Engineered Microstructure Granules for Tailored Drug Release Rate

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Statement of Purpose: We developed specifically structured granules for controlled drug release rate, porous and hollow hydroxyapatite (HA) spherical granules conjugated with dexamethasone (DEX) loaded poly(lactic-co-glycolic acid) (PLGA) nano-particles. Our developed bone graft materials met the requirements of basic characteristics found in natural bone. Therefore, our biomaterials exhibit the potential for hard tissue regeneration and can be made patient-specific by controlling the DEX concentration.

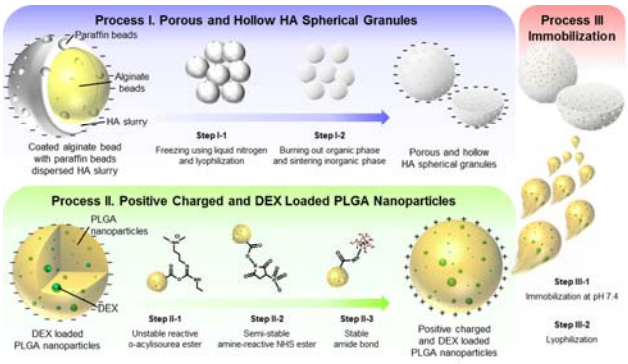

Figure 1. The representative scheme of this study.

Methods: Porous and hollow HA spherical granules were fabricated using a template method. Prepared alginate beads were coated with HA slurry (containing specific sized paraffin beads) and subsequently dropped into the liquid nitrogen. The HA coated beads were lyophilized and then organics were burned out by sintering process. DEX-loaded PLGA nanoparticles were fabricated and their surface was modified to positive charge by using EDC/NHS chemistry. These surface modified nanoparticles were immobilized to in- and outside of the HA granules which charge negatively.
We performed 1) physico-chemical analyses, 2) thermal analyses, 3) morphological analyses, 4) DEX release profiles, and 5) biological evaluations.

Results: The specific structured HA granules, containing the drug both in- and outside of the granules, showed the controlled drug release rate compared to the granules, which contain the drug only outside of the granules. The micro pores for insertion of drug carrying nanoparticles also had effects on the MC3T3-E1. These cells were able to migrate into the granules, resulting higher cell seeding efficiency compared to the granules that had no micro pores. The increased cell seeding efficiency consequently influenced the cellular behavior; the first was that the cell proliferation and DNA concentration on the specific structured HA granules were higher than the control until one week of cell seeding whether the granules contained DEX or not. The second was that the early stage of cell differentiation and the expression level of type-I collagen were higher until 2 weeks. The effect of controlled release rate of the drug was evident even after 2 weeks resulting in alkaline phosphatase activity and the expression levels of osteocalcin and runt-related transcription factor 2.

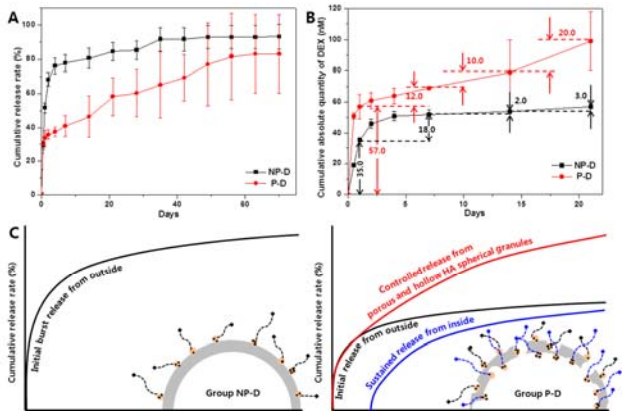

Fig. 2. (A) DEX release profiles from groups NP-D (non-porous with DEX) and P-D (porous with DEX). (B) Conversion to cumulative absolute quantity of DEX from relative release rate to compare with the results of ALP activity test. (C) These virtual graphs express that the multiple origins of drug show up the stepwise drug release kinetics and these result in controlled release.

Conclusions: These bone graft materials met the requirements of basic characteristics found in natural bone. There is no doubt the fact that the spherical shape of the granules can be filled into the complex bony defects. Micro pores helped the nano-sized drug carriers and the cells to migrate into the granules and these resulted in the increase of the drugs and cells seeding efficiencies more than the non-porous granules. It also could be expected that the vascularization and neo tissue growth would be progressed well through them. The other important purpose of this study was to control the drug release rate and we could control the rate by designing the stepwise drug release. DEX was adapted as biological factors to enhance the osteoinductivity of the HA spherical granules. From the results, these biological functioned bone grafts can be made patient-specific by controlling the drug concentration. These bone grafts also exhibit the potential for hard tissue regeneration.

References: Abbott A. Nature 2003;424:870-872.
Hong MH. J Mater Sci Mater Med 2011;22:349-355.