

Hydroxyapatite Nanoparticles in Drug Delivery

Subjects: Biochemical Research Methods

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Definition

A biomaterial is a synthetic material used to replace part of a living system or a material meant to be in contact with living tissue. In this sense, biomaterials can be categorized into polymers, liposomes, micelles, dendrimers, and calcium phosphate (CaP) nanoparticles, where each will show a different type of bioactivity. Hydroxyapatite (HAP) has been the gold standard in the biomedical field due to its composition and similarity to human bone. HAP nanoparticles have been used as vehicles for delivery due to their affinity to DNA, proteins, several drugs, and proper release activity.

1. Interactions in Drug Delivery with HAP Nanoparticles

HAP nanoparticles have been used as vehicles for delivery due to their affinity to DNA, proteins, several drugs, and proper release activity (**Table 2**) [1]. Although there are no conclusions on which HAP nanostructure is more suitable for which kind of molecule, the adsorbed amount is a function of the functional groups interactions, surface area, porosity, pH, and the surrounding medium [2][3]. Regarding the porosity and pore structure effect on nanoparticles' ability to adsorb and retain the cargo, it is known that mesoporous inorganic materials with high pore volume and adequate pore size are able to adsorb higher amounts of therapeutic molecules and ensure a sustained release [2][4]. Although the synthesis process influences pore size and structure, factors such as the amount and size of the pores are primarily a function of the composition of the raw materials and the sintering conditions. A sintering process up to 1350 °C maintains the HAP phase while promoting pore formations [3]. However, sintering procedures at higher temperatures makes other phases such as TCP appear due to HAP decomposition. Where the TCP band appears at a sintering temperature of 1400 °C in a study by Sofronia et al. [5]. Regarding the effect of particle size, it is known that for solid drug delivery systems, it has a strong impact on its dissolution and drug absorption. Given the large surface area of nanoparticles, an increase in the bioavailability of poorly soluble drugs can be seen in several studies [6][7][8]. A study to correlate the influence of particle size specifically with HAP was performed by Rouahi et al., where they found that HAP nanopowders containing 100 nm particles adsorbed more proteins than 1 µm [9]. This was directly attributed to the difference in superficial surface area, where smaller nanoparticles had higher superficial surface areas than micro-scale HAP particles. The results of these studies suggest that a higher superficial surface area leads to higher protein adsorption, which is also reported in other studies [10].

2. Proteins

As it is essential to tailor the characteristics of HAP nanoparticles to control the affinity of the cargo with the delivery system, several authors have studied the relationship between different physicochemical properties and protein adsorption on the surface [11][12][13][14]. CaPs are able to adsorb more protein than other materials, as calcium and phosphate ions are present as preferential binding sites for proteins. Several authors studied the protein adsorption potential of HAP powders treated with heat, where it was found that there are two main correlations between the superficial surface area and the protein adsorption capacity of HAP: the higher the superficial surface area, the higher the protein adsorption; however, when HAP is sintered, intergranular microporosity is formed and less proteins can be adsorbed [9][15]. In a study by Rouahi et al., an HAP powder with agglomerated granules and a low value of surface area due to the partial fusion of the particles was synthesized. For the FTIR characterization, although the HAP composition was confirmed, the formation of TCP was not observed even though the sample was treated with high heat, which is contrary to other studies displayed in **Table 1**, where Sofronia et al. obtained TCP after sintering at 1400 °C [5]. However, the carbonate peak located around 1500 cm⁻¹ disappeared after the heat treatment. Nevertheless, the authors explained that the heat treatment did affect the protein adsorption potential and that the slight difference between samples was due to the surface area values, where the original samples that were not sintered had higher surface area values than those that underwent heat treatment. Finally, the ceramics prepared from the sintered samples had higher microporosity and intergranular microporosity, which explained the higher values of cells attaching on the surface. According to the previous study, increasing the surface area results in higher protein adsorption. Furthermore, as the microporosity decreases, the lower the protein adsorption and cell attachment rates become [5].

Table 1. Vibration frequencies in FTIR spectrums from different HAP samples sintered and treated at different temperatures.

Sintering Temperature	-	-	60 °C	600 °C	950 °C	1250 °C	1350 °C
Sample	Natural HAP (cm ⁻¹)	Si-HAP (cm ⁻¹)	HAP-p (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)
	1540	-	1540	1462.48	1456	-	1540
C-O	1548	-	-	-	-	-	-
	1418	-	-	1418.2	876	-	-
C=O	1653	-	1650	1621.94	-	-	-
C-N	1560	-	1560	-	-	-	-
N-H	1560	-	1560	-	-	-	-
Peptide	-	-	1400	-	-	-	-
P-O	1087	1089	1020	1100	1091	1100	1087
O-H	3569	3570	-	3571	3572	3575	-
	-	881	-	-	-	-	-

Sintering Temperature	-	-	60 °C	600 °C	950 °C	1250 °C	1350 °C
SiO ₄ ⁴⁻ Sample	Natural HAP (cm ⁻¹)	Si-HAP (cm ⁻¹)	HAP-p (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)	HAP (cm ⁻¹)
	-	498	-	-	-	-	-
Reference	[5]	[16]	[17]	[18]	[5]	[9]	[15]

HAP: hydroxyapatite, Si-HAP: SiO₄⁴⁻ substituted HAP, HAP-p: HAP conjugated with peptide.

Another study that discussed the relationship between the calcination temperature and the adsorption and controlled release of bovine serum albumin (BSA) was carried out by Dasgupta et al. [19]. The authors reported a process of synthesis of nano-HAP using a reverse micelle template system and protein loading through electrostatic interactions between the nanoparticle surface and the charged amino acids of BSA. The release profiles were evaluated at three different pH solutions. During the physicochemical characterization, when the particles were calcined at 600 °C, pure HAP was formed instead of TCP, which forms at higher temperatures and is explained by the absence of the OH⁻ bending frequency in FTIR spectra. This phase transformation happening at higher temperatures was noticed because of the disappearance of the HPO₄²⁻ at 870 cm⁻¹ and the OH⁻ band at 3569 cm⁻¹. The authors also mentioned that this change was reflected in the XRD pattern [19]. In the case of particle size analysis, it was found that at higher calcination temperatures, the particle size increased as well. The HAP nanocrystals calcined at 600 °C showed the highest surface area (73 m²g⁻¹) and aspect ratio. For the loading experiments, those studied at a pH higher than 7.5 maintained high stability because at a lower pH, the dissolution of nano-HAP could destroy the stable interface between the BSA and the nanoparticles. This interface was formed by the positive calcium ions and the negative polar heads of the BSA molecule. Since the pH of the BSA and CaPs suspension was above the isoelectric point of each BSA, TCP, and HAP, both the BSA and the nano-HAP carried negative charges on their surface. The stern layer of anions [A⁻, (H₂PO₄)⁻, OH⁻] attached to Ca²⁺ ions was the source of negative charges on the CaP nanoparticle surface. This interaction gradually decreased as the pH increased from 7.5 to 8.5 and 9, due to an enhanced electrostatic repulsion force between the particle surface and the BSA. The surface area was the main factor of interaction, as the higher the surface area, higher the surface charge density of the nanoparticles, resulting in a higher degree of electrostatic interactions. Since the surface of HAP materials cannot be easily modified through surface treatments to form hydroxyl-, amino-, or carboxyl- groups as is possible with metals and polymers, peptides can be adsorbed on HAP by modifying the surface [15]. This was also the case in a study by Kojima et al., where several peptide-HAP complexes were made to adsorb cytochrome c, myoglobin, and BSA [17]. Firstly, the complexes were made by adding peptides during the HAP synthesis process along with the calcium ions source. The peptides contained amino groups on their structures (glutamic acid and lysine) and were easily detected through FTIR spectroscopy, where two major bands of amide I and amide II stretching groups appeared at 1650 and 1560 cm⁻¹, signals that according to **Table 1** are not found among other HAP examples. Then, selective adsorption was proven with a lysine-HAP complex and the acidic protein BSA. The authors report that the selective adsorption was due to electrostatic interactions between the peptides on HAP surface and the proteins, as adding the peptides changed the surface potential [17]. As carbonate ions can be found in HAP samples sintered at low temperatures, the authors did not discuss whether the small signal they found at 1650 cm⁻¹ was due to a possible carbonate substitution on the HAP structure. Even though it is not discussed in the paper, as the signal is smaller than those HAP samples with high carbonate content, it can be assumed that the complex was made between the peptide and HAP. As seen in **Table 1**, increasing the sintering temperature can reduce the carbonate concentration, thus affecting peptide and protein adsorption as there are less ions for the biomolecules to interact with [20]. In the case of the study by Kojima et al., protein and peptide adsorption was still possible because of the electrostatic interactions between the side chains of the peptide and the proteins [17]. For these reasons, it is important to take into consideration which groups are meant to interact via electrostatic forces and set an appropriate pH to set the expected charges of each groups.

2. Peptides

Peptides are smaller, cheaper to produce, less susceptible to degradation, and have advantages over proteins [15]. Even if proteins and peptides are both able to promote different cell functions, such as cell adhesion, nanoparticle-mediated peptide delivery is known to enhance the bioavailability of these proteinaceous compounds [21] and protect the peptides from enzymatic degradation [22][23][24][25]. As mentioned in previous sections, the level of peptide adsorption on the nanoparticles can be altered through the presence of carbonate within the structure and changes in surface morphology. In work by Segvich et al., different peptide sequences with preferential adsorption towards HAP, carbonated apatites, and bone-like minerals were identified, and they studied how surface morphology changes and carbonate incorporation could alter peptide adsorption [15]. According to data reported by Tamerler and Sarikaya [26], three 7-mer peptide sequences are specific to HAP, and adsorption experiments were carried out to prove this preferential adsorption. Peptides APWHLSSQYSRT [A], SLTPIPHFSRE [S], and VTKHLNQISQSY [V] were identified with phage display, and peptide EEEEEPRGDT [E] was known to be found in the bone sialoprotein [27]. Peptide E can be found in proteins that contain a high proportion of acidic amino acids, such as glutamic and aspartic acids, whereas peptides A, S, and V do not present strings of acidic amino acids. It is reported that compounds with acidic groups are adsorbed on HAP surfaces due to the interaction with calcium surface cations [28]. The BET surface areas for bone-like material, HAP, 5% carbonate apatite (CA5) and 10% carbonate apatite (CA10) were 121.55, 0.05, 0.11, and 0.19 m²g⁻¹, respectively. Regarding surface feature sizes, HAP, CA5, and CA10 had granular surfaces, whereas bone-like material illustrated more evident plate-like features. The FTIR characterization showed characteristic type A carbonate peaks at 1455 cm⁻¹ for CA5 and CA10 but not for HAP. For XRD characterization, the narrow and distinct signals, because of the high sintering temperature peaks were correlated with HAP. Peaks from TCP phase were found on the CA5 and CA10 samples at around 29.7 and 37.3°, which were also not present on the HAP sample. It was seen that at the same morphological scale, the carbonate concentration differences were less than 2 wt%, which indicated that the differences between peptide adsorption were present due to morphological differences rather than compositional, which is a known phenomenon as reported in other studies [10]. The authors mentioned that a better control on the surface morphology could determine whether carbonate incorporation had an effect on peptide adsorption. In the case of the effect of the peptides' pH and the amount of acidic amino acids on the structure, as this study demonstrated that peptides without acidic amino acids showed preferential adsorption towards HAP even though it was reported that acidic peptides had a higher affinity, based on the electrostatic attraction, the acidic proteins should preferably be adsorbed on the calcium site-based surfaces, basic proteins preferentially adsorbed on the P/OH site-based surfaces; acidic residues preferably bonded to the Ca²⁺ sites, basic residues preferentially bonded to the P/OH sites [10].

In another study, computational studies were made to understand the interaction between the tripeptide HYP-PRO-GLY with HAP. This peptide is known for being present in collagen protein and might have a growth-modifying effect on HAP surfaces. This peptide contains hydrophilic and hydrophobic side groups, and the results showed that it interacts mainly with the (0110) plane rather than the (001) plane. The main interactions found in this study were located on the surface calcium ions; these were more pronounced than the more thermodynamically stable (001) plane [29]. On another study, peptides HYP-PRO-GLY, PRO-HYP-GLY, PRO-LYS-GLY, and PRO-HYL-GLY interactions with HAP (0001) and (0110) surfaces were studied through molecular dynamics [13]. The four peptides adsorbed strongly to (0110), showing a proton transfer from the peptides to the reactive surface. On the (0001) surface, this transfer only happened when the amino acid residue had a charged polar group (PRO-LYS-GLY and PRO-HYL-GLY). In this particular case, the proton of the LYS and HYL amine group migrated to the basic phosphate group. With these studies, the authors showed that peptide adsorption onto HAP depends on the crystallographic phases [13]. Inhibited crystal growth of HAP has been attributed to the molecular adsorption of certain amino acids on the surface at active growth sites due to the affinity and the nature of each amino acid [30][31][32]. It is reported that amino acids with polar uncharged side groups have a high adsorption affinity for the surface of HAP, which is also the case for aspartic acid, phosphoserine, histidine, and imidazole derivatives [33].

3. Drugs

Different types of HAP nanoparticles have been used for the delivery of several drug molecules, composites, coatings, and paramagnetic particles. Abbasi Aval et al. developed superparamagnetic HAP-coated Fe₂O₃ nanoparticles, aiming to prevent the agglomeration and oxidation of superparamagnetic particles with the coating [34]. The authors synthesized mesoporous HAP with 12 nm sized pores and a surface area of 148 m²g⁻¹ to adsorb a large amount of doxorubicin, a small hydrophobic drug, on the surface of Fe₂O₃ nanoparticles. The nature of the pores was determined by nitrogen sorption isotherms, where, due to a relatively sharp slope of the adsorption-desorption diagram, the presence of cylindrical pores with open ends was confirmed. Under neutral conditions, the positive nature of the HAP surface is caused by the specific adsorption of excess calcium ions and their solubility [28]. The amount of doxorubicin adsorbed on the surface was almost 93%; however, the authors do not mention in which solution or conditions, and the release profiles were studied at pHs 5.5 and 7.4. Within 24 h, in pH 7.4, only 10% of the loaded doxorubicin was released, whereas in the pH 5.5 environment, about 70% of the drug was released, this means that HAP and doxorubicin had a higher affinity when HAP carried positive charges rather than negative [35]. This conjugation with doxorubicin was also seen in another study by Yang et al., with a different morphological approach [36]. The authors synthesized hollow mesoporous HAP nanoparticles with a surface area of 163.2 m²g⁻¹ and a pore size of 3.3 nm. The samples were placed in phosphate buffer at pH 7.4, and the vehicles showed a fast release for the first 30 min and slow release from 0.5 to 50 h, which corresponds to a pseudo-first-order release profile. They also mentioned that due to this behavior, it could be assumed there was no interaction between the HAP matrix and the doxorubicin molecules, and the release was significantly higher on mesoporous hollow nanoparticles than normal nanoparticles and higher at pH 4.5 than pH 7.4. However, in a study by Storm et al., doxorubicin was encapsulated in higher amounts on negatively charged liposomes than on neutral ones [37]. The main mechanism of adsorption of doxorubicin, in this case, may not be caused by electrostatic interactions but rather hydrogen bond interactions between the OH⁻ group of doxorubicin and the OH⁻ group of HAP. This is reasonable because, in a study by Yulia et al., by combining quantum chemistry calculations and spectroscopic techniques, an ibuprofen/nanoHAP complex was studied [38]. The authors reported that the main interactions of the system were the hydrogen bonds between both OH⁻ groups of HAP and ibuprofen and a strong interaction between ibuprofen's carbonyl group and the Ca²⁺ center of HAP [38]. Moreover, even though it has been proved that electrostatic interactions play a major role in adsorption onto HAP surfaces, it does not fully account for the adsorption of biomolecules. For example, the adsorption of human serum albumin occurs under conditions where the adsorbent and the adsorbate are negatively charged. This process was dominated by entropy, structural rearrangements, changes of hydration, and co-adsorption of electrolytes. Moreover, studies suggest that the secondary structure of the biomolecules and desorption of water also play critical roles [39][40].

In a study by Barroug and Glimcher, the anti-tumor drug cisplatin was adsorbed by HAP crystals of 93 × 29 nm [41]. The authors mentioned the effect of the solution's composition and ionic strength, in which an increase in the ionic strength of the solution significantly reduced the affinity between the HAP surface and the cisplatin molecules. This dependence of adsorption on the solution composition is driven by electrostatic interactions, as the surface is covered by adsorbate, and charge neutralization and adsorbate-adsorbate repulsion occur as well. In these experiments, the HAP samples synthesized at a pH close to 10 had isoelectric points at around 7.0, and the highest uptakes were observed after equilibrium with phosphate buffers rather than Tris buffers due to the presence of phosphate ions, which can also be explained by the hydrolyses of cisplatin in aqueous solutions [41]. The authors also reported that under the conditions of the experiments (pH 7.4, phosphate 10 mM), the HAP crystals and the cisplatin were oppositely charged, which resulted in an electrostatic attraction between both surfaces. With this being said, the medium in which the adsorption between HAP and the drug occurs plays a major role in its performance and release, as the hydrated derivatives and the presence of different ions can cause displacements in the native forms of the drugs.

As the structure of HAP contains negatively charged OH⁻ groups, these can interact with positive groups such as amine groups, sodium, and hydrogen ions. These interactions were employed in a drug delivery system using HAP and sodium ampicillin. In a study by Queiroz et al., they made a comparison between HAP and HAP composites that contained other crystalline phases such as TCP. The authors explained that pure HAP adsorbed more ampicillin than the composites with 16 and 57 wt% TCP because of a greater amount of OH⁻ groups in HAP, which are bridging agents to ampicillin. The higher solubility of TCP also played a major role in decreasing the ampicillin adsorbed, causing ampicillin resorption during the loading process, making it harder for ampicillin to adsorb on the composite surfaces compared to the HAP sample, which was relatively insoluble [42].

4. Genetic Material

HAP can be used as a vector for gene delivery due to their strong affinity and the ionic interactions between calcium ions and the gene backbone [43]. This allows the use of HAP delivery systems for the attachment of regulatory sequences and movement across the cell membrane. One of the main disadvantages of using HAP as a delivery system is that the sintering process can cause the agglomeration of particles, which in the case of gene delivery decreases its transfection efficacy. In a study by Han et al., well-dispersed HAP nanoparticles were obtained by a simple ultrasound-assisted precipitation method with the assistance of glycosaminoglycans [44]. The nanocrystalline nature of the particles was confirmed by the broadening and merge of the three major peaks (211), (112), and (300) at around 2θ = 30,

which are characteristic of HAP. They were also able to confirm the presence of carbonate ions due to the peaks at 603 and 567 cm^{-1} , which are phosphate bands appearing in different sites [44]. The size for the rod-like particles was about 20 × 50 nm and had a zeta potential of -60.9 mV, which improved stability, as mentioned in previous sections. The authors also mentioned that the acoustic cavitation caused by the ultrasound processing dispersed the HAP nanoparticles. The addition of glycosaminoglycans improved the electrostatic interaction between their negatively charged groups and the calcium ions of HAP, resulting in the overall negative charge of HAP nanoparticles. A novel strategy for gene therapy involves the use of biominerals through the nucleation of HAP on a DNA template. The rationale behind this stems from the relation between DNA and HAP in other biological systems and a strong interaction between both materials. As a specific binding activity of HAP exists for DNA, these kinds of complexes are less susceptible to degradation by serum and nucleases [45]. In a study by Bertran et al., DNA was encapsulated into HAP nanoparticles through the fabrication of nanocapsules and crystalline nanorods with DNA inside. The experiments suggested that HAP grew around the DNA matrix [45].

Table 2. Drug delivery applications for HAP and its respective cargos.

Cargo	Heat Treatment		Size (nm)	Potential (mV)	SSA (m^2g^{-1})	Porosity (%)	Pore Volume (cm^3g^{-1})	Morphology (-)	Amount Adsorbed (mg)	Application	Reference	
	(°C)	(h)										
Fibrinogen				-	2.53	2.39	-	Spheres	2.93 mg/m^2			
Insulin	80	overnight	60						2.24 mg/m^2	Diabetes	[4]	
Col-I									1.12 mg/m^2			
BSA	1250	4 h	1000	-37	0.9	micropores	-	Granules	65.7 $\mu\text{g}/\text{mL}$		[9]	
BSA	1000	15 h	100	0	25.4	micropores	-	Granules	78.3 $\mu\text{g}/\text{mL}$			
BSA	600	3 h	39	-0.55	40	-	-	-	4.0 mg/m^2			
Proteins	MG	600	3 h	39	-0.55	40	-	-	1.0 $\mu\text{g}/\text{m}^2$	Blood compatibility	[20]	
	BSA	700	3 h	43	-0.9	20	-	-	9.8 mg/m^2			
	MG	700	3 h	43	-0.9	20	-	-	1.5 $\mu\text{g}/\text{m}^2$			
BSA	600	4 h	32	-	73	-	-	89 $\mu\text{g}/\text{mg}$				
BSA	700	4 h	36	-	66	-	-	85 $\mu\text{g}/\text{mg}$	Delivery	[19]		
Cyt c	60	3 h	60 × 30	-24	96		0.79	Rod	60 $\mu\text{g}/\text{mg}$			
MGB									43 $\mu\text{g}/\text{mg}$	Delivery	[17]	
BSA									78 $\mu\text{g}/\text{mg}$			
Peptides	APWHLSSQYSRT	1350	1 h	-	-	0.05	-	Granules	1 nmol			
	STLPIPEFSRE			-	-				2.4 nmol	Delivery	[15]	
	VTKHLNQSISQSY			-	-				2.5 nmol			
Drugs	Doxorubicin	100	24 h	400 × 600	-	163.2	mesopores	0.53	Oval	3 × 10 ⁵ mol/g	Breast cancer	[36]
	Ibuprofen	1000	2 h	79	-	-	-	-	Plates	-	Arthritis	[38]
	Cisplatin	80		93 × 29	-	96.8	-	-	Plates	2.4 mg/g	Cancer	[41]
	Ampicilin	1200	1 h	8-9 × 10 ³	-	-	Mesopores		Spheres	6.5 mg/g	Bacterial infection	[42]
DNA	Fish sperm DNA	80	1.5 h	20	-	-	-	-	Spheres	11 $\mu\text{g}/\text{mg}$	Gene therapy	[45]
	EGFP-N1 pDNA	170	2 h	40-60	-	-	-	-	Rod	0.02 $\mu\text{g}/\mu\text{g}$	Gene therapy	[46]
	CDglyTK	35	72 h	23-34	+16.8	-	-	-	Feather	-	Antitumor	[47]

SSA: superficial surface area, Col-I: type I collagen, BSA: bovine serum albumin, MG: macroglobulin, Cyt c: cytochrome c, MGB: myoglobin.

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