Bilayered Calcium Sulfate Space-Making Composites with Multiple Drug Delivery Capabilities

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Introduction

The capacity to quickly regenerate or augment bone lost as a result of resorption is crucial to ensure suitable application of prosthetics for restoring masticatory function. To achieve this ideal end point, however, the treatment may need to be designed on a patient-to-patient basis utilizing the combination of multiple drugs and release approaches. Bilayer calcium sulfate (CS)-based composites are being developed that will act as 'tenting' barriers to soft tissue infiltration, while allowing a well-tailored delivery of a variety of treatment specific drugs directly loaded in a CS matrix and/or embedded in poly(β-amino ester) biodegradable hydrogel particles. Release of simvastatin that was directly loaded into different components of bilayered implants as well as simultaneous release of directly loaded simvastatin and metronidazole loaded in hydrogel particles from single-layered devices was investigated.

Methods

Bilayered CS composites were produced in a multi-stage process. Using calcium sulfate hemihydrate as the main structural component, cores were produced by mixing 1 gram CS powder with 800µL of deionized (DI) water and injected into a mold with an average diameter of 2.4mm and a height of 6.5mm, kept at 43°C for 24 hrs. Finished cores were suspended in a larger mold that allowed for a CS mixture to be injected, completely surrounding the CS cores. Finalized samples had an average diameter of 4.7mm and a height of 9.5mm. Fig.1 demonstrates the fabrications process. To test the release of drug from different CS layers, 16mg of simvastatin was directly mixed into 1g of CS and combined with 800µL DI and used to produce either the shell only, core only, or both. To determine the composites' ability to deliver different drugs simultaneously, a single-layered system was made with directly loaded simvastatin and H6 poly(β-amino ester) hydrogel (HG) particles [*J. Appl. Polym. Sci.* 122:1420, 2011] containing metronidazole. To make these samples, 0.1 g (10% of total composite mass) HG, 2mg simvastatin, 0.8 g CS, and 900 µL DI water were mixed and injected into a mold having an average diameter of 4.7 mm and a height of 6.5 mm. The mold was placed in a 43ºC oven for 24 hrs. All release studies were performed in 4mL phosphate buffer saline (PBS) at 37°C.

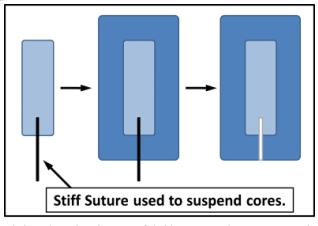

Figure 1: Graphic depiction of bilayered composite fabrication.

Results and Discussion

Fig. 2 shows the cumulative release of simvastatin from bilayered composites. Simvastatin loaded into the shell had a sustained release during the first 12 days of the study. The majority of drug loaded into the core was released after day 12, during which the core was exposed due to dissolution of the CS shell. When summed together, these two plots equaled the total amount of drug released from the entire composite.

Fig. 3 shows the cumulative release of directly loaded simvastatin and metronidazole that was loaded into biodegradable HG particles embedded in CS. The experiment demonstrated a sustained release of simvastatin, whereas the release of metronidazole had a large burst followed by negligible release for the remainder of the test. Sustained release of simvastatin was not altered by the presence of another drug or the hydrogel delivery vehicle. The lack of a controlled release of metronidazole from HG, however, may be affected by the simultaneous drug release and will need to be investigated further.

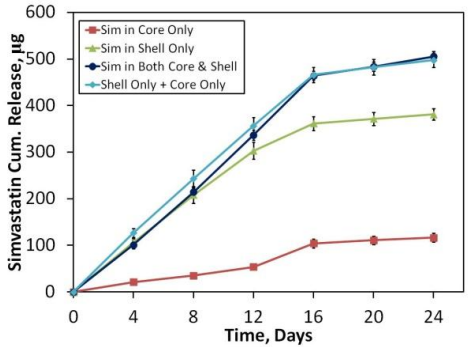

Figure 2: Cumulative release of simvastatin directly loaded into different components of bilayered implants.

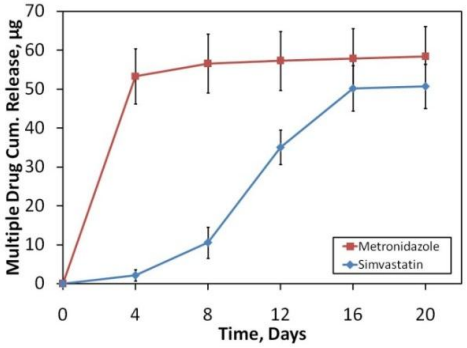

Figure 3: Cumulative release of directly loaded simvastatin and metronidazole loaded in HG.

Conclusion

Having the ability to tailor the release of multiple drugs from bilayered CS composites can be useful to help rapidly regenerate tissue. Further release studies will investigate altering drug loadings as well as release of multiple agents from layered composites to enhance the delivery capabilities of the devices.

Acknowledgement

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