

**Research Article**

## **BIOENGINEERED SCAFFOLDS FOR USE IN MAXILLOFACIAL DEFECTS**

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### **ABSTRACT**

Patients present with large defects of the face and the oral cavity following maxillofacial surgeries. Conventional treatment includes the use of artificial appliances. Surgical closure of these defects is also advocated routinely. Regrowth of the tissues within the defects is possible with the advancement of tissue engineering methods. The use of scaffolds has emerged as a promising alternative approach in the treatment of these defects. This paper discusses the different materials and techniques used in tissue engineering for scaffold fabrication.

**Key Words:** *Maxillofacial Defects, Scaffold Tissue Engineering*

### **INTRODUCTION**

Patients having undergone maxillofacial surgeries tend to present with large defects involving parts of the mouth and the face (Figure 1). An interdisciplinary treatment approach of surgical reconstruction and prosthetic rehabilitation of these defects has been advocated.



**Figure 1: Patient presenting with a Maxillofacial Defect**

Aramany (1978, 2001) and McKinstry (1985) have suggested conventional methods of treating such defects by using prosthetic (artificial devices) appliances. However these prosthetic treatment options are not able to replace all the functions of a damaged or lost organ or tissue. Modern approaches to restore such defects are aimed at regenerating the lost tissue rather than trying to replace it by artificial means.

Grafting these defects with various biocompatible materials has been carried out. Usually grafting is carried out by the hard tissues obtained from the patient itself. These grafts are referred to as autogenous grafts. However the inherent disadvantages of the autografts include the need for surgeries to harvest the graft and the chance of the donor site morbidity as reported by Raghoobar (2001). Other graft types like allogenic grafts (grafts from the same species), xenografts (grafts from animal sources) and alloplasts (powdered ceramic grafts) have documented disadvantages as reported by Eid K (2001).

Current trends of re-growing tissue in these defects revolve around using scaffold matrices to promote bone growth using tissue engineering techniques. These procedures involve the use of cells (with growth

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potential), certain signalling molecules and drugs. These agents need to be fabricated and delivered either sequentially or together onto the scaffold. Langer (1993) has suggested that these three methods should be adopted to create new tissue.

A 3-dimensional fill of the defects can be achieved by the use of scaffolds. Scaffolds are matrices which are essentially porous in nature in which the required cells can be seeded. The ideal requirements of these scaffold as stated by Sachlos (2003) are that they (1) should be incorporated with pores of appropriate size to favour tissue integration and vascularisation, (2) be made from material with controlled biodegradability or resorbability so that the scaffold forms the desired tissue, (3) possess the chemical composition to favour cellular attachment and proliferation and (4) be biocompatible so that no adverse response is induced.

This paper will discuss the newer trends in scaffold fabrication with respect to the techniques and the materials used.

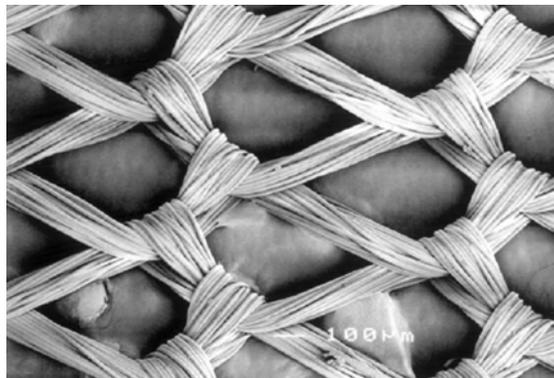
#### **The Microarchitecture of the Scaffold**

The success of a scaffold largely depends on its microstructure. This includes the pore size, pore distribution and the interconnectivity between the pores. The interconnectivity of the pores to form a network is for vascularization, the growth of the desired cells and for the transport of the nutrients and the metabolic waste products. The interconnecting network of these pores increases the surface area to the volume ratio of the scaffold. The pore size plays a substantial part in vascularization of the scaffolds. Chiu (2011) studied the role of the size of the pores on vascularization in PEG hydrogels. They reported that pores of 25-50  $\mu\text{m}$  in size provided with cell and vessel perfusion only onto the external surface. Larger pores (50-100 and 100-150  $\mu\text{m}$ ) permitted mature vascularized tissue formation throughout the entire material volume. Kovacina (2011) has described various modifications in the technique parameters to increase the sizes of the pores. Sultana (2011) obtained highly organized three-dimensional porous scaffolds by modification of fabrication parameters.

#### **Material Science**

According to Holzwarth (2011), apart from the high porosity, the other requirements that a scaffold must present with are mechanical integrity and biodegradability. These properties are greatly dependant on the choice of the scaffold material. Various materials have been used for the fabrication of scaffolds. A wide range of polymers have been used for the use of bone tissue engineering. These polymers can be classified as natural and synthetic polymers.

The synthetic polymers include polyesters, polyanhydride, polyorthoester and polycaprolactone (PCL). The more commonly used synthetic polymers are the polyesters such as poly (glycolic acid) (PGA), poly (lactic acid) (PLA), and their copolymer of poly [lactic-co-(glycolic acid)] (PLGA). (Figure 2) These polymers are easier to fabricate and modify. However they lack the required bioactivity as documented by Holzwarth (2011).

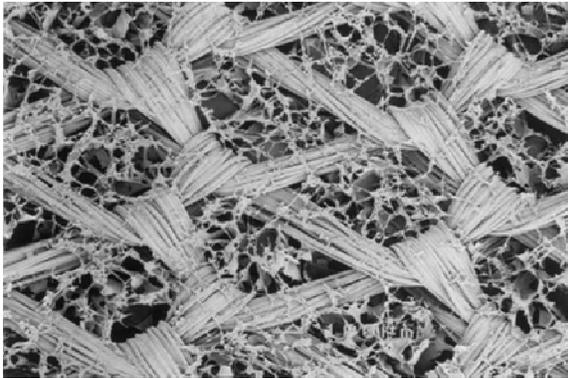


**Figure 2: PLA Scaffold**

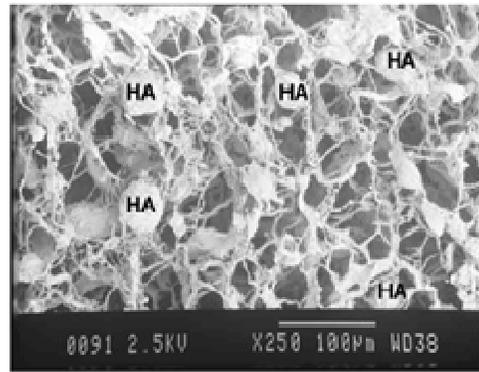
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This is however not an issue with the use of natural polymers. The natural polymers used for tissue engineering are collagen, silk, gelatin and chitosan amongst the other materials. They have promoted cell adhesion and proliferation as an inherent property. Kohara and co-workers (2011) induced bone formation when they used gelatin sponges with bone morphogenetic proteins. They also concluded that the use of gelatin scaffold incorporating multiple osteoinductive agents could be effective in inducing bone formation.

However since both the polymers have certain advantages, a combination of them can be used to create composite scaffolds with significantly better biological and mechanical properties. Yang (2009) combined PCL with chitosan to create bioactive nanofibers. This novel hybrid scaffold takes advantage of the physical properties of the synthetic polymer and the bioactivity of the natural polymer while minimizing the disadvantages of both. A collagen and PLA hybrid scaffold with parallel collagen fibres embedded within a PLA matrix has been fabricated by Dunn and co-workers 1997(Figure 3).Scaffolds with mineral content have been explored for better bone tissue engineering. Hydroxyapatite (HA) has been frequently used for the same (Figure 4).



**Figure 3: PLA + Collagen Scaffold**



**Figure 4: Collagen Scaffold + Hydroxyapatite (HA)**

Calcium phosphate ceramics, calcium phosphate cement and Bioglass are amongst the other mineralized materials that have been used. They not only improve the skeletal integrity of the scaffold but also make the scaffold osteoconductive. The calcium phosphate cements can be injectable and hence they have better delivery to the defect site. Lanao and co-workers (2011) studied the efficacy of these injectable calcium phosphate cements containing PLGA microparticles and documented excellent biocompatibility and osteoconductivity.

The minerals can be added to the polymer scaffolds. Marelli (2011) used the combination of dense nanofibrillar collagen and nano-sized bioactive glass to produce scaffolds for bone tissue engineering purposes. Wei (2004) created a scaffold of nano-hydroxyapatite in PLA (30:70) by the Thermally-induced phase separation (TIPS) technique. Seyedjafari and co-workers (2010) compared electrospun PLA scaffolds without hydroxyapatite and showed no calcium deposition and were surrounded by a granulomatous inflammatory response while scaffolds with hydroxyapatite showed significant mineralization with little inflammatory response.

### **Engineering Techniques Employed for Scaffold Fabrication**

The main techniques that are used for bone tissue engineering according to Holzwarth (2011) are Electrospinning and Phase separation. As discussed earlier, electrospun scaffolds of a combination of minerals and synthetic polymers have been fabricated. Boland (2001) readily electrospun Poly (glycolic acid) fibres ranging from about 0.15 to 1.5  $\mu\text{m}$  in diameter. These fine fibres were considered to be an attractive option of tissue engineering. However the challenge in maxillofacial rehabilitation is to create a scaffold that three-dimensionally fills in the defect with the desired tissue. It remains difficult to create

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clinically relevant three-dimensional constructs beyond a relatively two-dimensional mat. The problem posed by electrospinning is somewhat overcome by the process of phase separation. The polymer solutions used in tissue engineering are thermodynamically unstable at certain temperatures. The Thermally-Induced Phase Separation (TIPS) is a technique that uses this property of the polymers for fabrication of scaffolds.

The size and the shape of a maxillofacial defect can be diagnosed using advanced imaging procedures like Computed Tomography scan (CT scan) or a Cone Beam Computed Tomography scan (CBCT) and Magnetic Resonance Imaging (MRI). Using these images a Stereolithographic model of the defect can be fabricated. The shape of the scaffold as a whole can be hence controlled. Bone defects are never uniform in geometry so the ability to create a custom mold and scaffold for each patient allows for a smooth transition onto the operating table. The versatility of stereolithography has showed techniques for fabrication of porous scaffolds. Melchels and co-workers (2010) have showed how stereolithography fabrication methods can be used to accurately prepare tissue engineering scaffolds with designs that can be modelled according to various geometries.

However in spite of the actually macro geometry of the scaffolds, the key is to control the pore geometry. According to Park (2011), Solid Freeform Fabrication technique is capable of controlling the geometry of the pores. They fabricated computer aided hydrogel scaffolds using a solid freeform fabrication system (3-dimensional cell plotting). Solid freeform fabrication (SFF) uses layer-manufacturing strategies to create physical objects directly from computer-generated models. It can

improve current scaffold design by controlling scaffold parameters such as pore size, porosity and pore distribution, as well as incorporating an artificial vascular system, thereby increasing the mass transport of oxygen and nutrients into the interior of the scaffold and supporting cellular growth in that region.

With the constant improvement in technology and the advent of newer techniques various experiments have been conducted to create the most favourable scaffold. Diagnostic images obtained from CT/MRI and using them in solid freeform fabrication are the two most important technologies in computer aided tissue engineering. As mentioned before, a combination of both makes it possible to design and manufacture an arbitrarily-shaped complex human bone scaffold model for use in maxillofacial rehabilitation. By introducing a hybrid new method based on the distance field and Triply Periodic Minimal Surface (TPMS), Dong Yoo (2011) has reported that a variety of porous scaffolds can be fabricated.

### **CONCLUSION**

The engineering techniques for scaffold fabrication have seen a tremendous growth in the last few years. The exponential growth in tissue engineering towards regenerating lost human body parts has led to increase interest in development of newer techniques.

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