Antibacterial and Biomedical Applications of Metal doped Hydroxyapatite: A Review

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ABSTRACT

Recently metallic doped Hydroxyapatite has drawn attention due to their safe use and greater antibacterial properties in the field of biomedical. Researchers synthesized nickel-substituted hydroxyapatite nanoparticles with improved antioxidant characteristics and inhibition of *Pseudomonas aeruginosa* growth. The antibacterial activity and cytotoxicity of titanium and copper-substituted analogs of hydroxyapatite varied. The chemical precipitation of fine hydroxyapatite powder resulted in poor antibacterial activity when combined with ciprofloxacin. The antibacterial properties of Ag-Nano crystalline hydroxyapatite were unique with regard to *Staphylococcus aureus*, *Escherichia coli* and *Candida albican*. A new composite coating made of silver and zinc doped hydroxyapatite in chitosan matrix showed substantial antibacterial activity while being biocompatible. Higher zinc concentration enhanced hardness and antimicrobial capabilities in zinc-doped hydroxyapatite that was produced by wet precipitation, which had antibacterial effects against *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Drug delivery, treatment of bone infections and antimicrobial applications all involve hydroxyapatite nanoparticles. Ciprofloxacin delivery for bone regeneration was made possible by hydroxyapatite scaffolds that have functionalized with hydroxypropyl/Cyclodextrin gelatin/HAp nano composite showed drug release kinetics. Biological properties were enhanced when neodymium, cerium, magnesium and zinc ions were substituted with hydroxyapatite. Manganese and selenium-doped hydroxyapatite nanoparticles can interact with osteoblasts and have antibacterial and blood compatibility properties. These results support numerous possibilities of use of hydroxyapatite as antibacterial agent. The methods and techniques of metal doped hydroxyapatite are also reviewed to confirm the findings.

Keywords: Metal doped Hydroxyapatite, Antibacterial activity, Biomedical Applications, Ciprofloxacin, Biocompatible

1. INTRODUCTION:

Treatment of bacterial infections brought on by bone injuries necessitates the creation of biocompatible materials with improved antibacterial and medication delivery characteristics. The primary component of bone, hydroxyapatite (HAp) possesses antibacterial qualities and has been utilized in a variety of ways for bone filling. According to studies adding metal and antibiotics to HAp increases its antibacterial effect. The combined effect of nickel and ciprofloxacin doping on the antibacterial and drug-release characteristics of HAp nanoparticles has not been fully examined. Antimicrobial properties are enhanced when

hydroxyapatite, nickel and antibiotics are combined. Nickel harms microbial cells by disruption and protein disruption. By swapping out necessary metals in metalloproteins, it can also block enzymes. Nickel also has antioxidant qualities because it uses electron transfer processes to scavenge free radicals by injecting nickel [1]. The main inorganic component of bones and teeth is HAp a ceramic having chemical formula $Ca_{10}(PO_4)6(OH)_2$ is good for surface coating implants to encourage osteointegration. The effectiveness of these implants depends on their ability to fight off immune problems brought on by local microorganisms. Numerous uses, including antibacterial implants, protein purification, radioactive leakage barriers and catalysts, have been made possible by detailed studies of crystal structure of HAp and ability to alter its properties through ion replacement. The antibacterial characteristics of HAp modified with metal ions including Ag^{+}, Zn^{2+}, Cu^{2+} and Ti^{4+} have been the subject of recent studies. Excellent antibacterial activities were demonstrated by Ag+ replaced HAp but results for Cu^{2+} doped HAp varied and various synthesis techniques may affect CuHAp toxicity [2]. A biocompatible and bioactive ceramic known as HAp is frequently used in implants, coating materials, drug delivery, improved efficacy, safety, regulated release and predictable therapeutic response are some of its benefits. For local drug delivery, meso-porous HAp is thought to be the best drug carrier. Its potential to manage septic arthritis and stop infections is being researched. Due to its biocompatibility and porous nature, HAp has been studied with various morphologies and surface characteristics for drug administration. According to research Brij 35, a non-ionic surfactant, was used to create Nano-hydroxyapatite rods with porous architectures. The study concentrated on antibacterial activity against Gram-positive and Gram-negative bacteria as well as drug loading and leaching kinetics [3]. The study of biomaterials is particularly difficult since researchers are working to create new and better materials that are highly biocompatible and antimicrobial. It has been studied how silver nanoparticles interact with biological macromolecules as possible bioactive substances with antibacterial characteristics. Ciobanu *et al.*, 2013 wanted to assess how well Ag-doped hydroxyapatite nanoparticles (AgHAp-NPs) inhibited the growth of several bacterial and fungal strains in their investigation. The samples were created using the co-precipitation technique at 100°C. XRD, TEM, SEM and FTIR were among the methods used to characterized the structure, morphology and optical characteristics. Antimicrobial studies yielded encouraging results [4]. The goal of the work was to create AgZnHApCs, a new composite material with improved biocompatibility and substantial antibacterial characteristics. The composite was made of chitosan, which has antibacterial and antioxidant properties, mixed with hydroxyapatite that has been doped with zinc and silver. The goal of the study was to produce a homogenous coating that is uniform and maintained the biological characteristics of a composite solution [5]. The creation of pure HAp and HAp doped with zinc at the nanoscale was the main goal of this investigation. The phase composition, shape and incorporation of zinc into HAp were examined using various techniques. As a result of reduced grain size in Nano hydroxyapatite and enhanced zinc addition, the results showed that very little zinc remained in the hydroxyapatite matrix, improving the antibacterial

characteristics [6]. The production and evaluation of zinc-doped hydroxyapatite and nano hydroxyapatite as ciprofloxacin drug delivery vehicles. The drug loading percentage and release profile of drug-loaded carriers were also examined. Additionally, the antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* was assessed. The finding showed that these carriers can deliver drugs locally, increasing therapeutic effectiveness and minimizing negative effects [7]. In an aging society, the development of biotechnology for bone healing is essential since bone tissue diminishes with age and lowers quality of life. Due to its bioactivity and biocompatibility, HAp is a promising biomaterial utilized for bone healing that has a variety of uses. However, the presence of microbes on the surface of biomaterials is of concern. A study exhibited a novel and straight forward chemical method for the synthesis of HAp nanoparticles, which have promising antibacterial effects against a variety of bacteria [8]. HAp a popular ceramic, can have its characteristics improved by adding metal ions. The bioactivity, biocompatibility and antibacterial activity of HAp can all be enhanced by changing the ions in its lattice. Due to its stability, mechanical characteristics and biocompatibility, lithium-substituted HAp (Li-HAp) has drawn interest for its potential in hard tissue applications and therapeutic usage. Li-HAp can be produced more cheaply and safely using the sonochemical process. The preparation, characterization and biological activities of Li-HAp are examined with results that are encouraging for biomedical applications [9]. The drug is released at a controlled rate for a longer length of time with sustained-release formulations, which have an advantage over conventional drug delivery techniques. It also reduces negative effects while localizing drug release, increasing therapeutic index and efficacy. It is difficult to treat bone infections like osteomyelitis because biofilms shield germs from immune reactions. By delivering antibiotics directly to the site, sustained drug delivery systems that make use of biocompatible non-carriers such as hydroxyapatite aid in the treatment of bone infections. When coated with polymers like polyvinyl alcohol and sodium alginate, hydroxyapatite nanoparticles maintain drug release, improving bioavailability and therapeutic responsiveness. This approach of layer-by-layer coating guarantees extended medication administration, making it efficient for the treatment of bone infections [10]. Antibiotics are frequently given during bone regeneration procedures to reduce infection risk and hasten bone mending. However, due to high and prolonged concentrations needed in damaged bone tissue, localized antibiotics administration is constrained. By enabling the regulated release of medicines like ciprofloxacin, implantable biodegradable platforms might improve effectiveness. Local antibiotics administration is made easier by solid scaffolds with high loading capacities and slow drug release. Bone injuries activate a system that leads to the production of new tissue and bone regeneration involves intricate processes. The use of tissue engineering and bone grafting necessitates surgery and increase the risk of bacterial adhesion, which can result in problem like osteomyelitis. During orthopedic surgery, local antibiotics administration lowers bacterial burden at the site and lowers the likelihood of infection. Cyclodextrins (CDs) offer high local drug concentration and showed potential for improving antibiotics

administration. Due to its osteoconductive nature, HAp is a good material for scaffolds, however, its drug release qualities can be enhanced. Ciprofloxacin is a promising choice because of its interaction with CDs, which helps functionalized HAp with CDs to increase antibiotic transport and release. The goal of study is to develop CD-functionalized HAp microparticles that enhance ciprofloxacin transport and release. These microparticles can be employed alone or combined with scaffolds to provide local antibiotics for the treatment of osteomyelitis [11]. Antibiotics like amoxicillin are used as a treatment for periodontitis, an oral condition that results in alveolar bone loss surrounding teeth. Antibiotics should be administrated locally rather than systemically because they have fewer negative effects and are more focused. Numerous dental applications use synthetic HAp which imitates natural bone minerals; nevertheless, because of its mechanical limits, a composite material containing polymer has been investigated. Gelatin and other biodegradable polymers are prized for their capacity for controlled release and biocompatibility. The purpose of the study is to develop an amoxicillin-controlled release drug delivery system employing HAp gelatin nanocomposite. The nanocomposite can improve drug entrapment, release and resembles natural bone components. Various processing paths are investigated an impact [12]. Because of its biocompatibility, bioactivity and osteoconductivity, HAp is frequently employed in orthopedic and orthodontic areas. However, the mechanical and solubility properties of synthesized HAp have their drawbacks, ionic substitution, which permits alteration such as neodymium (Nd), Cerium (Ce), magnesium (Mg) and zinc (Zn) substitutions, that has come to be used as a method to improve the properties of HAp. These modifications alter qualities including cell proliferation, antibacterial activity and electrical conductivity The bone formation increased electrical conductivity, potential used in electromagnetic fields and bone fracture repair when neodymium-substituted HAp is used. Cerium which has a reputation for being healthy, can imitate enzymes and lessen reactive oxygen species. The bioactivity, osteoblastic activities and tissue regeneration are improved by magnesium and zinc substitutions as well. The wet chemical precipitation method was used for HAp. The structural and biological effects of replacement were examined using X-ray diffraction, infrared spectroscopy, microscopy and spectroscopy. The work also looked at how osteosarcoma and normal cells responded to substituted HAp's antibacterial, antifungal and cellular effects [13]. A flexible bone substitution noted for its biocompatibility, capacity to produce bone and use in orthopedic and dentistry applications is calcium-deficient HAp. Although HAp has advantages such as osteoconductivity and osteoinductivity. It also has drawbacks such as poor bioactivity, weak mechanical strength and a low rate of resorption. By incorporating different ions such as magnesium (Mg), gallium (Ga), copper (Cu), zinc (Zn), cobalt (Co), silver (Ag), europium (Eu), strontium (Sr), manganese (Mn), and selenium (Se) into HAp lattice. The effect of manganese-doped HAp (Mn-HAp) on bone and muscle metabolism, bone mineralization and collagen-type synthesis has been demonstrated. It was demonstrated the higher cell adhesion and improved thermal and mechanical stability and osteoblast proliferation potential. HAp (Se-HAp) doped with selenium has shown an advantage in the

treatment of bone cancer, antibacterial action and a decrease in reactive oxygen species. It promoted healthy cell development while causing osteosarcoma cells to undergo apoptosis. The systematic synthesis and characterization of HAp nanoparticles doped with various amounts of manganese and selenium ions is the main objective. Wet-co-precipitation method is used. The microstructural, physiochemical, and biological characteristics of produced nano powders are compared, as well as their antibacterial effects and compatibility with osteoblast cells. Understanding how to create ion-substituted HAp Nano phase with improved bioactivity, biocompatibility, and antimicrobial activity would help with prospective uses in bone regeneration and implantation [14].

2. EXPERIMENTAL METHODS

Different methods have been used to synthesized HAp powder and then doped with other metals. Among them coprecipitation was used to create nanoparticles of HAp and cationic substituted HAp. To speed up the reaction, calcium nitrate tetrahydrate is combined with a solution containing cetyltrimethylammonium hydrogen phosphate at a particular flow rate and pH, following overnight development, the precipitates were thoroughly cleaned before gel-like byproduct was dried to produce HAp powder. Different amounts of nickel (II) nitrate hexahydrate were employed for $Ni_{x=0.3,\ 0.5}$ HAp. The FTIR, XRD and FESEM methods were used to characterized the synthesized materials. Asghar *et al.*, 2023 used HAp and $Ni_{x=0.3,\ 0.5}$ HAp nanoparticles with a drug solution containing ciprofloxacin hydrochloride to examine drug loading and release. The mixture was stirred for varied amounts of time and at various temperatures. The amount of drug loading was calculated [1]. By using a wet chemical process, metal ion substituted HAp was created. To create pure hydroxyapatite, calcium hydroxide [Ca $(OH)_2$] and phosphoric acid (H_3PO_4) were first combined. At pH 6 and 98.5°C, metal salt solutions comprising Cu^{2+} and Ti^{4+} were added to the HAp slurry to produce metal-substituted HAp. Ortho-phosphoric acid was gradually added to calcium hydroxide while stirring in a wet chemical precipitation reaction to create hydroxyapatite nanoparticles. It was then washed and dried to produce a white powder. Zn $(NO_3)_2$. $6H_2O$ was used to create zinc-doped hydroxyapatite samples with various zinc concentrations [7].

3. TECHNIQUES USED FOR CHARACTERIZATION

Different techniques were used to characterized the synthesized HAp. The samples were examined by various techniques using the Field Emission Scanning Electron Microscope to look at their physical appearance, X-ray diffraction to determine their crystal phases and Fourier Transform infrared spectroscopy (FTIR) to analyzed bond interactions. The weight percentage of Cu and Ti in the samples was calculated using inductively coupled plasma emission spectrometry. *Escherichia coli* (*E. coli*) was used to test the sample's antibacterial abilities [2]. Wet chemical synthesis of HAp was used in investigation by Padmanabhan *et al.*, 2019. To make solutions with a pH of 11, calcium nitrate and ammonium dihydrogen orthophosphate were dissolved in water. One of the solutions was blended with the non-ionic surfactant Brij 35, and the combined effects produced a white precipitate. To obtained pure phase nano HAp, the HAp product was collected, cleaned with ethanol, dried and powdered before being calcined at 800°C. To see

how Brij 35 affected the HAp characteristics, the synthesis was carried out again both with and without Brij 35 at various concentrations. By combining 30% weight of ciprofloxacin hydrochloride (CPF) with 70% weight of HAp, drug loading was carried out. The resulting mixture was then pressed into pellets. The pellets contained drugs [3]. According to study of Ciobanu *et al.*, 2013, coprecipitation was used to create Ag^{+} doped HAp. Without additional purification, the initial chemicals, such as calcium nitrate, ammonium dihydrogen phosphate, and silver nitrate were employed. By bringing the pH of the $Ca^{+}Ag$-containing solution to 10 and gradually adding the P-containing solution, the HAp ceramic powder with varied silver doping levels (xAg) of 0.2,0.3 and 0.4 was created. The Ag^{+} doped HAp nanoparticles were obtained by washing and drying the resultant precipitate. Different methods were used to characterized the generated samples. $Ca_{10}xxAg$ $(PO_4)6(OH)_2$ samples' phase purity and crystallinity were examined using X-ray diffraction (XRD) techniques. The surface morphology and elemental content were examined using energy-dispersive X-ray analysis (EDX), scanning electron microscopy (SEM) or transmission electron microscopy (TEM) [4]. In a chitosan matrix, created silver-and zinc-doped hydroxyapatite (AgZnHAp) with particular amounts of chitosan, calcium nitrate, zinc nitrate, and silver nitrate, Predoi *et al.*, 2020 employed a coprecipitation technique. The resulting AgZnHApCs slurry was tested for stability before being used to create coatings using the dip coating technique on glass substrates. The coating was cured for 24 hours at 100°C variety of methods were used to characterized the samples of produced AgZnHApCs. Their crystal structure was examined using X-ray diffraction (XRD), while their molecular structure was investigated using FTIR-ATR spectroscopy. Measurements from XPS (X-ray photoelectron spectroscopy) allowed for additional surface examination. The surface morphology of the coating was studied using optical and metallographic microscopy, atomic force microscopy (AFM) and other techniques. Also assessed was the cytotoxicity of the AgZnHApCs solutions and coatings. In general, the Predoi *et al.*, 2020 sought to created, described, evaluated the cytotoxicity and antibacterial qualities of AgZnHApCs coating. The study conclusion might be useful in a number of biological and antibacterial domains [5]. By gradually adding an aqueous suspension of orthophosphoric acid drop by drop to an aqueous suspension of calcium hydroxide while stirring, hydroxyapatite nanoparticles were created. After washing and drying the result might slurry, samples of Zinc-doped hydroxyapatite with various zinc concentration were created by various techniques, including XRD, TEM, FTIR, Raman, hardness testing and antibacterial activity tests against certain bacterial strains were used to characterized the samples. The findings shed important light on the composition, characteristics and prospective uses of zinc-doped hydroxyapatite nanoparticles [6]. XRD was used to determine the crystalline phase composition, while TEM was used to investigate the crystal form and structure. Functional groups were examined using FTIR and Raman measurements and microhardness was assessed using hardness testing. Ciprofloxacin was dissolved to perform drug loading [7]. By gradually incorporating orthophosphoric acid into a calcium hydroxide solution while vigorously swirling it at 70°C for three hours, maintaining a molar ratio of 1.67 for Ca to P, hydroxyapatite nanoparticles

were created. A white precipitate of HAp gel was formed after 4 hours of aging. Nearly all of the HAp nanoparticles were obtained by separating, washing and drying the HAp solid products. The final goods were produced by heating the solid materials in an electric furnace for one hour at 700°C. Utilizing a variety of methods, the produced HAp nanoparticles were characterized. To determine the makeup of the crystalline phase, X-ray diffraction was used. To investigate the functional groups found in nanoparticles, infrared spectra were obtained. Scanning and transmission electron microscopy were used to examine morphology and structural elements [8]. Nanoparticles of hydroxyapatite (HAp) and lithium-substituted hydroxyapatite (Li-HAp) were created. Ammonia was used to prepare calcium nitrate and ammonium phosphate aqueous solutions and get their pH values to 11. The phosphate precursor solution was added dropwise while the calcium precursor solution was agitated and continued to be sonicated. Methanol was used to filter, wash and clean the resultant precipitate. The precipitate was dried to obtain pure HAp and various lithium nitrate solution concentrations were then added to the calcium nitrate solution to produce Li-HAp with varying lithium concentrations. Utilizing a variety of methods, the produced HAp and Li-HAp nanoparticles were characterized. Functional groups were examined using Fourier transform infrared spectroscopy (FTIR) and phase purity was assessed using X-ray diffraction or Scanning electron microscopy (SEM) [9]. Orthophosphoric acid and calcium hydroxide were combined and the mixture was agitated for two hours at room temperature. The pH was maintained at 11. The slurry was then thoroughly cleaned before being dried at 80°C. Using this method, hydroxyapatite nanoparticles of a specific substance were produced. This data was obtained from a study conducted in 2011 by Devanand Venkatasubbu and associates. Water was used to dissolved the polymer known as polyvinyl alcohol. For two hours HAp nanoparticles were introduced and mixed. Centrifugation was used to separate the mixture and it was then examined using a variety of techniques using a specialized tool to conduct an X-ray diffraction (XRD) analysis to examined the material's structure. The size of the particles was determined using TEM and SEM to take pictures. The functional groups of HAp were identified using FTIR experiments in micro-Raman scattering with a particular spectrometer and laser examination. All of these procedures assisted the research in comprehending the characteristics of composite alginate. Polyvinyl alcohol-coated hydroxyapatite nanoparticles were introduced and mixed. After adding amoxicillin, the mixture was swirled for two hours. Centrifugation was used to separate the mixture and it was then dried at room temperature. Amoxicillin concentration was determined using a spectrophotometer at a wavelength of 231nm to assessed drug entrapment effectiveness. By producing solutions with various concentrations an amoxicillin standard graph was produced. The effectiveness of amoxicillin's capture within the HAp/polyvinyl alcohol sodium alginate nanocomposite was determined by this procedure in the research on medication release. At 37°C and pH 7.4 a 100mg sample was put into a glass container with 100 mL of phosphate buffered saline (PBS). The drug's release was monitored during a 30-day period 5mL of the solution was removed for analysis on a regular basis. The deleted solution was switched out for 5mL of fresh PBS. A spectrophotometer operating at a wavelength of 231 nm was used to

determine the amount of amoxicillin present in the samples that were collected. This research aided in our understanding of how in a controlled setting, amoxicillin is gradually released from samples. The potential of nanocomposite to combat microorganisms was evaluated against *Klebsiella pneumoniae* and *Bacillus subtilis*. Different concentrations of nanocomposite (50g, 100g, 200g, 500g per well) were applied using the agar well diffusion method. The microorganisms were dispersed across plates of nutritional agar. The plates were drilled with a cork borer to form wells. The plates were then kept at 37°C for a further 24 hours. It was determined whether the well had a region called an inhibition zone that prevented bacterial growth. This study provided insight into the effectiveness of nanocomposite in inhibiting growth [10]. The chemicals include methanol, sodium hydroxide, ciprofloxacin hydrochloride, 1,2,3,4-butane tetracarboxylic acid (BTCA), 1,2 hydroxypropyl Cyclodextrin (HBP) and phosphate-buffered saline. These chemicals are employed in an analytical setting and are obtained from several manufacturers in France and Spain. The procedure entailed employing a modified technique to functionalize HAp particles with 1,2-hydroxypropyl-Cyclodextrin (HBP). Phosphate disodium, BTCA and various concentrations of HBP were combined with HAp particles to generate the dissolutions, which were then dried. To remove unreacted substances the particles were heated, ground and washed. After that ciprofloxacin (CPX) was added to the HAp sample by dipping them in a drug solution, stirring, filtering, washing and drying to complete the loading procedure. In order to create ciprofloxacin-loaded HAp-HPB microparticles, a reaction to create HAp was used. Creating a suspension then splitting it into four batches. In addition to ciprofloxacin (CPX), additional additives like BTCA and HPB were present in different batches. The loaded medication was identified using methanol and aqueous NaOH solutions after these mixes were sprayed and dried. HAp particles were added to buffer phosphate saline at pH 7.4, shaken and incubated at 37°C for drug release research. A UV spectrometer was used to measure the antibiotic concentration at 271 nm. Trials were carried out in triplicate [11]. Amoxicillin, calcium nitrate tetrahydrate, di-ammonium hydrogen phosphate, gelatin, glutaraldehyde and ammonium solution were some of the compounds utilized in the experiment. The solvent used was deionized water. 0.5 M Ca $(NO_3)_2.4H_20$ and 0.3 M $(NH_4)_2HPO_4$ solutions were produced in a 1.5% gelatin solution with a pH above 10 to create the composites. Using glutaraldehyde, the solutions were combined, aged and cross-linked. The composite known as HG was made by separating, washing and drying the resulting foam. In contrast, HAp was made without the use of gelatin. Mineral phase analysis with X-ray diffraction, interaction analysis with FTIR and morphological observation with SEM were all used in the characterization process. Using thermogravimetry (TG) analysis, the amount of amoxicillin present in the samples was determined. In order to determine cytocompatibility, human osteoblast-like cells were used. MG-63 was grown in a medium that also contained serum, penicillin and streptomycin as supplements. The cells were plated in 96-well plates and treated for 48 hours with various dosages of composite samples. Cell viability was evaluated by MTT staining and the results were quantified by using optical densities. Amoxicillin was integrated into the matrix for drug loading using direct and in situ

loading techniques. HAp/HG was combined with amoxicillin and formed into pellets for direct loading. Amoxicillin was mixed in a gelatin solution used to create HAp during in situ loading. Using UV-vis spectrometry, the amoxicillin encapsulation efficiency was determined. The drug-loaded pellets were submerged in a phosphate-buffered solution at body temperature to perform in vitro drug release. Three copies of each experiment were run [12]. An aqueous solution of nitrate salt including calcium, neodymium, cerium, magnesium, and zinc ions is needed to create substituted hydroxyapatite. Under regulated pH and temperature conditions, a solution of $(NH_3)_2HPO_4$ is produced separately and introduced dropwise to nitrate salt solution. Following the pH being lowered it is progressively raised and the solution is aged for 24 hours while being stirred. The resultant mixture is cleaned, dried, sintered, and ground after being filtered to remove water by products. Nano Nd-Ce-Mg-Zn substituted hydroxyapatite was the product of this method. Several procedures were used in the characterization testing for substituted hydroxyapatite (Nd-Ce-Mg-Zn/HAp). X-ray diffraction analysis was performed to determine the components of substituted HAp and to confirm its production. CuK radiation was utilized and XRD patterns between 10° and 80° were produced in 2θ, with peak positions measured against model references. Using potassium bromide pellets, FTIR was used to characterized the functional groups in Nd-Ce-Mg-Zn/HAp. The spectral range, 4000 to 500 cm^{-1}, revealed details on the chemical makeup of substances. The morphology and size of the sample were assessed by field emission scanning electron microscope (FE-SEM) and the existence of Ca, Nd, Mg, Zn, P and O was confirmed by energy dispersive spectroscopy (EDS). Data from EDS was used to calculate the Ca^+ M/P ratio. In relation to biological tests, the antimicrobial activity of both Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus mutants*) and Gram-negative (*Escherichia coli*) bacteria as well as *Candida albicans* were evaluated for antibacterial and antifungal capabilities of produced HAp. Well diffusion was used to gauge biological activity. Nystatin and gentamicin were employed [13]. The National Center for Cell Sciences in India provided human osteoblasts-like cells (MG63). A Wet co-precipitation technique with modifications based on Muthusamy *et al.*, 2021 was used to create Se and Mn-doped HAp. In order to establish a mole ratio of 1.67 for Ca^+ Mn/P^+ Se, the precursor compounds were employed. Separate suspensions of calcium hydroxide and phosphoric acid were made throughout this process. Nano powders of HAp were created. By mixing the basic suspension at room temperature with the acidic suspension. By separately adding sodium selenite and manganese chloride tetrahydrate to the basic suspension and then drop wise to acidic suspension, Se-HAp and Mn-HAp nano powders were created. To get the finished product, the reaction mixture was aged, cleaned, centrifuged and dried. After applying gold sputter coating, the surface morphology was studied using SEM. At 15kV, SEM imaging was done. High-resolution transmission electron microscopy (HRTEM) was used to analyzed samples suspended in ethanol on copper grids to determine their morphology and size distribution. On tiny pellets, FTIR spectroscopy was used to capture infrared spectra. By mixing the basic and acidic suspension at room temperature. By separately adding sodium selenite and manganese chloride

tetrahydrate to the basic suspension and then dropwise to the acidic suspension. Se-HAp and Mn-HAp nano powders were created. The morphology of surface-waned CuK radiation was used to measure X-ray diffraction (XRD) patterns in order to quantify crystal size. A spectrometer was used to record the spectra of electron paramagnetic resonance (EPR). Thermo gravimetric analysis (TGA) was used to evaluate thermal degradation patterns using weight loss measurements up to 800°C. After doing a qualitative assessment of the ions using inductively coupled plasma optical emission spectrometry [14].

4. CONCLUSION

The improved biomedical anti-antibacterial properties of metal doped hydroxyapatite (X-HAp) where X=Ni, Cu, Ti have been reviewed in detail. It is demonstrated in recent studies that improved drug delivery and antibacterial activity are two benefits of metal-doped HAp. Studies have shown that Ciprofloxacin-loaded pure HAp nanoparticles and those with variable amounts of nickel doping may successfully attack both Gram-positive and Gram-negative bacteria. Together with the antibacterial properties of nickel and Ciprofloxacin-doped HAp, this sustained and prolonged drug delivery method is shown to be used for effectively treating and preventing chronic osteomyelitis brought in by certain bacteria. These results call for additional investigation for in vivo studies and point to possible therapeutic uses for metal and HAp composite antibacterial therapies. The development of various metal-doped HAp coatings for implant surfaces was another area of investigation. Copper-doped HAp, demonstrated bacterial properties however copper-doped HAp (Cu-HAp) was found to be cytotoxic to osteoblasts, making it unsuitable for implants. The titanium-doped HAp (TiHAp) on the other hand showed antibacterial properties and a low toxicity level, making it more suitable for implant coating TiHAp might stop bacterial infections. Findings of studies suggested that titanium HAp coating could successfully prevent bacterial infections ensuring success and disability of implants. Nano HAp rods were created using a low-cost wet chemical method. Nanorods serve as effective drug transporters and have porous network structures that allow for controlled drug release. This regulated released method lessens bacterial adhesion improves antibacterial activity and guards against biofilm development and bone infection. Silver-doped HAp nanoparticles were studied for their antibacterial capabilities.

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