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In vivo performance of microstructured calcium phosphate formulated in novel water-free carriers

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ABSTRACT

Osteoinductive calcium phosphate (CaP) ceramics can be combined with polymeric carriers to make shapeable bone substitutes as an alternative to autologous bone; however, carriers containing water may degrade the ceramic surface microstructure, which is crucial to bone formation. In this study five novel tricalcium phosphate (TCP) formulations were designed from water-free polymeric binders and osteoinductive TCP granules of different particle sizes (500–1000 μm for moldable putty forms, and 150–500 μm for flowable paste forms). The performance of these novel TCP formulations was studied and compared with control TCP granules alone (both 150–500 and 500–1000 μm). In vitro the five TCP formulations were characterized by their carrier dissolution times and TCP mineralization kinetic profiles in simulated body fluid. In vivo the formulations were implanted in the dorsal muscle and a unicortical femoral defect (Ø = 5 mm) of dogs for 12 weeks. The TCP formulation based on a xanthan gum–glycerol carrier exhibited fast carrier dissolution (1 h) and TCP mineralization (7 days) in vitro, but induced inflammation and showed little ectopic bone formation. This carrier chemistry was thus found to disrupt the early cellular response related to osteoinduction by microstructured TCP. TCP formulations based on carboxymethyl cellulose–glycerol and Polyoxyl 15-hydroxystearate–Pluronic® F127 allowed the in vitro surface mineralization of TCP by day 7 and produced the highest level of orthotopic bone bridging and ectopic bone formation, which was equivalent to the control. These results demonstrate that water-free carriers can preserve the chemistry, microstructure, and performance of osteoinductive CaP ceramics.

1. Introduction

The clinical use of synthetic bone graft substitutes has steadily grown due to improved material performance and an aging population which requires more bone grafting procedures annually [1,2]. These substitutes are used as an alternative to autograft tissue, which is in limited supply and can engender donor site pain, morbidity, and infection [3,4]. Currently bone graft substitutes such as calcium phosphate (CaP) ceramics can be applied as bone void fillers and are used to treat a variety of cranio-maxillofacial [5], foot and ankle [6], long bone [7], and vertebral bony defects [8].

The bone repair potential of CaP ceramics was first documented by Albee and Morrison in 1920, when they applied injectable tricalcium phosphate to repair one-quarter inch radial defects in rabbits [9]. More widespread development and use came later, in the 1970s [10], ranging from periodontal to orthopedic applications [11,12]. In the early 1990s the intrinsic capability of some CaP ceramics to induce bone formation in non-osseous (ectopic) sites without the addition of committed osteoblasts, stem cells, or growth factors, defined as osteoinduction, was described, confirmed, and characterized by various authors [13,14]. The precise mechanism of osteoinduction by biomaterials is unknown, but current understanding emphasizes the importance of the micro- and nanostructure of the ceramic surface for bone formation [15]. The clinical utility of osteoinductive CaP ceramics have been demonstrated in critical sized bone defects, showing that these materials are better orthotopic bone void fillers than those that are merely osteoconductive, which guide bone formation given the presence of committed osteoblasts but do not induce its formation through the differentiation of stromal precursors [16,17].

In many clinical applications the preferred handling properties of a bone graft substitute are cohesive moldability or injectability in order to fill complex volumetric defects, as in mandibular alveolar ridge reconstruction [18], or span between bony surfaces, as in spine fusion [19]. For this purpose CaP cements have been developed as alternatives to the classical granular or block forms [20–22], but inherent drawbacks include unstable flowability, which

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