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Hydroxyapatite as Delivery and Carrier Material: Systematic Literature Review with Bibliometric Analysis

Atiek Rostika Noviyanti[1,], Qurratu Aini Alya Adzkia[1], Indrika Novella[1], Irwan Kurnia[1], S. Suryana[2], Azman Bin Ma'Amor[3], Ferli Septi Irwansyah[4,*]*

[1]Department of Chemistry, Universitas Padjajaran, Indonesia
[2]Department of Biology, Universitas Padjadjaran, Indonesia
[3]Department of Chemistry, Universiti Malaya, Malaysia
[4]Department of Chemistry Education, UIN Sunan Gunung Djati Bandung, Indonesia
*Correspondence: E-mail: atiek.noviyanti@unpad.ac.id; ferli@uinsgd.ac.id

ABSTRACT

Hydroxyapatite (HA), a bioactive calcium phosphate compound, has garnered significant attention in biomedical and pharmaceutical research due to its remarkable properties as a delivery and carrier material. This review aims to comprehensively analyze the extensive research surrounding HA's applications in drug delivery and as a carrier for various therapeutic agents, encompassing various studies from scientific articles focusing on HA-based systems designed for drug delivery, tissue engineering, and other therapeutic applications. The review also investigates the HA synthesis and modification methods for tailored drug release profiles, as well as the interaction between HA and bioactive molecules. Key findings from the review include the versatility of HA as a biocompatible carrier, its ability to facilitate controlled drug release, and its potential to enhance tissue regeneration. The review identifies trends in HA-based delivery systems, highlighting recent advances and emerging research directions, as well as providing valuable insights into the current state of HA-based drug delivery and carrier materials, shedding light on the potential of HA to revolutionize the field of biomedicine. It serves as a valuable resource for researchers, clinicians, and pharmaceutical professionals seeking to harness the capabilities of HA in developing innovative therapeutic strategies.

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1. INTRODUCTION

Hydroxyapatite (HA) has been known as the main inorganic mineral constituent of human hard tissues, with its advanced properties in biocompatibility, bioactivity, osteogenic, osteoconductive, and osteoinductive, HA is often used in the medical field, especially as bone or dental regeneration and drug delivery and carrier (Kuśnieruk *et al*., 2016; Noviyanti *et al*., 2020). HA is also used in antibiotic delivery and carrier systems, due to its porous surface and biodegradable properties (Uskoković, 2020; Irwansyah *et al*. 2022). HA is a main mineral found in bones and teeth with a porous structure that allows for an effective antibacterial activity. Natural HA is abundant, non-toxic, and highly biocompatible. HA can be synthesized from natural resources such as eggshells, cow bones, and shells HA does not cause inflammatory reactions in the human body and is also non-toxic. Therefore, it is sufficient to assume that HA has the possibility of being used in the medical and food industries (Biedrzycka *et al*., 2021).

In addition, HA also Possesses on-immunogenic properties which are highly essential in the medical field (Pandharipande & Sondawale, 2016). Various biomaterial composites have been studied by numerous researchers to improve mechanical properties for their applications as they have low toxicity to humans and the environment. In this systematic literature review paper, since HA can be used as a material in the medical field, the authors summarized recent and relevant research about HA application for drug delivery and carriers.

The field of biomedical and pharmaceutical research has witnessed an ever-increasing demand for innovative materials that can serve as effective delivery and carrier systems for therapeutic agents (Tewabe *et al*., 2021). In biomedical and pharmaceutical research, these materials play a pivotal role in enhancing drug efficacy, enabling targeted therapies, and advancing regenerative medicine. Among the multitude of materials under investigation, HA has emerged as a particularly promising candidate.

HA, a calcium phosphate compound with a chemical structure akin to the mineral component of human bone and teeth, possesses several remarkable properties that render it highly suitable for such applications (Irwansyah *et al*., 2022). Its biocompatibility, osteoconductive nature, and bioresorbability make it an attractive option for tissue engineering and regenerative medicine. Not only does it serve as a therapeutic carrier, but it also possesses the capability to transport a diverse range of materials, including bacteria, genes, and proteins (Munir *et al*. 2021). The distinctive capacity to be absorbed by the physiological environment confers an advantage in interaction with biological molecules (Pal *et al*., 2018; Hassanzadeh-Tabrizi *et al*., 2021). Furthermore, HA's porous structure and ability to adsorb and release various therapeutic agents allow for precise control over drug delivery profiles, promising improved treatment outcomes and patient compliance (Lara-Ochoa *et al*., 2021). Besides being used as a carrier for various drugs, based on its inherent properties, HA also positions itself as a satisfying solution for various issues requiring the filling or coating of hard tissue (Rial *et al*., 2021). As the demand for personalized medicine and targeted therapies continues to grow, the exploration of HA's capabilities as a delivery and carrier material has gained significant momentum. This systematic literature review seeks to consolidate and analyze the extensive body of research on HA in biomedical and pharmaceutical contexts, shedding light on the versatile applications of HA and its potential to revolutionize healthcare solutions (Irwansyah *et al*., 2022a; Noviyanti *et al*., 2023). **Table 1** shows previous studies about HAP as delivery material on SLR with bibliometric and **Table 2** shows qualitative findings on SLR with bibliometric.

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The primary objective of this systematic literature review is to provide a comprehensive overview of the current state of knowledge regarding the use of HA as a delivery and carrier material. To achieve this, we have set forth the following specific goals: to systematically review and synthesize relevant articles from peer-reviewed journals, patents, and conference proceedings, categorize and analyze the findings from these articles, identify key trends, innovations, and challenges, assess the implications of HA-based delivery and carrier systems in the fields of drug delivery and tissue engineering, and identify gaps in the existing literature and areas for future research. Understanding the capabilities and limitations of HA as a delivery and carrier material is of paramount importance in the quest to develop more effective and personalized healthcare solutions. By synthesizing the wealth of research findings in this area, this systematic literature review not only contributes to the existing body of knowledge but also offers valuable insights that can inform future research endeavors, drive innovation, and ultimately benefit patients worldwide.

2. METHOD

This paper presented a Systematic Literature Review (SLR) and meta-analysis studies on HA as a delivery and carrier material. In September 2023, the literature search was limited to open-access articles that were published between 2020 and 2023. The keywords used to search for articles in research databases at Scopus, MDPI, ScienceDirect, and Pubmed are “Hydroxyapatite as delivery material” and “Hydroxyapatite as carrier material”.

The Preferred Reporting Item for Systematics Reviews and Meta-Analytic (PRISMA) technique was used to guide the search. The selected publications were screened based on the year of publication, document type, keywords, and source type. The inclusion criteria are (1) studies about delivery material, and (2) studies about HA as carrier material. The exclusion criteria are (1) studies about HA with other doping materials and (2) articles containing a literature review. Research procedure in this study can be seen in **Figure 1**.

There were 459 studies in total that mentioned “hydroxyapatite as delivery and carrier material”, from Scopus, 123 articles; MDPI, 17 articles; Pubmed, 47 articles; and ScienceDirect, 272 articles. After screening through the duplicates, abstracts, and irrelevant papers were excluded, the author's collaboration resulted that there were 12 studies that relevant to the topic of HA for delivery material.

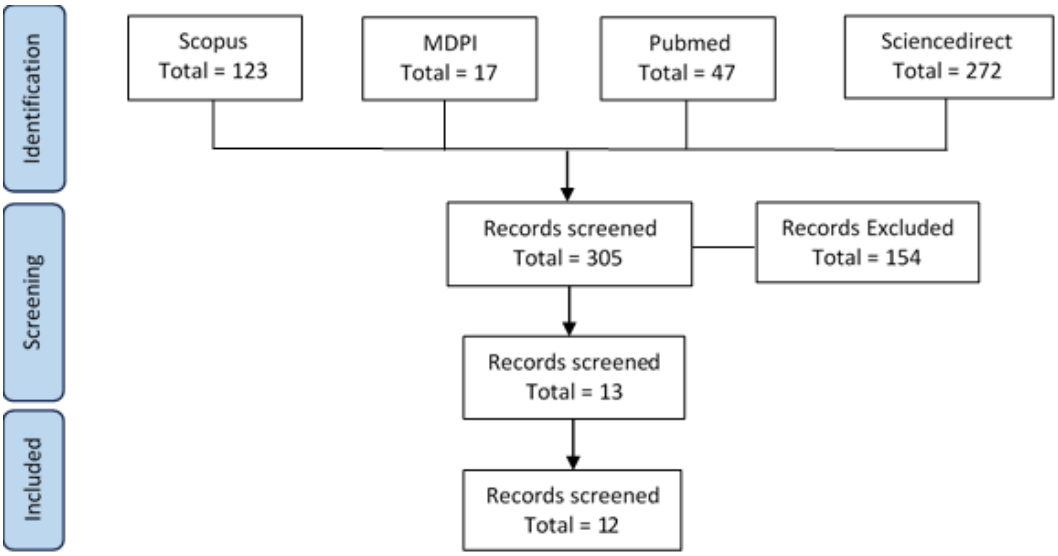

Figure 1. Flow diagram summary of systematic literature review.

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Table 1. Previous studies about HAP as delivery material on SLR with bibliometric.

Synthesis Method	Composite	Size (nm)	Potential (mV)	Morphology	Application	Result	Bioactive substance	Ref.
Wet chemical precipitation	HA-SCTNPs	72.42 ± 7.190	-29.6 ± 0.8	Spherical	Bone targeted delivery	10 mg/dL 6 mg/dL	Calcium Phosphorous	(Kotak & Devarajan 2020)
Co-precipitation	HA HA-Ni	43.595 40.53	-	Hexagonal	Drug delivery	86 ± 0.2% 95 ± 0.2%	Ciprofloxacin	(Asghar *et al.* 2023)
Ligand exchange reaction	HA-HE-PEI	~ 20	-13.87	Spindle	Drug delivery	31.83%	Doxorubicin hydrochloride	(Wan *et al.* 2022)
Wet chemical precipitation	HA-PCL-NPs	90.12 ± 20.36	-	Spindle	Drug release	94.77 ± 1.23%	Doxycycline	(El-Habashy *et al.*, 2021)
Electrospinning	HA-PLA	320 ± 12	-	Scaffold	Drug delivery	92.7% 576.3 mg/g	Doxycycline	(Farkas *et al.*, 2022)
Copolymerization	HA-Alginate	-	-	Scaffold	Drug release	43.92%	Bovine serum albumin Bone morphogenetic protein	(Levingstone *et al.*, 2021)
Lyophilisation techniques Hydrothermal method	Collagen-HA	-	-	Scaffold	Femorat defect healing	5% 10%	Bone morphogenetic protein-2/7 (BMP)	(Liu *et al.*, 2023)
Computational study (COMSOL Multiphysics model)	Ca-ALG-CHI-HA & Ca-ALG-HA	-	-	Nano-rod shape, hydrogel	Drug delivery	HA : 100% ALG : 87,27% CHI-ALG : 45,46%	Propranolol hydrochloride (Prop) and cloxacillin sodium salt monohydrate (Clox)	(Rial *et al.*, 2021)
High-energy Ball mill & Vibration process	PEI-HA (pEH)	<500nm	-		Dental pulp stem cells	-	BMP-2 gene	(Lee *et al.*, 2021)
	Commercial HA	Micro HA: 1-10µm Nano HA: 20-50 nm	-	Rod shape	Bone cancer treatment	-	Doxorubin (DOX)	(Liu *et al.*, 2022)
	Commercial HA	30 mm	-	Granule	Drug-eluting agent	65.42 µg/g, 16 µg/g 16.01 µg/g	Gentamicin, Vancomycin, and Amoxycyllin	(Simon *et al.*, 2020)
	Commercial HA	1-10 µm	-	Spherical and porous	Proliferative human osteosarcoma	28 & 36 % (in vitro) 63% (in vivo)	Doxorubin (DOX)	(Liu *et al.*, 2021)

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Table 2. Qualitative findings on SLR with bibliometric.

Synthesis Method	Composite	Application	Bioactive substance	Summary	Ref.
Wet chemical precipitation	HA-SCT-NPs	Bone targeted delivery Drug release	Salmon Calcitonin	The release of drug SCT loaded in HA-NPs showed maximum capacity of 85% at 24 h. HAP-NPs in bone-targeted delivery show a significant improvement in serum markers (ALP, Cal, Phosp) with an increase in bone mass and mechanical strength. This shows that there is a direct impact on homeostasis of bone resorption and bone formation, HAP-SCT-NPs have the potential to be an antiresorptive material.	(Kotak and Devarajan 2020)
Co-precipitation	HA HA-Ni	Drug delivery	Ciprofloxacin	HAP and HAP-Ni can be used as a drug delivery material, the increase of nickel concentration is directly proportional to the increase in cumulative drug release. The maximum release shown when stirring time is 420 h.	(Asghar et al. 2023)
Ligand exchange reaction	HA-HE-PEI	Drug delivery	Doxorubicin hydrochloride	HAP-HE-PEI shows a good in-vitro release with the maximum release of DOX at pH 5.4 (31.83%) that was significantly higher than at pH 7.2 (9.90%) for the maximum time in 48 h, which can still be used as an intracellular drug delivery material. This proves that pH regulation for targeted cancer cell uptake and therapy is needed.	(Wan et al. 2022)
Wet chemical precipitation	HA-PCL-NPs	Drug release	Doxycycline	HAP-PCL-NPs resulted in the highest reported entrapment efficiency (94.77 ± 1.23%) of Doxycycline. The developed composite system achieved the controlled release of the water-soluble DX over 24 days. The composite also managed to significantly ameliorate DX cytotoxicity on bone marrow stem cells, as well as enhance its overall proliferation potential.	(El-Habashy et al. 2021)
Electrospinning	HA-PLA	Drug delivery	Doxycycline	The adsorption of HAP-PLA in Doxycycline is mostly influenced by the concentration of the Doxy solutions, the adsorption capacity increased when the concentration of the initial Doxy solutions increased. the adsorption capacity of HAP was 120.86 mg/g and 576.3 mg/g for (in the case of) 3 g/L and 12 g/L Doxy, respectively. The cumulative Doxy released 92.7% within the first 6 hours.	(Farkas et al. 2022)
Copolymerization	HA-Alginate	Drug release	Bovine serum albumin Bone morphogenetic protein	The addition of HAP become HAP-Alg composite increased the release rates of BSA and BMP, confirming for the first time the role of HA as a sonosensitizer and also be used in minimally invasive bone repair applications.	(Levingstone et al. 2021)
Lyophilization techniques Dehydrotermal method	Collagen-HA	Femorat defect healing	bone morphogenetic protein-2/7 (BMP)	The CHA (Collagen-HA) scaffold offers prolonged delivery of molecules and aids in the absorption of Bone Morphogenetic Protein (BMP). BMP2/7 delivered alongside CHA exhibits greater osteoinductive properties compared to BMP2 alone	(Liu *et al.*, 2023)

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Table 2 (Continue). Qualitative findings on SLR with bibliometric.

Synthesis Method	Composite	Application	Bioactive substance	Summary	Ref.
Computational study (COMSOL Multiphysics model)	Ca-ALG-CHI-HA & Ca-ALG-HA	Drug delivery	Propranolol hydrochloride (Prop) and cloxacillin sodium salt monohydrate (Clox)	Ca-ALG-CHI doped with HA demonstrates a gradual drug release capability and slow adsorption, influenced by the drug's stronger affinity for the negatively charged surface of HA nanorods	(Rial *et al.*, 2021)
High-energy Ball mill & Vibration process	PEI-HA (pEH)	Dental pulp stem cells	BMP-2 gene	Utilizing a pEH core. Specifically HA, in conjunction with PEI (polymer) is recognized for enhancing bone differentiation, facilitating osteogenic differentiation, exhibiting superior gene transfer capabilities compared to PEI, and also demonstrating low toxicity	(Lee *et al.*, 2021)
	Commercial HA	Bone cancer treatment	Doxorubin (DOX)	Exploration of the accretion mechanism polarization of a cytostatic DOX, containing hydroxyl groups, with different sizes of HA particles both in vitro and in vivo. DOX delivery with nHA proves more efficient than free DOX, nHA+DOX induces mitochondrial dysfunction, resulting in decreased cellular ATP compared to free DOX. Moreover, nHA+DOX exhibits stronger tumor inhibition compared to mHA. DOX delivery with HA induces a higher rate of apoptotic cells (cell death). Various delivery pathways emerge when DOX is delivered with HA of different sizes. HA features two binding sites : C via Ca^{2+} and P via PO_4^{3-} (both with affinities for macromolecules like proteins). With its numerous hydroxyl groups, DOX readily interacts with HA. The interaction between HA and DOX is reversible and electrostatic, potentially influenced by pH (acidic environment)	(Liu *et al.*, 2022)
	Commercial HA	Drug-eluting agent	gentamicin, vancomycin, and amoxicillin	HA can undergo ionic modifications, and its osteoconductive properties can facilitate the regeneration of bone tissue. Furthermore, it can develop additional calcium phosphate layers on its surface, enabling tissue integration and preventing the formation of fibrous tissue, which could enhance drug release	(Simon *et al.*, 2020)
	Commercial HA	Proliferative human osteosarcoma	Doxorubin (DOX)	A two-phase biphasic material serves as a drug delivery system wherein HA is submerged in a sulfate solution. Based on the obtained results, this system indicates rapid apoptosis and significantly inhibits tumors even at low doses	(Liu *et al.*, 2021)

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3. RESULTS AND DISCUSSION

3.1. Bibliometric Data of the Reviewed Articles

Depending on the findings of the review, the articles are released through various publishers. **Figure 2** represents the publishers where the articles were published. The total number of published articles is 12, with both Science Direct and Scopus having the most at 41.6% (n = 5). The remaining articles were published by Pubmed (n = 1) and MDPI (n = 1).

The year with the highest number of articles published is 2023 (n = 2), 2022 (n = 3), 2021 (n = 5) and 2020 (n = 2). It is also crucial to notice the number of countries and institutions represented by the main authors of the articles in the context of the review, as this provides a clear picture of the diversity and geographical extent of the research conducted on the topic. Furthermore, there are nine countries recognized, thus the study was conducted by country rather than continent. Sweden has the most university participation in research articles, at 25%, followed by India at 16.7%, then Australia, South Korea, Romania, Ireland, Egypt, Pakistan, and Spain.

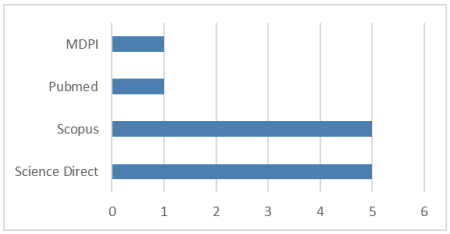

Figure 2. Bibliometric data counted by publisher name.

3.2. Synthesis Method

HA can be obtained from natural sources, and the removal of organic compounds or the synthesis of HA can be carried out with several choices of methods. Different synthesis methods will result in different shapes, sizes, morphologies, and ionic substitutions as well. Hence, the morphology of HA depends on the synthesis method and impacts the physical properties. The expectation of HA mechanical and physical properties can be controlled by choosing the right methodology of synthesis by using existing methods or even modifying existing methods with some new routes. Some choices of synthesis methods, namely sol-gel, wet chemical precipitation, hydrothermal, solid-state method, electrospinning, copolymerization, and thermal decomposition (Lara-Ochoa *et al*., 2021). Thus, depending on the synthesis method, HA particles can result in different physical properties, as presented in **Table 3**. Different charge and arrangement counterparties endow HA with regulated structural characteristics and multiple shapes (Kotak & Devarajan 2020).

Various synthetic methods have been used for the HA synthesis process which includes top-down and bottom-up processes producing HA with favorable properties (Abdulrahman *et al*. 2014; Gomes *et al*. 2019). Various synthesis methods are employed to produce HA with controllable properties tailored to the intended applications. One of the challenges in the process of synthesizing HA is the occurrence of agglomeration, which can be unfavorable for certain applications (Lee *et al*. 2021). As a result, several studies combine HA with various other materials to enhance its properties for specific applications, such as the fabrication of HA composite, creation of HA scaffolds, coatings of HA with other materials and also combine synthesis methods to generate HA with distinctive properties and structures. Moreover, some employ a blend of computational and experimental techniques in the HA synthesis process (Liu *et al.,* 2023; Rial *et al*., 2021). A variety of precursors are employed in the synthesis of HA, spanning from commercial HA to the use of waste materials with different morphology

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as presented in **Figure 3** (Lee *et al*., 2021; Liu *et al*., 2021). Modification of HA with a polymer (A) HA tends to agglomerate in water & B HA coated with a polymer allows for better particle distribution. Adopted from the references (Lee *et al*. 2021). The SEM characterization results of HA also indicate that HA synthesized under different treatments yields varying shapes and sizes.

Table 3. Comparison between the HA synthesis method to its properties.

Synthesis Method	Composite	Size (nm)	Morphology	Ref.
Wet chemical precipitation	HA-SCT-NPs	72.42 ± 7.190	Spherical	(Kotak & Devarajan 2020)
Co-precipitation	HA	43.595	Hexagonal	(Asghar *et al*. 2023)
	HA-Ni	40.53		
Ligand exchange reaction	HA-HE-PEI	~ 20	Spindle	(Wan *et al*. 2022)
Wet chemical precipitation	HA-PCL-NPs	90.12 ± 20.36	Spindle	(El-Habashy *et al*. 2021)
Electrospinning	HA-PLA	320 ± 12	Scaffold	(Farkas *et al*. 2022)
Copolymerization	HA-Alginate	-	Scaffold	(Levingstone *et al*. 2021)
Lyophilisation techniques	Collagen-HA		Scaffold	(Liu *et al*., 2023)
Dehydrotermal method				
Computational study (COMSOL Multiphysics model)	Ca-ALG-CHI-HA & Ca-ALG-HA		Nano-rod shape, hydrogel	(Rial *et al*., 2021)
High-energy Ball mill & Vibration process	PEI-HA (pEH)	<500nm		(Lee *et al*., 2021)
	Commercial HA	Micro HA : 1-10µm, nano HA : 20-50 nm	Rod shape	(Liu *et al*., 2022)
	Commercial HA	30 mm	Granule	(Simon *et al*., 2020)
	Commercial HA	1-10 µm	Spherical and porous	(Liu *et al*., 2021)

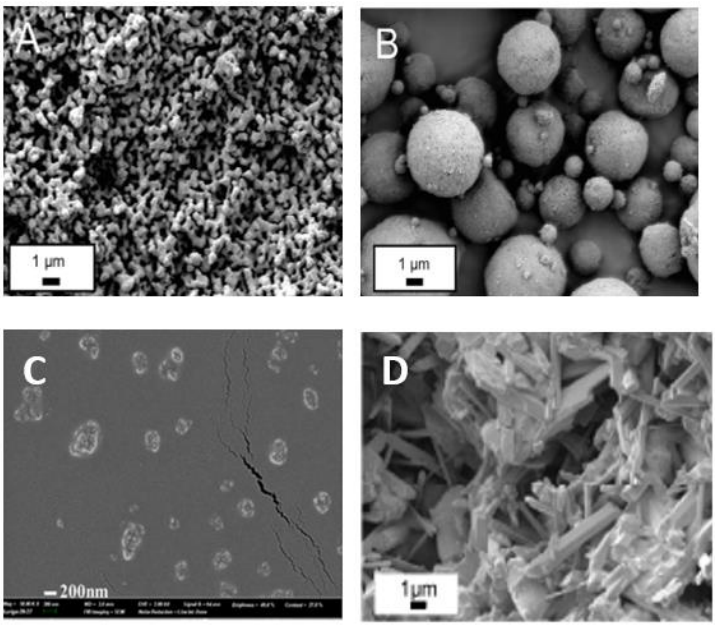

Figure 3. The particle morphology of HA was examined using SEM under different conditions (A) Nano-sized HA particles, (B) Micro-sized HA particles (Liu *et al*., 2022) (C) Polymer-coated HA (Lee *et al*., 2021), and (D) HA composite with calcium sulfate (Liu *et al*., 2021).

3.3. Characterization

HA characteristics can be determined using several characterization techniques depending on which properties are needed. Analysis of HA characteristics is shown **in Table 4**.

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Table 4. HA characterization techniques.

Characterization	Properties	References
FTIR	Fingerprint region of composite composition, interaction between materials	(Asghar *et al.*, 2023; El-Habashy *et al.*, 2021; Farkas *et al.*, 2022; Kotak & Devarajan 2020; Levingstone *et al.*, 2021; Liu *et al.*, 2021; Wan *et al.*, 2022)
XRD	Crystallinity, fingerprint region of composite composition, crystal structure, crystallinity, purity, and microcrystalline of HA	(Asghar *et al.*, 2023; El-Habashy *et al.*, 2021; Farkas *et al.*, 2022; Kotak & Devarajan, 2020; Wan *et al.*, 2022; Liu *et al.*, 2022; Lee *et al.*, 2021)
SEM	Surface morphology, average particle size, particle size distribution, surface area, and comparison of structure and surface of HA	(Asghar *et al.*, 2023; El-Habashy *et al.*, 2021; Lee *et al.*, 2021; Farkas *et al.* 2022; Kotak & Devarajan 2020; Liu *et al.*, 2022)
TEM	Morphology, particle size distribution	(Wan *et al.*, 2022; Liu *et al.*, 2022)
DLS	Surface charge	(El-Habashy *et al.*, 2021)
TGA	Mass percentage, composite stability	(Farkas *et al.*, 2022)
XPS	Chemical composition	(El-Habashy *et al.*, 2021)
BET	Surface morphology, pore size	(Farkas *et al.*, 2022; Irwansyah *et al.*, 2023, 2024)
XRF	Chemical composition	(Lee *et al.*, 2021)

3.3.1. Infrared spectroscopy

Fourier Transform Infrared (FTIR) is usually used to analyze purity and different functional groups present in compounds or composites (Asghar *et al.*, 2023). Furthermore, FTIR spectra are used to study the chemical bonding and validate the synthesis being successful (Wan *et al.*, 2022). The composite purity was identified through a specific peak on each compound as seen in **Table 5**. On FTIR spectra, the presence of HA can be seen at various characteristic peaks, this can be correlated to the different compounds or copolymer on each composite. The obtained material that corresponds to a carbonated HA showed at 1476, 1447, 1079, and 1244 cm^{-1}. Additionally, the substitution of O-H bonds observed at 1637, 3305, and 3000 cm^{-1} correspond to absorbed water. The bond of C=O was identified at various peaks, namely 1615, 1702, 1724, 1700, and 1641 cm^{-1} which could have been the result of contamination from atmospheric CO_2 or the composite carrier.

Table 5. Vibration frequencies in FTIR spectrums from different HA composites.

Composite	HA-SCT-NPs (cm^{-1})	HA-Ni (cm^{-1})	HA-HE-PEI (cm^{-1})	HA-PCL-NPs (cm^{-1})	HA-PLA (cm^{-1})	HAP-Alginate (cm^{-1})
HA	1033 604	1067	1045 598	653	~1080	~800 - 1200
C-O	1476	1447	-	-	1079	1244
C=O	1615	-	1702	1724	1700	1641
C=C	1480	-	-	-	1600	-
C-N	1265	-	-	1217	-	-
C-H	-	2850	2900	2869	-	2919
N-H	1656	-	-	1669	-	1539
O-H	-	1637	-	3305	3000	3000
Reference	(Kotak & Devarajan, 2020)	(Asghar *et al.*, 2023)	(Wan *et al.*, 2022)	(El-Habashy *et al.*, 2021)	(Farkas *et al.*, 2022)	(Levingstone *et al.*, 2021)

3.3.2. X-Ray diffraction

XRD diffractogram is used to reveal the presence of HA in the composite. As shown in **Table 6**, different composites showed HA characteristic fingerprint region regions within 25 to 33°, this confirmed the presence of HA in each composite.

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Table 6. X-ray diffraction of HA fingerprint region from different composites.

Composite	2θ (°)	Reference
HA-SCT-NPs	26.12 32.3	(Kotak & Devarajan 2020)
HA-Ni	28.22 32.34	(Asghar *et al.*, 2023)
HA-HE-PEI	25.8 31.7	(Wan *et al.*, 2022)
HA-PCL-NPs	25.9 31.79	(El-Habashy *et al.*, 2021)

3.3.3. Scanning electron microscopy

Physical characterization techniques like SEM are used to identify surface morphology and average particle size. Different synthesis methods can result in various morphologies and sizes as shown in **Table 7**.

Table 7. SEM analysis of the effect of various synthesis methods on size and morphology.

Synthesis Method	Composite	Size (nm)	Morphology	Ref.
Wet chemical precipitation	HA -NPs	72.42 ± 7.190	Spherical	(Kotak & Devarajan 2020)
Co-precipitation	HA HA-Ni	43.595 40.53	Hexagonal	(Asghar *et al.*, 2023)
Wet chemical precipitation	HA-PCL-NPs	90.12 ± 20.36	Spindle	(El-Habashy *et al.*, 2021)
Electrospinning	HA-PLA	320 ± 12	Scaffold	(Farkas *et al.*, 2022)
Lyophilisation techniques Dehydrotermal method	Collagen-HA	-	Scaffold	(Liu *et al.*, 2023)
Computational study (COMSOL Multiphysics model)	Ca-ALG-CHI-HA & Ca-ALG-HA	-	Nano-rod shape, hydrogel	(Rial *et al.*, 2021)
High-energy Ball mill & Vibration process	PEI-HA (pEH)	<500nm		(Lee *et al.*, 2021)
-	Commercial HA	Micro HA : 1-10µm, nano HA : 20-50 nm	Rod shape	(Liu *et al.*, 2022)
-	Commercial HA	30 mm	granule	(Simon *et al.*, 2020)
-	Commercial HA	1-10 µm	Spherical and porous	(Liu *et al.*, 2021)

3.4. Discussion

3.4.1. Application

HA has an open porous structure, so it is known to have good potential as an antibacterial agent used to help prevent infections in medical implants and also as an injection material in bone and tooth regeneration because HA has structural components similar to human bones and teeth. Apart from that, HA is also used as an antibiotic drug delivery system and drug release material due to its porous surface and biodegradable properties (Lamkhao *et al.* 2019). HA also maintains osteoconductive properties, a high affinity with some drugs, and absorbs osteoblasts (Higino and França 2022). The microporous HA structure can act as a drug delivery system to transport drugs directly to the desired target (Asghar *et al.* 2023). Various applications of HA are presented in **Table 8**. When using HA as a carrier material, surface morphology can enhance the loading capacity of active substances to be delivered to specific targets. The loading of active substances on the surface of HA is also influenced by the physicochemical properties of HA without compromising its bioactivity (Abdul Halim *et al.*, 2021; Abdulrahman *et al.*, 2014; Family *et al.*, 2012; Gomes *et al.*, 2019).

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Table 8. Several applications of HA.

Composite	Application	Ref.
HA-SCT-NPs	Bone targeted delivery; Drug release	(Kotak & Devarajan 2020)
HA HA-Ni	Drug delivery	(Asghar *et al*., 2023)
HA-HE-PEI	Drug delivery	(Wan *et al*., 2022)
HA-PCL-NPs	Drug release	(El-Habashy *et al*., 2021)
HA-PLA	Drug delivery	(Farkas *et al*., 2022)
HA-Alginate	Drug release	(Levingstone *et al*., 2021)
Collagen-HA	Femorat defect healing	(Liu *et al.,* 2023)
Ca-ALG-CHI-HA & Ca-ALG-HA	Drug delivery	(Rial *et al.*, 2021)
PEI-HA (pEH)	Dental pulp stem cells	(Lee *et al.*, 2021)
Commercial HA	Bone cancer treatment	(Liu *et al.*, 2022)
Commercial HA	Drug-eluting agent	(Simon *et al.*, 2020)
Commercial HA	Proliferative human osteosarcoma	(Liu *et al.*, 2021)

3.4.2. Size and shape effect

Many studies have shown that the size and shape of a material composite affect its application performance as shown in **Table 9**. Numerous things affect the size and shape of composites, namely pH, synthesis method, temperature, time, concentration, and pressure. These parameters must be considered, so that will produce the best properties, such as size uniformity, greater amounts, and the expected particle shape (Kuśnieruk *et al*., 2016; Noviyanti *et al.*, 2020). Particle size and crystallinity were also influenced by different synthesis temperature conditions. The increase in processing temperature has a significant impact on HA to have larger particle size, greater homogeneity, and higher crystallinity (Noviyanti *et al*., 2020). HA-NPs are believed to show desired cell proliferation to enhance biological activity, a feature that is strongly reliant on the particle size. This discussion is critical in understanding HA-NP biological activity and hydrophilicity during biomineralization (Kuśnieruk *et al*., 2016). Nanoparticles have been demonstrated in previous studies to penetrate bacteria and their diffusion is directly related to the size and shape of the particles (Silva-Holguín & Reyes-López, 2020). HA usage in bone application, the smaller particle size can result in better performance. Large particle sizes may be cumulative in the bone marrow and cause bone toxicity (Kotak & Devarajan 2020). It is well-recognized that particle size has a significant impact on drug release and absorption in solid drug delivery systems. Because small-sized particles have a vast surface area, they can boost the bioavailability of poorly soluble medicines. This was directly attributed to the difference in superficial surface area, with smaller-sized particles having larger superficial surface areas. According to the findings of these investigations, a larger superficial surface area leads to more drug adsorption and release (Lara-Ochoa *et al*., 2021).

Therefore, the important parameters must be enhanced, to improve the range of particle size. This shows that precise control of the particle size can be maintained, and these parameters can still be controlled. The particle density and shape were discovered to be size-related (Kuśnieruk *et al*., 2016). Hence, the control of particle size and shape can be used to optimize HA properties for specific applications. HA has been employed as a carrier material in a wide range of delivery material applications. One crucial aspect that affects the efficient utilization of HA as delivery materials is its size since the size of HA can impact the release efficiency of the materials (Irwansyah *et al*., 2022a). Based on previous research, it has been shown that particle size significantly influences the delivery system. Particles that are too small tend to agglomerate, thus hindering the delivery process. However, on the other hand,

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small particle sizes result in a large surface area, which can enhance the dissolution process of the drugs. Therefore, appropriate particle size control is needed for delivery system applications (Mozar & Chowdhury, 2017). Liu *et al.* (2022) have reported that HA in the nanoscale range specifically 30-50 nm, demonstrates a significantly enhanced cellular uptake capability when compared to HA in the microscale and also has been reported that nanometer-sized HA, with its larger surface area, also exhibits a more significant binding effect on bioactive substances, measuring 63.3% compared to micro-sized HA, which measures 7.65%. Nano-sized HA, which exhibits a large surface area, also has a greater binding effect on bioactive substances, at 63.3%, compared TiO micro-sized HA at 7.65%. In addition to size, morphology is also a crucial characteristic in the use of a delivery system, where the morphology of HA significantly affects the attachment of the carried bioactive substance. HA synthesized in scaffold form demonstrates the attachment of bioactive substance to the scaffold walls (Liu *et al.,* 2023). The adsorption and de-sorption processes of bioactive substances are also influenced by the material's morphology, as reported by Rial et al., the spherical morphology of HA nanorods has a pronounced impact on the drug desorption process (Rial *et al*., 2021).

Table 9. HA size and shape effect on application.

Composite	Size (nm)	Morphology	Application	Result	Ref.
HA-SCT-NPs	72.42 ± 7.190	Spherical	Bone targeted delivery Drug release	85%	(Kotak & Devarajan 2020)
HA HA-Ni	43.595 40.53	Hexagonal	Drug delivery	86 ± 0.2% 95 ± 0.2%	(Asghar *et al.*, 2023)
HA-HE-PEI	~ 20	Spindle	Drug delivery	31.83%	(Wan *et al.*, 2022)
HA-PCL-NPs	90.12 ± 20.36	Spindle	Drug release	94.77 ± 1.23%	(El-Habashy *et al.*, 2021)
HA-PLA	320 ± 12	Scaffold	Drug delivery	92.7%	(Farkas *et al.*, 2022)
HA-Alginate	-	Scaffold	Drug release	43.92%	(Levingstone *et al.*, 2021)
Collagen-HA	-	Scaffold	Femorat defect healing	5 & 10%	(Liu *et al.,* 2023)
Ca-ALG-CHI-HA & Ca-ALG-HA	-	Nano-rod shape, hydrogel	Drug delivery	HA : 100% ALG : 87,27% CHI-ALG : 45,46%	(Rial *et al.*, 2021)
PEI-HA (pEH)	<500nm	-	Dental pulp stem cells	-	(Lee *et al.*, 2021)
Commercial HA	Micro HA : 1-10µm, nano HA : 20-50 nm	Rod shape	Bone cancer treatment	-	(Liu *et al.*, 2022)
Commercial HA	30 mm	granule	Drug-eluting agent	65.42 µg/g 16 µg/g 16.01 µg/g	(Simon *et al.*, 2020)
Commercial HA	1-10 µm	Spherical and porous	Proliferative human osteosarcoma	28 & 36 % (in vitro) 63% (in vivo)	(Liu *et al.*, 2021)

3.4.3. Bioactive substances

All bioactive substances can form an interfacial bond with bones or tissues, but the type of biomaterial influences the time dependence of bonding and the strength, thickness, and mechanism of bonding (Filip *et al*., 2022). Several bioactive substances used for HA application are shown in **Table 10**. Increasing the drug concentration improves the adsorption of the drug to the HA surface as an adsorbent (El-Habashy *et al*., 2021). In bone targeted delivery is heavily reliant on drug-loaded carriers. For maximum uptake in the bone, the

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intricate architecture of the bone tissue requires small particles that can easily penetrate the bone microarchitecture. Such small or nanoparticles' long circulation would also ensure their availability at the bone for such absorption (Kotak & Devarajan 2020). The drug choice for delivery also needs to have a small size to result in excellent penetration (Asghar *et al*., 2023).

Table 10. Bioactive substances used for HA application.

Composite	Application	Bioactive substance	Ref.
HA -NPs	Bone targeted delivery	Salmon Calcitonin	(Kotak & Devarajan 2020)
HA HA-Ni	Drug delivery	Ciprofloxacin	(Asghar *et al*., 2023)
HA-HE-PEI	Drug delivery	Doxorubicin hydrochloride	(Wan *et al*., 2022)
HA-PCL-NPs	Drug release	Doxycycline	(El-Habashy *et al*., 2021)
HA-PLA	Drug delivery	Doxycycline	(Farkas *et al*., 2022)
HA-Alginate	Drug release	Bovine serum albumin Bone morphogenetic protein	(Levingstone *et al*., 2021)

HA can serve as a carrier and delivery system for a wide range of bioactive substances, including genes, proteins, and drugs. This showcases HA's suitability as a carrier and delivery material. The attachment of HA to the material being transported is influenced by several factors, one of which is particle size. Smaller particle sizes lead to more favorable interactions and binding between HA and bioactive substances. HA also exhibits a greater affinity for nanosized particles compared to micro-sized ones (Liu *et al*., 2022; Rial *et al*., 2021).

The composition of the carrier and delivery material also has a significant impact on the binding of HA to bioactive substances. Calcium ions are particularly crucial contributors to HA, playing a pivotal role in binding with bioactive substances (Liu *et al*., 2022). The crosslinking reaction of Ca^{2+} ions with bioactive substances is notable. Additionally, calcium ions also play a vital role in tissue engineering by facilitating the formation of an extra layer of calcium phosphate on the surface of the tissue, an advantage of employing HA in the field of tissue engineering (Liu *et al.,* 2023). The interaction between HA and bioactive substances can manifest through various mechanisms such as electrostatic interaction, as well as chemical, physical, and mechanical binding processes, and this also demonstrates the bioactive of HA with various substances (Liu *et al*., 2021; Liu *et al*., 2022; and Liu *et al.,* 2023). Nevertheless, these interactions differ for each bioactive substance, underscoring the importance of a thorough understanding of the bioactive substances' chemical structure. One of the drug delivery mechanisms involves inhibiting ATP in mitochondria, which results in apoptotic (cell death) effects. This process is notably more efficient when facilitated by HA in comparison to the use of the drug alone (Liu *et al*., 2022). The sustained release of drugs is also influenced by the properties of the materials used, enabling the maintenance and control of drug release by binding doxorubin (dox) through hydrogen bonds. An acidic environment accelerates drug release because the ions in the acidic matrix expedite the breaking of hydrogen bonds between HA and dox when using a calcium sulfate (CaS/HA) carrier, a lower dox dose can be employed, leading to improved efficiency (Liu *et al*., 2021)

The osteoinductivity of HA is a significant advantage in utilizing HA as a delivery material for various bioactive substances like genes, proteins, and drugs in the context of bone tissue engineering applications, the use of HA promotes the growth of bone tissue (Liu *et al.,* 2023).

4. CONCLUSION

In conclusion, this systematic literature review underscores HA's remarkable versatility and promise as a delivery and carrier material. Its ability to facilitate controlled drug release,

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support targeted therapies, and foster tissue regeneration has the potential to reshape the landscape of biomedicine and pharmaceuticals. By addressing challenges and embracing emerging trends, we can harness the full potential of HA for the benefit of patients, ushering in an era of more effective and personalized healthcare solutions.

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6. AUTHORS' NOTE

The authors declare that there is no conflict of interest regarding the publication of this article. The authors confirmed that the paper was free of plagiarism.

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