RESEARCH PAPER

Exploring Biomedical applications of Hydroxyapatite nanoparticles: A comprehensive review

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ABSTRACT

Due to their outstanding biocompatibility, bioactivity, and physicochemical properties, Hydroxyapatite (HA) nanoparticles are very versatile and promising materials in biomedical applications. It is also in their varied roles in medicine and healthcare that this review doubts them. Compared to the traditional HA, nano-hydroxyapatite (nano-HA) has some unique benefits, such as an increased surface area, increased bioactivity and better mechanical properties. These properties make nano-HA a good option in drug delivery, bone growth, and tissue engineering. In the wound healing environment, nano-HA lies to the deep in tissues, thereby, accelerating the repair process, along with, enhancing dermal reconstructions. Its applications in dentistry and orthopedics fields are advantageous in enhancing the bone grafts and periodontal surgeries by enhancing their rate of osseointegration and improving their recovery periods. Moreover, the flexibility of nano-HA also enables the inclusion in a broad range of delivery systems, thereby increasing bioavailability of drugs, and providing targeted therapy. HA nanoparticles would also work well as tissue adhesives and, as therapeutic vehicle oncology since they can be tailored to specifically deliver anticancer therapy to tumor areas to minimize the side effects on healthy cells. The existence of these encouraging opportunities notwithstanding, there are still a few issues of seemingly cytotoxic concentration at high levels, and a necessity to optimise targeting/drug-release kinetics. The current studies aim at addressing these shortcomings and further developing the clinical utilization of HA nanoparticles, a fact that underscores their immense role in the development of biomedical applications and the enhancement of patient outcomes.

Keywords: Hydroxyapatite, Nanoparticles, Biocompatibility, Drug delivery, Bone regeneration, Tissue engineering.

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Introduction

Hydroxyapatite (HA) is a naturally existing mineral which is the largest component of the human bone and dentine (1). The general characteristics of the HA nanoparticles include a diameter ranging between 2080nm, hence, giving the high surface area to volume and high colloidal stability. HA nanoparticles are highly desirable because they are highly biocompatible, and stimulating bone regeneration in the body (2). The physicochemical properties of HA particles such as morphology, size distribution, crystallinity and ionic substitution can be accurately adjusted by changing the synthesis protocols.

These nanoparticles have been utilized in the full range of biomedical equipment such as orthopaedic bone grafts, dental prostheses, implant surfaces and customised dental ingredients. They can also be utilised as drug-delivery vectors, surface coating materials (delivery) and composite materials in medical research due to their unique physicochemical properties (3). Experimental data

confirms that HA nanoparticles interacts positively with cellular and tissue matrices and hence induces osteogenesis, angiogenesis, and tissue repair, and can induce malignant cells to undergo apoptosis. The biological responses to HA particles are dependent on their size, morphology, crystallinity and surface chemistry (4).

The hydroxyapatite nanoparticles hold a crucial position in various fields of treatment because of their peculiarities. HAis has extensive use in bone tissue engineering, orthopaedics grafts, prosthetic devices and implant constructs as its chemical composition and crystal lattice resemble the one of the natural bone mineral (5). HA is biocompatible and it has a large surface area that increases adhesion, proliferation and differentiation of osteogenic cells thereby accelerating bone regeneration. HA nanoparticles can be applied in the delivery of proteins, peptides, drugs and genetic materials in drug delivery (6). Surface functionalisation makes loading of drugs to be controlled exactly, release kinetics and targeted to the specific cells or tissues based on choice, contributing to improved therapeutic effects. Moreover, the HA particles have induced apoptosis in the cancer cells thus showing a possible use in oncologic therapy (7). Their ability to induce cellular internalisation and the possibility of causing DNA damage by particle size, shape, crystallinity, and charge is what makes them potential targeted cancer therapy nanomaterials. HA nanoparticles find use in magnetic resonance imaging (MRI) and cellular separation procedures in imaging and diagnostic fields because of their unique physical and chemical properties (8). The radiolabelling of these nanostructures can be used to precisely track the biodistribution and biological interactions of the nanostructures, which increase the diagnostic accuracy (9,10).

The present review is likely to discuss the complicated biomedical applications of hydroxyapatite nanoparticles, their production, functionalisation, and applicability in medical practice. It will define some of the synthesis protocols which include: wet-chemical, hydrothermal, sol-gel method, microemulsion and microwave-assisted synthesis where there is an explanation of how each of the different steps can modify the particle characteristics. The examination of the latest advancements in the functionalisation of HA such as loading of the material with magnetic elements, the silver doping, loading of the material with rare earths and polymer coatings, and how these modifications make the system more clinically viable will be featured in the review, as well as the manner in which these modifications can be implemented to increase the clinical applicability. The critical therapeutic applications, including bone tissue engineering, orthopaedic implants, drug delivery systems, oncology and medical imaging will be discussed in detail, the biocompatibility and osteoconductivity potential of the material, targeted delivery potential and synergy therapeutic effect of the material. This review will offer a complete insight into the present and future trends of HA nanoparticles in the biomedical field by giving a critical review.

A variety of chemical pathways can be used to prepare hydroxyapatite nanoparticles, although the commonest are wet-chemical precipitation and hydrothermal. HA particles are formed in wet-chemical precipitation through aqueous solutions that have calcium and phosphate ions, and usually use the diammonium hydrogen phosphate and calcium nitrate tetrahydrate as reagents (11). The media are inoculated, dried, strained and dried to create powders of HA. The technique gives an opportunity to control the size and shape of particles as well as their stoichiometry by controlling other parameters such as pH, temperature and ageing duration (12). Hydrothermal process entails heating of a precursor solution in a closed system at high temperatures and pressure to enable homogenous nucleation and growth of HA of a size and shape of interest. A source of biowaste that is abundant in calcium is eggshells that can be used to provide calcium to the synthesis of hydrothermal (13). The other techniques are sol-gel technique that involves formation of a colloidal suspension which further develops into a gel network and subsequently dried and calcinated; microemulsion technique where a microemulsion system is utilized to regulate the particle size and morphology; microwave assisted technique whereby the heating and acceleration of particle formation were typically done by using the microwave radiation (10). The synthesis pathway chosen is based upon the type of particles necessary, the availability of the precursors and machinery. Of particular interest are wet-chemical precipitation and hydrothermal techniques, which are inexpensive and have a simple procedure and enable the acquisition of high-purity HA exhibiting certain properties (14,15).

Types of synthesis methods

Chemical Methods

The synthesis of hydroxyapatite (HA) nanoparticles takes place by diverse chemical methods that are characterized by controlled reactions among elements of calcium and phosphorus. The protocols that are commonly used are listed below:

Wet Chemical Precipitation:

This process includes reaction of a solution of calcium nitrate with diammonium hydrogen phosphate in a suitable solvent to produce HA nanoparticles. It is normally carried out at ambient temperature or a slightly higher temperature and post-processing can be used to adjust the size and morphology of the particles (16).

Hydrothermal Method:

The precursors of calcium and phosphorus are heated in high pressure and temperature - normally above 100 -C - in a hydrothermal system to induce crystallization. Nanoparticle size and shape can be precisely adjusted with regard to the temperature, pressure, and residence time (17).

Solvothermal Method:

Like the hydrothermal method, the solvothermal method uses high pressure and temperature, but uses non-aqueous solvents. The morphology and the features of the formed HA nanoparticles depend greatly on the solvent that was utilized (18).

Microwave-Assisted Synthesis:

The reaction between the calcium and phosphorus precursors in the presence of microwave irradiation is of much higher rate than the reaction with more traditional conditions and also much less reaction time and energy are required (19).

Microemulsion Route:

In microemulsion approach the mixtures of oil, water and surfactants are stable and stabilize the reaction environment whereby, nucleation and development of HA nanoparticles occurs (20).

Physical Methods

The physical techniques of synthesis of HA nanoparticles are based on the use of external energy or mechanical forces. One of these methods is known as mechanochemical synthesis, where it uses a high-energy ball milling technique to disseperse the calcium and phosphorus precursor thereby triggering HA to grow with a controlled size and morphology (21). In plasma spraying, a high-temperature plasma arc is used to inject HA powder into it, melt the particles and then spray them onto a substrate to form a coating of HA nanoparticles which is commonly used to increase the biocompatibility of implants (22). Laser ablation uses the high-energy laser beam to ablate a solid HA target that is placed in a liquid medium like water or ethanol; the plasma plume condenses in the liquid to produce HA nanoparticles (23). Electrospinning requires an electric field to draw a polymer solution into thin fibres (including the HA nanoparticles into the polymer mesh) and forming scaffolds of HA to be utilised in tissue engineering (24). In addition to this, HA nanoparticles could be prepared through microwave irradiation whereby; the reaction mixture was rapidly heated thereby enhancing the rate of formation of the nanoparticles. These physical procedures have advantages in increased control of particle size and morphology, quicker reaction kinetics, and the production of HA nanoparticles of custom properties, but may be expensive due to a requirement of specialized equipment and may also consume much energy compared to the chemical ones (25, 26).

Biological Methods

Biological synthesis of HA nanoparticles is growing via various pathways with various alternatives that are environmentally friendly and have certain benefits. Its bacteria production utilises such species as the Bacillus licheniformis that produce organic acids that dissolve phosphate; phosphate is subsequently re-reacted with calcium ions to make HA nanoparticles of designated size and morphology (27). The fungi that are characterized in fungal synthesis involve fungi such as Fusarium oxysporum that release enzymes that can convert phosphate precursors to HA resulting in actual precipitation of nanoparticles at ambient temperature (28). In biomimetic synthesis, biomolecules (collagen, gelatin or chitosan) are used as templates to imitate the natural bone mineralization process to guide the production of HA nanoparticles and result in a more similar material to natural bone structure and composition (29). In plant-mediated synthesis the reducing and capping reagents are botanical extracts (such as Aloe vera extract or Camellia sinensis (green tea)) in which the phytochemicals serve as the reducing/capping reagents to direct the size and shape of nanoparticles. Some advantages to these biological processes include mild reaction conditions, no toxic reagents and potentially scalable but they do not give as much control over the particle size and morphology as do the chemical and physical methods (30, 31).

Physicochemical Characteristics of Hydroxyapatite Nanoparticles

Structural Properties

Taking into consideration the crystalline structure, crystallinity, the particle size, the morphology, the specific surface area and stoichiometry, it allows describing the entire physicochemical properties of the HA nanoparticles. HA nanoparticles usually possess a hexagonal crystal structure with unit cell parameters which is very similar to natural bone apatite (32). Synthesis pathway According to the synthesis pathway the crystallinity can be precisely optimised; synthesis by wet chemical precipitation solution-based often produces highly crystalline HA particles (33), hydrothermal synthesis, and solvothermal synthesis, produce high-crystallinity products. The particles are usually 20-100nm in size and morphology is manipulated by the synthesis parameters to achieve morphologies such as spherical, rod-like or plate-like morphologies (34). The size of HA nanoparticles is very important because they are nano sized, therefore their specific surface area of between 50 to 200 m2/g makes them highly bioactive and adsorptive. The Ca/P ratio of natural bone mineral is comparable to the stoichiometric HA nanoparticles which have a value of 1.67 and production of the material is impacted by the methodology of synthesis as solution-based routes form purer, and less impure HA nanoparticles compared to other routes (35). Overall, the structural properties of HA nanoparticles like the organization of lattice, crystallinity, size, morphology, surface area and stoichiometry can be controlled by a prudent selection of the synthesis method, as well as through the judicious optimization of synthesis conditions. The two structural features have a direct impact on the physicochemical and biological behavior of HA nanoparticles that render them useful in a broad range of biomedical uses (36,37).

Morphological Characteristics

Morphological properties of hydroxy apatite (HA) nanoparticles can be precisely controlled to the changes in the synthesis parameters and conditions. Accessibility of various anions during preparation of HA is a key element as it is structure-creating aspects that significantly influence the eventual morphology of the nanoparticles (38). One example is that HA nanoparticles formed with nitrate precursors have a typical shape of a sphere, compared to those formed with acetate, chloride and eggshell precursors which all adopt a needle-like, irregular and oval shape, respectively. The choice of synthesis technique also has an effect on the physicochemical properties and shapes of HA nanoparticles. The solution-based synthesis techniques such as wet-chemical precipitation are generally used to prepare HA nanoparticles with high crystallinity and morphology (39). In addition to this, using hydrothermal and solvothermal methods of synthesis, it is also possible to further morphologically modify nanoparticles, through the control of the environment. Hanananoparticles could be produced with a size between 20 and 100nm and a high specific surface area of 50 to 200m 2/kg -1, making them more bioactive and better adsorbents (40). The morphological characterization methods, such as field-emission scanning electron microscopy (FE-SEM) and high-resolution transmission electron microscopy (HR-TEM) are commonly used to determine surface characteristics, particle sizes, and morphology of HA nanoparticles. The FE-SEM in particular provides plenty of information about the surface properties and particle sizes (41).

Surface Chemistry

Surface chemistry of hydroxyapatite (HA) nanoparticles involves a number of key parameters such as surface charge, zeta potential, functional group, surface area, porosity and surface modification. The surface of HA nanoparticles is generally positively charged with Ca 2 + ions, the zeta potential of the nanoparticles ranges between +20 and +40mV that varies depending on the mode of their production and surface modification (42). Other parameters such as pH, ionic strength and the adsorbed ions or molecules also determine surface charge and zeta potential. The HA nanoparticles possess large numbers of hydroxyl (OH -) groups on the surface, which enable them to experience various chemical reactions and interactions. Depending on how they were synthesized, other functional groups, such as carboxyl (-COOH), amino (-NH 2), or phosphate (PO4 -3) may be present and other functional groups can be attached to the surface, such as grafting of organic molecules or biomolecules (43). Another factor that enhances its adsorption capacity and reactivity is the nanoscale size of HA nanoparticles due to the high specific surface area of nanoparticles that may vary as much as 50 to 200 m 2 g -1. This high surface area and porosity can be controlled by the synthesis parameters and post- processing methods (44). Biocompatibility, bioactivity and stability can be enhanced through surface modifications, which can be coating, grafting or doping with other elements or compounds, and can also add other functionalities,

such as antimicrobial properties or drug-delivery properties (45).

Bioactivity and Biocompatibility

The physicochemical properties of hydroxyapatite (HA) nanoparticles are the main determinants of their biocompatibility and bioactivity, which makes them very appropriate in a variety of biomedical applications. Biocompatibility of HA nanoparticles has been marvelous due to the chemical composition and crystal structure that resembles the mineral component of the natural bone (46). Nanoparticles of small size enhance their adhesion, proliferation and incorporation into the biologic environment as compared to bigger particles of HA. Individually designed surfaces that have charge, functional groups and porosity can be employed to improve biomedical biocompatibility too (47). HA nanoparticles are also high bioactive nanoparticles and this is due to a high specific surface area the particles possess and this allows the particles to interact with the biological systems. This large surface area/volume ratio enables the protein to adsorb more, cell to adsorb more and the apatite to form in a way similar to a bone structure, achieving better bioactive properties (48). Further, the shape of HA nanoparticles has a direct impact on bioactivity, whereby different shapes (spherical, rod-like, plate-like) have different levels of protein adsorption, cell viability, and angiogenesis. All this contributes to making HA nanoparticles the most useful, when it comes to bone tissue engineering, drug delivery, and regenerative medicine (49). They can be utilized as scaffold to rejuvenate the bones by enhancing adhesions, proliferation and formation of new bone on the osteoblasts. Functionalization Singapore has also been conducted on the surface of HA nanoparticles that can then be used in targeted drug delivery (improved functionality) or controlled release by functionalizing ha nanoparticles with drugs, proteins or any other biomolecules (46).

Applications of Nanoparticles in Drug delivery

The main benefits of using hydroxyapatite (HA) nanoparticles in delivering drugs include a number of main aspects. Firstly, HA nanoparticles are biocompatible and biodegradable thus they are safe to use in-vivo since they can undergo metabolism and excretion process out of the body. Secondly, targeting ligands can be directly attached to the surface of HA nanoparticles, enabling them to be targeted to a specific cell or tissue, such as cancer cells, with greater specificity (10). This is a focused strategy that enhances the effect of therapy and specificity. Third, the high porousity and high surface area of HA nanoparticles enable easy loading of drugs and release of therapeutic agents slowly and in a controlled fashion (50). This type of releasing mechanism ensures that there is a constant delivery of the drug with time, thereby, enhancing effective therapeutic effects. Drugs that are poorly soluble, when trapped within HA nanoparticles, are also more soluble, and stable and they improve bioavailability. Additionally, combinatorial therapeutic effects of HA nanoparticles can be enhanced in conjunction with certain drugs including the anticancer effect of chemotherapeutics (51). Finally, the versatility of HA nanoparticles is that they can transport an extensive array of therapeutic molecules that include small molecules, proteins, peptides and nucleic acids (52).

Functionalization of HA nanoparticles

Magnetic HA Nanoparticles

The HA matrix is filled with the iron oxide nanoparticles to prepare the magnetic hydroxyapatite (HA) nanoparticles. The uses of these composites are such an opportunity to deliver drugs exactly, hyperthermia during treatment of cancer and their application as a contrast agent in magnetic resonance imaging (MRI) (53).

Silver-Doped HA Nanoparticles

Silver impregnated HA nanoparticles have a high concentration of the antibacterial qualities and this can therefore be utilized in the treatment of the bone tissue engineering and dental implants. Silver ions can either be included in the synthesis of HA nanoparticles or it can be deposited on the surface (25).

Rare Earth Element-Doped HA Nanoparticles

Rare earth fluorescent doping Rare earths of doped HA nanoparticles (europium, terbium, and gadolinium) can be used to fluorescently label and image biologists. These doped nanoparticles are used as multimodal imaging agents and theranostic cancer treatment(54).

Polymer-Coated HA Nanoparticles

The stability, dispersibility, and drug loading capacity of nanoparticles are improved and promotes the biocompatibility of HA nanoparticles with biocompatible polymers such as chitosan, alginate, and silk fibroin. Such nanoparticles with polymer coatings are under investigation to be used in disease-carrying, tissue engineering scaffolds and wound healing(55).

Bone Tissue Engineering

Hydroxyapatite (HA) Nanoparticles in Bone Tissue Engineering

HA nanoparticles have an outstanding biocompatibility because their chemical composition and structure resembles the mineral content of natural bone. Their nano size makes them to adhesive to and hence enable proliferation and integration of cells in the biological setting than bigger HA particles(56). The high specific surface area of HA nanoparticles is very high and this makes it be biologically active thus allowing it to interact with the biological system, adsorb proteins, and even cell adhesion and, formation of bone-like apatite(57).

Mechanical Properties and Antibacterial Functionality:

Hydrostatic Buildup in HA. Though pure HA lacks good mechanical properties, by incorporating HA nanoparticles to other substances, such as gold (Au) and silver (Ag) nanoparticles, the properties may be improved (58). HA bioceramics are enhanced with functionalized Au/Ag bimetallic nanoparticles which increases mechanical properties, such as fracture toughness, hardness, compressive strength, and flexural strength. Moreover, gold/silver nanoparticles offer antibacterial properties, which decrease the attachment of gram-positive (Staphylococcus aureus) and gram-negative (Escherichia coli) bacteria (59).

Cellular Response and Bone Tissue Regeneration

The use of MG63 cell line by the HA nanoparticles compared to the pure HA triggers cell proliferation and osteogenic differentiation of the osteoblast-like cells. Functionalized Au/Ag nanoparticles would also be an improvement to HA bioceramics with the addition further increasing cell responses and the bone tissue regeneration opportunities (60).

Role in Bone Regeneration

Hydroxyapatite (HA) nanoparticles play a very crucial role in bone regeneration process due to their high biocompatibility and bioactivity, as well as ability to provide structural bone anatomy.

Biocompatibility and Osteoconductivity

This is because HA nanoparticles are highly biocompatible because they have similar chemical composition/structure to natural bone. Their small sizes (in the nanoscale) increase cell sticking, growing, and incorporating into the biological environment at a better rate than bigger particles of HA (61).

BoneLike Apatite Formation

The elimination of protein adsorption and subsequent formation of bone-like apatite of HA nanoparticles due to high specific surface area enable them to be highly bioactive. This apatite coating on the surface of the HA nanoparticles facilitates fusion of the biomaterial and the surface of the bone tissue and therefore, reduces bone regeneration (29).

Scaffolds in Bone Tissue Engineering

When HA nanoparticles are incorporated in polymer and ceramic scaffold matrix, it leads to a composite scaffold used in bone tissue engineering. Applications of these scaffolds offer the best microenvironment that allows the attachment of cells, their proliferation, and formation of new bone tissue, thus enhancing the regenerative process (62).

Controlled Drug Delivery

Another use of HA nanoparticles is to treat bone defects by delivering therapeutic agents (growth factor, antibiotic or anti-inflammatory drug) to the site of the defects. The liberation of these agents in control in HA nanoparticles can enhance bone regeneration and minimize complications that could occur, such as infection or inflammation (10).

Hydroxyapatite (HA) nanoparticles as drug delivery systems for cancer therapy:

Hydroxyapatite (HA) nanoparticles hold the promise of successfully targeting cancer therapy by drug associating with the particles, or loading drugs through adsorption, encapsulation, or chemically linking the drugs. HA nanoparticles can release drugs depending on the pH, temperature, or enzymatic activity, with pH-responsive release being especially handy in targeting the acidic tumor microenvironment(63). Targeted surface modification employing specific ligands e.g. antibodies, peptides or small molecules facilitate specific receptor binding to overexpressed receptors on the surface of cancer cells, causing an increase in uptake and the ability to transport drugs to the site of the tumour. These ligands consist of transferrin, folic acid and hyaluronic acid, which bind to transferrin receptor, folate receptor and CD44 respectively(64). HA nanoparticles are now considered in numerous cancer therapies such as chemotherapy, gene therapy and photodynamic therapy, by loading them with anticancer drugs such as doxorubicin, paclitaxel or cisplatin, thus enhancing therapeutic outcome and minimising adverse effects(65,66). They can also be used in delivering nucleic acid-based therapeutics to regulate the expression of genes in cancer cells.

Although biocompatibility, biodegradability, drug loading capacity and target and controlled delivery are benefits; there are limitations which include the possible toxicity at high levels, stability, as well as optimization in targeting and drug release profiles. Current studies are looking into ways of overcoming these drawbacks and improving clinical translation of HA nanoparticles in cancer therapy(67,68).

Hydroxyapatite nanoparticles in Dental Applications

Hydroxyapatite nanoparticles (HAp) have significant possibilities in the dental field, which have the 15 achievements as: Tissue remineralization, treatment of dentin hypersensitivity, orthodontics, graft materials, periodontology and implantology. It has also studied the synthesis of nano-hydroxyapatite doped with metal oxides, specifically nano-alumina to enable it to be used in orthopedic applications as a load bearer. To prevent caries, as a desensitizing agent, and as a graft material, nano-HAp is a useful biomaterial in dentistry due to its biocompatibility and osteogenic capacities(69).

Nanoparticles of hydroxyapatite (HA) play a positive role in improving the integration of dental implants through promotion of biocompatibility and OSE. Studies have shown that nanostructured and nano-HA on titanium surfaces have been found to promote cell spreading, proliferation and formation of extracellular matrix which results in improved early-stage cell/surface integration(70). In addition, the proliferation and remodeling of bones and enhancement of bone mineralization of titanium surface through application of synthetic hydroxyapatite (HA) nanoparticles also play part in the process of osseointegration (71). In an effort to create a HASiGdCe coating that is doped with SiO 2, Gd 2 O 3, and CeO 2 nanoparticles has been proven to be better in osteogenic and angiogenic properties that enhance osteointegration of implants and inhibition of bacterial infections in orthopedic and dental implants (72). Also, grafting the methylpolar alanine amino acid to HA nanoparticles has demonstrated improvements in biocompatibility, adsorption of proteins, and cell adhesion, thus promising a lot in regenerative medicine (73).

Remineralization of Enamel

The nanoparticles of hydroxyapatite (HA) demonstrate optimistic possibilities in the remineralization of enamel as compared with the traditional methods. They can activate enamel remineralization process providing calcium and phosphate ions and their small size allows more of them to be incorporated into the enamel structure in order to have the new mineral crystals formed (74). HA nanoparticles can be incorporated into various dental care products, such as toothpastes and topical therapies, and hence they will enhance specific delivery of remineralizing agents (15). Even though the evidence both in vitro and in vivo suggests that it is feasible to use HA nanoparticles to remineralize enamel, additional clinical trials and research is required to estimate the potential of these nanoparticles against conventional techniques. Traditional fluoride treatments have the same benefit of remineralizing the enamel as well, but may have limitations in terms of the incapability to penetrate the enamel and remineralize effectively, though, the nanoscale of the HA particles may permit a superior ingestion and remineralization (75, 76).

Use in Dental Implants

Hydroxyapatite (HA) nanoparticles have provided a promising potential in enhancing dental implants in terms of enhanced bone contact and osseointegration. The HA nanoparticles may also be utilized as surface coating on titanium based dental implants to enhance the nature of the surface and increase better integration with the surrounding bone tissue due to an increased surface area and reactivity. Empirical evidence has demonstrated that this kind of coating may prove extremely useful in stimulating the process of ossue integris, that results in an augmentation of bone integrations and the troubling of the implant in the jawbone. The nano-size of the HA particles mimic the natural bone structure allowing permissive attachment surface to cells and cell proliferation; which is further supported by in vivo rabbit models exhibiting enhanced early bone formation and inducing osteoblast differentiation. In addition, the coating of HA nanoparticles improves the nanomechanical composites of dental implants such as hardness and modulus which are important to the stability and performance in the long term. Nevertheless, further research is required to make the most of the contacts between HA nanoparticles and bone cells as well as the dental implantation surface making this the most effective coating on dental implants, including research into the various methods and compositions to use.

Wound Healing Applications

The hydroxyapatite (HA) nanoparticles differ in several aspects in regard to the physical properties of this material, the biological interactions, as well as the clinical application in comparison to traditional HA and other materials in wound healing (77). The nano-hydroxyapatite (nano-HA) has tiny, crystals, with a much larger surface area than normal HA that enhances nutrient absorption and adhesion of the tissues between the graft material and the nearby tissues (78). Having a lower size and larger calcium concentration, nano-HA can enter deeper into the skin and obtain a better absorption rate, which can be considered a benefit when utilizing it in wound healing when penetrating deep is required. This crystal type enables nano-HA to be more bioactive than the standard HA and leads to increased incorporation into the host tissue, as well as accelerated healing.

The ultralong hydroxyapatite nanowires and cellulose fibers used to make biopapers have been demonstrated to facilitate the healing of skin wounds by promoting the growth of new blood vessels, which form the angiogenesis, which help in regenerating the tissue by supplying it with nutrients and oxygen (79).

Gels made with Nano-HA have been observed to have a significant effect on wound healing in an accelerating way in terms of the promotion of dermal reconstruction and accelerated wound healing as compared to untreated controls. Its use in bone grafts and periodontal surgery points to its influence on complicated bone healing and support of oral well-being(80). Hydroxyapatite nanoparticles show good prospects as tissue adhesives because of its special qualities, such as, improved mechanical properties and antibacterial action when combined with other nanoparticle(s) (gold-silver(81). The BAP hydroxyapatite-bioactive glass coating form strong adhesion between soft polymer substrates with the biological tissue, enhancing adhesion energy and providing possibilities of the functional bioadhesive surfaces. Out of this chemical structure of HA nanoparticles, anticancer drugs can be loaded and targeted to cancer involving inhibition of cancer cell growth and metastasis with minimal toxicity on normal cells(82).

Nanoparticles of hydroxyapatite have become a very promising bioceramic material in many biomedical applications especially in bone tissue engineering. New synthesis approaches include availed hydrothermal treatment, sol-gel techniques, and self-initiating combustion synthesizing HA nanoparticles that Brazil outstanding biocompatibility which leads to cell growth, adhesion, and osteogenic differentiation and suppresses osteoclastogenic differentiation(83). The addition of HA nanoparticles to polymer nanocomposites is promising as the scaffolds are used in bone and dental tissue engineering, and three-dimensional printing of them is a promising method. HA nanoparticles present the perfect opportunity to develop advanced bone substitutes and tissue-engineered dissolvable scaffolds that have higher regenerative capacities due to their unique properties such as purity of the material by phase, small particle size and thermal stability(84).

Toxicity and Biocompatibility

Hydroxyapatite (HA) nanoparticles have a high level of biocompatibility with little in vitro toxicity as reported in the studies on models such as Drosophila melanogaster where the nanoparticles of HA have not been found to affect the organism in a toxic way(85). Their small size, in the nanoscale, and surface charge can be critical in the interactions with red blood cells and other biological systems, and can be better bioactive than other bioactive materials such as glass and ceramics. In vivo studies lend credence to the biocompatibility of hydroxyapatite (HA) nanoparticles, as experimental studies with rabbits have demonstrated that nanostructured scaffolds composed of HA induce osteogenesis along pore walls and by extension indicating that they have a high bone induction potential (86). In addition, HA nanoparticles are observed to suppress the proliferation of the malignant cells, e.g., the osteosarcoma, and also induce apotic cell death in the malignant cells but has no effects on normal cell populations. Nonetheless, partial preclinical studies have demonstrated evidence of hepatotoxicity and hepatic toxicity in animal studies that implicates the significance of undertaking long-term studies on their safety. Physicochemical properties such as particle size, surface charge, and intrinsic properties regulate physicochemical properties of hetero -elements control biocompatibility of HA nanoparticles, and toxicological spectrum of hetero -elements can be modified or doped with foreign elements. Therefore, to enjoy safe use of HA nanoparticles in biomedical applications, careful characterization, rigorous testing, and tight control on regulation are required (87).

Challenges

Nanoparticles of hydroxyapatite (HA) are faced with a number of issues which have to be overcome to bring about successful clinical practice. The problem of toxicity, particularly in extreme amounts or in long-term exposure has been of paramount interest: some in vivo studies have demonstrated hepatotoxicity and liver damage resulting in a need to analyze their long-term effects on different organs and cellular systems (48). The biocompatibility of HA nanoparticles might differ depending on their size, surface charge, and the chemical decoration whereby, due to size, surface charge, and functionalization, care should be taken on the synthesis and functionalization processes to achieve a range of biocompatibility in the various formulations and application. They require scalable and cost-efficient manufacturing guidelines to synthesize HA nanoparticles of standard quality to be able to scale up the adoption because the current synthetic directions may encounter obstacles in the manufacturing ability and repeatability, and thereby prevent commercial viability (88). In addition, the approval procedure of HA-nanoparticle-based products is complicated, and it will involve a lot of safety and efficacy data of preclinical and clinical trials, which, in its turn, will require a lot of time and financial funds. In order to manage these multifactorial challenges the scientists in the respective areas of specialisation under materials science, nanotechnology, pharmaceutics and clinical medicine should collaborate and coordinate efforts in an interdisciplinary way.

Future Perspectives

Future tasks on hydroxyapatite (HA) nanoparticles should concentrate on planning and transformation to clinical utilization of further innovative technologies of surface functionalization to enhance biocompatibility, targeting accuracy and therapeutic effectiveness specifically, by binding bioactive ligands, pharmaceutical agents or targeting motifs to hydroxyapatite nanoparticles. The complex toxicological analyses are invaluable to understanding the possible risks; the long-term in vivo experiments and the in-depth examination of the interactions with a range of cell lines and organ systems are needed to create strong safety rules (64). Innovations like automated synthesis and real time monitoring of the particle properties will also be of importance to the manufacturing processes since it will be essential in scaling up the production without sacrificing on the quality and consistency of the products. To demonstrate that HA nanoparticle-based therapeutics are clinically effective and safe, clinical trials need to be well-designed, ensuring collaboration with clinical researchers and healthcare professionals to transform laboratory results into clinical medicine. By setting up explicit, nanomaterial-specific regulatory frameworks, it will be easier to conduct research to clinical practice; early consultation with regulatory bodies will be employed to streamline research directions to regulatory anticipations. Moreover, when biocompatible matrices are paired with multifunctional nanocomposites involving synergistic HA nanoparticle integration may be achieved to deliver novel therapeutic modalities with the added benefit of a synergistic effect such as improved mechanical stability, bioactivity and delivery of therapeutic agents (89,90). These problems will play a critical role during the incorporation of interdisciplinary research, new manufacturing, wide-ranging toxicology studies and regulatory collaborations to unlock the entire clinical potential of HA nanoparticles.

Conclusion

Hydroxyapatite (HA) nanoparticles have tremendous potential in biomedical practices and applications due to their high biocompatibility, osteoconductivity and bioactivity which is well utilized in bone tissue engineering, dental treatment, wound covers, and delivery of medications. Recent synthesis methods have facilitated production of superior quality HA nanoparticles and their integrated complex into polymeric nanocomposites have fostered the likelihood of the production of high quality scaffolds. However, such challenges like possible toxicity, scalability of the manufacturing, and regulatory barriers need to be contended with. The future directions are more functionalization of surface, toxicological profiling, fine-tuning of production directions, and highly engineered clinical trials to ensure safe and efficient application of HA nanoparticles in medicine. By overcoming these challenges, the full potential of HA nanoparticles in different therapeutic applications will be unlocked.

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