

# SCAFFOLD FABRICATION FOR DRUG DELIVERY SYSTEM USING LAYERED MANUFACTURING METHODS

W. S. Chu\*, B. S. Jung\*, and S. H. Ahn†

\*School of Mechanical and Aerospace Engineering, Seoul National University, Seoul, Korea

†School of Mechanical and Aerospace Engineering & IAMD, Seoul National University, Seoul, Korea

Reviewed, accepted September 15, 2009

## Abstract

To fabricate functional shape of drug delivery system (DDS), various processes are used. In this research, based on layered manufacturing, two different processes of 1) replication and 2) direct deposition were used to fabricate scaffold type implantable DDS. For replication process, hot embossing process for fabrication of patterned layers and bonding for construction of three-dimensional shape were used. As a direct deposition process, nano composite deposition system (NCDS) was used. Various scaffolds were fabricated with different filament size, pore size, and shape. It is observed that the scaffold type of implantable DDS is more stable than non-porous DDS through the *in vivo* test.

## Introduction

Drug delivery system (DDS) refers to formulation of the drug, its delivery vehicle, and its method of administration. Nowadays many drug delivery systems have been studied, and for effective delivery of drugs, implantable drug delivery systems have been introduced. Implantable DDS has many advantages in less side effects, small number of doses/injections, controlled release, etc. Figure 1 shows the comparison of conventional drug delivery (left) and controlled drug delivery (right).

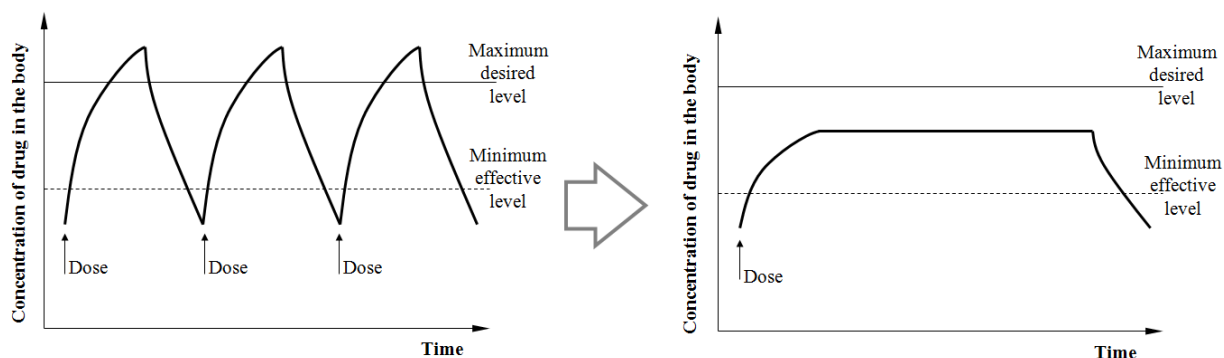


Figure 1. Comparison of conventional drug delivery (left) and controlled drug delivery (right)

Many researchers have been studying to fabricate functional structures using various types of materials to control the release of drug. Using the advantages of various micro-fabrication technologies, various implant DDSs were fabricated with various materials such as PZT (lead zirconate titanate), silicon, and polymers [1-6]. Although these DDSs give a good control in drug release, DDSs need to be removed after the drug is completely released. Biodegradable materials, on the other hand, such as, polycaprolactone (PCL), polylactic acid, polyglycolic acid and their co polymer poly(lactic/glycolic) acid (PLGA) are removed over long time without additional

surgery.

For implantable DDS, it is important to control the release of the drug. Moreover, this DDS needs to avoid immune system from the host. In this research, porous structure as the shape of DDS and composite material to control the release of drug were used to fabricate implantable DDS.

Based on layered manufacturing (LM) many rapid prototyping (RP) technologies are introduced to fabricate complicated 3-dimensional structures. Fabricating layer by layer, it is easy to fabricate porous (scaffold in this research) structure as well as complicated structures. Two different processes of replication and direct deposition were used as the fabrication process in this research. Various scaffolds were fabricated and tested *in vivo* environment.

## Materials

### *Composition of materials*

To fabricate implantable DDS, the materials were formed into drug-polymer composite. 5-fluorouracil (5-FU), which is an anti-cancer drug, was used as drug. Hydroxyapatite (HA) particle was used as additive to control the drug release. As a matrix, PLGA(85:15) was used to combine the drug and HA particles. These two particles and polymer were mechanically mixed at 120 °C into the raw DDS material. PLGA has about two years of degradation time and amorphous melting temperature. 5-FU melts at 280~282 °C and HA is a bio-ceramic. Through the *in vitro* test, drug concentration was measured using HPLC (High Performance Liquid Chromatograph System, HITACHI, Japan), and it maintained its physical and chemical characteristics.

## Fabrication methods

Using the micro-fabrication processes, various shapes of DDS were fabricated. In this paper, the replication and direct deposition processes were used as the micro-fabrication process.

### *Replication method*

For replication process, hot embossing and bonding processes were used. Hot embossing process has an advantage in fabrication of patterned structures. To fabricate patterned structure for scaffold DDS, the micro mold tool was designed (figure 2 (a)). The designed mold tool has draft angle to have an advantage in demolding (figure 2 (b)). Figure 2 (c) shows the picture of micro machined micro mold. The tool was micro machined on the brass plate using micro endmill with diameter of 100 μm.

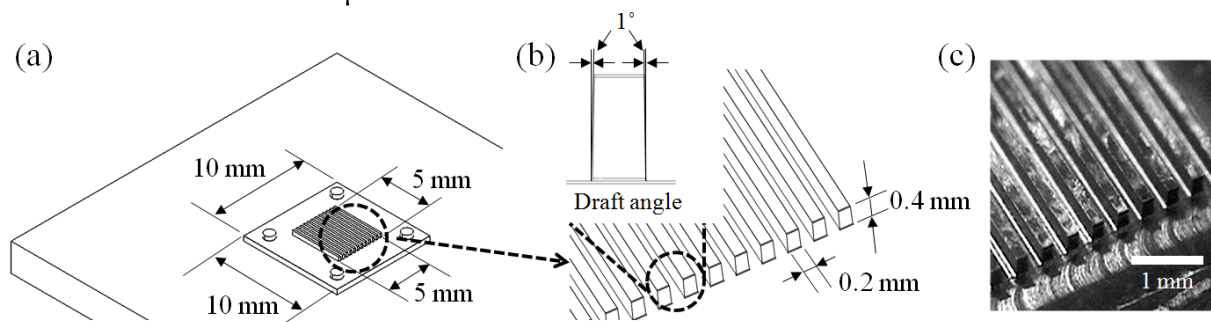


Figure 2. A schematic diagram of designed micro mold for hot embossing process and micro machined micro mold

To construct three-dimensional shape, patterned layers by hot embossing were stacked and bonded each other by thermal bonding process. Figure 3 shows the fabricated implantable DDS by replication process.

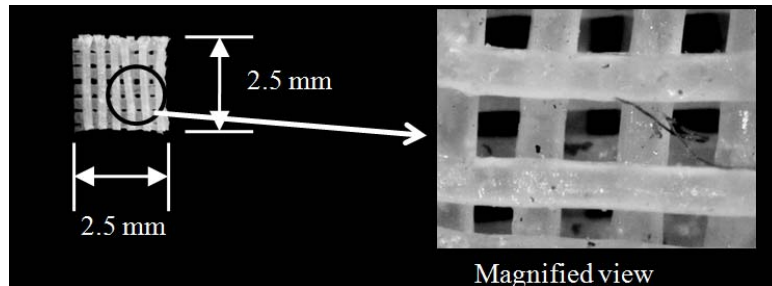


Figure 3. A implantable DDS using replication process

*Direct deposition method*

Nano composite deposition system (NCDS) was used as direct deposition process to fabricate scaffold shape [7]. NCDS has a hybrid process which is combined machining and deposition process. In this research, only deposition process was used with  $\phi$  300  $\mu$ m micro nozzle and 1  $\mu$ m resolution of 3-axis micro-stage. Molten (120 $^{\circ}$ C) drug-polymer composite material was deposited at the controlled position in the three-dimensional space. Figure 4 show the NCDS hardware with  $\phi$  300  $\mu$ m micro nozzle. Figure 5 shows the fabrication sequence of three-dimensional scaffold structure.

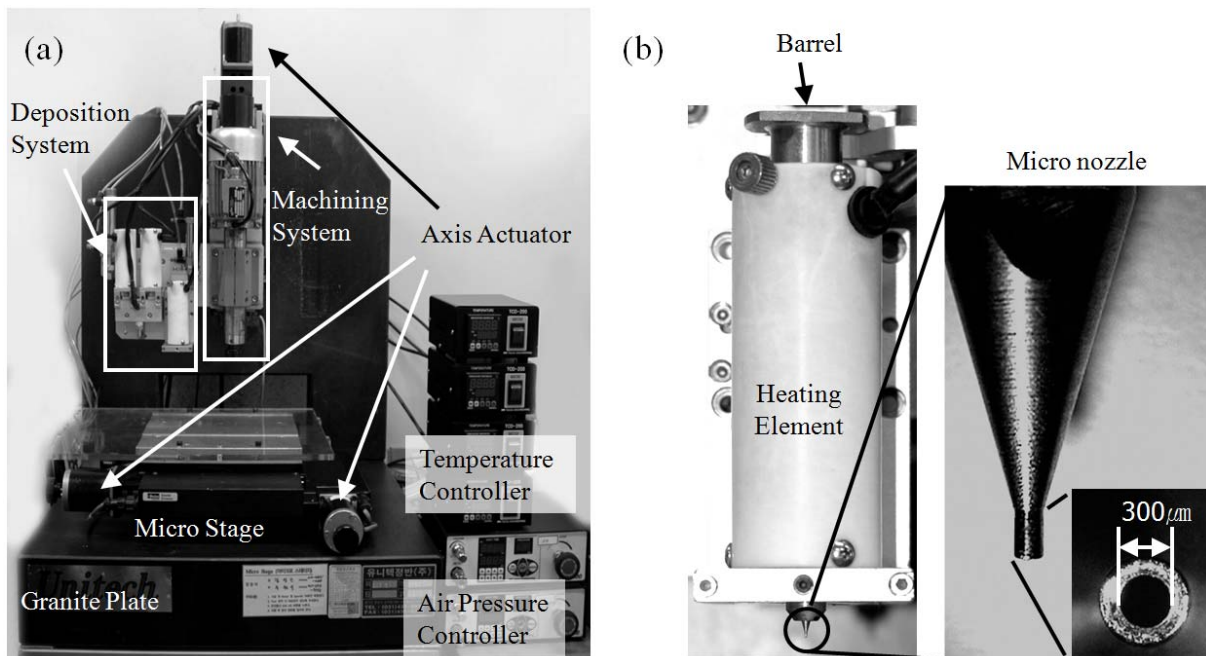


Figure 4. NCDS (a) hardware and (b) heating element and micro nozzle of  $\phi$  300  $\mu$ m. [7]

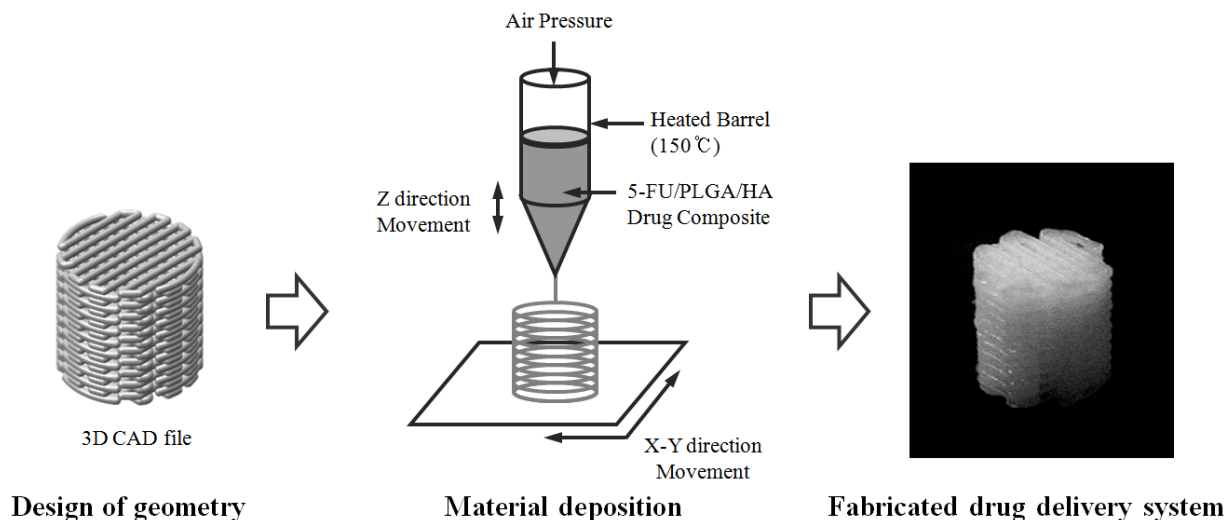


Figure 5. A sequence of fabrication process of three-dimensional scaffold structure [8]

### Evaluation

To evaluate the structure, the specimens were tested *in vivo* environment. Through the two weeks *in vivo* test, the changes of shape were observed using optical micro scope (Sometch, ICS-305B, Korea). Three different shape of implant DDS were compared. Cylindrical DDS without pore, cylinder-shape scaffold, and hexahedron-shape scaffold were implanted into the Sprague-dawley rat. Each specimen was implanted into the back of rat, and extracted and collected two weeks after implanted (figure 6).

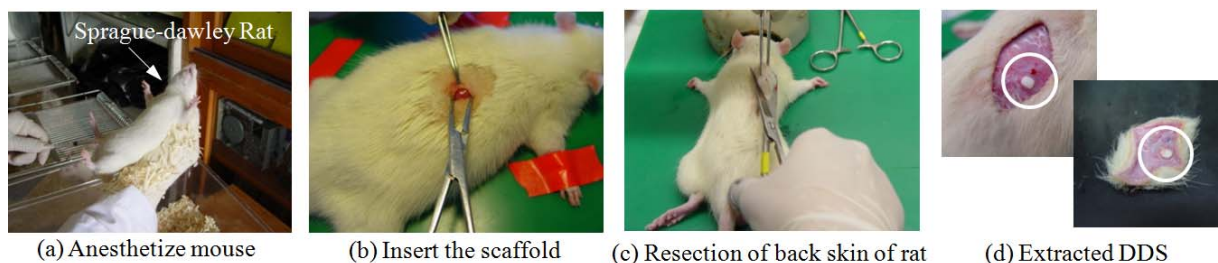


Figure 6. A sequence of implantation, extraction, and collection of DDS [9]

### Results

Through the test, their morphological changes in the *in vivo* environment were measured as shown in figure 7. The effect of pressure inside the body markedly altered the morphology of the non-porous DDS. The DDS with the 200- $\mu\text{m}$  pore size more-or-less maintained its shape over two weeks of implantation. The hexahedron-shape DDS maintained almost the same dimensions as its original shape. This might be affected by the body fluid in the pores inside of DDS. Figure 8 shows the cumulative amount of released drug *in vivo* environment that indicates cylinder-shape drug DDS with the 200- $\mu\text{m}$  pore size gives faster drug release than reference DDS.

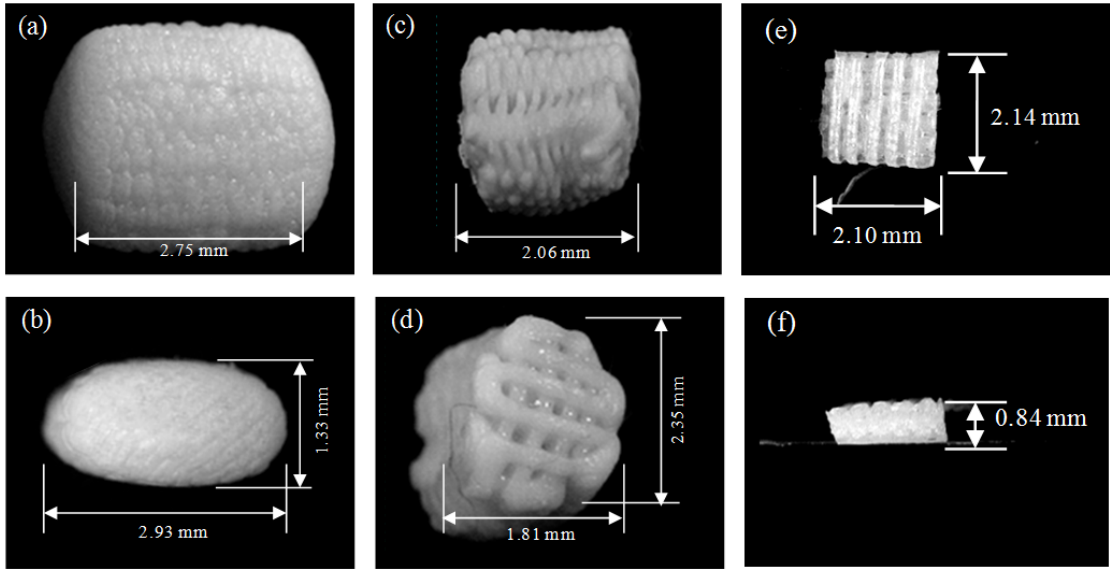


Figure 7. Implanted DDS after two weeks of *in vivo* test, (a and b) reference, (c and d) cylinder-shape with 200- $\mu$ m pore, and (e and f) hexahedron-shape

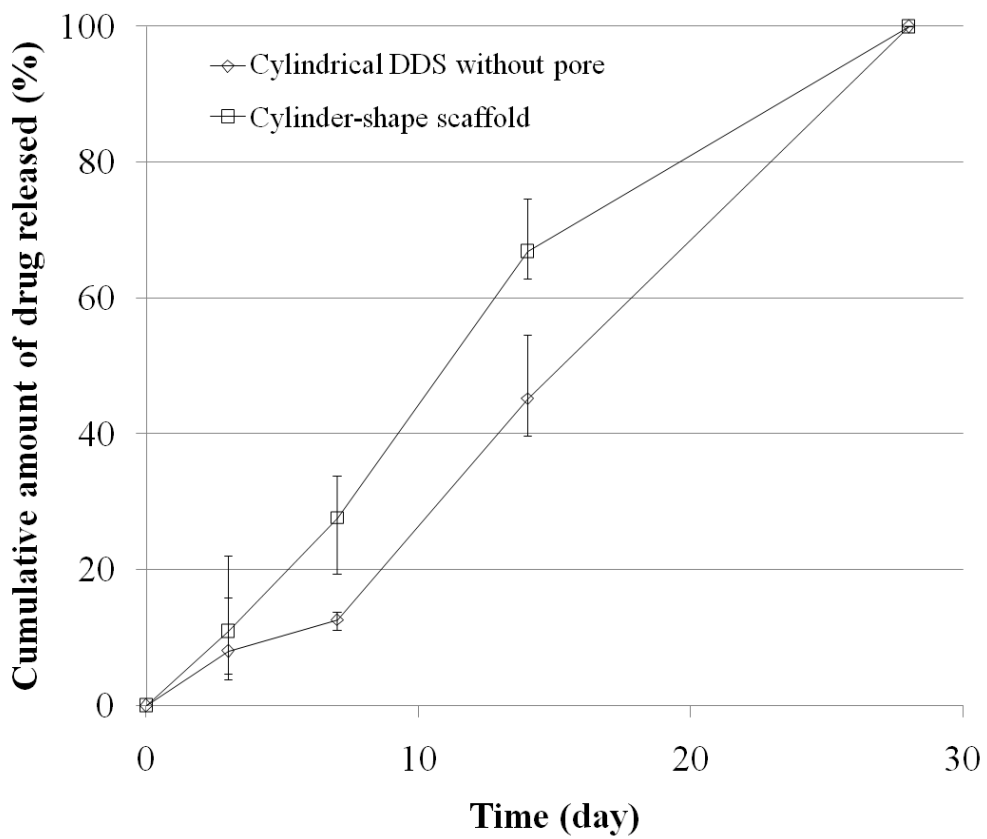


Figure 8. Cumulative amount of released drug *in vivo* environment for 2 weeks

### Conclusions

To fabricate porous structure as implantable DDS, based on LM, two different fabrication processes were used. Using the replication process and direct deposition process, three different types of DDS were fabricated and evaluated *in vivo* environment of rat. Scaffold DDS was more stable *in vivo* environment. The replication process has an advantage in mass production while direct deposition process has an advantage in fabrication of complicated shapes.

### Acknowledgement

This work was supported by ERC (Micro-Thermal System Research Center), Second stage of Brain Korea 21 of Seoul National University, and grant R01-2006-000-10699-0 from the Basic Research Program of the Korea Science & Engineering Foundation.

### References

1. Santini, J. T. Jr., Langer, R. and Cima, M. J. A., "Microfabricated Controlled Release Device," in: 10th Int. Conf. on Solid-State Sensors and Actuators Tech. Digest, pp. 746-747, 1999.
2. Ryu, W. H., "Micro-fabrication Technology for Biodegradable Polymers and Its Applications," PhD Thesis, Department of Mechanical Engineering, Stanford University, 2005.
3. Ryu, W. H., Vyakarnam, M., Greco, R. S., Prinz, F. B. and Fasching, R., "Fabrication of Multi-Layered Biodegradable Drug Delivery Device Based on Microstructuring of PLGA Polymers," Biomedical Microdevices, Vol. 9, No. 6, pp. 845-853, 2007.
4. Ryu, W. H., Huang, Z., Prinz, F. B., Goodman, S. B. and Fasching, R., "Biodegradable micro-osmotic pump for long-term and controlled release of basic fibroblast growth factor," Journal of Controlled Release, Vol. 124, No. 1-2, pp. 98-105, 2007.
5. Chu, W. S., Kim, S. G., Jung, W. K., Kim, H. J. and Ahn, S. H., "Fabrication of Micro Parts using Nano Composite Deposition System," Rapid Prototyping Journal, Vol. 13, No. 5, pp. 276-283, 2007.
6. Vincent, C., Benoit, R., and Onori, M., "Implantable Drug Delivery Systems - Design Process," International Journal of Precision Engineering and Manufacturing, Vol. 7, No. 4, pp. 40-46, 2006.
7. Chu, W. S., Jeong, S. Y., Kim, S. G., Ha, W. S., Chi, S. C. and Ahn, S. H., "Fabrication of biodegradable drug delivery system with controlled release mede of PLGA/5-FU/hydroxyapatite," Rapid Prototyping Journal, Vol. 14, No. 5, pp. 293-299, 2008.
8. Cho, K. J., Koh, J. S., Kim, S., Chu, W. S., Hong, Y., and Ahn, S. H., "Review of Manufacturing Processes for Soft Biomimetic Robots," International Journal of Precision Engineering and Manufactuirng, Vol. 10, No. 3, pp. 171-181, 2009.
9. Chu, W. S., Jeong, S. Y., Pandey, J. K., Ahn, S. H., Lee, J. H., and Chi, S. C., "Fabrication of Composite Drug Delivery System using Nano Composite Deposition System and *in vivo* Characterization," International Journal of Precision Engineering and Manufacturing, Vol. 9, No. 2, pp. 81-83, 2008.