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CONVENTIONAL METHODS OF SCAFFOLDS PRODUCTION

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ABSTRACT

The main problem in conventional manufacturing processes is failure to provide the appropriate resolution to control the submicron internal architecture and bioactivity. In addition, conventional methods do not allow the production of material which is designed to mimic the microscopic structure of the tissue and does not allow the production of an individual scaffold with a precisely defined pore size and shape. Based on these knowledges were developed advanced manufacturing technologies to obtain the desired properties.

INTRODUCTION

Nowadays, there are many production methods for the creation of the scaffolds such as gas foaming, phase separation, fibre bonding, freeze-drying, and frost-freezing. Most of these techniques are referred as conventional methods and have been found to be unsuitable for preparation scaffolds to produce and regenerate tissues. Since most of the conventional techniques for production of scaffolds have certain limitations, adapted computer-aided design (CAD) technology and advanced manufacturing technologies have been developed. Based on this, it is now possible to use these add-on design concepts for production of new scaffolds or living tissues with exact architecture.

3D CAD data is compiled using software with algorithms to adapt the spatial properties of the final product. The software allows precise geometry based on end-user specific requirements from a CAD file or by generating 2D image data from medical scanning devices such as magnetic resonance imaging (MRI) or computer tomography (CT). There are several advantages of using additional production methods compared to common methods:

- the spatial elements of the scaffold at the submicron level are limited by specific technology
- the shape and size of the structure can be accurately designed to match the empty tissue (no cells)
- the unique submicron and micron architecture of the tissue can be created and reproduced at large design dimensions
- the structure may be formed from a wide selection of hydrophilic or hydrophobic polymers, either jointly or separately without affecting the spatial resolution of the proposed architecture
- a spatially-defined structure may be made of bioactive or cellular components.

SOLVENT-CASTING AND PARTICULATE-LEACHING

Solvent-casting and particulate-leaching involve the use of a polymer solution with uniformly mixed salt particles of a certain diameter. The solvent is evaporated from the entire matrix polymer. The composite is then immersed in salt water, allowing the formation of a porous structure. This technique allows to produce high-porosity scaffolds with a porosity of up to 93% and a pore diameter of 500 µm. The disadvantage of this method is that it can only be used to make thin membranes into 3 mm thick.

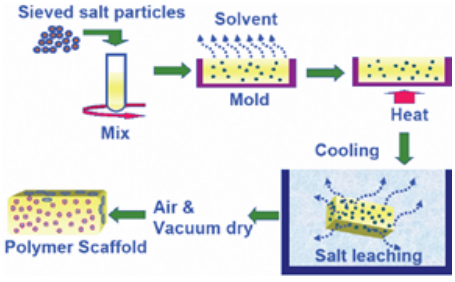

Figure 1: Solvent-casting and particulate-leaching Source: https://www.researchgate.net/publication/252777700_Bioinspired_Nanocomposites_for_Orthopedic_Applications/figures?lo=1

GAS FOAMING

During gas foaming, the compressed biodegradable polymer is under high pressure with gas-foaming (such as CO2 and nitrogen), water or fluoroform until the polymer is saturated. As a result, nucleation and gas bubble growth ranges from 100 µm to 500 µm. The advantage of this technique is that it is an organic process without solvents, but a significant disadvantage is the possibility of obtaining large unrelated pore and non-porous outer surface.

Figure 2: Gas foaming Source: https://www.researchgate.net/ publication/252777700_ Bioinspired_Nanocomposites_for_Orthopedic_Applications/figures?lo=1

PHASE SEPARATION

During the phase separation process, the polymer solution is disintegrated and passes through the liquid-liquid phase separation to form two phases:

1. polymer-enriched phase
2. polymer-degraded phase

The polymer enriched phase solidifies and the phase with a smaller

proportion of polymer is removed, leaving only a highly porous polymer network. The micro and macrostructure of the resulting scaffold is controlled by changing process parameters such as polymer concentration, temperature and quench rate. The process is carried out at low temperatures which are beneficial for the incorporation of bioactive molecules in the construct. By using the phase separation technique, a nanofibrous structure is created that mimics the ECM architecture and provides a better environment for cell attachment.

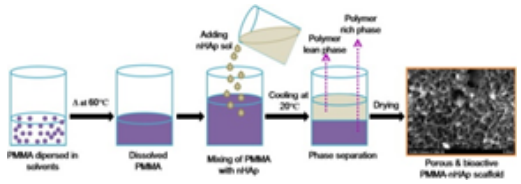

Figure 3: Phase separation Source: https://www.sciencedirect. com/science/article/pii/S092849311631284X

MELT MOLDING

This process consists of filling the mold with a polymer powder and a porogenous component and heating above the glass transition temperature of the polymer upon application of the pressure to the mixture. During the manufacturing process, the materials bind together to form the proposed specific external shape. After the mold is removed, the porogen is flushed and the porous scaffold is dried.

Melt molding with porogen leaching is a solvent-free process that allows independent control of morphology and shape. Disadvantages include the possibility of residual porogen and high processing temperatures, which excludes the possibility of incorporating bioactive molecules.

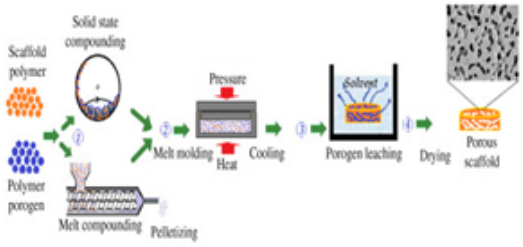

Figure 4: Melt molding Source: https://www.sciencedirect. com/science/ article/ pii/B9780081009796000045

LYOPHILIZATION - FREEZE DRYING

Polymeric porous scaffolds may be formed by freeze-drying. In the freezing phase, the polymer solution is cooled to a temperature at which all the materials are frozen and the solvent is crystallized, forcing the polymer molecules to clump to the interstitial spaces. In the second phase, the solvent is removed under pressure. If the solvent is completely sublimed, a dry polymeric crosslinked pore is formed. Porosity of the scaffold depends on the concentration of the polymer solution, the pore size is affected by the freezing temperature. This technique is used not only for the production of a porous scale, but also for the drying of biological samples to protect their bioactivity.

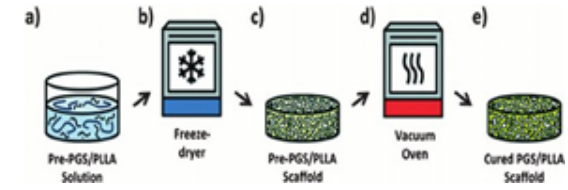

Figure 5: Lyophilization Source: https://www. researchgate. net/publication/282450405_Polyglycerol_sebacate_biomaterial_synthesis_and_biomedical_applications/figures?lo=1

ELECTROSPINNING

It is an electrical charge manufacturing technique to create fine fibers in the nanometric range. By using this method, it is possible to create rafters from different materials. Electrospinning technology is used to make porous scaffolds with a nanofibrous architecture that mimics the structure and function of ECM. It is possible to generate fibers with a diameter of from about 2 nm to several microns, using both natural and synthetic polymers, with small pore size and high surface area. The basic components for electro pinning include three parts: an injection pump comprising a polymeric material, a high voltage source, and a fiber collection collector. During fabrication of the scaffold important parameters for fiber morphology are:

- in polymer solution - viscosity, molecular weight of polymer, polymer conductivity, surface tension
- in the process of processing - applied voltage, distance between peak and collector, flow
- in the environment - humidity, temperature

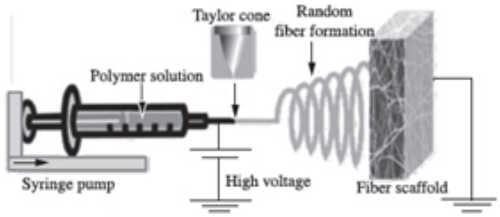

Figure 6: Electrospinning Source: http://www. scielo. br/scielo. php?script=sci_arttext&pid=S1516-14392011000300006

FIBER CONNECTION

Polymer fibers are a feasible material for the formation of scaffolds as they exhibit an excellent surface area to volume ratio for cell attachment. The primary tissues engineering dumps were fibrous grids with poor mechanical integrity for organ regeneration. To overcome this problem, a fiber-bonding technique has been developed that firmly binds the fibers at the crossing point. The first example of the skids was made of PLLA and PGA. PGA fibers are arranged and placed in a non-woven grid. When the temperature is raised to the melting

temperature of the material, the fibers are joined at their contact surface. PGA filaments are encapsulated before the heat treatment to prevent potential collapse of the molten polymer. PLLA is dissolved in methylene chloride and then seeded and dried on the fibers in the grid to form a PGA-PLLA composite matrix. The main advantages of fiber bonding include the simplicity and preservation of the original properties of PGA fibers. The disadvantages are the difficulty of controlling the pore size and porosity, the limited availability of solvents, and the lack of mixing of the two polymers in the molten state.

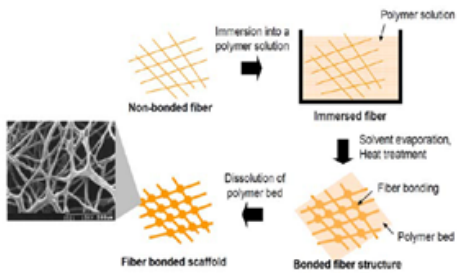

Figure 7: Fiber connection Source: https://www.google. com/ url?sa=i&rct=j&q=&esrc=s& source=images& cd=&ved=2ahUKEwj9hanl0prgAhXMxYUKHUevD48Qjhx6BAgBEAI&url=https%3A%2F%2Ftsukuba.repo.nii.ac.jp%2F%3Faction%3Drepository_action_common_download%26item_id%3D19498%26item_no%3D1%26att ribute_id%3D17%26file_no%3D2&psig= AOvVaw2nhLzD2Ll3IvkmTSCE1mRH&ust=1549113196064248

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CONCLUSIONS

This paper provides a brief overview of different production methods to create bioactive porous scaffolds supplemented by advanced manufacturing technologies. Each method contains from the basic principle of functioning supported by visualization and comparation of advantages and disadvantages.

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