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Classifications, surface characterization and standardization of nanobiomaterials

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Abstract

Biomaterials metrology and standardization are necessary for suitable use in medical industries. Nanobiomaterials are used in living creature body, taking into account their biocompatibility, nontoxic and non-carcinogenic effects. These requirements are conditions imposed on many available engineering materials and may lead to eliminate some of them. Thus, the Nanobiomaterials must have accurate and precise assessment to possess adequate physical and mechanical properties and surface characteristics to serve as augmentation or replacement of body tissues. This paper discusses classification and surface assessment of different biomaterials and their reference standards according to proposed development strategy in micro- and nano-scale for use in bioengineering applications in details.

Keywords: *Biomedical engineering, standards, developed strategy, metrology; surface characteristics.*

1 Introduction

Metrology is the measurement science and its applications in any field, especially in engineering materials. The special material used in medical engineering is called biomaterial. Biomaterial is a material implanted stable to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body [1]. Biomaterial can partially or totally replaces one or more parts of the body. Many researches are potentially going forward by using biomaterials in the medical field. Medical implants and devices are still the main and most valuable research area of the biomaterials science and engineering [2]. Performance of biomaterials in the body can be defined in several ways due to the rapid development and expansion of biomaterials science. Biomaterials classifications are necessary for suitable use in medical industries according to reference standards. It was found in synthetic and natural types while these structures may be found in solid and sometimes liquid. Those used in medical artificial organs are designed to resolve partially or totally of biological function when failure in the organ happens (disorder). There are three generation terms in which a biomaterial described in or classified into will represent the tissue responses [2-5]:

i- First generation is called "Bioinertness" (1950's-1960). Bioinertness means no trigger to any reaction in the host neither rejected nor recognized. It combines the ability to be tolerated by the body with mechanical properties sufficient to withstand the anticipated physiological stress. While providing an effective immediate solution for many patients, the outcome is often time-limited. It includes natural and synthetic biomaterials.

ii- Second generation called "Bioactivity" (1970's-2000). This generation ensures a more stable performance in a long time or for the period you want. The examples of this generation are such as biodegradable polymers, hydrogels, bioactive and biodegradable ceramics.

iii- Third generation is called "Regeneration functional tissue" (2000's-Present). This continuous generation deals with tissue engineering scaffolds. It can be chemically degraded or decomposed by natural effectors (weather, soil bacteria, plants, animals) with micro- or nanotechnology, micro- or nanofabrication.

Therefore, biomaterials metrology and standardization are necessary for suitable use with biological systems. So, the nanobiomaterial must meet the specific requirements during accurate and precise assessment to satisfy the physical and mechanical properties and surface characteristics.

2 Classification of biomaterials

Actually, there are different common classification types of biomaterials implanted with human biological systems. These types can be classified into two main categories. The first category is based on *natural biomaterials*, while the second category of biomaterials is based on *synthetic engineering biomaterials*. With the advanced technology of engineering biomaterials tissues, a new third category is created, called *combined of biomaterials.* This type plays between these two categories. Nanobiomaterials are new term means materials constituent from one or more elements having dimensions not more than 0.1 µm. From the authors view, Fig.1 shows new simple block diagram of nanobiomaterials classification, where nanobiomaterials are new term constituent one or more elements of dimension not more than 100 nm. Nanobiomaterials are produced from Allah creatures as a natural cosmic (not artificial) or from manmade innovation (artificial).

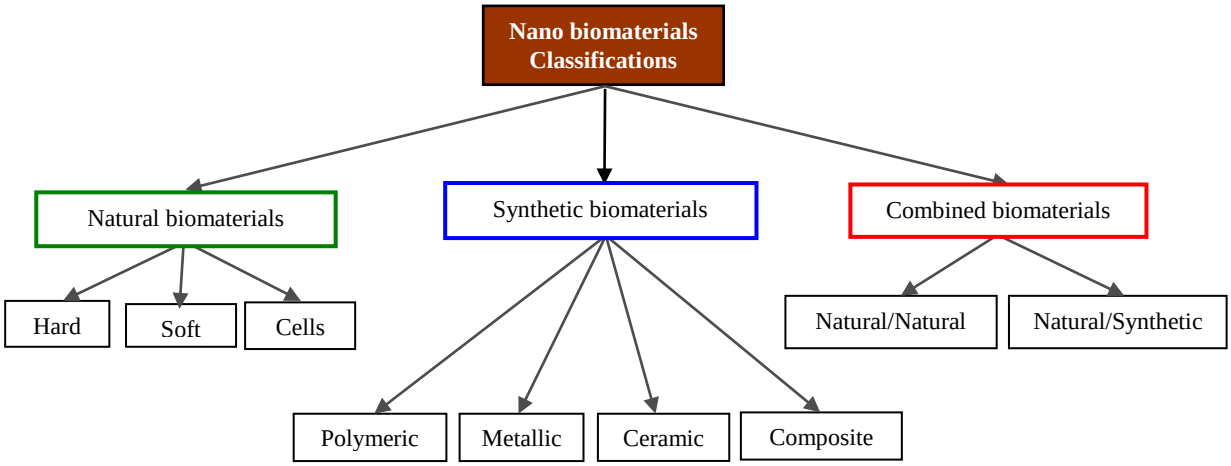


Fig.1: Classifications of nanobiomaterials.

2.1 Natural biomaterials

Human natural biomaterials are materials that contain similar architectures to the native tissue they are replacing with donor natural elements needed for proper tissue reconstruction. Natural biomaterials in the human biological system are classified into three types (soft, hard and cells). The natural soft tissue likes skin, tendon, pericardium, cornea, nerve, muscle and so on. The natural hard tissue is a kind of connective tissue likes bone, collagen, dentine and cuticle. While the natural blood and lymph cells are the stem cells. Natural materials (hard or soft) have important role in tissue engineering and organ regeneration. The use of natural biomaterials has typically required chemical or physical pretreatment aimed to: (1) Preserving the tissue by enhancing the resistance of the material to enzymatic or chemical degradation, (2) reducing the immunogenicity of the material, and (3) sterilizing the tissue.

The main advantage of natural biomaterials provides mechanical and shape compatibility compared to synthetic scaffolds [6]. The advantages and disadvantages of natural biomaterials (for example natural polymers) are shown in Table 1. Natural polymers include extracellular matrix (ECM), proteins derivatives, and some materials derived from plants and seaweed that help to build up the required material [7-8]. An example of natural polymer is rubber, that made mostly from the latex of the Hevea brasiliensis tree and the chemical formula is the same as that. Natural rubber was found to be compatible with blood in its pure form [9]. Many advanced nanometrology techniques are used for characterization of nanobiomaterials [10]. The structure of natural polymers and some relational functions between cells, polymers, and tissues are also shown in Fig.2 [7].

Table 1: The advantages and disadvantages of natural polymers [7]

Advantages	Disadvantages
No problem with toxicity or foreign body response.	A major issue is immunological reaction. Body's immune system recognizes foreign material and tries to destroy it.
Can function biologically at molecular level, not just macroscopic level.	High natural variability.
If desired, natural degradation can occur in the body via natural enzymes. Can also add cross-links to make less degradable.	Structurally more complex than traditional materials. Technological manipulation is more elaborate.

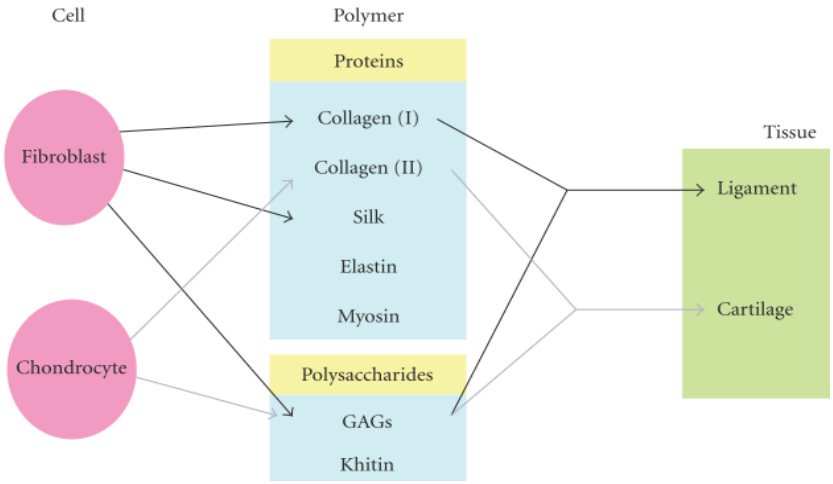


Fig.2: Structure and function of natural polymers

2.2 Synthetic biomaterials

There is a big demand for biomaterials to assist; replace organ or function for improving quality of life. Synthetic biomaterials are artificial engineered materials, used to replace or restore function to a body tissue and continuously directly or indirectly in contact with body fluid conditions. One of the primary reasons that synthetic biomaterials are used is to physically replace hard or soft tissues that have become damaged or destroyed through some pathological process [5]. Synthetic engineered biomaterials can be classified into four main types: metallic biomaterials, ceramic biomaterials, polymeric biomaterials and composite biomaterials. Metallic biomaterial includes stainless steel (St 316L), cobalt-chromium-molybdenum based alloy (Co-Cr-Mo), titanium alloy (Ti), gold and platinum. The applications of metallic biomaterials are used in many fields such as: cardiovascular (stent, heart artificial valve), orthopedic like bone fixation (plate, screw pin), and in artificial joints and dentistry (orthodontic wire, filling) [11]. Ceramic biomaterials include: alumina (AL_2O_3), zirconia (ZrO_2), carbon calcium aluminates (Ca (Al_2O_4)). An example of AL_2O_3 application is its use in vertebrae spacers, extensors (which is any number of specific muscles in arm, hand, leg and foot) and in dental applications like orthodontic anchors [12]. Polymeric biomaterials like ultra-high molecular weight polyethylene (UHMWPE), silicon (Si), polyurethane (PU). UHMWPE material is used for artificial joints and bio-absorbable polymers for surgical applications and adhesives for medical applications. Composite biomaterials contain carbon fiber/polyetherether-ketone (CF/PEEK), carbon fiber/ultra-high molecular weight polyethylene (CF/UHMWPE) and carbon fiber/ polymethylmetacrylate (CF/PMMA). The implementation of composite biomaterials into the medical field using continuous carbon fiber and PEEK as matrix (CF/PEEK) initiates the development of orthopedic implants with outstanding fatigue properties and optimized visualization in various imaging technologies [13].

2.2.1 Metallic biomaterials

Implants of metallic biomaterials are fabricated from a wide variety of metallic materials include stainless steel, cobalt-chrome (Co-Cr) alloys and titanium alloys. The biocompatibility of the metallic implant is of considerable concern because these implants can corrode in an in-vivo environment. The consequences of corrosion are the disintegration of the implant material, which will weaken the implant and the harmful effect of corrosion products on the surrounding tissues and organs [14]. Stainless steel is the generic name for a number of different steels used primarily because of their resistance to a wide range of corrosive agents due to their high chrome (Cr) content. It has several types and the most mainly used for manufacturing implants is stainless steel 316L. Stainless steel implants are often degraded due to pitting, crevice, corrosion fatigue, fretting corrosion, stress corrosion cracking and galvanic corrosion in the body. Stainless steel has been used for wide range of application due to easy availability, lower cost, excellent fabrication properties, accepted biocompatibility and great strength also widely used in traumatological temporary devices such as fracture plates, screws and hip nails [15]. Cobalt-chromium (Co-Cr) alloys can be basically categorized into two types; one is the cobalt-chromium-molybdenum alloy (Co-Cr-Mo) (which is usually used to cast a product) , while the second one is cobalt-nickel-chromium-molybdenum (Co-Ni-Cr-Mo) alloy (useful in surgical implant). The Co-Cr-Mo alloy has been used in dentistry for long time and recently in making artificial joints. The wrought cobalt-nickel-chromium-molybdenum (Co-Ni-Cr-Mo) alloy is an excellent wear resistance, and has been used for making heavily loaded joints such as ankle implants [16]. Cobalt-based alloys are highly resistant to corrosion even in chloride environment due to spontaneous formation of passive oxide layer within the human body environment. These materials have superior

mechanical properties such as high resistance to fatigue and cracking caused by corrosion with a good wear resistance. Also, they are not brittle because they have a minimum of 8% elongation. Titanium Ti and Ti Alloys implants date back to the late 1930s. There are three structural types of titanium alloys: Alpha (α), Alpha-Beta (α-β) and Beta (β).The β phase in Ti alloys tends to exhibit a much lower modulus than α phase and also it satisfies most of the other necessities or requirements for orthopedic application. Ti alloys due to the combination of its excellent characteristics such as high strength, low density (approximately 4700 Kgm^{-3}), high specific strength, good resistance to corrosion (due to the formation of an adhesive TiO_2 oxide layer at the surface), complete inertness to body environment, enhanced biocompatibility, moderate elastic modulus of approximately 110 GPa are a suitable choice for implantation. Ti and its alloy also have this ability to become tightly integrated into bone [15]. Porous Nickel-Titanium (NiTi) has been considered as one of the promising biomaterials in surgical implants which have been used in medical fields in Russia and some other countries. The porous materials have many applications, ranging from spinal fixation to acetabular hip prostheses, dental implants, permanent osteosynthesis plates. Porous biomaterials are divided into two categories: solid substrate with porous coating and integral porous body. Porous NiTi has good biocompatibility, comparable to conventional porous stainless steel and titanium implant materials. Metallic biomaterials have several advantage and disadvantage as shown in Table 2 according to its application on biomedicine.

Table 2: Advantages and disadvantages of metallic biomaterials [2]

Advantages	Disadvantages
High strength	High modules
High hardness	High corrosion
Fatigue & impact resistance	High wear rate and friction coefficient
Easy fabrication	High density (low strength /weight ratio)
Easy to sterilize	Metal ion sensitivity and toxicity
---	Electrical and thermal conductivity

2.2.2 Ceramic biomaterials

It is a nonmetal structures and has have traditionally been synthesized by fusion or sintering of complex mixtures of inorganic compounds such as metal oxides [17]. Nonabsorbable or relatively bioinert bioceramics maintain their physical and mechanical properties while in the host. They resist corrosion and wear and have all the properties. An example of bioceramics like alumina extensive research on Al_2O_3 was done during the 1950s and 1960s. It was used as a coating for the articulating surface in total hip replacement as it has very favorable wear and corrosion properties as well as good biocompatibility. However, its use was discontinued after complaints of post-operative pain. Hydroxyapatite (HAp) is well known as a valuable material for bone. It is one of a few bioactive implantation materials capable of creating a direct bond with bone tissue. Zirconia ceramics have several advantages over other ceramic materials, due to the transformation toughening mechanisms operating in their microstructure that can give to components made out of them, very interesting mechanical properties. The research on the use of zirconia ceramics as biomaterials started about twenty years ago. The use of zirconia to manufacture ball heads for total hip replacements (THR) but developments are in progress for application in other medical devices [17]. Carbons can be made in many allotropic forms: crystalline diamond, graphite, noncrystalline glassy carbon and quasi- crystalline pyrolitic carbon. Among these, only pyrolitic carbon is widely utilized for implant fabrication, it is normally used as a surface coating. It is also possible to coat surfaces with diamond. Although the techniques of coating with diamond have the potential to revolutionize medical device manufacturing, it is not yet commercially available [18]. The concept of using synthetic resorbable ceramics as bone substitutes was introduced in 1969**,** resorbable ceramics, as the name implies, degrade upon implantation in the host. The rate of degradation varies from material to material. Calcium Phosphate has been used in the form of artificial bone. This material has been synthesized and used for manufacturing various forms of implants, as well as for solid or porous coatings on other implants. Aluminum-calcium-phosphate (ALCAP) has insulating dielectric properties but no magnetic or piezoelectric properties. ALCAP ceramic is unique because they provide a multipurpose crystallographic system where one phase of the ceramic on implantation can be more rapidly than the others. ALCAP is prepared from stock powders of aluminum oxide, calcium oxide and phosphorous pent oxide. Coralline coral is a natural substance made by marine invertebrates. It is used as bone implants and selected on the basis of structural similarity to bone, coral provides an excellent structure for the in growth of bone. Tricalcium phosphate (TCP) ceramic is multicrystalline porous form of β-tricalcium phosphate (β-Ca_3 $(PO_4)_2$) has been used successfully to correct periodontal defects and augment bony contours. Zinc-calcium-phosphorous oxide (ZCAP) ceramic zinc is essential for human metabolism and is a component of at least 30 metalloenzymes**,** (ZCAP) was synthesized to repair bone defects and deliver drugs. Zinc-sulfate-calcium-phosphate (ZSCAP) ceramic is prepared from stock powders of zinc sulfate, zinc oxide, calcium oxide and phosphorous pent oxide. Ferric-calcium-phosphorous-oxide (FECAP) ceramic is prepared from powders of ferric (III) oxide, calcium oxide and phosphorous pent oxide. Bioactive or surface-reactive ceramics have the ability to form strong bonds with adjacent tissue, for example dense nonporous glasses, bioglass and

hydroxyapatites. The surface-reactive ceramics are used for coating of metal prostheses in reconstruction of dental defects for filling space vacated by bone screws, donor bone, excised tumors, and diseased bone loss. Also, it is used in replacing subperiosteal teeth [18]. A bioceramics for example, calcium orthophosphate-based is found in a variety of different applications throughout the body, covering all areas of the skeleton as dental implants, percutaneous devices and use in periodontal treatment, healing of bone defects, fracture treatment, total joint replacement, orthopedics, cranio-maxillofacial reconstruction, otolaryngology, ophthalmolo-gy, spinal surgery, and samples of calcium orthophosphate applications [19]. It is of great interest to know whether the inert ceramics such as alumina undergoes significant static or dynamic fatigue to determine the deterioration of ceramics. Even for the biodegradable ceramics, the rate of degradation in vivo is of paramount importance. The fatigue strength of alumina is reduced by the presence of water. This is due to the delayed crack growth, which is accelerated by the water molecules. Reduction in strength occurs if water penetrates the ceramic. Decrease in strength was not observed in samples which did not show water marks on the fractured surface. The technique used to fabricate the bioceramic device will depend greatly on the ultimate application of the device, whether it is for hard tissue replacement or the integration of the device within the surrounding tissue [18]. Table 3 illustrates the advantage and disadvantage of bioceramic materials [2].

Table 3: Advantage and disadvantage bioceramic materials

Advantage	Disadvantage
High compression strength	High modulus (mismatched with bone low)
Wear & corrosion resistance	Low strength in tension
Can be highly polished	Low fracture toughness (very brittle)
Bioactive/inert	Difficult to fabricate

2.2.3 Polymeric biomaterials

Synthetic polymeric materials have been widely used in medical disposables. The main advantages of the polymeric biomaterials compared to metal or ceramic materials are ease of manufacturability to produce various shapes (latex, film, sheet, fibers, etc.), ease of secondary process ability, reasonable cost and availability with desired mechanical and physical properties. The required properties of polymeric biomaterials are similar to other biomaterials that have biocompatibility, sterilizability, adequate mechanical, physical properties and manufacturability [2, 20]. Polymerization is a chemical process of condensation in order to link the small molecules and force them to lose their electrons and controlling the reaction temperature, pressure and time in the presence of catalyst. Because they are easily to be synthesized, only ten to twenty polymers are mainly used in medical device fabrications from disposable to long-term implants. The types and applications of polymers are as follows: Polyvinylchloride (PVC) is an amorphous, rigid polymer due to the large Cl,(chloride) to prevent the thermal degradation of the polymer, and applied as thermal stabilizers such as metallic soaps or salts. PVC sheets and films are used in blood and solution storage bags and surgical packaging.

Polyethylene (PE) is available commercially in five major grades: (1) high density (HDPE), (2) low density (LDPE), (3) linear low density (LLDPE), (4) very low density (VLDPE) and (5) ultra-high molecular weight (UHMWPE). HDPE is used in pharmaceutical applications, nonwoven-disposable. Laminated LLDPE is frequently employed in pouches and bags due to its excellent puncture resistance, and VLDPE is used in extruded tubes. UHMWPE has been used for orthopedic implant fabrications, especially for load-bearing applications such as an acetabular cup of total hip and the tibial plateau and patellar surfaces of knee joints.

Polypropylene (PP) can be polymerized by a ziegler-natta stereospecific catalyst which controls the isotactic position of the methyl group. Thermal and physical properties of PP are similar to PE. PP has an exceptionally high flex life and excellent environment stress-cracking resistance; hence it had been tried for finger joint prostheses with an integrally molded hinge design. PP is used to make disposable hypothermic syringes, blood oxygenator membrane, packaging for devices, solutions, drugs, suture, artificial vascular grafts and nonwoven fabrics. Polymethylmet-acrylate (PMMA) is a commercial and an amorphous material with good resistance to dilute alkalis and other inorganic solutions. PMMA is best known for its exceptional light transparency (92% transmission), high refractive index, and has good weathering properties as one of the most biocompatible polymers. PMMA is used broadly in medical applications such as a blood pump and reservoir and membranes for blood dialyzer. Polystyrene (PS) have a good surface properties and dimensional stability. It is used in clamps, blood dialyzers and diagnostic test kits [20]. Polyesters such as polyethyleneterephthalate (PET) are frequently found in medical applications due to their unique chemical and physical properties. PET is so far the most important of this group of polymers in terms of biomedical applications such as artificial vascular graft, sutures. Polyamides (Nylons) are known as nylons and are designated by the number of carbon atoms in the repeating units. Fluorocarbon polymers are best known as fluorocarbon polymer is polytetrafluoroe-thylene (PTFE), commonly known as teflon. Synthetic rubbers have been used for the fabrication of implants. Polyurethanes are usually thermosetting polymers where they are widely used to coat implants. Polyurethane rubbers are produced by a reaction between a prepared prepolymer chain with an aromatic to make very long chains possessing and give active

isocyanine groups for cross-linking. The application of biodegradable polymer is in biomedical area particularly in the field of tissue engineering and controlled drug delivery. Degradation is important in the biomedical area if the following conditions are met:

- The mechanical properties must match the application and remain sufficiently strong until the surrounding tissue has healed.
- The degradation time must match the time required.
- It is metabolized in the body after fulfilling its purpose.
- It is easily processable in the final product form with an acceptable shelf life and easily sterilized [3-21].

There are several biodegradable polymers such as polylactide (PLA), polyglycolide (PGA), poly(glycolide-co-lactide) (PLGA), poly(dioxanone), poly(trimethylene carbonate), poly(carbonate). They are used or tested on a wide range of medical applications due to their good biocompatibility, controllable biodegradability and relatively good process-ability [20]. Sterilizability of biomedical polymers is an important aspect of the properties because polymers have lower thermal and chemical stability than other materials such as ceramics and metals. Consequently, they are also more difficult to sterilize using conventional techniques. Commonly, sterilization techniques are dry heat, autoclaving, radiation and ethylene oxide gas. Table 4 shows main advantages and disadvantages of polymeric used in medical fields [2; 22-24]. Figure(3) shows some examples of polymeric applications in biomedical engineering.

Table 4: Advantage and disadvantage of polymeric biomaterials

Advantage	Disadvantage
Biodegradable	Leachable
Easy to manufacturing and produce	Absorb water & proteins
Tailorable properties	Surface contamination
Surface modification	Wear & breakdown
Immobilize Cells	Biodegradation
---	Difficult to sterilize

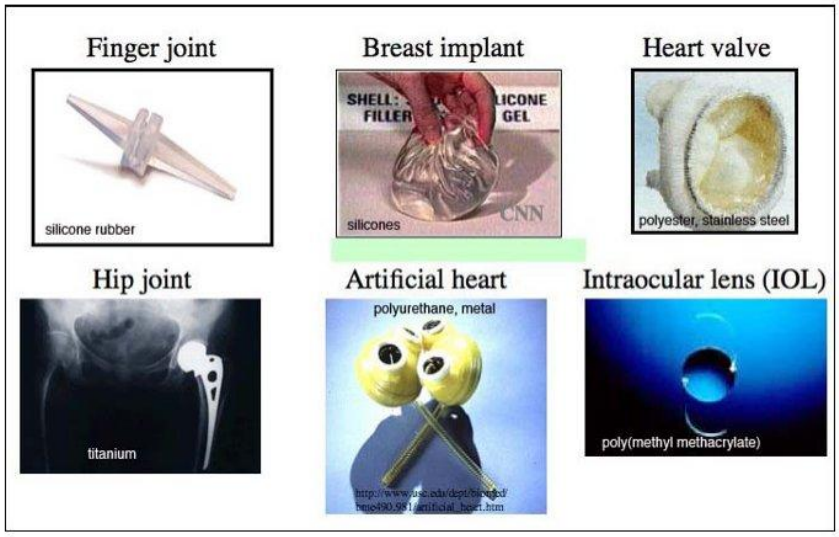


Fig.3: Polymers in biomedical engineering applications [25].

2.2.4 Composite biomaterials

The term "composite" is taken from its common form as a structure consisting of two or more distinct materials or phases, on a scale larger than the atomic. Properties such as the elastic modulus are significantly altered in comparison with those of a homogeneous material. Composite materials offer a variety of advantages in comparison with homogeneous materials. These include the ability for the scientist or engineer to exercise considerable control over material properties. There is a potential for stiff, strong, lightweight materials as well as for highly resilient and compliant materials. In biomaterials, it is important that each constituent of the composite be biocompatible. Some applications of composites in biomaterial applications are: (1) dental filling composites, (2) reinforced methyl methacrylate bone cement and ultra-high molecular weight polyethylene and (3) orthopedic implants with porous surfaces. The properties of composite materials depend very much upon structure. Composites differ from homogeneous materials in that considerable control can be exerted over the larger scale structure. The properties of a

composite material depend upon the shape of the heterogeneities, upon the volume fraction occupied by them and upon the interface among the constituents. The shape of the heterogeneities in a composite material depends on its categories. The principal inclusion of shape categories are: (1) the particle with no long dimension, (2) the fiber with one long dimensions and (3) the platelet or lamina, with two long dimensions [26]. Anisotropy is a characteristic of composite materials. The relationship between stress σ_{ij} and strain ε_{kl} in anisotropic material is given by the tonsorial form of Hooke's law equation as follows:

$$\sigma_{ij} = \sum_{k=1}^{3}\sum_{l=1}^{3} C_{ijkl}\,\varepsilon_{kl}$$

Where C_{ijkl} is the elastic modulus tensor.

Bone can be viewed as a composite of collagen with the principal organic component; hydroxyapatite, and the inorganic mineral component; water and small amounts of other organic phases. Improvement in regeneration has been observed in composite constructs mimicking the composition and structure of bone. Synthetic polymers used for bone regeneration include poly (lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic) acid (PLGA), polypropylene fumarate (PPF) and the polyhydroxy-alkanoates (PHAs).

Figure (4) shows combining polymer with ceramic creating bioactive scaffolds that enhance tissue formation with greater initial strength. A common methodology of fabricating ceramic-polymer composite scaffolds is promoting the deposition of a mineral layer on its surface from a solution with ion concentrations similar to that of human plasma [27]. Important advantages and disadvantages of biocomposites materials are presented in Table 5 [28].

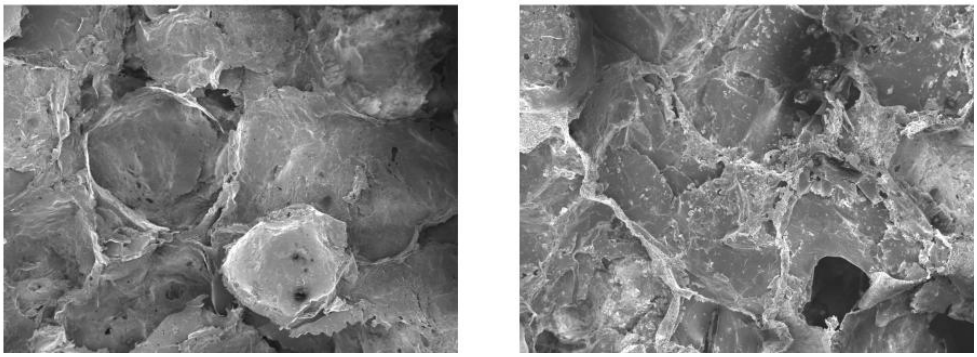


Fig.4: Typical macro surface structural of composite biomaterials use in bone tissue engineering: (a) poly-lacticco-glycolic (PLG) and two bioceramics; (b) PLGA-hydroxyapatite composites.

Table 5: Advantages and disadvantages of biocomposite materials

Advantages	Disadvantages
Good durability in small to moderate restorations	Low leakage if properly bonded
Moderate resistance to fracture in high load restorations	Recurrent decay depends on maintenance of tooth-material bond
Moderate resistance to wear	---

2.3 Combined biomaterials

During the last decades, researches reached to advanced form and dimensional stability of biomaterials. Using natural/synthetic combination or natural/natural is combination of biomaterials. The first form includes many combinations between natural/synthetic materials which is Hydroxyapatite (Hap)/Collagen (Col) bone in cylindrical dense form with central hole were implanted into segmental defect of tibia 20 mm in length as shown in Fig.5 [22; 29]. Aliphatic polyesters poly(lactic acid), poly(glycolic acid) and their copolymers used in sutures, drug-delivery systems and in tissue engineering. Also poly(hydroxy butyrate), poly(e-caprolactone) poly(alkylene succinates) and copolymers are used as biodegradable, as a matrix for drug-delivery systems, cell micro-encapsulation.

Properties can be changed by chemical modification, copolymerization and blending. Also hydrogels polymerized are obtained from a variety of synthetic and natural materials using typical and novel synthetic methods [14]. While natural/natural combination of biomaterials includes bone, wood, dentin, cartilage, skin and collagen, it is used as absorbable sutures; sponge wound dressing, drug delivery microspheres, poly (amino acids). It exhibits hierarchical structures in which particulates, porous and fibrous structural features. Usually poly (amino acids) such as poly (lysine) is used as drug carriers and protein-based polymers, typically elastic materials as implants and in tissue engineering [30]. Table 6 explains the strong points and the drawbacks of using combined materials.

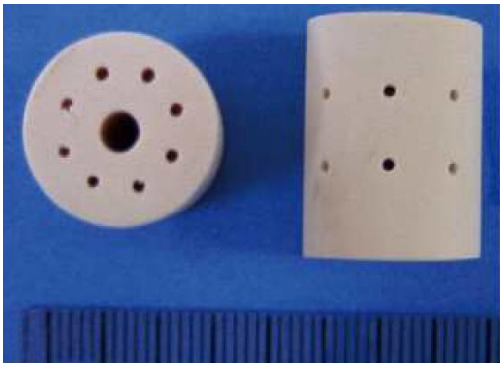


Fig.5: Typical product and dimension of dense synthetic-natural materials: HAp/Col bone-like nanocomposite with central and satellite holes [29]

Table 6: Specification of combined biomaterials [31]

Advantages	Disadvantages
Excellent biocompatible	Allografts and xenografts are associated with infection and inflammation and have perceived ethical
Easily degraded and resorbed	Insufficient supply and morbidity

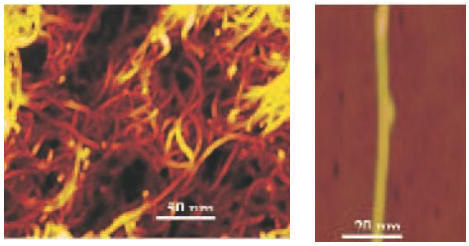
3 Nanobiomaterials

Nanobiomaterials are new term describing biomaterials with constituent or surface feature sizes less than 100 nm; provide extraordinary materials with unique structures and properties to solve most traditional biomedical puzzles. Getting knowledge and principles toward understanding biology, medicine and materials science, the nanobiomaterials derived from the science of measurement at the nanoscale is called nanotechnology [3; 21-24]. A naturally occurring nanobiomaterial is inorganic bone matrix which is composed of hydroxyapatite crystals. Nanobiomaterials can provide the cells with the desired matrices that mimic the native environment of the cells. Correlations of surface properties with stability, toxicity, and biodistributions are essential for in vivo applications. The potential fields of nanobiomaterials varies widely from tissue engineering to biosensing and diagnostics to drug delivery, disease therapy, hip replacements, fracture plates, bioresorbable sutures, tissue engineering scaffolds and drug delivery devices. These materials provide sites for cell adhesion and initiation of matrix-generated signal transduction pathways. Examples of some types of nanobiomaterials applications are (a) nanohydroxyapatite for orthopedic implants and drug carriers for bone diseases, (b) carbon nanotubes and nanofibers as novel drug delivery devices, (c) gold nanoparticles for cancer diagnostics and (d) quantum dots as biological sensors. The use of carbon nanotubes and various types of nanoparticles in medicine is very prevalent in research [32].

Carbon nanotubes (CNTs) are considered as the most suitable candidates to reinforce composites, especially polymer composites. This is because of their outstanding magnetic, mechanical, electrical, thermal and optical properties together with their extraordinary chemical stability, low density and very high and tunable aspect ratio [21-23; 33]. Types of CNTs are single wall carbon nanotubes (SWCNTs), double wall carbon nanotubes (DWCNTs), multi wall carbon nanotubes (MWCNTs). This is the reason why composite materials containing CNTs have recently attracted so much attention [24; 34]. Chemical and physical functionalization of multi-walled carbon nanotubes (MWCNT) has been practiced to achieve better behavior in medical fields, for example dispersion of carbon nanotubes (CNTs) in polymer matrix. Functionalization methods include (acid-treatment, non-ionic surfactant treatment with TritonX-100) [35].

There are different modern types of advanced nanometrology techniques for biomaterials characterization. Scanning Tunneling microscopy (STM) used to characterize synthesized CNTs as show in Fig.6: (a) CNTs as total amount, (b) sample of CNTs. TEM applications are illustrated in Fig.7 for various sizes of CNTs [36]. CNTs dispersion in different three types of polymer matrix composites show symmetric scuttle and the powerful interfacial bonding and cross-linking between CNTs and polymer matrix, as shown Fig.8. The functionalized coherent body form concluded how CNTs play a role as a reinforcing agent in polymer matrix. It can be indicates that CNTs suit well the in polymer matrix for synthesizing competent composite for different applications.

Other implementation is dispersion 2% of CNT into polymeric UHMWPE matrix have better and stronger interfacial bonding, as SEM image of CNT/UHMWPE composite particles are shown in Fig.9 at different scales. CNTs are explained clearly in Fig.9 (d–f). It seemed that CNTs had not been cut short obviously. It has achieved coating of CNT on the surface of UHMWPE particles [38].



(a) Total of CNTs (b) CNT sample

Fig.6: STM images for CNTs syntheses [36].

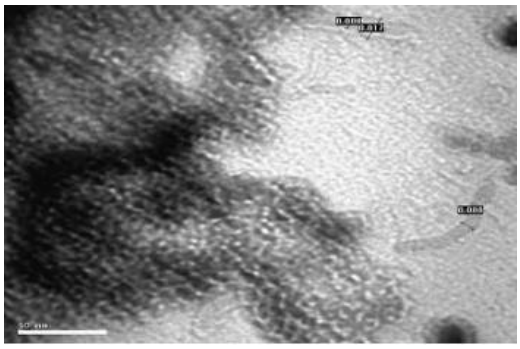
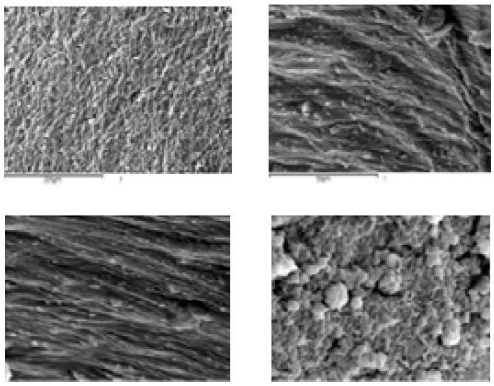
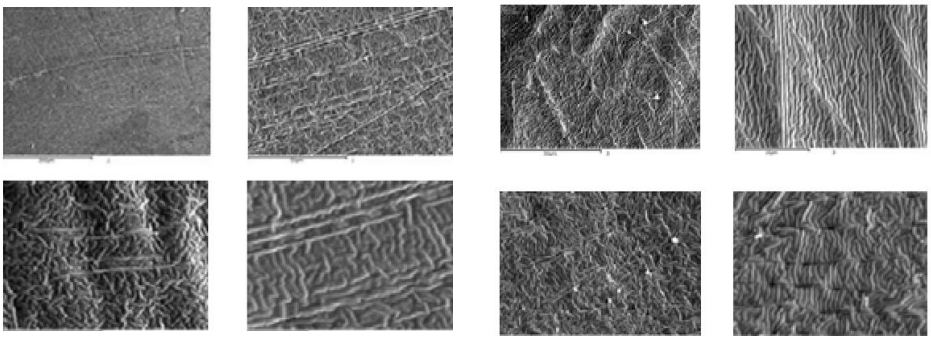


Fig.7: CNTs under TEM



(a) CNTs/PVC



(b) CNTs/PMMA (c) CNTs/PS

Fig.8: Different types of polymeric composed with CNTs using SEM technique [37].

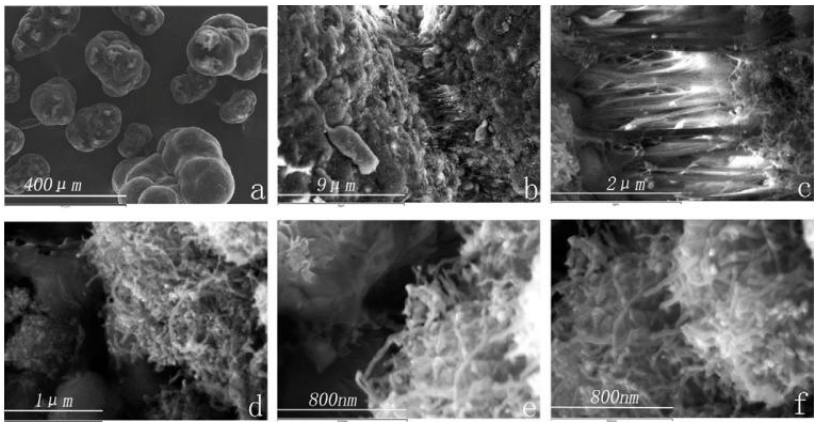


Fig.9: CNTs/UHMWPE by SEM technique.

4 Standardization of biomaterial

The International Standards Organization (ISO) was established to determine uniform worldwide standards. The ISO developed a standard for biological evaluation of medical devices. ISO in 1995 which is a 20-part standard used to evaluate the effects of medical devices and their component materials on the body [39]. The primary aim of the standard document (ISO 10993) is the protection of humans from potential biological risks arising from the use of medical devices [40]. The most influential guideline for biocompatibility is the first part of this standard, "ISO 10993- Part 1: Evaluation and Testing," which provides a methodology for choosing the proper biological evaluation test program. Typically, material characterization and analysis of a device's components are conducted prior to any biological testing. This involves extracting leachable materials from the device or components at an elevated temperature and analyzing the leachable extracts for potentially harmful chemicals and cytotoxicity. Once in vitro testing has been completed, in-vivo, biological testing can be done based upon the device's intended for use. This testing can range from skin irritation testing to hemocompatibility and implantation testing. Identification of biomaterials constituents done as flows [41]:

1. Change of a material over time
2. Change with exposure to different environments
3. Lot-to lot consistency for manufacturing purposes

On the other hand, the ISO technical committee (TC 150) in the field of implants for surgery and their required instrumentation covers terminology, specifications and methods of tests for types of implants and for the materials both basic and composite used in their manufacture and biomedical application. It is applied on objects or devices which are surgically implanted in the body either temporarily or permanently for diagnostic or therapeutic purposes [42]. In biomaterials community, there has been an increasing interest for standardization to be suitable for biomedical applications like tissue engineering. Eventually, it is be clear that the standardization of biomaterials is very important issue. Biocompatible and inexpensive, as well as safe and affordable material that responds to the medical requisites of the surgeon is also important to provide patient needs [43].

5 Recent development of standard reference biomaterial

Standard reference material (SRM) is defined as a material or substance, one or more of whose property values are sufficiently homogenous and well established to be used for the calibration of an apparatus. Reference material used for supporting measurements concerned with chemical composition, biological, clinical, physical, engineering properties to ensure their global acceptance. The variability associated with most of the biological evaluations is relatively large and necessary hence experimental controls are frequently employed to ensure that the results are reliable. These experimental controls, either positive or negative controls, could be considered as reference materials in the context of biological evaluation. Specified properties need a certified reference material which is a reference material characterized by a metrological valid procedure, also associated with uncertainty and a statement of metrological traceability. In biological materials, the success of any material in the biological environment is defined by its reaction to and from the surrounding environment. In general, a biomaterial is required to perform with appropriate host response in a specific application. Hence no single test can be used for conforming the biocompatibility of a material and a material cannot be categorically stated as biocompatible. But it can be concluded, through a series of properly selected qualification studies, that a material is suitable for use in a specific application. The most popular and accepted series of standards in this area

is ISO 10993: Biological evaluation of medical devices. Regular use of reference material ensures the accuracy (to mean the closeness of the agreement between the result of a measurement and a true value of the measurement) and repeatability (to mean closeness of agreement between results of successive measurements carried out under same conditions of measurement. Many efforts have been initiated around the globe to resolve this problem. National institute of standards and technology (NIST), national institute of health (NIH) and the national heart, lung, and blood Institute (NHLBI) in USA were the pioneers in this area. Some of the commonly used reference materials in the biological evaluation are listed in the Table 7 [44]. Before using any materials to be reference there is some primary specifications, and it depends on requirements like ISO 10993-6: Tests for local effects after implantation for example in commercially pure titanium as given in Table 8.

Table 7: Commonly used reference biomaterials

Test	Positive control	Negative control
Cytotoxicity	Polyvinylchloride (PVC), Zinc diethyl dithiocarbamate (ZDEC); Natural rubber latex	Polyethylene, Silicone rubber; Alumina
Blood compatibility	---	Polypropylene; Silicone rubber
Implantation	PVC, ZDEC; Natural rubber latex	Polyethylene, Silicone rubber, Titanium, Stainless Steel 316L, Alumina; Calcium phosphates

Table 8: Primary specification of proposed commercially pure titanium reference materials [44]

No.	Property	Value
1-	Material grade	American Society for Testing and Materials (ASTM)
2-	Length	10 ± 0.5 mm
3-	Diameter	0.05 mm
4-	Surface finish	Better than 0.1 µm
5-	Sterilization method	Ethylene oxide (EO)

The various stages involved in the development of a reference material are described in the following sections [44]. The first step in the development involves the planning and identification of the requirements and development of appropriate set of specifications for the material samples as shown in Fig.10. The structural homogeneity of the material with respect to the required properties is established. This call for a series of studies will reach to the repeatability and reproducibility of the relevant properties within the batch. Inter laboratory comparisons also is employed to generate this information. Once the homogeneity is established, the material needs to be characterized for all properties. This is done in order to provide data on material such as (safety, physic-chemical properties, biological characteristics and ageing behavior). The material is assigned with a reference value (which could be qualitative or quantitative depending.

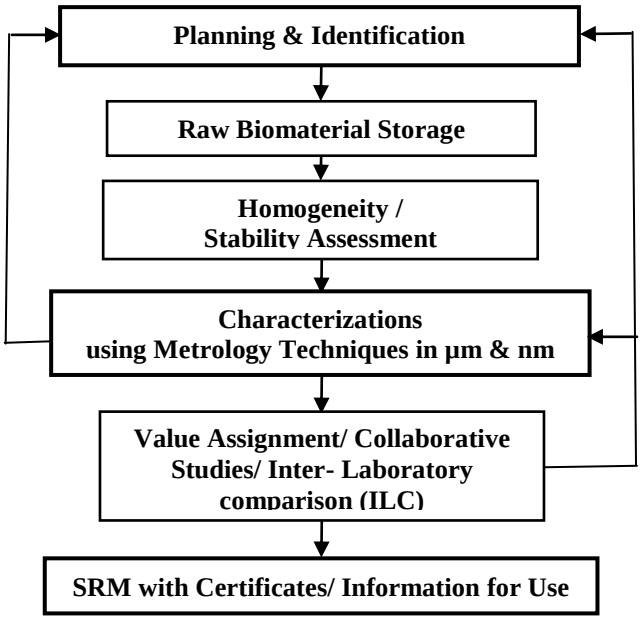


Fig.10: Proposed procedures strategy of standard reference test for SRM.

6 Conclusions

Before using nanobiomaterials in any medical applications, it is necessary to put in mind that, which categories they are belonging to avoid any negative effect in the body. Also it is necessary to follow standards with respect accurate and precise measurements for suitable use within biological system to provide patient needs. Main attentions are giving to generations of biomaterials based on their classifications to witness numerous developed types of nanobiomaterials to natural, synthetic. Based on last up to date, they classify combined biomaterial to include natural-natural or/and natural-synthetic material. Physical, mechanical, tribological, biological properties and their influences on the stability of dimensional and surface characteristics are very important parameters. Moreover, biocompatibility and sterilizability of nanobiomaterials are very important in line with ISO standards. It is necessary to classify and give accurate assessment for new nanobiomaterials according to developed procedures strategy for stable use in the medical engineering applications.

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