Materials Science and Engineering C 70 (2017) 976–982

Contents lists available at ScienceDirect

Materials Science and Engineering C

journal homepage: www.elsevier.com/locate/msec

Low-temperature deposition manufacturing: A novel and promising rapid prototyping technology for the fabrication of tissue-engineered scaffold

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ARTICLE INFO

Article history:
Received 30 January 2016
Received in revised form 19 March 2016
Accepted 4 April 2016
Available online 12 April 2016

Keywords:
Low-temperature deposition manufacturing
Prototyping technology
Tissue-engineered scaffold
Three-dimensional scaffold
Cartilage regeneration

ABSTRACT

Developed in recent years, low-temperature deposition manufacturing (LDM) represents one of the most promising rapid prototyping technologies. It is not only based on rapid deposition manufacturing process but also combined with phase separation process. Besides the controlled macropore size, tissue-engineered scaffold fabricated by LDM has inter-connected micropores in the deposited lines. More importantly, it is a green manufacturing process that involves non-heating liquefying of materials. It has been employed to fabricate tissue-engineered scaffolds for bone, cartilage, blood vessel and nerve tissue regenerations. It is a promising technology in the fabrication of tissue-engineered scaffold similar to ideal scaffold and the design of complex organs. In the current paper, this novel LDM technology is introduced, and its control parameters, biomedical applications and challenges are included and discussed as well.

1. The introduction of LDM

Scaffold is one of the key elements in tissue engineering and plays an important role in cell behaviors including: attachment, proliferation, infiltration and differentiation [1,2]. It plays a crucial role in the integration with tissue and tissue regeneration after implanting into defected site [3,4]. Ideal scaffold must be biocompatible and have proper pore size, controlled biodegradability, similar mechanical properties to the targeted tissue and controlled structure and morphology [5]. To fabricate scaffold with controlled pore size and structure, various novel technologies have been reported, including rapid prototyping manufacturing (RPM), since the concept of tissue engineering was proposed by Vacanti and Langer [6–8]. RPM is a set of manufacturing processes that fabricate scaffolds with complex structure and controlled pore size by the aid of computer design model [9–11]. Low-temperature deposition manufacturing (LDM) is a new RPM developed by Tsinghua University. It was firstly reported in 2001, and then a commercialized system was introduced and named as Tissue Form™ [12,13]. To control the material composition, a multi-nozzle system extruding both natural and synthetic polymers was developed in 2008 [14]. In 2012, a LDM system which could fabricate core-sheath structure composite scaffold was reported, and at the same year, LDM and electrospinning were combined together to fabricate multi-scale tissue-engineered scaffolds [15,16].

As shown in Fig. 1, based on the computer-aided design data, LDM is employed to build scaffold layer by layer on a platform in a low temperature chamber where the temperature is below 0 °C, and then the scaffold is freeze-dried to remove the frozen solvent. LDM process is a non-heating liquefying processing of materials and belongs to green manufacturing [17]. It is not only based on rapid deposition manufacturing process but also combined with phase separation process [13]. Besides the controlled macropore size, tissue-engineered scaffold fabricated by LDM has inter-connected micropores in the deposited lines due to the phase separation process [13].

Compared with fused deposition modeling (FDM) and selective laser sintering (SLS), LDM is a more robust technology to fabricate scaffold [17]. It preserves the bioactivities of the materials due to its non-heating feature. Natural biopolymers such as collagen type I (COLI), gelatin, sodium alginate and chitosan were printed successfully without the compromise of their bioactivities [16,18–22]. Synthetic biopolymers such as poly(lactic-*co*-glycolic acid) (PLGA), polyurethane (PU), poly(D,L-lactide) (PDLLA) and poly(L-lactic acid) (PLLA) were dissolved in 1,4-dioxane (DIO) and have been processed into scaffolds [16,23–25]. Moreover, inorganic particles such as nano-hydroxyapatite (nHA), tricalcium phosphate (TCP) and magnesium particles have been

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http://dx.doi.org/10.1016/j.msec.2016.04.014
0928-4931/

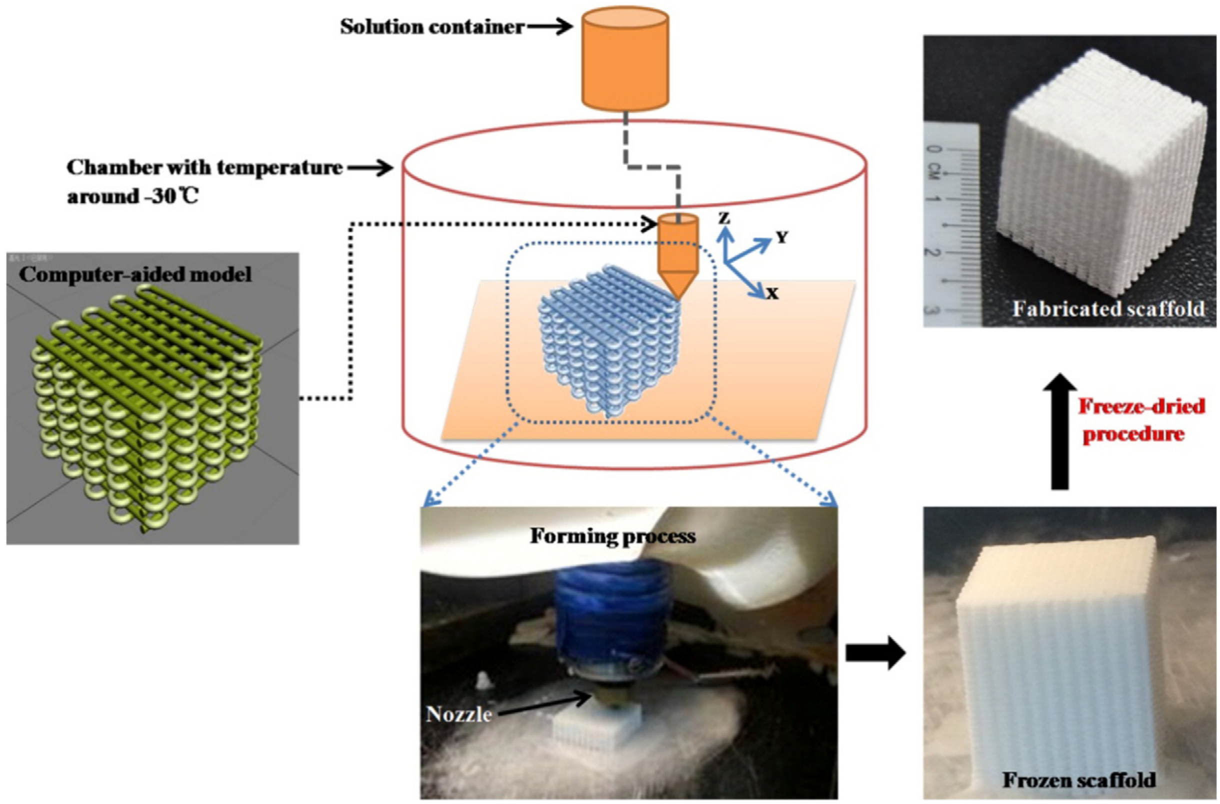

Fig. 1. Schematic illustration of the fabrication procedure of the scaffold by LDM system.

incorporated into the solution of biopolymers before processed [25,26]. They can enhance the biological and mechanical properties of the scaffolds. However, the size of the particles should be in a micron or nanometer manner because of the limitation of the printing nozzle diameter. By now, LDM has been employed to fabricate tissue-engineered scaffolds for bone, cartilage and vascular tissue regenerations. Researchers even tried to print a multi-channel liver organ [27].

2. The parameter control of LDM

The pore size and structure of the scaffold influences cell behaviors and tissue regenerations [28,29]. It is necessary to adjust the parameters of the LDM system for the fabrication of ideal scaffold. Firstly, an electrical model should be fine designed by software. It determines the shape and architecture of the scaffold. Secondly, material properties and the proportion of the composite materials are also related to the structure and morphology of the scaffold [30]. With other conditions and parameters fixed, scaffolds with different polymer matrices have been fabricated and different micro-cellular morphology was observed [31]. Moreover, when polymeric materials are dissolved in the solvent at higher concentrations, micropores of the scaffolds get smaller and the wall of the micropores get thicker [25]. As the proportion of the materials changes, the structure of the scaffold is influenced. Hu et al. added TCP or pearl powder in PLGA to prepare solutions containing different weight ratio of materials. They found that pure PLGA scaffold, PLGA/pearl at 5:2 and PLGA/TCP at 5:2 had better continuous porous structure than that of other scaffolds [30].

Thirdly, the parameters of the LDM device should be adjusted for the fabrication of fine scaffolds. Usually, the temperature in the forming chamber is maintained around −30 °C during the forming process to ensure that the extruded material slurry is frozen. The temperature of the nozzle should be much higher than the chamber temperature, so the extruded lines can be integrated with the previous layer. The nozzle with too low temperature will cause the extruded lines detaching from the previous layer [32]. Other parameters such as nozzle diameter, nozzle scanning speed, extrusion rate, and the viscosity of the material solution define the final structure and morphology of the scaffold [33,34]. The nozzle diameter, nozzle scanning speed and extrusion rate determine the diameter and the morphology of the extruded slurry lines. Higher nozzle scanning speed and lower extrusion rate may decrease the diameter of the lines and eventually lead to broken lines [27]. Another reason for line broken is related to the viscosity of the material solution. A study showed that after the first few layers, the highly concentrated polymer solution blocked up the extrusion nozzle, and then a mess of polymer solution was squeezed out [31]. Due to its high viscosity, the highly concentrated polymer solution was difficult to be squeezed out of the nozzle, resulting in the broken fibers. But a study showed that the solution viscosity was influenced by the nozzle temperature and it decreased with the increase of nozzle temperature [35]. It indicates that a scaffold with fine structure and morphology can be achieved by adjusting the nozzle temperature. Besides the decrease of the polymer solution concentration and the increase of nozzle temperature, a piston-extrusion nozzle could solve this problem successfully as well [31].

3. The improvements of LDM

Since the LDM was proposed, improvements had been made for the fabrication of more complex scaffolds or tissue-engineered organs. These improvements exhibit promising ways to fabricate tissue-engineered scaffolds, complex organs and drug release systems. Those can easily be achieved by the changing of the nozzle or combining with electrospinning system to fabricate multi-scale tissue-engineered scaffold.

Natural materials have better biocompatibility and synthetic materials show better mechanical properties [36,37]. However there is no one solvent which can dissolve the natural and synthetic polymers together when LDM is applied to fabricate scaffolds. In 2008, Liu et al.