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# Low temperature additive manufacturing of three dimensional scaffolds for bone-tissue engineering applications: Processing related challenges and property assessment

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ABSTRACT

In the last two decades, additive manufacturing (AM) has made significant progress towards the fabrication of biomaterials and tissue engineering constructs. One direction of research is focused on the development of mechanically stable implants with patient-specific size/shape and another direction has been to fabricate tissue-engineered scaffolds with designed porous architecture to facilitate vascularization. Among AM techniques, three dimensional powder printing (3DPP) is suitable for fabrication of bone related prosthetic devices, while three dimensional plotting (3DPL) is based on extrusion of biopolymers to create artificial tissues. In the present review, we aim to develop a better understanding of the science and engineering aspects of these low temperature AM techniques (3DPP and 3DPL) in the context of the bone-tissue engineering applications. While recognizing multiple property requirements of a 3D scaffold, the central theme is to discuss the critical roles played by the binder and powder properties together with the interplay among processing parameters in the context of the physics of binder-material interaction for the fabrication of implants with predefined architecture having structural complexity. An effort also has been exerted to discuss the existing challenges to translate the design concepts and material/binder formulations to develop implantable scaffolds with a more emphasis on bioceramics and biopolymers. Summarizing, this review highlights the need to adopt intelligent processing approaches and targeted application-specific biocompatibility characterization, while fabricating mechanically stable and biologically functionalized 3D tissue equivalents.


**Contents**



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## 1. Introduction

Bone-tissue engineering is the application of biological, chemical, and engineering principles to repair the living tissues using biomaterials, cells, and growth factors, alone or in combination [1]. The strategies are often categorized into three groups: (1) direct injection of cells into the tissue of interest, (2) implantation of cell-scaffold constructs (3D tissue structure), and (3) scaffold-based delivery of drugs and/or signaling molecules such as growth factors, capable of stimulating cell migration, growth, and differentiation [2]. The clinical applications of bone tissue engineering offer the opportunities for treating traumatized or diseased skeletal tissues by deliberately manipulating cellular and biological processes [3]. The bone fractures and skeletal disorders caused by trauma or diseases such as tumors or osteoporosis are traditionally treated by the reconstruction of bone using temporary and/or permanent implants [4]. The materials and the mechanical properties of these implants are critical for the long term performance under physiological environment [5]. In case of large bone defects, so called critical size defects, bone is not able to regenerate even after mechanical support which results in a non-union of bone [6,7].

It is worthy to mention that, the human bone is characterized by a compressive strength of ~170–193 MPa and ~7–10 MPa for cortical and cancellous bone, respectively [8,9]. Therefore, a biomaterial with mechanical properties similar to the bone is required to ensure the stability of the implant [1,10]. In this context, metal devices like plates, screws, nails or an external load-bearing fixation were used in case of implant weaker than the bone for the stability [1]. Furthermore, to mimic the gradient structure of bone, a scaffold with varying in porosity across the scaffold can allow the stiffness variation through the structure [11]. However, it is important to remember that the mechanical properties of a scaffold depend on the multitude of parameters, such as phase composition, microstructure and pore architecture [12,13]. For instance, in an open-cell foam, the elastic modulus and elastic collapse stress are directly proportional to the geometry of the cells, elastic modulus of the strut material, and relative density of the scaffold [14].

For the restoration of damaged bone and faster regeneration, scaffolds should ideally have the following characteristics, (i) biocompatible and bioresorbable constituents, (ii) an architecture promoting the formation of the native anisotropic tissue structure, (iii) a highly porous structure with micro- and macro-porosity for the cell attachment, migration, bone growth, and vascularization [15], (iv) interconnected pores network to promote oxygen, nutrient and waste exchange, (v) a porous architecture that can absorb the impact energy, and (vi) clinically relevant implant geometry and size to influence osseointegration [2,16]. For instance, pores smaller than 75 $\mu$m favor the formation of fibrous tissue. However, pores in the range of 75–100 $\mu$m support the formation of tissue with unmineralized osteoid. A relatively coarser pores (>200 $\mu$m) facilitate enhanced bone ingrowth and vascularization [17]. Apart from these, a scaffold should mimic the natural tissue to support the mechanical stimuli as well as chemical and topographical cues [18,19].

As will be discussed in this review paper, a complex internal pore network can be constructed using the additive manufacturing process [20]. Furthermore, the build-on-demand nature of additive manufacturing provides the flexibility to create a patient-specific implant with custom-made architectures [20–22]. Therefore, in order to reconstruct the damaged tissue, scaffolds fabricated by additive manufacturing methods are reported to be more advantageous over conventional 3D scaffolds. This is in view of the fact that because additive manufacturing enables the incorporation of drugs/proteins as well as cells during scaffold manufacturing and to produce very complex architecture similar to bone [22–24].

Conceptually, additive manufacturing technology is a layer-by-layer fabrication technology of three-dimensional physical models directly from computer-aided design (CAD) [25–27]. Additive Manufacturing (AM), also known as "Rapid Prototyping" is said to be the next global industrial and technological revolution [28,29]. In most sectors of industry, the utilization of AM is