Fabrication of Composite Drug Delivery System Using Nano Composite Deposition System and *in vivo* Characterization

Won-Shik Chu[1], Suk-Yong Jeong[1], Jitendra Kumar Pandey[1], Sung-Hoon Ahn[2,#], Jae-Hoon Lee[3] and Sang-Cheol Chi[3]

1 School of Mechanical and Aerospace Engineering, Seoul University, 599 Gwanangno, Gwanak-gu, Seoul, South Korea, 151-142
2 School of Mechanical and Aerospace Engineering & Institute of Advanced Machinery and Design, Seoul University, 599 Gwanangno, Gwanak-gu, Seoul, South Korea, 151-142
3 College of Pharmacy, Sungkyunkwan University, 300 Cheoncheon-dong, Jangan-gu, Suwon, South Korea, 440-746
Corresponding Author / E-mail: ahnsh@snu.ac.kr, TEL: +82-2-880-7110, FAX: +82-2-883-0179

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The Rapid Prototyping (RP) technology has advanced in many application areas. In this research, two different types, cylinder and scaffold, of implantable Drug Delivery System (DDS) were fabricated using Nano Composite Deposition System (NCDS), one of the RP systems. The anti-cancer drug (5-fluorouracil, 5-FU), biodegradable polymer (PLGA(85:15)), and bio ceramic (Hydroxyapatite, HA) were used to form drug-polymer composite material. Both types of DDS were evaluated in vivo environment for two weeks. For evaluation, the cumulative drug release and shape stability were measured. Test results showed that the scaffold DDS provide higher cumulative drug release and has better stability than cylinder DDS.

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1. Introduction

Rapid prototyping (RP) technology is widely used for product function test, evaluation of performance, and simulation of operation, as well as for new product development.[1-5] In the bio-medical field, the RP technology is applied to surgical operation and development of artificial organs, so called tissue engineering.[6]

Implantable DDS has been developed for controlled drug delivery. It can be implanted directly to treatment region, reducing side-effect, and improving effectiveness of drug. Typically, a drug is delivered by oral administration, intravenous injection, intramuscular/ subcutaneous injection, etc. Fig. 1 shows the typical drug delivery (top) and controlled drug delivery (bottom) by implantable DDS. Controlled drug delivery can avoid the toxic level concentration of drug in the body and multiple dosages. Using the advantages of RP and micro-fabrication technologies, various implantable DDSs were fabricated with materials such as PZT (lead zirconate titanate), silicon, and polymers.[7-12] But these DDS materials are required to be removed by another surgery after the treatment is over. To overcome this problem, biodegradable polymers that can be degraded in the human body were used for DDS. Polylactic acid, polycaprolactone, and poly(lactic/glycolic) acid (PLGA) are commonly used in DDS. These materials can be used to fabricate DDS using replication, RP, and laser micro fabrication technology.

In this research, two types, cylinder and scaffold, of DDS were fabricated and tested *in vivo* environment. Nano composite deposition system (NCDS) was applied to fabricate DDS. Anti-cancer drug particle, biodegradable polymer, and bio ceramic nano particle were mixed to form a drug-polymer composite of DDS. The Sprague-dawley Rat was used to evaluate the controllability of drug release

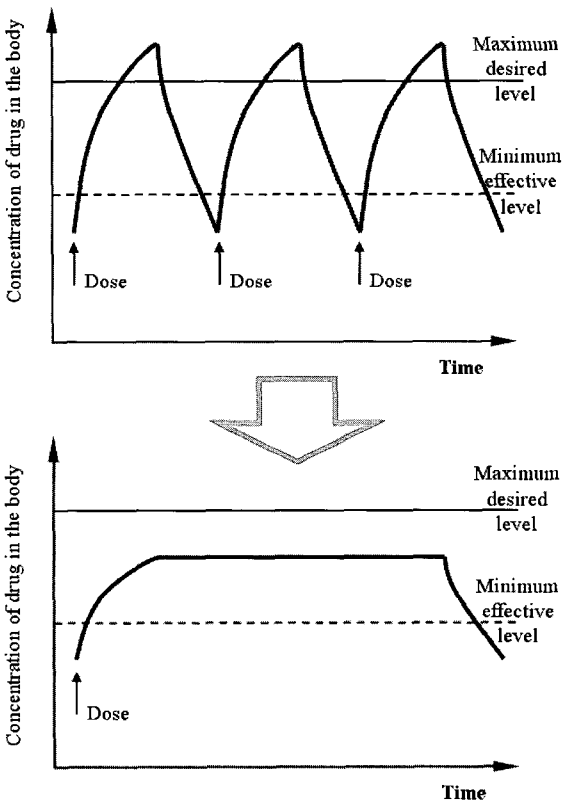


Fig. 1 Comparison of conventional drug delivery (top) and controlled drug delivery (bottom)

rate and shape changes of the DDS *in vivo* environment.

2. Materials and Methods

2.1 Composition of Materials

Drug-polymer composite was used in this research to fabricate shapes of DDS. An anti-cancer drug (5-fluorouracil, 5-FU) with tens of micrometer diameter was used as drug particles. The melting temperature of 5-FU is 280~282 ℃. PLGA(85:15), thermo-plastic, was used as polymer matrix of the composite. PLGA(85:15) has about two years of degradation time and amorphous melting temperature (it melts around 60 ℃). HA, a bio ceramic (average diameter is 300 nm), was used as the additive material to control drug release rate and to improve the strength of the drug-polymer composite. These three materials were mixed mechanically at 120 ℃ into the raw DDS material. Through the drug release test (*in vitro/in vivo*) the drug concentration was measured using HPLC (High Performance Liquid Chromatograph System, HITACHI, Japan). The drug was maintained its physical and chemical characteristics after the test.

2.2 Nano Composite Deposition System (NCDS)

NCDS consists of two main parts; 1) material deposition part using precision nozzle and 2) material removal part using micro endmill (fig. 2).[11] The 3-axis micro-stage has 1 ㎛ resolution at each axis, and it is controlled by the multi-tasking digital signal process board. Through the ϕ300 ㎛ micro nozzle, molten (120℃) drug-polymer composite material was deposited at the controlled position in the three-dimensional space. Fig. 3 shows a fabricated scaffold DDS and its cross section. The typical release mechanism of DDS is governed by diffusion of drug into body fluid.

3. Experimental Results and Discussions

The specimens were fabricated into two different shapes. One was without pore as reference (cylinder DDS), and the other was with 200 ㎛ pores (scaffold DDS). To evaluate the drug release rate *in vivo* environment, Sprague-dawley Rat was used. Each DDS specimen was implanted into the back of rat, and the specimens were extracted and collected three days, one week, and two weeks after implantation. Fig. 4 shows the process of implantation and collection of the DDS.

To analyze the drug concentration, Each sampling scaffolds were dissolved in 1 ㎖ of methylene chloride. Then, PLGA was precipitated by adding 9 ㎖ of water and after centrifugation under a condition of 3000 rpm for 10 min. Finally, content of residual 5-FU was analyzed using HPLC with 200 ㎕ of aliquots of supernatant.

Fig. 5 shows cumulative amount of drug release *in vivo* environment during two weeks. Each test was repeated three times. On 14th day, the released drug amounts were 32.16wt% without pore and 37.84wt% with 200 ㎛ pore respectively. Two-week result shows almost linear shape of release rate, and cumulative drug release rate of scaffold DDS was higher than that of cylinder DDS. This was probably caused by the larger surface area of scaffold DDS, and the immune system might covered more of the cylinder DDS surface. The structures were relatively weak because these DDS mainly consists of biodegradable polymer which has low modulus. Thus, after two weeks of implantation, the stability was measured using optical micro scope (Sometech, ICS-305B). Fig. 6 shows that the scaffold DDS was more stable, or remaining the original cylindrical shape, than cylinder DDS. This might be affected by the body fluid in the pores inside of DDS.

4. Conclusions

To fabricate scaffold type and cylinder type DDSs, NCDS was applied. From the measurements of *in vivo* environment, scaffold DDS showed higher cumulative drug release and provided better stability than cylinder DDS. This experimental data showed controllable drug release rate of the implantable DDS made of three-phase composite materials. The effects of shape, pore size, and filament size on the characterization of DDS are under investigation.

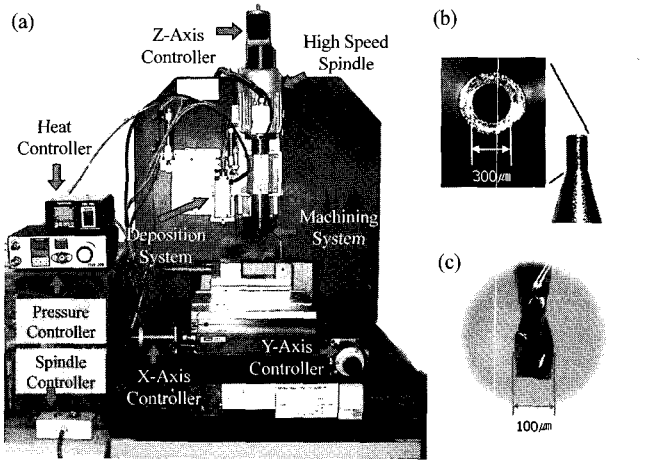


Fig. 2 Nano Composite Deposition System: (a) over all system, (b) Micro needle, and (c) Micro endmill

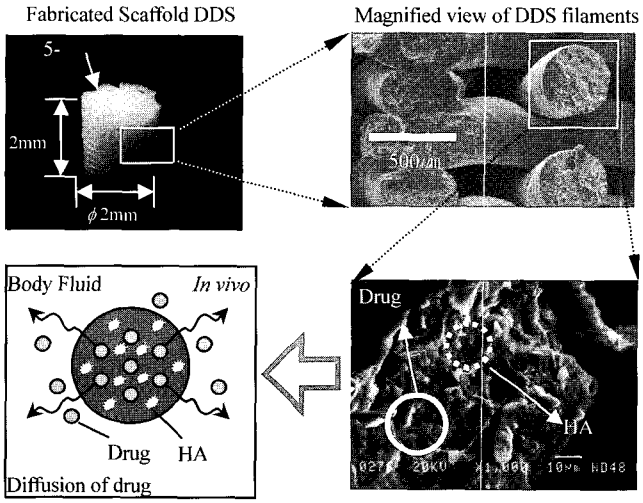


Fig. 3 Fabricated DDS and cross section of filament

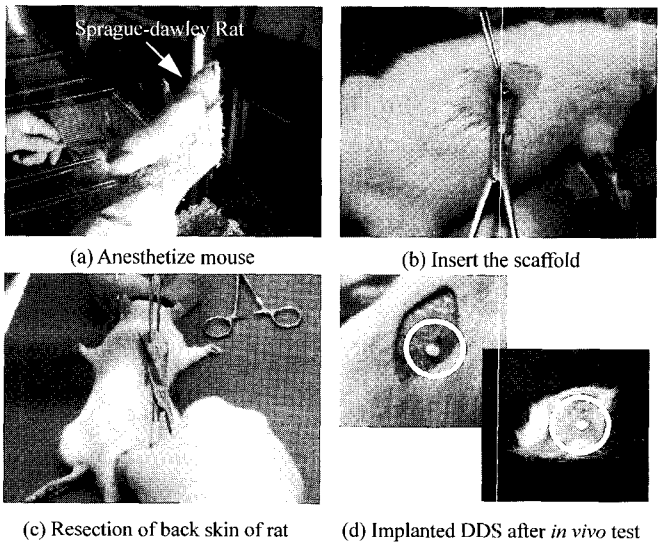


Fig. 4 Implantation and collection of DDS in the back of rat

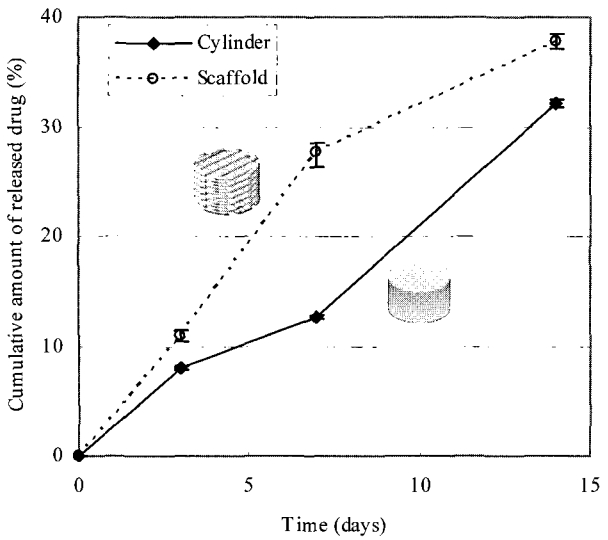
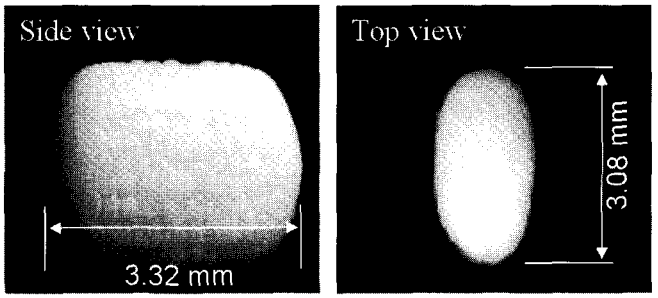
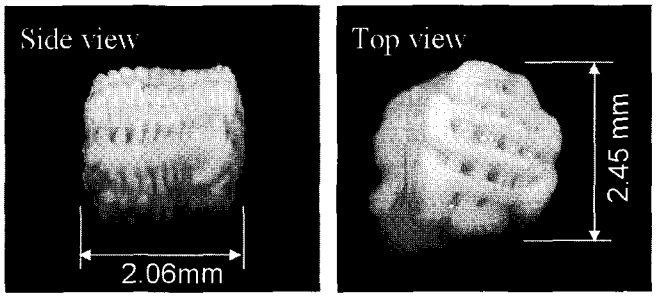


Fig. 5 Cumulative amount of drug release *in vivo* environment



(a) Cylinder type DDS



(b) Scaffold type DDS

Fig. 6 Shape changes in DDSs after two weeks of *in vivo* implantation

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