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Biomaterials

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1. Introduction

Biomaterial can be described as a combination of substances originating from natural, inorganic or organic materials that is biocompatible in exactly or partially contact with the body for healing time. They involve complete or part of a living organism or biomedical device which performs, augments or replacements any natural function [1].

Biomaterial is a nonviable substance used in a medical device intended to interact with biological systems. Their usage within a physiologic medium needs the characteristic features such as efficient and reliable. These characteristic features have provided with a suitable combination of chemical, mechanical, physical and biological properties [2]. Nowadays, biomaterials are commonly used in various medical devices and systems; synthetic skin; drug delivery systems; tissue cultures; hybrid organs; synthetic blood vessels; artificial hearts; cardiac pacemakers; screws, plates, wires and pins for bone treatments; total artificial joint implants; skull reconstruction; dental and maxillofacial applications [3].

Metals and their alloys, polymers, ceramics and composites are commonly used for biomedical applications. These materials that have different atomic arrangement present the diversified structural, physical, chemical and mechanical properties and so different properties offer alternative applications in the body. The mechanical properties of metals and their alloys such as strength, elasticity coefficient and fatigue life makes them attractive materials for many load-bearing biomedical systems. Metallic materials tend to degradation in a corrosion process and even as the corrosion reactions of releasing some side products such as ions, chemical compounds and insoluble components that may cause adverse biological reactions.

Ceramic materials are desirable biomaterials due to the biocompatible properties such as bioactive, bioinert and biodegradable, however they have significant disadvantages such as brittleness, low strength etc. [1-4].

Polymers are attractive materials for biomedical applications such as cardiovascular devices, replacement and proliferation of various soft tissues. They are also used in drug delivery systems, diagnostic supports and as a reconstructive material for tissue engineering. The

current applications of them include cardiac valves, artificial hearts, vascular grafts, breast prosthesis, contact and intraocular lenses, fixtures of extracorporeal oxygenators, dialysis and plasmapheresis systems, coating materials for medical products, surgical materials, tissue adhesives etc. [3]. The composition, structure and organization of constituent macromolecules specify the properties of polymers.

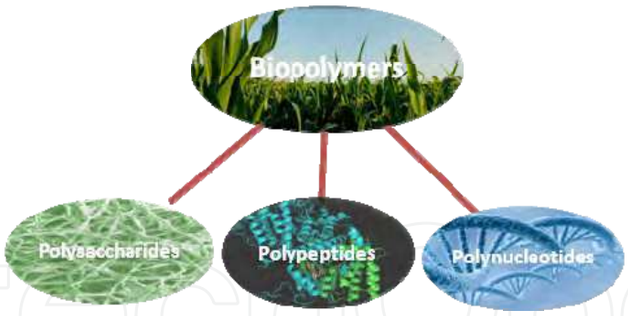
Composite is a material comprised of two or more metal, polymer or ceramic structures which are separated by an interface. Composite materials have been widely used for a long time in innovative technological applications due to their superior mechanical properties. The bones, tendons, skin, ligaments, teeth, etc. are natural composite structures in the human body. The amount, distribution, morphology and properties of structure components determine the final behavior of resultant tissues or organs. Some synthetic composites can be used to produce prosthesis able to simulate the tissues, to compromise with their mechanical behavior and to restore the functions of the damaged tissues. Composites are usually classified based on their matrix components like metals, ceramics, polymers or reinforcement components like particulates, short or long fibers, microfillers, nanofillers. Many matrix and reinforcement components of composite materials have been tried by several researchers in tissue engineering to advance the mechanical features, biologic functions and to deliver special molecules. Biocompatible polymers have been mostly applied as matrix for composite materials associated with ceramic fillers in tissue engineering. Although ceramics are generally stiff and brittle materials, polymers are known to be flexible and exhibit low mechanical strength and stiffness. Composites aim to combine the properties of both materials for medical applications [1-9].

There are currently thousands of surgical materials, hard and soft tissue products, biomedical devices, pharmaceutical and diagnostic products and disposable materials at the medical market. The recent biomaterial applications were aimed to engineered tissues, intelligent materials, tissue cultures, drug delivery systems, artificial organs, biomimetic systems and materials in addition to traditional medical applications. Nowadays, modern clinical procedures such as preventing and curing main genetic diseases are become significant and new medical demands cause the change of the biomaterial products. Materials scientists and engineers need researchers who work effectively in professional teams such as molecular biologists, biochemists, geneticists and physicians and they also aim for the materials which are recognised by cells, biochemical structures, molecules and genetic issues [4].

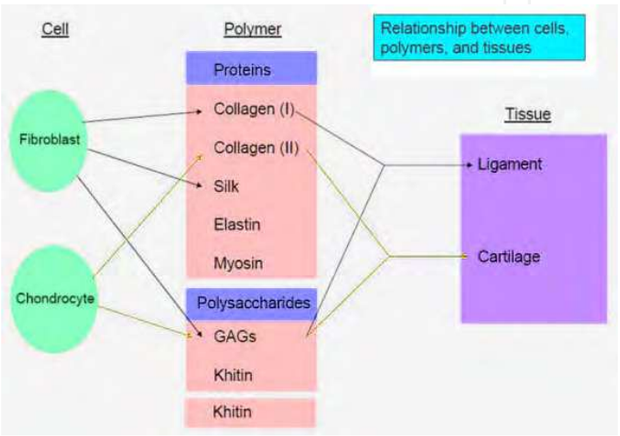
2. Materials used in medicine

2.1 Natural materials

Biopolymers are natural materials such as carbohydrates, proteins, cellulose, starch, chitin, proteins, peptides, DNA and RNA produced by living organisms [10]. Generally, the synthesis procedure of them involves enzyme-catalysed polymerization reactions of activated monomers and chain growth which are characteristically formed within cells by complex metabolic processes [11]. Figure 1 shows classification, structures and functions of biopolymers. Table 1 also presents incidence and physiological functions of certain natural polymers.



(a)



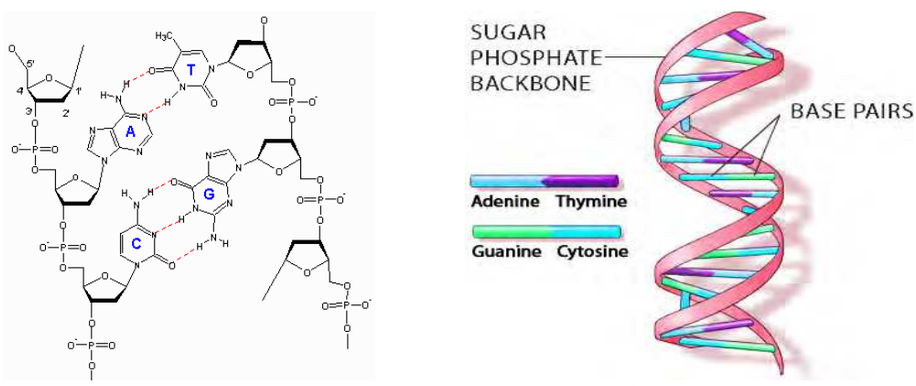
(b)

Fig. 1. (a) Classification of biopolymers and (b) structure and functions of biopolymers [12].

	Polymer	Incidence	Physiological Function
Proteins	Silk	Synthesized by arthropods	Protective cocoon
	Keratin	Hair	Thermal insulation
	Collagen	Connective tissues (tendon, skin, etc.)	Mechanical support
	Gelatine	Partly amorphous collagen	
	Fibrinogen	Blood	Blood clotting
	Elastin	Neck ligament	Mechanical support
	Actin	Muscle	Contraction, motility
	Myosin	Muscle	Contraction, motility
Polysaccharides	Cellulose (cotton)	Plants	Mechanical support
	Amylose	Plants	Energy reservoir
	Dextran	Synthesized by bacteria	Matrix for growth of organism
	Chitin	Insects, crustaceans	Provides shape and form
	Glycosaminoglycans	Connective tissues	Contributes to mechanical support
Polynucleotides	Deoxyribonucleic acid (DNA)	Cell nucleus	Direct protein biosynthesis
	Ribonucleic acid (RNA)	Cell nucleus	Direct protein biosynthesis

Table 1. Incidence and physiological functions of certain natural polymers [12].

DNA is a natural polymer that has a great importance in all living creatures. DNA can be involved in the nucleus of every human cell and determines all of the physical characteristics through genes. Genes consist of a sequence of nucleotides that a specific protein is to be made. Hence the proteins carry out all of the functions of living organisms. Nucleotides are the monomers of DNA and each nucleotide consists of a 5-carbon sugar, a base and a phosphate. There are four bases named as Adenine(A), Thymine(T), Cytosine(C) and Guanine(G). The purines (Adenine and Guanine) have 5 carbons and the pyrimidines (Thymine and Cytosine) have 3 carbons. Purines are nitrogen containing bases consisting of two rings and pyrimidines are nitrogen containing bases with just one ring consisting of carbon and nitrogen. The nucleotides are linked covalently by carbon atoms and covalent bonding occurs between the sugar of one nucleotide and the phosphate in the backbone of the next. Each nucleotide is then paired up with their corresponding base (A to T and C to G). A weak hydrogen bond only holds the two base pairs together which makes DNA very easy to split and replicate. The linked nucleotides become a polynucleotide and named as the polymer of DNA (Figure 2a and 2b) [13].



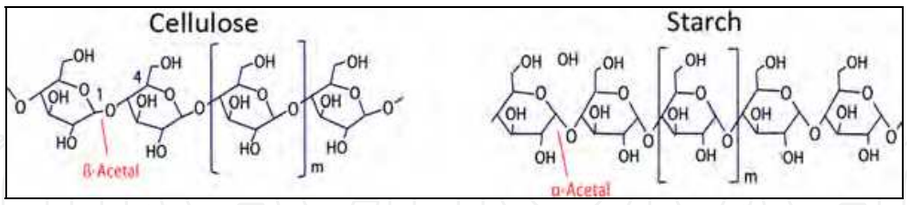
(a) (b)

Fig. 2. (a) DNA structure [14] and (b) double helix [15].

Polysaccharide is a macromolecule consisting of a large number of monosaccharide chains joined to each other by glycosidic linkages. Polysaccharides are made up chains of monosaccharide molecules which are linked together by glycosidic bonds and occurred by the condensation reaction. The linkage of monosaccharides into chains creates of greatly varying length ranging from chains of just two monosaccharide that make a disaccharide to the polysaccharides which consists of many thousands of the sugars. The polysaccharides play different and significant roles within the biological processes. [16]. The assembly of the polysaccharide is conducted by enzyme-driven reactions. It is the most spacious polysaccharide in nature and acts as a storage carbohydrate in many different parts of a plant. Starch, cellulose, glycogen and chitin are the basic polysaccharides used for medical applications. Starch is a combination of branched and linear polymers of D-glucose molecules generated by plants (Figure 3a). Starch contains only a single type of carbohydrate (glucose) [11].

Cellulose is the most common carbohydrate in the world and is the main substance that forms most of a plant's cell walls. Its structure consists of long polymer chains of glucose units bonded by a beta acetal group. Cellulose structure has mostly a linear chain due to the

bond angles in the beta acetal group. The repeating monomer unit in starch structures is alpha glucose. Starch-amylose forms a spiral structure because of the bond angles in the alpha acetal groups (Figure 3b) [17].

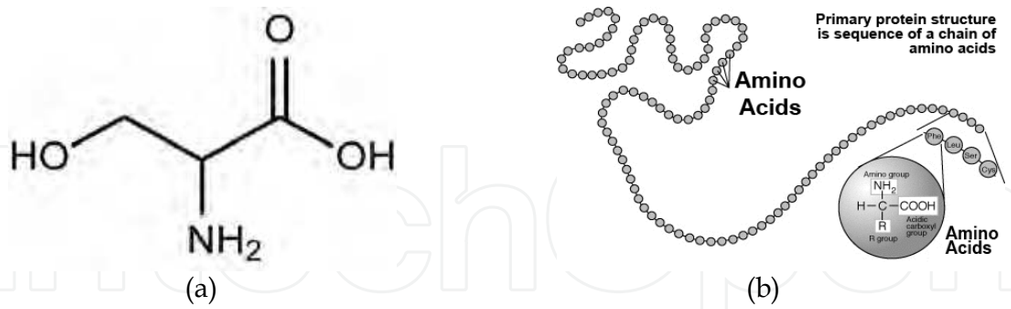


(a) (b)

Fig. 3. Structure of (a) starch and (b) cellulose [17].

Collagen is a main structural protein located in the body. It provides homogen strength to the tissues and organs of the body and comprises 90% of the organic matrix of bone together with the mineral, manages through the biomechanical properties and functional integrity of tissues. Collagen that is in the shape of elongated fibrils is mostly included in fibrous tissues such as tendon, ligament and skin, and is also abundant in cornea, cartilage, bone, blood vessels and intervertebral disc. The collagen molecule has a distinctive feature that consists of three polypeptide chains. Proline, hydroxyproline and Gly-Prol-Hyp amino acids are the most common triplet found in collagen. The repeating sequence of these amino acids allows the chains to form a triple-helical structure. The arrangement of triple helices in fibrils is provide high tensile strength to this biopolymer [18].

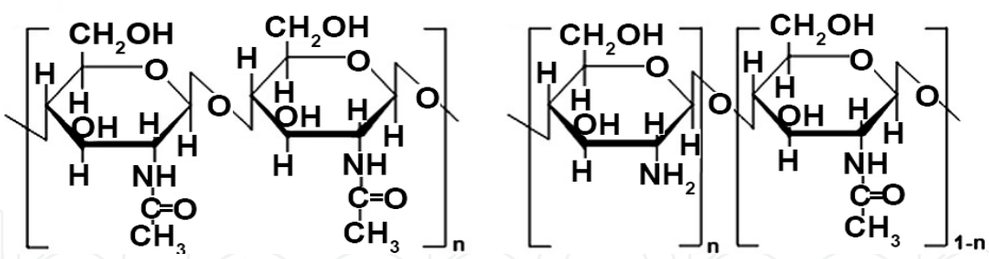
Proteins are complex biopolymeric structures that are composed of up to 20 different amino acids. These amino acid units are sequenced by the template specific reamer of the polymerization process. Protein chains can contain a few hundreds or thousands of amino acid units (Figure 4).



(a) (b)

Fig. 4. (a) Amino acid molecule (serin) and (b protein structure [13].

Chitin is a biopolymer of b(1/4)-linked N-acetyl-D-glucosamine residues (Figure 5a). Chitin is the second most abundant polysaccharide in nature and it is the basic structural component of the exoskeleton of invertebrates such as crustaceans, insects and spiders. It can also be found in the cell walls of most fungi and many algae. Chitosan is obtained from the alkaline deacetylation reaction of chitin and is a linear polysaccharide consisting of N-glucosamine and N-acetyl glucosamine units linked by b(1/4) glycosidic bonds (Figure 5b). The deacetylation degree (DD: glucosamine/N-acetyl glucosamine ratio) usually can vary from 30 to 95% depending on the source.



(a) (b)

Fig. 5. Chemical structure of chitin (a) and chitosan (b).

Alginate is the name given to linear polysaccharide family found in brown algae and is composed of guluronic and manuronic units. Alginate contains homopolymeric sequences such as polymer of (1-4) - β -D-mannuronopyranosyl and (1-4)-L-guluronopyranosyl units in a copolymer [18]. Table 2 shows some applications of natural biomaterials.

Application	**Natural Biomaterial**
Artificial heart valves	Bovine pericardium, intact porcine aortic valves
Hernia repair devices	Porcine small intestinal submucoa, porcine urinary bladder mucosa, porcine dermal grafts
Sutures	Catgut (porcine or bovine intestinal wall), porcine dermal grafts
Skin repair/ wound care	Dermal allograft, porcine small intestinal submucoa, porcine dermal grafts
Vascular prostheses	Bovine ureter, porcine small intestinal submucoa, ovine arteries
Urethral repair	Porcine bladder
Breast reconstruction	Dermal allograft
Ligament repair	Dermal allograft, porcine small intestinal submucoa, fetal bovine skin
Spinal fusion/bone healing	Bone allograft

Table 2. Some applications of natural biomaterials [19].

Natural products have many applications in the field of medicine, pharmaceuticals, diagnosis and treatment, food industry and agrochemicals etc. and they have a beneficial for the treatment of particular diseases on the human body. The recent research in natural biomaterials tends to many applications in various biomedical fields.

2.2 Metals

Metallic implant materials have significant economic and clinic importance on the medical applications for a long time. Many of metal and metal alloys such as stainless steel (316L), titanium and alloys (Cp-Ti, Ti6Al4V), cobalt-chromium alloys (Co-Cr), pure metals, precious metals, aluminium alloys, zirconium-niobium and tungsten heavy alloys were used for medical requirements (Table 3). The rapid growth and development of the many specialties of medicine has created whole new medical industry which was to supply more than a trillion dollars of medical products such as dental implants, craniofacial plates and screws;

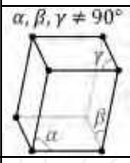
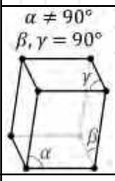
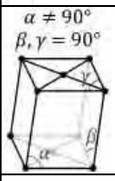
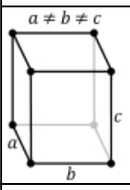
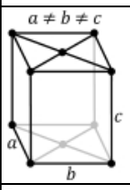
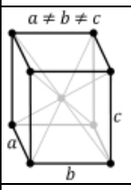
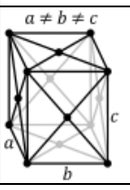
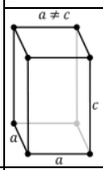
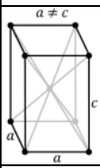
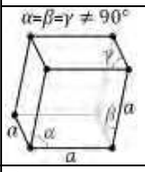
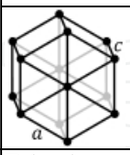
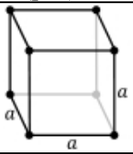
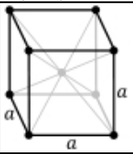
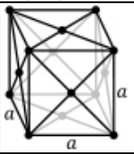
parts of artificial hearts, pacemakers, clips, valves, balloon catheters, medical devices and equipments, bone fixation devices, dental materials, medical radiation shielding products, prosthetic and orthodontic devices, tools of machining metallic biomaterials. The main criteria in selection of metal-based materials for biomedical applications are their excellent biocompatibility, convenient mechanical properties, good corrosion resistance and low cost [4].

Medical Alloys	**Product Forms**	**Medical Applications**
Stainless Steel	Tube, pipe, wire, bar, strip, sheet, plate, screw, profile, clips, fixation devices, nails and pins, joints	Dental and surgical instruments, medical devices
Titanium	Wire, spring	Surgical implants, medical prostheses, dental implants, maxillofacial and craniofacial treatments, cardiovascular devices, surgical instruments
Cobalt-Chromium	Foil, strip, sheet, bracket, screws, surgical instruments	Medical equipment
NiTiNol	Wire, Bar, rod, strip	Surgical instruments, orthodontics, robotics
Pure Metals	Plate, profile	Bone fracture fixation devices
Precious Metals	Forgings, castings	Dental materials
Aluminium Alloys	Fasteners	Medical radiation shielding products
Zirconium-Niobium	Machined parts	Prosthetic and orthodontic devices
Tungsten Heavy Alloys	Prosthetic components	Tools of machining metallic biomaterials

Table 3. Medical metals and alloys for surgical implants and medical devices [5].

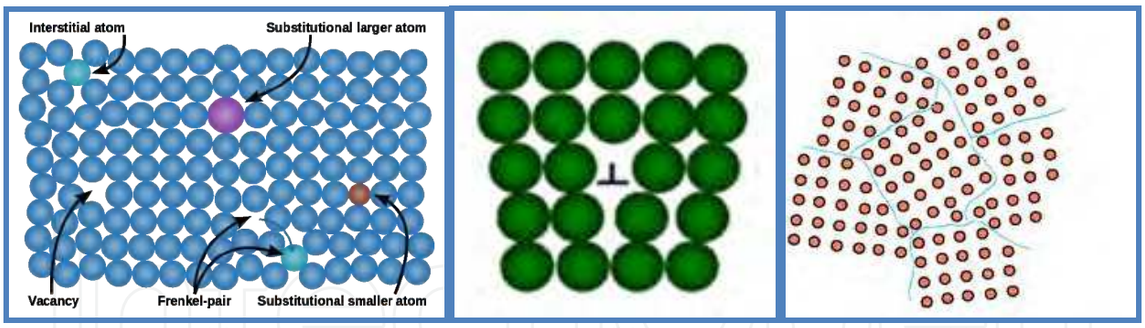
At the present time, the compatibility of improved diagnostic instruments and developments about the information on materials are supposed greater significance as well as on medical procedures [8]. Metals are used as biomaterials due to their excellent electrical, thermal and mechanical properties. Metals have some independent electrons which can transfer an electric charge and thermal energy fastly. These mobile free electrons act as the bonding force to hold the positive metal ions together. This strong attraction has proved by the closely packed atomic arrangement resulting in high specific gravity and high melting points of most metals. Since the metallic bond is not essentially directional, the position of the metal ions can be altered without destroying the crystal structure resulting in a plastically deformable solid [9].

Metallic biomaterials such as stainless steel, cobalt-based alloys, titanium and its alloys etc. form either face-centered cubic, hexagonal close-packed or body-centered cubic unit cells at body temperature with ideal crystal lattice structures as shown in Table 4. The most of metal crystals, in contrast to these ideal atom arrangements, contains lattice defects such as vacancies, dislocations, grain boundaries etc. (Figure 6). The presence of point, line and planary defects in metal internal structure has a strong effect on mechanical, physical and chemical properties.

Lattice Systems	**Bravais Lattices**				**Examples**
Triclinic	P 				$K_2Cr_2O_7$ $CuSO_4.5H_2O$ H_3BO_3
Monoclinic		C 			Monoclinic Sulphur $Na_2SO_4.10H_2O$
Orthorhombic	P 	C 	I 	F 	Rhombic Sulphur KNO_3 $BaSO_4$
Tetragonal	P 	I 			White Tin SnO_2 TiO_2 $CaSO_4$
Rhombohedral	P 				$CaCO_3$ HgS
Hexagonal	P 				Graphite (C) ZnO CdS
Cubic	P (pcc) 	I (bcc) 	F (fcc) 		NaCl Zinc Blende (ZnS) Cu

P: Primitive centered that includes the lattice points on the cell corners only; I: Body centered which finds one additional lattice point at the center of the cell; **F:** Face centered that consists one additional lattice point at center of each of the faces of the cell; **A, B or C:** Base centered which has one additional lattice point at the center of each of one pair of the cell faces.

Table 4. The distribution of the 14 Bravais lattice types into 7 lattice systems [20].



(a) (b) (c)

Fig. 6. Defects of crystal structures: (a) point defects (substitutional or interstitial elements, vacancies) [21], (b) line defects (edge dislocation) [22] and (c) planar defects (grain boundaries) [23].

Interatomic bonding in solids occurs by strong primary ionic, covalent, and/or metallic bonds and weaker secondary interatomic bonding by van der Waals and hydrogen bonds. Metals are characterized by metallic interatomic bonding with valance shell electrons forming an electron cloud around the atoms/ions. As a result of the close positioning of neighboring atoms and the shared valence electrons, the non-directional interatomic bonding and electron movement within metal crystal lattices is easier than in ionic or covalently bonded materials. This fundamental distinctive feature of metals results in the relative ease of plastic deformation as well as the high electrical and thermal conductivities of metals. Most of the metals used for implant production have either close-packed atomic structures with face-centered cubic (fcc) or hexagonal close-packed (hcp) unit cells or nearly close-packed structures forming body-centered cubic (bcc) structures. The equilibrium distance between atoms defining the unit cells of these crystals and the strength of their interatomic bond is determined by intrinsic factors such as atom size and valency as well as extrinsic factors such as temperature and pressure. In addition to ease of deformation to desired shapes, the ability of deforming plastically at increasing loads results in another very important characteristic namely an ability to decrease sharp discontinuities through plastic deformation there by reducing local stress concentrations resulting in relatively high fracture toughness. These desirable features are dependent on proper selection of processing conditions for material and part formation [24].

Type of metal used in biomedical applications depends on functions of the implant. 316L type stainless steel (316L SS) is still the most used alloy in all implants part ranging from cardiovascular to otorhinology. However, when the implant requires high wear resistance such as artificial joints, Co-Cr-Mo alloys is better served. Table 5 summarizes surgical implant alloy compositions used for different biomedical applications [4].

The chemical properties of materials also are due to their atomic bonding types. Atomic bonding type changes the chemical, physical and mechanical properties of metallic materials. The surfaces of metallic medical products can be degraded in living systems and their changed surfaces can release some by-products to biologic medium. As a result of this releasing process, interactions between cell and tissues with metallic implant surfaces occur. For this reason, recent research gives great importance to surface properties of metallic products for the development of biocompatible materials.

Element	316L Stainless Steel (ASTM F138,139)	Co-Cr-Mo (ASTM F799)	Grade 4 Ti (ASTM F67)	Ti-6Al-4V (ASTM F136)
Al	-	-	-	5.5-6.5
C	0.03 max.	0.35 max.	0.010 max.	0.08 max.
Co	-	Balance	-	-
Cr	17.0	26.0-30.0	-	-
Fe	Balance	0.75 max.	0.30-0.50	0.25 max.
H	-	-	0.0125-0.015	0.0125 max.
Mo	2.00	5.0-7.0	-	-
Mn	2.00 max.	1.0 max.	-	-
N	-	0.25 max.	0.03-0.05	0.05 max.
Ni	10.00	1.0 max.	-	-
O	-	-	0.18-0.40	0.13 max.
P	0.03 max.	-	-	-
S	0.03 max.	-	-	-
Si	0.75 max.	1.0 max.	-	-
Ti	-	-	Balance	Balance
V	-	-	-	3.5-4.5
W	-	-	-	-

Table 5. Surgical implant alloy compositions (wt %) [6,7].

The mechanical properties of materials have a great importance during the design of the load-bearing dental and orthopaedic implants. With a few exceptions, the high tensile strength and fatigue limit of metallic materials make them the materials of chosen materials for implants that carry mechanical loads compared with ceramics and polymeric materials. It should be noted that, in contrast to the nanophase, composite nature of their constituent macromolecules. The properties of metallic biomaterials as hard tissue implants are compared below [25]:

Stainless steel (SS)

- cheaper than other metals,
- has high strength, ductility and toughness,
- easy machining,
- can be corrosion problem,
- can be less bone bonding than other metals,
- may create nickel ion sensitivity.

Co-Cr-Mo alloys

- cast alloy forms have lower cost than wrought or forged forms,
- cast alloys forms have higher elastic modulus than wrought or forged forms,
- wrought or forged forms has the highest strength/wear resistance,
- hardest to fabricate,
- may produce cobalt or chromium ion sensitivity/toxicity.

Titanium alloy (Ti-6Al-4V) versus Titanium (Ti) metal

- titanium alloy is stronger than titanium metal,
- both have relatively low elastic modulus,

- neither is as wear resistant as SS or Co-Cr-Mo alloys,
- both have the best corrosion resistance,
- both have excellent bone bonding.

Types of Alloys Used in Medical Devices

Several alloys are used in many medical devices; (1) silver-tin-mercury-copper alloys for dental amalgam fillers; (2) cobalt-chromium alloys for dental applications, cardiac valves, bone fracture and joint components; (3) titanium alloys for conductive leads, screws, joint components and nails and (4) stainless steels for bone fracture and joint components, stents and prosthetic materials (Table 6 and Figure 7).

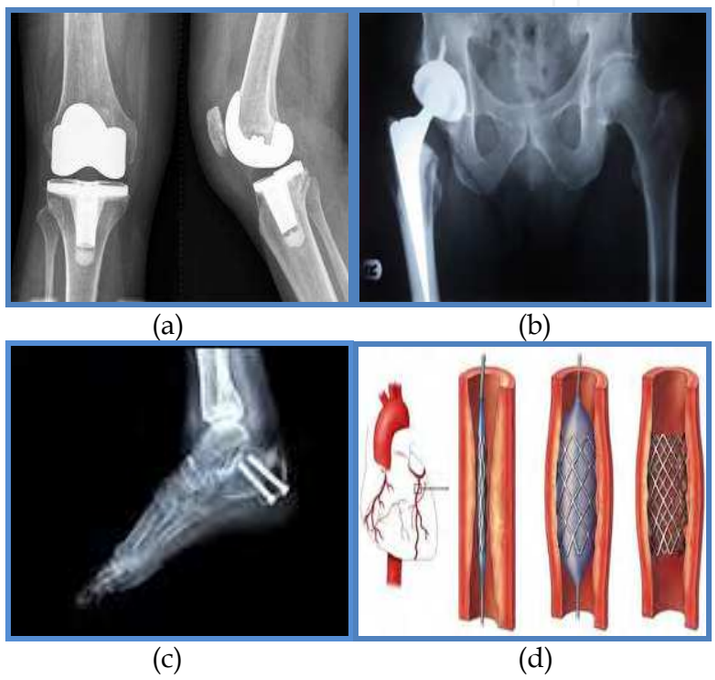


Fig. 7. (a) Nanostructured diamond coatings [26]; (b) ceramic and metal hip implant [27]; (c) metal ankle implants[28]; (d) coronary artery, metallic stent and stent procedure [29].

Application	**Metal**
Conductive leads	Titanium and its alloys
Dental amalgams	Silver-tin-copper alloys, gold and platinum fillings
Dental applications	Cobalt-chromium alloys
Fracture plates	Stainless steel, cobalt-chromium alloys
Guide wires	Stainless steels
Heart valves	Cobalt-chromium alloys
Joint components	Cobalt-chromium alloys, titanium alloys
Nails	Cobalt-chromium alloys, titanium alloys
Pacemaker cases	Titanium alloys
Screws	Cobalt-chromium alloys, titanium alloys
Vascular stents	Stainless steel, nitinol

Table 6. Medical applications of metals [30].

Mechanical properties of metals used in medical applications are given in Table 7. Stainless steel has ultimate tensile strength values that range from 480 to 860 MPa and ultimate tensile strain values from 12 to 45%. In comparison, cobalt-based alloys have ultimate tensile strength values that can exceed 1,500 MPa and ultimate tensile strain values between 8% and 50%. Titanium alloys have ultimate tensile strength values up to about 900 MPa and ultimate tensile strain values between 10 and 24%. In comparison to polymers, metals have higher ultimate tensile strength and elastic modulus but lower strains at failure. However, in comparison to ceramics, metals have lower strengths and elastic modulus with higher strains to failure [30].

Type and Condition	Metal	UTS (MPa)	Yield at 2%[a]	US (%)
F55, F138 (annealed)	Stainless steel	480-515	170-205	40
F55, F138 (cold worked)	Stainless steel	655-860	310-690	12-28
F745 (annealed)	Stainless steel	480 min.	205 min.	30 min.
F75 (cast)	Cobalt-based alloy	655	450	8
F90 (annealed)	Cobalt-based alloy	896	379	30-45 min.
F562 (solution annealed)	Cobalt-based alloy	793-1,000	241-448	50
F562(cold worked)	Cobalt-based alloy	1,793 min.	1,586 min.	8
F563 (annealed)	Cobalt-based alloy	600	276	50
F563 (cold worked and aged)	Cobalt-based alloy	1,000-1,586	827-1,310	12-18
F67	Titanium alloy	240-550	170-485	15-24 min.
F136	Titanium alloy	860-896	795-827	10 min.

Note: UTS = ultimate tensile strength; US = ultimate strain; min. =minimum; [a] Yield strength at 2% offset in MPs.

Table 7. Mechanical properties of metals used in medical applications [30].

Nowadays, some metal implants have been replaced by ceramics and polymers due to their excellent biocompatibility and biofunctionality. However, the properties of high strength, toughness and durability are required for the metals. On the other side, clinical application of the promising research in using bioactive polymers and ceramics in regenerative medicine is still far away from practice. The future trend seems to combine the mechanically superior metals and the excellent biocompatibility and biofunctionality of ceramics and polymers to obtain the most desirable clinical performance of the implants.

2.3 Polymers

Polymers have been used widely in medicine and biotechnology [31], surgical devices [32], implants [33], drug delivery systems, carriers of immobilized enzymes and cells [34], biosensors, bioadhesives, ocular devices [35], dental materials [36], surface modification [37], biosensors [38], components of diagnostic assays [39], tissue adhesives [40] and materials for orthopaedic and tissue engineering applications [41]. This versatility requires the production of polymers prepared in different structures and compositions and appropriate physicochemical, interfacial and biomimetic properties to meet specific applications. The main advantages of the polymeric biomaterials compared to metal or ceramic materials are ease of manufacturability to produce various shapes such as membranes, films, fibres, gels, sheets, hydrogels, capsules, spheres, particles and 3D-structures (scaffolds) (Figure 8) and ease of secondary processability, reasonable cost and availability with desired mechanical

and physical properties. The required properties of polymeric biomaterials are biocompatibility, sterilizability, convenient mechanical and physical properties, and manufacturability as given in Table 8. Different polymeric materials and their biomedical applications are also presented in Table 9. The main types of polymers for biomedical applications derived from natural or synthetic organic sources.

Table 10 presents the most important natural and synthetic origin polymers and their main biomedical applications. The principal disadvantages of these polymers are related to the difficulties in the development of reproducible production methods, because their complex structure often renders modification and difficult purification. In the case of synthetic polymers, these are available in a wide variety of compositions with modified properties.

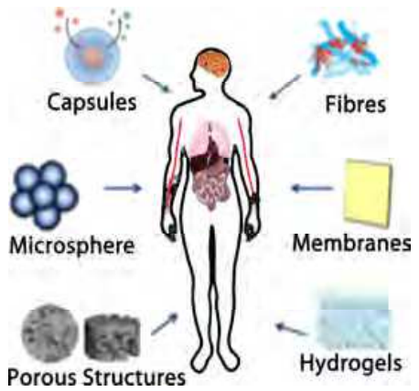


Fig. 8. Natural polymers used in biomedical applications such as tissue regeneration and drug delivery systems [42].

The main disadvantage of synthetic polymers is the general lack of biocompatibility in the majority of cases, often associated with inflammatory reactions [42]. For this reason, the recent researches have focused on the usage possibilities of natural origin polymers such as chitosan, carrageenan, alginate etc.

Property	**Description**
Biocompatibility	Noncarcinogenesis, nonpyrogenicity, nontoxicity, nonallergic response
Sterilizability	Autoclave, dry heating, ethylenoxide gas, radiation
Physical property	Strength, elasticity, durability
Manufacturability	Machining, molding, extruding, fiber forming

Table 8. Required properties of polymeric biomaterials [9].

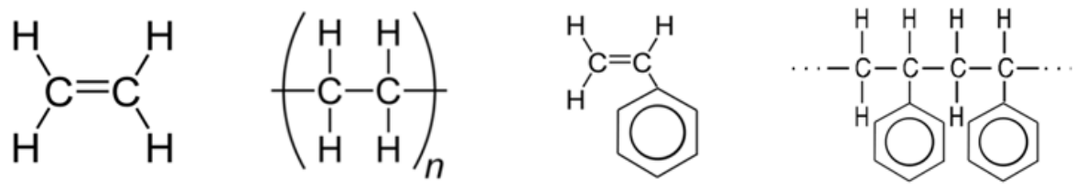
Polymer	**Application**
Poly(methyl methacrylate)	Intraocular lens, bone cement, dentures
Poly(ethylene terephthalate)	Vascular graft
Poly(dimethylsiloxane)	Breast prostheses
Poly(tetrafluoroethylene)	Vascular graft, facial prostheses
Polyethylene	Hip joint replacement
Polyurethane	Facial prostheses, blood/device interfaces

Table 9. Biomedical applications of different polymeric materials [43].

Synthetic Polymer	Main Applications and Comments
Poly(lactic acid) poly(glycolic acid) and their copolymers	Sutures, drug delivery systems and in tissue engineering, biodegradable, regulate degradation time during copolymerization
Poly(hydroxyl butyrate) poly(caprolactone) and copolymers poly(alkylene succinate) etc.	Biodegradable, used as a matrix for drug delivery systems, cell microencapsulation, to change the properties of materials by chemical modification, copolymerization and blending
Polyamides (nylons)	Sutures, dressing, haemofiltration and blending
Polyethylene(low density)	Sutures, catheters, membranes, surgical treatments
Poly(vinyl alcohol)	Gels and blended membranes for drug delivery and cell immunoisolation
Poly(ethylene oxide)	Highly biocompatible, different polymer derivatives and copolymers for biomedical applications
Poly(hydroxyethyl methacrylate)	Hydrogels as soft contact lenses, for drug delivery, for skin coatings and immunoisolation membranes
Poly(methyl methacrylate)	This and its copolymers in dental implants and bone replacements
Poly(tetrafluroethylene) (Teflon)	Vascular grafts, clips and sutures, coatings
Polydimethylsiloxanes	A silicone, implants in plastic surgery, orthopaedics, blood bags and pacemakers
Poly(ortho esters)	Surface eroding polymers, application in sustained drug delivery, ophthalmology
Polyanhydrides	Biodegradable, useful in tissue engineering and for the release of the bioactive molecules

Table 10. Main properties and applications of synthetic polymeric biomaterials [42].

Polymers are large organic macromolecules consist of repeating units called ‘‘mers’’ which are covalently bonded chains of atoms. These macromolecules interact with one another by weak secondary bonds such as hydrogen and van der Waals bonds to form entanglement structure. Polymers exhibit weak thermal and electric properties because of the covalent interatomic bonding within the molecules. The mechanical and thermal behavior of polymers is influenced by several factors, including the composition of the backbone, chemical side groups, chain structures and different molecular weight. Plastic deformation that occurs when applied the mechanical forces cause the movement of macromolecule chains to one another. Changes in polymer composition or structure increase resistance to relative chain movement, so this resistance increases the strength and decreases the plasticity of the material (Figure 9). Substitutions into the backbone that increase its rigidity limit the chain movement. Large side groups also make disentanglement more difficult. Growing macromolecule chain also makes it less mobile and hinders its relative movement [6].



(a) (b) (c) (d)

Fig. 9. Structure of (a) ethylene [44], (b) polyethylene [44], (c) styrene [45] and (d) polystyrene [44].

Polymers can be classified according to the polymerization techniques of the monomers. In bulk polymerization, only the monomer and possibly catalyst and initiator are fed into the reactor without solvent. At the end of the polymerization, process a nearly solid mass is removed as the polymer product. Bulk polymerization is employed widely in the manufacture of condensation polymers, where reactions are only mildly exothermic and viscosity is mostly low thus enhancing ready mixing, heat transfer and bubble elimination. Solution polymerization involves polymerization of a monomer in a solvent in which both the monomer (reactant) and polymer (product) are soluble. Suspension polymerization refers to polymerization in an aqueous medium with the monomer as the dispersed phase. Consequently, the polymer producing from such a system forms a solid dispersed phase. Emulsion polymerization is similar to suspension polymerization but the initiator is located in the aqueous phase (continuous phase) in contrast to the monomer (dispersed phase) in suspension polymerization. Besides, in emulsion polymerization the resulting polymer particles are considerably very smaller than those in suspension polymerization [46].

All polymers follow a degradation sequence in which the polymer is first converted to its monomers and then mineralization of monomers occurs. Most polymer molecules have too large size to pass through the cellular membranes, so firstly they have to depolymerize to smaller monomers before microbial cells absorbe them in biological system. The begining of polymer degradation during the chemical hydrolysis process can result different physical, chemical and biological forces. Physical forces such as heating/cooling, freezing/melting or wetting/drying can cause mechanical cracking of polymeric materials. These physical forces deteriorate the polymer surfaces and reveals the new surfaces for reaction with chemical and biochemical agents. This feature is a critical phenomenon in the degradation of solid polymers but the chemical and biological forces of fluid polymers are more important [47,48].

In recent years, advances of innovative technologies in tissue engineering, regenerative medicine, gene therapy and drug delivery systems have promoted through the need of new biodegradable biomaterials. Biologically and synthetically derived biodegradable biopolymers have attracted considerable attention. Polysaccharides and proteins are typical biologically derived biopolymers while aliphatic polyesters and polyphosphoesters are typical synthetic biopolymers. Specific biopolymers needed for in vivo applications are required because of the diversity and complexity of in vivo environments. Nowadays, synthetic biopolymers have become attractive alternative materials for biomedical applications for three reasons for most biologically derived biodegradable polymers: (1) may induce an immune response in the human body; (2) difficulty in chemical modifications; (3) change of the bulk properties after chemical modifications. To achieve the specific properties, properly designed synthetic biopolymers require further modifications without altering the bulk properties [49]. Table 11 lists the potential applications of these biodegradable polymers in tissue engineering.

Polymer	**Tissue engineering**
Polyanhydrides	Bone
Polyurethane	Vascular, Bone
Polyelectroactive materials	Nerve
Polyphosphoester	Bone
Poly(propylene fumarate)	Bone
Polyesterurethane	Genitourinary

Table 11. The potential applications of biodegradable synthetic biopolymers [49].

2.4 Ceramics

Ceramics are used as parts of the musculoskeletal system, dental and orthopaedic implants, orbital and middle ear implants, cardiac valves, coatings to improve the biocompatibility of metallic implants. However, these biomaterials have been preferred less commonly than either metals or polymers. Some medical ceramics have presented are listed in Table 12 [6]. Ceramics used for repair and replacement of diseased and damaged parts of skeletal systems are named as biocompatible ceramics or bioceramics. Bioceramics have become a diverse variable class of biomaterials presently including three basic types: bioinert ceramics, bioactive ceramics which form direct chemical bonding with bone or even with soft tissues in biological medium, bioresorbable ceramics that actively participate in the metabolic activities in organism. Alumina (Al_2O_3), zirconia (ZrO_2) and carbon are bioinert ceramic materials; bioglass and glass ceramics are bioactive and also calcium phosphate ceramics are categorized as bioresorbable. Bioceramics became attractive materials for medical applications, mainly in orthopaedics, maxillofacial surgery and dental implants. The biological evaluations of bioceramics are examined from the viewpoint of cytotoxicity, tissue irritability, bioceramic-tissue interface and cell adhesion to biomaterial surface in literature [50-52]. Figure 10 shows the main characteristics of ceramic materials [6].

Ceramic	Chemical Formula	Comment
Alumina Zirconia Pyrolytic carbon	Al_2O_3 ZrO_2	Bioinert
Bioglass	$Na_2OCaOP_2O_3$-SiO	Bioactive
Hydroxyapatite Hydroxyapatite Tricalcium phosphate	$Ca_{10}(PO_4)_6(OH)_2$ (sintered at high temperature) $Ca_{10}(PO_4)_6(OH)_2$ (sintered at low temperature) $Ca_3(PO_4)_2$	Biodegradable

Bioinert: material property that retains its structure in the body after implantation and does not induce any immunologic host reactions; **Bioactive:** material property that form bonds with living tissue; **Biodegradable:** material feature that degrade by hydrolytic breakdown in the body while they are being replaced by regenerating natural tissue; the chemical by-products of the degrading materials are absorbed and released via metabolic processes of the body.

Table 12. Ceramics used in biomedical applications [6].

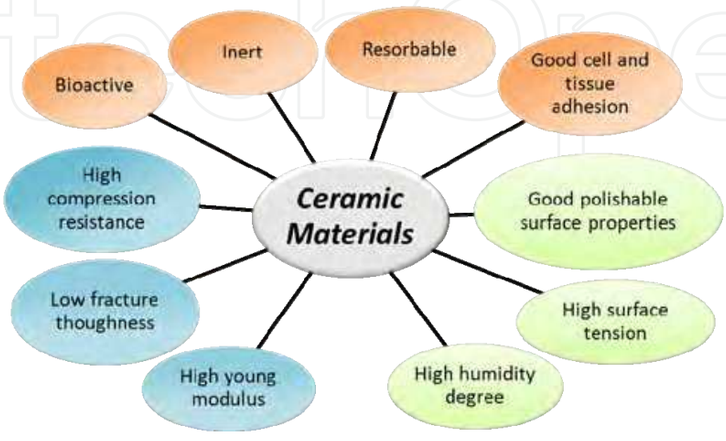


Fig. 10. Main features of ceramic materials [53].

The brittleness of bioceramics has severely restricted their field of application, leaving aside alumina (Al_2O_3) and zirconia (ZrO_2), which are being used for hip joint prostheses. Bioceramics, phosphates in particular, could be used to manufacture ideal biomaterials due to their high biocompatibility and bone integration, as well as being the materials the most similar to the mineral component of the bones [54]. Alumina ceramic has desirable characteristics such as bioinert, high hardness, good abrasion resistance, excellent wear and friction behavior. These properties are associated with its surface energy and smoothness. This biomaterial has only one thermodynamically stable phase and a hexagonal structure with aluminium ions at the octahedral interstitial sites. The mechanical features of ceramic biomaterials are prescribed in Table 13. Good abrasion resistance, strength and inert behaviour of alumina in chemical medium have made it desirable ceramic material for hard tissue implants. The biocompatibility of alumina and zirconia ceramics have been tested and evaluated by many researchers. The results of these researches showed negative indication of implant rejection or prolapse of the implanted piece after many weeks of implantation and separately, fibroblast proliferation, vascular invasion and tissue growth in the pores of the implant were reported [52].

Material Name	**Young's Modulus (GPa)**	**Compressive Strength (MPa)**	**Bond Strength (GPa)**	**Hardness**	**Density (g/cm^3)**	**Klc ($MPam^{1/2}$)**
Inert Al_2O_3	380	4000	300-400	2000-3000 (HV)	>3.9	5.0-6.0
ZrO_2 (PS)	150-200	2000	200-500	1000-3000 (HV)	≈6.0	4.0-12.0
Graphite(LTI)	20-25	138	NA	NA	1.5-1.9	NA
Pyrolitic Carbon	17-28	900	270-500	NA	1.7-2.2	NA
Vitreous Carbon	24-31	172	70-207	150-200 (DPH)	1.4-1.6	NA
Bioactive HAP	73-117	600	120	350	3.1	<1
Bioglass	≈75	1000	50	NA	2.5	0.7
AW Glass Ceramic	118	1080	215	680	2.8	≈2
Bone	3-30	130-180	60-160	NA	NA	NA

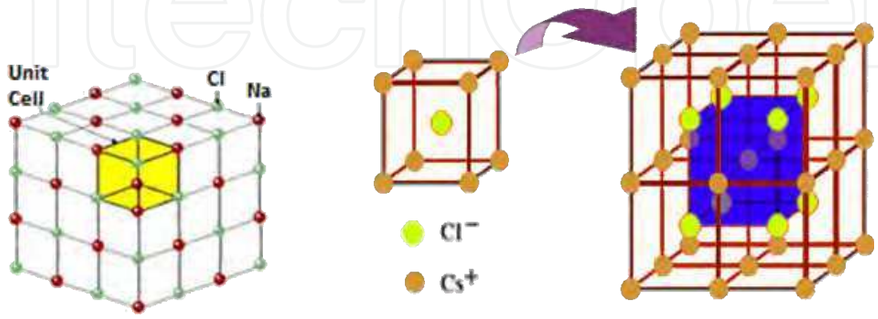
PS: Partially Stabilized; **HA:** Hydroxyapatite; **NA:** Not Available; **AW:** Apatite-Wallastonite; **HV:** Vickers Hardness; **DPH:** Diamond Pyramid Hardness

Table 13. Mechanical features of ceramic biomaterials [54].

Ceramics are represented structurally ionic compounds such as sodium chloride. Atoms in sodium chloride are ionized by electron transfer making an ionic compound as a result of coulombic attractions. Negatively charged ions have increased atomic radii because they gain an electron and positively charged atoms have smaller radii because they lose an electron. The electronic attraction of the counter ions in the crystal structure gives rise to its stability. The simple and face-centered cubic structures of sodium and cesium chloride ions can be given as an example (Figure 11), respectively [30].

Structure-property relations of ceramic materials are composed of metallic and nonmetallic elements held together by ionic and/or covalent bonds. The interatomic bonds in ceramics

result in long-distance and three-dimensional crystalline structures but glass materials do not exhibit long-distance order. The electrons in ionic and covalent bonds are circumscribed between the constituent ions/atoms of the metallic bonds; therefore ceramics show the nonconductive property. The strong ionic and covalent bonds make ceramics hard and brittle, because the planes of atoms/ions cannot move one through another. For this reason, ceramics and glasses are sensitive to the presence of cracks or other defects during plastic deformation. The ionic and/or covalent nature of ceramics also influences their chemical behavior [6].



(a) (b)

Fig. 11. Unit cells and crystal structures of (a) sodium chloride (NaCl) [55] and (b) cesium chloride (CsCl) [56] crystals.

Although ceramics and glasses resist to corrosive effects when exposed to the physiological environment, components of the ceramic structure make them sensitive to degradation media. The rate and mechanism of degradation depend on the structural properties of ceramic. Although alumina ceramic has mostly a bioinert character, its strength decreases in time during the immersion in simulated body fluids and after implantation. Some cracks and crack propagation may accelerate dissolution of impurities so ceramic material degrades in the biological structure.

Bioactive ceramics and glasses are also degraded in the body. [52]. Generally, degradation rate of materials depends on material composition, their functions and components of biological medium. The biodegradable (resorbable) ceramics are used for applications such as drug delivery systems, repairing of damaged or diseased bone, bone loss, filling the implant system vacations, donor bone, excised tumors, repairing vertebra, herniated disc surgery, treatment of maxillofacial and dental defects [53].

The brittleness and poor tensile strength properties of ceramic and glass implants are the main disadvantages. Although they can have exceptional strength during the compression loadings, ceramics and glasses fail at low stress under the mechanical loading such as tension or bending. Alumina and zirconia have the highest mechanical properties among biomedical ceramics. Low friction coefficient and wear rate are other advantageous properties of alumina. These properties of alumina and zirconia ceramics are used as a load-bearing surface in joint replacements [6].

Most of scientific works have been devoted to the interfacial reactions of biological systems with hydroxyapatite ceramic having chemical structure very similar to the mineral phase composition of bone. Hydroxyapatite is a popular surface coating material for stainless

steels, titanium and its alloys implants. In the recent time, researchers have investigated the probability of its use in composite forms that integrate polymers with ceramic or metal/ceramic combinations. There are significant researches performed on coating techniques, in-situ and biomimetic synthesis of apatites and the implications for ceramic properties and microstructure. The thermal and chemical stability of ceramics, high strength, wear resistance and durability properties contribute to making ceramics good candidate materials for surgical implants [57].

Calcium phosphate-based biomaterials and bioceramics are now used in a number of different applications throughout the body, covering all areas of the skeleton. Applications include dental implants, transdermic devices and use in periodontal treatment, treatment of bone defects, fracture treatment, total joint replacement, orthopaedics, cranio-maxillofacial reconstruction, otolaryngology and spinal surgery depending upon a bioresorbable or a bioactive material (different calcium orthophosphates). Figure 12 shows some commercially available ceramic medical products [58] and Table 14 also presents calcium phosphate based ceramics arranged by Ca:P ratio [54].

(a) (b) (c) (d)

Fig. 12. Ceramic products for medical applications (a) ceramic crown [59]; (b) hydroxyapatite block ceramic [60]; (c) ceramic implant systems [61]; (d) bio-eye hydroxyapatite orbital implants [62].

The mechanical properties of calcium phosphates and bioactive glasses make them unsuitable as load-bearing implants. Clinically, hydroxyapatite has been used as filler for bone defects and as an implant in load-free anatomic sites such as nasal septal bone and middle ear. In addition to these applications, hydroxyapatite has been used as a coating material on metallic orthopaedic and dental implants to promote their fixation in bone. In this case, the fundamental metal surfaces to the surrounding bone strongly bonds to hydroxyapatite. Delamination of the ceramic layer from the metal surface can cause serious problems and results in the implant failure [6]. Intracorporeal implantable bioceramics should be nontoxic, noncarcinogenic, nonallergic, noninflammatory, biocompatible and biofunctional in the biological structure.

Chemically, calcium orthophosphate bioceramics are based on HA (hydroxyapatite), β-TCP (β-tricalcium phosphate), α-TCP (α-tricalcium phosphate) and/or BCP (biphasic calcium phosphate). The BCP concept is determined by the optimal phase ratio between HA with α-TCP or β-TCP phases. Desirable bone tissue should have two clinical requirements: (1) pores size of the bone tissue grafts should be about 100 μm for biodegradation rate comparable to the formation of bone tissue between a few months with about two years and (2) their mechanical stability should be sufficient for clinical demand. HA is a more stable phase under the physiological conditions compared to α-TCP and β-TCP phases, as it has a lower solubility and a slower resorption rate. Calcined HA-based implants are applied for

Name	Abbreviation	Formula	Ca/P
Tetracalcium phosphate	TetCP	$Ca_4O(PO_4)_2$	2.0
Hydroxyapatite	HAp	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Amorphous calcium phosphate	ACP	$Ca_{10-x}H_{2x}(PO_4)_6(OH)_2$	
Tricalcium phosphate (α, β, γ)	TCP	$Ca_3(PO_4)_2$	1.50
Octacalcium phosphate	OCP	$Ca_8H_2(PO_4)_6.5H_2O$	1.33
Dicalcium phosphate dihydrate (brushite)	DCPD	$CaHPO_4.2H_2O$	1.0
Dicalcium phosphate (monetite)	DCP	$CaHPO_4$	1.0
Calcium phosphate (α, β, γ)	CPP	$Ca_2P_2O_7$	1.0
Calcium pyrophosphate dihydrate	CPPD	$Ca_2P_2O_7.2H_2O$	1.0
Heptacalcium phosphate	HCP	$Ca_7(P_5O_{16})_2$	0.7
Tetracalcium phosphate diacid	TDHP	$Ca_4H_2P_6O_{20}$	0.67
Calcium phosphate monohydrate	MCPM	$Ca(H_2PO_4)_2.H_2O$	0.5
Calcium metaphosphate (α, β, γ)	CMP	$Ca(PO_3)_2$	0.5

Table 14. Calcium phosphates arranged by Ca:P ratio [54].

repair of the bone defects after implantation for many years, bioceramics made of β-TCP, α-TCP, CDHA (calcium-deficient hydroxyapatite) or BCP are more preferable for medical purposes. According to both observed and measured bone formation parameters, calcium orthophosphates were arranged as low sintering temperature BCP (rough and smooth) ≈ medium sintering temperature BCP ≈ TCP > calcined low sintering temperature HA > non-calcined low sintering temperature HA > high sintering temperature BCP (rough and smooth) > high sintering temperature HA (calcined and non-calcined). Figure 13 shows some randomly chosen examples of commercially available calcium orthophosphate bioceramics for use as bone grafts [63].

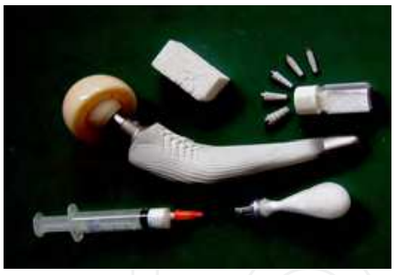


Fig. 13. Various commercial calcium phosphate-based bioceramic products [63].

Bioresorption and bioactivity are the most important properties of calcium phosphate-based biomaterials. Even though the bone mineral crystals have a very large surface area, beside this, calcium phosphate bioceramics present lower surface area and strong crystal bonding. Because of this reason, disintegration of particles into crystals and the dissolution of crystals are involved in a resorption process. While cell activity forms the dissolution stage of crystals, insoluble calcium phosphates such as apatite or calcium pyrophosphates cannot be eliminated easily by cells and can reveal infected properties in other tissues. High sintering temperature (>900°C) decreases the resorption rate of HA ceramics, on the contrary (<900°C) increases [52]. Although HA sintered ceramics show osteoconductivity, their bioresorbability is low and HA remains in the body for a long time after implantation. Implanted materials should exhibit resorbable property through the bone regeneration followed by complete substitution for the natural bone tissue after stimulation of bone

formation. Therefore, recent research has been tend to TCP ceramics as scaffold materials for bone regeneration [64].

Calcium phosphate ceramics exhibit nontoxic behavior to tissues, bioresorption and osteoinductive property. Since ceramic/ceramic, ceramic/metal, ceramic/polymer composites include the different solid particle stiffeners, they need to the choice of more materials for implant applications. Consequently, the biological activity of bioceramics has to be known by various in vitro and in vivo studies and also data on mechanical feature would determined using by standard test methods to make the implant application and the choice of the bioceramic depending on the site of implantation easier [52]. Eventually, implantable bioceramics should be nontoxic, noninflammatory, nonallergic, noncarcinogenic, biocompatible and biofunctional for its working time in the host tissue.

In consequence of bioceramics have generally structural properties and functions; they were used as joint or tissue replacements, coating materials to improve the biocompatibility of metal implants, temporary structures and frameworks to rebuild the damaged tissues in the body, drug delivery system for the treatment of damaged living organism.

2.5 Composites

Composites are engineering materials that contain two or more physical and/or chemical distinct, properly arranged or distributed constituent materials that have different physical properties with an interface separating them. Composite materials have a continous bulk phase called the matrix and one or more discontinuous dispersed phases called the reinforcement which usually has superior mechanical or thermal properties to the matrix. Separately, there is a third phase named as interphase between the matrix and reinforced phases such as coupling agent coated on glass fibers to achieve adhesion of glass particles to the polymer matrix [65].

Solid materials basically can be classified as polymers, metals, ceramics and carbon as a separate class. Both reinforcements and matrix materials are divided into four categories. Composites are usually classified as the type of material used for the matrix. The four main categories of composites are polymer matrix composites (PMCs), metal matrix composites (MMCs), ceramic matrix composites (CMCs) and carbon/carbon composites (CCCs). Recently, PMCs are the most commonly preferred class of composites. There are important medical applications of other types of composites which are indicative of their great potential in biomedical applications [66].

The composite material usually includes reserved distinct phases that are separated on a scale larger than the atomic size. A synthetic composite material also consisted of continuous polymeric matrix phase and a ceramic reinforcement phase like natural biological materials such as bone, dentin, cartilage, skin. The properties of this phase such as the elastic modulus are significantly altered when compared with a homogeneous structured material. Reinforced polymer matrices are fiberglass or natural materials such as bone. Bone, wood, dentin, cartilage and skin tend to be natural biological composite materials, beside these; natural foams include lung, cancellous bone, wood, sponge etc. Natural composites have hierarchical structures particulate, porous and fibrous structural features which are seen on different micro-scales [9].

Composite materials consist of mixtures of polymers, metals and ceramics to form materials such as fiberglass, a mixture of glass fibers coated with a polymeric matrix. In recent years, scientific research tends to develop biomedical composite materials because of these materials present new alternative solutions for load-bearing tissue components. Composite materials are used limitedly in medicine for example high-modulus carbon fibers embedded in a polymeric matrix such as poly(lactic acid) and carbon-fiber-reinforced high molecular weight polyethylene are widely studied for tendon, ligament, joint and facial implants [30].

The structural properties are main feature of composite materials. Composites are different from homogeneous materials because of considerable control can be exerted over the larger scale structure, and hence over the desired properties. The properties of a composite material depend on the shape of the reinforcements, the volume fraction of them and interaction level of the interfaces of constituents. The categories of basic dispersed phase shape in a composite material are (1) particle; (2) fiber; and (3) platelet or lamina as shown in Figure 14. The dispersed phases may vary in size and shape within all category. For example, particulate dispersed phases may be spherical, ellipsoidal, polyhedral or irregular. If any phase consists of voids filled with air or liquid, the material is known as a cellular solid. If the cells have polygonal shapes, the material is a honeycomb form; if the cells have polyhedral shape, material has a foam form. These particulate shapes are necessary to construct the biomaterial to distinguish the above structural cells from biological cells which occur only in living organisms. Moreover, produced composite structure has to include random orientation and preferred orientation [67].

(a) (b) (c)

Fig. 14. Morphology of basic composite inclusions: (a) particle, (b) fiber, (c) platelet [67].

Metals have high strength, ductility and wear resistance properties. Most of many metals have low biocompatibility, corrosion, high stiffness and density, and metal ion releasing when compared to tissues. However the ceramic materials are exhibited good biocompatibility and corrosion resistance and high compression resistance, they also show brittleness, low fracture strength and production difficulties. But polymer composite materials provide alternative route to improve many undesirable properties of homogenous materials mentioned above.

In general, tissues are grouped as hard and soft tissues, the bone and tooth are examples of hard tissues and skin, blood vessels, cartilage and ligaments are some of the soft tissue examples. The hard tissues have higher elastic modulus and stronger tensile strength than the soft tissues. Metals or ceramics chosen for hard tissue applications together with polymers prefferred for the soft tissue applications have to exhibit structural and mechanical compatibility with tissues. The elastic modulus of metal and ceramic materials is 10-20 times greater than values of the hard tissues. This difference is a major problem in orthopedic surgical materials between the bone and metallic or ceramic implants. Because of load

sharing between the bone and implant, it can create different stress distribution directly related to their stiffness [68].

Bone consisting of apatite mineral on collagen fibrils in different mass ratios form a composite material structure (Figure 15). Composite structure with a bioactive component will induce tissue growth to the implant and the formation of a strong bond between the tissue and implant after implantation process. [69].

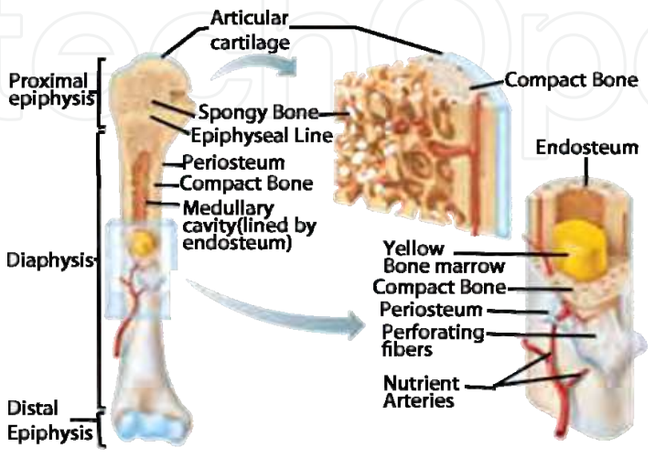


Fig. 15. Bone structure [70].

Shape, size and distribution, volume ratio, bioactivity properties of the reinforcement or matrix phases; matrix properties such as molecular weight, grain size and distribution; ratio of the reinforcement in the matrix and reinforcement-matrix interfacial situation are largely affected to the properties of biomedical composites. Among these factors, properties of constituent materials have significant influence. However, architectural features of the composites such as the reinforcement percentage, distribution and orientation, etc. and reinforcement-matrix bonding condition also have strongly important roles. The mechanical and biological performance of bioactive composites relates to response various clinical requirements. The physical characteristics of the reinforcement such as shape, size and size distribution determines the mechanical properties of a composite. Spherical reinforcement shape which determined by mathematical modelling results achieved in the idealised situation provides good mechanical behavior for particulate composite material (Fig. 16a). Substantially, reinforcing bioactive particles may have to different shapes like irregular, platelet or needlelike. And the irregular shapes facilitate to the penetration of the molten polymer into gaps on the particle surface during high temperature composite processing. Thus, mechanical interlock between reinforced particle and polymer effectively form at the ambient or body temperature and even if a tensile stress is applied (Fig. 16b). The reinforcing bioactive glass or glass–ceramic particles which are made via the conventional glass–making method such as melting and quenching have sharp corners and take up the shape shown in Fig. 16c. These irregular shapes with sharp corners that cause stress concentration in the composites around are not preferred. The platelet shape is rarely encountered for particles in bioactive composites (Fig. 16d). Generally, particles prepared using by the precipitation procedure have to nanometer size and the needlelike shape are directly used for the composite materials (Fig. 16e) [69].

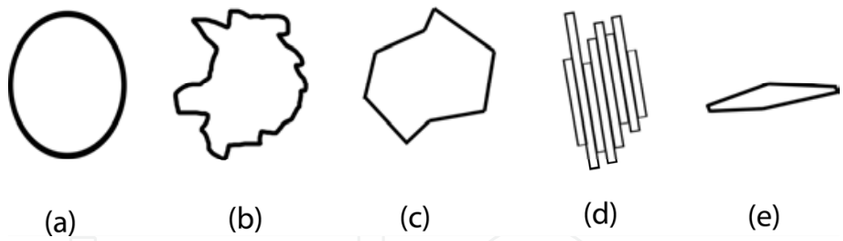


Fig. 16. Shapes of bioceramic particles for biomedical composites: (a) spherical, (b) irregular flake, (c) irregular flake with sharp corners, (d) platelet, (e) needlelike [68].

Polymer composites are combination of two or more materials such as fillers, polymer matrix and binders especially structurally supplemental substances as if metal, ceramic, glass and polymer combine to produce structural or functional properties none of any specific component. Although the constituents protect identities of them and do not dissolve or merge completely into one another, they protect the rules of the integrity. Normally, the components of the composite body form an interface between two phases. The composites are divided in four main categories as composites with particles; composites reinforced with fibers; layered composites and sandwich structured composites [71].

The most contribute factors to the engineering performance of the composite are: (1) materials that make up the individual components; (2) quantity, form and arrangement of the components and (3) interaction between the components. The shape, size, orientation, composition, distribution and manner of incorporation of the reinforcement system in a composite material strongly determine the desirable properties of material. Composite materials can also be simply classified as fiber-reinforced and particle-reinforced composites. Thus, there are four classes of composites: polymer-matrix composites (PMCs), ceramic-matrix composites (CMCs), or metal-matrix composites (MMCs). MMCs are prefferred rarely in biomedical applications and mostly used for high-temperature applications [65].

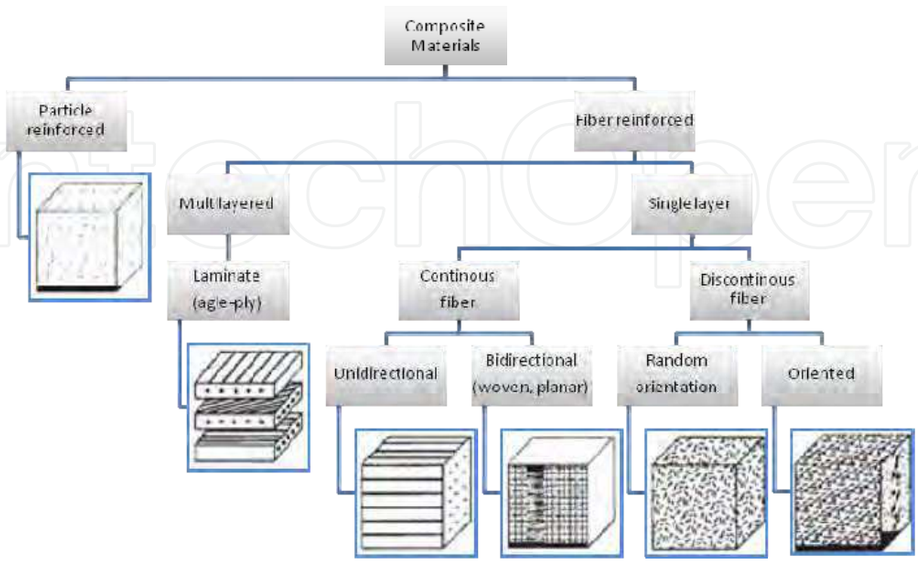


Fig. 17. Classification of composite materials [65].

Figure 17 shows main types of biocomposites according to their reinforcement forms. Three kinds of reinforcements as short fibers, continuous fibers and particulates are typically used in preparation of the medical composites such as screws and total hip replacement stems made from short fiber reinforcements [68].

A typical external fixation system comprises of wires or pins that are pierced through the bone and keep under high tension by screws to the external frame. The wires oriented at different angles across the bone and their tensions are adjusted to provide necessary fixation rigidity. The external fixators are designed with high rigidity and strength to ensure the stability. Traditional designs are made of stainless steel which are heavy and cause patients to feel uncomfortable carrying the system for several months. CF/epoxy composite material is a good alternative for external fixator's construction and gain currency owing to the fact that their lightweight, sufficient strength and stiffness [68]. Biocomposites used in the body are shown in Figure 18.

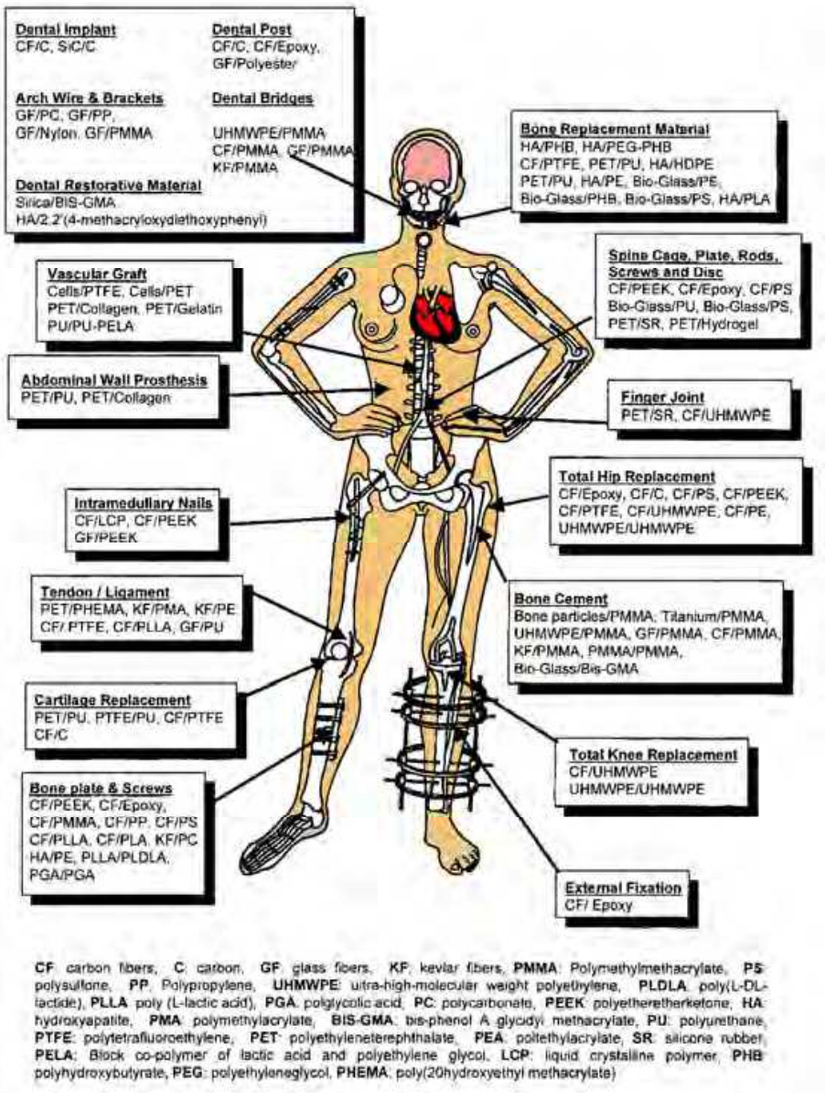


Fig. 18. Biocomposites used in the body [68].

The matrix determines the environmental durability of the composite by resisting chemical, hygroscopic and thermal stresses and protecting the reinforcement from these stresses. The matrix also greatly influences the processing characteristics of a composite material. Common matrices and reinforcements in biomedical composites are listed in Table 15. Thermoplastics are selected as matrix materials due to their nonreactive nature to produce biomedical composite materials. In spite of the thermosets have to inert feature; reactivity, flexibility and strength properties of some thermoplastics have redesigned to provide biodegradable behavior. Resorbable matrices are temporarily convenient to prepare a composite implant, but they are attractive to design a stiff reinforcing material that have a comparable degradation. Good compressive properties and bioactive possibilities of ceramics have also presented new matrix opportunities to produce the modified composite structures [65]. New matrix materials are developed constantly instead of ready for sale materials for medical applications.

Composites can be made from constituents that have similar linear expansion constants. If they have distinct linear expansion constants, contact area (interface) between reinforcement and matrix materials can generates large voids through the contact surface, therefore bone tissue engineers which produce the composite scaffolds have to behave more sense for the selection of the polymeric and bioceramic materials. The nature of the materials in a composite material usually requires the essential mechanical and/or chemical properties for the polymers and ceramics (and glasses). Materials that have the ability to degrade in vivo are ideal candidates for composite scaffolds which gradually degrade. During the degradation of calcium phosphate or bioactive glasses, the polymeric byproducts that form due to low pH values buffered to prevent the formation of inconvenient environment conditions for cells.

Matrix	Fibers	Particles
Thermosets	***Polymers***	***Polymers***
Epoxy	Aromatic polyamides	Polylactide, and its copolymers
Polyacrylates	Poly(ether ketones)	with polyglyocolide
Polymethacrylates	Polyesters (aramids)	Collagen Silk
Polyesters Silicones	UHMWPE	***Inorganic Glass***
Thermoplastics	Polyesters	Alumina
Polyolefins (PP, PE)	Polyolefins	***Organic***
UHMWPE	PTFE	Polyacrylate
Polycarbonate	***Inorganic***	
Polymethacrylate	Carbon	
Polysulfones		Glass
Inorganic	Hydroxyapatite	
Hydroxyapatite	Tricalcium phosphate	
Glass ceramics	***Resorbable polymers***	
Calcium carbonate ceramics		
Calcium phosphate ceramics		
Carbon Steel		
Titanium		
Resorbable polymers		
Polylactide, polyglycolide and their copolymers		
Polydioxanone, Poly (hydroxy butyrate)		
Alginate, Chitosan, Collagen		

Table 15. Constituents of biomedical composites [1].

Bioceramic and glass materials are mechanically stronger than polymers and have a critical significant in providing mechanical stability to construct prior to synthesis of new bone matrix by cells. However, ceramics and glasses tend to destructive failure depending on to their intrinsic brittleness and defect sensitivity. It is required to obtain good chemical and/or physical bonding between polymer and inorganic phase to optimise the biological and mechanical performance of bioactive polymer/ceramic composites.

Table 16 lists selected typical biodegradable and bioactive ceramic/glass-polymer composites that are designed for bone tissue engineering scaffolds and their mechanical properties. Literature reported an important composite scaffolds group that are tailored combinations of bioglass particles and biodegradable polymers such as PLGA, PDLLA, PHB having high application potential. These composites with porous structure have such mechanical properties that are close to cancellous bone and the high bioactivity is conferred by the bioglass particulate filler.

Biocomposite		**Percentage of Ceramic (wt%)**	**Porosity (%)**	**Pore size (μm)**	**Compressive (C) Tensile (T) Flexural (F) Strength (MPa)**	**Modulus (MPa)**
Ceramic	**Polymer**					
Non-crystalline CaP	PLGA	28-75	75	>100		65
ß-TCP	Chitosan-Gelatine	10-70	-	322-355	0.32-0.88 (C)	3.94-10.88
ß-TCP	PLGA	30	-	400(macro) 10(micro)	-	-
HA 	PLLA PLGA PLGA	50 60-75	85-96 81-91 30-40	100x300 800-1800 110-150	0.39 (C) 0.07-0.22 (C) -	10-14 2-2.75 337-1459
nHA	PA	60	52-70	50-500(macro) 10-50(micro)	13.20-33.90 (C)	0.29-0.85
HA	PCL	25	60-70	450-740		76-84
HA	PLAGA	50-87	-	-	80 (C)	Up to 120
Bio-glass®	PLGA	75	43	89	0.42 (C)	51
	PLLA	20-50	77-80	100(macro) 10(micro)	1.5-3.9 (T)	137-260
	PLGA	0.1-1	-	50-300	-	-
	PDLLA	5-29	94	100(macro) 10-50(micro)	0.07-0.08(F)	0.65-1.2
CaP glass	PDLLA	20-50	93-96.5	80-450	-	0.05-0.2
A/W Phosphate	PLA-PDLLA	40 20-40	93-97 85.5-95.2	98-154	0.017-0.020 (C)	0.075-0.12
Glass	PDLLA	-	-	-		
Human cancellous bone	-	-	-	-	4-12 (C)	100-500

Table 16. Typical biodegradable and bioactive ceramic-glass-polymer composites for bone tissue engineering applications and their mechanical properties [73].

Many studies suggest well-dispersed nanostructured composites that may offer surface and/or chemical properties closer to native bone and therefore they might represent ideal substrates to support bone regeneration. Recently, nanosized bioactive ceramic and glass particles have become available which can be considered as ideal fillers for tissue engineering scaffolds. However, problems associated with poor interfacial bonding and particle agglomeration may be more pronounced when using nanosized particles. Coupling agents have been employed as well as titanates and zirconates to improve the bonding between inorganic particles and matrix [72].

Fibre reinforced composite materials are widely prefferred for hard-tissue applications such as skull reconstruction, bone fracture repair, total knee, ankle, dental, hip and other joint replacement applications [73]. Considerably, the mechanical properties of composite materials depend on the direction of loading and the volume fraction of fibers. Low volume fraction of fibers decreases the modulus of the composite and requires a critical volume fraction approach for the modulus of the composite fibers. The modulus of cartilage and collagen fiber in a matrix of glycosaminoglycan and the tensile strength of skin, thick collagen fiber and glycosaminoglycan can be given as examples of the mechanical properties of composites. Biomedical composites which show continuous progression are very attractive and promising engineering materials made from two or more constituents with different physical properties [74].

3. Components of living systems

3.1 Structure and properties of cells and tissues

Cells the smallest living unit of an organism and each cell maintains all necessary functions to survive and represent the organism's genetic code in its linear chemical cord (deoxyribo nucleic acid -DNA). They also evolve by the time or environmental changes; keep those records of experiences and can transfer this information to surrounding neighbor cells or next generations. Cells act like a power plant that requires raw material to produce energy and function. Each cell has a programmed life-span and predetermined function organized by the genetic code. According to their encoded function cells differentiate and develop specific features both functionally and physically during the intrauterine life.

All cells have certain components that enable them to maintain their vital life processes. Those components are responsible to carry out different functions of the cell [75,76]. Cell membrane is a bilayered phospholipid barrier that separates the interior colloidal suspension (cytoplasm) of all cells from the outside environment (Figure 19).

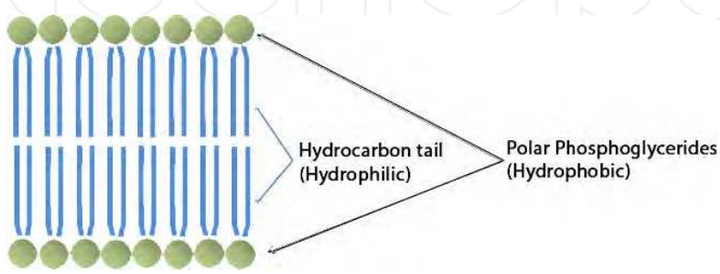


Fig. 19. Lipid bilayer model of a cell membrane. Circular polar portions making internal and external borders are made of phosphoglycerides (hydrophobic lipid), while inner portion of the molecule is hydrocarbon (hydrophilic).

Exterior and interior surfaces of cell membrane are lined with lipid pole of phospholipid molecules, while hydrophilic phospho-poles locate in the middle zone of the membrane. Randomly spread protein molecules, acting like a gated between inner and outer spaces, located in that bilayered cell membrane, of which main function is transportation of some molecules (Figure 20). Carbohydrates take place at cell membrane in combination with proteins as glycoproteins and fat acids as glycolipids. Both these carbohydrate containing molecules (glycocalyx) cover outer surface of cell and repulse negative charged molecules or cells.

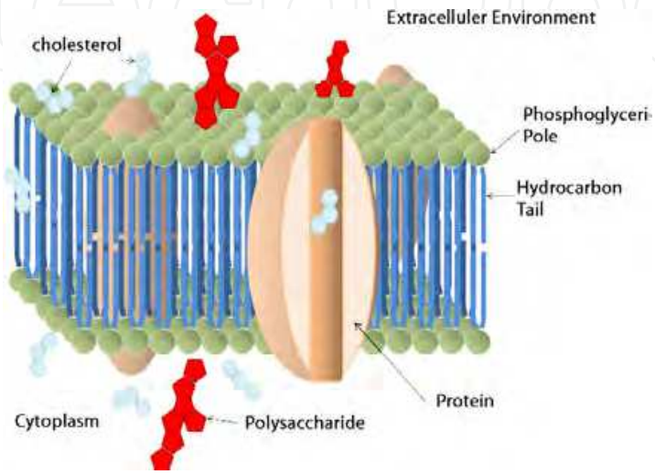


Fig. 20. Fluid-mosaic model of cell membrane. Phospholipid is the major component of the bilayer lipid structure. Protein molecules float within this bilayered structure.

Filtering substances is a selective operation, which essential to maintain homeostatic environment inside the cell to keep vitality of the organism. Even though cell membrane is selective barrier fulfilling passive diffusion, it may not be able to keep the equilibrium between inner structure and outer environment (homeostasis). Certain ions or molecules may require to be moved in or out with enforcement of transporter molecules of cell. This active transportation procedure requires energy.

Common components of functioning cells (organelles) are:

- Nucleus: contains DNA and controls functions of cell,
- Mitochondria: power generator of the cell and control water and mineral level of cytoplasm and responsible from metabolic functions,
- Endoplasmic reticulum: Tubular network among nucleus and cell membrane, responsible from inner transportation and storage,
- Golgi apparatus: Responsible from sorting and storage of protein products of the cell,
- Lysosome: Digestion of proteins, lipids, and carbohydrates and transportation of waste materials to cell membrane,
- Ribosomes: Function for protein synthesis.

Organized gathering of similar cells providing a specific function as a part of organ or organism is called as tissue. Tissues have their own purposeful union to fulfil their main function. Several types of tissues assemble in structural unit to serve a common function and named as “organ”. In an organ usually there is a main tissue (parenchyma), which executes

the organ function. In order to maintain vital functions and integrity of parenchyma supportive tissue (stroma), vessel tissues and nerve tissues take part in an organ. "Organ system" term is used for collection of several organs working together to fulfil a function, for example digestive system [75,76].

3.2 Biomolecules and their behaviors

Biomolecules are main components of living cells (also their raw digestion materials) and at the same time their end-products, can also have an important role in signal transmission inside the cell or among other cells. Those molecules are also responsible from many functions like regeneration, survival and death. Several classifications can be made for their structures and functions. They can be a single molecule or in polymer form as well.

Roughly saccharides, lipids, amino acids are the basic counterparts of more complicated molecules like proteins, vitamins, hormones and enzymes. Fundamental functions like digestion and replication are performed in a programmed cascade via several molecules under the control of DNA molecule. DNA is a double stranded polymer of the same four types of monomers (nucleotides). A base molecule, which may be either adenine (A), guanine (G), cytosine (C) or thymine (T) binds to a sugar (deoxyribose) with a phosphate group attached to it, forms this nucleotide monomer, which also can be called as building block of a single DNA strand (Figure 21). Those monomers bind one another with sugar phosphate linkages.

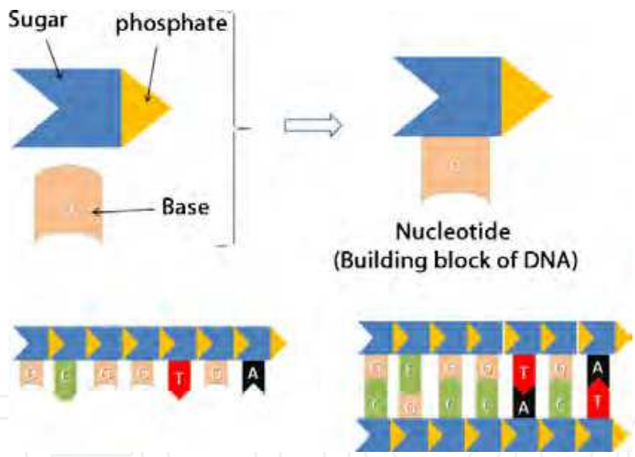


Fig. 21. Structure of DNA.

A DNA strand attached its pair with weak hydrogen links (adenine to thymine, cytosine to guanine), which permits two DNA strands to be separated without breakage. Each those DNA strands are templates for the synthesis of a new DNA strands during cell division to produce new cells.

DNA has more responsibilities than replication but also synthesis of protein and ribonucleic acid (RNA) to maintain its vital functions. This process begins with transcription of some DNA segments and forms RNA polymers that are used as templates for several molecules like proteins or enzymes. In other words DNA contains templates of all molecules that it is responsible to produce.

Amino acids, in other terms backbones of protein polymers, present diversity from DNA or RNA and 20 types of amino acids are used as base monomer for protein (polypeptide) synthesis. This variety brings different structural and behavioral nature diversity for proteins, like maintaining structures via enzymatic activity, movement of cell, sensing any inner or outer signal. According to their genetically encoded nature each protein molecule is responsible from a specific function. Enzymatic action of proteins is mainly dependent their amino acid arrays and location which determines the nature of the enzyme (destruction, digestion, catalization or synthesis function) [76].

3.3 Host response to materials

3.3.1 Inflammation, wound healing, and the foreign body response

Simply, tissue response to any kind of injury can be named as inflammation. Injury is the starting point of protective biomechanism, which triggers wound healing to restore the damaged part of organism.

- Physical trauma, like traffic accidents,
- Thermal injuries, like sun or fire burns and electrical burns,
- Chemical injuries, like contact with acidic or alkali solutions or poisoning or chemically irritant material, and
- Biologic invasion (infections) by microorganisms, like bacteria, virus or fungi can cause tissue injury. Owing that information; it is important to emphasize a common mistake that infection is not a synonym for inflammation, but one cause of inflammation.

Following sudden onset of signal injured vessel system and some local blood cells produce initial response by releasing some biochemical molecules that give first protective reaction to the injury cause and some other produce a chemical signal to attract the white blood cells, which are responsible from body defence, to let them migrate to the injury site. Inflammation stage can also be considered as the first step of wound healing. If the integrity of vessel is interrupted by the injury platelets (thrombocytes) begin to adhere the wound edges and one another to produce clot plug. By the aggregation of platelets they also release some molecules trigger clotting mechanism to produce clot plug. Those vessels or platelet originated molecules increase vessel permeability leading transfusion water from vessel lumen into the injured tissue site, which causes swelling of the tissue (edema). To ease arrival of chemically induced migrating (chemotaxis) of white blood cells; those released biomolecules also loosen muscles surrounding vessels, which are responsible to control blood flow via altering diameter of vessels, and increase vessel diameters. Therefore, the site looks reddish due to dilated blood vessels. Fibroblasts, likewise white blood cells, have the ability of chemotaxis to infiltrate the injury area to start reparatory phase. Some of these released molecules are pain mediators to warn our nerve system to attract our attention to take care our wound.

As the white blood cells arrive the site they begin to struggle with the target caused injury and beside begin to resorb the blood clot to restore vessel lumen, so that blood stream to be maintained. Some white blood cells release molecules to neutralize the threat chemically and some others try to resorb the foreign material in small pieces to relive it (see section 3.4.2). Simultaneously fibroblasts begin to produce connective tissue, which will be replaced with clot until local tissue regeneration takes place. Epithelial cells (responsible to cover our

body and make a barrier in between outer environment and inner medium) begin to replicate and grow to create a new cover over the wound area [75,76].

As the source of injury (foreign body) is eliminated and the tissue is regenerated and take the action again wound healing process is completed. However, if the foreign body, sometimes implant or biomaterial, remains inside the body. On that point; it is critically important that whether the material giving threatening chemical signals, or not. If the remaining material is biocompatible, following the initial acute response, it can get along well with the surrounding tissues and may survive inside the organism.

On contrary if the chemical signals of implanted material are recognized as a threat and cannot be terminated, defence system activates rejection mechanism (foreign body reaction) to withdraw the foreign body. Inflammatory reaction continues beside work out of fibroblasts, which knit a connective tissue net around the foreign body to isolate and put this material in quarantine for any possible further threats. As release of inflammatory biomolecules continues swelling, pain and reddish appearance sustains until the withdrawal. This process is called as foreign body reaction and presents a chronic development.

3.3.2 Immunology and the complement system

Our environment is rich of bacteria, viruses, fungi, and parasites and we are in contact with these external threats continuously via our skin, eyes, digestive, respiratory and genitourinary systems. Each attack of those organisms could have been lethal for us, if our body had not got any protection mechanisms. Defence system of human organism against hazardous factors is immune system. This system is not only responsible to fight with those invader organisms, but also has the obligation to neutralize chemical agents sensed as a threat for the organism. This system is sensitive to the dangers developing internally, like tumoral pathologies and sometimes can struggle with our natural structure itself.

Immune system is consist of two major components; cellular and biochemical reactions. Cellular reaction is carried out by the white blood cells produced partly bone marrow and lymph vessels. Polymorphonuclear neutrophils, polymorphonuclear eosinophils, polymorphonuclear basophils, monocytes, lymphocytes, and plasma cells act like soldiers in this battle. They destroy invading microorganisms by engulfing (phagocytosis), especially neutrophils and macrophages.

Second defence mechanism to eliminate or inactivate biologic or chemical agents is biochemical defence. This neutralization process can be innate or adaptive (acquired). Some natural secretions of our organ systems, like acid release of stomach, some digestive enzyme secretion of several organs of digestive system can kill the bacteria entered to our digestive canal. A mucolytic polysaccharide, lysozyme, which is a component of sweat and tear, can dissolute the microorganisms or some basic polypeptides can react with and inactivate certain types of gram-positive bacteria.

The complement system of about 20 proteins including serum proteins, serosal proteins, and cell membrane receptors, generally synthesized by the liver, is found in the blood as inactive precursors. When stimulated by one of several triggers system that can be activated to destroy bacteria. Triggered system can initiate a chain reaction forming antibodies and

sensitized lymphocytes to destroy the responsible target. They account for about 5% of the globulin protein fraction of blood serum.

Immunoglobulins (antibodies) are synthesized by B-lymphocytes. These glycoprotein molecules can tag a microorganism, infected cell or chemical-threat agent (antigen) and deactivate them. Antibodies can be non-specific as found in normal blood stream or can be synthesized to destroy one target selectively.

3.3.3 Systemic toxicity and hypersensivity

Of the most important features of biomedical materials non-toxicity, in other terms material must not harm the living organism. Damage of substance to the organism may vary from mild local response to (sometimes) lethal generalized reactions. Acute toxicity can be explained as damaging affects to an organism with a single or short-term exposure. Any natural or artificial substance (animal or plant secretions or extracts, inorganic materials, drugs) may damage the living tissues gradually related with their potency, doses and administration way and metabolism. Even materials like inevitable components of cells, like water, or even oxygen, may be harmful for our organism in higher doses. Pure substances may have toxicity risk solely, correspondingly compound materials, that contain more than one component have a different risk rate for each ingredient. Some components may induce toxicity rate of each other or may act a synergic action to harm organism. The damage to living structures, correspondingly with the amount of substance, may occur in many cascades of internal or external cell functions or structures.

Chronic toxicity is the ability of a substance to cause harmful effects over an extended period (sometimes for the entire life), usually on repeated or continuous exposure. Therefore, corrosion, degradation or decomposition of material placed inside the body is, unless designed to act in this direction, is not desired due to the risk of local or systemic toxicity risk. As the toxicity occurs; depending its damage level, patients' complain may vary from local irritation to life-threatening severe condition clinically until the reason of toxicity is removed or neutralized.

Deactivation process of any molecule sensed as a threat (antigen) by immune system is allergic reaction. Several defence mechanisms are initiated locally and neutralize the antigen. However; sometimes, no matter what the amount of antigen entered to the body it may trigger chain-reaction over the normal limits and carries the reaction via chemical signalling all around whole body and described as hypersensitivity reaction. The patient could have been pre-sensitized by multiple exposures to the antigen until that time. No or mild previous reactions due to the antigen contact can be reported by the patient and sudden onset of hypersensitivity may occur at a severe level. On the other hand; the organism may have a genetic potential to generate this over-reaction, which means hypersensitivity reaction may occur during the first introduction with the antigen material and can be lethal.

3.3.4 Tumorogenesis and biomaterials

Reproduction of healthy cells is division of cells (mitosis). DNA controls the frequency of mitosis, likewise all functions of cell. During the life span of a healthy cell DNA carries a

code to end cell life and programmed cell death (apoptosis) occurs. However, some external factors, like chemical agents, radiation, some bacteria or virus infections, may cause a change on the DNA structure (mutation) or pre-determined genetic code is deteriorated during normal life span [75,76]. These mutagenic alterations lead DNA to lose its inhibitory control on mitosis or moreover induce continuous cell division. Additionally or on the other hand; the genetic mutation may clear apoptosis order of the nature and continually dividing cells can survive forever. Both mechanisms cause unstoppable cell number increase inside the body, called as tumourogenesis (tumour formation).Some substances induce cell division via DNA mutation and cause tumour formation, while some, like ethyl alcohol and oestrogen, may promote mitosis and lead cancer. Similarly; continual physical, chemical, electrical or electromagnetic stimuli, behave as chronic irritation and trigger the healing mechanism, which means inducing cell division to repair the injured area. Unless the factor reasoning promoted cell division is relieved cancer out-breaks would be faced. Those are the mainly accepted carcinogenic theories, which give the clues to be considered, while biomaterial production is concerned.

3.3.5 Implant-associated infection

A material or object placed in to an organism to restore a function, mass loss or to measure, diagnose or treat any condition is called as "implant". Implants' success is directly related to their survival. Life expectancy of the implants can be interfered with several endogenous or exogenous factors [77]. Least but not the last issue considering implant failure is the infection. Implant, as a foreign material has a risk to undergo rejection. Therefore; implants are produced of biocompatible materials and sterilized before placement into the body. As antimicrobial body protection is carried out by our skin and mucosal barrier, inner environment of the body is sterile, except some parts like digestive system canal etc. Microorganisms are always in contact with this shield and are not let go inside. However, any kind of injury may break the integrity of the skin-mucosa barrier and can open a gate to the microorganisms to enter body. Following their entry, they replicate themselves and retain at a weak part of organism (colonization). During the proliferation process the also synthesize and release some toxins to damage the host to weaken its defence or to make the environment more proper for their survival. Inoculation of microorganism to the implant material can be via direct contact or blood stream can act like a high-way to transport the microorganisms from a distant entry point to the implant. Either way of exposure can easily initiate colonization of the microorganisms on the implant, in other words infection. Implant, itself, has a risk of rejection and invasion by the microorganisms would lead and hasten withdrawal of the implant. Especially mouth, as a wet and warm atmosphere full of food debris, is an ideal environment for bacteria colonization. That makes it a unique part of the body, with the highest type-multiplicity of microorganism and highest microorganism concentration in one unit of saliva. Those factors mentioned above increase the infection risk of dental implants placed in edentulous jaw bones to restore chewing, phonation functions and aesthetic. Implant surface roughened intentionally to increase bone-implant contact area for more stability and longer survival in the bone cavity. Rough surface provide an ideal environment for bacteria colonization with its retentive topography and can facilitate increase of bacteria count on dental implant. Moreover; incidence of dental implant placement is the higher than all other types of implants. This high frequency of application also increases the infection coincidence of dental implants. Dental implant infections can be as high as 31,2% [78].

Overcoming implant associated infections is another focus of current researches. Previous efforts focused on killing already-colonized microorganisms via several antimicrobial agents like antibiotics [79] or debriding the colonies with several techniques like scratching, chemical cautery or damaging the colonies via photo thermal effect of laser energy. However current concepts have centered on prevention of colonization or may be killing the microorganism as they contact the implant. Those studies showing positive effect of antibiotic use on infection treatment grounded the idea of keeping antibacterial agents around the implant site during healing process. Initial attempts aimed administration of antimicrobials, like tetracycline, ciprofloxacin, vancomycin, rifampin/minocyclin, cefoperazone, penicillin/streptomycin, gentamicin, around the implant to prevent infection. However; those local administration of antibiotics to the implant site topically had limited release time and couldn't prevent development of infection in long term. Idea of gradual release of the antimicrobial substances by the implant has leaded coating titanium surface with antibiotics with restricted success limited time of degradation process of antimicrobial drug coating [80]. Several local drug delivery vehicles like (glycolic, lactic acid, caprolactone, methyl methacrylate polymers, chitosan, agarose/hydro-gels, bioactive ceramics, collagen, nanotubes), have been studied to prolong releasing period of the antibiotic [81-83]. Choice of delivery medium is dependent on:

- Type of tissue to be placed (whether soft tissue or bone)
- Environment of the implant to be protected (mouth, skin, bone, vessels, heart, genitor-urinary system, aero digestive system, cranium or any place inside the body)
- Required releasing time (slow or fast)
- Biodegradation mechanism
- How many drugs will be used (single or multiple) and
- Compatibility with antimicrobial agent to be sustained.

Simultaneously; antimicrobial prevention concepts have evolved innovative surface technologies based on the knowledge that certain metal ions like silver, copper, bismuth and zinc have oligodynamic effect (toxic effect on living organisms) on microorganisms [84,85]. Target of those researches centered on modifying the titanium dental implant surface with these above mentioned metal ions to wall-up a defensive line on the titanium surface and protect themselves against bacterial attacks. Similarly zirconium doped titanium presents antimicrobial activity beside high epithelial cell attraction and mediate healthy cell proliferation to promote formation epithelial cell barrier over the implant surface.

Development of carbon-nanotube systems grown on implant surface can give the capability of controlled release of any drug implanted. It has been shown that they can act as sensing probe for various (electrical, thermal, photo or chemical) stimuli. These triggering factors can be redox reactions of bone-forming cells (osteoblasts) or connective tissue-forming cells (fibroblasts) or any substance specifically released from bacterial wall. As impulses are sensed, such materials can release any given drugs to potentially fight bacterial infection, reduce inflammation, promote bone growth or reduce fibroblast functions [85, 86].

3.3.6 Blood coagulation and blood materials interactions

Any kind of injury may disrupt integrity of blood vessels and cause bleeding. Coagulation (hemostasis) mechanism is to stop blood loss, which can also be named as a protective mechanism. Injury of the vessel initiates physical, cellular and biochemical chain reaction.

Physical change due to trauma (rupture) of vessel walls leads a reflex at surrounding muscles of the vessel and they constrict diameter of vessel, so that blood flow thru narrower lumen decreases gradually and contribute success of co-working hemostatic mechanisms. Besides external trauma, internal biochemical stimulus released by platelets (thromboxane A_2), has an additive effect on vasoconstriction [75,76].

Cellular part of hemostasis mechanism is fulfilled by platelets, formed in the bone marrow and release into blood stream as a member of blood cell population. Platelets, though lack of reproduction capability and nuclei in their cytoplasm, contain thrombosthenin, that contract the platelet cell initially. They can store calcium ions in their cytoplasm and synthesize several molecules act actively in inflammation process (pain mediators).

Main action of platelets in hemostasis mechanism is aggregation via adhesion on another and to injured vessel walls. Glycoprotein layer on cell membrane presents a selective adhesiveness to the platelet. Under normal conditions this layer rebuff adhesion to healthy vessel wall tissue (endothelial cells), while in presence of any injury glycoprotein promotes adhesion to the damaged endothelium, collagen bundles supporting vascular wall and one another. This increased adherence occurs simultaneously with changing their form as swelling and presenting multiple protrusions on their cell membrane and degradation of several substances of some attract more platelets and lead increase of those cells in number. Increased irregularity of their form and sticky nature of the membrane ease their adhesion capability to accumulate at the damaged vessel window. These aggregation and adhesion behavior of platelets yield initial clot formation to stop bleeding.

The third method playing a role in hemostasis mechanism simultaneously with vascular response and platelet plug formation is biochemical coagulation cascade. Basically; over 50 substances found in blood or tissue take place in blood coagulation (procoagulants) or anticoagulation (anticoagulants) equilibrium. Procoagulant factors of those substances (Table 17) are present in inactive (precursor) form and any stimulus originated traumatized vascular endothelium or platelet derivates can activate them to start the coagulation mechanism. These extrinsic and intrinsic pathways activate those factors and each activated substance either activates another or catalyse their activation process. Final steps of the cascade are change of fibrinogen to fibrin via thrombin and formation of fibrin network as an end product.

Factor I	fibrinogen
Factor II	prothrombin
Factor III	tissue factor or tissue thromboplastin
Factor IV	calcium ion
Factor V	proaccelerin, labile factor or Ac-globulin
Factor VII	serum prothrombin conversion accelerator, proconvertin or stable factor
Factor VIII	antihemophilic factor, antihemophilic globulin, antihemophilic factor A
Factor IX	plasma thromboplastin component, Christmas factor or antihemophilic factor B
Factor X	Stuart factor or Stuart-Prower factor
Factor XI	plasma thromboplastin antecedent or antihemophilic factor C
Factor XII	Hageman factor
Factor XIII	fibrin-stabilizing factor
Fletcher factor	Prekallikrein
Fitzgerald factor	High-molecular-weight kininogen
Platelets	thrombocytes

Table 17. Factors in blood coagulation mechanism

Blood clot (thrombus) piece can be detached from a main clot mass or sometimes may occur spontaneously without any injury effect. High blood viscosity, high procoagulant serum levels or vascular malformations etc. increase intravascular thrombus formation risk. Any free thrombus piece can easily be transferred via circulatory system until get stacked in a narrower vessel lumen and obliterate an artery (of heart, brain, kidney eye etc.), which may cause a severe damage due to occluded blood circulation of the related the tissue. Especially, thrombus formation can easily occur on irregular vascular surfaces covered with cholesterol plaques or around any vascular implants or grafts like stents used in cardiovascular interventions. For a healthy person; anticoagulation mechanism is a protective equilibrium that impedes coagulation of whole blood in the vascular system spontaneously, which may mean end of life. In other case, as the clotting cascade begins due to any reason, anticoagulation mechanism obviates dissemination of the coagulation chain thru whole circulation system. Anticoagulant substances found in our body like vascular surface cover, glycocalyx, helping platelet or clotting factor repelling, or thrombin binding protein thrombomodulin. Fibrin fibers formed during coagulation consumes thrombin and eliminates it from the environment. Additionally alpha globulin protein (antithrombin-heparin cofactor or antithrombin III) also removes thrombin and hinder or delay coagulation. In our daily life; anticoagulation is an equilibrium is maintained via vascular surface integrity, presence of those anticoagulant substances in the blood or with some drugs.

On the other hand, in case of lack of any of those clotting factors or a deficit in platelet structure, function or count lead disturbed coagulation function, which means unstoppable bleeding reasoning death. Anticoagulation kept in normal limits is desired to avoid intravascular coagulation especially in patients with vascular malformations, vascular grafts or stents, atherosclerosis etc. Therefore, those patients are prescribed anticoagulant, like heparin, coumarin or 1,3-indandionederivates, to increase coagulation threshold within safety limits.

3.4 Evaluation of materials behavior

Prior to clinical use of any substance (biomaterial or drug), which is going to be in contact with our organism, it should be strictly tested and proven to be non-hazardous for us. Those processes to examine this biomaterial can be classified in 3 parts. First requirement is the matching physical and chemical properties of the substance, desired to be the same or at least compatible with the organism. These materials, therefore, are produced according the tissue features, where they are going to be used. According to tissue type; physical strengths (tensile, compressive, shear strength, elasticity modulus), thermal properties, photoreactivity or translucency, colour, calcification potency, surface structure, chemical features, or degradation resistance are modified for ideal adaptation to the environment. Those features are examined under laboratory conditions before biologic behavioral tests [87].

3.4.1 In vitro assessment of tissue compatibility

Proofed materials in laboratory examinations are ready to be evaluated for their biologic performance. According to the tissue(s) which is(are) going to be the environment of the

material, related tissue cells are selected to evaluate if the material has a potential to damage them, or not. Even materials previously proven to be safe to be use inside the body, should be tested if any chemical or major physical modification has been carried out. With this aim cell culture systems are the first step evaluation process to assess toxicity of the material for related cell types. In vitro term is used to define a test setup that produces cells extracted from a living organism outside the body in controlled laboratory conditions. This method is helpful to assess the biologic behavior of a material without killing plenty of animals used in experiments. Additionally, these in vitro study settings result rapidly, can be performed in many different models and can be repeated in a short time. Initially cells are harvested from a living organism (animal, human or even plants), kept in proper environmental conditions containing all necessary organic and inorganic substances, water, temperature etc., to maintain their survival. They should be isolated from other cell groups or microorganisms to gain a pure cell population with equivalent features, so that cellular response could be same in this population. Genetic structure can be modified to give them immortality to keep their production continuously. Gene modification can be used to transform those cells to cancer cells to work on such illnesses. Then cultured cells are passaged and exposed to test material or can be stored at -196°C for further studies. Time depended toxicity rate can be measured as the count of surviving cells, their physical appearance, functions like replication rate or energy production ability (mitochondrial activity) [88].

Additionally, biologic behavior of a material is not only toxicity but also can be an altering effect on cell structure. Especially mutation effect on cell DNA due to test material exposure may also change cellular behavior or character and cause cancer. Therefore, such mutagenity evaluations can also be made for further investigation. With this purpose morphological change can be scanned with scanning electron microscopy or ultrastructural transformations can be visualized with transmission electron microscopy. Cellular affinity to the substance is eventually another point of interest to measure. Cellular extracts are lined on the prepared surface and incubated for a certain period to wait for cell adhesion. Then cultured specimens are washed out with water and examined to count attached cell numbers.

Some behavioral and structural alterations can be monitored with various biochemicals, spectrophotometric, immunoassay techniques (ELISA-Enzyme-Linked Immunosorbent Assay) or dynamic imaging methods like confocal microscopy. These techniques can detect presence of a defined substance with various methodology in a sampled moment or in real-time.

On the other hand, some materials like bone grafts are used as a scaffold for tissue engineering procedures that mainly act as a carrier of implanted cells and biomolecules. In advanced applications; differentiation of root (stem) cells planted in/on those graft materials to bone cells is another desired feature expected from a bone graft material. Hence, differentiation effect of test material can also be examined with undifferentiated stem cells.

Besides cell cultures; bacterial or fungi cultures can also be used to evaluate antimicrobial effect of the test material. On microorganisms cultured at a medium (on a surface or in a solution) are exposed to the test material and surviving microorganisms are counted to evaluate their lethal efficacy [89,90].

3.4.2 In vivo assessment of tissue compatibility and animal models

Third step of biologic behavioral tests are in vivo (animal) experiments. Only approved substances with in vitro examinations are subjected to in vivo experiments, so that excessive scarification of experiment subjects is minimized. Depending on the purpose of biomaterial; the substance is tested whether it cause any allergic reaction (sensitization), tissue inflammation and rejection reaction (irritation). It is also implanted under the skin (intracutaneously) or in a prepared bone cavity (intrabony) to evaluate local tissue response. Additionally following administration in to the body (no matter what way of administration was chosen) acute or subacute damages to all organ systems (systemic toxicity) are evaluated after implantation via examining each organ with microscopic imaging or biochemical analyses. Genotoxicity potential of the studied material is investigated with changes of genetic structure of the cells exposed to the material. Changes of the healthy tissue can be assessed with comparison of those tissue samples exposed to the substance with healthy tissue structures of the same spice with different methodology. Tissue morphology can be evaluated with microscopic techniques like light microscopy, scanning electron microscopy, transmission electron microscopy, confocal microscopy etc. or some physical tests (tensile strength, shear strength or compression tests) can be used to evaluate physical strength of hard tissues like bone and tooth, or even (sometimes) soft tissues. Biochemical alterations, before and after application of the researched material, can also be compared to evaluate tissue response or its reaction path to the material. Additionally calcified tissues like bone or tooth can be followed up via X-ray images (radiographically). Study designs can be based on time dependent comparative research methodology and can use assessment of half-life of radioactively singed atoms implanted to the study substance to be placed in to the body [91].

Samples to be examined should be free of any contamination (pure), packed properly and sterilized according their structure (with gamma-radiation, steam+heat, ethylene oxide or plasma). Local reaction to the material can be measured with comparison of healthy tissue, physiologic tissue healing or healing process of a standard material well-known and documented previously. In such methodology, unless systemic efficacy is not in consideration, more than one substance can be tested in one organism to make a healthy comparison. However, at least 6 subjects should be studied for each group for statistical analysis. If time depended results are required one group of animals should be prepared for each time interval. Examinations regarding systemic effect of the substance necessitate use of one material on one animal each time, which eventually increase number of animals. Regarding systemic toxicity, irritation or hypersensitivity repetitive dose applications can be used, which also means raised animal number. Following application of test material, the subjects are kept in a convenient habitation conditions. Responses are monitored after scarification or real-time with suitable probing in tissues and body fluids histologically, radiologically, chemically, thermally or immunohistochemically etc. For evaluation of results; obtained raw data is analysed statistically with parametric and nonparametric tests.

Physical or chemical tests can be performed to evaluate structural, chemical or physical strength changes of the material itself after using in the organism. Especially force bearing materials like bone plates or metallic prosthesis or dental implants can be examined regarding corrosion potential, micro/macro cracks or plastic deformation, so that survival of material can be estimated under compressive, tensile and shear strengths besides corrosive effect of body fluids [92].

3.5 Dental implants

Other than restorative dentistry the rehabilitation of teeth losses is a major concern for clinicians. Replacing the teeth with human-made one has been one of the greatest challenges in field of dental medicine. Mechanical features like macro anatomy, micro surface topography of dental implants necessitate a special concern to give a life-long service in an environment where repeating bite or chewing forces are loaded from different directions. These physical design properties are expected to neutralize those loaded chewing forces or at least should minimize compressive stresses on the bony bed where they were implanted. Moreover; regarding resistance against metal fatigue choice of material is highly important in case of cycling compressive, shear and tensile loads. Dental implants are partly placed into the jaw bones where in contact with blood and also have a part left in the oral cavity where exposed to saliva. Those body fluids that have lipophilic and hydrophilic affinity and enzymatic activity potentially dissolve and corrode materials. Hence corrosion resistance of the dental implant material should be high enough both to sustain their physical strength in acceptable limits and also to minimize local or systemic toxicity risk due to corrosion particles. However; first place for significance ranking of dental implant material, likewise in all biomaterials, is its compatibility with the surrounding tissues (biocompatibility). Therefore; several materials and alloys have been tried for decades to find out the ideal biocompatibility with excellent physical features. Titanium and zirconium elements have been well documented and presented to have better tissue biocompatibilities and acceptable physical properties, when compared to others [93,94]. It is been shown that alloys of these materials can present augmented biologic and physical features while corrosion aspect of those alloys is still questionable. With this regard Ti-6Al-4V, Ti-6Al-7Nb, Ti-5Al-2Nb-1Ta, Ti-30Ta and Ti-Zr alloys have been studied in several studies to enhance mechanical and biologic properties of titanium or zirconium [95-99]. Those alloys have been used as base material or as coating for augmented features. More recent studies focusing on Ti-Zr alloy have promising results which show evidences of elimination of disadvantages of both substances while improving biocompatibility.

Except using alloys to improve biocompatibility several techniques have been used to modify implant surface that is in contact with bone. Changing micro-structural, chemical or ionic structure of dental implant material to make it more attractive for surrounding bone cells (osteoblast) and allow it to bind calcium and phosphate ions of neighboring bony bed [100].

Following preparation of a place in the jaw bone dental implant is placed into the cavity and left for healing. During the healing process blood clot cover implant surface which is not in close contact with bone. Those two different neighboring structures (bone and blood clot) initiate healing process which means integration of implant to surrounding bone tightly. Parts of implant surface at direct bony contact may develop chemical connection with calcium and phosphate of bony hydroxyapatite crystal. Developing a bone contact on the implant surface exposed to blood clot needs more time to have bony connection. Overlaying clot undergoes transformation turn into bone tissue, so that implant connects to surrounding bone (osteointegration). Both titanium and zirconium materials and their alloys are capable to show osteointegration. Considering this process, implant surface must be available for osteoblast habitation, in other terms implant surface should have an optimum surface roughness values to let the bone cells attach on tightly. Surface treatment also helps

to increase surface magnitude with roughening, which also contribute extension of bone-to-implant contact area. Following adhesion; cells synthesize osteoid bone matrix (immature bone) that acts like a template leading calcium hydroxyl apatite crystal precipitation in (calcification). Therefore, osteoblastic attachment is inevitable for osteointegration, which also means "success" [101]. Therefore; increasing surface roughness has been worked out with different techniques, like sand blasting, acid etching, abrading with SiC paper, microarc oxidation, spark erosion, lasering or their combinations [102,103]. Sand blasting is a well-documented method to improve surface porosity, as well as altering several physical properties of the metal (fracture, fatigue, tensile strength etc.) [104].

Various parameters have been modified for optimization both for roughness and bone cell (osteoblast) adhesion to the surface. Different materials like aluminium oxide, TiO_2, hydroxyapatite, calcium phosphate and zirconium oxide have been studied in different particle sizes in combination or separately [105]. Parameters like blasting speed, particle diameter, and particle ratio in the blowing air, blasting atmosphere and temperature can affect surface topography. Type of blasting material is also important with the respect that during the blasting process some particles can be stacked into the titanium surface due to high velocity and may remain on even after cleaning processes following blasting. It should be considered that those blasting particles remaining on the implant surface can alter tissue reaction to the implant material in positive or negative direction. With this regard, choice of blasting materials among biocompatible ones would accelerate osteointegration process, while substances with low or no biocompatibility can be expected to influence this process negatively [106]. It should also be considered that these blasting materials remaining on the implant surface may undergo corrosion and may result rejection of the implant or toxicity by the time as well [107]. Therefore, analysis of the titanium surface following blasting can be advised to evaluate any remnants of blasting materials if such susceptible material had been used for blasting. Owing that; several chemicals or their combinations have been tried out and some are currently used to modify implant surface to enhance roughness. Phosphoric acid and its derivates, HF, HNO_3, HCl and H_2SO_4 the most frequently used chemical etching agents to modify titanium surface solely or in combination. It is also noted that temperature is an important factor that increase the corrosive effect of chemicals [108]. Even though several research groups showed that acid treatment is more useful then alkali solutions to improve surface roughness of titanium [109], there are studies showing that alkali solutions are efficient for surface treatment of titanium implants in nanoscale and moreover can be advantageous to give hydrophilic structure on the implant surface, which provide augmented tissue affinity to the titanium surface [110]. It is also been stated that alkali- and heat-treated titanium surface can accelerate and improve bone-implant contact area due to increased surface roughness [111]. As understood from those results; alkali treatment can be attributed as less aggressive than acid etching method, but can be used following acid treatment and forms nanoroughness on the titanium surface that can attract bone cells to attach on. Hydrogen peroxide, likewise alkali treatment, and heat treatment can improve cell adhesion and create hydrophilic nature for titanium [112]. Moreover; alkali (NaOH) treated titanium surfaces can induce biomimetic apatite debris formation on the implant surface, which can be attributed as chemical binding of titanium and bony apatite. This bone-like apatite focuses act as bone calcification nuclei and initiate bone formation.

Surface treatment with previously mentioned methods, sand blasting and acid or alkali etching, do contaminate the titanium surface, of which remnants cannot be avoided,

eradicated or neutralized totally all the time. However, laser energy can modify the titanium or titanium alloy surfaces without contamination [113]. Laser energy can change the titanium or its alloys with heat (photothermal) effect or intense pulsed wave form of laser energy (photomechanic) effect like embossing. For this purpose, certain wavelengths, like neodymium: yttrium aluminium garnet (Nd-YAG) laser-355 nm and carbon dioxide laser-10600 nm, have been well documented [114] and taken an inevitable place in industrial surface treatment industry. Pulsed Nd-YAG laser with 10 Hz repetition rate has been demonstrated to give the opportunity to control micro-topography as desired [115]. However, those wavelengths work with photothermal effect and modify the titanium surface via melting. Even laser surface treatment is defined to give the control for desired surface topography melting method does not create a perfect surface structure. Therefore, shorter (femto or pico second) pulses can generate more controlled surface shape due to lower heat formation [116]. Femtosecond laser pulses can engrave surface topography at micro or nano scales, which give the 100% control facility of surface texturing. Control of roughness depth and geometry on the implant surface also gives the possibility for selective cell attraction to the implant surface. Such laser-treated surfaces can distract inflammatory cells, responsible from tissue response to implant surface, and contribute to suppression of early inflammatory events, which may lead rejection [117]. Similarly, laser-texturing can make it possible to attract certain cells of which long-term function is a prerequisite for their adhesion, like epithelial cells and osteoblasts. Those cells attach directly to the implant surface, if convenient roughness values can be yielded with treatment. Connective tissue cells (fibroblast) tend to attach less roughened surfaces, when compared with bone cells (osteoblasts) [118]. Wavelengths proven to be innocuous to the titanium surface like erbium: yttrium aluminium garnet (Er:YAG) laser-2940 nm, recently, have been documented as a laser type that may modify the titanium surface at certain power settings as low as 200 mJ/10Hz [119]. On the other hand, degree of surface roughness can alter surface adhesion potential of several microorganisms as well as body cells [120]. Owing that affinity potential, implant surfaces can be modified gradually according to the location where cell adhesion is targeted, while microbial attacks are repulsed.

Titanium surfaces treated with micro-arc (plasma electrolytic) oxidation (MAO) can also improve surface porosity and its alloys, contributing cellular activity for osteointegration [121]. Correspondingly; MAO procedure facilitates cell adhesion capability of titanium surface with enhanced hydrophilicity [122].

4. Summary

In conclusion, physical, chemical and biologic features of biomaterials are chosen and determined considering their function and required durability in situ besides biocompatibility. Accelerative development in material science, especially in nano and optoelectric sciences makes exploration of new materials or enhancement of conservative biomaterials.

5. Acknowledgements

The authors would like to thank Dr. Kadriye Atıcı Kızılbey and Chem. Çağdaş Büyükpınar from Yıldız Technical University, Science and Technology Application and Research Center (Turkey) for their kindly assistance in arrangements of the present chapter.

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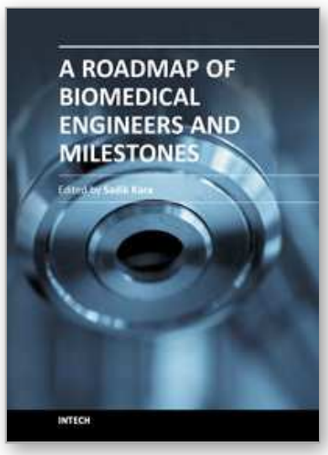

A Roadmap of Biomedical Engineers and Milestones

Edited by Prof. Sadik Kara

ISBN 978-953-51-0609-8
Hard cover, 230 pages
Publisher InTech
Published online 05, June, 2012
Published in print edition June, 2012

This book is devoted to different sides of Biomedical Engineering and its applications in science and Industry. The covered topics include the Patient safety in medical technology management, Biomedical Optics and Lasers, Biomaterials, Rehabilitat, Ion Technologies, Therapeutic Lasers & Skin Welding Applications, Biomedical Instrument Aopplication and Biosensor and their principles.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

A. Binnaz Hazar Yoruç and B. Cem Şener (2012). Biomaterials, A Roadmap of Biomedical Engineers and Milestones, Prof. Sadik Kara (Ed.), ISBN: 978-953-51-0609-8, InTech, Available from: http://www.intechopen.com/books/a-roadmap-of-biomedical-engineers-and-milestones/biomaterials

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