in vivo* environment mimicry, in which the seeded cells interact with their parent's cells, after implantation, and with the supporting matrix through adhesion by cytokines regulation. This complex biosystem of interactions between cells, signal molecules and structural molecules gives rise to the microenvironment presented in the tissues.[80,81]

Cell culture in monolayers was the mainstay for all current knowledge about cell biology and allowed approximations on the mechanisms governing individual cell behavior.[82] Although 2D culture has proved to be a simple and economical tool for the study of cellular behavior, its limitations become increasingly noticeable.[13,83,84] Since the last decade, a growing number of studies have suggested that cell culture in three dimensions, in contrast to the monolayer system, represents more accurately the actual cells microenvironment.[80,83–89] Indeed, in the *in vivo conditions* most cells are surrounded by other cells and the extracellular matrix (ECM) is a three-dimensional (3D) framework. Cell culture in monolayers is not able to mimic this environment and therefore the results obtained by this culture may not provide predictive data for *in vivo* responses.[13,83] According to Dzobo,[90] cultivation on a planar surface decompensates cell signaling, division and differentiation, since communication between cells is restricted to the periphery only, compromising migration, polarization and differentiation.[90–92] The 3D structure, on the other hand, allows scaffolds to present larger pores and porosity, providing an ideal surface for gas exchange, migration, higher rates of cell adhesion and proliferation, with degradation rates compatible with the rate of tissue formation. Three-dimensional culture is also characterized by its viscoelasticity, hydrophilicity, biocompatibility, biodegradability and mechanical strength, ideal for mimicking the in vivo environment of cells.[91,93] Furthermore, in two-dimensional cultivation conditions, the cell migration is governed by the equilibrium between adhesion and contractile forces. While in the 3D culture, in addition to this balance of forces, the extracellular matrix (ECM) features, such as rheological properties, heterogeneity, porosity and fibers size may interfere in the cell's movement.[89,94] These spatial and physical aspects affect signal transduction from the outer side to the inside of the cells and ultimately influence gene expression and cellular behavior. It has been reported by Shield[95] and Zietarska[96] that cell responses in 3D cultures are more analogous to *in vivo* behavior than 2D cultures.

In three-dimensional conditions, the ECM can be remolded by proteolytic properties or by tensile forces exerted by the cells.[97,98] Such remodeling can be used as a parameter to evaluate the force exerted by the cells. In situations where the ECM imposes physical barriers to cell migration, as in cases where its pores are smaller than the size of the cell, it may excrete proteolytic enzymes for its degradation.[86,89,98]

It has been shown that gene expression can be altered by the culture environment.[88] In the case of human mammary fibroblasts, seven of the eight proteins HGF, IL6, IL8, FGF2, TNFa, TGFa, TGF-p1 e VEGF were expressed in higher concentrations when grown in a three-dimensional environment compared to those grown in a monolayer. One of the seven proteins expressed in higher concentration was HGF, a multifunctional cytokine that stimulates mobility, morphogenesis and metastasis. However, invasive breast cancer cells did not show variations in the expression of these proteins in 3D and 2D cultures, suggesting that some cell types are more affected by the characteristics of the microenvironment in which they are adhered.[88] Cultures of melanoma cells under three-dimensional conditions also showed increased expression of chemokines CXCL1, CXCL2, CXCL3, IL-8 and CCL20.[99] Thus, in different cell types, the change in ECM can induce variations in gene expression, such as those related to signal propagation and transduction.

In addition to physical factors, ECM provides cells with signal molecules that influence cell signaling processes. The results reported by Weigelt *et al.*[100] indicate that mammary gland cells, when cultured in three-dimensional environments, show a closer signaling mimic *in vivo* than in 2D culture. In addition, Niero[101] report that some cell types become more resistant to cell death by apoptosis when in contact with other cells or the extracellular matrix.

Regarding the response to drugs, the use of three-dimensional cultures is emerging as an attractive approach for the evaluation of new drugs.[102,103] As an example, we can mention the works of Dong[104] and Loessner,[105] reporting that human ovarian cancer cells, when cultured in 3D culture to mimic ascites, form clusters of cells resistant to paclitaxel, a drug that stabilizes microtubules in their polymerized form, resulting in cell death.[101,104] Another example of the increased resistance of cells grown in 3D was reported by Yang,[106] who showed the resistance of lung cancer cells to Bortezomib, known as the first protease inhibitor, tested in humans.

One hypothesis for 3D cultures to be more resistant to drugs than in 2D is related to the increase in cell adhesion and matrix elements synthesized under these conditions, making it more difficult for the anti-cancer drug to penetrate the cell spheroids grown in the 3D environment.[107] However, some studies point out that certain drugs, such as doxorubicin, can penetrate and be incorporated in the cell nuclei.[101]

The three-dimensionality of these cultures becomes the crucial characteristic that leads to the different cellular responses, influencing not only the spatial organization of the cell surface receptors involved in the interactions with the surrounding cells, but also inducing physical limitations to the cells.[13,83]

EXTRACELULAR MATRIX

The spatial distribution of cells in the *in vitro* environment is an important variable to obtain a system that responds to stimuli in a similar way to what occurs in the extracellular matrix (ECM).[94] The ECM is essential for cellular physiology of the tissue, being mainly composed of fibrillar (collagens, fibronectin, laminin and elastin) and non-fibrillar proteins (proteoglycans and non-collagenous glycoproteins).[108]

Collagen is the most abundant component of the extracellular matrix, presenting more than twenty variants, each with distinct

physical and chemical properties that contribute to provide an ideal environment for cell growth. This variety of molecules in different concentrations is tightly related to the type of connective tissue (skin, bone or cartilage), being the main challenge for manufactured *in vivo* environments.[109,110]

Fibronectin, the second major component of ECM, is present in several isoforms and has binding adhesives that contribute to tissue repair.[111,112] These ligands consist of motifs such as the Arginine-Glycine-Aspartate trimer that function as specific recognition sites for transmembrane receptors, such as integrins, that promote the interaction between the actin cytoskeleton and the ECM during cell movement.[113] Laminin is a crosslinked trimeric polypeptide (α1, β1, γ1), whose main function is the formation and maintenance of vascular structures.[114,115]

The glycosaminoglycans, other important components of the ECM, are responsible for binding of growth factors and cytokines, water retention and gel properties of ECM. They are composed of chondroitin sulfates A and B, heparin, heparan sulfate and hyaluronic acid.[116,117] Whereas, the proteoglycans function as a reservoir for a variety of molecules, such as growth factors, adhesion molecules, matrix components, enzymes and enzyme inhibitors.[118]

Binding sites that promote cell adhesion are called junctions, which are connected to the cellular cytoskeleton in such a way to transmit stresses to the cell, provoking specific responses to mechanical stimuli from the surrounding environment. Anchoring junctions promote cell-cell and cell-matrix adhesion and can connect to both the actin filaments and the cytoskeletal intermediate filaments.[119]

MIMICKING THE ECM

Considering the above-mentioned features, the extracellular matrix structure and composition are essential for the fabrication of scaffolds, for tissue engineering. Different biocompatible materials, both natural and synthetic polymers, have been studied for this purpose, among which: collagen,[4,120–122] chitin,[18,120] chitosan,[4,18,123] cellulose,[124–127] biodegradable polyesters (PCL, PLA, PGA, among others)[6,62,128] and their blends.[6,129]

The development of an artificial *in vivo* tissue strongly demands the scaffold to promote, in a synergistic way, cell-cell and cell-scaffold interactions, in an appropriate culture environment inside preferentially a bioreactor (Figure 1).[44,130] However, given the complexity of the extracellular matrix and its important functions, it is still a challenging issue to produce fully functioning and suitable scaffolds for tissue generation.[44,130]

The characteristics required for scaffolds, as well as their composition, will depend on the type of tissue to be cultivated. In addition, factors such as biocompatibility, biodegradability, pore size and their interconnectivity, mechanical properties and functional chemical groups are of paramount importance for the viability of cellular and tissue development.[130,131]

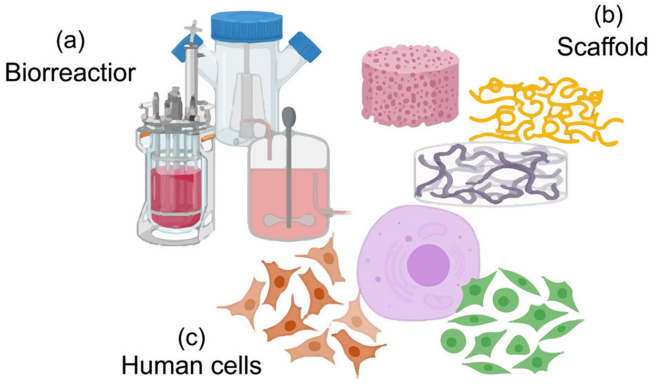

Figure 1. *Basic conditions for Tissue Engineering. a) Controlled environment provided from Bioreactors, b) Scaffolds properly to support Tridimensional organization of tissue intended, and c) Type cellular to tissue intent*

The scaffolds can be obtained from biological tissues, by the removal of cells, using physical, chemical and enzymatic methods, followed by washing and sterilization processes. Recently Caires-Junior (2021) investigated the use of by pre-coating decellularized tissue scaffolds with HepG2-conditioned medium to improve liver scaffold recellularization.[132] Decellularized matrices are considered as excellent models for *in vitro* tissues; however, their use presents certain disadvantages, such as variability of composition and structure, due to the factors involved, ranging from the preparation of the framework to the structural relationship between the decellularized matrices obtained from different individuals, together with the risk of promoting immune rejection.[130,133]

A variety of techniques can be used to obtain scaffolds, such as: hydrogel, leaching of particles, lyophilization, phase separation, gaseous foam formation, 3D printing, self-assembly, electrospinning and centrifugal (or rotary jet) spinning.[42] Electrospinning is the most reported technique to produce fibrous mats, due to its easy use, relative low cost and great potential. However, centrifugal spinning and airbrushing are emerging as alternative techniques to electrospinning, that show undoubted advantages such as simplicity of execution, high voltage-free operation, besides promoting a high yield production of micro and nanofibers.[42]

SYNTHESIS AND MANUFACTURING PROCESS OF SCAFFOLD

Hydrogels

Hydrogels are a special class of polymer matrix, that can be defined as a crosslinked polymer network capable of adsorbing and retaining a large amount of water or fluid within its 3D structure. Such feature is due to the presence of hydrophilic groups, such as, for example, amino, carboxyl and hydroxyl groups, in the polymer chains.[134,135]

Hydrogels can be manufactured by physical and chemical processes, for their use in tissue engineering. In chemically crosslinked gels, the different polymer chains can be linked through covalent bonds, by radical polymerization crosslinking, high radiation energy, chemical reactions of complementary groups (using aldehydes, addition reactions and condensation reactions) and enzymes. Whereas, physical hydrogels are shaped by a crosslinking mechanism involving non-covalent bonds, such as hydrogen bonds, electrostatics interactions, crystallization (homopolymer crystallization and formation of stereocomplexes), protein interactions (using genetically modified proteins and antigen-antibody interactions) and amphiphilic blocks and graft copolymerization.[136]

Hydrogels produced by chemical methods have greater durability compared to those produced by physical methods. However, a specific adjustment is indispensable, since covalent bonds must be established *in situ* with considerable rapidity to prevent dilution and/or dispersion, but, slow enough to provide injection and minimal heat generation. In the other side, hydrogels produced by physical methods have the advantage of reacting to environmental stimuli, such as temperature or pH, but as drawback, a faster reabsorption/erosion after injection associated to the dynamic equilibrium of the non-covalent crosslinking. The conjunction of chemical and physical crosslinking in a single hydrogel was shown to be an alternative to obtain hydrogels with better biostability, maintaining in breathability.[137] Figure 2 shows the crosslinking forms in the construction of hydrogels and their respective advantages.

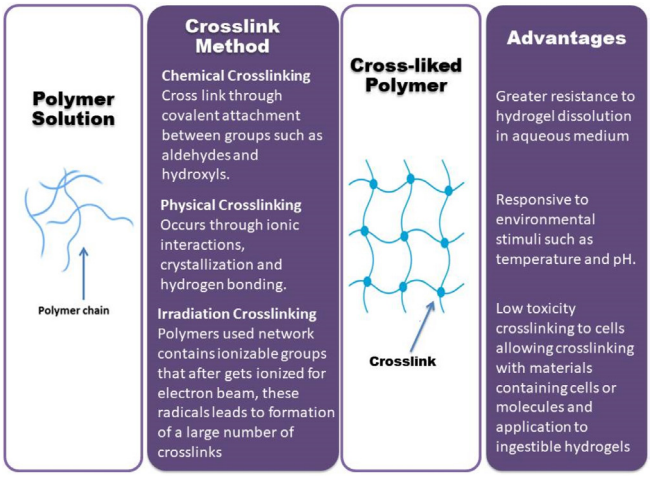

Figure 2. *The crosslinking forms in the production of hydrogels and their respective advantages*

For the production of hydrogel scaffolds, techniques such as leaching of particles, solvent casting, lyophilization, phase separation and gas foaming are used to provide scaffold architecture to the hydrogel through the formation of pores.[138,139] The agent that promotes pore formation is inserted before the crosslinking process and removed after this step. Hydrogels are also widely used for the construction of scaffolds using 3D printing. The combination of biostability with precise adjustment of the degradation time and mechanical properties makes the hydrogel system attractive for the ECM mimicry.[134] In injectable hydrogels, the crosslinking process could perform *in vivo*, in the target site. When exposed to mechanical stress, heat or pH, rheological characteristics can be altered, including a shift to a firmer shape when injected in the target site.[134]

Currently, the use of gelatin microgels has been proposed for the construction of an injectable hydrogel. The scaffold tested on a swine cornea tissue was found to be promising for application in regenerative medicine, due to suitable pores, surface migration and cell proliferation.[140]

Porogen leaching process

The leaching process is based on the casting of a polymer solution together with a porogenic agent. Once a dried polymer film is formed, the porogenic agent is then removed by a dissolution process, given raised to a porous membrane. The pores size and density depend directly on the porogen agent size and concentration in the polymer solution, respectively.[141] Various hydrosoluble particulates may be used as porogens, such as sodium chloride and sugar microcrystals, for hydrophobic polymer scaffolds fabrications.

Mikos *et al.* have reported that the pores density affects the cellular adhesion and should be higher than 80%.[142] It is worth to underline that a porous scaffold makes more efficient the incorporation of bioactive molecules (proteins, growth factors, drugs, etc.) and the cells infiltration across the scaffold.

Silva has investigated the morphological properties of PCL and PLLA based dense and porous polymer membranes, produced by a casting process.[143] The polymer pellets were dissolved in chloroform as solvent, under mechanical stirring. Microparticles of sodium chloride (NaCl) were dispersed in the polymeric solutions, with a NaCl/Polymer mass ratio of about 60%. The solvent was then allowed to evaporated overnight at room temperature to obtain a dried polymer film, which was uncast from the container (glass molds) for the porogen removal. The porogen size range was achieved by sieving the NaCl particles between 75 and 150 μm. To leach out the salt, the membranes were completely immersed in individual glass containers filled with 500 mL of deionized water, under magnetic stirring, at room temperature. The water was changed every 8 h. After 5 days of leaching, the salt-free membranes were then dried in a vacuum oven for 2 days and stored in a desiccator under vacuum for posterior use (Figure 3). In Figure 4 is shown the SEM images of the PCL membranes, in top and cross-section views, with and without the leaching process. The authors highlighted the formation of highly density of interconnected porous membrane as a result of the leaching process. Such porous structure was used for the incorporation of an antibiotic drug, hydrochloride tetracycline, for wound dressing application.

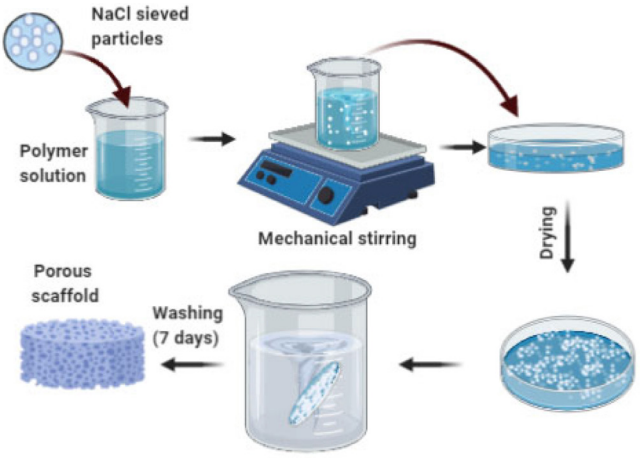

Figure 3. *Illustration scheme of the leaching process*

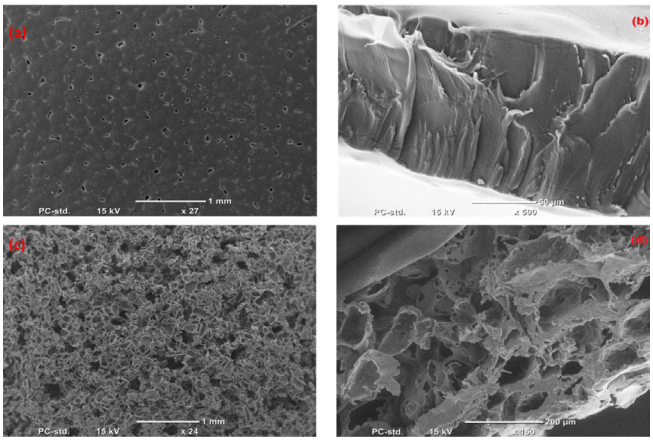

Figure 4. *SEM images of top view of PCL membranes without and with leaching (a) and (c), respectively; and cross-section view of PCL membranes with leaching (b) and (d), respectively*[143]

3D Printing

By targeting several applications, including tissue engineering, 3D printing is conceived as a splendid innovative manufacturing technology.[144] Overall, 3D printed biomedical devices are built in a layer-by-layer process, involving the following steps: (a) design of a 3D computer model; (b) fractioning of the 3D computer model into a 2D image construction file; (c) manufacturing by a computer-controlled layer-by-layer process and (d) post-processing, such as surface modification for nanoarchitecture.[145]

Unlike the traditional 3D printing methods that are employed to print free-cells scaffolds for use in surgeries, bioprinting demands a different approach that is harmonious with the deposition of living

cells. During the 3D bioprinting process, cell units and biomaterials are simultaneously released with micrometric precision to form tissue-like structures.[146] The three main methods used for 3D biofabrication are inkjet, extrusion and laser-assisted bioprinting. Inkjet-based bioprinting was the first method to emerge, by a simple adaptation of the well-established conventional inkjet printers for the bioink (cells-loaded biomaterial) deposition to build the functional tissue.[147] Extrusion-based bioprinting consists of the ejection and deposition of the bioink from a nozzle by an automated robotic system.[148] Newly Backes used extrusion-based bioprinting to procuce a bioactive composite scaffolds based on the combination of aliphatic polyester and calcium phosphates that showed elevated level of printing accuracy and applicability for bone tissue regeneration.[149] Light-assisted bioprinting is based on the use of photopolymerization of biomaterials, printing a diversity of cells with good cell viability. There are two light-assisted bioprinting systems: laser-based and digital light processing based (DLP-based) printers.[147]

According to Aguilar,[150] the Kenzan bioprint is the highest quality technique reported in the literature. The Kenzan matrix is an arrangement of stainless-steel needles 10 mm long and 170 mm in diameter, spaced 400 μm in a standard 9x9x9 or 26x26x26. First, the vision system in the 3D printer confirms that the set of needles are bent or missing, and only then does the process start. The system also scans the nozzle, which is responsible for removing the tissue constructs from the culture medium to another location. Subsequently, it checks each spheroid to match the diameter, rounding, and location according to the limits specified by the user. Once the spheroid is checked, it is pulled slightly to the tip of the nozzle using the pressure system also in the printer. If the spheroid is no longer seen by the vision system, it is assumed that the spheroid is not in the mouthpiece, which will move to the place in the series of needles, lowering into a preselected needle, impaling the spheroid needle. The entire process is checked after each placement of spheroids using the machine vision system, until the entire structure designed by the software is constructed.

Although it is a simple and apt technique to generate specific structures without the need of scaffolding, it still requires the improvement of some essential points such as optimization of production time, minimization of costs and errors.

Electrospinning

Due to the vast interest of the researchers in the technique of electrospinning, the mechanisms and phenomena in the process were well characterized.[151,152] The general principle of electrospinning is the use of an electric field to provide a driving force that promotes the elongation of a fiber from a drop of polymer solution or molten polymer. Other techniques applied to electrostatic precipitation and some pesticide sprayers use the principles that strong repulsive electric forces can be used to overcome surface stress forces.[153]

The typical apparatus for carrying out the technique is composed of a high voltage supplier, a tube system connected to a peristaltic pump or syringe, a spinneret having at its end a capillary and a grounded collector plate, Figure 5.[153,154] During the electrospinning process the polymer containing feedstock is pumped into the capillary of the metallic needle, forming a droplet at its end. This droplet is subjected to an electric field by means of a potential difference applied between the needle and the grounded collector, inducing the formation of free charged in the polymer droplet.[154] As the electric field intensity increases, the droplet surface at the capillary end elongates to form a conical shape called the Taylor's Cone, with accumulation of charges induced in this region.[155] Increasing the field strength further yields a critical value that overcomes the surface tension of the droplet and then a jet of the fluid is ejected from the needle.[153] Along the flying path of the jet in the direction of the collector, only in the region close to the Taylor's Cone a stable behavior is observed; after a short distance the jet is subjected to stretching processes and instabilities that promote the evaporation of the solvent and the reduction of the diameter of the jet, ending to a quite dried fibers at the collector.[134,153]

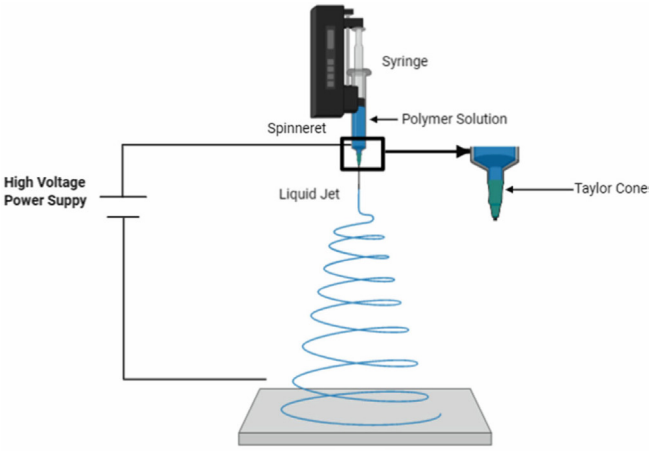

Figure 5. *Electrospinning*

Due to its ease of operation, electrospinning has been considered as an alternative for large-scale production of nanofibers.[156] However, electrospinning presents some drawbacks that need some attention and that may restrict its application in industrial scale, such as the need for high voltages of 10 to 30 kV,[157] a suitable choice of the solvent, beside a relatively low yield of about 0.1 g h^{-1}.[158]

Therefore, strategies for the improvement of the electrospinning technique have been proposed in order to increase its performance using, for example, multichannels or porous tubes to allow the simultaneous ejection of a large number of fibers.[157,159] Alavarse used the electrospinning method to produce scaffolds composed of chitosan, PVA and tetracycline hydrochloride (TCH), as fibers that make up or scaffolding with average measurements of about 309 nm. In addition to presenting antibacterial activity, the authors analyzed a cell test by means of a draft test, which demonstrated that the scaffolds had good cytocompatibility. Figure 6 shows how images from the Scanning Electronic Microcopy of PVA, PVA / Chitosan and PVA / Chitosan / TCH scaffolding before and after the crosslinking process with glutaraldehyde (GA).[70]

Solution Blow Spinning (SBS)

As seen previously, the electrospinning process is based on an electrical fields generated between the needle and the collector. Thus, often the fiber deposition process can be susceptible to the behavioral conditions of the polymeric solution facing the electric field. If a polymer blend shows phase separation, the jet instability can suffer different conformations and, consequently, the deposition of fibers with variable diameters. In addition to the electric field, a Taylor cone-shaped polymeric jet can be obtained through pressurization by air in the drop of the needle. This process is known as solution blow spinning (SBS) and can be applied to polymer solutions with high or low electrical conductivity. As in the case of electrospinning, a peristaltic pump controls the flow of the polymeric solution located in a syringe. The needle is interconnected to a cylindrical tube with air or gas passage (Figure 7), and the drag force is directed towards the fiber collector. For the polymeric jet to be launched into the collector, the critical force should be greater than the surface tension forces of the solution (in this case, air flow pressurization forces), so that the solvent is evaporated and fibers are deposited.[160] Thus, the

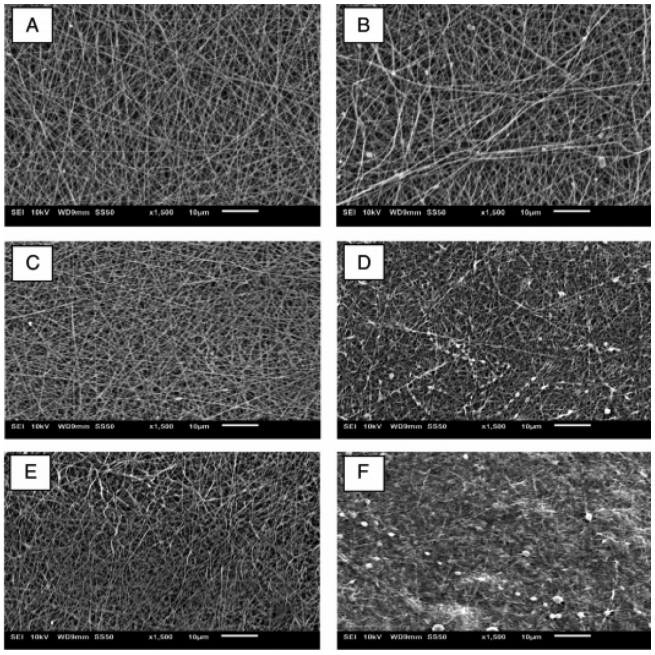

Figure 6. *Scanning Electronic Microcopy imagens scaffolds obtained with (A) Pure PVA, (B) PVA/GA, C) PVA/CS, (D) PVA/CS/GA and (E) PVA/CS/TCH and (F) PVA/CS/TCH/GA*[70]

morphology of the fibers obtained also depends on the viscosity of the solution, the distance between the needle and the collector, the gas and solution flow rates.

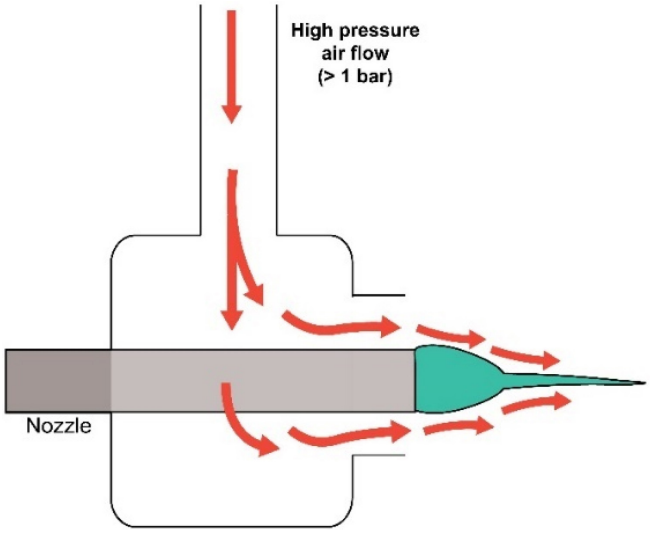

Figure 7. *The formation of Taylor's cone by SBS process provoked by the high-pressure air flow pivoting in the drop of polymeric solution*

PLA fibers formed through SBS process were investigated varying the polymer concentration and equipment setup. As expected, the concentrated PLA solution at 12% resulted in larger diameter fibers (>310 nm), PLA solution at 10% intermediary diameter fibers (174-216 nm) and smaller diameter fibers (110-179 nm) for PLA solution at 8% even when varying other parameters. In concern of the applied air flow rate (40-80 psi), the study shows that the fiber morphology depends when the feed solution rate reaches 50 μL mL^{-1}. The results were supported by statistical analysis of Box–Behnken design, having significant values ($p < 0.05$) for quadratic and liner model for concentration and air flow rates.[161] Another advantage of the SBS process is the practicality and even the opportunity to synthesize fibers *in situ*. Gao and collaborators designed an apparatus capable of producing fibers up to 400 mg min^{-1} of Polyvinyl butyral (PVB). For this, the bottom an aerosol spray (with orifice inner diameter of 2.8 mm) was connected to a dust removing tank (in this case as an air reservoir). The syringe containing the polymeric solution was placed axially to the aerosol (the syringe nozzle also was modified to fit on properly the air flow).[162] Thus, the apparatus can be transported to other places such as operating rooms, being used as an emergency device (example: bleeding situations, application of fibers with hemostatic feature) or even inserting directly into the target tissue.

Centrifugal spinning

Recently, centrifugal spinning has been proposed as one of the most promising alternative technique to overcome the low productivity of the electrospinning.[163] Centrifugal spinning is based on the formation of nanometric and submicrometric fibers by centrifugal force, requiring no electric fields neither electrically charged solutions. It is worthy to stress that, although we use the term centrifugal spinning in the present review, this technique is treated through different appellations in the scientific literature, namely Rotary Jet Spinning and Forcespinning™, introduced by the brand FibeRio® Technology Co.[164] The term Centrifugal spinning was recently reported in the literature, by Badrossamay[165] and Sarkar.[166] However, the phenomena of fiber formation on a nanometer scale using centrifugal force was unexpectedly discovered by Weitz[167] in a coating process with polymethyl methacrylate (PMMA). Using a conventional spin coater apparatus, the authors noted the formation of fibers of diameters up to 25 nm.

The principle of using centrifugal force to promote a motive force that allows the polymeric fluid to overcome the viscous forces and surface stresses involved in centrifugal spinning is already applied in the production of cotton candy[164] and glass fibers used as thermal insulation in refrigerators and stoves.[168] Although the principle involved in centrifugal spinning has already been used in other areas, its recent application in the production of polymer nanofibers has boosted its use and the investigation of the influence of the parameters involved in the technique.[165,168] The rising brand involving centrifugal spinning technique can be perceived by the booming of patents filed by important companies such as BASF Aktiengesellschaft, Owens Corning Fiberglas Technology and Akzo Nobel NV.[168]

Several models of centrifugal spinning equipment have been reported in the literature from commercial equipment.[165,169,170] However, some components are required for operation and are common to all centrifugal spinning equipment used as a spinner located in the center of the equipment which contains predetermined radius holes, whereby the polymeric fluid is expelled, a motor which rotates the spinneret, a system coupled to sensors and speed controllers, and a collector where the fibers is deposited, Figure 8.[158,166,171]

One of the great concerns during the centrifugal spinning process is the control and the optimization of the process variables, to modulate the characteristics of the final fibrous mat such as fibers diameter and orientation, porosity and homogeneity. In this sense, other components have been added such as heating and temperature control,[166] flexible sheets in the lower region of the nozzles to generate an airflow that prevents the fibers from depositing immediately at the bottom of the collector[158,168] and mobile collectors, which allow the variation of the distance between the collector and the die.[164]

During the centrifugal spinning process, the polymeric fluid is fed to the spinneret by a pump or syringe at a predetermined rate. After the feeding, three steps of the process can be considered: (i) the spinneret rotation induces a centrifugal force that, above a given

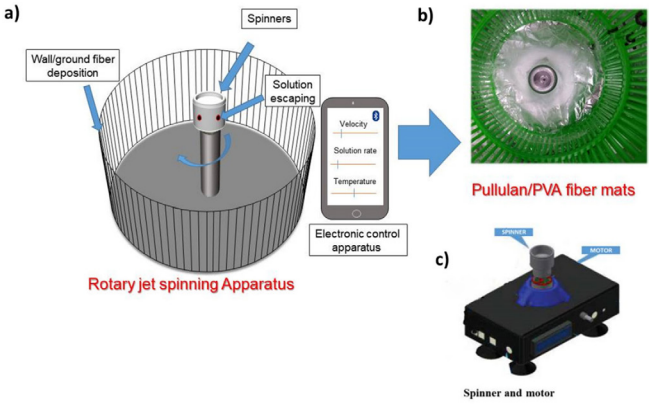

Figure 8. *Centrifugal Spinning Equipment. A) Collector and spinneret. B) Collector with PVA Fibers. C) Spinner and motor*

threshold intensity, overcomes the capillary and viscous forces, provoking the ejection of the polymer jet; (ii) the jet is extended towards the collector by the rotation and resistance movement imposed by the viscosity of the fluid, at a molecular level, the polymer chains are stretched and intertwined, promoting their thinning of the fiber, due to the inertia of the rotation the jet travels in an undulatory trajectory and (iii) concomitantly to elongation of the jet the evaporation of the solvent occurs, promoting the solidification of the jet.[164,172]

Due to the wide range of applications for the polymer nanofibers and the superiority in centrifugal spinning performance in detriment to the electrospinning, there is a great interest to get o better understanding of the fiber's formation mechanisms and the influence of the different parameters of the process on the final fibrous mat architecture.[173,174] Eventually, defects may occur beside and/or along the fibers such as beads, agglutination and alignment or not that may be unwanted for the final application of the fibers. Therefore, it seems of paramount importance to focus restless efforts to study the best strategies to precisely tune the different involved parameters to match the fibers morphology to a specific application.[165,172]

During the centrifugal spinning process, rotational velocity, viscoelasticity of the polymer, evaporation rate, temperature, spinning radius, collector distance to the spinneret and feed rate of the polymeric fluid are the main parameters that influence the morphology and diameter of the fibers.[174] De Souza *et al.* used RJS to produce pullulan and PVA fibers with different diameters, changing the process parameters as collector distance and solution parameters as solvent volatility and polymers composition. Beyond influence, the diameter of the fibers these variables can module diameters distribution and fibers aspects within mats. This work shows that polymer solution proprieties besides concentration and viscosity, as viscoelasticity, influence spinnability, and fibers aspects.[173]

The volatility of the solution is a relevant parameter of the process since a crucial step is the evaporation of the solvent from the polymer jet for the formation of the fiber. Golecki *et al.*[172] have reported the hypothesis that the formation of smooth and bead-free fibers is mainly due to the effect of the rapid evaporation of the solvent. The solvent evaporation from the jet is a mass transfer process that can occur in two stages: a predominantly convective and a purely diffusive step. The first step occurs as the jet travels towards the collector and is dependent on the speed of rotation; the second stage occurs by the diffusion of the solvent remaining through the polymer matrix when the fibers are already deposited in the collector. However, as in many cases, after the centrifugal spinning, the mat is removed and submitted to other processes, only the first stage is in generally considered.[172] For instance, the volatility can be changed by increasing the proportion of chloroform in a PLA solution in order to produce fibers with lower diameter.[172]

Badrossamay[165] has reported the influence of the rotation speed in the process. They showed that the diameter of PVA fibers dropped from 1143 ± 50 nm to 424 ± 41 nm, by increasing the rotation from 4000 rpm to 12000 rpm.[165] Ren and Kotha[175] showed a similar behavior for BaTiO3 fibers, achieving a mean diameter of 1497 nm and 788 nm, using a speed of 7000 rpm and 9000 rpm, respectively, evidencing an inversely relation between the speed of rotation and the mean diameter of the fibers.

The rheological properties of the polymeric fluid are of great importance for the centrifugal jet spinning process, influencing the formation or not, as well as the morphology of fibers.[165] The viscosity can be understood as the degree of interlacing of the polymer chains, promoting greater resistance to shear stresses. When the viscosity value of the polymeric fluid is below a critical value, the degree of entanglement between the polymer chains is not sufficient to provide resistance for the jet stretching, provoking the jet rupture and the formation of beads.[175] By increasing the polymer concentration, the viscosity is enhanced, allowing an overlapping of the polymer chains to takes place, and leading to more rigid chains conformations, favorable for the spinning capacity of the solution; however, higher rotation speeds are required for the fiber's formation.[176]

Vida *et al.*[177] showed, by comparing fibrous scaffolds produced by centrifugal spinning and electrospinning, that the latter technique gives rise to thinner fibers; however, both techniques allow suitable biocompatibility and cell viability, for tissue engineering. Furthermore, the authors emphasize that the worrisome drawback associated to the use of fibrous scaffolds in tissue engineering is the control of the architecture obtained by these processes.[177]

Airbrushing

Airbrushing or Blow Spinning just like Centrifugal Spinning is an alternative technique for the production of polymeric fibers. The technique is based on the use of pressurized air to promote the extrusion and traction of a polymeric solution that will give rise to the fibers.[178,179] This technique requires a simple apparatus such as an air compressor, hoses and a pump for the polymeric solution; despite being a simple equipment, there are commercially available airbrush apparatus.[179,180]

During the fiber manufacturing process, two fluid streams concentrate, the polymer solution in the center and the surrounding air jet.[178] The flow pressurized air promotes the displacement of the polymeric solution producing a polymeric jet, the airflow also provides the rapid solvent evaporation present in the jet, leading then to the formation of the polymeric fiber. The use of heated air further favors the drying process of the polymeric jet.[180]

Among the advantages of the technique can be mentioned productivity up to ten times higher than electrospinning, without the need for an electric field or solvents with specific dielectric constants. In addition, as the air flow remains around the polymeric solution, the solution does not come into contact with the nozzle of the equipment, which minimizes the occurrence of clogging of the equipment nozzle, which can occur more frequently in electrospinning and centrifugal spinning.[179,180] Another advantage of the technique is the possibility of depositing the fibers directly on a desired surface, be it flat or with different topographies.[180] Airbrushing has shown promise for the production of scaffolds for tissue engineering.[181–183]

The Table 1 shows examples of scaffolds produced of different polymers and by different techniques for applications in Tissue Engineering.

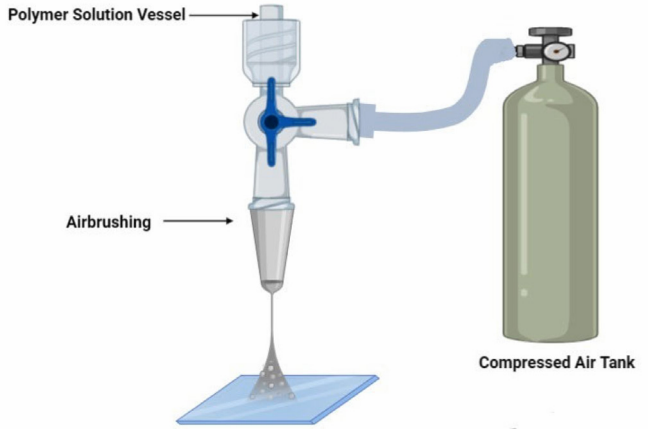

Figure 9. *Airbrushing*

COMBINATION OF DIFFERENT SCAFFOLD-FORMING PROCESSES

Wei *et al.* have investigated the combination of 3D printing and particulate leaching techniques to produce alginate scaffolds with both controlled macro and micropores. The authors claimed that the combination of these two techniques allow the obtention of versatile scaffolds for different tissues with suitable properties using alginate-based bioink.[254]

Yan et al. also argue that the combination of different processes overcomes some limitations of single isolated processes, for scaffolds manufacturing. The authors proposed the integration of 3D printing, as macro-structure forming process, and near-field electrospinning (NFES) process, as micro-structure forming process. The experimental results show that the two processes could be switched to get a multi-scale scaffold of 3D printed of gelatin and chitosan together with electrospun chitosan and PVA.[255]

Mayer et al. have investigated the release profile of two pain relief drugs (diclofenac sodium – DCS and lidocaine -LID), incorporated in both a 3D printed and electrospun scaffolds, for wound dressing applications. The authors proposed, on the basics of their experimental results, an integrated bi-layered scaffold, based on a top 3D printed layer loaded with DCS, and an inner layer filled with LID in contact with the wound. Such combination could allow an immediate pain relief by the LID release, followed by a prolonged DCS release, until

Table 1. Scaffolds of different polymers produced by different techniques

Material	Scaffold Production Technique	Application
Poly (ethylene glycol) (PEG)	Hydrogel	Cartilaginous tissue;[184–186] Tissue vascularization.[187]
Poly (ethylene glycol) – Chitosan	Hydrogel	Wound healing;[188,189] Cartilage tissue engineering;[186] Bone tissue engineering.[190]
Poly (ethylene glycol) - hydrophobic poly-ε-caprolactone	Hydrogel	Formation of neocartilage;[191] Cell delivery.[191]
Chitosan-Agarose	Hydrogel	Brain injury repair;[192] Skin regeneration;[193,194] Repairing soft tissue;[195] Cartilage tissue engineering.[196]
Pectin–chitin	Hydrogel	Bone regeneration and drug delivery.[197]
Chitosan-hyaluronic acid	Hydrogel	Abdominal tissue regeneration;[198,199] Cartilage tissue engineering;[190,200] Adipose tissue regeneration.[201]
Pullulan-collagen	Hydrogel	Skin tissue engineering.[202,203]
Alginate – gelatin	Hydrogel	Skin tissue engineering;[204] Tissue engineering.[205]
Alginate – gelatina	3D printing	Cartilage tissue engineering;[206,207] Bone tissue engineering;[208,209] Tissue engineering;[210] Vessel-like structures;[211] Skin tissue engineering.[212]
Poly(ε-caprolactone) (PCL)	3D printing	Bone regeneration;[213] Tissue engineering;[214] Skin tissue engineering;[215] Cardiac tissue engineering;[216] Bone tissue engineering.[215]
Poly(lactic) acid (PLA)	3D printing	Bone tissue engineering.[217–221]
Alginate – Agarose	3D printing	Cartilage tissue engineering.[222,223]
Polylactic acid-co-glycolic acid	Electrospinning	Development of skin grafts. [224,225]
Polylactic acid-co-glycolic acid/chitosan	Electrospinning	Tissue engineering.[226]
Polylactic acid-co-glycolic acid/collagen	Electrospinning	Bone tissue engineering;[227–229] Skin tissue engineering.[229–231]
Gum tragacanth/poly(vinyl alcohol)	Electrospinning	Skin tissue engineering.[232,233]
Polyether urethanes Z3A1 and Z9A1 and Polyurethane-Hydroxyapatite	Electrospinning	Bone matrix formation.[234,235]
Poly (vinyl alcohol) Gelatin/Carica papaya	Electrospinning	Wound healing.[236]
PCL/Gelatin	Electrospinning	Tendon healing;[237,238] Vascular tissue engineering.[239–241]
Cellulose acetate/ Pullulan (PUL/CA)	Electrospinning	Skin tissue engineering;[242] Bone tissue engineering.[243]
Poly(ε-caprolactone) (PCL)	Centrifugal Spinning	Tendon healing;[237] Bone tissue engineering;[244] Tissue engineering.[244]
Polyurethane (PU)	Centrifugal Spinning	Tissue engineering.[245]
Polyurethane/gelatin (PU/Gel)	Centrifugal Spinning	Tissue engineering.[246,247]
Poly(d,l-lactide) (PLA)	Airbrushing	Bone tissue engineering.[248,249]
Poly(ε-caprolactone) (PCL)	Airbrushing	Tissue engineering.[250,251]
Poly(ε-caprolactone) (PCL)	Solution blow spinning	No specific tissue.[251]
PLLA/hydroxyapatite	Solution blow spinning	Bone tissue.[252]
PVP/PCL	Solution blow spinning	No specific tissue.[253]

Table 2. Comparison of diferent scaffold-forming process

Technique	Advantages	Limitations
Hydrogel	• Simple method;[138] • High water adsorbing and retaining;[138,258] • Can be injectable into the body.[134,138]	• Usually mechanically weak;[138,259] • The cross-linking process can make it difficult to incorporate cells and biomolecules during production;[138,259] • Handling difficulties;[138,259] • Sterilization difficulties;[138,259] • Closed pore structure in the resulting matrix;[138,260] • Difficulty modulating pore size and shape.[138,260]
3D Printing	• Controlled pore structure;[261,262] • Customized production;[262] • High productivity;[262] • Cells and hydrogels can be printed;[261,262] • Solvent not required.[261,262]	• Limited filament resolution;[138,262] • Expensive.[138,261,262]
Leaching	• Facile process; • Additional components or techniques can be inserted to fitting final product;[35,263] • Interconnected pores; • Green.[264]	• Pore uniformity.[263,265]
Electrospinning	• Highly interconnected pores;[153,266] • Huge surface area to volume ratio;[153,156] • Both random and oriented fibers possible.[267,268]	• Limited scaffold thickness;[138] • Low productivity;[158] • Need for electric field;[153,157] • Need for specific solventes;[153] • Unscalable.[153,157,158]
Centrifugal Spinning	• Highly interconnected pores;[174,244,269] • Huge surface area to volume ratio;[174,244,269] • Scalable, high productivity and low cost;[168,270] • High resolution.[271]	• Depends on the rheological aspects of the polymeric solution;[158,272] • Too many parameters;[158,172,174,272] • Non oriented fibers.[158,172,174,272]
Airbrushing	• Highly interconnected pores;[181,249] • Huge surface area to volume ratio;[181,249] • Scalable, high productivity and low cost;[181,273] • High resolution;[179,180] • Deposition on surfaces with different topographies.[180]	• Non oriented fibers;[178] • Polymer beads formation;[274,275] • Too many parameters.[276]

the wound dressing removal after 2 days of application.[256]

Techniques to produce fibrous scaffolds shows difficult to control of the architecture obtained, this limitation may possibly be overcome by the method, reported recently by Wang *et al.*,[257] for nanofibers production based on the combination of electrospinning and centrifugal spinning. In this innovative strategy, the centrifugal spinning was used to simultaneously generate fibers of two distinct polymers, and the electrospinning to induce an alignment of the collected fibers.

It seems that the combination of different processes for scaffolds manufacturing could overcome the draw backs of each isolated process, for specific tissue engineering applications and is pointing, seemingly, to interesting future scaffolds design with tunable features. The Table 2 shows the pros and cons of different scaffold-processes related on this review.

CONCLUSIONS

Based on previous reported works, important aspects of the scaffold design have been highlighted in this review. We have focused on important features for the development of a 3D framework that mimics the extracellular matrix in both the morphological and functional character, imposed by the *in vivo* environment for cells adhesion and proliferation. To face this challenge, innovative strategies for the scaffold fabrication have discussed. Among the different techniques, polymeric fibrous mats production plays an important role for tissue engineering applications. To sum up, considering the diversity of materials that can be used for scaffold fabrication, we gave a special emphasis on the interactions between the scaffold on the biological environment, that are essential for cell adhesion, growth, and proliferation. For broad clinical applications, the large production scale with competitive cost may be achieved considering both the nanostructured material functionality and innovative strategies based, for instance, on the combination of two or more fabrication techniques.

LIST OF ABREVIATIONS

WHO - World Health Organization
GODT - Global Observatory on Donation and Transplantation
3D - Three-Dimensional
2D - Two-Dimensional
PMMA - Poly (methyl methacrylate)
FDA - Food and Drug Administration
PLA - Polylactic acid
PGA - Polyglycolic acid their
PLGA - Polylactide-co-glycolide
PCL - Poly (ε-caprolactone)
PVL - Poly(γ-valerolactone)
PEG - Polyethylene glycol
PEO - Polyethylene oxide
PU - Polyurethane
PVA - Poly (vinyl alcohol)
ECM - Extracellular matrix
T_g - Glass transition temperature
HGF - Hepatocyte growth factor
IL6 - Interleukin-6
IL8 - Interleukin-8

FGF2 - Fibroblast Growth Factor 2
TNFa - Tumor Necrosis Factor Alpha
TGFa - Transforming Growth Factor Alpha
TGF-p1 - Transforming Growth Factor-p1
VEGF - Vascular endothelial growth fator
CXCL1 - C-X-C Motif Chemokine Ligand 1
CXCL2 - C-X-C Motif Chemokine Ligand 2
CXCL3 - C-X-C Motif Chemokine Ligand 3
CCL20 - Chemokine (C-C motif) ligand 20
RJS - Rotary Jet Spinning
SBS - Solution Blow Spinning

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