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Bioerodible devices for intermittent release of simvastatin acid

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Abstract

The association polymer system of cellulose acetate phthalate (CAP) and Pluronic F-127 (PF-127) was used to create intermittent release devices for mimicking the daily injection of simvastatin that has been reported to stimulate bone formation. To enhance solubility in water, prodrug simvastatin was modified by lactone ring opening, which converts the molecule to its hydroxyacid form. CAP/PF-127 microspheres incorporating simvastatin acid were prepared by a water–acetone–oil–water (W/A/O/W) triple emulsion process. Devices were then fabricated by pressure-sintering UV-treated blank and drug-loaded microspheres. Using a multilayered fabrication approach, pulsatile release profiles were obtained. Delivery was varied by changing loading, number of layers, blend ratio, and incubation conditions. To determine the cellular effects of intermittent exposure to simvastatin acid, MC3T3-E1 cells were cultured with either alternating or sustained concentrations of simvastatin acid in the medium, and DNA content, alkaline phosphatase activity, and osteocalcin secretion were measured. For all three cell responses, cultures exposed to simvastatin acid showed higher activity than did control cultures. Furthermore, cell activity was greater for cells cultured with intermittent concentrations of simvastatin acid compared to cells that were constantly treated. These results imply that devices intermittently releasing simvastatin acid warrant further study for locally promoting osteogenesis.

Keywords: Intermittent release; Controlled release; Pulsatile release; CAP/PF-127 system; Simvastatin acid

1. Introduction

The need to treat bone defects resulting from degenerative diseases, trauma, and reconstructive surgery continues to increase at a significant rate. More than 500,000 bone grafting procedures are performed annually in the United States (Popovic, 2001). Harvesting autogenous tissues requires an additional surgery at the donor site that can result in its own complications, such as inflammation, infection, and chronic pain. Also, the total amount of bone that can be harvested is limited and creates a supply problem. Although allograft tissue is treated by freezing, freeze-drying, gamma irradiation, electron beam radiation, or ethylene oxide, because it is obtained from a donor, a risk of disease transmission from donor to recipient exists (Boyce et al., 1999). These problems have led to development of drug delivery devices, synthetic materials, and tissue engineered constructs for use as alternatives to autografts and allografts in bone repair.

Simvastatin is a well-known member of the statin family. Statins are potent pro-drugs of hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors that block conversion of HMG-CoA to mevalonic acid, which is needed for cholesterol biosynthesis (Sugiyama et al., 2000). Simvastatin occupies a portion of the binding site for HMG-CoA, thus blocking access of substrate to the active site (Istvan and Deisenhofer, 2001). Mevalonic acid is a precursor not only of cholesterol but also of isoprenoids, such as geranyl pyrophosphate, which is important in the control of osteoclast-mediated bone resorption (Casey and Seabra, 1996). Statins offer additional benefits, such as promotion of new blood vessel growth (Kureishi et al., 2000) and anti-inflammatory effects (Davignon and Laaksonen, 1999). Most relevant to the present work, Mundy's group originally demonstrated that statins induce expression of bone morphogenetic protein 2 (BMP-2) and that they stimulate bone formation on the calvaria of mice following daily subcutaneous injections (Mundy et al., 1999). Subsequent studies have shown

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