Industrial Engineering and Applications
L.-C. Tang (Ed.)

doi:10.3233/ATDE230027

Implant Development Using 3D Printing with Polylactic Acid-Based Polymer

Weidong HUANG[a,*], Zihan WANG[b,*], Bo WANG[a], Xianli LIU[a,1], and Xiaoju LU[a,2]
[a] *School of Chemistry and Chemical Engineering, Hubei Polytechnic University, Huangshi, China*
[b] *School of Chemistry and Chemical Engineering, Wuhan University of Science and Technology, Wuhan, China*

Abstract. In this paper, a unique implant containing Gentamicin sulfate with biocompatible poly-lactide powders was developed by using such 3D printing (3D printing) process. The implantable drug delivery system prototypes, which were constructed with matrix structure; double-layer structure and sandwich structure, were manufactured with different processing parameters. The cross-sectional morphology of the implant was characterized by three dimensional video microscopic system and environmental scanning electron microscope. The microscopic morphologies and the in vitro releasing experiments of the implants fabricated by both 3D printing technique and conventional technique were investigated to evaluate the performance of the implant devices. At about 60-day release of the implants in vitro, the drug concentration was measured and the profiles were made. The release behavior and the microstructure were subsequently compared between the samples prepared using the 3D printing technology and the conventional technology. The as-described 3D printing technology in this work allows for the design and fabrication of implants with a sophistically micro- and macro-architecture, and thus having unambiguous advantage over the conventional technology.

Keywords. Three-dimensional printing, implant, gentamicin sulfate, fabrication, release in vitro

1. Introduction

Three-dimensional printing(3D printing) process, a solid freeform fabrication technique, employs powder processing in the construction of parts in a layer-wise manner. Nowadays, 3D printing technique has been used by drug specialists to produce products with the optimal control of the structure and internal architecture. Controlled release of drug delivery devices fabricated using this methodology was initially demonstrated by Massachusetts Institute of Technology[1]. Using dyes as model drugs, several oral drug

[1] Corresponding Author: Xianli Liu, School of Environmental Science and Engineering, Hubei Polytechnic University, Huangshi, China; Email：liuxianli@126.com.

[2] Corresponding Author: Xiaoju Lu, School of Chemistry and Chemical Engineering, Hubei Polytechnic University, Huangshi, China; Email：64194816@qq.com.

*These authors contributed equally to the work.

delivery devices that release multiple drugs or release a single drug in multiple phases in a controlled way were prepared [2-3].

Implant, also called implantable drug delivery system, may be prepared by the mixtures of drugs, added in the form of powder or emulsion, and the excipients via vacuum foaming process and lost mould method in implants production traditionally[4-6]. While these methods have merits, there may be problems with very minimal control over the structure and internal architecture of the implants. Unlike other conventional pharmaceutical processing technologies, 3D printing technology allow the design and fabrication of implants with a novel micro- and macro-architecture, which enables complex drug release profiles, dosage control, and drug or materials matrix distribution in one dosage form[7-10]. The versatility of the technology has allowed for various shapes and internal architectures to be incorporated[11].

In order to develop implants with complicated architectures using 3D printing, this study evaluated the feasibility of using implants fabricated by nonconventional 3D printing technology for controlled delivery of Gentamicin sulfate (GS), a broad spectrum fluoroquinolone antibiotic. The biocompatible poly-L-lactide (L-PLA) powder was developed for the 3D printing process. Implants prototype was manufactured by employing different processing parameters. The morphology of the implants was characterized and the in vitro release profiles of GS were studied.

2. Materials and Methods

2.1. Materials and Implants Design

Poly (l-lactic acid) (L-PLA), Mw＝100kD, was gifted from Dikang Biomedical Co., Ltd (Chengdu, China). Polymer L-PLA powders were milled, vacuum-dried and hand-sieved with stainless steel sieves at 150 μm before fabrication. Gentamicin sulfate (GS) powder was obtained from Handan Pharmaceutical (Hebei) Co., Ltd. All other chemicals were of analytical grade or pure and purchased from commercial suppliers.

Three cylindrical implants were designed as illustrated in Figure1I-III, the names and dimensions of the designs being summarized in Table 1. L-PLA was chosen as the mainly matrix material because of its well–established biocompatibility and biodegradability and was already used clinically and FDA approved for biomaterial.

Table 1. Implants Designed to Fabricate

	I	II	III
Implant design	Matrix structure	Double-layer structure	Sandwich structure
Drug Distribution	Homogeneous	Homogeneous in lower portion	Homogeneous in middle core portion

All implants have been designed with the external dimension of 8 mm in diameter. The implant I in Figure 1 was a single matrix structure of 6 mm in height with GS homogeneously distributed in L-PLA matrix. Implants with complicated architectures was designed as shown in Figure 1 II-III. The implant II was made of a double structure, which comprised an L-PLA matrix portion of 2 mm in height and a portion of 4 mm in height with GS homogeneously distributed in L-PLA matrix. The implant III has a sandwich structure in Figure1, which the core portion of 4 mm in height, with GS

homogeneously distributed in L-PLA matrix, was surrounded respectively by upper and lower L-PLA matrix of 1 mm in height.

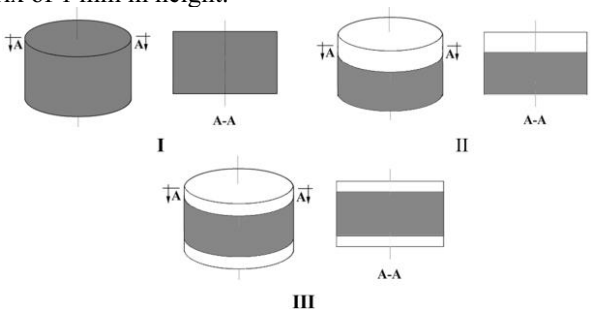

Figure 1. Schematic diagram of the design of the implants.

2.2. Implants Manufacture Process and assay

The implants I were fabricated by the conventional process according to a single matrix structure . The implants II-III used in this study, with sophisticated structure that cannot be fabricated by conventional technologies, were manufactured by machine LTY-I presented in Figure 2, a kind of solid freeform fabrication 3D printing technique developed at MIT[1].

The essential elements of this device are a z-piston as a building box, an x-y plotter for moving the printing device, the spreading unit, and several electronic control devices. The process of 3D printing was used to create a solid object by ink-jet printing a binder onto selected areas of sequentially deposited layers of powder or particulates.

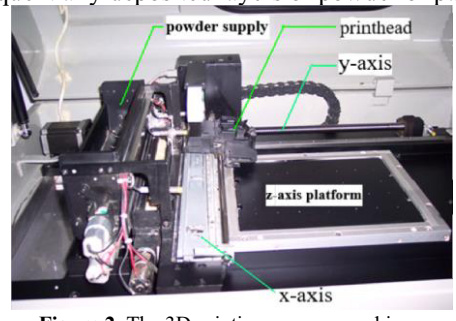

Figure 2. The 3D printing process machine.

The implants external structures were examined by 3-D stereoscope microscopy (QUESTAR KH-1000). The samples were dried and coated under an argon atmosphere with gold-palladium and examined by Environmental Scanning Electron Microscope (ESEM, FEI Quanta 200) at 20 kV. The concentrations of GS in each released sample lot were analyzed by using UV spectrophotometer at 335 nm[12]. The in vitro release medium was composed of physiological salting, and maintained in water bath at 37 °C. The release medium was sampled at preselected times and replaced with fresh physiological salting.

3. Results and Discussions

3.1. Determinations of 3D printing parameters

In this study, L-PLA was used as the polymer phase, which was soluble in acetone. GS was slightly soluble in acetone but soluble in ethanol. The solubility of GS in different ratios of ethanol and acetone is developed in order to optimize the balance of high drug concentration and polymer dissolution ability of the binder solution. The mixtures of ethanol and acetone (10:90, 20:80, 30:70, 40:60, V/V) were investigated. A homogeneous implant is achieved by these binder's solution, which is deposited on a bed of L-PLA. As was showed in Table 2, it is determined that a 30:70 mixtures of ethanol and acetone was optimal for dissolving the polymer L-PLA.

Table 2. Binder composition of 3D printing process

	Binder composition	***Binder ability***
A	acetone	Cannot print
C	Acetone+10%ethanol	Print and bind; loose
D	Acetone+20%ethanol	Print and bind; normal
E	Acetone+30%ethanol	Print; bind; excellent
F	Acetone+40%ethanol	Print; bind; poor

The optimal 3D printing parameters for implants were determined before the fabrication. According some previously published explanation of the 3D printing technique from literatures[13-15], several operating parameters are available to alter the implant properties. The layer thickness and spacing between printed lines are optimized to provide adhesion between lines and layers. Flow rate of the liquid binder and fast axis speed determine the quantity of binder deposited per unit line length. The layer thickness, spacing between printed lines, binder printed speed and flow rate of the liquid binder of 3D printing process were selected. From the results listed in Table 3, those optimized operating parameters mentioned above were 200 μm, 150 μm, 150 cm/s and 1.4 g/min, respectively.

Table 3. 3D printing processing parameters for the implants

Powder layer height(μm)	*Binder line spacing(μm)*	*Binder printed speed(cm/s)*	*Binder flow rate(g/min)*	*Quality**
200	50	100	1.0	2
200	100	120	1.2	4
200	150	150	1.4	5
400	200	110	1.5	2
200	220	160	1.8	3

The implants fabricated by 3D printing were showed in Figure 3. It is obvious that all implants have the external dimension of 6 mm in height and 8 mm in diameter. Each section of the structure of implants gives smooth and dense structure.

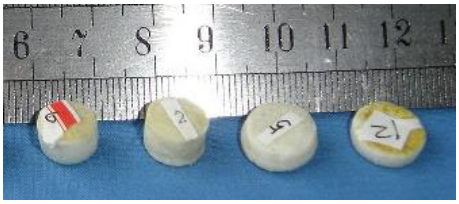

Figure 3. The implants fabricated by 3D printing.

3.2. In vitro evaluation

The release studies for each of the implant designs were achieved to gain a better insight into the mechanisms by different fabrication processes. The in vitro release profiles compared in Figure 4 indicated that all the implants released GS continuously throughout the 60-day study for implant I-III.

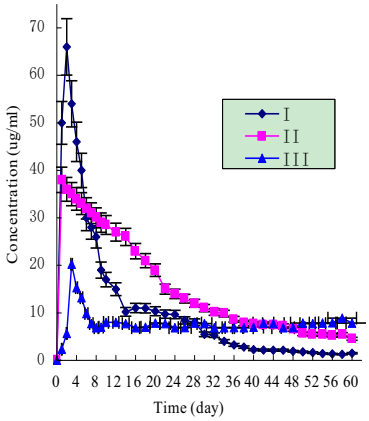

Figure 4. The daily dose of GS of implant I-III.

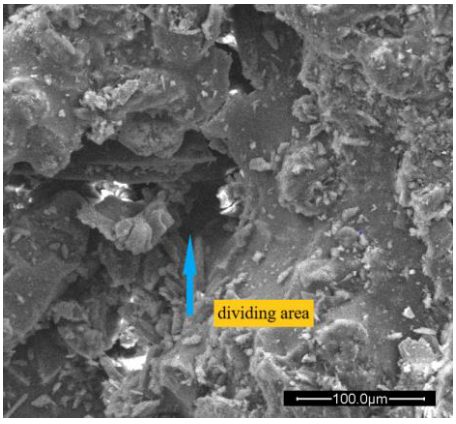

Figure 5. The 3D-stereoscopes of implant I.

Figure 4I showed that a burst release of GS took place within 3 days. The release of implant I appeared maximum concentration of 65 g/ml at 2nd day. After about 10 days

releasing at the concentration of about 15 g/ml, the concentration of GS was below 10 g/ml at 15th day. The structure of implant I was simple because of the fabrication process' limitation. Based on the mechanisms of bioerosion-modulated drug release reported in the literature[16], it is showed that with the conventional compress process the implant would be seen with the distinct dividing area, which could lead to the implant to split into several sub-units, between the sections as shown in Figure 5. The structure prepared by the traditional process is not uniform, and there is still a relatively large gap, so there is a relatively high release. Later, due to the sharp reduction of the dosage, the effective concentration of release can no longer be maintained.

The result in Figure 4II indicated that burst release happened with a lag time of 1 day at 3rd day. The concentration of GS release maintained about 15 g/ml for 30 days before declining gradually. The dual-layer of implant II can prolong the steady release of GS in some extent compared to the matrix structure of implant I. This is caused by the rapid release of drug molecules on the surface and outer layers of PLA, and of course some internal drug molecules are released in the form of diffusion through microporous structures.

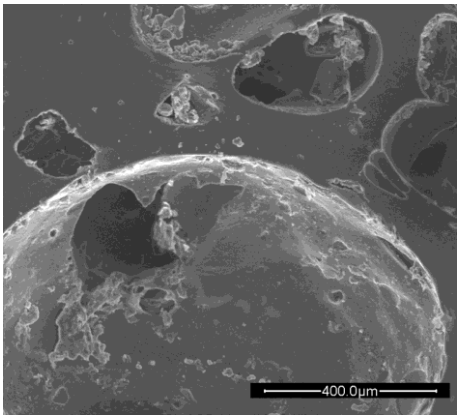

Figure 6. The ESEM of implant after releasing by 3D printing process.

The GS release indicated that implant III released a higher daily dose of drug than implant I and II except the burst releasing dose. Figure 4III showed the profiles of implant III fabricated by 3D printing process. From 10th day to 50th day implant III achieved a GS concentration above 10 g/ml, with the maximum of 20 g/ml at 4th day. Implant III was observed to gain a steady release in a single implant in 60 days releasing above 12 g/ml which archived a longer drug release than implant I and II. The implantable gentamicin preparation prepared by 3D printing technology has tight internal structure and uniform pore size distribution, so it can maintain slow drug release after sudden release. Implant III after release was characterized with many connected hole by Environmental Scanning Electron Microscope (ESEM) in Figure 6. It may induce that the release was controlled by a combination of passive diffusion and erosion from L-PLA matrix.

From Figure 4-6, there is degradation of carrier material polylactic acid in gentamicin preparations prepared by the two methods, especially after a certain time of release, the internal structure and pore size of the preparation will be affected. In other words, more space is created so that more internal drug molecules can be released more quickly. The sophisticated release profiles of implants III may suggest that the 3D printing technique possesses the ability to produce implants device that cannot be

fabricated by conventional manufacturing techniques. Since the 3D printing technique can give the implant the desired internal macroscopic architecture, the implants could be created with many regions, each with materials and architectures that are different than the architectures and materials used in other regions of the same implant.

4. Conclusion

GS implants with complex release profiles have been successfully fabricated with 3D printing technique. The 3D printing process parameter was optimized and in vitro release test of implants fabricated by 3D printing and conventional compress process had been investigated. The as-described 3D printing technology in this paper allows for the design and fabrication of implants with a sophistically micro- and macro-architecture, thus having unambiguous advantage over the conventional technology. Our further work will deal with the evaluation of these implants in vivo, optimization of the release performance and mechanisms of the drug release before the use in human body. With the benefits obtained from such implantable drug delivery and the rapid advances in biodegradable and biocompatible materials and 3D printing processing technology, these implantable drug delivery systems will be clinically applicable for local treatment in the bone and related disease.

Acknowledgment

This research was supported by the National Natural Science Foundation of China (Nos. 51803121 & 51402099); The Foundation of Central Guidance on Local Science and Technology Development (2022BGE252); the Technical Innovation Project (Major Project) of Hubei, China (2016ACA176); University-Industry Collaborative Education Program (201902313008); Hubei Provincial Department of Education (B201306); The Hubei Key Laboratory Foundation (2012107& 2013105). Authors also gratefully acknowledge the reviewers of this article.

References

[1] Cima LG, Chim MJ. Preparation of medical devices by solid free-form fabrication methods [P]. US Pat: 5490962, 1996-02-13.
[2] Lamprou D A, Dennis D, Andrews G P, et al. 3D printing in pharmacological and pharmaceutical sciences[J]. Journal of Pharmacy and Pharmacology, 2022(10):10.
[3] Liaskoni A, Wildman R D, Roberts C J. 3D Printed Polymeric Drug-Eluting Implants[J]. International Journal of Pharmaceutics, 2021:120330.
[4] Seidlitz A. 3D-Printing of Drug-Eluting Implants: An Overview of the Current Developments Described in the Literature[J]. Molecules, 2021, 26.
[5] Sarah LT, Tejal AD. Microfabricated drug delivery systems: from particles to pores [J]. Advanced Drug Delivery Reviews, 2003, 55, 315.
[6] Weidong HUANG, Qixin ZHENG, Xiangliang YANG, et al. Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique [J]. International Journal of Pharmaceutics, 2007,339, 33–38.
[7] T.M.Gabriel, David G,Scott J, et al. Mechanical and in vivo performance of hydroxyapatite implants with controlled architectures [J]. Biomaterials, 2002, 23, 1283–1293.

[8] Mohamed Arinate, Ilham Elayachi, Omar Akourri, The Process of Optimization of Spot-Welding Conditions and Analyze of the Effect on the Nugget Diameter by Using Taguchi Methodology, International Journal of Materials Science and Engineering, 2020, 8(4): 118-129.
[9] Cui M, Hu N, Fang D, et al. Fabrication and evaluation of customized implantable drug delivery system for orthopedic therapy based on 3D printing technologies[J]. International Journal of Pharmaceutics, 2022, 618:121679.
[10] Tota B, Sh B, Bb C, et al. Extrusion and 3D printing of novel lipid-polymer blends for oral drug applications[J]. Biomaterials Advances, 2022, 137, 212818.
[11] Tagami T, Ito E, Kida R, et al. 3D printing of gummy drug formulations composed of gelatin and an HPMC-based hydrogel for pediatric use[J]. International Journal of Pharmaceutics, 2021, 594:120118.
[12] Sampath S, Robinson DH. Comparison of new and existing spectrophommetric methods for the analysis of tobramvin and other aminoglycosides [J]. J Pharm Sci. , 1990, 79 (5), 428–431.
[13] I Bácskay. Manufacturing and Examination of Vaginal Drug Delivery System by FDM 3D Printing[J]. Pharmaceutics, 2021, 13.
[14] Teoh J H, Tay S M, Fuh J, et al. Fabricating scalable, personalized wound dressings with customizable drug loadings via 3D printing[J]. Journal of Controlled Release: Official Journal of the Controlled Release Society, 2022(341-):341.
[15] Awad A, Fina F, Goyanes A, et al. Advances in powder bed fusion 3D printing in drug delivery and healthcare[J]. Advanced Drug Delivery Reviews, 2021, 174.
[16] Willemen N, Morsink M, Veerman D, et al. From oral formulations to drug-eluting implants: using 3D and 4D printing to develop drug delivery systems and personalized medicine[J]. Bio-Design and Manufacturing, 2022(001):005.