Design and development of Three-dimensional scaffolds for biomedical application by rapid prototyping

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ABSTRACT

Tissue engineering is a concept whereby cells are taken from a patient, their number expanded and seeded on a scaffold. The appropriate stimuli (chemical, biological, mechanical and electrical) are applied and over a relatively short time new tissue is formed. This new tissue is implanted to help restore function in the patient. The scaffold is a three-dimensional substrate and it serves as a template for tissue regeneration. The ideal scaffolds should have an appropriate surface chemistry and microstructures to facilitate cellular attachment, proliferation and differentiation. In addition, the scaffolds should possess adequatemechanical strength and biodegradation rate without any undesirable by-products. Research in this area has been intense over the past 10 years or so on biopolymer formulation andon scaffold fabrication. Rapid prototyping methods embrace a family of latest technological methods that are developed to speed up manufacturing especially for biomedical applications. The sole needed input for production of porous biomedical parts. Its biomedical application production characteristics and the geometric part complexity that can be achieved due to these novel methods have extended the applicability/research areas of these methods beyond prototyping. Local pore formation in part that occurs as a result of the discrete manufacturing nature of rapid prototyping methods can be viewed as an opportunity for material development. In this paper, the manufacturing-internal (porous) structure-mechanical property relations of porous materials are being investigated. These porous parts are produced via Selective Laser Sintering (SLS), fuse deposition manufacturing (FDM) which is a rapid prototyping method. The elastic modulus, tensile strength, rupture strength and Poisson's ratio of uniform porous specimens with known porosities may be determined through standardized mechanical tests for various materials. The mechanical property variation profiles in graded materials are determined using the mechanical properties of uniform parts. The mechanical behaviour of uniform and graded materials under applied loads are modelled using finite element method and simulation results are compared to the results of mechanical tests performed on graded material .In addition, feasibility of producing resin filled composite parts from this uniform and graded porous parts are sought. Porous parts (both uniformly and graded) that areInfiltrated with epoxy resins have been characterized mechanically and the results have been compared with the infiltrated porous parts.

KEYWORDS: *Scaffold; tissue engineering; Rapid Prototyping*

INTRODUCTION

The basic requirements for biomaterials used for scaffoldsare their biocompatibility and appropriate surface properties to favour cellular attachment, proliferation and differentiation. An ideal scaffold should have thefollowing characteristics: (1) an extensive net-work of interconnecting pores so that cellscan migrate, multiply and attach deep withinthe scaffolds; (2) channels through whichoxygen and nutrients are provided to cellsdeep inside the scaffold, and the waste products can be easilycarried away; (3) biocompatibility with a high affinity for cells toattach and proliferate; (4) right shape, however complex asdesired by the surgeon; and (5) appropriate mechanical strength and biodegradation profile. Tissue engineeringwould greatly benefit from such scaffolds. Synthetic biomaterials (bio ceramics and biopolymers) are theprimary materials use for scaffold fabrication in various tissueengineering applications.Scaffold materials can be either natural or synthetic. However,synthetic biopolymers offer an advantage over naturalmaterials in that they can be tailored to give a wide rangeof properties and which are more predictable. In particular, many investigations have concentrated on synthetic biodegradablepolymers that are already approved by the foodand drug administration (FDA). The most common biodegradablepolymers being used or studied include polylacticacid (PLA), polyglycolic acid (PGA), polyanhydrides, polyfumarates (PF), polyorthoesters, polycaprolactones (PCL)and polycarbontes (Vail et al., 1999). PLA, PGA and their co-polymer, poly(DL-lactic acid-co-glycolicacid) (PLGA) are widely used in the fabrication of scaffolds. Scaffolds fabricated by electrospinning PLGAnanofibres on to the surfaces of a knitted PLGA demonstrateda good mechanical strength and internal hierarchical.

OBJECTIVE

These architectures may then be used *in vitro* and *in vivo* to evaluate the effect of design on selection by biological systems for porous structure. The following goals are proposed:

SPECIFIC AIM #1

To determine the effect of material organization (strut length, strut diameter, connectivity, material volume) on the architectural properties (structural stiffness, strength, structural modulus, ultimate stress) of solids based on regular, porous architectures.

HYPOTHESES

- A deliberate arrangement of architecture can be used to density as the dominant controlling factor of strength
- For a constant density, tailored mechanical properties can be obtained through reorganization of architecture.
- Rapid Prototyped models can be used as accurate representations of modelled cellular solids and can replicate finite element modelling results of the structural and material properties of the porous architectures.

SPECIFIC AIM #2

To determine the effects of void phase organization (pore size, surface to volume ratio, pore architecture, total void volume) on the architectural properties (structural stiffness, strength, structural modulus, ultimate stress) and flow properties of solids based on particulate leached systems with defined pore architectures.

HYPOTHESES

- A derive relationship exists between surface to volume ratio of a void architecture and its resulting permeability.
- A derive relationship exists between surface to volume ratio of void architecture on the structural properties of a random porous architecture.
- A derive relationship exists between porosity and permeability for defined architectural parameters and porosity values.

SPECIFIC AIM #3

To apply the derived relationships in Specific Aim 1 and 2 through material rearrangement towards the design of porous structure employing the steps of Computer Aided Tissue Engineering.

ENGINEERING OBJECTIVES

- Utilize architectures characterized in Specific Aim 1 in the design of porous structure scaffolds for a load-bearing system to determine the dominant design principles governing the success of such an implant.
- Utilize derived relationships from Specific Aim 2 in the design of implants which will require fluid transport and determine the dominant design principles governing the success of these implants.
- Determination of the dominant design principles governing tissue invasion into porous scaffolds for the architectures examined and the important characteristics of those scaffolds.

LITERATURE REVIEW

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Tiebing Chen, Yuwen Zhang (1) in their worknumerical results are validated by experimental results and a detailed parametric study is performedabout Laser sintering of a metal powder mixture that contains two kinds of metal powders with significantly different melting points under a moving Gaussian laser beam is investigated numerically. The continuous-wave laser-induced melting accompanied by shrinkage and resolidification of the metal powder layer are modelled using a temperature-transforming model. The liquid flow of the melted low-melting-point metal driven by capillary and gravity forces is also included in the physical model. Craig Schroeder et al (2) in their work shows that porous structure can be described as a heterogeneous structure consisting of 3D extra-cellular matrices (made from biodegradable material) and seeded donor cells and/or growth factors. The design and fabrication of such heterogeneous structures requires new techniques for solid models to represent 3D heterogeneous objects with complex material properties. There work representation of model density and porosity based on stochastic geometry. Porosity is a new problem for bio-medical CAD critical for modelling replacement bone tissues. A.J.H. FRIJNS AND E.F. KAASSCHIETER (3) in there paper describes about NUMERICAL MODELLING OF CARTILAGE AS A DEFORMABLE POROUS MEDIUM and about the biphasic mixture theory is investigated. In this theory, the mechanical behaviour is described by mass and momentum balances and constitutive equations. As a result a system of coupled, time-dependent, Non-linear equations is obtained. These equations are discretized in space by a mixed-hybrid finite element method and in time by a suitable implicit time integrator. A. Jafari, S.H. Seyedein& M. Haghpanahi (4) describes about Modelling of heat transfer and solidification of droplet in micro casting SDM Process In the study attempts were made to numerically model the heat transfer and phase change within the droplet/substrate, making a better understanding of process performance. Thus, making a brief literature review, a 2-D transient heat transfer Finite Element Analysis was carried out by the use of ANSYS multiphysics, in which solidification is handled using apparent capacity method. Verification was done by available experimental data in the open literature to ensure model predictions. The model was run under various process parameters and obtained results presented in the form of temperature fields, solidification profiles, cooling curves and remelting history curves. It was concluded that 1) the process is not sensitive to convection/radiation effects from the surface. 2) The main parameter that can control the maximum remelting temperature is initial temperature of the droplet. The more drop temperature, the more remelting. This parameter also affects cooling rate during solidification. 3) Increasing substrate temperature showed a decreased cooling rate in solid, which can be used to reduce residual stresses, but it had a minor effect on the cooling rates during solidification. A. Simchi (5)In his work, the densification and microstructural evolution during direct laser sintering of metal powders were studied. The empirical sintering rate data was related to the energy input of the laser beam according to the first order kinetics equation to establish a simple sintering model. The equation calculates the densification of metal powders during direct laser sintering process as a function of operating parameters including laser power, scan rate, layer thickness and scan line spacing. It was found that when melting/solidification approach is the mechanism of sintering, the densification of metals powders (D) can be expressed as an exponential function of laser specific energy input (ψ) as $\ln(1-D) = -K\psi$. The coefficient K is designated as “densification coefficient”; a material dependent parameter that varies with chemical composition, powder particle size, and oxygen content of the powder material. C. Casavola, S.L. Campanelli, C. Pappalettere (6) in their work modeling has been done for the thermal energy supplied by a focused laser beam. In order to reach high density, metallic powder particles are fully molten by the laser beam. However, the laser melting process is difficult to control. The most important drawback is the generation of highly variable residual thermal stresses during the process. study the effect of positioning powders in the platform and part thickness on residual stresses of SLM-fabricated

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components. S.J. Hollister et al. (7) in hispaper describe an image-based homogenization approach that can design porous microstructure, scaffold material and regenerate tissue microstructure to meet conflicting design requirements. In addition, constraints to ensure adequate cell/gene delivery can be introduced using a minimum porosity threshold. Homogenization theory was used to compute relationships between scaffold microstructure and effective stiffness. The functional relationships were used in the MATLAB optimization toolbox to compute optimal pore dimensions and scaffold material such that the scaffold and regenerate tissue effective stiffness matched that of native bone stiffness. The scaffold design was converted into .STL format for solid free-form fabrication. Damien P. Byrne et al(8) perform experimental studies to determine the optimal properties for a scaffold for use in bone tissue engineering .optimal parameters, e.g. scaffold porosity, Young's modulus, and dissolution rate. In their work a fully three-dimensional approach is used for computer simulation of tissue differentiation and bone regeneration in a regular scaffold as a function of porosity, Young's modulus, and dissolution rate and this is done under both low and high loading conditions. The mechanoregulation algorithm employed determines tissue differentiation both in terms of the prevailing biophysical stimulus and number of precursor cells, where cell number is computed based on a three-dimensional random-walk approach. The simulations predict that all three design variables have a critical effect on the amount of bone regenerated, but not in an intuitive way: in a low load environment, a higher porosity and higher stiffness but a medium dissolution rate gives the greatest amount of bone. F. Niebling, A. Otto, M. Geiger (9) presented macroscopic FE-model allows to analyze the thermal fields and the resulting stress built up during Selective Laser Sintering. Process and material parameters are focused on Direct Metal Laser Sintering (DMLS). The FE-model is introduced and the assumptions for the model are given. Three different geometric models are discussed. The 3Dmodel shows the sintering of a single line, whereas 2D-models are used for longitudinal and crosscuts of the sintering process. Aim of the investigation is a more basic knowledge about the process, which will lead to a stabilization and optimization of the process. Pei-Xue Jiang et. Al.(10) has studied Forced convection heat transfer of water and air in sintered porous plate channels was investigated experimentally. The effects of fluid velocity, particle diameter, type of porous media (sintered or non-sintered), and fluid properties on the convection heat transfer and heat transfer enhancement were investigated. The results showed that the convection heat transfer in the sintered porous plate channel was more intense than in the non-sintered porous plate channel due to the reduced thermal contact resistance and the reduced porosity near the wall in the sintered material, especially for convection heat transfer of air. For the tested conditions, the local heat transfer coefficients in the sintered porous plate channels were increased up to 15 times for water and 30 times for air. The heat transfer enhancement due to the sintered porous media with air intensified sharply with increasing flow rate. However, the influence of particle diameter on the convection heat transfer in the sintered porous media was not great. The effective thermal conductivity of the sintered porous media was found to be much higher than for non-sintered porous media due to the improved thermal contact caused by the sintering process. PallaviLal, Wei Sun (11)A computer modeling approach for constructing a three-dimensional microsphere-packed bone graft structure is presented. The modeling approach consists of both geometric and CAD-based computer modeling. The geometric model uses two extreme microsphere packing models (minimum-density packing and maximum-density packing) and a statistical packing model to determine the number of microspheres packed in a synthesized bone graft. The pore size of the packed internal porous structure is predicted, and a parametric study of the effect of microsphere diameter on the number of microspheres and pore size is conducted. Based on the results obtained from the geometric model, a CAD modeling approach for designing randomly microsphere-packed three-dimensional bone grafts was developed. The hierarchy of the CAD model and the steps for constructing a bone graft model are described, and application of the CAD-based bone graft model in internal structural examination, visualization, prediction

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and comparison with in vitro bone ingrowth is presented. Jiri Brozovsky ,PankajPankaj (12)modeling has been for Trabecular bone comprises of a complex arrangement of plates and struts at micro level that make it anisotropic. Osteoporosity is a common problem in old age which makes the bone weak due to increased porosity. Considerable two dimensional data in the form of images is available on the porous structure of the bone, however this needs to be related to the macro-level anisotropic properties. This preliminary study aims to examine whether topological anisotropy can be related to elastic anisotropy. Simple three dimensional structured meshes comprising of elements with different material properties are used to simulate the porous structure. Homogenised elastic properties are evaluated and these are compared with a two dimensional topology anisotropy indicators. For the simple problems considered it appears that topological anisotropy cannot be directly linked to elastic anisotropy. Ki-Hoon Shin et. Al. (13) Introduces an integrated design and fabrication system for heterogeneous objects, especially Functionally Graded Materials (FGMs). We first describe the variant design paradigm and a constructive representation scheme for heterogeneous objects. A discretization-based process planning method, which converts continuous material variation into stepwise variation, is then described. Next, Direct Metal Deposition (DMD), a laser based LM method that can take advantage of the proposed process planning method, is described in detail.

METHODOLOGY

There are two main approaches to this problem: those using Rapid Prototyping (RP) techniques.This approach will require diverse range of skills to be successful and so a more conventional engineering approach was followed. This led to the initial approach of examining the readily available RP machines for their suitability to manufacture a novel porous structure.

EXPERIMENTAL WORK USING RAPID PROTOTYPING METHODS

The process of mimicking the native structure of porous structure has been simplified greatly by recent advances in three dimensional (3D) imaging. The STL file is then converted into the file format for the relevant RP machine using Magics (Materialise) and the 3D model was then constructed. Initial experimentation may intended to determinewhich RP processes were capable of direct replication of the bone sample and thus besuitable for further research. A number of RP techniques were attempted including stereolithography (SLA), three dimensional printing (3DP), selective laser sintering (SLS) and selective laser melting (SLM).This research takes a fluid dynamics approach to improve the print quality or *Print Resolution* of the RP. This will be achieved through analyzing the extruder subassembly (Figure 1). The print material is biocompatible material, as it is the currently preferred FDM thermo polymer for the RP. The cylindrical rod section near the end of the extruder is called the liquefier, which is connected to heating elements that melt the polymer prior to extrusion. The brass liquefier is actually the central area of focus since its internal geometry serves as the flow channel for the melt. It is a critical parameter that constitutes the performance of the RP, and is governed directly by the following three variables:

TEMPERATURE OF MELT FLOW

It is important not to overheat the bio material melt to an excessively high temperature because the fluidity will increase, which in turn will cause excessive filament elongation and inconsistent filament diameter upon exit. This degrades the surface finish of the printed part.

PRESSURE DROP (ΔP)

The pressure drop directly affects the amount of force required to push the filament through. Controlling the amount of force applied to the filament will prevent any buildup of material melt within the liquefier which can cause a feedback effect, further increasing the pressure drop. Controlling the force can keep the exit extruded melt as a consistent stream with non-varying thicknesses. Any changes in layer thickness can contribute to overall part defects.

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NOZZLE EXIT DIAMETER (d)

In order to maintain a fine filament diameter, the nozzle exit diameter needs to be a small as possible.

THE LASER EXPOSURE PARAMETERS

The parameters of contour exposure are also the parameters of hatchingexposure, but at different values. However hatching exposure has some additionalparameters. Below, all the parameters relevant to laser exposure are discussed.

LASER POWER

In the process software, the laser power is input as a percentage of themaximum laser source power. The input value depends on the type of the materialand the layer thickness, with which the part is built. The corresponding value inW can be determined on the basis of the laser power curve. The laser power curveis a characteristic of the machine, recorded by the service technician during theinstallation of the machine, which is given in Figure .The resulting laser power is dependent on the power setting of the laser source.

LASER SCANNING SPEED

The laser scanning speed is also a process parameter that can be adjusted. In Standard applications, the recommended laser scanning speed during contouring is 700 mm/s, whereas for the hatching this standard value is 4500 mm/s.

EFFECTIVE DIAMETER OF THE LASER BEAM

In SLS systems, the produced laser beam is focused down to a certain beam diameter where it contacts the powder surface. This diameter is 0.4 mm. However, the diameter of the region where the particles are sintered (effective sintering range) is larger than the physical beam diameter. This range is denoted as the **effective diameter of the laser beam**, **De,** which is proportional to the laser power and inversely proportional to the scanning speed of the laser.

BEAM OFFSET (DISPLACEMENT)

During the scanning a layer, the laser beam centre does not move all the way to the edge of the layer, but stops before it. The distance between the centre of the laser beam and the edge of the layer is called the **beam offset**. In the SLS system, the beam offset can be entered separately for contouring and hatching. In order for the powder at the edge of the boundary to be completely exposed to the laser beam, for the contouring the value of the beam offset, (**dc**), should be set to the half of the **Dec**. If the beam offset for contour is less or greater than half the effective beam diameter, then there is the possibility of sintering powder outside the layer edge or not sintering part of the intended edge region, which would disrupt the dimensional accuracy of the part.

THREE-DIMENSIONAL MODELING OF RP METAL COMPONENT

Numerical solution of a three dimensional quasi-steady-state melting and resolidification problem in a two-component metal powder subjected to a movingGaussian laser beam will be considered. The effects ofthe powder-layer thickness, moving heat source intensity, and scanning velocity on the sintering depth and the formation of theliquid pool in a three-dimensional metal powder layer investigated.

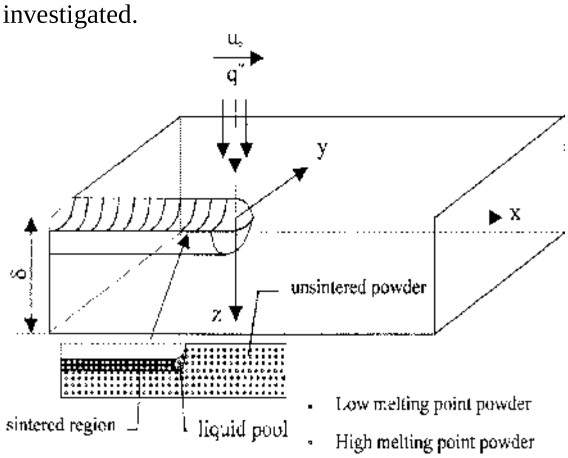

Fig.1 Physical model

The physical model of the problem under consideration is shown in Fig. 1. A circular

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Gaussian laser beam moves at a constantrelative velocity $u_b$over the surface of a two-component metal powder layer with finite thickness. A moving coordinatesystem of which the origin is fixed at the center of the laser beam is employed. The initial temperature of the powder layer is below the melting point of the low-melting-point powder *Tm*. As the laser beam interacts with the powders, the temperature of thepowders is brought up to *Tm*, then melting occurs. A liquid pool is formed under the laser beam, and the melted metal infiltrates theunsintered powders driven by capillary and gravitational forces. Adensified heat affected zone (HAZ) is formed after the laser beammoves away and the liquid pool resolidifies. Significant densitychange due to the shrinkage accompanying melting is also takeninto account.The problem is formulated using a temperature-transformingmodel, which converts the enthalpy-based energy equation into a nonlinear equation with a single dependent variable—temperatureThe dimensionless energy equation in the moving coordinate system is:

$$\nabla\varphi_l V_l C_l T - U_b \frac{\partial}{\partial X}[(\varphi_H + \varphi_s C_l)T] + W_s \frac{\partial}{\partial Z}[(\varphi_H + \varphi_s C_l)T] = \nabla.(K\nabla T) - \left\{\frac{\partial}{\partial \tau}[(\varphi_l + \varphi_s)S] + \square.(\varphi_l V_l S) + W_s \frac{\partial}{\partial Z}[(\varphi_s)S] - u_b \frac{\partial}{\partial X}[\varphi_l + \varphi_s]\right. \quad (1)$$

The dimensionless shrinkage velocity *Ws*, heat capacity *C*, source term *S*, and thermal conductivity *K*, can be given by:

$$W_s = \left\{\frac{\varphi_{si}}{1-\varepsilon}\left(\frac{\partial \eta_{st}}{\partial \tau} - u_b \frac{\partial \eta_{st}}{\partial X}\right) Z \leq \eta_{st} \leq \Delta \quad OZ > \eta_{st}\right. \quad (2)$$

$$C = (\varphi_s + \varphi_l) C_L + \varphi_H \quad (3)$$

MATHEMATICAL MODELLING OF THE GOVERNING EQUATIONS OUTLINE OF THE COMPUTATIONAL DOMAIN

The computational domain of the pile up problem is shown in Figure.2. Since the problemconsidered is assumed axisymmetric only half of the cross-section has to be taken intoaccount. The entire domain is divided into four regions. For the solution of the fluidmechanics equations, only the domain of the impacting droplet as well as the boundary of the presolidifieddroplets are considered. The solution of the energy equation covers all four regions in Figure 1. The heat transfer solution method contains special features necessitated by the two indicated interfaces. Governing Equations for the Fluid Flow The pile up is modeled as an unsteady, viscous, incompressible flow with constant density and constant dynamic viscosity. Thus, the flow is governed by the following Navier-Stokes equations, written in vector notation, and in Lagrangian form.

Continuity equation: $\rho\nabla.(\vec{u}) = 0$

Momentum equation:

$$\rho\partial_t u_i + \square p - \mu\Delta\vec{i} - \rho\vec{g} = 0, i \in \{r, z, \theta\}$$

Experimental Parameters used in the experiments

Sample No.	Peak Power (W) ᴬ	Pulse length (ms)	Period (ms)	Duty Cycle ᴮ	Powder mass flow rate (g/s)
1	1500	20	50	0.4	0.358
2	857	35	50	0.7	0.358
3	600	-	-	1	0.358
4	1500	20	50	0.4	0.586
5	857	35	50	0.7	0.586
6	600	-	-	0.1	0.586
7	1500	20	50	0.4	0.674
8	857	35	50	0.7	0.674
9	600	-	-	1	0.674

[A] Mean power = 600 *W* in all cases

[B] Duty cycle = pulse length / period

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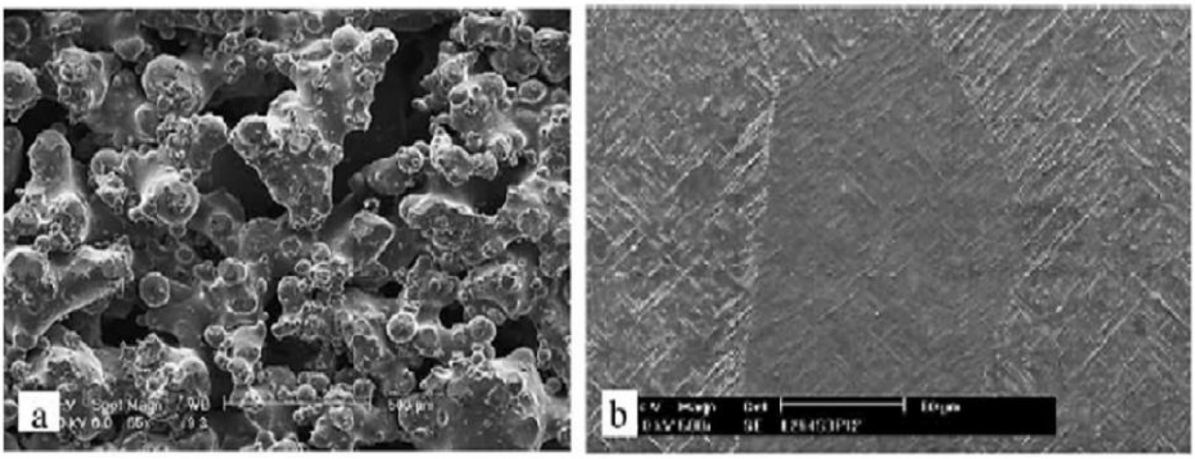

Fig. 2 Porous and fully dense structure obtained at 180 and 264 W

CONCLUSION

Many techniques exist to process these biomaterials intotissue engineering scaffolds. The utility of each techniquefor engineering of specific tissues will ultimately depend onseveral design criteria including mechanical stability, chemicalcomposition, degradation, cellular organization and nutrientrequirements. The hierarchical structures of the scaffoldshave important influence on the cellular behaviour of cells,and on direct the macroscopic process of tissue formation,therefore it is vital to manufacture scaffold with hierarchical structure ranging from nanometre to millimetre scales. However, current processing techniques, such as particulateleaching, gas forming, fibre binding and phase separation and so on, cannot precisely control the architecture of thescaffold. SFF techniques have the potential to fabricate scaffoldwith controlled structure, however scaffold design theoryhas not yet advanced to design scaffolds with hierarchicalstructure, added by the limitation of machine's resolution[direct SFF techniques cannot control fine structure of scaffold (scales less than 100 mm)]. Among these scaffold fabricationtechniques, the indirect SFF technique (Sacholset al., 2003a) has the ability to control the architecture ofcollagen scaffold and to integrate cell/growth factors withthe scaffold fabrication process.

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