

Antimicrobial ionic liquids in bioactive sol-gel hydroxyapatite for bone tissue engineering

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Introduction: Bacteria and fungi can often adhere to biomaterials and have the capability of forming biofilms on foreign bodies. The detachment of cells from these biofilms can result in the development of systemic infections in patients. It has been suggested that the local application of antimicrobials can provide higher local antibiotic concentrations than those through intravenous application, and can also avoid the toxicity accompanied with high plasma levels. Thus, an effective approach would be creating a material able to regenerate the tissue in the bone defect and at the same time presenting antimicrobial activity, which was the goal of this study. It has been demonstrated that some imidazolium, pyridinium and quaternary ammonium ionic liquids (IL) have antimicrobial activity against a panel of clinically significant bacterial and fungal pathogens. Moreover, innovative hybrid materials can be synthesized via the sol-gel method using IL either as solvent, co-solvent or template. The in situ application of IL into sol-gel processes allows nanoparticles' structure control, driven by the IL' self-assembling property and selective IL-substrate interactions while preserving their specific properties. In this work IL were incorporated in hydroxyapatite (HA) during the sol-gel process in order to obtain an injectable material with bioactive, biocompatible and antimicrobial properties.

Materials and Methods: The HA/IL gel materials were obtained by re-suspending IL [C_nMIm]Cl with different chain-lengths in the gelling HA water solution. Physicochemical and mechanical investigations of these hybrids were performed to evaluate the composition, chemical interactions among the phases and the effect of IL on the rheological properties. TEM analysis was used to evaluate the HA nanoparticles morphology changes after interacting with IL. The biological properties in terms of cytotoxicity, proliferation and osteogenic differentiation of hMSC, were investigated.

Results and Discussion: In general, the insertion of IL into the setting gels induced a shorter gelification at room temperature and an increase in crystallinity in comparison with the neat HA system. TEM investigations (Fig. 1) demonstrated an important role of the IL-structure on the nanoparticles size and HA morphology. IL interact with the growing particles through the hydrogen bond "co- π - π stacking" mechanism, which creates an IL-layer on the HA surface. Thus, differences in the size, geometry and Coulomb coupling forces between ILs' anions and cations contribute directly to the

final HA particle size and morphology. Additionally, the hydrophobic tail-tail interactions in IL with longer cation side-chains caused the formation of bigger agglomerates than in the case of shorter alkyl chains. The biological analyses showed no cytotoxic effects and good biological response on hMSCs.

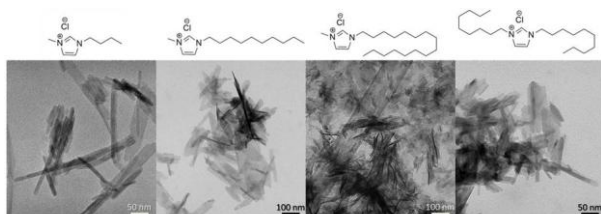


Fig. 1 HA morphology changes depending on IL applied.

Conclusions: Injectable hydroxyapatite gels of IL with different chain-length can be synthesized at room temperature by the sol-gel approach. Hybrids of IL with longer cation side-chains in HA gels demonstrated good antimicrobial properties. The presence of IL doesn't influence the effect of HA on the hMSC differentiation process in osteoblast-like cells, thus suggesting the potential of these biomaterials to prevent bacterial infections and improve bone formation in treated defects.

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