Functionalization of oligo(poly(ethylene glycol)fumarate) hydrogels with finely dispersed calcium phosphate nanocrystals for bone-substituting purposes

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Statement of Purpose: From an engineering point of view, bone tissue is best described as a nanocomposite consisting of a polymeric matrix of collagen fibers, which is reinforced by a mineral dispersion of nanosized, apatitic calcium phosphate (CaP) crystals. In that respect, biodegradable polymers that can be processed into injectable hydrogel matrices are promising candidates for bone-substituting purposes, especially when degradable CaP particles and growth factors are incorporated into these hydrogel matrices. In that way, a fully degradable bone construct can be designed which stimulates the formation of new bone by the surrounding tissue, thereby compensating for the loss of structural integrity of the degrading synthetic bone-substitute.

Generally, a major challenge in synthesis of nanoceramic-reinforced polymers is the achievement of a fine dispersion of nanoparticles throughout the polymer, since the unique properties of nanocomposites are lost when nanoparticles aggregate. Therefore, composite hydrogels, consisting of oligo(poly(ethylene glycol)-fumarate) (OPF) matrices and CaP dispersions of varying crystallinity, were developed in the current study using physical or chemical preparation strategies in order to investigate the influence of the mixing step on the final dispersity of the produced hydrogels.

Methods: OPF hydrogels were synthesized according to an established method[1]. The conversion of PEG to OPF was confirmed by means of GPC, FTIR, and NMR analyses. A classical, wet-chemical precipitation method was used to synthesize apatitic nanoparticles with varying crystallinity by dripping phosphoric acid into a suspension of calcium hydroxide[2]. Two methods of component mixing were employed: the first method involved physical incorporation of dried, micron-sized CaP powders into OPF matrices by means of vortexing and sonication of the mixtures prior to crosslinking, whereas the second method involved chemical mixing of CaP nanoparticles with OPF upon CaP precipitation in the presence of dissolved OPF macromers. The hydrogels were characterized using microcomputed tomography, scanning electron microscopy, and infrared spectroscopy. Physically and chemically mixed OPF/CaP hydrogels were soaked in SBF (Simulated Body Fluid) for four weeks to study the influence of CaP incorporation on hydrogel swelling behavior.

Results/Discussion: Physical mixing of dried, micron-sized CaP powders resulted into formation of irreproducible composites with a highly heterogeneous dispersion of large and agglomerated CaP microparticles throughout the OPF matrix. On the contrary, reproducible and homogeneous hydrogels were fabricated using a chemical mixing strategy, whereby CaP crystals were formed in the presence of dissolved OPF macromers. This co-precipitation technique resulted into a much higher degree of dispersion of the CaP crystals, which can enable higher CaP contents in organic matrices such as OPF. By using these CaP suspensions instead of dried powders, the nanosized structure of separated CaP crystals was preserved (Fig. 1), resulting into a higher reactivity of the CaP phase, as indicated by reduced swelling behavior of these composite hydrogels.

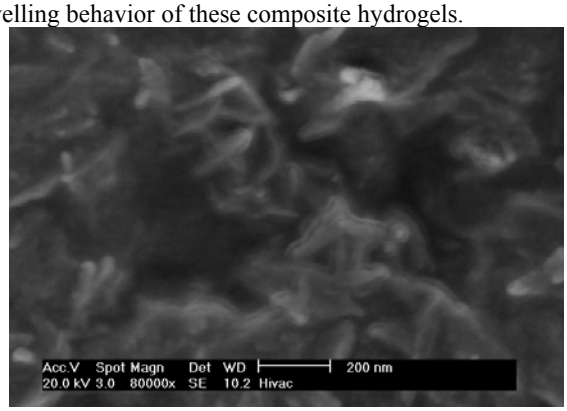

Figure 1: SEM image of a nanostructured OPF/CaP composite hydrogel after lyophilization for 24 hours.

This effect was most likely caused by a physicochemical interaction between Ca^{2+} and unreacted COOH-endgroups, thereby leading to increased physical crosslinking of the composite hydrogels.

Conclusions: Composite hydrogels, consisting of OPF matrices and a CaP dispersion of varying crystallinity, were successfully developed using two preparation strategies. Physical mixing of dried, micron-sized CaP powders resulted into formation of irreproducible composites with a highly hetereogeneous dispersion of large and agglomerated CaP microparticles throughout the OPF matrix. On the contrary, reproducible and homogeneous hydrogels were fabricated using a chemical mixing strategy, whereby CaP crystals were formed in the presence of dissolved OPF macromers. This co-precipitation technique resulted into a much higher degree of dispersion of the CaP crystals, and a higher reactivity of the CaP phase due to the preservation of the CaP nanostructure.

References:

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