Introduction to Biomaterials

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Abstract

Biomaterials are biocompatible materials designed to interface with both living tissue and the environment. They are manufactured from natural sources (living tissue such as silk) or synthetic sources (artificial, such as ceramics, metals and polymers) and can be classified into ceramic, metallic, polymeric, composites (e.g. polymer and metal) and semiconductors (biosensors, implantable microelectrodes). Biomaterials are used in various medical applications to support damaged tissue, replace worn out tissue or enhance biological functions. Biocompatibility is an essential characteristic of a biomaterial but they can also be bioinert, biodegradable or bio-absorbable. They are used in a diverse range of anatomical sites and their applications range from stick-to-skin medical devices, implants, prostheses, transplants to tissue and regenerative engineering.

A wide variety of materials and composites are used due to the broad range of chemical, physical and mechanical properties required. However, biomaterials used in the human body are required to possess certain properties and characteristics so they are not rejected by the patient and the patient does not react to them. These properties and characteristics have to be taken into consideration during the development and manufacturing stages and in the assessment or analysis of their suitability for use. Biomaterials are used in medical devices to save lives and/or improve quality of life. Achieving the right balance is essential and determined by the area of application. Similar to all medical devices, biomaterials must undergo stringent tests to ensure they comply with the legal requirements of the relevant regulating bodies. Advancement in the area of

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biomaterials has progressed from purely interacting with body tissue to influencing biological processes towards the goal of tissue regeneration. Evolving applications include patient-specific 3D printing, drug delivery devices, skin/cartilage, shape memory, tissue engineering-bio printing, wound healing, bioresorbable adhesives and biosensors. 3D printing of patient-specific parts is recently beginning to make important contributions towards improving the safety, biocompatibility and performance of bioresorbable implantable medical devices across a range of application areas.

The field of tissue engineering continues to grow and evolve, heading towards the current goal which is to grow bespoke organs for patients.

Keywords

Biomaterials · 3D Printing · Biomedical applications

1.1 Introduction to Biomaterials

A biomaterial is a material that is compatible with living tissue and is designed to interface with both living tissue and the environment. Biomaterials are manufactured from natural sources (living tissue such as silk) or synthetic sources (artificial, such as ceramics, metals and polymers) and are used in medical applications to support, enhance or replace damaged tissue or a biological function. Biomaterials are used in medical devices to save a patient's life or improve their quality of life [1, 2]. The history of biomaterials can be traced as far back as the late 1800s when polymers were used in aseptic surgery followed by the 1900s when metal implants were used to support fractures, hip replacements and polymers for use in cornea replacement surgery, artificial hearts, glass lens and synthetic skin [1]. Further development has resulted in the use of polymers surpassing the use of other biomaterials in medical applications. The term biomaterials came into effect in the 1970s and further advancement led to the development of the Society of Biomaterials in 1974 and various academic institutions and companies within the field [3].

The evolution of the multidisciplinary field of biomaterials started with physicians attempting to find solutions to life-threatening medical problems. Followed by researchers and engineers in medicine, material science, biology and chemistry investigating the nature of biocompatibility. The evolution of biomaterials can be said to have gone through three major stages. The first stage focused on the development of the structural properties of the implants, followed by innovations in bioactivity and soft tissue replacement and most recently the regeneration of functional tissue [2]. Recently the focus has been on the function and resorption/degradation of biomaterials. The function of a biomaterial is measured by how well it performs a specific action and how it will be used. The resorption and degradation of a biomaterial consider what happens to the biomaterial as it performs its function and once it has achieved its function. They are also used as tools to facilitate treatment in the area of drug delivery, tissue repair and replacement.

Biomaterials are used in implants, prostheses, transplants, tissue and regenerative medicine. Implants are medical devices inserted or embedded surgically in the body. Prostheses are medical devices used inside the body to replace a diseased or damaged part. Transplants involve the transfer of a tissue or an organ from one body or body part to another. These applications can be grouped under the areas with life sciences known as biotechnology, bioengineering, tissue and regenerative engineering.

1.2 Characteristics of Biomaterials

Biomaterials used in the human body are required to possess certain characteristics so they are not rejected by the patient and the patient does not react (i.e. not toxic) to them. When a biomaterial makes contact with a living tissue or system, this living tissue is referred to as the Host. The reaction(s) of the living tissue to the presence of the biomaterial is referred to as tissue/host response and commonly described as the tissue response continuum [5–7].

The host response may vary depending on the location and the nature of the biomaterial. Thus there are two broad phenomenon taking place after every biomaterial interacts with living tissue especially in the case of implants—these are tissue response and biomaterial response [6–8]. The following are the characteristics of biomaterials based on tissue response.

1.2.1 Biocompatibility

This is the ability of a material to be compatible with living tissue and not produce a toxic or immunological response when exposed to body tissue or fluids. In essence, the material performs with an appropriate biological response to a specific application [9].

A biomaterial is considered to have good biocompatibility if it does not trigger too strong of an immune response, resists build-up of proteins and other substances on its surface that would hinder its function and is resistant to infection [4]. The dynamic interplay between the host cells/tissue and the biomaterial decides the level of biocompatibility [6, 8].

1.2.2 Biotolerant

Biotolerant materials are those that are not necessarily rejected when implanted into the living tissue. They are surrounded by a fibrous layer in the form of a capsule [10].

Examples of biotolerant metals are Co-Cr alloys, stainless steels, gold, zirconium, niobium, tantalum and biotolerant polymers are polyethylene, poly-tetrafluoro-ethylene, polyamide, poly-methylmethacrylate and polyurethane.

1.2.3 Bioinert

Bioinert materials have minimal interaction with surrounding tissue and are generally encapsulated by a fibrous layer hence its bio-functionality relies on tissue integration through the implant and direct bone apposition at the implant interface [11]. Examples are stainless steel, alumina, ultra-high molecular weight polyethylene, partially stabilized zirconia-ZrO2 (PSZ), and titanium, Ti alloy, alumina and zirconia.

1.2.4 Bioactive

Bioactive refers to a material, which upon being placed within the human body interacts and develops chemical bonds with the surrounding bone and soft tissue. An ion-exchange reaction between the bioactive implant and surrounding body fluids results in the formation of a biologically layer on the implant that is chemically equivalent to the mineral phase in bone. Examples are calcium phosphate cement (CPC), glass ceramics, synthetic hydroxyapatite [12].

1.2.5 Bioresorbable

Bioresorbable materials such as calcium oxide, polylactic–polyglycolic acid copolymers and tricalcium phosphate [$Ca_3(PO_4)_2$] start to dissolve (is resorbed) once placed in the body, the by-products are non-toxic and the biomaterial is slowly replaced by advancing tissue (such as bone) [9].

1.3 Properties of Biomaterials

The properties of a biomaterial are very important and essential in the development and manufacture of the biomaterial and in the assessment or analysis of its suitability for use. Biomaterials are predominantly used in implants such as artificial joints for the replacement of worn or injured body parts. Thus biomaterials are not only required to exhibit the above characteristics but they are also required to remain stable under high loads and survive/withstand the rigours of everyday living in the form of varying multi-axial and cyclical mechanical loads. These loadings can be considerably high and put the biomaterial under stress and strains. They must also be high wear-resistant, to survive the environment in the body (corrosive saline body fluids) and last the duration of their applications (typically 20 years). These properties can be grouped into bulk and surface properties.

1.3.1 Bulk Properties

Stability and longevity of a biomaterial goes hand in hand with its structural and mechanical properties (strength and the mechanics). The structural integrity of a biomaterial takes into consideration the following factors:

1.3.1.1 Modulus of Elasticity (E)

Measure of the change in the dimensions of the biomaterial in response to applied stress. The elastic modulus of an implant should be as close to that of the tissue it is replacing and those around the implant. This is to ensure an even distribution of stress and prevent the relative movement at the implant-bone interface. The elastic modulus of a biomaterial interacting with bone should be similar to that of bone which is 18 GPa.

1.3.1.2 Tensile Strength

This is the ability of a material to resist a pulling force. A biomaterial used in an implant requires high tensile strength.

1.3.1.3 Ultimate Tensile Stress (UTS)

Stress is the force applied on a material per unit area. The UTS is the maximum tensile load a material can withstand per its cross-sectional area, prior to failure [1]. In general, metals possess good tensile strength, whereas in order to compensate for the poor tensile strength of ceramics, they are combined with reinforcement polymeric materials such as glass and Kevlar.

1.3.1.4 Compressive Strength

This is the ability of a material to resist pushing forces and is assessed by the maximum force/load a material can withstand per its cross-sectional area prior to failure. A biomaterial used in an implant requires high compressive strength. Ceramics generally have high compressive strength.

1.3.1.5 Shear Strength

Ability of a material to withstand sliding forces. A biomaterial used in an implant requires high shear strength. Shear strength takes into consideration the maximum shear load a material can withstand per cross-sectional area prior to failure. This property is most relevant in the case of sutures and adhesives.

1.3.1.6 Yield Strength

The stress at which a material exceeds its Yield Point, i.e. no longer returns to its original state due to changes from its region of elastic deformation to its region of plastic deformation as a result of an applied force. Biomaterials used for implants are required to have a high yield strength.

1.3.1.7 Fatigue Strength

When a material is exposed to recurring forces, the stress at which the material fractures is referred to as the fatigue strength. Biomaterials used for implants are required to have a fatigue strength.

1.3.1.8 Young Modulus

A modulus is the value that represents a physical property of a material. The modulus of elasticity represents the easy of stretch or deformation.

1.3.1.9 Ductility

A measure of the degree of plastic deformation prior to fracture when a tensile stress is applied.

1.3.1.10 Hardness

Ability of a material to resist permanent indentation or penetration to its surface. The higher the hardness, the less the wear and tear of the material.

1.3.1.11 Toughness

This is the amount of energy required to fracture a material. The higher the toughness of a material, the less likely it is to fracture.

Stress: force per unit area.

The formula used for calculating stress (σ) is

$$\sigma = P/A,$$

where σ stress, P load, A cross section area

1.3.1.12 Strain

The degree of deformation of a material due to an applied force.

The formula used for calculating stress (ε) is

$$\varepsilon = dL/L,$$

where ε strain, dL extension produced in the rod, L original length

To analyse the strength of a material, a tensile test is performed on the material using a tensile testing machine which applies a tensile load on one end of a specimen of the material and that is fixed at the opposite end. The load and extension graph is then used to calculate and produce a stress–strain curve. Hooke's law states that stress is directly proportional to strain.

1.3.1.13 Surface Properties

The surface properties of a biomaterial is essential as it affects its degree of biocompatibility with its surrounding tissue [13, 14]. The surface properties of a material/implant dictate its level of corrosion resistance as well as the cytotoxicity of the corrosion products. The environment inside the human body can be highly

corrosive to implants. Corrosion is a type of failure in a material. Corrosion Resistance is the ability of a material not to deteriorate as a result of its reaction with its environment. More specifically, corrosion can be defined as the chemical or electrochemical degradation of metals due to their reaction with the environment.

There are different types of corrosion observed in relation to implants:

a. Stress corrosion—This is a crack as a result of increased tensile stress and corrosive environment.
b. Crevice corrosion—Occurs where there is a gap/crack between adjoining surfaces.
c. Pitting corrosion—Similar to crevice corrosion but the holes are produced in the material and blocked by the corrosion product.
d. Fretting corrosion—Failure resulting from corrosion and surface rub.
e. Galvanic corrosion—Occurs as a result of the coupling of two different materials.

1.3.1.14 Cytotoxicity of Corrosion Products

The biocompatibility of a biomaterials improves with an increase in its corrosion resistance and decrease in its toxicity. The toxicity of a biomaterial is determined by the toxicity of its corrosion product. When a biomaterial undergoes corrosion, the residue or corrosion product can be toxic. The degree of toxicity depends on various factors such as the amount of material dissolved by corrosion per unit time, the amount of corroded material removed by metabolic activity in the same unit time and the amount of corrosion particles deposited in the tissue [9]. Surface Characterization: Interaction between host tissue and biomaterial primarily occurs at the implant surface [6, 9]. Thus characterization/preparation of implant surface to suit clinical needs is extremely important to avoid metallosis (metal poisoning), osteolysis (weakening of bone), inflammatory responses and implant loosening, which can be aggravated by metal allergies and sensitivity [13, 15]. Surface characterization can be accomplished by several techniques: Passivation (chemical treatment of a material with a mild oxidant), acid etching (surface treated with nitric or hydrofluoric acid), and sand blasting (sand particles used to get a roughened surface texture which increases attachment at bone implant surface) [9]. Surface coatings involve covering implant surfaces with porous coatings to increase their surface area, roughness, attachment strength at bone implant interface, increase load bearing capacity and biocompatibility [9]. Several coating techniques exist. The plasma sprayed technique is the most commonly used and there are two major types: Plasma sprayed titanium and plasma sprayed hydroxyapatite.

1.4 Balancing the Characteristics and Properties of Biomaterials in Medical Devices

Balancing the characteristics, bulk and surface properties of biomaterials are essential. For example, with regard to a heart valve the proper balance can help avoid complications such as tissue degeneration, mechanical failure, post-operative

infection and the induction of blood clots. Vascular grafts also illustrate this principle because they are required to be flexible, porous structures and come in a range of permeabilities. They must also maintain their structural integrity under repeated loads, have a low tendency to clotting, be biostable as well as achieve and maintain homeostasis.

Metal stents commonly used to keep blood vessels open can cause long-term complications, including re-narrowing of the vessel, blood clots and bleeding [4]. Thus recent research has looked into developing a bio-absorbable zinc stent that harmlessly erodes away over time, minimizing the normal chronic risks associated with permanent stents [4]. Metallic biomaterials are predominantly used in orthopaedic implants because of their material and structural properties. Internal fixators such as screws and plates require stability and high bending/pull-out strength hence there are various types of screws to meet the required load bearing needs. Although the artificial hip joint is made out of a combination of biomaterials (Metallic or ceramic femoral head, metallic femoral stem, polyethylene or ceramic insert, metallic acetabular cup and composite bone cement) the implant undergoes high cyclic mechanical stresses that lead to wear.

With regard to tooth filling materials, some general criteria in relation to bulk and surface properties are mechanical strength, wear resistance, minimal dimensional changes on setting and biocompatibility, i.e. non-irritation to pulp, low toxicity, does not dissolve or erode in saliva as well as good aesthetic properties. Artificial skin must prevent the loss of fluids, electrolytes and molecules, it is required to be flexible enough to adapt to the wounded area and movement of the body yet resist storing moisture under the graft. Possible materials used for artificial skin are polymeric or collagen based membranes due to the ability to regulate their properties, however, they are not effective in all burn wounds [16].

1.4.1 Bio-adhesives

Tissue adhesives are used to repair fragile, non-suturable tissue in anatomical parts such as livers, kidneys, lungs. The important criteria for tissue adhesives is that they are able to be wet and bond to tissue, they are capable of onsite formation by the rapid polymerization of a liquid monomer without producing excessive heat or toxic by-products [5], they are absorbable, do not interfere with the normal healing process and are easily applied during surgery [5]. They are manufactured from alkyl-o-cyanoacrylates which are low strength and restricted to use in traumatized fragile tissue (e.g. kidney) or fibrin derived from fibrinogen-clotting component of blood and limited mechanical strength. Due to their limited strength wound site leakage sometimes occur and as a result, current research is focused on the use of photothermal therapy, a laser-welding technique for colon repair as an alternative to suturing or stapling [4]. The procedure is minimally invasive and uses photothermal nanocomposites—nano-sized material and gold rods embedded in a matrix that when heated with a laser can fuse with ruptured tissues [4, 17]. Recently a bioadhesive has been developed that is able to bond biological gel to damaged

cartilage in the knee. Cartilage has been very difficult, if not impossible, to repair due to the fact that cartilage lacks a blood supply to promote regeneration [4]. This gel/adhesive combo has been successful in regenerating cartilage tissue following surgery. The biological gel is injected into a cartilage defect and the adhesive helps to keep the gel and newly regrown cartilage in place. In order to avoid adhesive failure, the application of the adhesive must be considered before it is manufactured and the chosen adhesive must be compatible with the manufacturing process intended to mass produce the final product. The adhesive must also be able to withstand the speed and friction of a specific method or the liner materials could break during production, which may compromise integrity. With regard to stick-to-skin products, it is usually the adhesive's main job to keep the device adhered to the user's skin for a specified wear time. Adhesives must also be compatible with the other materials used in the device [18, 19].

1.4.2 Materials Property Chart

In order to pick the right material for an application, it is helpful to be able to compare the properties. The wide variety of materials and their varying properties lend itself to the difficulty of comparing them. A materials property chart is a common method of displaying and comparing the properties of various materials [20].

1.4.3 Regulations and Standardization

It is a legal requirement that all biomaterials and medical devices must be tested and comply with the requirements of the relevant regulating bodies before they are introduced into the market. The ISO 10993 document highlights the main recommendations for testing a biomaterial or medical device [21].

1.5 Classification of Biomaterials and Their Applications

Biomaterials can be classified into ceramic, metallic, polymeric, composites (e.g. polymer and metal) and semiconductors (biosensors, implantable microelectrodes).

Their applications range from stick-to-skin medical devices, implants, prostheses, transplants to tissue and regenerative engineering. Also a wide range of materials are used due to broad range of chemical, physical and mechanical properties required. They are used in a diverse range of anatomical sites.

1.5.1 Ceramic Biomaterials

1.5.1.1 Bioceramics

Ceramics are inorganic, non-metallic materials. Bioceramics can be classified as bioinert, bioactive or glass ceramics [22].

1.5.1.2 Bioinert Ceramics

These ceramics show direct bone apposition at implant surface (i.e. close together/side by side) but do not show chemical bonding to bone. They are full oxides, i.e. bulk and surface thus excellent bio compatibility, have good mechanical strength, low ductility which results in brittleness and have similar colour to hard tissue [9]. Examples are aluminium oxide, titanium oxide, zirconium oxide. They are not suitable for load bearing dental implants due to inferior mechanical properties. They are used as surface coatings over metals to enhance their biocompatibility increase the surface area for stronger bone to implant interface [9].

1.5.1.3 Bioactive Ceramics

Bioactive ceramics are not used for load bearing implants due to lack of mechanical strength.

They are used as bone graft material for augmentation of bone and as bioactive surface coating for various implant material to increase biocompatibility and the strength of tissue integration [9]. Examples are calcium phosphate ceramics—(CPC), hydroxyapatite (HA), tricalcium phosphate (TCP), etc. CPC have biochemical composition similar to natural bone. General properties of bioactive ceramics include excellent biocompatibility, lower mechanical tensile and shear strength, lower fatigue strength, lower ductility and brittleness. Though the pores decrease the strength they increase the surface area providing additional regions for tissue ingrowth [9].

1.5.1.4 Glass Ceramics

These ceramics chemically bond to bone due to the formation of a calcium phosphate surface layer. They have high mechanical strength but their low resistance to bending and tensile stresses make them extremely brittle. They are not used as load bearing implants but more often as bone graft material. They also make weak coating bonds between coating and metal substrates. Example is bioglass.

1.5.1.5 Bio Ceramics

With carbon and carbon silicon compounds are biocompatible with a modulus of elasticity similar to that of bone. They are brittle and susceptible to fracture under tensile stress, however, they are used as surface coatings and facilitate osseointegration at bone implant interface.

1.5.1.6 Applications of Bioceramics

Bioceramics are used in bone replacements, heart valves, dental implants (alumina, calcium phosphate), ceramic crowns (glass ceramics + alumina, mica or leucite),

tooth filling materials and hip/knee joint replacement prosthesis (ceramic femoral head, ceramic insert), to name a few.

1.5.1.7 Metallic Biomaterials

Metallic biomaterials are mainly used for load bearing applications such as knee or hip replacement implants, orthopaedic fixation plates and some parts of dental implants. Metallic implants are commonly made from metal alloys comprising of a combination of pure metals. As a result they generally possess a combination of enhanced chemical and mechanical properties. Metallic biomaterials are extracted from other materials such as aluminium from bauxite, however, few materials such as copper and precious metals are naturally found in in their metallic state. Examples of metal and metal alloys are titanium, cobalt, surgical steel (iron, chromium, nickel alloy), molybdenum alloy (vitallium), precious metals (gold, platinum, palladium).

1.5.1.8 Strength of Pure Metals vs. Alloys

Pure metals are tightly packed particles of the same size atoms arranged in an organized pattern. As a result the bonding at the grain boundaries tends to be weaker and susceptible to dislocation when a lateral force is applied. On the other hand, alloys comprise two different sizes of metal elements randomly organized and the difference in size helps prevent the physical dislocation of the lattice structure. The presence of atoms of other metals that are of different sizes disturb the orderly arrangement of atoms in the metal. This reduces the layer of atoms from sliding. Thus, an alloy is stronger and harder than its pure metal [9].

1.5.1.9 Metal Structure and Properties

The area of application in which a metal is used is determined by its physical properties. These physical properties are largely determined by the strength of the metallic bond (degree of attraction) between the closely packed positive metal ions and numerous delocalized electrons. Metallic bonds are naturally strong and the free electrons facilitate the conduction of electricity. Other advantages of metallic biomaterials are that they can be moulded into various forms and complex shapes using a wide range of fabrication techniques, e.g. casting, forging, machining. Their high level of fracture resistance also enables them to bear high loads. The major disadvantages are their susceptibility to corrosion and stress shielding. Stress shielding occurs when metals take the stress off the bone resulting in weakening the bone tissue, hence one of the main aims of metal alloys is to resolve this challenge.

1.5.1.10 Titanium (Ti)

Titanium (Ti) is the highest standard in implant materials. Commercially pure titanium is usually composed of 99.75% Titanium, 0.1% Oxygen, 0.05% Carbon, 0.05% Iron, 0.03% Nitrogen and 0.012% Hydrogen. Titanium Alloy Ti6Al4V consists of titanium, 6% Aluminium—alpha stabilizer, and 4% Vanadium—beta stabilizer. It has excellent corrosion resistance, oxide layer formed is resistant to charge transfer thus contributing to biocompatibility, the modulus of elasticity is 5.6

times that of the bone thus more distribution of stress and the strength of titanium alloy is greater than pure titanium—6 times that of bone hence thinner sections can be made. Titanium Alloys Ti6Al4V also has sufficient ductility and exhibits osseointegration [9].

Titanium Alloy Ti-9Cr-0.2O is used in scoliosis surgery. Its properties include: High stiffness in deformed parts, low stiffness in the non-deformed parts, high strength and good flexibility. These properties make the implant more controllable and surgery easier.

1.5.1.11 Cobalt, Chromium and Molybdenum Alloy

Is a composition of 63% Cobalt, 30% Chromium (CrO provides corrosion resistance) and 5% Molybdenum (strength). The properties of cobalt, chromium and molybdenum alloy are high mechanical strength, good corrosion resistance and low ductility (solid material's ability to deform under tensile stress). It is used in the fabrication of custom designs due to ease of castability and low cost [9].

1.5.1.12 Iron, Chromium and Nickel Based Alloy

These are surgical steel alloys. They have a long history of use as orthopaedic and dental implant devices. They are composed of iron, 18% chromium (corrosion resistance) and 8% nickel (stabilize austenitic steel). The properties of iron, chromium and nickel based alloy are high mechanical strength and high ductility. They are used in various applications. They are susceptible to pitting and crevice corrosion and hypersensitivity to nickel has been observed. Bone implant interface has also shown fibrous encapsulation and ongoing foreign body reactions [9].

1.5.1.13 Precious Metals

Precious metals (noble metals) such as gold, palladium and platinum are unaffected by air, moisture, heat and most solvents. They do not depend on surface oxides for their inertness. Their properties include low mechanical strength and very high ductility [9]. However they do not demonstrate osseointegration and cost more per unit weight.

1.5.1.14 Applications of Metallic Biomaterials

Metallic biomaterials are used in dental implants, i.e. pure titanium screws replacing roots for crowns and bridges, orthopaedic screws/fixation, for example, hip/knee joint replacements and spinal implants use titanium, titanium alloys, stainless steel, bone plate are made from stainless steel. Stainless steel is used in heart valves; platinum electrodes are used in cochlear replacements; Staples made of titanium facilitate closure of large surgical incision produced in caesarean procedures.

1.5.1.15 Polymeric Biomaterials

Polymers are organic compounds that consist of chains of molecular units. Examples of polymers: proteins, carbohydrates, plastics, etc. The basic unit of a polymer is a monomer. Examples of monomers: lactic acid, amino acids, glucose, etc. The way monomers are connected/shaped has a very large influence on their properties. They

can be graft, star, multivalent, dendrimer, or dendronized shaped polymers [23, 24]. Polymers are named after the bonds between the monomers. E.g. Polyesters, Polyamides, etc.

There are also various types of polymers, namely Homopolymers (polymers consisting of one type of unit), Copolymers (A polymer consisting of two), Random (units are randomly linked), Alternating (where two units alternate), Block (where blocks comprising of the same units are linked to blocks comprising of different units) and Graft polymers. Polymers can also be referred to as macromolecules since they consist of large molecules. Polymers with low molecular masses and fewer monomers are called Oligomers, for example, peptides [25]. Polymeric Biomaterials have high molecular masses and high melting and boiling points. They are easily modified to various applications and can be polymerized to create synthetic polymers [24]. Although they are biodegradable they are not easily sterilized and they can be subject to surface contamination and leachable compounds. Biopolymers can be grouped into natural or synthetic [25].

1.5.1.16 Natural Polymers (Protein Based)

Natural polymers occur in nature and can be extracted. They are often water-based. They can be divided into functional (DNA, RNA and globular proteins) and structural (Fibres—cellulose, silk, wool or gels and rubbers, e.g. agar and gelatin). Natural polymers can also be classified based on their source, i.e. plants (polysaccharides, e.g. cellulose, starch, alginate), animals (proteins, e.g. gluten (gelatin), albumin and polysaccharides, e.g. chitin (chitosan), hyaluronate) and microbes (polyesters, e.g. poly (3-hydroxylalkonate) derivatives and polysaccharides, e.g. hyaluronate) [9]. Developments in biomaterials have led to additional natural polymers such as reflectins for optical devices, amyloids for biosensors and various plant proteins for tissue regeneration. Together with their genetic variants generated by protein engineering, these natural proteins enable the possibility of creating a combination of properties [26]. Examples of applications of natural polymers are in heart valve replacements (e.g. pig valves), collagen is used in corneal bandage and artificial skin [27]. Absorbable Surgical Sutures made from natural collagen (beef intestine) and fibres (silk) [28]. They are also used in drug delivery [29], prosthetic implants and in tissue engineering for multiple organs.

1.5.1.17 Synthetic Polymers

Synthetic polymers can be grouped into Fibres (polyester, nylon and acrylic), plastic (polyethylene, poly (vinyl chloride), polystyrene, and bakelite) and rubbers (cis-1,4-polyisoprene). They can be degradable or non-degradable. Examples are polyamides (PA), poly (methyl methacrylate) (PMMA), poly (ethylene) (PE)—plastic bags, poly (vinyl chloride) PVC—PVC pipes, polylactic acid (PLA)—plastic bottles, food containers, disposable bags, plastic utensils—polylactides (biodegradable polymer such as those used in brain wafers), polyurethanes (PU)—coatings, adhesives and sealants, automotive building and construction, footwear, appliances [29].

1.5.1.18 Thermoplastic Polymers

These are polymer materials that are consistent in their chemical and mechanical properties regardless of the number of times they are softened when heated and harden when cooled.

1.5.1.19 Thermosetting Plastics

These are polymer materials made of cross-links, they harden when heated and cannot be remoulded once cooled.

1.5.1.20 Elastomers

Elastomers are low crosslink density network polymers (have weak intermolecular forces) that can be stretched easily and recovers upon stress withdrawal. They can be both thermoplastic and thermosets. E.g. rubber

1.5.1.21 Polymer Composite

A polymeric composite is made up of a combination of a polymer and other synthetic biomaterials. It consists of two phases, e.g. glass fibre reinforced plastic. Their main advantage is that their properties can be altered to suit clinical applications.

Bone is an example of a natural polymer composite of collagen (a protein) and apatite (a ceramic). Composites may be isotopic (have the same properties in all directions) or anisotropic (different properties in different directions).

The type of polymer used can be customized to specific applications by considering the type of monomer composition, the molecular weight, the polymer microstructure and architecture and the end group. The substrates used are required to meet the specifications for application and be able to meet the requirements of the scale of production. These substrates come in different forms: granules, powder, filaments, tubes, mono- and multi-filament yarns, sutures, meshes and tapes, foils/membranes/nonwovens, etc. [28]. Within the wound healing and paediatric markets in particular, conventional bioresorbable polymers have lacked the combination of high mechanical strength and the ability to degrade rapidly. As a result, companies seeking to develop bioresorbable wound closure devices such as stomach or ligating clips and vascular closure devices have been forced to either utilize traditional metal-based materials or make compromises in the use of polymeric-based materials that may adversely affect functional performance. For paediatric applications with accelerated bone regeneration, such as for craniomaxillofacial (CMF) implants, imbalanced degradation times could significantly impair the ability of the device to match the natural healing process. Recent innovation has led to the development of PLA-PEG copolymers for use with implantable medical devices. By combining the hydrophobic properties of PLA polymers with the hydrophilic properties of PEG to increase water uptake, the new platform of tri-block (PLA-PEG-PLA) copolymers is able to replicate the mechanical strength of standard, equivalent material grades but degrade up to six times faster [30]. Bioresorbable medical device in orthopaedic applications include: Craniomaxillofacial implants (for skull fractures), sutures anchors (for rotator cuff injury), thorac-lumbar fusion (spinal injury), spinal disk implants (for spinal injury), fixation plates (bone fractures), meniscal darts (for knee injury),

interference screws (for ACL tears), pushlock suture anchor (for anterior knee pain), smart nail (for bone fractures), Achilles implants (for Achilles tendon ruptures), subtalar implants (for flat foot) and hammertoe repair (for hammertoes), biocomposite distal biceps (for tendon rupture), dental membrane (for bone and tissue regeneration), tracheal implant (for airway obstruction), cardiovascular stents (for clogged arteries), breast implants (for breast reconstruction), shoulder balloon (for rotator cuff injury), tissue scaffold (for tissue regeneration), ligating clip (for general surgery) [30]. Evolving applications are patient-specific 3D printing, drug delivery devices, skin/cartilage, shape memory, tissue engineering-bioprinting, wound healing, bioresorbable adhesives and biosensors. 3D printing of patient-specific parts is now beginning to make important contributions towards improving the safety, biocompatibility and performance of bioresorbable implantable medical devices across a range of application areas [31–33]. For example, the orthotic and prosthetic (O&P) field has experienced developments in 3D printing enabling O&P clinicians to seamlessly design and create bespoke devices that are functional, lightweight, affordable, and comfortable for patients, more easily and efficiently than they can with traditional methods [33]. Many of the materials used in the O&P market today, such as carbon fibre sheets, are not the most comfortable. Silicon liners can be used as an alternative to provide a better fit and better comfort, however, this can increase the cost and waiting time for a full prosthesis. 3D printing offers alternatives to carbon fibre and silicon which provides reliable strength and comfort. Currently 3D printing of bioresorbable implants can be done via a bioplotters using granule based gel, inks. Implants can also be 3D printed via SLS using print powder [31].

Recent research is looking into bioplastics as a substitute for single-use plastics. The overall aim with bioplastics is that they are reusable or biodegradable and their mechanical, chemical and physical properties can be tuned to adapt to various applications [1, 34]

1.5.1.22 Semiconductor Biomaterials

Semiconductor biomaterials are used in biosensors and implantable microelectrodes. In the case of the structural design of implantable medical devices and delivery systems, the device should be adequate for handling the electronic data and be the right size to insert in the human body [32]. The delivery methods of the devices are via incision and the use of tools.

Smart wound dressings are a recent development. They combine electronics, wound healing, microfabrication, biomaterials and drug delivery [29]. The dressing integrates sensors and actuators in close contact to skin [4] for the treatment of chronic diabetic ulcers. The smart wound dressing delivers oxygen and blood vessels promoting biochemical factors while monitoring healing and reducing unnecessary dressing replacements and visits to medical facilities [4].

1.6 Transplants, Tissue Engineering and Regenerative Medicine

Biomaterials have advanced from purely interacting with tissue to influencing biological processes toward the goal of tissue regeneration [35–38].

Organ transplantation is the process of surgically transferring a donated organ to someone diagnosed with organ failure. Organ transplants performed include kidney, liver, heart, lung and pancreas transplants [16, 27, 32, 39, 40]. The regenerative capacity of tissues can help replicate their biological function in relation to the desired geometry and mechanical properties [21, 32].

Recent research into transplantation proposes bioprinting organs as an alternative to organ donation.

Tissue engineering is a practice within the field of biomaterials that combines scaffolds, cells and biologically active molecules into functional tissues [4].

The goal of tissue engineering is to assemble functional constructs that restore, maintain or improve damaged tissues or whole organs. Artificial skin and cartilage are examples of engineered tissues that have been approved by regulatory organizations; however, currently they have limited use in human patients [4, 17].

Regenerative medicine is a broad field that includes tissue engineering but also incorporates research on self-healing—where the body uses its own systems, sometimes with the help of foreign biological material to recreate cells and rebuild tissues and organs [4, 17].

Tissue Engineering applies engineering principles to either maintain existing tissue structures or enable tissue growth. With regards to the field of engineering materials, tissues can be described as multiple systems of cellular composites each comprising of three main structural components organised into functional units, the extracellular matrix (ECM) [41] (initiates crucial biochemical and biomechanical cues that are required for tissue morphogenesis, differentiation and homeostasis) [42] and scaffolding architecture (highly porous scaffold biomaterials, which act as templates for tissue regeneration, to guide the growth of new tissue), e.g. hydrogels [38, 43]. Currently research is being done to combine silk with tropoelastin, a highly elastic and dynamic structural protein to construct a panel of protein biomaterials. These materials must mimic the elasticity of diverse tissue structures and, consequently, control biological function, particularly the differentiation of stem cells [4, 17].

The main materials for the matrix (scaffold) are synthetic polymers, e.g. polylactic and polyglycolic acid—self-assembling proteins and natural polymers, e.g. fibrin, collagen, collagen-glycosaminoglycan copolymer [44]. Scaffolds and constructs must be biodegradable to enable cells to develop their own extracellular matrix [44, 45]. Ideally, the mechanical properties of the scaffold should be the identical to that of the host tissue and have the strength to withstand the implantation process [38]. In orthopaedic and cardiovascular applications, producing ideal scaffolds is of specific importance and an ongoing challenge because the durability of the implanted scaffold is required to last the

duration of the remodelling process and the rate of healing varies with the age of the patient [38].

Recent developments in 3D bioprinting have combined the processes of tissue and regenerative engineering to address one of the major challenges with transplants by enabling blood vessels to be inserted into new organs thereby maintaining the survival of the organs during transportation from the donor to the receiver [17].

1.6.1 Supramolecular Biomaterials

Standardization is another challenge in the field of regenerative medicine as reproducibility is difficult due to physiological differences and changes over time. Therefore, current advancements are in the direction of the development of biomaterials that can be adjusted (tuned) in response to physiological cues or that mimic natural biological signalling [4]. These are called supramolecular biomaterials, they are composed of a combination of molecules engineered to sense and respond, they combine the functionality of the biomaterial and physiological parameters to produce patient-specific applications [17, 46]. The field of Tissue Engineering continues to grow and evolve, heading towards the current goal which is to grow bespoke organs for patients [17, 46].

1.7 Conclusion

In conclusion, Biomaterials play an integral role in medicine today—restoring function and facilitating healing for people after injury or disease [4]. The modern field of biomaterials combines medicine, materials science and more recently tissue and regenerative engineering. Biomaterials may be natural or synthetic and can be reengineered into various forms for use in biomedical products and devices. These devices are used in medical applications to support, enhance or replace damaged tissue or a biological function such as heart valves, hip joint replacements, dental implants or contact lenses [4]. They are biocompatible and can be bioinert, biodegradable or bio-absorbable. Doctors, researchers and bioengineers use biomaterials for a broad range of applications [4] and continue to work together towards a common goal.

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