Advanced Materials Research *Online: 2011-09-02*
ISSN: 1662-8985, Vols. 328-330, pp 658-661
doi:10.4028/www.scientific.net/AMR.328-330.658

The Use of Rapid Prototyping to Fabricate Liver Tissue Engineering Scaffold

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Keywords: Tissue engineering, Rapid prototyping, PDMS mould, Scaffolds, Biomaterial

Abstract. In this papers, the authors described a rapid prototyping method to produce vascularized tissue such liver scaffold for tissue engineering applications. A scaffold with interconnected channel was designed using CAD environment. The data were transferred to a Polyjet 3D Printing machine (Eden 250, Object, Israel) to generate the models. Based on the 3D Printing model, a PDMS (polydimethyl-silicone) mould was created which can be used to cast the biodegradable poly (L-lactic-co-glycolic acid) (PLGA)material. The advantages and limitations of Rapid Prototyping (RP) techniques as well as the future direction of RP development in tissue engineering scaffold fabrication were reviewed.

Introduction

Currently, the only effective and permanent treatment to restore lost tissue function is transplantation. This has led to an increase in the demand for organs suitable for transplantation. At present, the number of people awaiting transplantation greatly exceeds the number of organs available. Tissue engineering proves to be a temporary treatment for patients suffering from hepatic failure [1].

Tissue engineering is the process of creating functional 3D tissues using biological cells, and biomaterials to retore, maintain physiological functions lost in diseased or damaged tissue. A pre-fabricated scaffold can either act as a supportive prosthetic material to regenerate tissue in vivo, or seeded with cells and cultured in vitro to form tissue before implantation[2–4]. For example, cells are seeded onto a three–dimensional (3D) scaffold, a tissue is cultivated in vitro, and finally the construct is implanted into the body as a prosthesis[5].

During the early years of tissue scaffold research, there was limited capability in being able to control the scaffold architecture due to the lack of automation and computer integrated fabrication. Initially, chemical based methods such as fibre bonding, solvent casting, melt moulding, Gas foaming, emulsion freeze drying, Solution Casting, melt molding, membrane lamination, thermally induced phase separation, Freeze drying[6-26], were used to fabricate scaffolds that resulted in a random pore generation and distribution. Limited architectural control was achieved by adjusting the chemical fabrication parameters[27]. None of these conventional techniques has allowed researchers to build scaffolds with a completely interconnected pore network with large interconnection channels, a highly regular and reproducible scaffold morphology[28].

The imperfection of the conventional techniques has encouraged the use of a rapid prototyping techniques, such as 3D printing, multi-phase jet solidication, and fused deposition modeling (FDM) in the scaffold design and fabrication stages of tissue engineering[28-31]. RP techniques are computerized fabrication techniques that can produce highly complex three-dimensional physical objects layer-by-layer using data generated by computer aided design (CAD) systems or computer-based medical imaging modalities. This technique allows the production of scaffolds that are customized in size and shape according to specific requirements which are highly reproducible. It can improve current scaffold design by controlling scaffold parameters such as pore size, porosity and pore distribution.

Biodegradable porous scaffolds can be fabricated directly by a melt–dissolution deposition process using fused deposition modeling (FDM)[28] or 3-D fiber-deposition[32], or by a particle bonding technique such as 3-D printing (3DP)[33, 34]. Scaffolds can also be produced indirectly by casting in a mold and employing techniques such as melt deposition, droplet deposition, and photo-polymerization [35].

In this paper, the author describe the fabrication techniques of scaffolds using RP technique, and review the advantages and limitations of current RP techniques as well as the future direction of RP development in tissue engineering scaffold fabrication.

Material and Method

An indirect fabrication process was used, in which the PDMS mould was obtained from RP model. A scaffold with interconnected micro capillary network was designed using commercial CAD software (Unigraphics) as shown in fig.1a. The STL file from the virtual CAD design were transferred to a 3D printer (Eden 250, Object, Israel) to generate the resin scaffold model (fig.1b). Objet machines create parts layer by layer combining inkjet technology with photo-polymerisation (UV curing) process. The head printer moves back and forth along the X-axis, similar to a line printer, depositing a single super-thin layers of photopolymer onto the build tray. Immediately after building each layer, UV bulbs alongside the jetting bridge emit UV light, immediately curing and hardening each layer. The building tray moves down and the jet heads continue building, layer by layer, until the model is completed. When the build is fnished, a WaterJet easily removes the support material, leaving a smooth surface and the part is removed from building tray for post-processing operations.

The PDMS molds were made by mixing a PDMS prepolymer and a curing agent at 10:1 weight ratio. The PDMS mixture is degased under vacuum until no bubbles appear (20~30 min). Once almost all the bubbles have cleared from the mixture, the mixture is pour on the rapid prototyping resin pattern. The PDMS is Baked in the oven at 60^{o}C for approximately 40 minutes, and freezed for a few minutes. This will shrink the PDMS slightly and will help peeling the PDMS replica off from the resin pattern (fig.1c).

Biodegradable poly (L-lactic-co-glycolic acid) (PLGA) was dissolved in dioxane to form a 3wt% polymer solution. The polymer solution were cast into PDMS moulds and freeze-dried at −50◦C for 12 hours to completely remove the solvent.

In this method, the PLGA solution was deposited on the PDMS mold and placed under vacuum for 2min. During this time the polymer filled the microchannels present in the mold and displaced any air present. Once the polymer had filled the mold, excess PLGA was removed by dragging the edge of a glass slide across the top of the mold. The filled mold was baked for 30min at 60^{0}C. When cooled, the PLGA pattern was easily. The Multi-layer of 2D scaffolds are stacked on top of each other to create the 3D tissue engineered scaffold (fig1.d)

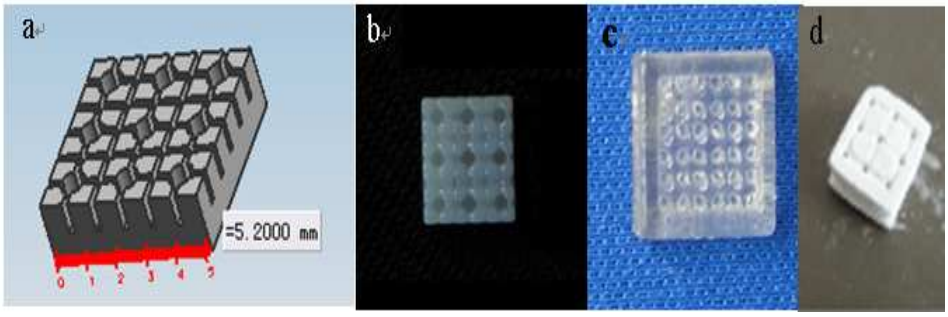

Figure 1 a) Scaffold CAD model; b) RP model; c) PDMS mould; d) PLGA scaffold

Discussion

Several methods have been developed for processing biodegradable polymers to create highly porous scaffolds. The conventional methods include particle leaching, gas (CO2) foaming, freeze-drying, thermal induced phase separation (TIPS), liquid/liquid phase separation in combination with freeze

extraction, electrospinning, and particle sintering. Also combinations of these techniques have been described [6-26]. All this fabrication techniques for tissue engineering scaffold have shown limited reproducibility and low control of the micro environment needed to sufficiently sustain nutrient concentrations.

The conventional scaffold fabrication techniques are incapable of precisely controlling pore size, pore geometry, pore interconnectivity, spatial distribution of pores, and construction of internal channels within the scaffold.

Rapid Prototyping (RP) technique can overcome the shortcomings of conventional techniques by producing scaffolds with customized external shape and predefined internal morphology. This paper presents a rapid prototyping technique combine with PDMS mold fabrication to create 2D interconnected porous scaffolds. Multi-layer of 2D scaffolds must be stacked on top of each other to create the 3D tissue engineered scaffold. Compared to the existing 3D manufacturing approaches, this technique has a "maskless" nature that significantly simplifies the fabrication process and reduces the design-to-fabrication turnaround time.

The RP technique enabled solid free form fabrication directly from a computer-aided design (CAD) model, and can manufacture in One-step a complex 3D scaffold structure with desired porosity and inter-connectivity without using an additional mould. RP can create complex structures with functional components that are difficult, if not impossible to create with conventional tissue scaffold fabrication techniques. This distinct advantage makes RP a technique with excellent potential for fabricating scaffold with controlled hierarchical structures for use in tissue engineering.

One of the major drawbacks of RP is that only a selected range of materials can be processed directly. however, most materials used in the commercialized RP systems are so far neither biocompatible nor biodegradable and are not suitable for direct use in the fabrication of scaffolds. The limitation of RP technique to directly fabricate biocompatible and biodegradable scaffold restrict their scope of applications in tissue engineering. To overcome these limitations, it is desirable to use indirect RP methods in which RP master pattern is used to create the mould to cast a wide range of biomaterials. The indirect RP fabrication method extend the range of materials that can be used in tissue engineering including biocompatible and biodegradable polymers, either biosynthetic or naturally derived, can be processed to satisfy specific condition of scaffolding.

Conclusion

Although the RP technique has its advantages, the manufacturing processes limit the number of polymeric materials that can be used for direct RP fabrication. In particular, in the field of biomedical applications molding techniques have to be used to obtain biocompatible and/or biodegradable scaffold. Direct printing of biopolymers and biocomposites material can overcome the limitation RP in scaffold manufacturing. The Direct printing methods enable the fabrication of customized tissue engineering scaffolds with complex features both inside and outside the scaffold, so future development in the RP field should be based on the development of photopolymerizable, biocompatible, and biodegradable liquid polymer, which can fulfill the requirements of tissue engineering.

Acknowledgements

The authors acknowledge the support provided by Dongguan Science and Technology Project (2007108101007) in this study.

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10.4028/www.scientific.net/AMR.328-330

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