FABRICATION OF BIODEGRADABLE DRUG DELIVERY SYSTEM USING NANO COMPOSITE DEPOSITION SYSTEM

W. S. Chu*, S. G. Kim*, H. J. Kim*, S. H. Ahn, W. S. Ha***, and S. C. Chi*****
***School of Mechanical and Aerospace Engineering, Seoul National University**
****School of Mechanical and Aerospace Engineering & Institute of Advanced Machinery and Design, Seoul National University**
*****College of Pharmacy, Sungkyunkwan University**

Abstract

The rapid prototyping (RP) technology has advanced in various fields such as verification of design, and functional test. Recently, researchers have studied bio materials to fabricate functional bio RP parts. In this research, implantable Drug Delivery System (DDS) was fabricated by Nano Composite Deposition System (NCDS).
NCDS uses biocompatible or biodegradable polymer resin as matrix and various bio-ceramics or drugs to form bio-composite materials. To apply a drug delivery system (DDS), Cylinder and scaffold type of drug delivery devices were fabricated using Poly(DL-lactide-co-glycolide acid) containing anti-cancer drug 5-fluorouracil. To control drug release, different structure and different composition of drug/polymer/additive composite were used. Test in vitro results showed a possibility of controlled release of scaffold DDS over 50 days.

1 Introduction

Utilizing the advance of micro/nano fabrication technology, implantable drug delivery system (DDS) was developed [1]. Existing micro-devices for bio and medical implants have been made from silicon, glass, silicone elastomer [2], and plastic materials [3].

For the fabrication of freeform shape DDS, the rapid prototyping (RP) technology was employed. The RP technology has advanced in product development cycle for more than 25 years. Relatively new applications of RP research include bio and medical fields where simulation of operation is performed using RP models, and artificial bones made by RP process are implanted into human body [4, 5]. An implantable drug delivery system (DDS) was also developed using micro/nano fabrication and RP techniques [6~8].

Such implanted devices would permanently remain in the biological tissue if not removed surgically. Because of the inherent difficulty associated with retrieving small-scale devices from tissues, it is advantageous to apply biodegradable polymers, such that the micro-devices would naturally degrade and disappear in tissues over a desired period of time.

On the material issue, wide acceptability of the biodegradable system can be appreciated from the fact that biodegradability can be manipulated. Biodegradation can be enzymatic, chemical or of microbial origin or simply by hydrolysis [9].

Among biodegradable polymers, polylactic acid and poly (lactic/glycolic) acid (PLGA) have been the most commonly used in sustained-release drug delivery, because they degrade by simple hydrolysis of the ester bonds into natural metabolites, glycolic and lactic acid. These polymers are, therefore, biocompatible, biodegradable and considered safe [10]. Polycaprolactone (PCL), an aliphatic polyester, is one of the most important biodegradable polymers in medicine. Some of the applications of PCL are sutures and biocompatible medical devices [11].

In this research, a nano composite deposition system (NCDS) was developed to fabricate DDS. As a drug material, 5-fluorouracil was used to form a polymer-drug composite. Hydroxyapatite (HA) was used to control drug release rate.

2 Composition of Material

In this research, 5-fluorouracil (5-FU) with 5~10 ㎛ diameter was used as anti-cancer drug (grinded using Jetmill (Model Jet-O-Mizer 000, Plumsteadville, USA) (Table 1 and Fig. 1.)).

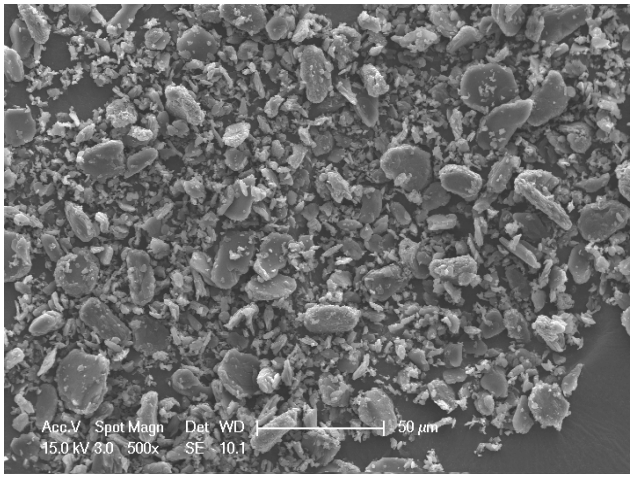

Fig. 1. The SEM photomicrographs of 5-FU particles grinded with jet-mill ×500

It is a white crystalline powder and slightly soluble in water and ethanol, and practically insoluble in chloroform and ether. PLGA (Poly(DL-lactide-co-glycolide)) and PCL (Poly(*e*-caprolactone)) were used as polymer. PLGA was used for matrix material of DDS and PCL was the materials of container of DDS. Table 2 and 3 shows the properties of each polymer. HA is chemically similar to the mineral component of bones and hard tissues in mammals. Table 4 shows the properties of HA. In this research HA was used to control drug release.

Table 1. Properties of 5-fluorouracil

Property	Value
Intratumoral Implant	Hepatomas
Melting Point (℃)	220 ~ 282
Molecular Weight	130.077
Absorption (%)	20 ~ 100

Table 2. Properties of PLGA

Property	Value
Synonym	Lactel BP-0100
Inherent viscosity (dL/g (lit.))	0.15-0.25
Melting temp (℃)	60.0
Molecular Formula	$[-OCH(CH_3)CO-]_x[-OCH_2CO-]_y$

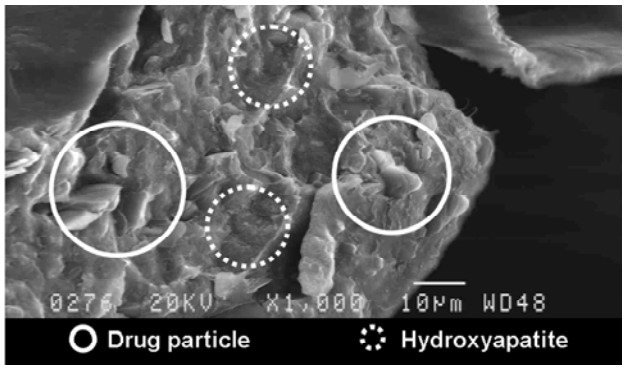

Fig. 2. SEM picture of drug/HA/PLGA composite

Table 3. Properties of PCL

Property	Value
Synonym	6-Caprolactone polymer
Hardness	55 (Shore D, ASTM D 2240-75)
Melting temp (℃)	60.0
Molecular Formula	$(C_6H_{10}O_2)_n$

Table 4. Properties of hydroxyapatite

Property	Value
Molecular Formula	$Ca_{10}(PO_4)_6(OH)_2$
Density (g/㎤)	3.16
Avg. diameter (㎚)	ϕ 100 ~ 300
Application	bone ingrowth, repair, regeneration

2 Fabrication System

The hardware system of NCDS consists of two main parts (Fig. 3 (a).), one is deposition system and the other is machining system. The stage has 3 axes (X, Y, and Z) with linear encoders at each axis and the stage was controlled by PMAC control board.

The fabrication process is as follows: 1) deposits the nano composite or polymer, 2) cures the resin by UV (ultra violet λ= 365 *nm*) light when using a photo-curable polymer, and 3) cuts out the unnecessary deposited materials by micro machining. Repeating deposition mechanism and material removal process for each layer, final freeform 3-dimensional part could be manufactured. Fig. 3 (b) and (c) shows the tools for deposition and micro machining respectively. Table 5. shows the specifications of the hardware components.

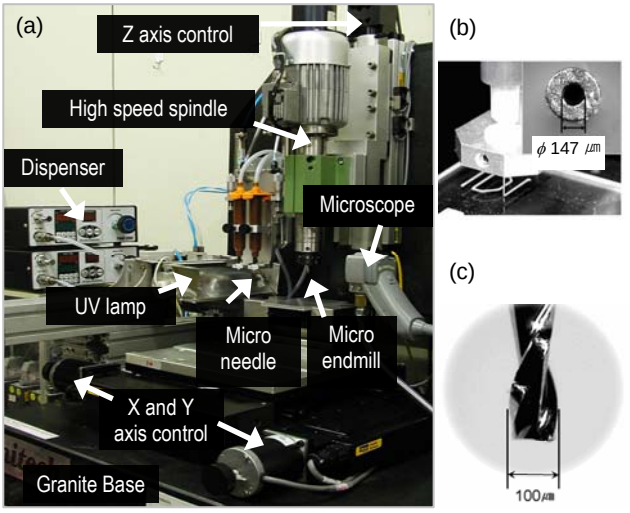

Fig. 3. Hardware system of NCDS (a) nano composite deposition system, (b) deposition nozzle, and (c) cutting tool (endmill) [12]

Table 5. Specifications of hardware components

Process	Hardware	Specification
Deposition	Dispenser	15~700 *kPa*
	Micro needle (inner diameter)	ϕ 140 ㎛ ~ ϕ 500 ㎛
Machining	Micro endmill	ϕ 100 ㎛ ~ ϕ 1000 ㎛
	Spindle	0 ~ 46,000 *rpm*
Curing	UV lamp	0 ~ 400 *W*, λ= 365 *nm*

3 Fabrication of Drug Delivery System

3.1 Container type DDS

Container type samples loaded with 5-FU were prepared using the method described in Fig. 4. A pair of mold plates was made using NCDS. PCL containers were fabricated using these mold plates. Later, 5-FU/PLGA composite was deposited into the container (Fig. 5.).

3.2 Scaffold type DDS

Scaffold is a porous three-dimensional structure used in tissue engineering field to obtain the biological equivalent of defective organ, bone or tissue. Fig. 6. shows a modeled schematic and a fabricated scaffold shape DDS. Fig. 7. shows SEM images of a scaffold containing 10wt% 5-FU and 10wt % of HA. Fabricated scaffold type DDS shows almost uniform pore size. The structure of scaffold can easily change its fabrication parameter, such as porosity, diameter of filament, geometry and so on.

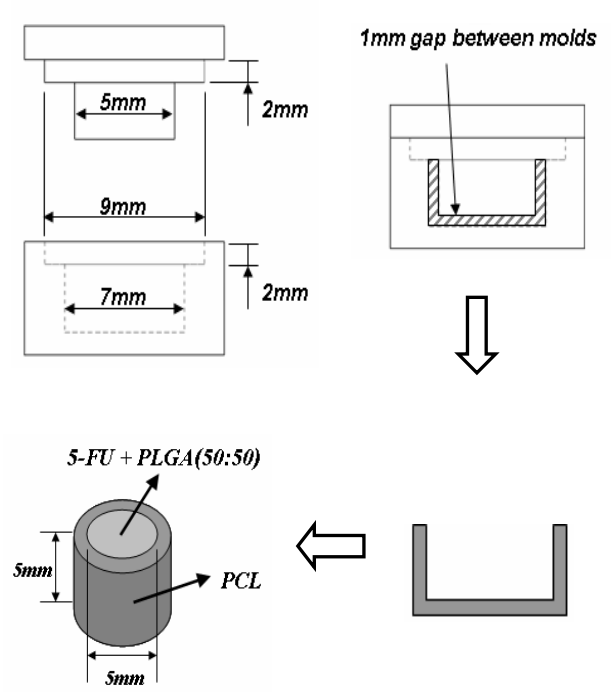

Fig. 4. Schematic diagram and figures of the method to manufacture container type structure [6]

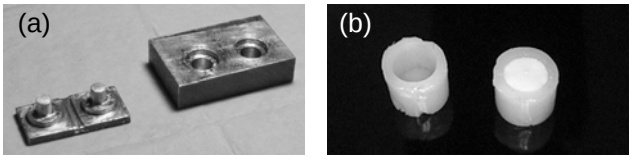

Fig. 5. (a) Fabricated mold plates PCL container and (b) 5-FU/PLGA (50:50) loaded in container [6]

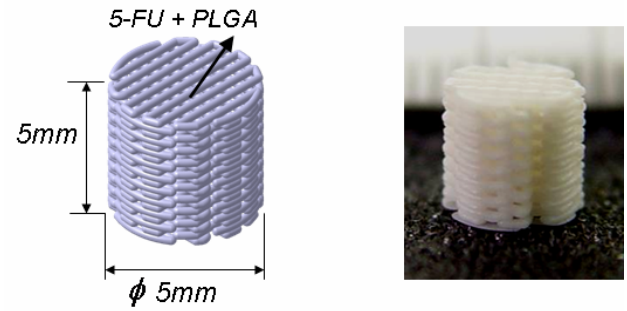

Fig. 6. Schematic diagram and figures of scaffold type DDS (15 layers, [0° $_8$/90° $_7$]) [6]

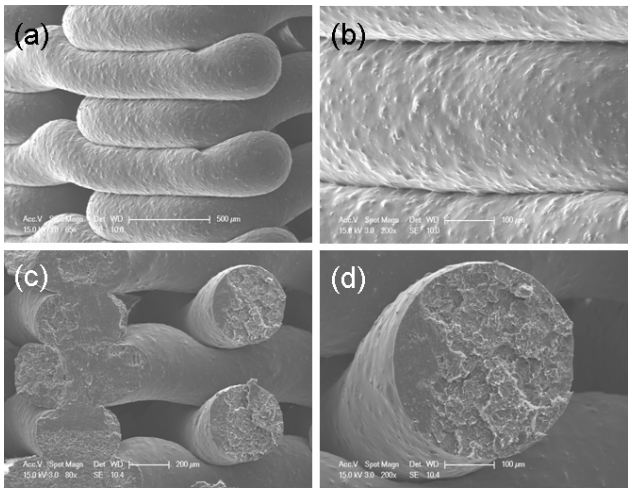

Fig. 7. SEM images of PLGA scaffold containing 10wt% 5-FU and 10wt % of HA.

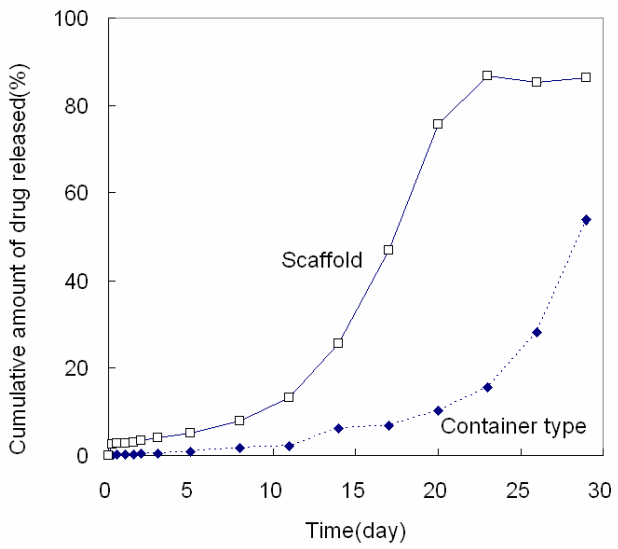

Fig. 8 Drug release test of container type of DDS and Scaffold (PLGA (50:50) composite)

4 Drug release test

Drug release rate was measured using a shaking water bath. Phosphate buffered saline (PBS, 0.05 M, pH 7.4) was used as the medium. The temperature and shaking rate were 37 ℃ and 50 *rpm* respectively.

Fig. 8. shows the result of drug release rate. The container type DDS is easy to test the release rate because of one-directional release through the open end of drug unlike the scaffold type DDS, which provides fast and complicated release. The pores of the scaffold provide large surface areas on the drug-polymer composite.

From the drug release test, it was found that PLGA (50:50)/5-FU scaffold was too weak to endure the mechanical stress under the drug release test (Fig. 9.). To improve the strength, PLGA (85:15) was also tested as the polymer matrix of the DDS composite. The changes in the shape of PLGA (85:15)/5-FU/HA scaffolds after the release tests are shown in Fig. 10. As expected, PLGA (85:15) kept the scaffold geometry better than PLGA (50:50) did. Fig. 11 shows the result of drug release rate of the PLGA (85:15)/5-FU/HA scaffold. In case of PLGA (85:15)/5-FU specimen, 5-FU was released slowly over 30 days and its release rate was then increased over time afterward. On the other hand, drug release within short periods was increased with higher HA contents. A significant increase in release rate was observed as the amount of HA increased from 10 to 20wt%. In case of 20wt% HA in the scaffold, as much as 80% of loaded drug was released after 10 days. From the test data, controllability of drug release rate by using additives such as HA is proved. The additives takes certain volume in the DDS and as the additives were separated from the DDS during polymer's degradation, surface area of the polymer/drug composite could be increased. The increased surface area may accelerate degradation and resulted release rate.

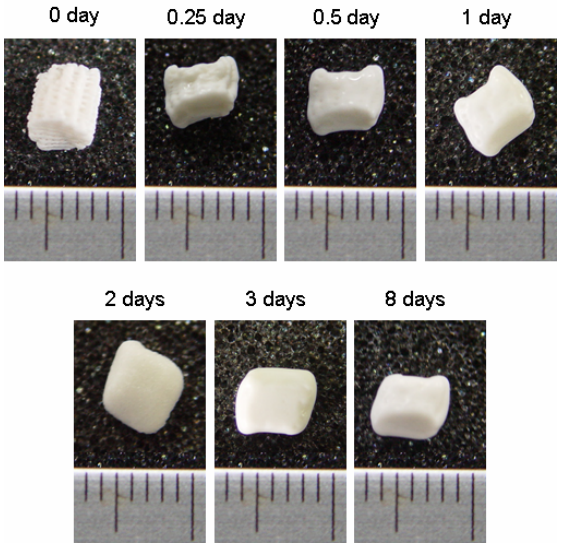

Fig. 9. Shape variation of PLGA (50:50) scaffold loaded with 5-FU during release test.

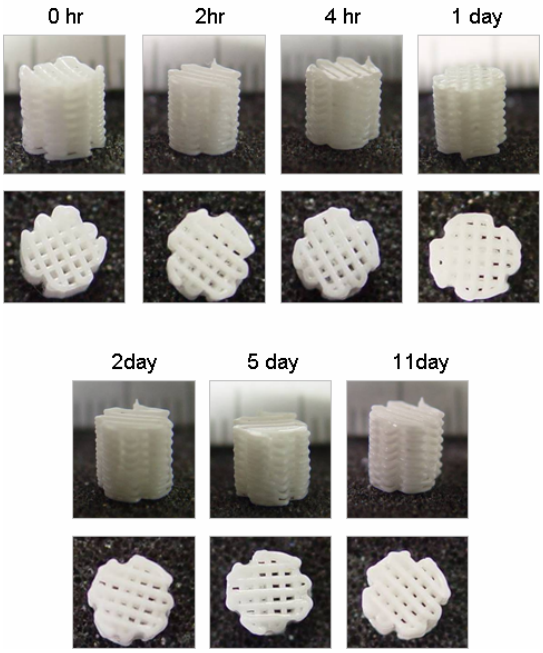

Fig. 10. Shape variation of PLGA (85:15) scaffold loaded with 5-FU during release test.

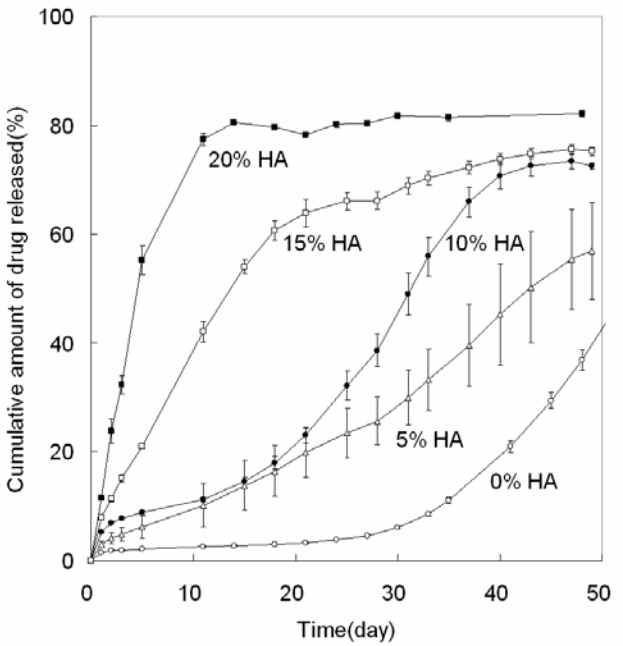

Fig. 11. Drug release test of Scaffold type of DDS as a function of HA Composition (PLGA (85:15), 10%5-FU, and HA composite)

6 Conclusions

The nano composite deposition system was developed to fabricate implantable DDS. The scaffold type DDS shows a faster and more complicated manner of drug release.

In this research, PLGA was used as matrix material. PLGA (85:15) is more stable than PLGA (50:50). Drug-polymer composite with HA showed the possibility of controlled release rate by changing the composition, especially by the portion of HA. About 5~20% HA contents seems reasonable amount of additives to affect release rate of the composite DDS. Further study of different polymer and additive materials is necessary for a better controlled drug delivery system.

7 Acknowledgement

This research was supported by grant R01-2006-000-10699-0 from the Basic Research Program of the Korea Science & Engineering Foundation, grant KRF-2004-041-D00066 from the Korea Research Foundation, Second stage of Brain Korea 21 and Micro Thermal System Research Center (ERC) of Seoul National University.

References

[1] Santini T. Jr, Langer R. and Cima J., "A microfabricated controlled release device". *10th Int. Conf. on Solid-State Sensors and Actuators,* Sendai, Japan, Tech. Digest, pp 746-747, 1999.

[2] Armani K., Liu C. and Aluru N. "Re-configurable fluid circuits by PDMS elastomer micromachining". *12th Int. Conf. on MEMS*, MEMS 99, Orlando, FL, pp 222-227, 1999.

[3] Boone D., Hooper H. and Soane S. "Integrated chemical analysis on plastic microfluidic devices". *IEEE Workshop on Solid-State Sensors and Actuators,* Hilton Head Island, SC, pp 87–92, 1998.

[4] Williams M., Adewunmi A., Schek M., Flanagan L., Krebsbach H., Feinberg E., Hollister J.and Das S. "Tissue Engineered Bone Using Polycaprolactone Scaffolds Made by Selective Laser Sintering". *Biomaterials* Vol. 26, pp. 4817-4827, 2005.

[5] Vozzi G., Flaim C., Ahluwalia A. and Bhatia S. "Fabrication of PLGA scaffolds using soft lithography and. microsyringe deposition " . *Biomaterials* Vol. 24, pp 2533-2540, 2003.

[6] Chu, W. S., Kim, S. G., Kim, H. J., Lee, C.S. and Ahn, S. H. "Fabrication of bio-composite Drug Delivery Device Using Rapid Prototyping". *Key Engineering Materials* Vols. 342-343 pp. 497-500, 2007.

[7] Kunou, N., Ogura, Y., Yasukawa, T., Kimura, H., Miyamoto, H., Honda, Y. & Ikada, Y. “Long-term sustained re-lease of ganciclovir from biodegradable scleral implant for the treatment of cytomegalovirus retinitis”. *Journal of Con-trol Release* Vol. 68, pp. 263-271, 2000.

[8] Santini, J. T., Cima, M. J. and Langer, R. “A controlled-release microchip”. *Nature* Vol. 397, pp 335-338, 1999.

[9] Uhrich E., Cannizzaro, M., Langer S., Shakesheff M. “Polymeric systems for controlled drug release” *Chem. Rev*. Vol. 99, pp 3181–3198, 1999.

[10] Kunou, N., Ogura, Y., Yasukawa, T., Kimura, H., Miyamoto, H., Honda, Y., Ikada, Y. “Long-term sustained release of ganciclovir from biodegradable scleral implant for the treatment of cytomegalovirus retinitis”. *J. Control Rel.* Vol. 68, pp 263-271, 2000.

[11] Armani K., Liu C. “Microfabrication technology for polycaprolactone, a biodegradable polymer”. *J. Micromechanics Microengineering* Vol. 10, pp 80-84, 2000.

[12] Chu, W. S., Kim, S. G., Jung, W. K., Kim, H. J., Ahn, S. H. and Friedrich B. Prinz, "Fabrication of Nano-composite Parts Using Hybrid Rapid Prototyping System ," *ASPEN 2005 International Conference on Precision Engineering and Micro/Nano Technology in Asia*, November 12-14, Shenzhen, P.R. China, 2005.