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HYDROXYAPATITE NANOPARTICLES: A REVIEW OF THEIR EMERGING ROLE IN DRUG DELIVERY APPLICATIONS

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REVIEW

Abstract. *This literature review assesses existing research on hydroxyapatite-based drug delivery systems, with a focus on evaluating their effectiveness. Researchers are actively exploring strategies to enhance drug loading capacity, involving surface modifications of nanoparticles and the innovation of novel drug encapsulation techniques. Elevating drug loading has the potential to clearly increase the therapeutic efficacy of these systems. Stability issues also present a challenge in the clinical translation of nanoparticle-based drug delivery systems. Furthermore, scientists are underway to minimize potential side effects by judiciously selecting biocompatible materials for nanoparticle synthesis and conducting comprehensive toxicity studies before advancing to clinical trials.*

Keywords: hydroxyapatite (HAp), targeted drug delivery
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1. Introduction

Hydroxyapatite (HAp), a widely recognized biomaterial, has experienced significant evolution, from a simple biocompatible material to an advanced

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functional material with different applications [1,2]. Initially acknowledged for exceptional biocompatibility and bioactivity [3,4], HAp found prominence in bone tissue engineering and dental applications [5–9], owing to its capacity for tissue integration, cellular adhesion promotion, and facilitation of osseointegration. Researchers expanded the potential use of hydroxyapatite beyond traditional biomaterial roles, so HAp's composition, morphology, and surface characteristics have been tailored, resulting in enhanced mechanical strength, controlled drug release, and improved biodegradability. These changes broadened HAp's applicability to drug delivery systems [10], biosensors [11], tissue engineering scaffolds, and regenerative medicine [12,13]. The exceptional biomineralization properties of HAp facilitated the inclusion of functional ions and molecules during synthesis, leading to bioactive coatings and composites with specific therapeutic functionalities. Functionalized HAp materials displayed potential in antimicrobial coatings, controlled release systems for growth factors and therapeutic agents, and catalytic roles in chemical reactions. Recently, HAp nanoparticles and nanostructured materials have gained attention for their distinctive physicochemical properties, becoming a focal point for research in targeted drug delivery, imaging, and theranostic applications [14].

2. Clinical applications of HAp – drug loading for medical applications

HAp nanoparticles have been recently used as carriers for controlled drug delivery due to their unique properties to enhanced therapeutic outcomes. HAp nanoparticles serve as effective carriers due to their capacity to adsorb and release therapeutic agents in a controlled manner. Ongoing research explores surface modifications and functionalization techniques to optimize the interaction between hydroxyapatite and biological environments. Coating HAp surfaces with functional groups and bioactive molecules aims to improve cell adhesion, promote specific cellular responses, and enable controlled drug release for enhanced performance of the biomaterial. HAp-based drug delivery systems have the potential to improve drug stability, extend drug release, and expand therapeutic outcomes while minimizing side effects [10].

2.1. Incorporation of the drug into the structure of hydroxyapatite

The development of a drug delivery system based on hydroxyapatite involves several key steps to benefit from its unique properties. HAp nanoparticles with specific morphology and surface characteristics are particularly designed to be suitable for drug delivery. The high surface area of hydroxyapatite is a crucial factor for maximizing drug loading capacity [15–17]. As HAp can be naturally found in bones [18], it has excellent biocompatibility and low cytotoxicity [19].

Surface modifications and functionalization techniques are employed to enhance the bioactivity and functional properties of the carrier. By coating the HAp surface with bioactive molecules, functional groups, or polymers, the biocompatibility and cellular adhesion are improved [20]. The drug is incorporated into or onto the HAp nanoparticles through methods as encapsulation, adsorption, or chemical conjugation, depending on the specific drug and desired released kinetics [21]. This process ensured that the drug is securely held within the HAp matrix.

Encapsulation can be performed using various methods, such as coacervation, co-precipitation, or self-assembly [22,23]. The coacervation process is defined by the associative phase separation process induced by an adjustment of the environment (such as ionic strength, temperature, pH or solubility), under monitored conditions. Two phases are involved into the process: coacervate phase and equilibrium phase [24]. During the encapsulation by coacervation technique, the nanoparticles are placed around the active ingredient [25]. Being an inexpensive method, the co-precipitation implies the simultaneous precipitation of both the nanoparticles and the drug [26]. The self-assembly uses the intrinsic properties of certain materials to form nanoparticles that encapsulate the drug.

By chemical conjugation, the active substance is chemically fixing to the surface of the nanoparticle, permitting the targeted delivery and controlled release [27].

This adaptability is essential for achieving the highest drug loading efficiency, while ensuring that the drug is successfully delivered by the nanoparticles to the desired site of action.

The tailored HAp-based drug delivery system is designed to interact with the biological environment, optimizing its performance for targeted drug delivery, including ensuring compatibility with the psychological conditions of the targeted tissue or cells [28]. Upon administration, the drug-loaded HAp nanoparticles navigate through the body to the target site. The controlled release of the drug is achieved by the interactions between the drug, HAp, and the biological environment. This controlled release mechanism helps accomplish prolonged drug release, enhanced stability, and reduced side effects.

3. Use of HAp-based nanomaterials in drug delivery systems

Hydroxyapatite nanoparticles can be functionalized by adding various substitution agents (Table 1) or even other biocompatible components, such as polymers, in order to obtain materials that can be used to improve actual bioimaging technologies and delivery systems [12].

Table 1. Substitution agents that can be added into HAp structure, suitable for medical applications

Element	*Applicability*
Silicon, Si	Biocompatibility and biodegradability properties, showed to promote drug loading efficiency [29]
Sulfur, S	pH-reactive system efficient for tumor-targeting drug delivery [30]
Selenium, Se	Cytotoxicity properties against prostate and breast cancer cells. Induces tumor cells death [31]
Strontium, Sr	89 isotope has luminescent properties [32]
Fluoride, F	Can be successfully used in medical imaging of soft tissues at PET and CT scans [33]
Zinc, Zn	Promotes the radiation of breast cancer cells [34]
Copper, Cu	Has the ability to improve the luminescent properties of hydroxyapatite, being appropriate for cancer imaging [35]
Europium, Eu	Can be used to track cancer cells [36-37]
Terbium, Tb	Photoluminescent properties [36]
Gadolinium, Gd	Can be used as a contract agent and drug carrier for cancer treatment [36]

3.1. Controlled drug release

For a drug delivery system to provide a slow, controlled, and constant release of the drug to the desired site, materials with high porosity and controlled pore size should be selected. HAp scaffolds are preferred in this area because of their higher porosity, hardness, and biocompatibility properties [2]. Recent studies demonstrated that the use of a biopolymer (incorporated into composite or just added as a coating layer) in the obtaining process of HAp scaffold can be efficient for controlling pore size and increasing the rate of drug retaining [38]. Also, chitosan was incorporated into HAp scaffolds and the obtained chitosan-HAp nanorods and chitosan-HAp microtubes showed the capacity of protection of regenerated new tissues from infections. The results obtained by the researchers indicates a very high drug loading capacity and an improvement of the mechanical properties [39]. Son et al. studied porous hydroxyapatite scaffolds coated with poly (lactic-co-glycolic acid) (PLGA) and loaded with dexamethasone for localized drug delivery systems. They observed an initial burst release of the loaded drug (44%), followed by a sustained release. In vivo studies confirmed that the dexamethasone-loaded HAp scaffolds increased volume and quality of the bone formation process, studied on the implantation in the femur defects of a beagle dog [40].

The aim of drug-targeted strategies is to reduce the dispersal of the therapeutic agent that is administrated in the treatment, while ensuring that the proper amount of active substance is provided, as needed [41]. In order to minimize the side

effects and to maximize the activity of the drug, drug delivery systems are specially tailored (Figure 1).

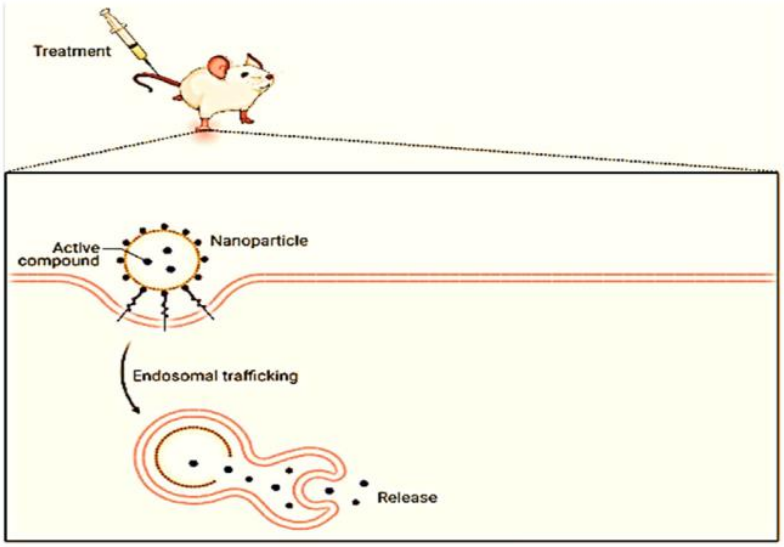

Fig. 1. The mechanism of drug release (Reprinted from [21], Copyright 2024, with permission from Elsevier)

3.2. Targeted cancer therapy and theranostic

Conventional therapies, such as chemotherapy and radiation therapy have significant disadvantages, including general toxicity and difficulty of the procedures that require extended recovery periods [42]. In the last decade, drug delivery methods based on nanoparticles have proven potential in addressing the limitations of the conventional cancer treatments due to their ability to increase treatment efficacy and potentially lower the risk of tumor recurrence. By delivering chemotherapy substances straight to targeted cancer cells using nanoparticles, the adverse effects on healthy tissues are reduced. The development made in this area can significantly enhance the prognosis of cancer patients [43–45].

In order to achieve advanced anticancer effects, either in conjunction with drug release or independently, particular therapeutic elements can be incorporated into the basic composition of HAp NPs [46]. This can be used to inhibit the growth and metastasis of cancer cells by activating specific cell signaling pathways. Studies demonstrated that nanoscale hydroxyapatite can be successfully used in nanomedicine for tumor treatment due to its capacity of inhibiting the tumors without affecting the normal cells [47–49]. Zhang et al. have developed

polyacrylic acid-coordinated hydroxyapatite nanoparticles using co-precipitation method and further grafted them with folic acid in order to overcome the current challenges appeared in the field of cancer cell-targeting nanoparticles. They demonstrated that adding a polymer can significantly improve the uniformity, stability, and dispensability of the synthesized system. The synthesis process has been controlled by adjusting the quantity of the polymer, the reaction time and precursor concentration. By inhibiting tumor spreading, HAP-PAA-FA nanoparticles can control the tumor microenvironment. Subsequently, calcium excess induces apoptosis in tumor cells by more than 80% [50]. Another study was published by Sun et al. in which doxorubicin-loaded hydroxyapatite nanorods were developed by in situ coprecipitation to be used in antitumor treatment, hence demonstrating a new method for drug loading in HAp nanoparticles. It has been proven that doxorubicin could be released in 24 hours in acid buffer solution at pH=6.0. In vivo tests on tumor-bearing mouse mode suggested that the system can be a promising agent for cancer treatment as it showed excellent tumor growth inhibition [51]. Moreover, multivalent ions as Fe^{2+}/Fe^{3+} can be released and renewed constantly when hydroxyapatite nanoparticles interact with biological fluids. The release of multivalent ions is crucial in for antitumor therapy and according to Fenton reaction can generate ROS in the tumor environment [52].

Conclusions

The development of multifunctional systems with therapeutic properties has great potential for clinical applications. Further research is needed to optimize the targeted drug delivery systems and nanoparticles have the potential to function as carrier system for therapeutic agents directly to the tumor sites, while minimizing the possible damage of the healthy tissues. The nanotechnology field is in a continuous development, and it may transform the cancer treatment by using personalized approaches taking into consideration the patient requirements.

Even if biomaterials based on HAp were extensively studied for applications in other fields, some challenges need to be addressed before using them for clinical applications. Different ions can be added into the structure of hydroxyapatite to provide additional functions for therapeutic applications. Due to their biocompatibility, specific morphology and surface characteristics, HAp is a promising material for therapeutic and diagnostic applications. Also, HAp can be successfully combined with polymers and other ceramics to obtain a promising system that can support and improve human health.

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