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Title: Collagen/multi-substituted apatite composite as a bone substitute material

Abstract

Bone tissue is a porous, hierarchical structure chemically composed of type I collagen, biological apatite (nanocrystalline calcium phosphate apatite) and water. It is often described as a natural composite with a specific microarchitecture that determines its unique properties: lightness while ensuring appropriate hardness and flexibility. A special feature of bone tissue is the ability to remodel and independently repair micro-damages. An imbalance between the processes of resorption and bone formation is responsible for the development of bone diseases. Many bone tissue diseases (cancer, cancer metastases, bone infections, osteoporosis or complicated fractures) require surgical intervention.

Modern implantology is looking for artificial bone substitute materials that can act as a scaffold for the newly formed bone tissue and, at the same time, are highly biocompatible, bioactive, bioresorbable and do not cause an immune response. Materials of this type must be characterized by appropriate porosity, mechanical strength and favorable physicochemical properties.

Commercially available bone substitute materials are often produced on the basis of synthetic, unsubstituted calcium phosphate apatite, which is characterized by low resorption and bioactivity. Recently, many research centers have been conducting research on modifying the structure of synthetic hydroxyapatite with ions, obtaining mono- and dual-doped materials. The physicochemical analysis of the obtained apatites proves that they are usually nanocrystalline and have much better solubility than pure, unsubstituted hydroxyapatite. Moreover, in recent years, there has been a growing interest in composite materials which, in addition to the mineral component, contain a synthetic or natural polymer that provides greater flexibility and durability.

The main research objective of this dissertation was to obtain a highly biocompatible and bioresorbable composite that resembled bone tissue in chemical composition, morphology and structure. In the present work, I focused on obtaining nanocrystalline calcium phosphate apatite that mimics biological apatite. I decided to introduce into its structure the most common "impurities" of bone apatite, namely Na^{+}, Mg^{2+} and CO_3^{2-} ions. Due to its well-

documented antiresorptive, osteogenic and antibacterial activity, I decided to incorporate Zn^{2+} ions additionally. The obtained powder materials were subjected to detailed physicochemical analysis and preliminary *in vitro* cytotoxicity tests.

Then, I used multi-substituted apatite to obtain composites based on a polymer of natural origin - collagen. I used various types of collagen to finally choose the most favorable formulation for obtaining multifunctional composite materials that also serve as drug carriers. Conventional pharmacotherapy of bone disorders is not easy and effective, among other reasons due to poor blood supply to bone tissue. Intraosseous drug delivery could increase the effectiveness of therapy, while negating the side effects that occur with systemic administration.

The next step was to enrich the composites with various biopolymers, which allowed to obtain a new form of biomaterial - three-dimensional granules. I investigated the impact of the presence of additional organic ingredients on the physicochemical properties of the materials, their biocompatibility, as well as the kinetics of drug and ion (Mg^{2+} and Zn^{2+}) release from the composite structure.

Based on the results, I concluded that the obtained composite materials could act as multifunctional bone scaffolds and dressings that would release the therapeutic substance and ions directly at the target site of action, treating inflammation after surgical procedures or inhibiting excessive bleeding, while restoring and regenerating bone tissue.

The results presented in this dissertation are of a basic nature. The obtained biocompatible materials inspired by the structure of bone tissue exhibit the desired physicochemical and biological properties. In further stages, *in vivo* tests should be planned to check the application possibilities of the obtained biomaterials, especially in dental surgery and for the regeneration of bone defects.

The research I conduct is interdisciplinary. They combine knowledge of modern pharmaceutics, biomaterials engineering, materials chemistry and physicochemical analysis. This dissertation consists of a series of published papers on the synthesis and physicochemical studies of powdered multi-substituted apatites and composite materials. The following chapters provide a concise description of the theoretical basis, research methodology and the results, which are extended and supplemented by the scientific monographs included at the end of this dissertation.

Keywords: biocomposite; collagen; hydroxyapatite; biomimetic material; bone tissue regeneration; multi-substituted apatite; drug delivery; zinc

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