



## Abstract **Preliminary Mechanosynthesis Map in the CaCO<sub>3</sub>-H<sub>3</sub>PO<sub>4</sub>-H<sub>2</sub>O System**<sup>+</sup>

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Calcium phosphates can be used, individually or combined, to clinically promote bone healing. This creates synthetic CaP-prevalent materials in bone tissue engineering, sustained by a range of properties: they are biocompatible and bioactive, promote osteoconductivity and a strong osteointegration, and their stability in body fluids can be tailored to render inert, bioactive and bioresorbable materials. Current applications in bone tissue engineering include bone substitution and filling, bone cements and remineralization intermediates, coating on orthopedic implants and grafts for spinal fusion. A range of dry, wet and high-temperature chemical processes is available to prepare synthetic calcium orthophosphates through a reaction between a Ca<sup>2+</sup> and a PO<sub>4</sub><sup>3-</sup> source. Yet, the very low reaction kinetics hinder the production of thermodynamically stable products, namely, of the most biomedical significance (including hydroxyapatite).

This work explores the ability of high-energy milling to enable a significant reactivity increase via the energy transferred to reagents when they are impacted. Mixtures of CaCO<sub>3</sub>,  $H_3PO_4$  and  $H_2O$  reagents complying with a Ca/P = 1.67 molar ratio and  $H_2O$  between 6 and 82 wt% were submitted to high-energy ball milling at 600 rpm from 0.5 to 12 h.

The synthesized calcium phosphates include hydroxyapatite, brushite and monetite in the form of nano or submicrometric particles. The produced materials exist within specific milling duration domains, while the liquid/solid ratio plays a major role in the onset of hydroxyapatite formation and the stability limits of monophasic hydroxyapatite. Obtained results were used to build a preliminary milling map for the system that allowed to adjust experimental parameters to obtain the desired final product under specific milling conditions. Overall, the ability of high-energy milling as an adequate route to produce calcium phosphates was demonstrated. This signals to a window of opportunity for the development of a reliable, scalable, fast and cost-effective production method for biomedically significant calcium phosphates.

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