# Nanoceramics: Synthesis, Characterizations and Applications

**S. Anne Pauline**

**Abstract** Nanoceramics are ultrafine particles with particle size less than 100 nm and have greater advantages over macroscale ceramics which are brittle and rigid. They are inorganic, metallic and non-metallic compounds that have high heat resistance. Their small particle size offers them unique properties which have led to their widespread use in various fields. Their improved properties include bioactivity, dielectricity, ferromagnetism, piezoelectricity, magnetoresistance and superconductivity. Hardness and strength of ceramics are greatly improved by reducing their particle size to be in the nanoscale. Nanoceramics can be conveniently prepared by various physical and chemical methods in various sizes and shapes such as nanoparticles, nanorods, nanotubes, nanoribbons, nanosheets and nanofluids which determines their properties. Characterization of nanoceramics can be carried out by surface characterization methods such as X-ray diffraction analysis, Infrared spectroscopy, Scanning electron Microscopy, Transmission Electron Microscopy, Atomic Force Microscopy, etc. Nanoceramic particles can be used for bone repair, drug delivery, energy supply and storage, communication, transportation systems and construction. The current article discusses in detail the nanoceramics, their preparation methods, various characterization techniques, their unique properties and their application in the biomedical field arising due to their excellent properties.

**Keywords** Nanoparticle · Bioactivity · Drug delivery · Scaffolds

## 1 Introduction

Nanoceramics are essentially ceramic materials whose length scale lies in the range of 1–100 nm at least in one dimension. Ceramics are inorganic solid materials that are characterized by heat resistance and are made of metallic as well as nonmetallic compounds. On macro scale, ceramics are rigid and brittle that breaks upon impact

---

S. A. Pauline (✉)
Department of Chemistry, Central Institute of Plastics Engineering & Technology, Chennai 600032, Tamil Nadu, India
e-mail: lillyanne68@gmail.com

T. S. Santra and L. Mohan (eds.), *Nanomaterials and Their Biomedical Applications*,
Springer Series in Biomaterials Science and Engineering 16,
https://doi.org/10.1007/978-981-33-6252-9_5

against other hard objects. However, in the nanoscale, their properties are unique, differ widely from that of macroscale ceramics and are of greater use in various fields. Ceramic nanoparticles have properties lying in between metals and non-metals. The improved properties include dielectricity, ferroelectricity, piezoelectricity, pyroelectricity, ferromagnetism, magnetoresistance and superconductivity [1]. Nanoceramics also have excellent mechanical, processing and surface properties such as biocompatibility, superplasticity, mechanical resistance, chemical resistance, strength and hardness at normal as well as high temperatures [2]. The properties of nanoceramics depend and vary based on the type of nanoceramic, its size and shape. The bonding between their constituent atoms defines their properties which are a combination of ionic and covalent bonds [3].

Nanoceramic materials were first discovered in the early 1980s using sol-gel method, a form of chemical solution deposition. Larger scale materials have flaws that make them brittle, but due to their small size, nanoceramics are flawless. Interest and research in nanoceramics are blooming since then owing to its varied properties and extensive applications. In the 2000s, synthesis methods evolved using heat and pressure in sintering process. The method of synthesis of nanoceramics plays a great role in determining the shape and size of the particles and hence its properties. During the past 20 years, research in nanoceramics has resulted in positive outcomes and the advanced materials prepared are being used in several industries such as sensors, batteries, capacitors, corrosion-resistant coatings, thermal barrier coatings, solid electrolytes, catalysts, cosmetics, automotive, optoelectronics, computers, electronics, biomaterials, etc. [4]. They have special applications in the field of medicine owing to their biocompatibility, bioactivity and hydrophilicity and hence are used as bioimplants, as drug delivery devices and also in cancer treatment as chemotherapy delivery vehicles [5].

Nanoceramics are characterized by large surface area due to their small particle size. This is especially useful in cases, where their surface properties play a role in its effective functioning. For example, when nanoceramics are used as catalysts, their small particle size increases the rate of reaction [6]. When they are used as bioimplants, nanoceramics facilitate faster bone-implant interface establishment and aids in faster healing. When used as drug delivery systems, the drug reaches the target site faster, does not get released in non-target sites, react with the target effectively and carry out the intended purpose.

The design and development of nanoceramics of different sizes and shapes by new techniques have garnered much attention as each of them come with unique properties. Till now, nanoceramics in different sizes and shapes such as nanoparticles, nanorods, nanoribbons, nanotubes, nanosheets and nanofluids have been synthesized [4]. Modification in various physical, chemical and biological properties can be bought about by modifying the nanoceramics size, shape, by doping different elements in their crystallographic sites as impurity or by creating defects using ion implantation method [7]. Advanced nanoceramics are of 3 major types: (i) oxides of alumina, zirconia, titania, ceria, beryllia, etc., (ii) non-oxides such as borides, carbides, nitrides, silicide, etc., and (iii) composite ceramics such as particulate reinforced, fiber reinforced combinations of oxides and non-oxides [8]. Advanced nanoceramics have profound surface properties as their surface to volume ratio is more than 10% when their particle size goes below 100 nm at least in one dimension [9].

## 2 Synthesis of Nanoceramics

Nanoceramics can be produced by various techniques that apply both wet and dry conditions. Most of the synthesis methods use liquid as media and factors such as type of suspension, packing of particles and their dispersion play a great role in their synthesis and outcome. The method of synthesis not only defines the size and shape of nanoceramics but also influences its characteristics such as crystal habits, specific surface area and state of agglomeration [10]. Further, size and shape of the nanoparticles can be molded by adsorbing organic molecules on the surface of growing nanoparticles [11]. Nanoparticles tend to agglomerate due to their high surface area and thermodynamic instability and the synthesis method adopted should involve strategies to overcome this for effective usage [12].

Synthesis of nanoceramics can be broadly classified into two approaches (i) Top-down approach where a large particle is broken down into nanosized particles and (ii) bottom-up approach where ions, atoms, molecules or nanoparticles are assembled in a controlled manner to form nanoparticles. There are various methods of synthesis which come under any of these two broad classifications. The synthesis method plays a great role in the functionality of the produced nanoceramics. The focus of this chapter is on nanoceramics and its application as biomaterials. Hence, we will limit our discussion to the different synthesis methods by which nanoceramics that are used as biomaterials are produced. The common methods of synthesis of nanoceramics include mechanochemical synthesis, co-precipitation, sol-gel method, spray pyrolysis, microemulsion method, physical vapour deposition, etc., which are discussed in detail below [13].

### *2.1 Physical Vapour Deposition*

Physical vapour deposition is a high vacuum coating technique that comprises vacuum deposition methods to produce thin coatings and films of pure metal or alloy. The material to be coated is heated and the metal in the condensed phase is converted to vapour phase [14]. In the vapour phase, the material gets supersaturated in an inert atmosphere to condense the metal nanoparticles and then deposits as thin adherent film of the condensed phase on electrically conductive material [15]. It is possible to develop a much thinner layer of the nanoceramic material over the implant surface with high adhesion strength. The porosity of the developed coatings could be close to that of the cortical bone which enhances osseointegration when the orthopaedic implant comes into contact with the cortical bone [16].

Titania coatings of different thicknesses were developed on machined Ti Screw shaped implants. New bone formation on the 120 nm coating was observed to be higher at the bone-implant interface compared to the 1430 nm coating implying that thinner PVD coating enhances a higher degree of bone growth soon after implantation [17]. Titania/silver combined coating has been developed by PVD method and it is reported to provide increased antimicrobial potency against microbial strains without affecting its mechanical performance [18].

### *2.2 Spray Pyrolysis*

Spray pyrolysis method is widely used for preparing metal and metal oxide powders [19]. It involves formation of solid metal oxide particles by first converting the reactants into micro-sized liquid droplets and spraying it onto a hot substrate in the furnace. The precursor gets decomposed and the desired nanostructure is produced. The size and shape of the nanostructure can be modified by controlling the reaction conditions such as spray energy, droplet size of the precursors, distance between the substrate and the spray gun, etc. [20]. Biocompatible nano calcium phosphate (CaP) was synthesized by the aerosol-derived flame spray pyrolysis method. The obtained nanoparticles have a particle size of 23 nm with increased crystallinity and specific surface area. It showed reduced cytotoxicity at 5–50 μg/ml and higher alkaline phosphatase (ALP) enzyme activity indicating that CaP synthesized by this method can be used in biomedical applications [21]. Nano-sized HAp was produced by ultrasonic spray pyrolysis using a salt-assisted decomposition method. The added $NaNO_3$ salt interrupts agglomeration and results in the formation of rod-type, single-phase, nano-sized particles with high crystallinity [22].

### *2.3 Chemical Vapour Deposition (CVD)*

Chemical vapour deposition is used to produce high-quality solid materials with better performance characteristics. The deposit can be produced on the substrate by depositing volatile precursors on its surface and then making them react or undergo decomposition in the presence of heat, light or plasma. Many CVD processes have been developed such as plasma-assisted chemical vapour deposition (PACVD), low-pressure chemical vapour deposition (LPCVD), laser-enhanced chemical vapour deposition (LECVD), plasma-enhanced chemical vapour deposition (PECVD), etc. Of these methods, PACVD is found to enhance biocompatibility, chemical stability and also increase corrosion resistance [23]. Nanostructured titania coating was developed on pure Ti implants by a metal-organic chemical vapour deposition method.

The coating is reported to accelerate the osseointegration rate and bone mineralization at the bone-implant interface [24]. Silica films were deposited onto titanium by PECVD and then functionalized with amino groups using 3-aminopropyl triethoxysilane (APTES). The functionalized coating was observed to have greater stability under physiological conditions and hence can be used as functional biomaterial coatings [25].

### 2.4 Mechanochemical Synthesis

Mechanochemical synthesis is a high-energy milling technique which involves the formation of nanoscale composites. This method involves coupling of chemical and mechanical phenomena on the molecular scale to produce ceramic nanoparticles. The application of mechanical action through ball mill enables the reaction to happen at room temperature or temperatures lower than the traditional methods avoiding external heating. It can be performed in the presence or absence of solvents. The precursor powders are milled together by placing them in a high-energy mill. Mechanically induced chemical reactions take place under a controlled atmosphere of high load and strain conditions. By modifying the reaction conditions nanostructured compounds having ultrafine grains and homogeneous composition can be produced [26]. Nanoceramics as small as 5 nm with high crystallinity without agglomeration can be produced by this method [27]. Precursors are normally a combination of salt and a metal oxide and they react during milling followed by a heating process. Nanocomposites of oxide, non-oxide as well as mixed ceramics can be prepared by this method.

Calcium phosphate can be synthesized by mechanochemical method under both wet and dry conditions. It was observed that wet grinding slowed down the reaction rate and increased powder contamination due to erosion and hence it is reported that dry mechanochemical synthesis is preferred for biomedical applications [28]. By milling $AlCl_3$ with $CaO_5$, nanoparticles of $Al_2O_3$ of size 10–20 nm can be formed [29]. Equal concentrations of lanthanum and silicate substituted apatite was produced by mechanochemical synthesis. Single-phase products can be produced by this method and the synthesized apatite was deposited on Ti substrate by micro-arc oxidation method. The resultant coating exhibited high biocompatibility and no cytotoxic action on mesenchymal stem cells [30].

Silver nanoparticles were successfully synthesized by combining this method and green synthesis using egg shell membrane or Origanum vulgare L. plant as the reducing agent. Silver nitrate was used as the silver precursor. The Ag nanoparticles synthesized by co-milling with Origanum plant exhibited higher antibacterial activity than the former one [31]. Hydroxyapatite with 20% Ti nanocomposite was synthesized by combining mechanochemical process with solid-state method. The resultant nanopowders exhibited high crystallinity, smaller size of about 25 nm and high purity and have improved bioactivity compared to calcium phosphate nanocomposites [32]. Calcium-deficient hydroxyapatite (CDHA) is used to prepare calcium phosphate ceramics and the CDHA with desired Ca/P ratio can be synthesized by mechanochemical synthesis method by varying the reaction conditions. Nano size crystals of hydroxyapatite of size around 20 nm and controlled Ca/P ratio was reported to be produced by this method [33].

## *2.5 Microemulsion Method*

Micelles are formed by self-assembly of surfactants or block copolymers when they are present above a critical concentration in air or aqueous solution. The synthesis of nanoceramics takes place inside the confined space in the micelle or microemulsion. A microemulsion is produced by dispersing an organic solution in an aqueous solution in the form of fine liquid droplets. The reactants are dissolved and are present in the organic droplets. The reaction happens at the interface between the organic and aqueous part [19]. The reaction will continue and nanoceramic will be produced till reactants are available inside the micelle. This method enables control of particle size, morphology, shape and surface area of the nanoceramic. Mesoporous HAp was prepared by microemulsion technique using hecadecyltrimethyl ammonium bromide (CTAB), cyclohexane and n-octyl alcohol. The HAp powders had well-ordered and uniform morphology with broader pore size distribution. The HAp powders had good biocompatibility at low concentrations and low toxicity at high concentrations and hence are suitable for bone tissue grafts, drug delivery and also for coating material [34]. Iron oxide nanoparticles are produced using the copolymer, poly(styrene-block-allyl alcohol) by microemulsion method. Hydrophobic nanoparticles are encapsulated into the iron oxide nanoparticles to obtain multi-functional nanocomposite. Fluorescent dye and anti-cancer drug molecules are loaded into them and it was observed that the nanocomposite enabled imaging-guided and magnetic targeted drug delivery [35].

## *2.6 Wet Chemical Deposition*

Wet chemical deposition method represents chemical reactions occurring in the solution phase using appropriate precursors and experimental conditions. Many wet chemical synthesis methods are known such as solvothermal synthesis, template synthesis, self-assembly, hot-injection, metal-organic decomposition, etc., by which nanomaterials can be effectively produced [36]. HAp nanostructures were synthesized by wet chemical synthesis method at different pH values and sintering temperatures. The rod and flake-like HAp structures that have formed have an enhanced Ca/P ratio of 1.83 and an increased crystallite size from 20 to 56 nm. Stable and porous Hap powders were synthesized by this method [37]. Needle-like and plate-like Mg-substituted Hap particles containing different amounts of Mg were prepared by wet chemical precipitation method from $Mg(OH)_2$/$Ca(OH)_2$ and $H_3PO_4$. It was observed that the specific surface area of the Hap powder increased with an increase in concentration of Mg [38].

## *2.7 Sol-Gel Process*

Sol-gel technique is used to produce high quality, homogeneous, and highly stoichiometric nanostructures. For the fabrication of nanoceramic oxides, the respective alkoxides are converted into a colloidal solution (sol) in the first step, which is then converted into an integrated network (gel) in the second step. The gel can be used as a precursor and can be coated on a substrate to form a film or can be subjected to other treatment methods to form nanosized powders. Nanoceramics can be prepared in different shapes such as nanospheres, nanorods, nanoflakes, nanotubes, nanoribbons, nanofibers and nanocoating's for different applications. Sol-gel prepared nanoceramics have varied applications in the biomaterial field such as fabrication of bioactive implant coatings and scaffolds for orthopaedic applications and drug delivery systems. Nanocomposite coatings with high homogeneity and purity can also be prepared by this method. Orthopaedic implant materials such as 316L SS and titanium and its alloys were coated with nanoporous nanoceramic oxides such as titania, niobia, silica, etc., and their ability to accelerate bone growth was studied. It was reported that these coatings enhance bioactivity as well as increase the corrosion resistance of the implant [39, 40].

The composite coating of tantalum oxide—carbon nanotubes was developed on Ti plates by sol-gel co-deposition method. The carbon nanotubes were loaded with bisphosphonic acid moieties. The composite coating material supported HAp growth as revealed by in vitro analysis [41]. Mesoporous silica-titania composites were obtained by sol-gel method assisted by hydrothermal method and the drug oxytetracycline was loaded onto the mesochannels. The drug release studies reveal that the drug was released slowly and steadily and the system exhibited good antimicrobial activity against Staphylococcus aureus [42].

## *2.8 Template-Based Synthesis*

Template-based synthesis is a simple procedure by which metallic particles in the nano size can be developed with the help of a host which has preexisting ordered porous structure. The developed nanoparticles will be of reduced dimension and also will be having the orientational order of the host material [43]. Different shapes of nanomaterials such as nanorods, nanowires, nanobelts, etc., can be developed with the help of templates using various methods such as electrophoretic deposition, filling of templates by capillary force, chemical conversion, etc. [44]. Silica-based mesoporous materials having a unique silica network of a well-ordered arrangement of pore system and cavities are developed by using surfactants as templates [45]. Nanoporous calcium phosphate ceramics were synthesized by a hard-templating method using ordered mesoporous carbon as the templating material. The developed calcium phosphate had disordered 3-D interconnected nanopores of 20–30 nm size with increased surface area and pore volume and exhibited higher charging capacity for antibiotics [46].

## *2.9 Biomimetic Deposition Method*

Biomimetic deposition method is a synthetic deposition method where a coating is developed on the implant surface by mimicking physiological conditions. It is done by immersing the implants in simulated body fluid (SBF) at a temperature of 37 °C. Biomimetic deposition happens in two steps. Nucleation followed by formation and growth of the coating. Such synthetic coatings can be developed on materials such as metals, bioactive glasses, glass-ceramics, and also on polymers [47]. Calcium phosphate coatings can be developed on the surface of metals, ceramics, or polymers by this method. These coatings improve load-bearing mechanical strength, bioactivity, and osteoconductivity. When biomolecules, proteins, or growth factors are incorporated along in these coatings it is found to improve osteoinductivity and also sustainably deliver these biomolecules, thus enhancing regeneration of bone tissue [48]. Octacalcium phosphate coating developed on zirconia oral implants by biomimetic method was found to have good reproducibility and improved tensile adhesion strength [49]. Hydroxyapatite coatings were developed on T-i6Al-4 V substrate by immersing the specimen in supersaturated Ca/P solution that has ionic composition similar to that of SBF. Homogeneous HAp coating was developed by this method in a few hours whereas it will require 14 days to develop similar coating from SBF. The deposited coating consists of HAp globular aggregates with fine lamellar structure than those deposited from SBF [50].

## *2.10 Electrophoretic Deposition*

Electrophoretic deposition includes many industrial processes such as cathodic electrodeposition, anodic electrodeposition, electrophoretic coating method, etc. In this process, the coating material is suspended in the form of a colloid in the electrolytic solution and under the influence of an electric field, it migrates and gets deposited onto the electrode. Materials such as ceramics, metals, pigments, polymers and dyes can be deposited by this method. Electroplating is a type of electrophoretic deposition. Graphene oxide reinforced calcium phosphate coating was developed on anodized Ti by pulse electrodeposition method. The graphene reinforced coating exhibited improved nano hardness, adhesion strength, crystallinity and decreased Young's modulus mismatch of the coating with the Ti substrate and hence offered better protection of anodized titanium against corrosion [51]. Cobalt substituted calcium phosphate coatings were developed on Ti-22Nb-6Zr alloy by electrodeposition method. The coating was observed to be made up of a low crystalline apatite phase and it protected the alloy against the corrosive Hank's solution [52]. Pure hydroxyapatite and HAp-$ZrO_2$-$TiO_2$ nanocomposite coatings were developed by merging two different electroplating methods. The coatings exhibited bioactive behavior and also had improved corrosion resistance as observed from decreased corrosion current density ($I_{corr}$) values [53].

# 3 Nanoceramics Characterization

Nanoceramics are key components finding application in different fields ranging from energy generation to applications in the biomedical field. New advanced technologies are developed continuously with the help of nanoceramics. Characterization of nanoceramics is essential as it helps us to understand and control the synthesis as well as discover possible applications. Nanoceramics can be characterized based on the conventional characterization methods and surface analysis techniques used for bulk materials and specialized techniques are being developed to study them in nanoscale too. In this section, let us briefly study the various characterization techniques, its significance, and outcome.

## *3.1 X-Ray Diffraction Analysis (XRD)*

X-ray diffraction analysis (XRD) is an important, accurate, and non-destructive experimental technique used to identify the crystal structure of solids, geometry, identify unknown samples, orientation of single crystals, etc. Various characteristics of a single crystal or polycrystalline material in the form of powder can be studied. In this, a beam of X-rays of wavelength 0.7–2 A° is made to fall on a small amount of the material. The X-ray gets diffracted at the crystalline phases in the material governed by the Bragg's law:

$$n\lambda = 2d \sin \theta$$

where, $\lambda$ is the X-ray wavelength, d is the spacing between atomic planes in the crystal and $\theta$ is the diffraction angle. The main disadvantage of XRD is that it is a time-consuming process and it requires large volume of sample compared to new advanced techniques.

### 3.2 Small Angle X-Ray Scattering

Small angle X-ray scattering is a surface analytical technique that measures the intensity of scattered X-rays as a function of the scattering angle. A very narrow and highly intense incident X-ray beam is focused on the material under study and the behaviour of X-rays that have undergone elastic scattering is studied. Measurements are made at very small angles in the range of < 5°. Nanoparticles in the size range of 1–100 nm even up to 300 nm can be measured [54]. Structural features and properties of nanomaterials such as particle shape, specific surface area, nanoparticle size distribution, pore size distribution, agglomeration behavior of nanoparticles can be studied. Any type of nanomaterial sample such as liquid nanoparticle dispersions, nanopowders, nanocomposites, etc. can be examined by this method.

### 3.3 Energy-Dispersive X-Ray Spectroscopy

Energy-dispersive X-ray spectroscopy (EDS or EDX) is also known as energy dispersive X-ray analysis (EDXA) or energy dispersive X-ray microanalysis (EDXMA). It is a microanalysis technique for identifying and measuring elemental compositions on specific particles, morphologies, or isolated areas of the material on nano-scale [55, 56]. It records the X-rays that are emitted from the material under study by bombarding it by an electron beam. The EDS detector measures the emitted X-rays as a function of their energy. The energy of the X-ray is characteristic of the elemental composition of the chemical substance. From this, the various elements present and their quantities can be determined [57]. The technique requires a very small sample quantity for analysis and it has less or no sample preparation. This technique is usually used in conjunction with SEM.

### 3.4 Thermal Analysis

Thermal analysis is a low cost and high-speed analysis method useful for verifying the morphology and composition of nanoceramics. Many properties of nanoceramics can be studied with the help of thermal analysis. In this method, nanoceramics are heated to higher temperatures and the changes in the material are studied as a function of temperature in the temperature range of −150 to 1600 °C. Properties such as purity, composition, crystallization behavior, glass transition, melting, phase changes, reaction enthalpies, surface area analysis, kinetics of reactive processes, etc., can be studied by thermal analysis [50]. The important thermal analysis techniques that are used to study nanoceramics are: (i) thermogravimetric analysis (TGA)—measures weight loss of the material during heating, (ii) differential thermal analysis—measures relative change in the material's temperature during heating, (iii) differential scanning calorimetry—measures the amount of heat required to raise the temperature of the material with respect to temperature, (iv) Brunauer-Emmett-Teller method—measures the specific surface area of the material, etc. New techniques are being developed which require less sample quantity which will extend the applications of thermal analysis in the characterization of nanoceramics.

## *3.5 Scanning Electron Microscopy (SEM)*

Scanning Electron Microscopy is used to study the surface features of the nanomaterials and nanostructured materials by focusing a narrow and high-intensity electron beam in the range of 5–100 keV over it [58]. The electron beam-sample interaction gives rise to a variety of signals including secondary electrons, backscattered electrons (BSE), photons, visible light etc. By collecting these signals with suitable detectors, high resolution and high-magnification images of the sample surface can be obtained. Secondary electrons give information about the morphology and the topography of the sample surface [59]. Backscattered electrons reveal information about the composition of multiphase samples whereas diffracted backscattered electrons can give information about the crystallographic orientation in the sample. SEM is a non-destructive analysis method requiring less or no sample preparation. Nonconductive samples can be studied by coating them with a thin layer of electrically conductive material such as carbon, gold, etc. in order to avoid or minimize negative charge accumulation from the incident electron beam [58].

## *3.6 Transmission Electron Microscopy (TEM)*

Transmission Electron Microscopy is a powerful tool used for studying nanoscale materials. A high energy beam of electrons is focused on a very thin specimen of thickness less than 200 nm [19]. The electron penetrates the sample and the subsequent electron—atom interaction results in either deflected or undeflected electrons carrying information about the crystal structure, composition, and defects such as dislocations and grain boundaries. A high magnification from 50–$10^6$ can be obtained by this method revealing finest details of the material even as small as individual atoms. High resolution—Transmission Electron Microscopy (HRTEM) has a resolution of approximately 0.08 nm. The diffraction pattern of a small selected area of the sample can be recorded with Selected area electron diffraction (SAED) from which information about the structure and orientation of the material can be obtained [60].

## *3.7 Scanning Probe Microscopy (SPM)*

Scanning Probe Microscopy is a quantitative measuring instrument to study the physical, chemical and surface properties such as topography and nanotribology at the nanoscale [61]. It uses a physical probe to scan the surface of the sample and it can image several interactions simultaneously. Three dimensional (3-D) topographical images of the sample surface with high atomic-scale resolution as well as chemical information can be generated by this method as the sample surface is felt and not just seen with electrons or light waves. This technique includes a group of instruments such as Scanning tunneling microscope (STM), Atomic force microscope (AFM), Lateral force microscope (LFM), magnetic force microscope (MFM), scanning thermal microscope (SThM), Electrical force microscope (EFM) and Near-field scanning optical microscope (NSOM). Different characteristics of the sample can be studied by changing the material, configuration of the probe and by modifying the detection scheme [62]. STM is the most powerful microscope and is used to study the surface of nanomaterials and biological samples related to microelectronics. STM can only scan electrically conductive samples.

AFM is a high-resolution type SPM with resolutions of the order of fractions of a nanometer. AFM is used to study smoothness, texture, presence and size of pores over the sample surface. Shape and topography of different nanoceramics can be investigated with AFM [63] AFM can scan any solid surface such as insulators, conductors, semiconductors, etc., and does not essentially require the sample surface to be conductive [19].

## *3.8 Brunauer-Emmett-Teller (BET) Analysis—Physical Gas Adsorption*

Brunauer-Emmett-Teller analysis is an important analysis technique for measuring the specific surface area, size of particles and pore size distribution of nanomaterials. Gas molecules are made to adsorb on the sample surface and the physically adsorbed gases are removed by reducing the partial pressure. The amount of gas required to fill the pores is measured with respect to gas pressure and the plot is known as gas adsorption isotherm. Evaluation of the adsorption and desorption branches of these isotherms and the hysteresis between them reveal information about the size, volume, and area of the pores. Specific surface area and pore volume of mesoporous or microporous materials can be particularly determined by measuring physical adsorption of gases [19]. The surface area measurement helps in predicting the bioavailability of the loaded materials into the nanopores.

### *3.9 Infrared Spectroscopy (IR)*

Infrared Spectroscopy is also known as vibrational spectroscopy. It is a powerful, sensitive and non-destructive tool for analyzing, characterizing and identifying both organic and inorganic molecules. It also helps in identifying functional groups present over a depth of about 1 μm [64]. When a sample is irradiated with light, the bonds present in the sample molecule absorbs light in the infrared region and start to vibrate. The absorbed light is characteristic of the bonds present in the molecule. IR spectrum is obtained by plotting the amount of light absorbed against wavelength in the region of 4000–400 $cm^{-1}$. This spectrum is known as 'molecular fingerprint' that helps to identify samples.

Fourier Transform—Infrared Spectroscopy (FT-IR) produces a spectrum with high spatial resolution, good signal-to-noise ratios and it also enables measuring a broad region of the spectrum in short duration [65]. Fourier Transform is a mathematical process carried out to convert the raw data into actual spectrum. Solid, liquid, or gaseous samples can be studied with FT-IR. Attenuated Total Reflection—Infrared Spectroscopy (ATR-IR) is used to study solid or liquid samples without further preparation. It uses the property of internal reflection to analyze the sample. The infrared radiation penetrates the samples to a depth between 0.5–2 mm. Rapid sampling and ease of handling are main advantages of this method.

### *3.10 X-Ray Photoelectron Spectroscopy (XPS)*

X-ray Photoelectron Spectroscopy is also known as electron spectroscopy for chemical analysis (ESCA). It is a surface-sensitive spectroscopic technique that does a quantitative elemental analysis of the surface of the sample. The elemental composition, empirical formula, chemical and electronic state of the elements present in the material can be measured by this method [66]. The sample surface is irradiated with a beam of X-rays and the kinetic energy of the emitted electrons from the top 1–10 nm of the material surface is measured [67]. The photoelectron spectrum is recorded by plotting the number of ejected electrons with respect to a range of electron kinetic energies. Atoms emitting particular energy is recorded as peaks. Identification and quantification of the different elements present on the material surface can be done by studying the energies and intensities of the peaks. XPS is a useful technique as it not only enables identification of elements present on the surface but also the elements it is bonded to and its oxidation state.

## 4 Biomedical Applications of Nanoceramics

Nanoceramic materials find a great deal of applications in various fields like electronics, energy storage devices, biomedical fields, catalysts, etc. It is widely used in the biomedical field owing to their mechanical properties, greater strength to weight ratio, biocompatibility and bioactivity. Their widespread application can be credited to its ability of being available in various forms such as powders, granules, dense and porous blocks, coatings, porous scaffolds, etc. [68]. Nano ceramics can function along with the physiological system without eliciting negative host response and get integrated with the host. Hence, nanoceramics are used to develop new biomedical systems to meet the increasing need for medical devices with increased functionality and extended lifetime. The various biomedical applications of nanoceramics are depicted in Fig. 1.

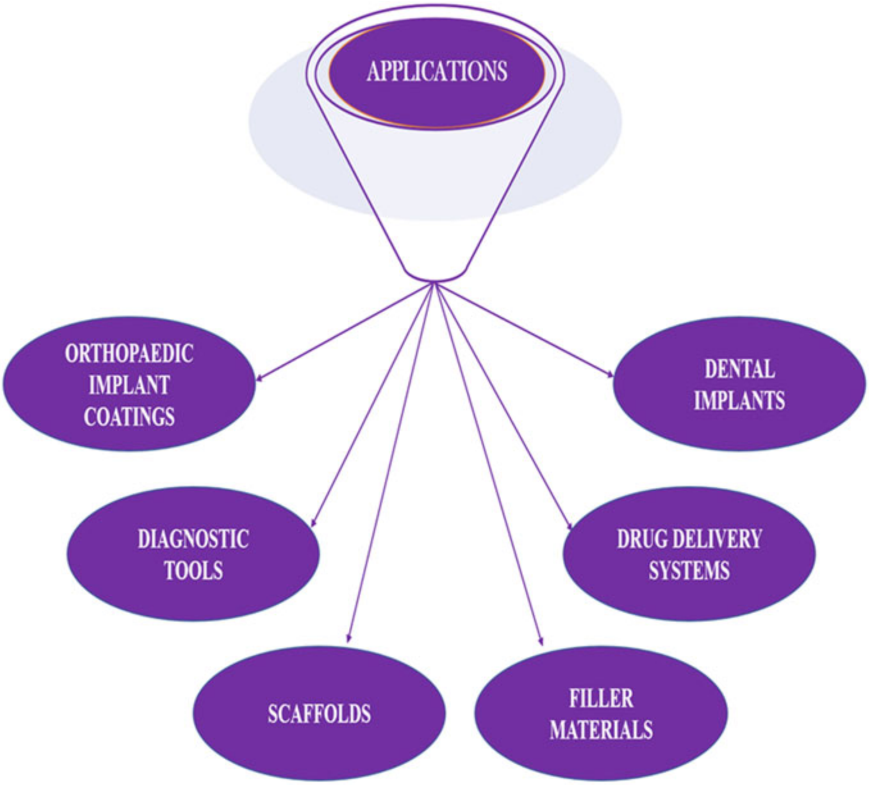

**Fig. 1** Biomedical applications of nanoceramics

## 4.1 Nanoceramics as Orthopaedic Implant Coatings

Implants are used to replace and restore the functions of diseased and/or damaged hard tissues such as bone and teeth. A good artificial implant material should be able to mimic the physical structure, chemical composition and biological function of the natural bone. The increase in the life expectancy of people along with those undergoing treatments for musculoskeletal disorders is on the rise every year. The biological environment is harsh and it leads to loosening of the metal implants, corrosion in the physiological medium, inflammation, loosening, wear and/or tear debris, autoimmune reactions and ultimately failure of implants in patients with traditional metallic implants [69, 70]. Improving the bioactivity and corrosion resistance of the implant material as well as facilitating faster bone-implant interface establishment is crucial to avoid early implant failure and increase the lifetime of an implant.

Modifying the implant surface is a simple and cost-effective method to effect osseointegration and increase the bioactivity of the implant. This can be done by applying biocompatible coatings, modifying the surface topography or by removing material from the existing surface to create new topography [71, 72]. Considering the constraints in the physiological environment, nanoceramics is a suitable material for different bone system-related applications such as dental, periodontal, cranial, maxillofacial, spinal surgery etc. Applying nanoceramics in the form of coatings over the implant surface is an effective methodology.

Numerous nano bioceramics have been developed and categorized based on their activity. The first-generation bioceramics such as zirconia ($ZrO_2$), alumina ($Al_2O_3$), etc., had good mechanical properties but were bioinert [73]. Copper and silver incorporated $ZrO_2$ coatings were developed on pure Ti implant by magnetron sputtering. The nanostructured coatings changed the structure of crystalline zirconia coating and the incorporation of Cu and Ag improved the antibacterial resistance of the implant material [74]. A thin layer of dense $Al_2O_3$ was developed by micro-arc oxidation method. The $Al_2O_3$ layer exhibited good adhesion to the Ti implant, had high Vickers hardness and it is suggested to be a preferred material for load-bearing applications such as artificial hip joint [75].

The second-generation nano bioceramics were based on their chemical reactivity, i.e., they had bioactivity. Bioactive ceramics can bond with the living bone without having adverse reactions such as inflammation and toxicity [76]. The high reactivity of this class of materials is the main advantage for being used in periodontal repair and bone growth. Hydroxyapatite, silica-based bioactive glasses, etc., are the important second-generation bioceramics. Hydroxyapatite coatings were developed over NaOH treated and untreated Ti-6Al-4 V by electrodeposition method and compared with that of plasma-sprayed Hap coated Ti-6Al-4 V. The new bone area value for HAp electrodeposited coating on alkali-treated material was highest at 12 weeks indicating enhanced osseointegration in vivo [77]. A new family of glasses was formulated by partially substituting CaO by MgO and $Na_2O$ by $K_2O$. The glass was deposited on the sample surface by a dip-coating method following by annealing. The glass coating's thickness was adjusted to be between 100–200 nm to have good adhesion and hence it does not crack or delaminate. The glass coating is highly bioactive with silica content of less than 60% [78]. It has been reported that 130 nm silica nanoparticles functionalized by amino group and silver nanoparticles aided the growth of human BMSCs [79].

The bioactivity of nanoceramics leads to the crystallization of hydroxyapatite (HAp) on the implant surface. HAp is similar to the bone tissue and this further facilitates the production of proteins and cell adhesion leading to a strong bond between the bone and implant. The third-generation bioceramics is based on its ability to activate genes that stimulate the regeneration of bone tissues. These can regenerate the bone tissue instead of acting as their substitutes [80, 81].

Silicon nitride ($Si_3N_4$) nano bio-ceramic exhibited less in vitro bacterial affinity than Ti. The ionic dissolution products contain Sr, Mg and Si ions and they increase the stimulatory effect for alkaline phosphatase activity. Increased bioactivity, no toxicity and reduced biofilm formation indicate that it can be applied as spinal fusion cages [82]. Magnesium based bioceramics are gaining a lot of attention owing to its ability to regulate ion channels, activate enzymes and stimulate cell growth and proliferation. Mg oxides, phosphates and silicates are employed in orthopaedic applications in the form of scaffolds, bone cements and also as implant coatings [83].

Nanostructured surfaces have been shown to elicit positive response from host, reduce inflammation and aid in faster bone-implant interface establishment [84, 85]. Growth factors, bioactive molecules, drugs, etc., can be loaded on to these nanoceramic coatings [86]. Ultrathin mesoporous $TiO_2$ coating was developed by evaporation-induced self-assembly method. Drugs like ibuprofen and vancomycin were loaded onto the pores in the coating. The coating exhibited excellent HAp growth and osteoblast adhesion indicating bioactivity while simultaneously eluting drugs from the coating. Thus, the coating exhibited improved therapeutic behavior for applications such as orthopaedic implants and drug delivery [87]. Recently, nanostructured composite materials have been developed in the form of coatings. Nanocomposites combine biodegradable or nonbiodegradable polymers or other compounds with nanoceramics to realize mechanical strength, effective biomineralization, and osseointegration [88]. Chitosan-bioactive glass nanocomposites with different concentrations of bioactive glass were developed over Ti-6Al-4 V by electrophoretic deposition method. Increasing the bioactive glass concentration leads to improvement in adhesion strength, roughness, wettability and also apatite growth. Good cell attachment and negligible cytotoxicity were observed during in vitro evaluation with osteoblast like MG 63 cell line confirming improved cellular performance of the nanocomposite coating [89]. Poly(3,4-ethylenedioxythiophene based nanocomposite coating with different concentrations of fluoro HAp nanoparticles) was developed on Ti-Nb0Zr alloy by an electrochemical deposition method. The uniformly distributed FHA nanoparticles lead to an increase in hardness and surface wettability. The coatings exhibited higher corrosion protection and increased cell adsorption and proliferation of MG 63 cells [90]. Silver particles are coated along with nano-titania on orthopaedic implants surface to prevent post-operative problems and infections [91].

### 4.2 Nanoceramics as Dental Implants

Ceramic materials have been used as dental implants due to their advantageous properties like compressive strength, wear resistance, radiopacity, color stability and biocompatibility. Many such ceramic dental implants have been developed in order to increase their durability and clinical lifetime. Dental implants get contaminated by settling of bacterial deposits especially the organic residues. Photocatalytic activity of $TiO_2$ can be used to degrade the organic residues and regain biocompatibility. A unique $TiO_2$ nanoceramic coating was developed on Ti implants by plasma electrolytic oxidation (PEO). The coating was able to decompose dyes like methylene blue, rhodamine B, and also pre-adsorbed lipopolysaccharide in the presence of visible light. The coating had good osteoconductivity than untreated Ti implant suggesting that it can be used in peri-implantitis treatments [92].

Feldspathic is an advanced ceramic material manufactured by high fusion and has excellent aesthetic properties, opacity and translucency. It is widely used in smile aesthetic recovery with the underlying tooth reinforcing the coating [91]. Feldspathic and alumina added Apatite-Wollastonite glass-ceramic were prepared by sintering $MgO\text{-}CaO\text{-}SiO_2\text{-}P_2O_5\text{-}Al_2O_3$ system at 1100 °C. The dental material produces an interface that is similar in characteristics to the commercially available dental material and hence is a suitable alternate [93]. Aluminized ceramics were prepared by incorporating metallic oxides. The recently developed glass-infiltrated aluminized ceramic with high alumina content has greater fracture resistance and they can be used for both anterior and posterior regions as prostheses [94, 95]. Zirconia based ceramics contain 69% aluminum oxide and 31% zirconium oxide. It's the best alternate for large metal-free fixed prostheses as it has good mechanical properties, clinical longevity and biocompatibility. Yttria-stabilized zirconia is developed by adding pure yttrium dioxide to zirconia. This material has high fracture toughness and it prevents crack propagation commonly observed in aluminized ceramics [90].

### 4.3 Nanoceramics as Drug Delivery Systems

Conventional drug delivery systems have a major limitation namely, limited drug solubility which leads to poor biodistribution, poor targeting, reduced efficacy, and serious side effects in non-target tissues. In some treatments, a definite amount of drug has to be maintained in the bloodstream over a stretch of time for effective treatment and faster recovery. With the conventional drug delivery method, this cannot be ensured as fluctuations in drug level is common. This leads to overdosage to achieve the result. Controlled and continuous in situ delivery of drugs is possible with biocompatible nanoceramics as they act as good drug delivery system (DDS) compared to the traditional ones such as lipids and polymers [96]. Their bioactive behavior along with their ability to control the rate and period of drug delivery and also target the release of drug in a specific area of the body makes them attractive for bone therapy purposes [97]. However, they suffer from certain disadvantages such as limited chemical stability, local inflammatory reactions, improper drug-release kinetics, etc. [71]. Bioactive calcium phosphates and bioactive glasses are widely used as matrices in drug delivery systems. Mesoporous silica-titania composites were developed to have ordered hexagonal array of pores. Antibiotic drug oxytetracycline was loaded onto the mesochannels by wetness impregnation method. Titania present on the silica surface enabled the composite to hold oxytetracycline through host-guest interaction and it avoided the initial burst release of the drug. It was observed that by controlling the distribution of titanium in the silica network it was possible to develop a drug delivery system with a controlled drug release profile [42]. Zeolites with different silica to alumina ratio was used as delivery vehicle for a chemotherapy drug, 5-fluorouracil. The molecular level interaction between the drug and zeolite was confirmed by FTIR spectroscopy. Alumina content played a key role in the drug release behavior and it was observed that greater the alumina content better the controlled drug release behavior [89]. Orthopaedic implants can also be coated with $TiO_2$ nanotubes that are loaded with anti-inflammatory drugs like Ibuprofen and antibiotics like gentamycin or antibacterial drugs like cefuroxime [99]. Thereby it is possible to control or prevent infection and inflammation without affecting the bioactive behavior of implant material which supports the adhesion of osteoblasts on to the implant surface [100].

## *4.4 Diagnostic Tools*

The physicochemical properties of ceramic nanoparticles such as improved cellular adhesion, greater osteoblast proliferation and increased biomineralization allow them to be used as diagnostic tools in addition to effective drug delivery systems [99]. Nanoceramics such as porous silica nanoparticles, $Fe_3O_4$ nanoparticles, quantum dots, etc., are some examples that can be used in imaging, magnetic hyperthermia, or photothermal ablation in addition to drug delivery systems [67]. Mesoporous $SiO_2$ coated with europium hydroxide, $Eu(OH)_3$ core-shell microspheres were used as a fluorescent probe for biomedical applications. FETEM confirmed that $SiO_2$ nanospheres were covered evenly with luminescent $Eu(OH)_3$. The microsphere emitted strong red emission peak when irradiated with ultraviolet light [101]. Composite film of $Fe_3O_4$/cellulose was prepared by co-dispersing $Fe_3O_4$ particles and cellulose in an aqueous solvent and then regenerating them. The composite film was flexible, strong, had excellent mechanical property and thermal stability. The composite film can sense towards UV light and magnetic field and can be used to prepare sensors [102].

## *4.5 Tissue Engineering Applications*

### 4.5.1 Scaffold

Bone tissue engineering involves usage of scaffolds in the oral cavity and craniofacial region and aims to restore alveolar bone after periodontal disease, peri-implantitis, and reconstructive surgery after trauma, after cancer, etc. Tissue engineering provides a suitable biochemical and physicochemical environment in which the osteoblasts can attach to the scaffolds providing mechanical support and also optimize cells osteogenic functions. With nanoceramics increased osteoblast adhesion and proliferation were observed on the material surface. Enhancement in their long-term function is also observed when their grain size is less than 100 nm [103, 84]. A good scaffold should be able to degrade in vivo at a specific rate combined with a controlled absorption rate that facilitates the formation of new bone in the space provided by the two processes. Nanoscale scaffold materials are preferred as they are porous, biodegradable and provide mechanical support during the process of bone repair [104]. Scaffolds for bone repair can be developed using ceramic, metal, polymer and composite materials. Nanoporous bioceramics have high mechanical strength, enhanced bioactivity and resorbability and hence are being used effectively in tissue engineering. Nanohydroxyapatite is now being clinically used on commercial scale. Biopolymers can be used along with HAp, bioactive glass, chitosan, etc., to modify the scaffolds properties such as porosity and growth factor delivering ability to have greater functionality [105]. Chitin, chitosan-based scaffolds, and those reinforced with nanoceramics such as hydroxyapatite (HAp), silicon dioxide ($SiO_2$), titanium oxide ($TiO_2$), etc., are being extensively used in bone tissue engineering applications [106]. Mesoporous silica nanocomposite scaffold loaded with BMP-7; enhanced differentiation of bone marrow-derived mesenchymal cells (BMSC) from osteocytes and initiated osteogenesis [107]. Three-dimensional (3D) periodic $TiO_2$ bio-ceramic scaffolds have finer feature size. The scaffold favoured cell growth and attachment for mouse osteoblastic cell line MC3T3-E1 indicating good biocompatibility of the scaffold. HAp scaffold with microporous structure and high interconnectivity is modified to have nanosheet, nanorod, or micro-nano-hybrids structure on the surface. The scaffold promotes cell adhesion, proliferation and osteogenic differentiation of adipose derived stem cells (ASCs) [108]. Nanoceramics such as HAp, β-tricalcium phosphate, and bioactive glass were combined with gelatin or chitosan to prepare composite scaffold material. The resultant scaffolds exhibited increased compressive strength, high bioactivity, osteoblast adhesion and proliferation and hence stimulated new bone regeneration [109]. Highly porous 3-D scaffolds of the Ag-bioactive glass system of type $58.6SiO_2$—$24.9CaO$—$7.2P_2O_5$—$4.2Al_2O_3$—$1.5Na_2O$—$1.5K_2O$—$2.1Ag_2O$ was found to have antibacterial property. The scaffold showed formation of Hap after 2 weeks of in vitro bioactivity study in SBF and had anti-methicillin-resistant Staphylococcus aureus (MRSA) effect on both direct and indirect exposure [110].

### 4.5.2 Filler Material

Bioactive glass-ceramic (BCG) is widely used as filler material for regenerating bone tissue as it can form strong interface between hard as well as soft tissue. Nano-bioglass ceramic particles doped with Calcarea phosphorica were formulated and their biological action in bone tissue engineering application was investigated [111]. Ca, Mg and Si-containing bioceramics such as calcium silicates have greater applications as they have better mechanical properties, controllable degradation rate, facilitate bone growth and aid healing [112]. Porous and non-porous calcium phosphate glass-ceramics were synthesized and used as injectable bone cement when added with xanthan gum for cell-based bone regeneration treatment. The possible damage of porous calcium phosphate during injection process is prevented by xanthan gum as a result of its viscoeleastic properties [113]. Surface pre-reacted glass is now increasingly used to fill tooth defects in dentistry. Various types of ions such as $Al^{+3}$, $BO^{-3}$, $Na^{+}$, $SiO3^{-2}$, $F^{-}$, $Li^{+,}$ etc., are released from these fillers and they exhibit high antibacterial activity and enhance osteoblast differentiation [114].

## 5 Summary

Nanoceramic materials are finding increased applications in the field of biomaterials owing to their biocompatibility, mechanical strength and greater surface area. They are increasingly used as implant coatings, scaffolds, bone grafts, drug delivery devices and biosensors. The various synthesis methods of nano bioceramics are discussed in this chapter. The characterization techniques used to study the various aspects of nanoceramics are briefly described. Nanoceramics are widely used as metal implant coatings to increase its functionality, bioactivity and resistance to corrosion and wear. Nanoceramic coatings play the dual role of in situ drug delivery system which deliver drugs directly in the implantation site and aid in faster healing and stronger bone-implant interface establishment. As nanoceramics have greater compressive strength and wear resistance they are successfully used as dental applications. The magnetic and radiopacity properties of nanoceramics are utilized in diagnostics and medical imaging. The nanoceramic's biodegradation property can be modified by converting them into nanocomposites with biopolymeric materials which are successfully used as scaffold materials. The application of scaffold as implant devices is increasing owing to its ability to biodegrade and aid natural bone growth in the defective site. Nanoceramics are being reinvented as filler materials in tissue engineering applications and the field is gaining momentum owing to its biocompatibility. Nanoceramics are continually implored in various capacities to bring out its advantageous properties to build functional biomaterials.

## References

1. Khalil KA (2012) Advanced sintering of nano-ceramic materials. In: Ceramic materials-progress in modern ceramics, InTechOpen, London
2. Smith KT (2019) What are nanoceramics and their applications? Accessed March 3. https://azonano.com/article.aspx?ArticleID=5143
3. Thomas SC, Harshita, Mishra PK, Talegaonkar S (2015) Ceramic nanoparticles: fabrication methods and applications in drug delivery. Curr Pharm Des 21:6165–88
4. Virk HS, Poonam S (2010) Chemical route to nanotechnology. Int J Adv Eng Technol 1:114–129
5. Kiani A, Rahmani M, Manickam S, Tan B (2014) Nanoceramics: synthesis, characterization, and applications. J Nanomat 2014:1–2
6. Sharma RK, Sharma P, Maitra A (2003) Size-dependent catalytic behavior of platinum nanoparticles on the hexacyanoferrate(III)/thiosulfate redox reaction. J Colloid Interface Sci 265:134–140
7. Miyake H, Yuba Y, Gamo K, Namba S (1988) Defects induced by focused ion beam implantation in GaAs. J Vac Sci Technol B: Microelectron Process Phenom 6:1001
8. Ting HT, Hossein KA, Chua HB (2009) Review of micromachining of ceramics by etching. T Nonferr Metal Soc China 19:1–16
9. Wakamatsu MH, Salomão R (2010) Ceramic nanoparticles: what else do we have to know? InterCeram: Inter Ceram Rev 59:28–33
10. Hiemenz PC, Rajagopalan R (1997) Principles of colloidal and surface chemistry, revised and expanded, 3rd edn. CRC Press, New York
11. Wakamatsu MH, Salomão R (2011) (Unintentional) synthesis of ceramic nanoparticles. InterCeram: Inter Ceram Rev 60:364–369
12. Rao CNR, Müller A, Cheetham AK (2004) The chemistry of nanomaterials: synthesis, properties and applications, vol 1. Wiley-VCH Verlag, Weinheim
13. Vashist SK (2013) Magnetic nanoparticles-based biomedical and bioanalytical applications. J Nanomed Nanotechnol 4:1000–1130
14. Xie L, Abliz D, Li D (2014) Thin film coating for polymeric micro parts, Vol. 7 comprehensive materials processing, reference module in materials science and materials engineering, Elsevier Publications, London
15. Rane AV, Kanny K, Abitha VK, Thomas S (2018) Methods for synthesis of nanoparticles and fabrication of nanocomposites. In: Synthesis of inorganic nanomaterials, micro and nano technologies, Woodhead Publishing, Massachusetts.
16. Goharian A (2019) Porous osseoconductive layering for enhancement of osseointegration. In: Osseointegration of orthopaedic implants, Academic Press, Cambridge, England.
17. Ballo AM, Bjoorn D, Astrand M, Palmquist A, Lausmaa J, Thomsen P (2013) Bone response to physical-vapour-deposited titanium dioxide coatings on titanium implants. Clin Oral Implants Res 24(9):1009–1017
18. Bazaka K, Jacob MV, Crawford RJ, Ivanova EP (2012) Efficient surface modification of biomaterial to prevent biofilm formation and the attachment of microorganism's. Appl Microbiol Biotechnol 95:299–311
19. Cao G (2014) Nanostructures & Nanomaterials: synthesis, properties & applications. Imperial College Press, London
20. Kumar DS, Kumar BJ, Mahesh HM (2018) Chapter 3—Quantum Nanostructures'. In: Synthesis of inorganic nanomaterials, micro and nano technologies, Woodhead Publishing, Cambridge, England.
21. Ataol S, Tezcaner Duygulu O, Keskin D, Machin NE (2015) Synthesis and characterization of nanosized calcium phosphates by flame spray pyrolysis and their effect on osteogenic differentiation of stem cells. J Nanopart Res 17:1–14
22. An GH, Wang HJ, Kim BH et al (2014) Fabrication and characterization of a hydroxyapatite nanopowder by ultrasonic spray pyrolysis with salt-assisted decomposition. Mater Sci Eng, A 449–451:821–824

23. Kulkarni M, Mazare A, Schmuki P et al (2014) Biomaterial surface modification of titanium and titanium alloys for medical applications. In: Nanomedicine, UK Central Press, Cambridge
24. Giavaresi G, Ambrosio L, Battiston GA et al (2004) Histomorphometric, ultrastructural and microhardness evaluation of the osseointegration of a nanostructured titanium oxide coating by metal-organic chemical vapour deposition: an in vivo study. Biomater 25(25):5583–5591
25. Szili EJ, Kumar S, Smart RSC, Voelcker NH (2009) Generation of a stable surface concentration of amino groups on silica coated onto titanium substrates by the plasma enhanced chemical vapour deposition method. Appl Surf Sci 255(15):6846–6850
26. Gennari FC, Gamboa JJA (2018) A Systematic approach to the synthesis, thermal stability and hydrogen storage properties of rare-earth borohydrides. In: Emerging Materials from Energy Conversion and Storage, Elsevier Publications, London.
27. Tsuzuki T, McCormick PG (2004) Mechanochemical synthesis of nanoparticles. J Mater Sci 39:5143–5146
28. Benabdeslam HEB, Ginebra MP, Vert M (2008) Wet or dry mechanochemical synthesis of calcium phosphates? Influence of the water content on DCPD-CaO reaction kinetics. Acta Biomater 4(2):378–386
29. Singh Z (2018) Nanoceramics in bone tissue engineering: the future lies ahead. Trends J Sci Res 3:120–123
30. Bulina NV, Chaikina MV, Prosanov IY (2018) Lanthanum-silicate-substituted apatite synthesized by fast mechanochemical method: characterization of powders and biocoatings produced by micro-arc oxidation. Mater Sci Eng, C 92:435–446
31. Balaz M, Daneu N, Balazova L (2017) Bio-mechanochemical synthesis of silver nanoparticles with antibacterial activity. Adv Powder Technol 28(12):3307–3312
32. Fahami A, Kahrizsangi RE, Tabrizi BN (2011) Mechanochemical synthesis of hydroxyapatite/titanium nanocomposite. Solid State Sci 13(1):135–141
33. BenAbdeslam HEB, Mochales C, Ginebra MP et al (2003) Dry mechanochemical synthesis of hydroxyapatites from dicalcium phosphate dihydrate and calcium oxide: a kinetic study. J Biomed Mater Res A 67A(3):927–937
34. Huang A, Dai H, Wu X, Zhao Z et al (2019) Synthesis and characterization of mesoporous hydroxyapatite powder by microemulsion technique. J Mater Res Technol 8(3):3158–3166
35. Xu H, Cheng L, Wang C et al (2011) Polymer encapsulated upconversion nanoparticle/iron oxide nanocomposites for multimodal imaging and magnetic targeted drug delivery. Biomater 32(35):9364–9373
36. Pottathara YB, Grohens Y, Kokol V et al (2019) Synthesis and processing of emerging two-dimensional nanomaterials. In: Nanomaterials synthesis, design, fabrication and applications, micro and nano technologies, Elsevier Publications, London
37. Lugo VR, Karthik TVK, Anaya DM, Rosas ER (2018) Wet chemical synthesis of nanocrystalline hydroxyapatite flakes: effect of pH and sintering temperature on structural and morphological properties. R Soc Open Sci 5(8):180962
38. Stipniece L, Ancane KS, Borodajenko N (2014) Characterization of Mg-substituted hydroxyapatite synthesized by wet chemical method. Ceram Inter 40(2):3261–3267
39. Pauline SA, Mudali UK, Rajendran N (2013) Fabrication of nanoporous Sr-incorporated $TiO_2$ coating on 316L SS: evaluation of bioactivity and corrosion protection. Mater Chem Phy 142:27–36
40. Pauline SA, Rajendran N (2014) Effect of Sr on the bioactivity and corrosion resistance of nanoporous niobium oxide coating for orthopaedic applications. Mater Sci Eng, C 36:194–205
41. Maho A, Detriche S, Delhalle J et al (2013) Sol-gel synthesis of tantalum oxide and phosphonic acid-modified carbon nanotubes composite coatings on titanium surfaces. Mater Sci Eng, C 33(5):2686–2697
42. Georgescu D, Brezoiu AM, Mitran RA et al (2017) Mesostructured silica-titania composites for improved oxytetracycline delivery systems. C R Chim 20:1017–1025
43. Foss CA (2003) Optical properties of nanoparticle pair structures. In: Encyclopedia of materials: science and technology, Elsevier Publications, London

44. Cao G, Liu D (2008) Template-based synthesis of nanorod, nanowire, and nanotube arrays. In: Springer handbook of nanotechnology, Springer, New York. 136(1–2):45–64
45. Regi MV (2010) Evolution of bioceramics within the field of biomaterials. C R Chim 13(1–2):174–185
46. Fan J, Lei J, Yu C (2007) Hard-templating synthesis of a novel rod-like nanoporous calcium phosphate bioceramics and their capacity as antibiotic carriers. Mater Chem Phy 103(2–3):489–493
47. Wang M, Guo L, Sun H (2019) Manufacture of biomaterials. In: Encyclopedia of biomedical engineering, Elsevier Publications, London
48. Shin K, Acri T, Geary S et al (2017) Biomimetic mineralization of biomaterials using simulated body fluids for bone tissue engineering and regenerative medicine. Tissue Eng Part A 23(19–20):1169–1180
49. Stefanic M, Krnel K, Pribosic I et al (2012) Rapid biomimetic deposition of octacalcium phosphate coatings on zirconia ceramics (Y-TZP) for dental implant applications. Appl Surf Sci 258(10):4649–4656
50. Bigi A, Boanini E, Bracci B et al (2005) Nanocrystalline hydroxyapatite coatings on titanium: a new fast biomimetic method. Biomater 26:4085–4089
51. Fathyunes L, Khalil-Allafi J, Moosavifar M (2019) Development of graphene oxide/calcium phosphate coating by pulse electrodeposition on anodized titanium: Biocorrosion and mechanical behavior. J Mech Behav Biomed Mater 90:575–586
52. Drevet R, Zhuova Y, Dubinskiy S et al (2019) Electrodeposition of cobalt-substituted calcium phosphate coatings on Ti-22Nb-6Zr alloy for bone implant applications. J Alloys Compd 793:576–582
53. Poorraeisi M, Afshar A (2018) The study of electrodeposition of hydroxyapatite-$ZrO_2$-$TiO_2$ nanocomposite coatings on 316 stainless steel. Surf Coat Technol 339:199–207
54. Pontoni D, Narayanan T, Rennie AR (2002) Tr-saxs study of nucleation and growth of sillica colloids. Langmuir 18:56–59
55. Ebnesajid S (2014) Chapter 4—Surface and material characterization techniques. In: Surface treatment of materials for adhesive bonding. William Andrew Applied Science Publishers, New York
56. Ismail AF, Khulbe KC, Matsuura T (2019) Chapter 3—RO membrane characterization. In: Reverse osmosis. Elsevier Publications, London
57. Bergstrom J (2015) 2—Experimental characterization techniques, mechanics of solid polymers. In: Theory and computational modeling. William Andrew Applied Science Publishers, New York
58. Ratner BD (2013) Chapter I.1.5—Surface Properties and Surface Characterization of Biomaterials. In: Biomaterials science (Third Edition), an introduction to materials in medicine. Academic Press, Cambridge, England.
59. Ven ALVD, Mack A, Dunner Jr K et al (2012) Chapter one—preparation, characterization, and cellular associations of silicon logic-embedded vectors. In: Methods in enzymology, vol. 508. Elsevier Publications, London
60. Bajpai OP, Panja S, Chattopadhyay S et al (2015) Process-structure-property relationships in nanocomposites based on piezoelectric-polymer matrix and magnetic nanoparticles. In: Manufacturing of nanocomposites with engineering plastic. Elsevier Publications, London
61. Cuenat A, Leah R (2014) Chapter 7—Scanning probe and particle beam microscopy. In: Fundamental principles of engineering nanometrology (2nd edn), micro and nano technologies. William Andrew Applied Science Publishers, New York
62. Ramakrishna BL, Ong EW (2001) Surface evaluation by atomic force microscopy. In: Encyclopedia of materials: science and technology (2nd edn), Elsevier Publications, London
63. Shi D, Guo Z, Bedford N (2015) 2-Characterization and Analysis of Nanomaterials. In: Nanomaterials and Devices, Micro and Nano Technologies. William Andrew Applied Science Publishers, New York
64. Causserand C, Aimar P (2010) 1.15—Characterization of filtration membranes. In: Comprehensive membrane science and engineering, vol. 1. Elsevier Publications, London

65. McCluskey MD (2017) High-pressure IR. In: Encyclopedia of spectroscopy and spectrometry (3rd edn), reference module in chemistry, molecular sciences and chemical engineering. Elsevier Publications, London
66. Ohara S, Adschiri T, Ida T, Yashima M et al (2012) Chapter 5 - Characterization methods for nanostructure of materials. In: Nanoparticle technology handbook (2nd edn). Elsevier Publications, London
67. Mather RR (2009) 13—Surface modification of textiles by plasma treatments. In: Surface modification of textiles. Woodhead Publishing Series in Textiles, Cambridge
68. Arcos D, Regi MV (2013) Bioceramics for drug delivery. Acta Mater 61:890–911
69. Smith AJ, Dieppe P, Vernon K et al (2012) Failure rates of stemmed metal-on-metal hip replacements: analysis of data from the national joint registry of England and Wales. The Lancet 379:1199–1204
70. Wang CJ, Huang TW, Wang JW et al (2002) The often poor clinical outcome of infected total knee arthroplasty. J Arthroplasty 17:608–614
71. Simchi A, Eng D, Tamjid E (2011) Recent progress in inorganic and composite coatings with bactericidal capability for orthopaedic applications. Nanomedicine 7:22–39
72. Duan K, Wang R (2006) Surface modifications of bone implants through wet chemistry. J Mater Chem 16:2309–2321
73. In HSF, Hench LL, Editors WJ (1993) An introduction to bioceramics. World Scientific, Singapore
74. Huang HL, Chang YY, Weng JC (2013) Anti-bacterial performance of Zirconia coatings on Titanium implants. Thin Solid Films 528:51–156
75. Khanna R, Kokubo T, Matsushita T et al (2016) Fabrication of dense α-alumina layer on Ti-6Al-4 V alloy hybrid for bearing surfaces of artificial hip joint. Mater Sci Eng, C 69:1229–1239
76. Hench LL (1991) Bioceramics: from concept to clinic. J Am Ceram Soc 74:1487–1510
77. Lakstein D, Kopelovitch W, Barkay Z et al (2009) Enhanced osseointegration of grit-blasted, NaOH-treated and electrochemically hydroxyapatite-coated Ti-6Al-4 V implants in rabbits. Acta Biomater 5:2258–2269
78. Esteban SL, Saiz E, Fujino S et al (2003) Bioactive glass coatings for orthopedic metallic implants. J Eur Ceram Soc 23(15):2921–2930
79. Tarpani L, Morena F, Gambucci M (2016) The influence of modified silica nanomaterials on adult stem cell culture. Nanomaterials 6:104–114
80. Hench LL, Xynos ID, Polak JM (2004) Bioactive glasses for in situ tissue regeneration. J Biomater Sci. Polymer Edition 15:543–562
81. Habraken WJEM, Walke JGC, Jansen JA (2007) Ceramic composites as matrices and scaffolds for drug delivery in tissue engineering. Adv Drug Deliv Rev 59:234–248
82. Fu L, Xiong Y, Carlsson G et al (2018) Biodegradable $Si_3N_4$ bioceramic sintered with Sr, Mg and Si for spinal fusion: surface characterization and biological evaluation. Appl Mater Today 12:260–275
83. Nabiyouni M, Bruckner T, Zhou H et al (2018) Magnesium-based bioceramics in orthopedic applications. Acta Biomater 66:23–43
84. Liu H, Webster TJ (2007) Nanomedicine for implants: a review of studies and necessary experimental tools. Biomater 28:354–369
85. Ainslie KM, Tao SL, Popat KC et al (2008) In vitro inflammatory response of nanostructured titania, silicon oxide, and polycaprolactone. J Biomed Mater Res, Part A 91:647–655
86. Luginbuehl V, Meinel L, Merkle HP et al (2004) Localized delivery of growth factors for bone repair. Eur J Pharm 58:197–208
87. Chao CS, Liu KH, Tung WL et al (2012) Bioactive TiO2 ultrathin film with worm-like mesoporosity for controlled drug delivery. Micropor Mesopor Mat 152:58–63
88. Couto DS, Alves NM, Mano JF (2008) Nanostructured multilayer coatings combining chitosan with bioactive glass nanoparticles. J Nanosci Nanotechnol 8:1–8
89. Mahlooji E, Atapour M, Labbaf S (2019) Electrophoretic deposition of Bioactive glass—chitosan nanocomposite coatings on Ti-6Al-4 V for orthopaedic applications. Carbohydr Polym 226:115299

90. Kumar AM, Adesina AY, Hussein MA (2019) PEDOT/FHA nanocomposite coatings on newly developed Ti-Nb-Zr implants: biocompatibility and surface protection against corrosion and bacterial infections. Mater Sci Eng, C 98:482–495
91. Goncalves SEP, Bresciani E (2017) Reconstructions using alloys and ceramics. In: Material-tissue interfacial phenomena. Elsevier Publications, London.
92. Wu H, Xie L, He M et al (2019) A wear-resistant $TiO_2$ nanoceramic coating on titanium implants for visible-light photocatalytic removal of organic residues. Acta Biomater 97:597–607
93. Pekkan G, Pekkan K, Park J et al (2016) A study on microstructural characterization of the interface between apatite-wollastonite based glass ceramic and feldspathic dental porcelain. Ceram Inter 42(16):19245–19249
94. Donovan TE (2008) Factors essential for successful all-ceramic restorations. J Am Dent Assoc 139:14S–18S
95. Koutayas SO, Vagkopoulou T, Pelekanos S et al (2009) Zirconia in dentistry: part 2. Evidence-based clinical breakthrough. Eur J Esthet Dent 4(4):348–380
96. Regi MV, Balas F, Arcos D (2007) Mesoporous materials for drug delivery. Angew Chem Int Ed 46:7548–7558
97. Regi MV, Balas F, Colilla M et al (2008) Bone-regenrative bioceramic implants with drug and protein controlled delivery capability. Solid State Sci 1:163–191
98. Datt A, Burns EA, Dhuna NA et al (2013) Loading and release of 5-fluorouracil from HY zeolites with varying SiO2/Al2O3 ratios. Micropor Mesopor Mater 167:182–187
99. Ozdemir V, Glatt BWJSJ, Tsuang MT et al (2006) Shifting emphasis from pharmacogenomics to theragnostics. Nat Biotechnol 24:942–946
100. Yi H, Rehman FU, Zhao C (2016) Recent advances in nano scaffolds for bone repair. Bone Res 4:1–11
101. Ansari AA, Hasan TN, Syed et al (2013) *In-vitro* cyto-toxicity, geno-toxicity, and bio-imaging evaluation of one-pot synthesized luminescent functionalized mesoporous $SiO_2@Eu(OH)_3$ core-shell microspheres. Nanomedicine 9:1328–1335
102. Yang W, Tian H, Liao J (2020) Flexible and strong $Fe_3O_4$/cellulose composite film as magnetic and UV sensor. Appl Surf Sci 507:145092
103. Shi Z, Huang X, Cai Y et al (2009) Size effect of hydroxyapatite nanoparticles on proliferation and apoptosis of osteoblast-like cells. Acta Biomater 5:338–345
104. Khan Y, Yaszemski MJ, Mikos AG et al (2008) Tissue engineering of bone: material and matrix considerations. J Bone Jt Surg 90:36–42
105. Dziak R, Mohan K, Almaghrabi B et al (2020) Nanoceramics for bone regeneration in the oral and craniomaxillofacial complex. In: Nanobiomaterials in clinical dentistry. Elsevier Publications, London
106. Deepthi S, Venkatesan J, Kim SK et al (2016) An overview of chitin or chitosan/nano ceramic composite scaffolds for bone tissue engineering. Inter J Biol Macromol 93:1338–1353
107. Luo Z, Deng Y, Zhang R et al (2015) Peptide-laden mesoporous silica nanoparticles with promoted bioactivity and osteo-differentiation ability for bone tissue engineering. Colloids Surf B 131:73–82
108. Xia L, Lin K, Jiang X et al (2014) Effect of nano-structured bioceramic surface on osteogenic differentiation of adipose derived stem cells. Biomater 35:8514–8527
109. Chen P, Liu L, Pan J et al (2019) Biomimetic composite scaffold of hydroxyapatite/gelatin-chitosan core-shell nanofibers for bone tissue engineering. Mater Sci Eng C: Mater Biol Appl 97:325–335
110. Marsh AC, Mellott NP, Chamorro NP et al (2019) Fabrication and multiscale characterization of 3D silver containing bioactive glass-ceramic scaffolds. Bioact Mater 4:215–223
111. Kumar SD, Abudhahir KM, Selvamurugan N et al (2018) Formulation and biological actions of nano-bioglass ceramic particles doped with Calcarea phosphorica for bone tissue engineering. Mater Sci Eng C: Mater Biol Appl 83:202–209
112. Shokrollahi H, Salimi F, Doostmohammadi A (2017) The fabrication and characterization of barium titanate/akermanite nano-bio-ceramic with a suitable piezoelectric coefficient for bone defect recovery. J Mech Behav Biomed Mater 74:365–370

113. Veloza AM, Hossain KMZ, Scammell BE (2020) Formulating injectable pastes of porous calcium phosphate glass microspheres for bone regeneration applications. J Mech Behav Biomed Mater 102:103489
114. Ali M, Okamota M, Komichi S (2019) Lithium-containing surface pre-reacted glass fillers enhance hDPSC functions and induce reparative dentin formation in a rat pulp capping model through activation of Wnt/β-catenin signaling. Acta Biomate 96:594–604