Calcium Phosphates in Drug Delivery: Adsorption and Release Kinetics of Lovastatin

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Introduction: Lovastatin, HMG-CoA reductase inhibitor, is a cholesterol lowering drug. HMG-CoA inhibition by lovastatin blocks the downstream pathway of cholesterol biosynthesis [1]. The immediate downstream metabolite intermediate mevalonate is believed to inhibit osteoblast activity. Another metabolite of this pathway, prenylated molecules, contributes in bone resorption by promoting osteoclast activity [2]. Scaffolds with 3D interconnected channels provide better mechanical interlocking between scaffolds and surrounding bone for improved cell-material interactions and pathways for micronutrients transfer. **Objective** of this research is to understand the chemistry of adsorption and release kinetics of lovastatin in 3D interconnected macroporuss calcium phosphate (CaP) scaffolds. Our **hypothesis** is that improved tissue material interaction in interconnected macroporous CaP scaffolds along with enhanced osteoblast differentiation and inhibited osteoclast activity by lovastatin will accelerate the healing time. The **rationale** is that once we understand the chemistry of adsorption and release of lovastatin on and from 3D interconnected macroporous CaP scaffolds, we should be able to design and tailor bone grafts to enhance osteoblast activity or decelerate osteoclast activity *based on application needs.*

Methods: Lovastatin was obtained from Sigma-Aldrich in its inactive lactone form and converted to active hydroxyl acid form by hydrolyzing with sodium hydroxide at 60 °C for 2h, and then neutralized by HCl to pH 7.2. **Fig. 1** shows the two forms of lovastatin. The final concentration of this water soluble hydroxyl acid form of lovastatin solution was 5 mM. Adsorption isotherm study was carried out at seven different micromole concentration, 10, 20, 30, 40, 50, 70, and 90 µM respectively. FTIR was carried out for lovastatin adsorbed CaP. Differential scanning calometry (DSC) was also performed on the TCP before and after lovastatin adsorption. Release study was done at three different pH, 7.4, 9, and 2 at 37 °C for up to 48h. For release measurement by UV spectrophotometer, solutions were withdrawn at certain time intervals.

Results: Adsorption isotherm obtained for lovastatin shows a sigmoidal shape, as shown in **Fig. 2**. This

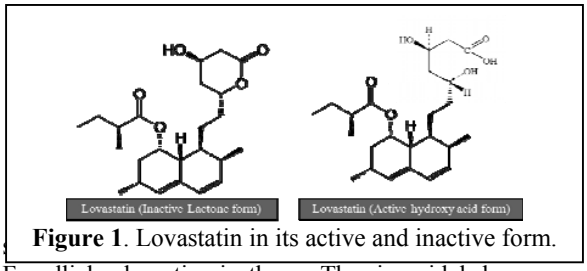

Figure 1. Lovastatin in its active and inactive form.

Frendlich adsorption isotherm. The sigmoidal shape indicates a cooperative effect, and cooperative effects are seen when there is interaction between neighboring adsorbed molecule. DSC thermogram, **Fig. 3**, shows

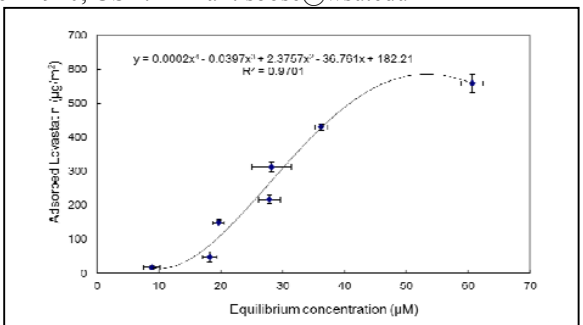

Figure 2. Adsorption isotherm of lovastatin on β-tricalcium phosphate (β-TCP) scaffold.

an endothermic peak at 184 °C due to adsorbed lovastatin on TCP. Release measurement at 239 nm did not detect any release at pH 7.4, 9, and 2.0. No release detection of lovastatin could be due to water insoluble complex formation of lovastatin with Ca^{2+}, and thus remains undetectable in the UV region due to its insoluble nature. The complex formation between calcium-lovastatin was further confirmed by reaction between lovastatin and $CaCl_2$, which showed a decreasing trend in λ_{max} with increasing $CaCl_2$ concentration. The sigmoidal adsorption isotherm also supports the complex formation. The complex formation might have led to the cooperative effect. A suitable analytical technique is under investigation to detect possible release.

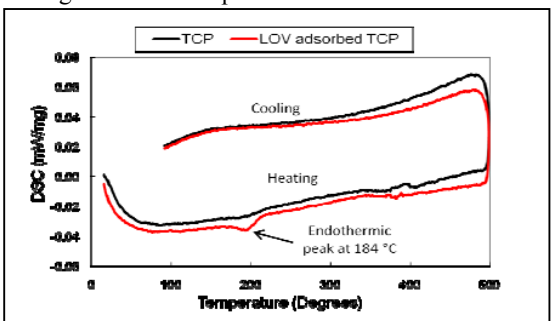

Figure 3. DSC thermogram of TCP and lovastatin adsorbed TCP.

Conclusions: DSC study shows lovastatin adsorption on CaP composites. The understanding of chemistry between lovastatin and calcium phosphate can open up new avenues to develop new drug delivery system for early stage healing or treating osteoporosis like diseases.

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References: 1. Demierre MF. Nature Reviewes: Cancer 2005; 5: 930-942; **2**. Hughes A. Calcif Tissue Int 2007; 81:403–413.