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Precise Control Delivery of Magnesium Ions thru sponge-like Monodispersed PLGA/nano-MgO-alginate Core-shell Microsphere Device to Enable In-situ Bone Regeneration

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ABSTRACT INTRODUCTION: Bone regeneration or fracture healing in particular to the patients with pathological bone diseases is challenging. Apart from the aid of growth factors, bone morphogenetic proteins and stem cells, our previous study evidenced that the magnesium ions at the range of 50-200 ppm in tissue microenvironment can significantly trigger new bone formation[1]. Hence, we propose to realize this concept by designing a novel delivery system to precisely control the magnesium ion delivery at the particular concentration in vivo in order to effectively stimulate in-situ bone regeneration. To achieve this objective, the sponge-like monodisperse PLGA/nMgO-alginate core-shell microsphere delivery system has been designed by using a customized microfluidic capillary device. A fixed amount of surface modified magnesium oxide (MgO) nano-particles is embedded within the poly(lactic-co-glycolic acid) (PLGA) matrix and the alginate is chosen to fabricate as the shell structure of core-shell microsphere.

METHODS: The PLGA/MgO-alginate core-shell microspheres were prepared by the oil/water/oil double emulsion method via the modified microfluidic capillary device. In brief, three kinds of fluids flowed into the modified microfluidic capillary device from different channels. The TMSPM-treated MgO nano-particles were suspended in 10%(w/v) PLGA solution (dissolved in DCM), named inner phase (oil phase). 10%(w/v) Span 80 in toluene was defined as the outer phase (oil phase), while 3%(w/v) PVA aqueous solution containing 1.5% (w/v) alginate was defined as the middle phase (water phase). The PLGA/nMgO inner phase flowed through the injected capillary and the alginate middle phase connected to the channel of square capillary. Then, the outer phase flowed through the channel between the collected capillary and square capillary and therefore the PLGA/MgO-alginate core-shell droplets can be yielded. The flow rates of inner phase, middle phase and outer phase had been accurately controlled at 500 μl/h, 800 μl/h and 2000 μl/h, respectively. The PLGA/nMgO-alginate core-shell droplets were then cross-linked with alginate to form the shell structure in a petri dish containing 0.1%(w/v) PVA calcium chloride aqueous solution. When DCM solvent evaporated, the PLGA/nMgO-alginate core-shell microspheres remained. Lastly, the core-shell microspheres were rinsed with deionized water and lyophilized for 48h.

RESULTS SECTION: The PLGA/nMgO-alginate core-shell microspheres measured in the diameter of 115.41±3.84μm were able to maintain the release of Mg\(^{2+}\) at ~50ppm per day for first 2 weeks and then ~100ppm per day until 28 days. With the aid of sustained and constant release of magnesium ions, the viability and proliferation as well as the osteogenic differentiation capability (i.e. ALP, Col I, Runx2 and OPN gene expression) of MC3T3-E1 pre-osteoblasts were significantly up-regulated, when cultured with PLGA/nMgO-alginate core-shell microsphere delivery system as compared with the control. Moreover, the new magnesium ion delivery system could effectively stimulate in-situ bone formation in vivo in terms of bone volume and trabecular thickness. Interestingly, higher bone mineral density (BMD) and increased Young’s modulus of newly formed bone were found in the PLGA/nMgO-alginate core-shell microsphere group after post-surgery eight weeks. The mechanical property of newly formed bone induced by this new delivery device was about 96% of that of the surrounding mature bone.

DISCUSSION: The positive effect of Mg\(^{2+}\) on osteogenesis has been demonstrated and the mechanism is thru either the enhancement of osteoblastic activities or the suppression of osteoclastic activities. However, high concentration of Mg\(^{2+}\)has detrimental effects on human osteoblast differentiation, osseous metabolism and homeostasis, thereby leading to defeated bone mineralization. Hence, it is a crucial step to precisely control the delivery concentration of Mg\(^{2+}\) into local tissue microenvironment if the concept of the use of Mg\(^{2+}\) to induce new bone formation is adopted clinically. While the sponge-like PLGA/nMgO porous core structure works as a reservoir of Mg\(^{2+}\), the alginate shell structure serves as physical barrier to reduce initial burst release of Mg\(^{2+}\) and facilitates the release of magnesium ions accurately via the chelation effect between Mg\(^{2+}\) and alginate hydrogel. Thus in-situ bone formation can be realized thru the stable release of Mg\(^{2+}\) by this customized delivery system.

SIGNIFICANCE: These results indicate that sustained and precisely controlled release of magnesium ions leads to enhanced osteoblastic bioactivity in vitro and apparent in-situ bone regeneration in vivo. Therefore, it is believed that this monodisperse PLGA/MgO-alginate core-shell microsphere system enabling precise control delivery of magnesium ions may provide a simple and cost-effective approach for local bone regeneration and healing clinically.


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IMAGES AND TABLES:

Fig. 1 Schematic diagrams of PLGA/MgO-alginate core-shell microspheres fabricated by microfluidic capillary device and their enhanced cytocompatibility and stimulation of in-situ bone regeneration