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Synthetic hydroxyapatite in pharmaceutical applications

Joanna Kolmas*, Sylwester Krukowski, Aleksandra Laskus, Maria Jurkitewicz

Medical University of Warsaw, Faculty of Pharmacy and Laboratory Medicine, Department of Inorganic and Analytical Chemistry, ul. Banacha 1, 02-097 Warsaw, Poland

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Abstract

Synthetic hydroxyapatite plays a key role in implantology, stomatology, and regenerative medicine. Thanks to its non-toxicity and biocompatibility with bone and mineralised dental tissues, it has found application as a bone substitute. The fact that porous granules and scaffolds can be made out of nanocrystalline hydroxyapatite, and that it has a high loading capacity, means that it can be used in pharmaceutical science as a carrier for drugs or a system for controlled drug release. The aim of this study is to present current trends in research on synthetic hydroxyapatite as a carrier for drugs used in the local treatment of bone tissue disorders (multifunction implants) and poorly soluble drugs, including those with limited bioavailability.

Keywords: Hydroxyapatite; Pharmacy; Drug delivery systems; Carrier; Multifunctional implant

1. Introduction

Synthetic hydroxyapatite (HA, general formula $Ca_{10}(PO_4)_6(OH)_2$) is a material commonly used in biomaterial engineering and regenerative medicine for bones [1,2]. It displays high biocompatibility with biological apatite, the main component of the mineral fraction of bones and dental tissues. Biological apatite is a nanocrystalline multi-substituted carbonated HA, deficient in calcium and with a reduced number of structural hydroxyl groups. This characteristic composition provides apatite with unique physicochemical and biological properties [3,4].

Synthetic HA, due to its non-toxicity and osteoinductive properties, is widely used as a component of bone fillers and bone supplements. It is also fairly frequently applied as an implant coating to facilitate osteointegration [2].

Modern biomaterial engineering involves modifying synthetic HA-based materials. The aim is to synthesise a material with properties that resemble biological apatite as closely as possible [5]. In order to achieve this goal, several ionic substitutions are proposed [6]. Moreover, ionic modifications may provide the material with additional, beneficial characteristics, e.g., antibacterial properties [7] or the ability to facilitate osteointegration [6,7].

Another direction of apatite bioengineering development is the production of drug delivery systems (DDSs) and controlled drug release systems that show good adsorption properties [8]. This concerns both apatite powders and various porous forms. Porous HA structures impregnated with the appropriate drug form a system that precisely delivers the drug to the affected area, and also constitutes a scaffold for the newly built bone [9]. This property is, of course, used in developing new DDSs in the therapy and prophylaxis of bone disorders, primarily osteoporosis, bone tumours, and bone metastases. Also of extreme importance is research on systems that deliver antibiotics directly to hard tissues (a necessary prophylaxis during bone surgeries) [8].

Apart from skeletal drug delivery systems, attempts are also being made to use apatites as carriers for other drugs, e.g., hormones, anti-inflammatory substances, or vitamins [8,9] (Fig. 1). The published works include numerous studies on HA used as a carrier for proteins and in gene therapy [8–10]. In this case, nanocrystalline HAs are the most popular

*Corresponding author. Tel.: +48 22 5720755; fax: +48 22 5720784.
E-mail address: joanna.kolmas@wum.edu.pl (J. Kolmas).

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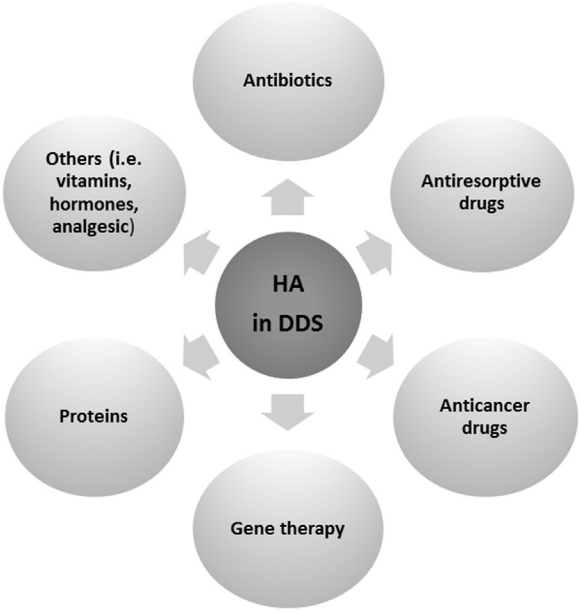

Fig. 1. Schematic illustration of pharmaceutical applications of hydroxyapatite.

materials; they are excellent nanocarriers, thanks to their biodegradability, non-toxicity and high loading capacity.

The DDS based on hydroxyapatite may be obtained by different ways, such as adsorption, chemical linking or physical and mechanical aspects. Preparation strategies are described in detail by Loca et al. [11].

It should be noted that, prior to clinical application, medical substances require proper preparation to create a suitable form of the drug, which will enable its delivery, release and absorption, and the initiation of a cascade of biochemical reactions resulting in the desired therapeutic effect [12]. This is why the current research aims to develop innovative, highly biocompatible, biodegradable and bioresorbable drug carriers that, in addition to their primary role as carriers, could restore lost tissue by forming a support that would allow the tissue to regenerate and stimulate remodelling processes.

Thus, the application of calcium phosphates (CaPs), especially HA, as carriers of drugs used in bone tissue disorders, seems particularly justified. The chemical properties of HA prevent the development of oral therapeutic systems, as the highly acidic gastric content would degrade the material instantly. A possible solution would be to develop an intestinal (pH 8–9) system with a controlled, targeted release. However, current research trends favour systems delivered locally, directly to the bone tissue, or as the coating of implants. In this case, apatite becomes a highly biocompatible and osteoinductive carrier for the active substance, which also restores tissue loss and allows the tissue to regenerate more quickly [8–12].

This work is a review of research directions for the use of HAs in pharmaceutical science, as delivery and controlled release systems for various drugs. HAs modified with therapeutically active ions – such as ions used in tumour treatment (magnetics) that induce hyperthermia, or ions with antibacterial properties – were excluded from consideration. The study reviews only HA/adsorbed drug systems, including current knowledge on the subject, trends in biomaterial engineering and pharmaceutical science, and benefits from using these systems.

Table 1
Division of antiresorptive drugs [13–15].

Group		Representatives	Mechanism of action
Bisphosphonates	Nitrogen-free	Clodronate Etidronate tiludronate	Osteoclast metabolism disruption and osteoclast apoptosis
	Nitrogenous	Alendronate Pamidronate Risedronate Zoledronate Ibandronate Neridronate Incadronate Olpadronate Minodronate	Cytoskeleton damage and inhibition of osteoclast activity without osteoclast apoptosis
Selective oestrogen receptor modulators (SERMs)		Raloxifene Lasofoxifene Bazedoxifene Ospemifene Arzoxifene	Oestrogen receptor modulation (agonist or antagonist effect depending on the tissue)
Hormones		Oestrogens	Reduced bone remodelling rate, calcium homoeostasis regulation (hormone replacement therapy)
		Calcitonin	Inhibition of osteoclast resorption activity, reduced release of calcium from bones, reduced ionized calcium concentration in the body
Monoclonal antibodies		Denosumab	Anti-RANKL antibody

2. Hydroxyapatite as a carrier for antiresorptive drugs

The pharmacological therapy of disorders involving bone tissue loss, depending on the therapy's aetiology and individual recommendations for each patient, has become possible thanks to the introduction of antiresorptive drugs into medical practice. The most frequent disorder resulting from disrupted bone metabolism is osteoporosis. Other disorders include osteomalacia, Paget's disease of bone, fibrous dysplasia, and disorders related to bone metastases [13].

The basic groups of antiresorptive drugs used in bone diseases are presented in Table 1 [13–15].

2.1. Bisphosphonates

The largest and most popular group of antiresorptive drugs among clinicians are bisphosphonates (BP). They are also the group most frequently combined with calcium phosphates (CaPs), with alendronate and zoledronate being the most popular subjects of research. Few studies have used other bisphosphonates so far. It should be noted that bisphosphonates, in addition to their application in osteoporosis and