Chapter 1

Introductory Chapter: The Testament of Hydroxyapatite: New Prospects in Regenerative Medicinal Treatments

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Additional information is available at the end of the chapter

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1. A terse testament of hydroxyapatite

The term 'Hydroxyapatite (HAp)' is a naturally occurring mineral and chemically identical to the mineral constituent of bones and solid tissues of mankind and mammals. As a mineral species, apatite was first known in 1786 by "the father of German geology" Abraham Gottlob Werner (1750–1817) and entitled by him on or after the antediluvian Greek *απατάω* (apatao)—"to mislead" or "to deceive" since it had earlier been does not specify one chemical opus. Though, the word "apatite" was revealed in the 1990s and is denoted as calcium orthophosphate, which would be a very infrequent heterogeneity of tourmaline, beryl and other stones [1]. The period of HAp in reformative science backdate to 1950s [2] furthermore for the filling of the bone defects, the bioceramics might be used as an inert scaffold. The history related to calcium orthophosphates dates back to 1770 [3] the mistaken for other minerals, such as beryl, tourmaline, chrysolite, amethyst, fluorite, etc., [1, 4, 5]. Currently, apatite is the term for a group of minerals with the same crystallographic structure and older history till 1950 could be delivered somewhere else in the published literature [6, 7]. On the basis of thorough literature survey of HAp, since 1950 in connection to its properties, production, composition and its applications were extensively studied and its usage in medicinal disciplines contributes many breakthroughs in contemporary technological developments in consideration with the interaction of materials on active species [8]. In the origin, HAp was used for grafting, which might not have reaction with neighbouring living cells. Far ahead, the development would change to the responsive nature of the material, also for the growth of bone the reactive material pretends as a conductive scaffold [7]. In recent trend, developing fabrication technology with the dawn of recognizing of regenerative medicinal growth in the field of nanotechnology and have transformed the appearance of bioceramics to a dissimilar facet [9–14].

S. No.	Methods/techniques	Outcome	Drawback	Refs.
1.	Dry	Well-crystallized	High temperature (1050°C in air)	[15, 16]
2.	Wet	High-yield, cost-effective, simple technique, and suitable for various pressure conditions	Non-crystalline and impure phase	[17]
3.	Co-precipitation	Crystalline, high-yield, cost-effective, template-assisted & various temperatures conditions	Requires high temperature annealing to yield product	[18–20]
4.	Sol–gel	Simple technique, low cost, crystalline nature	Dependent on solvent, the temperature and pH	[21, 22]
5.	Emulsion	More efficient, simple and particle agglomeration is less, Suitable for various surfactants, temperature conditions.	Dependent on ratio of aqueous and organic phases, pH and temperature	[23, 24]
6.	Hydrolysis	Simple technique, particle agglomeration is little high, sources are texture dependent	Precursors depend strongly on pH and temperature	[25]
7.	Hydrothermal	Highly crystalline micro or nano-sized structures, well-controlled morphology and porosity	Requires constant and uninterrupted temperature and pressure conditions	[26, 27]
8.	Alternate energy input (low-energy plasma spray)	Uniform thickness, good crystallinity, well-controlled morphology, porosity, micro hardness, and fracture toughness	Requires constant, uninterrupted temperature and pressure conditions. High temp. withstanding substrates and good cleaning process	[28]
9.	Microwave (MW)-assisted	Yield of perfectly, highly crystalline, homogeneous size, porosity and morphology	Requires constant, uninterrupted temperature conditions to yield product	[29]
10.	Ball-milling	Simplicity, reproducibility, and large-scale production	Requires high temperature annealing to yield product and little agglomeration	[30]
11.	Sonochemical	Nanosized products, elicits perfect control of morphology, porosity and size	Requires constant, uninterrupted temperature and pressure conditions.	[31]
12.	Others: a. Solvothermal process b. Spray pyrolysis	Yield of perfectly homogeneous size crystalline morphology	Requires organic solvents and hot zone of an electric furnace	[32, 33]

Table 1. Shows the key methods for the synthesis of hydroxyapatite (HAp).

Hydroxyapatite, HAp is an elementary calcium phosphate, and its chemical formula is $Ca_{10}(PO_4)_6(OH)_2$ present as main material of teeth, bones and mineral certainly with high bi-affinity. It is composited by below methods, and it is also applicable in various fields including biomaterials. In the meantime, amorphous HAp is no longer stable and could dissolve reliant on usage environment; a sintered body has been effectively used as a material in general. And, the sintered body could not dissolve so much owing to its high crystallinity. Because fusion and grain growth of each particle arose on its process stage are foreseeable, it has been hard to control configuration and grain diameter on a nanoscale impartial like initial particles of amorphous HAp. The synthesis of HAp, with its numerous morphologies, structures, and textures, has enthusing a prodigious deal of interest in academic and industrial research for numerous heterogeneous catalysis applications. In the past three decades, a numerous synthetic routes for producing HAp powders have been developed. Productions of HAp powders are classified under four different methods are enumerated in **Table 1** [34].

2. Topical advancements in reformative medicinal treatments in the new prospects of application of nanotechnology

HAp is considered as bioceramics that signifies the enormous amount of regenerative scion material persisting in the flea market. HAp is analogous to the bony-like apatite structure and is considered to be an important inorganic constituent for bone. However, in the organic matrix HAp is circumscribed, so that the existences of HAp in the normal bone in the form of extra inorganic trace elements [3]. Ailments related to the ablative and bone surgical treatment known as the abscission or removing a part of the bone, which ultimately needs renovation through various available measures. Since, the HAp has found increasing demand in regenerative medicine as a possible auxiliary material second to auto graft. HAp could also be used in occurrences, wherever the defects or voids present in bone. This process leads to curing of blocks, or beads by employing powders of the mineral being positioned into or on the defected parts of bone. From the time when it is bioactive, it reassures the bone to spot on the problem for further orientation of growth and this procedure may perhaps be an alternate to bone or dental implants, means that it can integrate into bone or dental structures and support growth with the no breaking down or dissolving in the human body. Though, HAp is still used for this purpose today and it is also applicable for other purposes too. Numerous advancements in nanotechnology oriented reformative medicine for the overhaul or improvement of dented tissues function in several organ systems. However, most studies concern the goings-on of topical advancements in nanomaterials used in regenerative medicinal treatments [35], as summarized in **Table 2**, with some more literatures in HAp, on the basis of regenerative medicine in various organ systems.

Applications of nanotechnology in regenerative medicine would require the entire prospective to reform tissue repair and regeneration [35]. Till now, to trigger the regeneration process the growth of impeccable nanomaterials accomplished of transfer signals to the diseased or damaged cells and tissues it remnants a dare. By employing nano-HAp based materials in regenerative medicine is a material of significant relate to the safety in relations to human health aspects, for the reason that this area is still in its developing platform. Erstwhile to human health based applications, a systematic research work in relevance to the noxious effect of these nanomaterials would be carrying through in excessive manner. In conclusion, at the nanoscale level to make acquainted about the original mechanisms of cell-biomaterial surface interfaces, and further implement the findings from bench to bedside, a manageable teamwork flanked by the scientists and clinicians is of highly necessary for the societal benign.

S. No.	Body part	Nanomaterials	Outcome (type of study)	Refs.
1.	Bone	Poly(epsilon caprolactone)	Improved cell attachment, proliferation, differentiation, and mineralization of osteoblasts (in vitro)	[36]
			Lineage restriction of progenitor cells by topographical cues (in vitro)	[37]
		Nanoscaled calcium phosphate	Large-sized blood vessel infiltration leads to bone formation (in vivo; canines)	[38]
		HAp-coated titanium	Enhanced and accelerated osseoimplant integration (in vivo; rats)	[39]
		Hybrid biomimetic collagen-hydroxyapatite composites	Crosslinking reactions for hard tissue engineering application with designed bioactive properties	[40]
		Nanostructured beta tri-calcium phosphate-coated over poly (lactic acid)	Enhanced osteoconductivity of scaffold (in vitro) and heterotrophic bone formation (in vivo; rabbits)	[41]
		Carbon nanotubes	Extracellular matrix calcification (in vitro); lamellar bone regeneration (in vivo; mice)	[42]
			Porous bone formation in bone defect (in vivo; rats)	[43]
		Silica nanofibers	Proliferation and maturation of MG63 cells (in vitro)	[44]
2.	Cartilage	Pentosan poly sulfate in poly (ethylene glycol) HA	Formation of cartilage like tissues by mesenchymal progenitor cells (in vitro)	[45]
		PVA/PCL [poly(vinyl alcohol) poly(caprolactone)]	Proliferation and chondrogenic differentiation of MSCs (in vitro); improved healing of cartilage defects (in vivo; rabbits)	[46]
		3D porous polycaprolactone (PCL)-hydroxyapatite (HAp) scaffold combined with MC	Improves the biological performance of 3D PCL-HAp scaffold	[47]
		POSS–PCU [polyhedral oligomeric silsesquioxane with polycarbonate polyurethane]	Enhanced survival, proliferation, and chondrogenic differentiation of adipose tissue derived stem cells (in vitro)	[48]
			Enhanced growth and proliferation of nasoseptal chondrocytes (in vitro)	[49]
3.	Peripheral nervous system	Electrospun collagen/poly (lactic-co-glycolic acid)	Axon regeneration, myelination, and action potential propagation (in vivo; rats)	[50]
		Poly(L-lactide-co-glycolide)/ chitosan/hydroxyapatite(PLGA/ chitosan/HAp)	In vivo application of PLGA/chitosan/ HAp conduits for nerve regeneration	[51]
		POSS–PCU–MWCNT	Novel biomaterial capable of electronic interfacing with tissue holds potential to promote nerve regeneration	[52]

S. No.	Body part	Nanomaterials	Outcome (type of study)	Refs.
4.	Central nervous system	Small interfering ribonucleic acid (Si-RNA) chitosan nanoparticles	Increased delivery of drugs by crossing BBB (blood–brain barrier) (in vivo; rats)	[53]
		Nano-HAPs on the growth of human glioma U251 and SHG44 cells in vitro and in vivo	Nano-HAPs have an obvious antineoplastic function in vitro and in vivo. It reduces the poisonous, adverse reactions to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), strongly cooperate with certain other chemotherapy drugs, decrease the toxicity, and might become a new clinical antineoplastic drug.	[54]
5.	Myocardial tissue/myocardial infarction (MI)	Insulin-like growth factor-1 (IGF-1) with poly(lactic-co-glycolic acid)	Increased protein kinase B phosphorylation and reduced infarct size (in vivo; mice)	[55]
		Electrospun (hb/gel/fb) [poly(hemoglobin/gelatin/fibrinogen)]	Cardiomyogenic differentiation of mesenchymal stem cells (MSCs) (in vitro)	[56]
		PGS [poly(glycerol sebacate)]	Increased transplant cell retention and survival (in vitro)	[57]
		Gold nanoparticles-loaded hybrid nanofibers	Cardiomyogenic differentiation of MSCs; superior biological and functional properties (in vitro)	[58]
		Calcium hydroxyapatite–based dermal filler into the infarct	Injection of an acellular dermal filler into an MI immediately after coronary occlusion reduces early infarct expansion and limits chronic LV remodeling.	[59]
6.	Skin	Silver nanoparticles	Reduced inflammation and promotion of wound healing (in vitro)	[60]
		Plasma-treated electrospun poly(lactic-acid) co-poly(epsilon caprolactone), and gelatin	Increased fibroblast proliferation and collagen secretion (in vitro)	[61]
		Titanium abutment (control) and one HA-coated abutment (case) interface	The HAp-coated abutment can achieve integration with the surrounding skin.	[62]
		Rosette nanotubes with PHeMA [poly(2-hydroxyethyl methacrylate]	Increased keratinocyte and fibroblast proliferation (in vitro)	[63]
7.	Eye	Polydimethylsiloxane	Topographical cue for formation of functioning corneal endothelium (in vitro)	[64]
		HAp, polytetrafluoroethylene (PTFE), polyhydroxyethyl methacrylate (HEMA), and glass (control)	Improving the initial cell adhesion environment in the skirt element of keratoprostheses may enhance tissue integration and reduce device failure rates.	[65]
		Super paramagnetic nanoparticles	Increased gene expression and neurite growth, subcellular organelle localization, and nano therapeutics delivery (in vitro)	[66]

S. No.	Body part	Nanomaterials	Outcome (type of study)	Refs.
8.	Lung	Deferoxamine	Regeneration of microvascular anastomosis in airways (in vivo; mice)	[67]
		HAPNs in both A549 and 16HBE cells	HAPNs might be a promising agent or mitochondria-targeted delivery system for effective lung cancer therapy.	[68]
		101F6 (tumor suppressor gene) nanoparticles	Increased tumor cell lysis (in vitro and in vivo; mice)	[69]

Courtesy: Reproduced from Ref. [35] with permission from Dove Medical Press, copyright 2014.

Table 2. Topical advancements in nanomaterials used in regenerative medicinal treatments [35].

3. Conclusion

In summary, hydroxyapatite is one of the well-studied biomaterials in the medical field for its established biocompatibility and for being the main content of the mineral part of bone, teeth and various organ systems. However the fact demonstrates that it has been more imperious towards ground-breaking research against novel medical applications for the cause of the society. It has all the typical topographies of biomaterials, such as, bioactive, biocompatible, non-toxic, osteoconductive, non-immunogenic, non-inflammatory, bioceramic coatings, bone void fillers for orthopedics, dental implant coating, HAp thin films, and resemblance to the inorganic component of human beings. In the midst of the major remarkable progress are in various fields of molecular biology, biochemistry, bioinformatics, microbiology, genetics, cytometry, medical diagnostics, drug & gene delivery, and the addition of nanotechnology are the most important worldwide challenges so far. The dispute of novel spectroscopic/microscopical innovation contains interdisciplinary areas that might endure to be enhanced for these innovative global developments in x-ray imaging, spectral imaging, time-correlated single-photon counting, fluorescence quenching, endo- and exo-thermic reaction rates, kinetic chemical reaction rates, *In vitro* and *In vivo* studies, visual implants, neurology and non-invasive optical biopsy. Thus, studies towards unique nano-hydroxyapatite used in regenerative medicinal treatments might give way to mechanisms of cell-biomaterial relations at the nanoscale level that may feasibly turn out to be the upcoming forerunners to human applications in the embryonic stage.

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Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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