Introduction to Ideal Characteristics and Advanced Biomedical Applications of Biomaterials

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Govinda Kapusetti, Namdev More, and Mounika Choppadandi

Abstract

Biomaterial intervention in healthcare is inevitable, rather required for a better life. They are well practiced from ancient times, and the successive evolution made them more potent, versatile, and easy for clinical practice. However, the mimicking of the materials is not at all absolute, and in some cases it is very minimal as compared to the native tissues. The course of development of a biomaterial needs a strong understanding of the basic characteristics of the material behavior in bioenvironmental. The chapter discusses the various types of biomaterials starting from polymers to composites, and it presents the detailed information about the required ideal characteristics of a biomaterial like biocompatibility, bio-inertness, bioactivity, bioabsorbable pattern, bio-adaptability, sterilization, etc. In contemporary medical technology, biomaterials play a major role to answer many complications with high accuracy. The chapter primarily focuses on the latest advancements in biomaterials for major areas like orthopedics, cardiovascular, ophthalmology, neuronal, etc. Further, the chapter gives special emphasis on tissue engineering aspect of biomaterials to the regeneration of tissues and therapy.

8.1 Introduction

Numerous materials abound on earth with a unique identity and application. Among biomaterials are a class of entities can able to interact with bioenvironment and tissues for various requisites. Biomaterials are evolving exponentially from the last 50 years, through the combined aspects of medicine, biology, chemistry, and

G. Kapusetti (✉) · N. More · M. Choppadandi
Department of Medical Devices, National Institute of Pharmaceutical Education and Research (NIPER)-Ahmedabad, Gandhinagar, Gujarat, India

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materials science. Majorly, the engineered material participated in disease diagnosis or therapy or both, and sometimes it acts as therapeutic as well. In this journey, the material must exhibit essential physicochemical, mechanical, and biological properties in order to augment or replace or support an organ or a tissue or a part of the body, to make the diseased/unhealthy part functional. To fulfill the function, the candidate must be biostable, biocompatible, and bio-tolerable as the immune system may treat the substance as a foreign material. The definition of biomaterials was framed in different ways, but most prominently "Biomaterials are a class of materials- be it natural or synthetic, alive or lifeless, and usually made of multiple components that interact with the biological systems. They are often used in medical applications to augment or replace a natural function."

Materials' intervention in human health is not a modern aspect since in ancient times multiple materials are used in the reconstruction of the human body. An ancient Hindu sacred book *Rigveda* (3500–1800 BC) was compiled with all sorts of medical amputations and augmentations with biomaterials. Sutures made from animal tendons, cotton, horsehair, leather, vegetable fiber, etc. were used for surgeries in those days. In ancient days, the Chinese first introduced gold in the dentistry, and now it is a well-established material for dental fillings. Earlier in the seventeenth century, brass sutures were used in fracture repairs. Later, nickel-, aluminum-, and platinum-coated devices were most prominent in orthopedics as plates and screws, whereas in the twentieth century, the carbon steel was being used in this persistence. Dr. Otto Rohm, a German chemist, developed poly(methyl methacrylate) (PMMA) in 1901 and patented as Plexiglas in 1933 (Arora et al. 2013; Hosseinzadeh et al. 2013). PMMA is widely used as a bone cement that fills the bone defects and also fills the space between the bone and prosthesis which ultimately results in uniform stress distribution. Hydroxyapatite (HA) is the highly consumed biomaterial being used from the last 50 years for musculoskeletal tissue regeneration and therapy. Collagen is an animal-derived biomaterial with a triple helical structure. Most of the connective tissues, such as bone, tendon, ligament, and skin, contain collagen; it is also commercially available as a wound-healing product (Agrawal 1998). In 1940, the cellulose acetate was first used in dialysis tubing. Dacron and polyether urethanes are used in vascular grafts and artificial pacemaker, respectively (Langer and Tirrell 2004). However, the biomaterials have been classified into a wide range of classification from ancient days, and till date there are a large number of materials and composite materials raised as a biomaterial for multiple applications in multiple approaches. When the material is implanted into the biological system, it may regenerate or repair or augment the organ or tissue, but they also produce some foreign body giant reactions or host reactions between the biological tissue and implant.

Biomaterials are used for several applications, such as joint replacements, bone plates, bone cement, artificial ligaments and tendons, dental implants for tooth fixation, blood vessel prostheses, heart valves, artificial tissue, contact lenses, and breast implants. In the future, biomaterials are expected to enhance the regeneration of natural tissues, thereby promoting the restoration of structural, functional, metabolic, and biochemical behavior as well as biomechanical performance.

8.2 Biomaterial Host Reactions

Biological response of a biomaterial on the target site of implantation is the most important factor to be understood. The interaction between the implant and biological system leads to the host defense mechanism in which it primarily causes nonspecific inflammation, infection, and specific immunological reactions such as immunity, inflammation, and blood coagulation to protect the body from foreign organisms. Generally, after implantation, the material is treated as a foreign substance and leads to the formation of nonspecific inflammatory reactions. Primarily, the foreign body reactions are initiated by macrophages. These macrophages activated in the process of interacting with the implant may intricate cytokines, which stimulate fibrosis. Biocompatibility is the important characteristic of biomaterial to decide the fate of the material for its medical use. It is opposite to the inflammation, more the biocompatible lesser the inflammation. Biocompatibility of a material is determined by various in vitro and in vivo assays (Schoen 2013; Samavedi et al. 2014). Biocompatibility of material is regulated by the International Standards Organization (ISO), Geneva, Switzerland. It comprises of standards for "Biological Evaluation of Medical Devices" in which ISO 10993 part-3 describes the in vitro and in vivo tests for genotoxicity, carcinogenicity, and reproductive toxicity. Genotoxicity tests also follow "organization for economic co-operation and development" guidelines (OECD 474, 1997; 475, 1997). ISO 10993 part-4 explains the selection of tests for interaction with blood such as thrombosis, coagulation, platelets and platelet function, hematology, and immunology. ISO 10993 Part-5 explicates about the in vitro cytotoxicity tests, i.e., tests on extracts (L929 elution test, neutral red uptake test, colony formation test, MTT, and related tests), direct contact test, and indirect contact tests (agar diffusion test, filter diffusion test). Biomaterial/medical device testing also follows the American Society for Testing and Material (ASTM) international standards.

8.3 Classification of Biomaterials

For a better understanding of applications of biomaterials by key characteristics, they are broadly classified into four major categories: polymers, ceramics, metals, and composites (Fig. 8.1). These materials are used in various processes of synthesizing to form an implantable medical device that is biocompatible, bioactive, and also sterilizable. Based on the severity of risk, medical devices are classified into four classes: they are class I (low risk), class IIa (medium risk), class IIb (medium/high risk), and class III (high risk). Class I medical devices are noninvasive devices, class IIa and IIb are invasive devices, and class III are active devices (Cheng 2003). Biomaterials are also classified based on the duration of contact with the tissue and named as class A (limited period ⍰24 h), class B (prolonged period 24 h–30 days), and class C (permanent >30 days). By modifying bulk raw material/material composites, it will be converted to an implantable medical device. Generally, in the synthesis of biomaterials from polymers or copolymers, ceramics, metals or

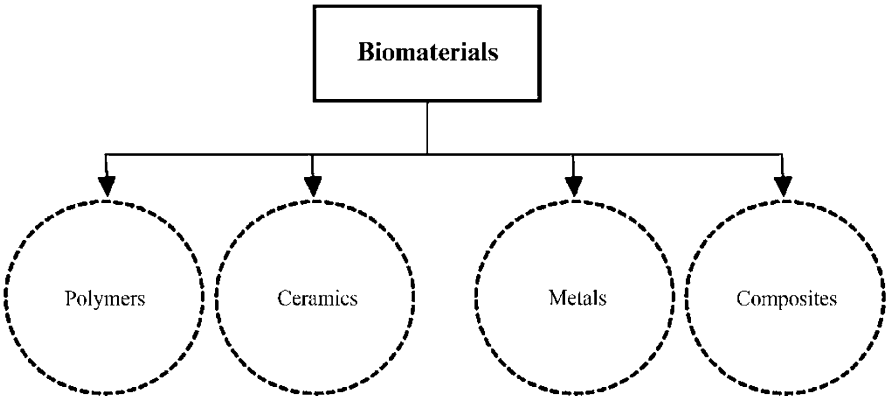

Fig. 8.1 The classification of biomaterials based on structural features (Teoh 2004; Kulinets 2015)

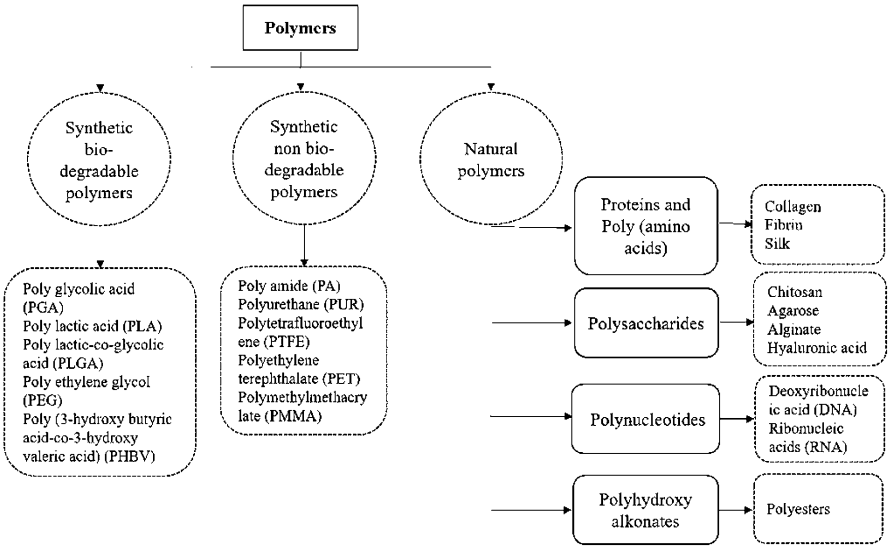

Fig. 8.2 The classification of polymers (Numata and Kaplan 2011; Pattanashetti et al. 2017; Teo et al. 2016)

alloys, and composites of polymers, ceramics, and metals are used individually or in combination to improve the physicochemical, mechanical, and biological properties.

By simplifying further, polymers are classified as natural, synthetic biodegradable, and synthetic nonbiodegradable polymers (Fig. 8.2). Polymers are the repetitive units of a single monomer. They are not only used as a scaffold material but they are also extensively used in the drug delivery systems. These natural polymers are rich in plant and animal source, and these materials have higher biocompatibility as

they already have binding sites from cells and adhesion molecules. Synthetic biodegradable polymers mostly help in repair and regeneration, whereas synthetic nonbiodegradable polymers are used as fillers, bone-fixing agents, and bone-supporting materials. In the case of synthetic biomaterials, the biocompatibility is questionable, and the material acts as a foreign substance, which leads to immune reactions. However, natural, synthetic, and the combination of natural and synthetic composite materials are used in biomedical applications (Numata and Kaplan 2011; Pattanashetti et al. 2017). Most of the polymers used in the biomedical applications are approved by FDA, namely, polylactic acid (PLA), polyglycolic acid (PGA), polylactic-*co*-glycolic acid (PLGA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), poly-*N*-vinyl pyrrolidone (PVP), poloxamer, starch, hyaluronate, gelatin, alginic acid, and collagen (Mansour et al. 2010).

Ceramics are natural or synthetic inorganic, nonmetallic, polycrystalline materials. Similarly, bioceramics are categorized into three classes: bioinert, bioactive, and bioresorbable ceramics (Fig. 8.3). Ceramics are mostly used as a dental-filling agent, vertebral bone cement (vertebroplasty and kyphoplasty), and cranial and maxillofacial fillings. Maximum ceramics are bioactive; they form a connection with the bone tissue processes known as osseointegration (Bohner 2008). Ceramics also play a major role in the biomedical applications such as alumina and zirconia yttria are used in top hip replacement, apatite wollastonite is used in vertebral reconstruction in tumor patient, and HA-based ceramics are used for teeth and bone (Bohner 2008; Kokubo 1991).

The metals are further classified into biodegradable and nonbiodegradable, and metals are known for high-strength applications (Fig. 8.4). Metals are mainly used in

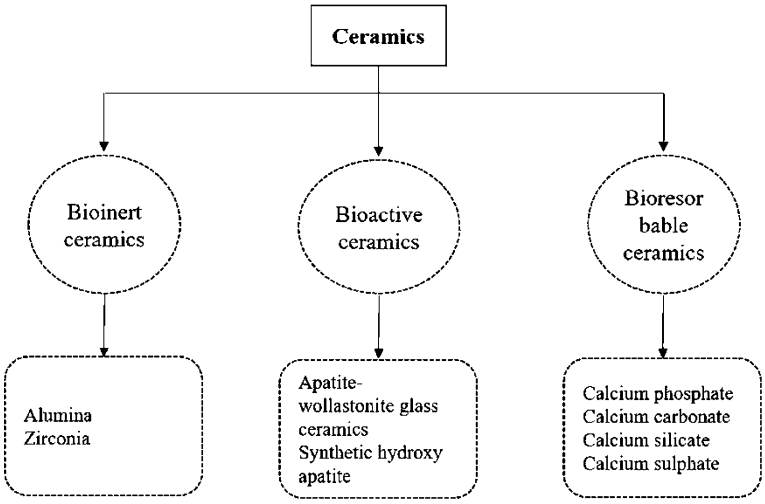

Fig. 8.3 The classification of ceramics with respect to interaction with bioenvironment (Bohner 2008)

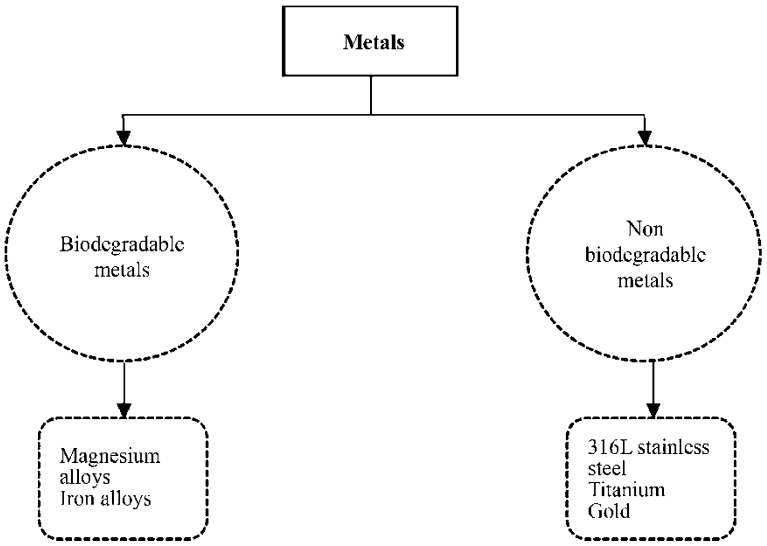

Fig. 8.4 The classification of metals based on biointegration (Niinomi 2002)

joint replacement, bone replacement, maxillofacial implants, dentistry, and cardiac stents. To avoid local inflammation or rejection, generally, metals are surface modified with a biocompatible material, which reduces the formation of biofilm. In the orthopedics fixation, plates, screws, and pins are used for bone healing, and they are made from 316 L SS, Ti (titanium), and Co-Cr-Mo (cobalt chromate and molybdenum) alloy. Amalgam, Au (gold), and Ti are used in dentistry. Cardiac stents are made from 316 L SS, Co-Cr-Mo, and Ti. The artificial eardrum is made up of 316 L SS (Hermawan et al. 2011; Niinomi 2002).

Composites (Fig. 8.5) are engineered materials composed of two or more different materials, often ones that have very different properties. The composites are intended for improvement of physicochemical, mechanical, and biological properties of the material in all aspects. Synthesis of composite materials provides with all specific properties in terms of osseointegration, degradation, porous structure formation, and adhesion property. Composites offer tuned properties based on the composition for required application; on the contrary, it is not possible in a single material. For instance, calcium phosphate and PLGA composite scaffold were prepared to modulate the degradability from poor degradable calcium phosphate and rapid degradable PLGA (Wang 2016). PLGA degrades hydrolytically and it results in the production of lactic and glycolic acid monomers. Due to the acidic nature of the monomers, the calcium phosphate cement degrades in the by-product environment by acidic dissolution.

All the Figures (1–5) described the classification of biomaterials with examples; the source of origin, structural features, ideal properties of biomaterial, and biomedical applications are explained in detail hereafter.

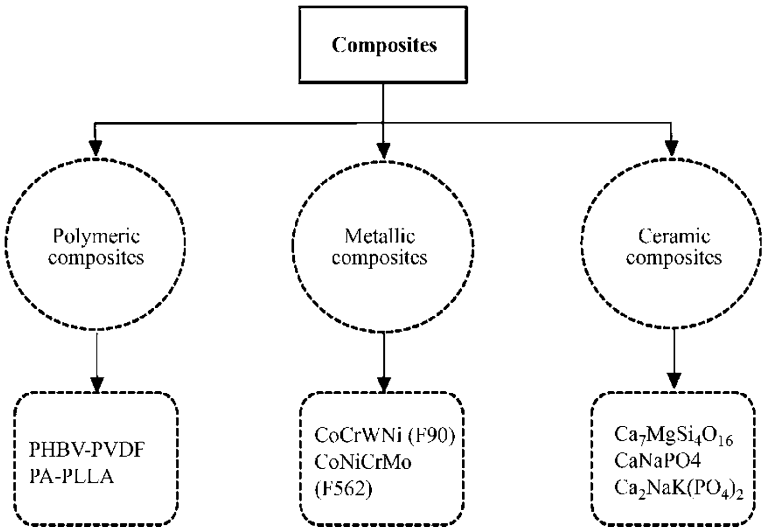

Fig. 8.5 Classification of composite materials from their matrix materials (Kulinets 2015; Ramakrishna et al. 2001)

8.4 Source of Origin

Natural biomaterials are obtained from the plant, marine, and animal source. For instance, the materials obtained from these sources are cellulose from a plant source, chitosan from a marine source, and collagen from an animal source. Metals are obtained from sources such as magmatic, sedimentary, and metamorphic rocks, soil, surface and groundwaters, and in the atmosphere (Bradl 2005), whereas ceramics are found from the geological origin, i.e., rocks and their interaction with elements (Velde and Druc 2012). Synthetic biomaterials are produced in the laboratories synthetically.

8.5 Structural Features

Structural features of polymers include general structure, polymeric structure, molecular weight, and tacticity. The general structure describes the building block of polymer like "mer" as the single unit of the polymeric chain and polymer is "many mers". The polymer is the repetitive unit of a single monomer. The polymeric structures may be linear, branched, cross-linked, and networked. The linear structure has the linkage of mers in a series fashion from one end to the other. During the synthesis procedure, the results in branches and this branched polymeric chain are known as a branched structure. The polymers that cross-link at a particular point

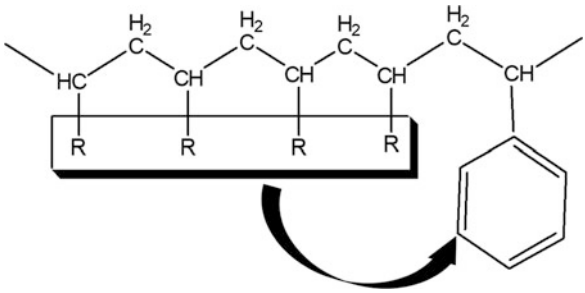

Fig. 8.6 Polystyrene structure explaining tacticity with R group

forming 3D polymeric structure or by covalent bonding is known as cross-linking polymers. The 3D polymeric network produces polymeric structures for the multifunctional approach in which multiple "mer units" bind together and form complicated network structures and are known as networked polymers. The molecular weight of the polymeric structure represents the degree of polymerization and the chain length of polymers. Generally, the degree of polymerization is represented by the letter "n" in the formula. The structural configuration of polymeric molecule is the primary part of the molecule and it can be modified only by reforming or breaking of primary bonds. In Scheme 6, "R" indicates the benzene ring in polystyrene. Consider "R" as the functional group; if the functional groups of "R" are arranged on the same side of the chain, then it is known as isotactic configuration. If the functional groups are in the alternative positions on either side of the chain, it is known as the syndiotactic configuration. If the "R" groups are situated randomly in the molecule, then it is said to be atactic configuration (Fig. 8.6).

Structural features of ceramics include the nature of the bond, crystal structure, high melting temperature, and low electrical conductivity. In the ceramics, the arrangement of bond linkage is with both ionic and covalent bonds. Due to this ionic and covalent bond, ceramics are responsible for unique properties like highest hardness, highest melting point, lowest thermal expansion, good chemical resistance, and brittleness (this leads to fractures unless the material is not reinforced with some reinforcing agent) (Society 2018).

Structural features of metals include crystalline nature and metallic bonding. Crystal structures are explained on the basis of unit cells. The unit cell is the configuration of atoms with a repetition of the crystal unit. Common crystal lattice structures in metals are face-centered cubic (FCC), body-centered cubic (BCC), and hexagonal close-packed (HCP) structures (Fig. 8.7). As the metallic bonding is nondirectional, there are some broad varieties of atomic configuration that creates crystal structure. Metals are widely used because of their structural properties such as strength, high melting point, ductility, toughness, and thermal and electrical conductivity. Therefore, these materials are extensively used for biomedical applications in orthopedics.

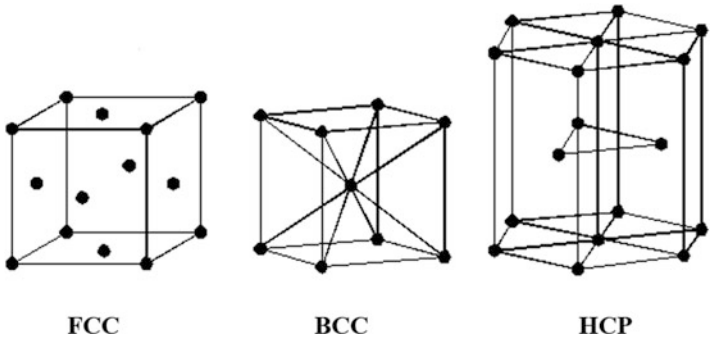

Fig. 8.7 Illustrations of different crystal lattice structures of metals

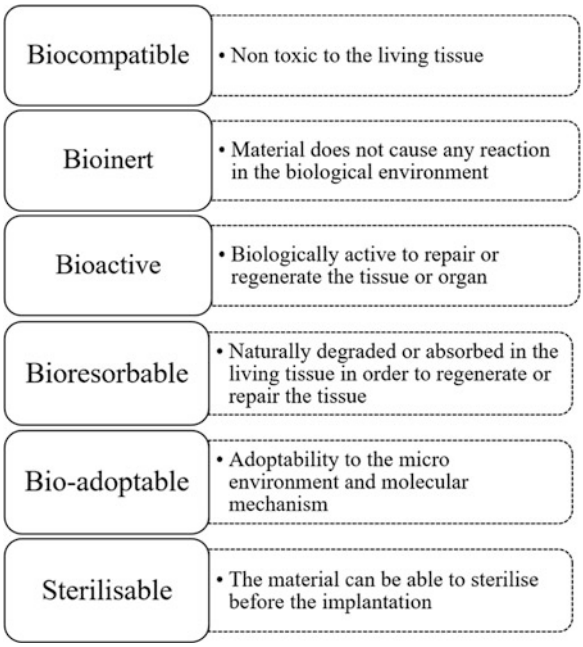

Fig. 8.8 The flow chart of the ideal characteristics of a biomaterial

8.6 Ideal Characteristics of Biomaterials

Ideally, biomaterial should be biocompatible, bioinert, bioactive, bioresorbable (biodegradable), bio-adoptable, and sterilizable (Fig. 8.8). The degree of the characteristics signifies the ability of the material for the biomedical application. Importantly, the ideal characteristics also influence in mimicking the microenvironment for the therapy or care.

8.7 Physicochemical Properties

The physicochemical properties highly control the microenvironment for cellular activities. The response is reflected in terms of cell adhesion, proliferation, and surface reactivity between the target site and the host. Physical properties include shape, size, microstructural features (amorphous/crystalline), porosity, surface area, and density. Whereas chemical properties include chemical composition and elemental distribution. The physical properties are determined by different microscopic techniques to analyze the surface properties (optical microscopy, scanning probe microscopy (SPM), transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), particle size (dynamic light scattering, DLS), porosity (porosimetry), surface area (gas adsorption), surface energy (hydrophilic/lipophilic property—contact angle measurements), and chemical properties such as chemical composition, and elemental distribution is evaluated by Fourier-transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), energy-dispersive X-ray spectroscopy (EDAX), and carbon, hydrogen, nitrogen, and sulfur elemental analysis (C/H/N/S elemental analysis, respectively). In order to maintain the structural stability and structural activity of a biomaterial, each of the abovementioned properties is very important (Ramalingam et al. 2016).

8.8 Mechanical Properties

Mechanical properties of material play a vital role in the biomedical applications. An implant may experience different kinds of functional loads, i.e., compression, tension, shear, and at times all the three parallelly. The compression strength is the application of loading force on both ends of the sample from the same direction, whereas tensile strength is the equal amount of force applied on the two ends of the sample from the opposite directions, and the shear force causes angular distortion due to the application of tangential force from the alternative surface. When all three forces are experiencing by the implant the distortion, frequency increases. Universal testing machine (UTM) is the instrument mainly used to check the mechanical properties of the biomaterials with respect to the ASTM standards. Hardness, strength, toughness, and viscosity elasticity of the material can be determined. The biomaterials of four different classes, i.e., polymers, ceramics, metals, and composites react differently to each of the applied loading forces. Polymers, metals, and composites exhibit both brittle and ductile nature based on their composition but most of the ceramics are in ductile nature. The scaffolds (films/fibers/sutures) are checked for the tensile strength; definitely shaped implants (metallic/polymeric/bioceramic/composites) are checked for the compression strength and shear stress (Roeder 2013).

8.9 Biological Property

The material which is used for the medical purpose be it organ replacement/tissue growth/drug release must possess characteristic biological properties such as biocompatibility, inertness, and biofunctionality. In addition to this, biomaterial must be sterilizable to avoid implant rejection, inflammation, and irritation. Biological characterization of a biomaterial is carried by ISO 10993 guidelines. The list of biological tests includes cytotoxicity, sensitization, hemocompatibility, pyrogenicity, implantation, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and degradation assessments (DOS Santos et al. 2017; Bandyopadhyay and Bose 2013).

8.10 Biocompatibility

Biocompatibility is a field of medical implants that explains the beneficial and risky interactions with the host tissue. Compatibility of the material with the biological system is known as biocompatibility and it is described as "the ability of a material to perform with an appropriate host response in a specific application" (Naahidi et al. 2017; Williams 2009). It can be evaluated by both in vitro and in vivo tests. In vitro studies give a rough idea about the appropriate cell type that survives in the presence of biomaterial. Although the biomaterial has shown good cell viable results in in vitro studies, it may not show the same effect in vivo due to host defense mechanism and may lead to inflammation at the site. In some cases, the cell interaction with host can induce the release of inflammatory chemotactic mediators at the target site (Naahidi et al. 2017; Kohane and Langer 2010; Williams 2008; Ziats et al. 1988). If the material is toxic, the surface modification of the material helps in reduction of toxicity. The surface modification is achieved by either physicochemical modification or surface coating with a bioactive material. The physicochemical modification is attained by etching, mechanical polishing, and chemical reactions such as oxidation, reduction, acetylation, and utilization of organosilanes. Surface coatings of the biomaterial include thin film deposition, grafting, and covalent and non-covalent coatings. This surface modification of biomaterial improves implantable device and tissue interaction and also provides biocompatibility and shows its bioactivity (DOS Santos et al. 2017).

8.11 Bioactivity

Bioactive materials are the materials that form chemical bonds with bone tissue known as osseointegration. It is a process through which the implant is connected to the bone tissue. There are some materials that show bioactivity in terms of regeneration, i.e., calcium phosphate and hydroxyapatite (DOS Santos et al. 2017). For instance, calcium phosphate bone cement produces great bioactivity; it was shown by the formation of apatite on the calcium phosphate cement surfaces when soaked

in SBF for 1 week (Xu et al. 2017; Sadiasa et al. 2014). When the calcium phosphate cement was implanted into rabbit femur, it shows the increased healing effect and bone ingrowth. These types of cement have the osteoconductive property that facilitates the attachment, ingrowth, proliferation, migration, and phenotypic expression of bone cells, which leads to the formation of new bone. Ideally, the scaffolds must have 60–80% interconnected porosity with 150–500 μm range pore size by which nutrient exchange, waste elimination, and cell penetration take place. Biodegradability of calcium phosphate scaffolds occurs by active (via cell-mediated process) and passive resorption (by chemical dissolution). Physical factors in degradability include bulk property of scaffold, crystallinity, porosity, and surface area, whereas chemical factors include chemical composition and ionic substitutions. Biological factors include activation of osteoclasts and macrophages (Lu et al. 2002). Calcium phosphate and PLGA-based scaffold are implanted into rabbit femoral bone defect model. The study reveals enhanced bone regeneration of >13% with >55% degradation in 6 weeks. Further, it shows >40% bone formation along with 90% degradation in 26 weeks (Grosfeld et al. 2016). The osteoconductive, osteoinductive, and biodegradability properties altogether explain the bioactivity of a biomaterial.

8.12 Bio-tolerability

Most of the metals and synthetic polymers are bio-tolerable; they form a fibrous layer surrounding the metallic or polymeric implant which forms by the release of ions, chemicals, and corrosive products. Some of the bio-tolerable materials are implanted as dental fillers, bone-supporting materials, and bone-fixing materials (DOS Santos et al. 2017). The chemical treatment enhances the bio-tolerability (electropolishing, acid cleaning, and chemical passivation); the chemical composition of 316 L stainless steel is C = 0.028%, Ni = 10.15%, Mo = 2%, and Fe, whereas 304 L stainless steel composition consists of C = 0.017%, Cr = 18.32%, Ni = 8.03%, Mo = 0.29%, and Fe. The bio-tolerable materials are considered as corrosion resistant and bioinert (Ghanavati et al. 2016).

8.13 Applications

Material interference in human healthcare is not a prerequisite; it is necessary for modern society lifestyle. The applications start from simple syringes to complex devices like artificial pacemakers and artificial organs. In ancient times, natural material like the wood was used to augment or repair the tissue or part of the tissue. In 21st century, the revolutionary changes in life science and materials science research are the fundamental base for the development of novel biomaterials. The biomaterials not only mimic the structure of the tissues but also exhibit the suitable microenvironment for fitting tissue response. Based on the applications, the biomaterials are broadly classified into various categories like tissue engineering,

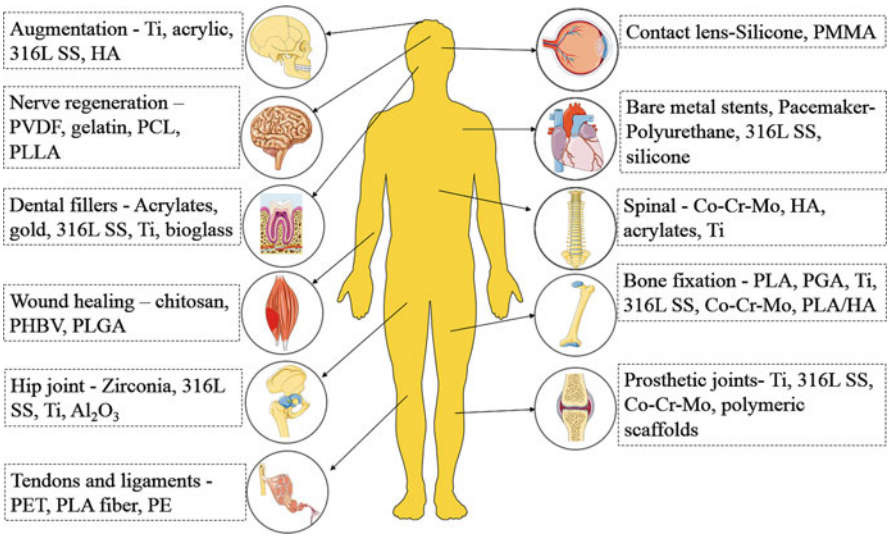

Fig. 8.9 The illustration of notable applications of biomaterials in human health

biosensors, and advanced drug delivery application. Figure 8.9 shows some of the applications of biomaterials in human health (O'brien 2011; Hubbell 1995).

8.14 Tissue Engineering

Tissue engineering is the groundbreaking field in healthcare which evolved from the biomaterials and acts as supporting structure for tissue regeneration and therapy. The practice is established by the application of the scaffold, cells, and bioactive molecule in the suitable microenvironment. Tissue engineering technology is broadly categorized into three classes based on the practice and regenerating tissues and the classification shown in Fig. 8.10. The major applications of tissue engineering serve major areas like orthopedics, cardiovascular, ophthalmology, etc. (Lutolf and Hubbell 2005).

8.15 Orthopedic Applications

Bone and cartilage are the key components of the skeletal system, of which 80% of the system is composed of bone and it contributes 18% of the total body weight (Ubelaker 1984). Bone serves a variety of functions like structural support, protection of internal organs, hematopoiesis, mineral homeostasis, and storage of triglyceride. Bone is a composite material composed of extracellular matrix and cellular system. The extracellular matrix contains inorganic component like calcium phosphate and calcium carbonate, and the organic components are collagen,

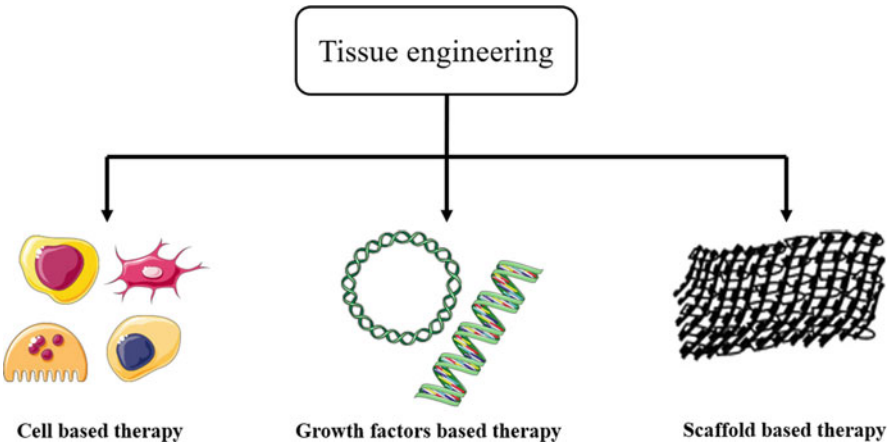

Fig. 8.10 Classification of tissue engineering by its practice with respect to the intervention of materials, molecules, and cells

proteoglycan, glycosaminoglycan (GAG), and other non-collagenous proteins. The cellular component comprises osteoblast, osteoclast, osteocytes, and osteogenic progenitor cells (Bilezikian et al. 2008). Osseous tissue continuously modifies in response to various stimuli such as electrical, mechanical, piezoelectric, etc.; every year 10% get replaced with a newly regenerated bone (Leppik et al. 2018; Robling et al. 2006). Though bone has self-healing capability, still the regeneration and repair are much more challenging and urge new therapeutic innervation. The major bone grievances occur due to mechanical trauma, accidental damage, and disease conditions like osteoarthritis, Paget's disease, osteomalacia, and cancer (Quarles 2008).

At the initial phase of tissue engineering, materials like metal and alloy such as iron and steel were employed for reconstruction of the osseous tissue. In the later stage, advanced metallic prosthetics were developed from cobalt-chromium alloy, gold-gold alloy, Mg-Mg alloy, and Ti-Ti-based alloy to minimize the adverse effects. However, the developed prosthetics indeed shows biological toxicity and poor mechanical performance. These issues are answered with ASTM-developed multicomponent stainless steel-based implantable material (Burg et al. 2000).

As the biomaterials are classified in accordance with tissue interaction, the first generation is intended to support the tissue, and the role of the second generation is to support the tissue and utilize as a carrier for the bioactive molecule. The third-generation material is biologically active material and has the intrinsic ability to stimulate the regeneration of the tissue. In order to enhance the bioactivity, the conventional metallic implants were surface modified and functionalized with osteoinductive material and functionalized the metal surface with a suitable chemical group. Most prominently, the osteoconductivity of an implant system was enhanced by simple coating of bioactive materials like bioactive glass (bioglass) (Hench 2006), HA (Swetha et al. 2010), carbon nanomaterials (CNT, nanodiamond, and

graphene) (Bhong et al. 2019), perovskites, calcium phosphate (Meroni and Ardizzone 2018), etc. Furthermore, the polymers such as chitosan, PCL, PLGA, PHBV, PLLA, collagen, silk fibroin, PMMA, etc. (Zhang et al. 2018; Choi et al. 2018; Ogueri et al. 2018; Ahmad et al. 2019) were also extensively used in bioactive coatings (Sharma et al. 2017). Apart from the conventional prosthetics, the engineered scaffolds for tissue engineering show overwhelming results but the clinical acceptance will be gone long. Tissue engineering is practiced in various categories like cell implanted, growth factor implanted, and smart material-based scaffolds. The development of the stem cell-seeded scaffold is the decedent choice for bone tissue repair and regeneration. Mostly, osteoprogenitor cells such as mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), pluripotent stem cells (iPSC), adult stem cells, and osteoblasts are directly incorporated or with carrier embedded at the site. The autologous chondrocyte implantation and the matrix-associated chondrocyte implantation are cell-based therapies which possess clinical importance in bone and cartilage regeneration (Meijer et al. 2007). In the second choice, the addition of growth factors in scaffolds is to stimulate cell growth and differentiation with certain biochemical cues. The growth factors such as bone morphogenic protein (BMP-2, BMP-7), transforming growth factor (TGF-α), vascular endothelial growth factor (VGEF), and insulin-like growth factor (IGF) are key candidates for bone and cartilage engineering (Lee et al. 2010; Cancedda et al. 2003). The growth factor-impregnated scaffolds demonstrated excellent preclinical results but limited for clinical application due to practical challenges. The challenges arise primarily dose optimization, unpredictable regeneration of the tissue, and an ethical concern associated with embryonic stem cells and the stability (More and Kapusetti 2017).

In order to astound the major glitches of traditional cell and growth factor-based strategies, in this contest, the polymeric scaffolds have huge potential to show a path for better therapy. The fabricated scaffolds exhibit tailored properties in porosity, mechanical strength, surface area, structure, surface architecture, etc. by its fabrication techniques (Petite et al. 2000; Hutmacher 2000; Hollister 2005). Various techniques are employed for fabrication which include freeze-drying, solvent casting, self-assembly, particulate leaching, injection molding, electrospinning, rapid prototype synthesis, template synthesis, and most advanced 3D printing (Roseti et al. 2017; Liu and Ma 2004). FDA-approved polymers involved in orthopedic applications include PLGA in the fabrication of the screw, nails, pins, and plates. Examples of the marketed products are FixSorb, NeoFix Resorption, Leadfix, MacroSorb System, etc. The PCL offers good mechanical strength, biocompatibility, and most interestingly long-lasting biodegradation. Apart from the synthetic polymers, the naturally derived polymers such as collagen, chitosan, silk fibroin, alginate, cellulose, and hyaluronic acid are the best choices of candidates for tissue engineering (Bose et al. 2012; Swetha et al. 2010). Among them, collagen is the key component of the extracellular matrix of the bone to provide structural integrity, and it plays a pivotal role in the maintenance of the mechanical strength. The collagen scaffolds are fabricated from a simple film casting technique to advanced 3D printing (Inzana et al. 2014). The scaffold promotes cell attachment and proliferation, thereby

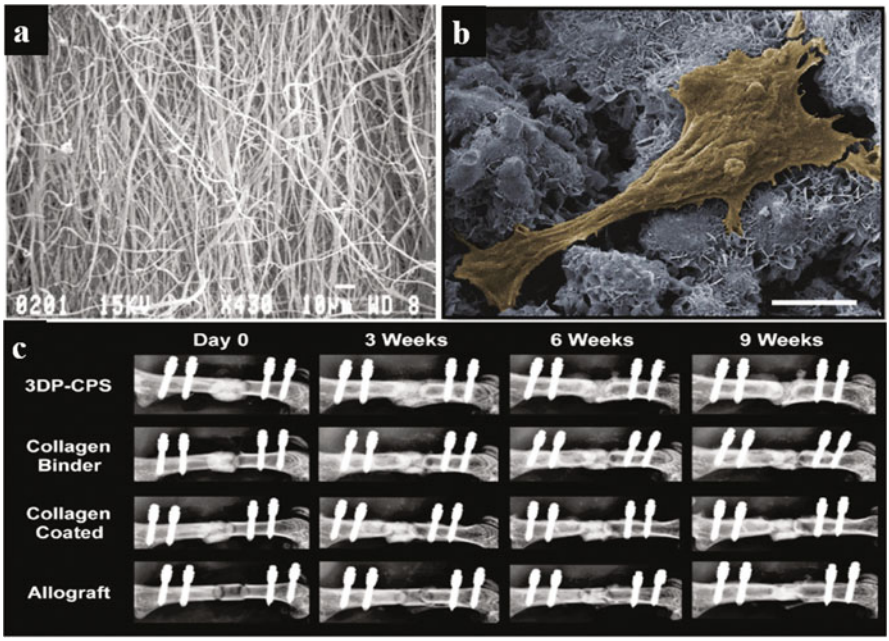

Fig. 8.11 (**a**) Fibrous morphology of the electrospun scaffold of collagen by SEM analysis (Matthews et al. 2002). (**b**) Well surface integrated osteoblast morphology on 3D-printed collagen-calcium phosphate scaffold (SEM image). (**c**) The X-ray images of murine femur implanted with various scaffolds including 3D-printed calcium phosphate-collagen scaffold (Inzana et al. 2014)

promoting tissue regeneration (Ferreira et al. 2012). Fig. 8.11a shows the electrospun scaffold of collagen with structural similarities with natural tissues (Matthews et al. 2002), and Fig. 8.11b and c shows the favorable osteoblast cell attachment on the 3D-printed collagen scaffold and X-ray digital images of scaffold implanted bone. The study reveals that the 3D-printed scaffold shows a similar kind of regeneration capacity as allograft (Inzana et al. 2014).

Unlike collagen, the silk scaffolds are fabricated by a combination of salt leaching and gas-foaming techniques for guided bone regeneration with an optimum pore size (Kim et al. 2005). Even though pristine polymeric scaffolds exhibit good passive regeneration capacity, still it lacks the bioactivity. The best possible method to enhance the bioactivity is to make a composite by the addition of bioactive fillers. The hybrid materials indeed enhance the bioactivity and also provide enhanced mechanical properties (Mieszawska et al. 2010; Gong et al. 2015). The inorganic fillers like calcium phosphate, bioglass, HA, CNT, graphene, nacre, barium titanate ($BaTiO_4$), zinc oxide (ZnO), wollastonite, and tricalcium phosphate are highly explored for bioactive composite preparation (Hajiali et al. 2018; Bhong et al. 2019; Rezwan et al. 2006). The amine functionalized graphene was reinforced in PMMA bone cement to enhance the osteoconductivity by Sharma et al. for better

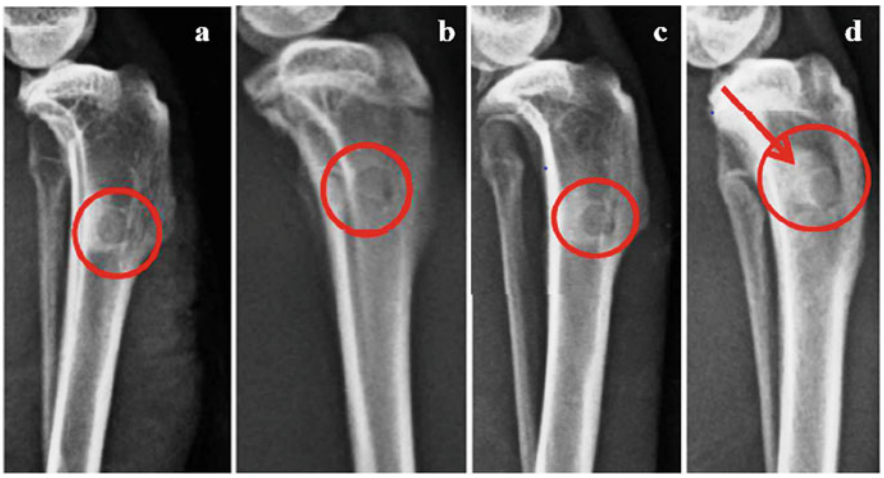

Fig. 8.12 The X-ray images of rabbit tibia at day 0. (**a**) Pristine PMMA bone cement, (**b**) Amine functionalized graphene reinforced PMMA bone cement, (**c**) Pristine PMMA bone cement, and (**d**) Amine functionalized graphene-reinforced PMMA bone cement at day 20 (Sharma et al. 2017)

integration in total joint arthroplasty (Sharma et al. 2017). Fig. 8.12 shows the X-ray digital images of rabbit tibia implanted with pristine bone cement and aminated graphene reinforced bone cement at day 0 (a and b) and day 20 postsurgery, respectively. The group reported that the reinforced bone cement-implanted tibia was healed completely within 20 days by clear observation calcium deposition, whereas in pristine bone cement the impression remains same as day 0.

Apart from the conventional biomaterials, the most advanced smart material approach is used for guided bone regeneration. The smart material or intelligent material has an intrinsic ability to respond to the external stimuli and help to tailor the biological environment. The piezoelectric, ferroelectric, magnetic, and the shape memory materials are considered as smart materials. As bone is a piezoelectric material which one of the biomechanical cues for the bone regeneration. The piezoelectricity is defined as the generation of electricity against mechanical pressure and vice versa. Piezoelectric materials such as PVDF, PLLA, collagen, PHBV, cellulose, and alginate along with inorganic materials like $BaTiO_4$, lead zirconate, and ZnO are used for the orthopedic application (Wei et al. 2011; Jacob et al. 2018; Tandon et al. 2018; Vasquez-Sancho et al. 2018).

8.16 Cardiovascular Application

The management of cardiovascular diseases like atherosclerosis, coronary heart myocardial infraction, and dysfunctioning of the heart valves is a major challenge in modern medicine. Conventionally, the cardiac diseases are treated with the drug intervention, but results are limited (Mohan 2005). The biomaterial used in the

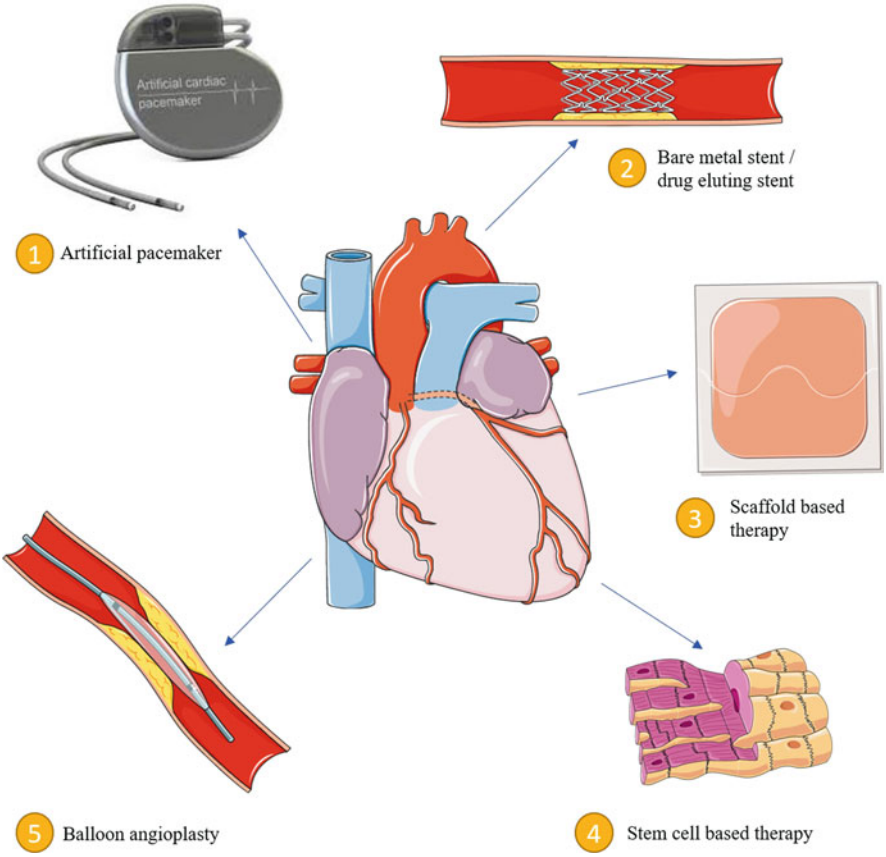

Fig. 8.13 The illustration shows the material intervention for various cardiovascular applications

management of the cardiac disease ranges from the cardiac patch to a coronary stent. Fig. 8.13 summarizes the various cardiovascular applications of the biomaterials.

Heart failure associated with myocardial infarction (MI) is a leading cause of death. Cardiomyocyte death associated with MI is a critical condition which is unable to be treated with the conventional drug therapy, but the cardiac patch has given meaningful results. Chitosan, cellulose, alginate, hyaluronic acid, gelatin, polyester urethane urea (PEUU), and PLGA are extensively used for fabrication of cardiac patches (D'Amore et al. 2016; Chi et al. 2013). Despite advancements in the polymer technology, the patches are compromised in mechanical strength. The new paradigm shifted to the development of composites to counter the limitations in cardiac patches, which not only improves the mechanical strength but also induces bioactivity in the pristine polymer. In this context, composite of PLGA-reinforced carbon fiber (Stout et al. 2011; Dvir et al. 2011), gold nanoparticle-added electrospun PCL, and gelatin nanofibrous scaffolds (Shevach et al. 2013) and

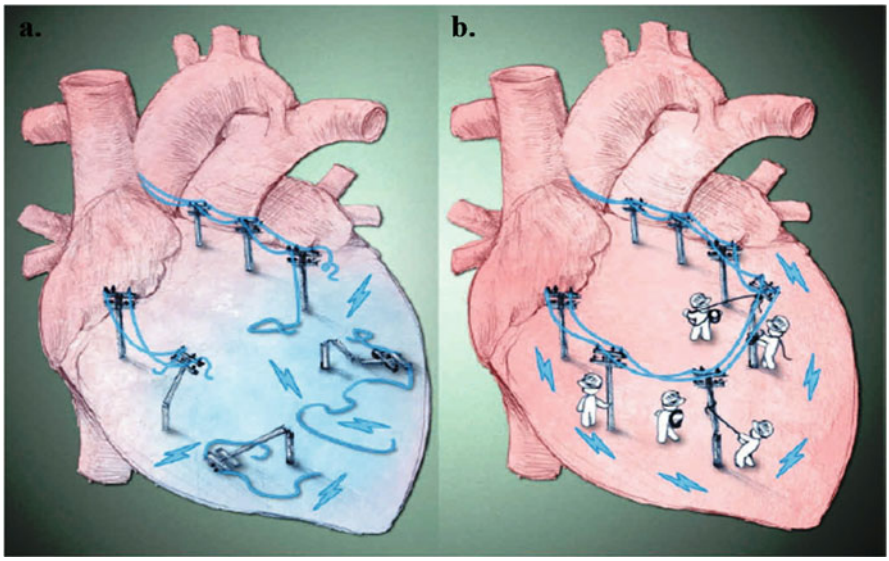

Fig. 8.14 The graphical representation of (**a**) Infracted heart and (**b**) Reconstruction of infarcted heart by using conducting polymer (Baino et al. 2014)

bioglass-reinforced PGS are developed (Souza et al. 2017). Similarly, bioactive Si patch (chitosan-reinforced calcium silicate) with enhanced conductivity was developed for the cardiac application (Wang et al. 2018). Figure 8.14 shows the graphic of infarcted heart and reconstruction by using conducting patch. However, the patches show significant enhancement in cardiac functions, but the complex surgical suturing limits the clinical applications. The development of 3D gold nanowire reinforced in albumin scaffold was demonstrated direct attachment on damaged without suturing by the eradication of NIR light. The NIR light absorption on material converts into thermal energy results in the strong attachment of the patch (Malki et al. 2018). Without thermal induction for the patch attachment, the paintable conductive patch was developed by using conductive polymer like polypyrol and dopamine through in situ polymerization (Liang et al. 2018).

Though bioinspired scaffolds have an ability to recover the damaged cardiac tissue due to lack of proliferation capacity, cardiomyocyte urges for the development of cell-loaded technologies. The skeletal myocytes, human embryonic stem cell (hESC), human-induced pluripotent stem cell (hiPSC), hematopoietic stem cells (HSCs), and human coronary artery endothelial cells (HCAECs) with suitable scaffolding material are used for the treatment of MI (Chaudhuri et al. 2017). In the following perspective, CNT-incorporated alginate framework with HCAECs seeded methacrylate collagen 3D scaffold was developed by the Izadifar and research group (Izadifar et al. 2018; Cui et al. 2016). Recently reported cell-based therapy includes MyoCELL® which comprises skeletal muscle myoblast cells and technology developed by BIOHEART, and it is in phase II/III trial in the USA

(Chaudhuri et al. 2017; Bejleri et al. 2018). Recently, two major research groups developed smart scaffolds based on piezoelectric and auxetic patches to avoid complex suturing and cell impregnation (Kapnisi et al. 2018; Arumugam et al. 2019).

In contrast to MI, another major cardiac disease is atherosclerosis which needs the coronary revascularization. The revolutionary milestone achieved in the treatment of coronary heart disease with the introduction of a cardiac stent. The major hurdle in treatment of coronary disease is restenosis after stenting. Initially, the bare metal stents were used to treat the condition made from 316 L (Iqbal et al. 2013; Bukka et al. 2018; Sabate et al. 2012), cobalt-chromium alloy, nitinol, tantalum, platinum, etc. The biocompatibility of bare metal stents is motivated by the inorganic coatings such as graphene, carbon nanodiamond, gold nanoparticle, nitride oxide, silicon carbide, etc. (Grill 2003; Chen et al. 2006). However, the amusing outcome of bare metal stents the major setback of the practice is restenosis. Immediate recoiling of the lumen of the blood vessel start followed by the series of sequence transpires leads to neointimal proliferation, which leads to the formation of thrombotic plaque. To avoid the initial consequence, the oral administration of pharmacological agents like probucol, rapamycin, cilostazol, etc. are recommended with prescribed doses (Hara et al. 2006). Due to lack of site specificity, conventional drug therapy is not the desired strategy. In the wake of drug-loaded medical devices, the drug-eluting cardiac stent came into existence. The antiproliferative drugs like paclitaxel, sirolimus, everolimus, ABT-578, tacrolimus, angiopeptine etc. were coated on the surface of the stent with suitable carriers for the desired realizing profile (Burt and Hunter 2006). The polymers such as PLLA, PLGA, chitosan, PCL etc. were well reported as carriers for drug-eluting stents. Table 8.1 summarizes major product of drug-eluting cardiac stents (Wache et al. 2003; Cui et al. 2016).

Another major cause of cardiac failure is dysfunctioning of the cardiac valve (mitral valve or tricuspid valve). The metallic and the plastic valves were used to treat the condition initially, but the poor clinical outcome has endorsed the development of the tissue-engineered valve. The idea involves the isolation of decellularized scaffolds from the allograft and xenograft procedures and conjugated with a bioactive ligand such as fibronectin, fibrin, etc., which helps in enhancement of cell adhesion and proliferation. Generally, decellularized scaffolds are obtained from

Table 8.1 The marketed product of drug-eluting stents with the brand and drug name

Sr. No.	Drug	Commercial name of the stent
1	Sirolimus	RAVEL, SIRIUS, SELECT
2	Paclitaxel	TAXUS 2, TAXUS4, ASPECT, ELUTES, EXPRESS, DELIVER, ACHIEVE
3	Everolimus	CHALLEGE
4	ABT-578	BiodivYsio
5	Dexamethasone	DEXAMET
6	Biolumis	BioMatrix flex™, BioMatrix™

human cadaver, pocrine, goat, and pig. The allograft and xenograft-derived cardiac valves exhibit significant drawbacks such as finite supply, infection, and transmission of the disease like HIV, HBV, immunogenic rejections, etc. Therefore, the most favorable strategy is a fabrication of polymeric scaffolds from highly biocompatible polymers like collagen, alginate, hyaluronic acid, polyalkenoate, etc. Similarly, PU- and PTEF-based valves also show good clinical performance. Some of the marketed polymeric cardiac valves are Sapien®, CoreValve®, Melody®, MAGNA MITRAL EASE VALVE, CENTERA, etc. (Claiborne et al. 2012).

8.17 Ophthalmology Applications

The eye is the most sensitive and complex organ and eases to surgical access by its anatomical position. The impairment vision arises basically from the malfunctioning of the eye portions like cornea, sclera, lenses, vitreous body, optical nerve damage, etc. Apart from that, impaired vision can be associated with the disease like impaired vision, myopia, hyperopia, astigmatism, presbyopia, cataracts, primary open-angle glaucoma, dry-eye syndrome, age-related macular degeneration, and diabetic retinopathy (Willoughby et al. 2010). Biomaterials are well recognized in the treatment of eye diseases in the form of contact lenses, intraocular lenses (IOL), keratoprosthesis, inlay-onlay, scleral buckling material, ophthalmic viscosurgical devices, vitreous replacement, and glaucoma shunt. PMMA is the best choice of biomaterial for the fabrication of contact lenses and other applications due to its better optical properties and biocompatibility. First, contact lenses and vitreous fluid are formulated from PMMA and PVP, respectively (Lloyd et al. 2001). The material requisite for the fabrication of contact lens is adequate oxygen permeability with the sufficient hydrophilicity, optically clear, and mechanical stability. PMMA, HEMA, silicone hydrogel, chitosan/gelatin, poly(4-methyl-1-pentene), and cellulose acetate butyrate are the best choice materials for the fabrication of contact lenses in contemporary times (Singh and Agrawal 1992; Mittal and Miranda 2018). The microbial keratitis is the potential risk associated with contact lens, and it has been countered by the development of antibiotic-loaded contact lenses. Silicon hydrogel loaded with drugs like levofloxacin, timolol, chlorohexidine, diclofenac, ketotifen fumarate, norfloxacin, vitamin A, etc. has been extensively reported for ophthalmic applications (Galante et al. 2018). Most advanced smart contact lenses are developed by using thermosensitive polymers, microfluidics techniques, and glucose sensing materials for controlled drug release (Park et al. 2018; Alvarez-Lorenzo et al. 2018). Similar to contact lenses, intraocular lenses (IOL) are used to treat myopia, cataract, and hyperopia. The choice of materials for the fabrication of IOL is PMMA, silicone hydrogel, polypropylene, polyimide, polyvinylidene fluoride (PVDF), and polysiloxane urea (Hayashi et al. 1997; Riehle et al. 2018; Stapleton et al. 2006). The practice keratoplasty is known as replacement of damaged or diseased cornea with artificial scaffold, and it is referred to as keratoprosthesis, PMMA, and PHEMA which are the choices for materials of keratoprosthesis. Biomaterials such as collagen immobilized with PVA hydrogel, HA-incorporated PVA hydrogel, graphite-

PVA hydrogel, and polyether ether ketone were used for keratoprosthesis (Myung et al. 2008; Pino et al. 2008).

Viscosurgical devices are the viscous non-active liquid materials used for the maintenance of fluidity in the anterior chamber of the eye during ophthalmic surgery, also known as phacoemulsification. Biomaterials such as hydroxypropyl methylcellulose, sodium hyaluronate, sodium chondroitin sulfate, and sodium hyaluronate are the best candidates for the viscosurgical devices (Bissen-Miyajima 2008). Glaucoma is the chronic eye disease reduces the intraocular pressure and results in permanent blindness. Glaucoma shunt is the best possible method when pharmacological and surgical innervation fails. The silicone and polypropylene are used to fabricate the shunts, and Ex-PRESS™ is the best know marketed shunt (Hendrick and Kahook 2008).

8.18 Wound Management

The injury or the physical alteration in the continuity to the biological tissue as the impact of mechanical trauma or certain pathological etiology leads to the wounds. The wounds are classified based on the duration of the healing as acute and chronic wounds. The mechanism of the wound healing is a dynamic and complex process, which involves a series of the sequential process, starts with hemostasis, inflammation, and proliferation and ends with tissue remodeling (Velnar et al. 2009). Although the physiologic mechanism contributes to wound healing, still it is a clinical challenge and needs for the development of new clinical approaches. The wound management is classified into two categories: passive and active intervention. The passive intervention is unable to regenerate the new skin cell, but it supports a local wound environment such as moisture, protection of prewound tissue, cleaning, and removal of dead tissue and minimizes the pain. Cotton, collagen patch, cellulose, and alginate are used for passive intervention. The active innervation is impregnated with active ingredients such as antibiotics, growth factor, bioactive molecule, etc. Tissue engineered scaffolds are fabricated by various methods such as freeze drying, particulate leaching, film casting, and 3D printing (Zhong et al. 2010). The chitin and chitosan are well known and gold standard polymer for wound management because of its strong antifungal and antibacterial activity (Dai et al. 2011; Ong et al. 2008). Apart from this, collagen, gelatin, fibrin, keratin, silk fibroin, eggshell membrane, PGA, PLLA, and polyacrylic acid are also extensively used for the active wound management (Zhong et al. 2010; Dainiak et al. 2010; Liu et al. 2017). In order to enhance active innervation, materials are reinforced with various additives like inorganic filler, drugs, and growth factors (Zhong et al. 2010). Table 8.2 presents the various polymers and additive for active wound management.

Table 8.2 The biomaterial with the bioactive agent used in active wound management

Sr. No.	Biomaterial	Bioactive agent	Method/type of scaffold	References
1	Chitosan	Montmorillonite	Intercalated film	Aguzzi et al. (2014)
2	Chitosan–PVP	Titanium dioxide nanoparticle		Archana et al. (2013)
3	PVA	Na-montmorillonite	Freeze–thawing scaffold	Kokabi et al. (2007)
4	Chitosan	Halloysite	Simple solid-dispersed scaffold	Sandri et al. (2017)
5	Eggshell membrane	Copper (Cu)-containing bioactive glass	Pulsed laser deposited scaffold	Li et al. (2016)
6	PCL-gelatin	*	Electrospun scaffold	Chong et al. (2007)
7	Chitosan	ZnO and castor oil	Casted film scaffold	Díez-Pascual and Díez-Vicente (2015)
8	PVA-chitosan	Minocycline	Freeze-thaw hydrogel	Sung et al. (2010)
9	Chitosan	Copper nanoparticle	Solid dispersion scaffold	Gopal et al. (2014)
10	Acrylic acid and *N*,*N*′-methylene bisacrylamide	Ag/graphene	Hydrogel	Fan et al. (2014)
11	Collagen	Gold nanoparticle	Cross-linked sponges	Akturk et al. (2016)
12	Collagen chitosan	Grafted *N*-acrylamide	Immobilized fabric	Wang et al. (2008)
13	Chitosan	AgZnO	Lyophilized sponges	Lu et al. (2017)
14	Gelatin	Polyurethane	Electrospun scaffold	Vedakumari et al. (2015)
15	Chitosan	Fibrin, quercetin	Electrospun scaffold	Vedakumari et al. (2017)
16	Chitosan–PEO	VEGF, platelet-derived growth factor-BB	Electrospun scaffold	Xie et al. (2013)
17	Cellulose	Kaolin	Film-casted scaffold	Wanna et al. (2013)
18	PVA	Glucose oxidase MCNT	Electrospun scaffold	Santos et al. (2014)
19	PCL	ZnO	Electrospun scaffold	Augustine et al. (2014)

(continued)

Table 8.2 (continued)

Sr. No.	Biomaterial	Bioactive agent	Method/type of scaffold	References
20	Chitosan-PVA	Curcumin-silver nanoparticle	Casted film	Vimala et al. (2011)
21	PVA	Calcium alginate	Electrospun scaffold	Tarun and Gobi (2012)
22	PVA	Cellulose nanowhiskers	Freeze–thawing	Gonzalez et al. (2014)
23	Polyurethane	PVDF	Electrospun scaffold	Guo et al. (2012)
24	Poly (3-hydroxybutyrate-*co*-3-hydroxyvalerate)	Collagen, graphene oxide	Electrospun scaffold	Zine and Sinha (2017)
25	Silk	Epidermal growth factor	Electrospun scaffold	Schneider et al. (2009)
26	Peg	Plasmid bFGF polyplex	Electrospun scaffold	Yang et al. (2011)
27	PLGA	Collagen	Electrospun scaffold	Liu et al. (2010)

* No information available
VEGF Vascular endothelial growth factor

8.19 Nerve Regeneration

The nerve injury or damage is still a major clinical challenge due to lack of self-repairing capability. Similar to bone nerve, tissue engineering is categorized as cell, scaffold, and the growth factor-based approaches. Earlier, allografts (epineural sheath, tendon, vein-decellularized muscle, skeletal muscle-filled Schwann cell) were frequently used to treat the neurological problem associated with nerve damage (Johnson et al. 2005; Ide et al. 1983). Undesired reactions and immunological rejections are the bottlenecks for the practice. The researchers have developed several biodegradable biomaterials to support nerve cell repair and regeneration since the last 50 years. PLGA and collagen are choice of material for fabrication of nerve conduction because of their good biocompatibility and biodegradability. The polymers like PCL, PCL-gelatin, PLLA, chitosan, etc., were also reported for the nerve regeneration (Ghasemi-Mobarakeh et al. 2011; Yang et al. 2005). In addition, the bioactive scaffolds such as Schwan cell-loaded PCL and PLGA foam encapsulated with the Schwan cell are also well established for nerve repair (Hadlock et al. 2000). Growth factors such as human glial cell-derived neurotropic factor (GDNF), brain-derived neurotropic factor (BDNF), insulin-like growth factor (IGF-1, IGF-2), platelet-derived growth factors, fibroblast growth factor, and ciliary neurotropic factor encapsulated into the engineered scaffolds for enhanced nerve regeneration (Dodla and Bellamkonda 2008; Wood et al. 2009).

In contrast to conventional polymer, the conducting polymers like polypyrrole (PPy), PDLA, poly(3,4-ethylenedioxythiophene), and polyaniline participated in

nerve signal conduction and regeneration (Ghasemi-Mobarakeh et al. 2011). Smart polymer PVDF is utilized for its piezoelectricity for nerve regeneration (Rajabi et al. 2015).

8.20 Cosmetic Applications

The cosmetic and aesthetic rejuvenation of the organs like lips, a facial fold, breast, and wrinkles are most frequently performed. The biomaterials like silicon, e-PTEF, collagen sponges, fats, and hyaluronic acid are extensively used in the aforementioned process (Niamtu 2006). Among them, the hyaluronic acid is mostly used as dermal filler in facial fine lines such as lip rhytides, extended radial cheek lines, and horizontal forehead furrows etc. (Fagien 2010). Surgisis is an acellular collagen (surgisis is derived from the ECM of the small intestine of the pig) reported for breast reconstruction, mastopexy, lip augmentation, nasolabial fold, labiomandibular folds, and glabellar folds etc. (Centeno 2009). Similarly, adipose-derived cells were used for the aesthetic surgery of lips and hand rejuvenation (Mehrabani et al. 2013). Beautification of an eye was being improved by wearing cosmetic contact lenses. Generally, the lenses are fabricted with PMMA in addtion of FDA approved pigment. An ocular prosthesis is a class of device used to replace the damaged eye with enhanced appearance. Initially, ocular prosthesis or damaged eye is directly replaced with pig eye; later on, it was fabricated from the glass, known as the glassy eye. Today, most of the orbital implants or ocular prostheses are made up of PMMA (Baino et al. 2014). Fig. 8.15 shows the PMMA ocular prosthesis, and biomaterials such as silicon, polyacrylamide gel, PLGA scaffold, and collagen were extensively used in breast augmentation (Siggelkow et al. 2003).

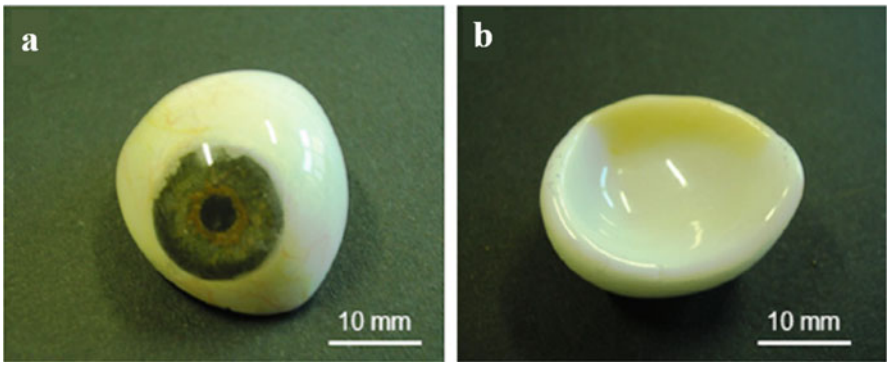

Fig. 8.15 The digital image of the hand-painted aesthetic PMMA orbital implant looks similar to normal eye: (**a**) Frontal view and (**b**) Lateral view of the prosthesis (Baino et al. 2014)

8.21 Biosensor and Bioelectronics

The biosensor is defined as the devices used to detect the biological substance into a measurable physical quantity. The key components of the biosensor are bioanalyte, bioreceptor, transducer, and the detector. There are different types of biosensors such as electrochemical, immunosensor, enzymatic, piezoelectric, microfluidic biosensor, etc. More emphasis of the biosensor is out of the scope of the present chapter. In the fabrication of electrochemical biosensor, conductive polymers like polypyrrole, polyaniline, and chitosan are used along with additive like CNT, ZnO, graphene, nanodiamond, etc. Some of the best-reported biosensors are chitosan combined with carbon nanotube and glucose peroxidase, cellulose zinc oxide composite, and chitosan-MCNT for glucose detection. Similarly, carboxymethylcellulose/ZnCdS, cellulose-graft-poly(*p*-dioxanone), and chitosan-folic acid-combined sensor were deployed for the detection of cancer. Graphene-modified cellulose-based biosensor was used to detect the HIV-I (Pérez et al. 2018).

Biomaterials in the wearable electronics have key attention due to flexibility, good mechanical properties, renewability, and biodegradability. The polymers like PLLA, which are obtained from the natural source like soybean, potato, and beets, have unique piezoelectric property and are used in the piezoelectric biosensor. Flexible polymers like polyurethane (PU) and polyhydroxyalkanoate (PHB, PHBV) polymers exhibit good flexibility, so they are used in the pressure sensor. Natural polymers like silk fibroin, cellulose, chitin, and chitosan are reported for the fabrication of flexible electronic devices (Sun et al. 2018).

8.22 Drug Delivery

A large group of biomaterials is vastly employed as drug carriers, and enormous advancements are reported on every day for drug delivery. Primarily, the polymers have a major stack in this category and demonstrated controlled and targeted drug delivery. The trending approach nowadays is drug-loaded implants for onsite delivery with controlled release. The approach is successfully employed in various applications, primarily drug-coated stents, antibiotic-loaded bone cement, drug-loaded hydrogels, etc. The antiproliferative drugs like paclitaxel and sirolimus are coated on the surface of bare metal stents by using polymers to treat restenosis (Oberhoff et al. 2002). The PVA, PEG, and poloxamer are the polymers used in the synthesis of hydrogels used as implantable scaffolds for drug delivery applications (Peppas and Huang 2002; Langer and Peppas 2003). From the last 10 years, plenty of literature is reported on nanostructured materials for drug delivery, but very few are accepted for clinical applications. The nanoformulations of polymers are well established for controlling drug delivery commercially against conventional formulations (Kumari et al. 2010). The polymers like PLGA, PCL, PLA, PCL, chitosan, gelatin, and poly(alkyl-cyanoacrylates) (PAC) are extensively explored for drug delivery in the form of nanoformulations.

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