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BIOMEDICAL APPLICATIONS OF CERAMIC NANOMATERIALS: A REVIEW

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ABSTRACT: A variety of Nano-biomaterials are synthesised, characterised and tested to find out their potentialities by global scientific communities, during the last three decades. Among those, nanostructured ceramics, cements and coatings are being considered for major use in orthopaedic, dental and other medical applications. The development of novel biocompatible ceramic materials with improved biomedical functions is at the forefront of health-related applications, all over the world. Understanding of the potential biomedical applications of ceramic nanomaterials will provide a major insight into the future developments. This study reviews and enlists the prominent potential biomedical applications of ceramic nanomaterials, like Calcium Phosphate (CaP), Tri-Calcium Phosphate (TCP), Hydroxy-Apatite(HAP), TCP+HAP, Si substituted HAP, Calcium Sulphate and Carbonate, Bioactive Glasses, Bioactive Glass Ceramics, Titania-Based Ceramics, Zirconia Ceramics, Alumina Ceramcis and Ceramic Polymer Composites.

INTRODUCTION: The field of nanotechnology is playing a pivotal role in the fields of electronics, biology and medicine. It also introduced several new concepts into medicine and thus makes these large cross disciplinary fields to join together. Nanomedicine encompasses many common technical issues like analytical tools, nanoimaging, nanomaterials and nano-devices, novel therapeutics and Drug Delivery Systems, clinical, regulatory and toxicological issues. Among the varieties of nanomaterials, nanostructured ceramics, cements and coatings are being considered for major applications in orthopaedic and dental treatments.

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Biocompatible Ceramics, also known as bioceramics, include of both macro and nano materials mainly used for bone, teeth and other medical applications. Understanding of the potential biomedical applications of ceramic nanomaterials will provide a major insight in to the future developments. It is under this context, this review has been made to enlist the potential biomedical applications of ceramic nanomaterials [1].

1.1 Nanomedicine: Applications of nano-technology in several areas of biomedical fields have provided a lot of opportunities and possibilities for the growth of nanomedicine. The major opportunities include superior diagnostic tools and biosensors, improved imaging techniques, innovative therapeutics and technologies to enable tissue regeneration and repair. The long term priorities are found to be in the design of synthetic, bioresponsive systems for intracellular delivery of macromolecular therapeutics (synthetic vectors for gene therapy), and bioresponsive or self-regulated delivery systems including smart nanostructures such as biosensors that are coupled to the therapeutic delivery systems [2].

There is also an urgent need to more clearly articulate and better communicate the potential benefits of Nanomedicine to the budding researchers as a whole. There are increasing challenges within the pharmaceutical industry to locate drugs more efficiently to their disease targets and treat them effectively. The major techniques and tools developed for analysis and diagnostics in the medical field have the potential for wider application [3, 4].

1.2 Nanobiomaterials: Nanobiomaterials are nanoscale materials utilized for various biological and biomedical applications such as drug and gene delivery, biosensors, bio-imaging, tissue engineering, bio-electronics, and for antimicrobial activities [5]. A variety of Nanobiomaterials are synthesised, characterised and tested to find out their potentialities by global scientific communities, during the last four decades [6]. A substantial amount of work has been carried out in the field of nanobiomaterials [7, 8].

The types of nanobiomaterials synthesized, produced and used are very highly heterogeneous with reference to their physical, chemical, biological and engineering properties. They pose not only many challenges in their design and development, but also provide ample opportunities to use them in several of the modern applications. Huge repositories of literature collections are available on the synthesis and characterisation aspects [9 - 10]. Nanobiomaterials include a wide range of nanoscale fine particles and devices that are fabricated with a prime focus on biological and biomedical applications [11]. The nanobiomaterials are classified into the following subgroups [12]:

1) Metallic nanobiomaterials
2) Ceramic nanobiomaterials
3) Semiconductor based nanobiomaterials
4) Organic/carbon based nanobiomaterials
5) Organic inorganic hybrid nanobiomaterials
6) Silica based nanobiomaterials
7) Polymeric nanobiomaterials including nano composites
8) Biological nanobiomaterials
9) Biologically directed / self-assembled nano-biomaterials
10) Bionanomaterials such as nanodiamonds.

Among these, nanostructured ceramics, cements and coatings are being considered for major orthopaedic, dental and other medical applications. The development of novel biocompatible ceramic materials with improved biomedical functions is at the forefront of health-related applications all over the world. Ceramics are also unique biomaterials used for repairing and regenerating several parts of the human body [13]. Modern ceramic substrates and packages are sophisticated combinations of glasses, ceramics, and metals that can form compact cost-effective solutions for a variety of applications [14]. In this work, the prominent applications of only the ceramic nanomaterials are discussed.

1.3 Properties of Ceramic Nanobiomaterials: Ceramics are compounds between metallic and non-metallic elements; they are most frequently oxides, phosphates, nitrides, and carbides. There are wide range of ceramic materials like clay minerals, cement, and glass used for various applications [15]. These materials are typically insulative to electricity and heat, and are highly resistant to harsh chemical environments than metals and polymers. With regard to their mechanical behaviour, ceramics are very hard and brittle. At nanoscale also, ceramic materials exhibit higher hardness, excellent heat and corrosion resistance, and electrical insulation properties [16].

Typical examples include china clay, firebricks, cements and glass. In addition to these properties, Fine Ceramics (also known as "advanced ceramics") have many advanced mechanical, electrical, electronic, magnetic, optical, chemical and biochemical characteristics. One of the major field of application of bioceramics is tissue generation. The major parameters considered to optimize the biomaterials for tissue generation include [17], a) Structural Components (physical, mechanical and chemical properties) and b) Biochemical Components (immobilized signals, diffusable signals, and living components).

The bioceramics have good biocompatibility, osteo conductivity, osteoinductivity, biodegradability, resorbability, and hydrophilicity. Yet another major field of application of bioceramic is clinical dentistry.

2.0 Types of Ceramic Nanobiomaterials: The widely used ceramic nanobiomaterials include **Fig. 1**, Calcium Phosphate (CaP), Tri-Calcium Phosphate (TCP), Hydroxy-Apatite(HAP), TCP+HAP, Si substituted HA, Calcium Sulphate and Carbonate, Bioactive Glasses, Bioactive Glass Ceramics, Titania-Based Ceramics, Zirconia Ceramics, Alumina Ceramcis and Ceramic Polymer Composites.

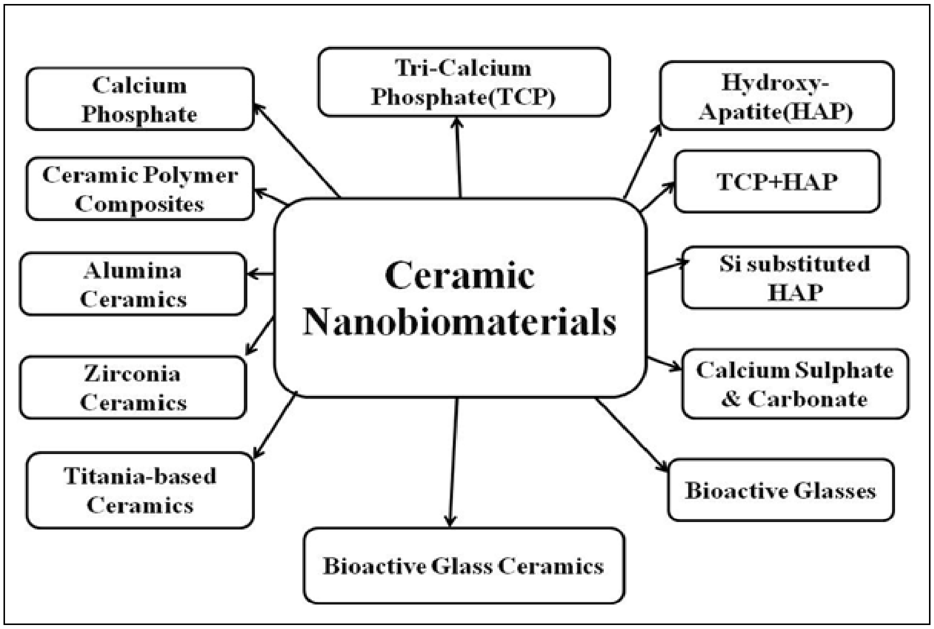

FIG. 1: WIDELY USED CERAMIC NANOBIOMATERIALS

Biomaterials are mainly used for orthopaedic applications [18]. Bioceramics are materials used to repair and replacement of diseased and damaged parts of musculoskeletal systems. Based on their inherent properties, they are classified into three major categories as [19]:

a) Bioactive ceramics (CaP, HAP, Bioactive Glass (BAG), and Glass Ceramics (GC) which form direct chemical bonds with bone or even soft tissues of living systems, b) Bioresorbable ceramics (TCP) that actively participate in the metabolic process of an organism andc) Bioinert high strength ceramics (alumina and zirconia)

Based on their applications, ceramic biomaterials are further classified into:

a) Cardiovascular biomaterials
b) Dental Biomaterials
c) Orthopedic bomaterials
d) Biomaterials to promote tissue generation.

Nanomaterials of CaP, HAP, TCP, BAG, GC and Calcium sulphate form good ceramic-based bone graft substitutes.

2.2 Applications of Ceramic Nanobiomaterials:

2.2.1 Calcium Phosphate (CaP): Calcium plays a very important role in the body. It is necessary for normal functioning of nerves, cells, muscles, and bones. If there is not enough calcium in the blood, then the body will take calcium from bones, thereby weakening bones. Tooth enamel is composed of almost ninety percent hydroxyapatite. Its solubility in cold water is 2 mg / 100 cc.

The Calcium phosphates occur abundantly in nature in several forms as:

a) Monocalcium phosphate - $Ca(H_2PO_4)_2$ occurring as monohydrate
b) Dicalcium phosphate (dibasic calcium phosphate), $CaHPO_4$ named as Dihydrate
c) Tricalcium phosphate (tribasic calcium phosphate or tricalcic phosphate), $Ca_3(PO_4)_2$, also named as calcium orthophosphate
d) Hydroxyapatite $Ca_5(PO_4)_3(OH)$
e) Apatite $Ca_{10}(PO_4)_6(OH, F, Cl, Br)_2$
f) Octacalcium phosphate $Ca_8H_2(PO_4)_6 . 5H_2O$
g) Tetracalcium phosphate, $Ca_4(PO_4)_2O$.

Calcium Orthophosphates have very useful properties and show several major biomedical applications. Regardless of the composition, all calcium phosphates are osteoconductive. Bone, which is similar to other calcified tissues, is an intimate composite of the organic (collagen and noncollagenous proteins) and inorganic or mineral phases [20].

The bioactivity and degradation behavior generally depend on the Ca/P ratio, crystallinity and phase purity. The biological calcium phosphates are mainly observed as components of natural hard tissues, that is, bone and teeth [21]. Ceramic nanobiomaterials, especially, calcium phosphate are used mainly as bone substitutes or scaffolds due to their good biocompatibility and also due to their compositional similarity with the inorganic components of human bone [22]. The major limitation of calcium phosphate- based ceramics lies in its load-bearing capability and their mechanical properties like brittleness, and poor fatigue resistance. Such factors are generally inadequate for many load-carrying applications [23].

Calcium Phosphate (CaP) biomaterials are used in the form of nanoparticles, coatings, cements, and scaffolds mainly in orthopedic and dental applications [24]. They are able to bind and concentrate bone morphogenetic proteins that are in circulation and may become osteoinductive (capable of osteogenesis) and can be effective carriers of bioactive peptide or bone cell seeds [25]. CaP biomaterials have outstanding properties based on which they are used for several kinds of biomedical applications [26, 27].

The current applications also include replacements for hips, knees, teeth, tendons and ligaments, as well as repair for periodontal disease, maxillofacial reconstruction, augmentation and stabilization of the jawbone, spinal fusion and bone fillers after tumor surgery [28].

The biphasic, triphasic and multiphasic (polyphasic) calcium orthophosphates are good biomaterials for reconstruction of bone defects in maxillofacial, dental and orthopedic applications [29].

The major applications of calcium phosphates are found to be:

a) Bone Grafts, Bone Reconstruction and Repair: Bone-grafting is usually required to stimulate bone-healing. In addition, spinal fusions, filling defects following removal of bone tumors and several congenital diseases may require bone grafting [30 - 32].

b) Bioactive Coatings for Orthopaedic Implants [33, 34].

c) Controlled Drug Release: Ceramics can be effective carriers of bioactive peptide or bone cell seeds and are therefore potentially useful in tissue engineering and drug delivery.

The calcium phosphate cements are used as carriers of different types of drugs, such as antibiotics, analgesics, anticancer and anti-inflammatory drugs [35 - 37]. The bioactive bone scaffolds are used as therapeutic drug carriers [42, 43],

d) Gene delivery and gene therapy [44, 45]

e) Dentistry

f) Bone tissue regeneration.

2.2.2 Tri-Calcium Phosphate: Tricalcium phosphate (TCP) is one of the most common and important members of the calcium phosphate family of minerals, which are made of calcium cations with different phosphate anions such as orthophosphates, metaphosphates or pyrophosphates. TCP is practically insoluble in water; insoluble in ethanol, soluble in dilute hydrochloric and nitric acid. It has three crystalline polymorphs α, α' and β. The α and α' states are formed at high temperatures. The α-tricalcium phosphate (α-TCP, $\alpha\text{-}Ca_3(PO_4)_2$) is receiving growing attention as a raw material for several injectable hydraulic bone cements, biodegradable bioceramics and composites for bone repair [46]. Tricalcium phosphate materials mostly behave like osteoconductive materials, which permits bone growth on their surface or into pores, channels, or pipes. It is a resorbable phase. Calcium phosphate exhibits some good properties to support bone growth [47]. The major field of applications are a) bone implant and replacement applications [48] and b) tissue engineering [49].

2.2.3 Hydroxy-Apatite (HAP): Hydroxyapatite (HAP) has been widely used as a biocompatible ceramic in many areas of medicine, but mainly for contact with bone tissue, due to its resemblance to mineral bone. HAP has exceptional biocompatibility and bioactivity properties with respect to bone cells and tissues. As a result of excellent favorable osteoconductive and bioactive properties, it is widely preferred as the biomaterial of choice in both dentistry and orthopaedics [50, 51]. The hydroxyapatite has a few favorable bioactive and osteoconductive properties which help in rapid bone formation, with a strong biological fixation to bony tissues. It also has very low mechanical strength and fracture toughness, which is an obstacle to its applications in load-bearing areas [52].

Due to its outstanding properties, the HAPs are employed in a variety of applications. They are [53]:

1. Bone tissue engineering, bone void fillers for orthopaedic, traumatology, spine, maxillofacial and dental surgery, orthopedic and dental implant coating,
2. Repair of mechanical furcation perforations and apical barrier formation,
3. Desensitizing agent in post teeth bleaching,
4. Early carious lesions treatment, and drug and gene delivery.

Biomedical Applications of Hydroxyapatite Nanoparticles [54] include

a. Bone regeneration and bone tissue engineering applications [55, 56]
b. Osteoblast and dental adhesion [57, 58]
c. Repair of dental enamel [59]
d. Controlled - release carrier of bone morphogenetic protein [60]
e. Intracellular Bio-imaging [61]
f. Photocatalytic applications [62]
g. Antibacterial applications [63]
h. Drug Delivery Systems.

HAP can incorporate the drug molecules either physically or chemically so that the drug retains intact until it reaches to the target site. It could also gradually degrade and then deliver the drug in a controlled manner over time [64, 65].

2.2.4 TCP+HAP: TCP and HA are used together since they both have bioactiveness and resorbability. Pure HA or TCP are not osteoinductive. Sintered hydroxyapatite-tricalcium phosphate (HA-TCP) ceramic material has more biomedical applications [66].

2.2.5 Si Substituted HAP: Silicon (Si) substitution in the crystal structures of calcium phosphate (CaP) ceramics such as hydroxyapatite (HAP) and tricalcium phosphate (TCP) generates materials with superior biological performance. Silica is an essential trace element required for healthy bone and connective tissues. It influences the biological activity of CaP materials by modifying material properties. Silica has direct effects on the physiological processes in the skeletal tissue [67 - 69]. The two main applications of silica-based materials in medicine and biotechnology are seen in bone-repairing devices and for drug delivery systems [70 -72].

2.2.6 Calcium Sulphate and Carbonate: Calcium sulfate (CS) is well-tolerated when used to fill bone defects and undergoes rapid and complete resorption without eliciting any significant inflammatory response. It is also used as a vehicle to deliver antibiotics. It is a good pharmacologic agents [73]. It has found wide use in orthopedics and dentistry, and has been used in a variety of clinical applications, including the periodontal defect repair, the treatment of osteomyelitis, sinus augmentation, and as an adjunct to dental implant placement [74, 75]. It has been found widely used in orthopedics and dentistry [76]. Calcium Sulphate Ceramics is a promising material for spinal cord scaffold fabrication. Since it is biodegradable, it has sufficient strength, and allows loading [77 - 80].

2.2.7 Bioactive Glasses (BG): Bioactive glasses are considered as attractive materials for biomedical applications. Materials consisting of calcium, phosphorous and silicate are classified as Bioactive Glasses (BG). These BGs are dense and hard. Most of the bioactive glasses have the characteristics of osteointegration and osteo-conduction. Bioactive glasses (BG) show great promise for bone tissue engineering based on their key properties, *e.g.* biocompatibility, bio-degradability, osteo-conductivity as well as osteogenic and angiogenic potential, which make them excellent candidates for bone tissue scaffolds and bone substitute materials. One of the most interesting features of BG is their ability to bond both to soft and hard tissues, depending on their composition [81].

Bioactive glass coatings are used for orthopaedic metallic implants [82]. A new class of bioactive glass, referred to as mesoporous bioglass (MBG), was developed 7 years ago, which possess a highly ordered mesoporous channel structure and a highly specific surface area [83]. Tissue engineering and Coatings for orthopaedic application are very promising fields in nanomedicine.

2.2.8 Bioactive Glass Ceramics: The recent studies include the development of bioactive biomaterials for bone regeneration. Development of sintered Na-containing bioactive glasses, borate - based bioactive glasses, and those doped with trace elements like Cu, Zn and Sr have been employed for bone tissue engineering [84].

2.2.9 Titania-Based Ceramics: Titanium comes under the category of Technical ceramics. The technical ceramics are divided into oxides and non-oxides like Aluminium Oxide, Ceramics, Carbide Ceramics, Nitride Ceramics, Oxide Ceramics, Silicon Carbide Ceramics, Silicon Nitride Ceramics, and Zirconium Ceramics Dioxide. The fact that titanium is strong, light, non-toxic and does not react without bodies makes it a valuable medical resource and used to make surgical implements and implants, such as hip joint replacements that can stay in place for up to 20 years. Although other photocatalytic materials are available, researchers have found that titanium dioxide provides the best performance in sunlight. Titanium nanomaterials has been clinically successful as an orthopedic or dental implant material.

2.2.10 Zirconia Ceramics: Zirconia Ceramics include Zirconium Dioxide Ceramics / Zirconia Ceramics / ZrO_2. Zirconium dioxide nanoparticles appear in the form of a white powder. It is non-magnetic and highly resistant against acids. It has a high thermal stability and has been proven to have excellent compatibility with bones and the surrounding connective tissue. The zirconium dioxide nanoparticles are non-toxic to the environmental organisms. The field of dentistry makes use of its special properties for manufacturing corona frames and bridge frames, tooth root studs, and metal-free dental implants. The major applications include

a) Coatings for metallic orthopaedic implants [85]
b) Stabilize Hydroxyapatite [86]
c) Dentistry [87].

2.2.11 Alumina Ceramics: Technical Ceramics includes mainly includes Aluminium oxides. It has very outstanding physical stability due to its high melting point (2050 °C), the highest hardness among oxides. It is strong and heat-resistant. It is the most widely used as the best-known fine ceramic material. The major applications of aluminium oxide ceramics include,

a) Dentistry
b) Anthroplasty
c) Treatment of hand and elbow fractures and
d) Antimicrobial activities [88]

2.2.12 Ceramic Polymer Composites: Ceramics have been successfully used for several decades for orthopædic prostheses. Ceramic composites are materials made from two or more constituent materials with significantly different physical or chemical properties. Currently, composites of polymers and ceramics are being developed with the aim to increase the mechanical scaffold stability and to improve tissue interaction. Limitations also exist with the difficulties of commercialisation, due to the scalability and the cost/benefits ratio [89]. A variety of bioactive composites have been investigated over the last two decades as substitute materials for diseased or damaged tissues in the human body. These ceramic nanobiomaterials are mainly used in, bone tissue engineering [91, 92], dentistry [93 - 98] and hip joint replacements [99].

2.2.13 Other Ceramic Nanobiomaterials: Magnetic oxides are also used in association with ceramic nanomaterials for therapeutic drug, gene and radionuclide delivery, cancer therapy and as contrast enhancing agents [100].

CONCLUSION: Applications of nanotechnology in several areas of biomedical fields have provided a lot of opportunities and possibilities for the future of nanomedicine. There are wide range of ceramic materials like clay minerals, cement, and glass used for various applications. Biocompatible Ceramics, also known as bioceramics, are mainly used for bone, teeth and other medical applications. The bioceramics have good biocompatibility, osteo-conductivity, osteoinductivity, biodegradability, resorbability, and hydrophilicity. the widely used ceramic nanobiomaterials are Calcium Phosphate (CaP), Tri-Calcium Phosphate (TCP), Hydroxy-

Apatite (HAP), TCP+HAP, Si substituted HAP, Calcium Sulphate and Carbonate, Bioactive Glasses, Bioactive Glass Ceramics, Titania-Based Ceramics, Zirconia Ceramics, Alumina Ceramcis and Ceramic Polymer Composites.

It is found that all these have shown a lot of applications in nanomedicine, orthopedics, dentistry, bone regeneration, tissue development and other biomedical activities in human body. Ceramic nanobiomaterials have excellent applications in several areas of health and medicine, and have a promising future in all commercial applications of nanotechnology.

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