Engineering Biomaterial Surfaces for Controlled Release of Therapeutics

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Statement of Purpose: The aim of this study was to develop a general approach for non-covalent immobilization of proteins onto polymeric and ceramic particulate surfaces. We utilized Bioplant®-HTR® (Bioplant Inc., New York, NY; by United States Surgical Corporation, Norwalk, CT), an FDA approved hard tissue replacement material that is currently used as a socket filler in dentistry. Bioplant-HTR is derived from poly(methymethacrylate) as a test substrate and has been shown to promote bone formation in dental osseous environment. Additionally, Bioplant-HTR can be dispersed into a photo-curable carrier for minimally invasive maxillo-facial reconstruction (Yukna RA J Periodontol. 1994; 65:342-349).

Methods: Bovine serum albumin (BSA) was mixed with lactose and the uniformity of the composition was verified. Formulated protein was mixed with a gelatin binder and forced through a sieve to yield granules (Baroli B. J Pharm Sci. 2002; 92:1186-1195). The protein granules were immobilized onto the HTR surface using water-soluble polymeric binders. In this study we explored two such binders: polyvinyl alcohol (PVA, Aldrich); and the poloxamer (Pluronic®, BASF Corporation, Mount Olive, NJ). Both PVA and Pluronic have sufficient biocompatibility in low concentrations and are deemed safe for in vivo use. In the first step, the HTR particles were coated with the binder and, then, following a brief drying step, the protein powder was immobilized by physical mixing in a pestle and mortar. Three different protein:binder (PB) ratios (0.5:1; 1:1 and 2:1 w/w) were studied. Protein release from HTR and dispersed into a hydrophilic photo-crosslinked poly(ethylene glycol)-diacrylate (PEG-DA) network were assessed. The protein release studies were carried out as follows. Briefly, HTR with PVA coating (HPV), HTR with Pluronic coating (HP), and HPV-PEGDA matrices were incubated in 10 ml PBS in a scintillation vial and the release buffer was removed periodically at pre-determined time-points, replaced with fresh release buffer, and protein content assayed using the Coomassie protein assay.

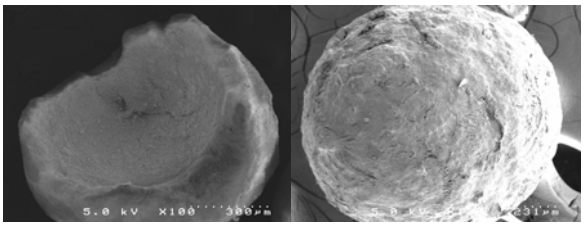

Figure 1: SEM images of the HTR particles: uncoated (left) and coated (right).

Results/Discussion The process yielded binding of 3.11±0.58, 4.07±0.88 and 9.05±1.99mg of BSA/100mg HTR in PVA system (HPV), and 2.84±0.83, 3.33±1.05 and 4.94±0.47mg of BSA/100mg HTR in the Pluronic system (HP), for 0.5:1, 1:1 and 2:1 PB ratios. In general increase in PB ratio resulted in increased BSA association with the HTR. HPV exhibited sustained release over 36-hours with 32, 28 and 20% released in 30 minutes for 0.5:1, 1:1 and 2:1, respectively; and 100% release at 36 hours. In the HP system, the release was of 25, 26 and 16% in 30 minutes with 100% released by 72 hours. In the HPV system upon incorporation into the PEGDA matrix, the initial burst at 24 hours was directly proportional to the amount of protein on the HTR grafting material, with a release of 93, 89 and 88% respectively. Interestingly, BSA release was observed up to one week, at which time 100% release was attained for all formulations. The release of other model proteins such as horseradish peroxidase (HRP) and growth factors relevant to bone tissue regeneration is currently being explored. These studies will additionally shed light the effect of the processing technique on activity of the protein

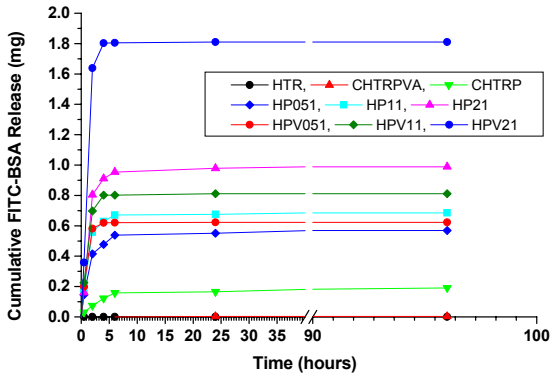

Figure 2: Cumulative BSA release from HTR particles. X axis: time (hours); Y axis: amount (mg).

Conclusions: A non-covalent strategy to immobilize proteins onto a biomaterial surface has been developed. Short term sustained release of a model protein from modified HTR surface has been demonstrated. Furthermore, enhancement of sustained release has been achieved by dispersing the HTR in a photocurable matrix. HTR surface modified with the appropriate osteogenic factors has the potential to offer superior clinical outcomes with respect to new-bone formation in reconstructive dentistry.

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