Trends in Biomaterials and Artificial Organs
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Review Article

Journey of Biomaterials: From Beginning to Future Development

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Biomaterials perform an indispensable role in modern medicine as medical devices fabricated by biomaterials are regularly utilized to restore the natural function and promotes healing process after damage or disease. The advancement of biomaterials is an emerging technology and rapidly progressive to address the continually-growing needs in healthcare and medicinal treatments. From first historic use of biomaterials as sutures from animal sinew, there is several folds increase its application due to consistent progression of biomaterials towards the degree of interaction with physiological environment. Three generation of biomaterials are clearly identified by their interaction with the host tissue and marked as bioinert, bioactive & bioresorbable. Present directions of biomaterials are mainly concerned in disease treatments including controlled and targeted drug delivery and cancer immunotherapy, are additionally marked. Thus, modern biomaterials combine medicine, biology, physics, and chemistry to address the challenges faced by biomaterials during its application in medical field and recently influences come from tissue engineering and regenerative medicine. This chapter is focused on the journey of biomaterials from bioinert to bio-functional materials as per the demands of the medical science as well as describe the future trends of biomaterials in modern medicine.

Introduction

In today's world, healthcare needs constant changing in terms of evolution. Due to advancement of biomaterials science life expectancy of people will increases remarkably as they provide necessary support in patient health [1,2]. Extended life should aim to be an improvement in life trait, both in terms of wellness and cost effective. Well-being is more than happiness and life satisfaction: a multidimensional analysis of 21 countries [3]. Therefore, biomaterials research and their continuous development can fulfil our dream and provide the right solutions. There is a stable demand for biomaterials not only for repairing large sections of disorders on hard and soft tissues but also replace the damaged or diseased tissues like bone, teeth, cartilage etc [4]. So, biomaterials play an intrinsic portrayal in present-day medicine i.e., reassuring action and promotes healing for people after injury or disease.

Biomaterial is either originated naturally or man-made biomedical material apart from drug that is used to support, augment, repair or replace the diseased or damaged tissue, organ to restore body's function in secure, stable, cost-effective, and physiologically bearable manner [5,6]. In addition, these materials can touch with body fluids and host tissues for prolong time without creating any adverse reactions [7]. Alternately, biomaterial is a medical substance of natural or synthetic origin made of multiple components having life or not modified to interact with physiological systems for therapeutic function like treat, strengthen, reconstruct, or supplant a natural action of damaged/diseased tissue of the body [8].

So, biomaterials are natural or synthetic materials which are designed to intervene with a biological system without any adverse effect to the host tissue. They play a vital role by providing a suitable framework for the cellular procreation, attachment, and growth, which ultimately guide towards the development of new tissue that subsequently helps to restore the functional aspects in a body after injury or damage [9]. All these properties of biomaterials are the probable reasons why they have been used in assisting healing applications, promote tissue function and rectify abnormalities within the system.

Biomaterial improve the attribute of human life by playing a pivotal role in present-day medicine on continuously increasing number of populations every year with thriving demands on biomaterials

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for better wellness to an older people by supporting, regaining task, and promotes healing mechanism for population having complications or diseases [10]. The first antique use of biomaterials as suture material which was made by ancient Egyptians from animal sinew. There is tremendous demand of biomaterials to repair and replaces hard tissues like bone, teeth etc, and collagen rich tissues such as skin, blood vessels etc as population ages and their life expectancy increases day by day [11]. The intention of biomaterial exploration is consummate with suitable mixed up of chemical and physical behaviours that mimicked with tissues recouped with minimal adverse response in the host [12,13].

There is enormous application of such research includes limb and joints replacements, artificial skin, contact lenses, artificial teeth, and dentures etc. Developing such medical materials to replace the ailing tissues extends the life expectancy of aged people and improve the quality of human beings by aesthetic manners [14,15]. The contemporary field of biomaterials incorporates medicine along with biology, physics & chemistry and later repercussion came from tissue fabrication and regenerative medicine respectively [16]. The space of biomaterials has grown substantially in the past decade due to exploration of tissue engineering as well as regenerative medicine and many others.

Evolution of Biomaterials

The ancient application of biomaterials includes binding of loose teeth with gold suture which create an artificial one around the neighbouring teeth [17,18]. After several thousand years later, bone plates made of stainless steel were successfully executed in the early 1900's to stabilise bone fractures and to accelerate their healing. While by the time of the 1950's to 60's, blood vessel replacement was in clinical trials and artificial heart valves and hip joints were in development [19]. Initially, autografts and allografts were considered as the gold source of biomaterials for hard and soft tissue substitute but these are not ideal because the rejection response from host immune system due biocompatibility mismatch, awful pain, and chance of infection [20,21]. While application, autologous grafts exhibit a remarkable bone resorption before reconstruction and allografts conferred noticeable possibility of infection and immune repudiation during implantation due to the transmission of contagious diseases [22,23]. These so-called problems associated with application of natural biomaterials in hard tissue replacement makes the space for searching a source of alternative biomaterials i.e., synthetic biomaterials [24,25].

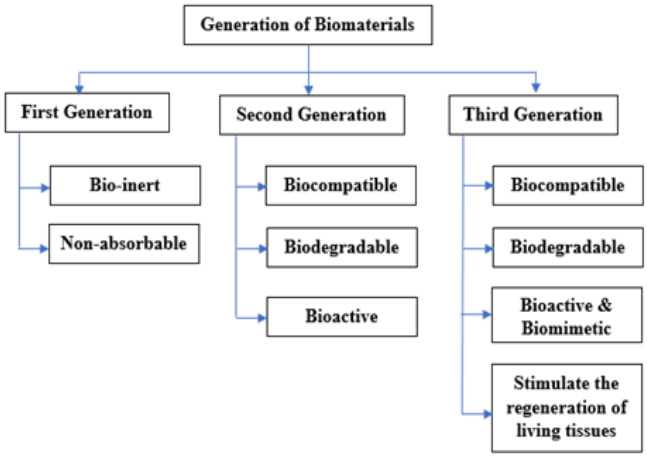

Figure 1: Different generation according to behaviour of biomaterials

Biomaterial applications have evolved through three generations. On evolution, progressive biomaterial generations are varied due to intricacy and their proficiency to combine with or adapt the physiological surroundings in the host tissue [26,27]. These biomaterials are convenient in the innate ambience of the host structure and used solely for restoration of organs [28]. Three distinct generations of biomaterials are clearly marked based on the behaviour that shown in figure 1.

First generation of biomaterials

The journey of such biomaterials begins in the years 1950s and continued until achievement of a favourable combination of functional behaviours that could mimic the properties of the recouped tissue without mischievous reaction by the owner [29]. Due to bioinert nature and considerable biocompatibility, the suitable combination of physical properties is effective and particular to the desired clinical application [30]. In between 1960's and 1970's, this class of materials was specifically designed and developed for internal use as prostheses which considered as the base for biomaterials research [31]. Professor Bonfield was first scientist to recognize the pioneering efforts to understand the relevance of mechanical behaviour of hard tissues, principally bone, to find out suitable skeletal prostheses [32]. Primary objective of each previous biomaterial development was to 'accomplish a satisfactory combination of physical properties which resembles the function of those reinstate tissue with minimal conflicting effect in the host environment', so bioinert or nearly inactive materials were used to diminish the chances of corrosion as well as releasing ions and particles after implantation for minimal immune response and foreign body reaction [33].

From beginning to 1980s, more than 50 different prostheses fabricated from 40 distinct materials were implanted for clinical use. During this period, as many as three million prosthetic parts were being inserted in patient body globally per year. Most of the materials used in the body were single-phase and biologically inert and they are considered from commercially available materials of high purity to eradicate the release of toxic by-products and minimize corrosion [34]. With the help of such implants made of inert biomaterials, more than ten million people have enhanced their trait of life for 25 years or more. Stainless steel, Co-Cr alloys, Ti & its alloys (Biometal); alumina & airconia (ceramics) and silicone rubber, acrylic resins (polymers) are the common examples of first-generation biomaterials.

Second generation of biomaterials

Origination of such biomaterials was designed in the 1980s to encourage a reasonable outcome within the tissues where such biomaterials were confined in order to engender a proper therapeutic response [35]. Bioactive materials like bio-glasses and calcium phosphate ceramics were used in a controlled, localized drug-release manner to orthopaedic and dental surgeries (e.g., drug-eluting cardiac stents used to limit restenosis followed by balloon angioplasty) [36,37]. This class of biomaterials also comprised with advanced biodegradable materials, with controlled rate of absorption which could be customized for requirements of a convenient utilization.

Second generation of biomedical materials utilizing the principles of bioactive materials i.e., competence to combine with the host surroundings to augment the biological reaction as well as tissue/ material bonding' and behaviour of resorbable biomaterials that has the capability to degrade with advanced tissue regeneration and ultimately rejuvenate [38]. Thus, the specific implant/ host tissue could be erased by proper tissue/implant bonding due to the

dissolution of foreign biomaterial within the system and ultimately degraded as nontoxic products by the host [39,40]. Illustrations for these generation of biomaterials include bioactive metals (Bioactive ceramic coated inert metal and/or chemically modified metal surface to induce proteins and cell adhesion and thus, secure tissue/material interactions); bio-ceramics (Bioglass ceramics and calcium phosphate ceramics); biodegradable polymers of synthetic and natural sources like poly-glycolic acid (PGA), poly-lactic acid (PLA) etc.

Third generation of biomaterials

The advancement of biomaterials development in this generation is mainly focuses on inspiring the regeneration of useful tissue in damaged soft tissue organs like urinary bladders, skin, corneal epithelium, and cartilage of living system [41]. These types of biomaterials exhibit a crucial nature in the briskly growing area of tissue engineering & regenerative medicine and act as a set of mechanisms at the interface between biomedical and engineering sciences which utilizes living cells to assist tissue construction or regeneration and ultimately create therapeutic or diagnostic benefit [42,43]. For example, cells are implanted on a porous 3D structure made of bioresorbable polymers in desired shape of engineered tissue that matured externally and adhered to cells. The newly build up tissue is implanted as prosthesis in a relevant anatomical site [44].

In these biomaterial generation, bioactive and biodegredable materials are used as interim 3D framework that can stimulate genes to trigger the regeneration of living tissue. The concept of combining effect of bioactivity and resorbability is the unique feature of this generation of biomaterials [45, 46]. Apart from bioactive, resorbable polymer and ceramics, only one metal has the ability to develop of porous structures i.e., Ti and its alloys.

Biomaterials Classifications

A biomaterial is a material that is entirely different from a biological materials and has been fabricated to act with biological constitutions in physiological environment for a medical function. So, functions of biomaterials is in close connection with living tissue and may replace a certain parts of a living system to reinforce, repair, or regain body function. The operations of biomaterials in the healthcare sectors have remarkably changed with the advancement of material science and technology [47].

Biomaterials can be categorized in various ways but they are mainly classified according to material properties and tissue response. The classification of Biomaterials is shown in figure 2.

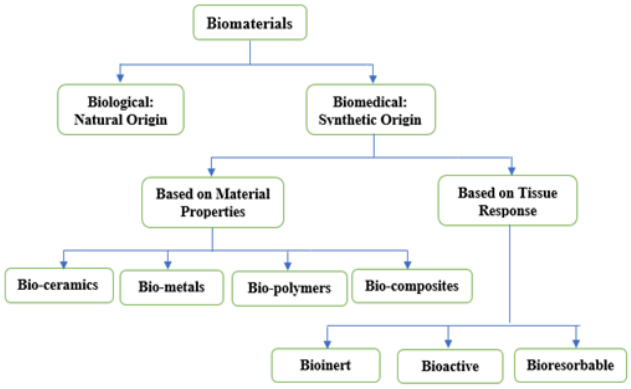

Figure 2: Classification of Biomaterials

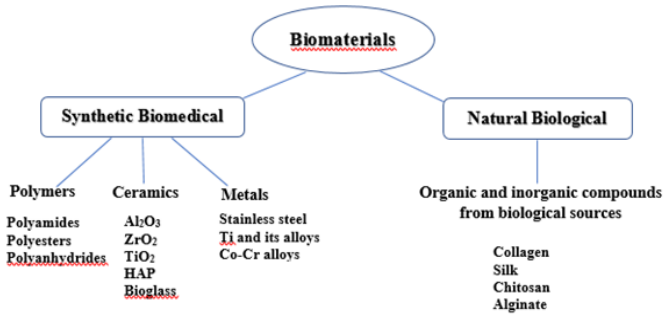

Figure 3: Biomaterials based on origin

According to origin, implantable biomaterials are of two types such as (figure 3) natural and synthetic biomaterials.

Natural biomaterials

This material is also known as biological material derived from living sources such as plants, animals, bacteria, and other microorganisms. Natural biomaterials are broadly categorized into three main non-exclusive groups based on their source such as – Plant, Animal and Microbial [48].

Synthetic biomaterials

Biomedical materials i.e., primarily engineered material fabricated in the lab and one of the prime examples being polymers derived from petroleum based on a synthetic route [49]. These types of materials are also divided as Biodegradable and Biostable depending on their degradation rate after implantation.

Based on material properties, synthetic biomaterials are classified into four distinct groups such as ceramic biomaterial, metallic biomaterial, polymeric biomaterial, and composite biomaterial [50]. Each of these types is described below

(a) Bioceramic biomaterials

Bioceramics is a class of non-metal structure that fabricated through sintering of inorganic compounds viz. metal oxides in complex mixture where covalent and/or ionic bonds are formed between non-metallic and metallic elements which is used for repairing or replacing damaged bone tissues [51,52]. Both the bonds between the ceramic elements create them hard, stiff, breakable, chemically stable and wear resistance which in turn make them highly biocompatible [53]. It has several advantages includes high biocompatibility and bioactivity, excellent compressive strength, corrosion resistant, minimal stress shielding, no disease transmission, and good reliability [54].

The major drawbacks are low fracture toughness and less strength in tension and brittle nature of such materials, which restricts them in load-bearing applications [55].

Bio-ceramic is considered as an alternate material to metallic biomaterials as it induces a strong bonding with bone and it plays a decisive role in the regeneration of hard tissue because it can precisely attach with the surrounding tissue, either by supporting tissue growth or persuasive brand-new tissue regeneration for bioactive ceramics [56]. Although various category of bioceramics is available in the market but the selection of bioceramics totally depends on the nature of defects to be repaired (figure 4). The mechanical property of bioceramics is best suited for varieties of applications such as reinforcing material, cements, implants etc.

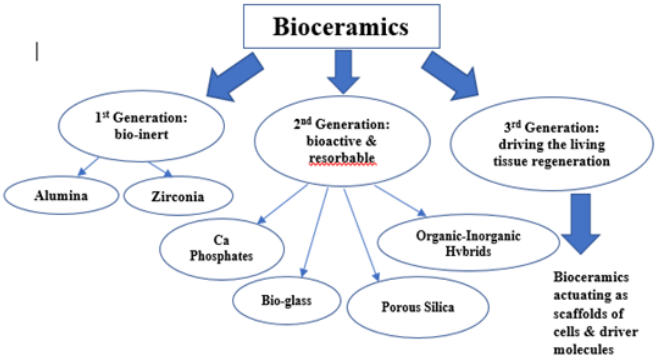

Figure 4: Types of Bio-ceramics

Bioceramic are classified in accordance with the structure, content, characteristics, and nature. The advanced bio-ceramics will not only deal with bone repair, but enhances its application area by loaded with active biomolecules. The name suggests that as a biomaterial, bioceramics must have several important characteristics like no inflammatory and allergic reaction, biofunctional, highly compatible with tissue, non-carcinogenic, and innocuous nature when it implanted in the recipient's body [57,58].

The common application of bioceramics is in the field of dental and orthopaedics as implants, surgical cermet's, and joint replacements. Coatings with bio-ceramic materials over polymeric and metallic biomaterials also reduces the wear and inflammatory responses of the base material [59]. These biomaterials are categorized into three different groups such as bioinert or non-absorbable ceramics (alumina and zirconia), semi-inert or surface and bioactive ceramics (bio-glasses and hydroxyapatite), and bioresorbable or biodegradable ceramics (calcium phosphates-based materials). Medical applications of three generation bioceramics is mentioned below in table 1. In addition, ceramics have been quite regularly used in dentistry for their nearly inactive behaviours to body fluids such as saliva, blood and have favourable aesthetic appearance and outstanding compressive toughness [60-62]. They are also practiced in pacemakers, dialyzer, respirators, extracorporeal devices, and modified bioreactors. Presently, bioceramics have shown extensive medical utilization such as in controlled drug delivery, gene therapy and cancer immunotherapy.

b) Metallic biomaterials

Metallic biomaterials are the widely accepted material for weight bearing implants such as hip prosthesis and knee joint replacements due to superior mechanical behaviour, exceptional erosion resistance properties, excellent thermal as well as electrical conductivity, good wear resistance properties, easy to manufacturing and sterilization, shape memory capabilities etc [63,64]. These kinds of biomaterials are also widely useful in synthetic heart valves, pacemaker leads and cardiovascular stents etc. Besides various advantages, they create some drawbacks on using such biomaterials inside the host body due to their high modulus, cytotoxic nature, prone to corrosion, and sensitivity of metal ion [65].

SS 316L, commercially pure titanium (Cp Ti) & its alloys, Co-Cr alloys, gold, silver, etc. are the most common biomaterials used in medical fields like cardiovascular, orthopaedic, ophthalmology, and dental applications. Metals are also used in different forms such as bone plates, screws, IM pins, IM rods etc. for fracture fixation of bone and total joint replacements for hips, knees, shoulders, and ankle joints, cardiovascular surgery, and dental implants, etc. (figure 5) [66].

Apart from pure metals, two or more elements containing metallic alloys are quite frequently enforced for fabricating medical implants and devices. These metallic admixtures are usually developed by

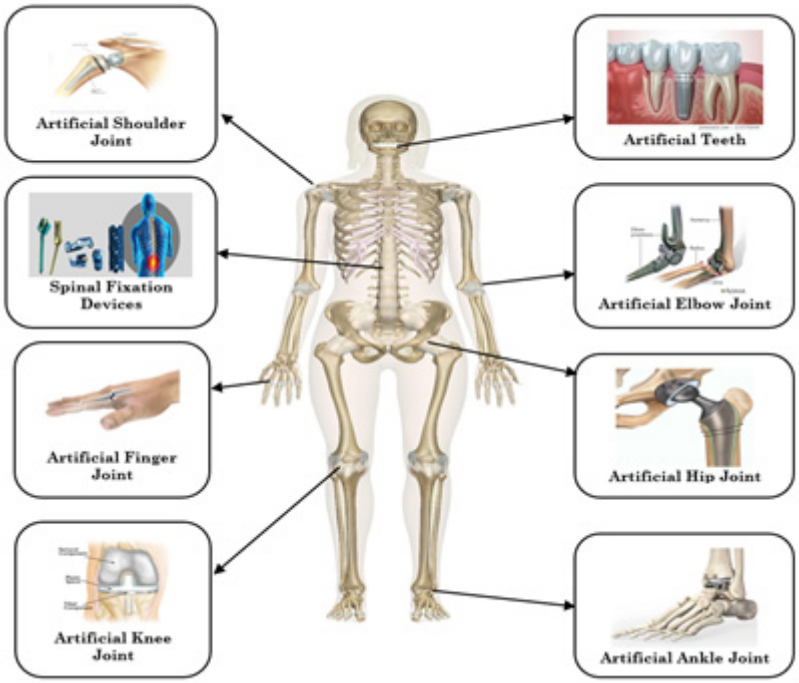

Figure 5: Medical applications of metallic biomaterials

Table 1: Types of Bio-ceramics with Example and Their Medical Application

Types of Bio-Ceramics	Example	Medical Application
Resorbable or biodegradable	Calcium phosphate ceramics	Artificial bones, dentistry, knee & hip joint replacement, tendons & ligaments restoration
	Calcium aluminate	Materials for dental restoration, orthopaedic applications
Surface reactive or bioactive	Calcium Hydroxyapatite	Filling materials for bone and teeth, bone grafts, bioactive coatings over metallic implants
	Bio-glass	Bone augmentation and restoration
Non-absorbable or bioinert	Al_2O_3	Dental and bone implants, hip prostheses
	Carbon/Graphite	Artificial Heart valves, Porous scaffolds for bone regeneration, cartilage reconstruction
	Silicon nitride	Implants for Spinal fusion
	ZrO_2	Hip prosthesis, Dental implants

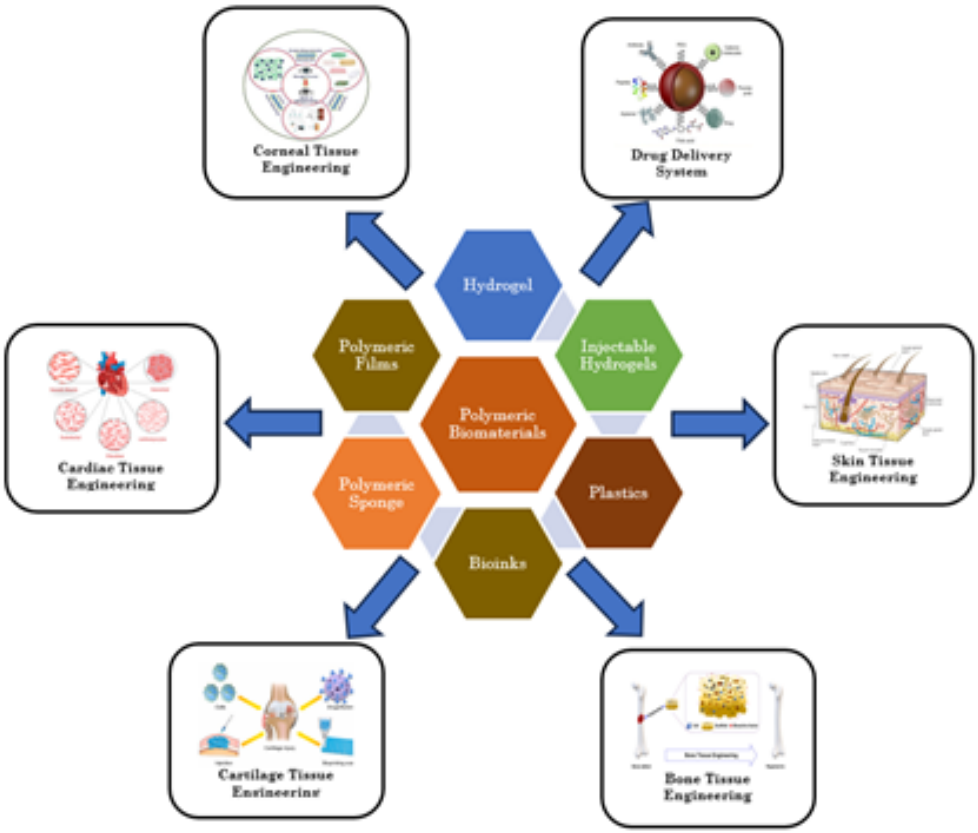

Figure 6: Types and applications of polymeric biomaterials

Table 2: Commonly Used Metallic Biomaterials & Their Applications

Types of Metallic Biomaterials	Medical Applications
Ti and Its alloys	Pacemaker leads, screws for fracture fixation, joint replacement etc.
SS 316L	Cardiovascular stents, bone plates for fracture healing, guided wires etc.
Alloys of Co-Cr	Dental implants & devices, mechanical heart valves, diarthrotic joint prosthesis, plates & screws for bone fracture fixation etc.

exterior surface alteration technique using bioactive ceramics coating and adhering thin polymeric films, or outer layer texturing, thus augmenting corrosion protection and strengthen the mechanical properties [67].

Presently, three common metallic biomaterials dominating in the medical applications such as: bioactive titanium (Ti) or titanium alloys (Ti-6Al-4V), stainless steel 316L, and alloys of Co-Cr because their suitable physical and mechanical properties, low cost, high corrosion resistance, excellent biocompatibility etc. [68]. Table 2 provides the various medical applications of such metallic biomaterials.

Table 3: Biomedical uses of commonly used synthetic non-degradable biopolymers

Name of Polymeric Biomaterials	Biomedical Uses
Polypropylene (PP)	Hernia correction, membrane for blood oxygenator, vascular grafts, bioresorbable sutures
Polyethylene (PE)	Medical implants, pipeline for waste removal, catheters, acetabular lining
Polymethylmethacrylate (PMMA)	Artificial crowns, implant fixing cement
Polytetrafluoroethylene (PTFE)	Cardiovascular grafts, mechanical heart valves
Polyurethane (PU)	Wound dressing materials, breast implants, cardiac patches, drug delivery carrier, vascular grafts etc.

c) Polymeric biomaterials

Polymeric biomaterials have replaced the other materials like metal, ceramics very easily due to their low cost, stability in physiological environment, easy to fabrication and exceptional corrosion resistance [69]. This type of biomaterials is either biodegradable or non-biodegradable polymer from naturally derived polymers and synthetically prepared polymers. Natural polymers like starch, collagen, and chitin are derived from plant & animal sources and periodically used as biomaterials for their biodegradable nature and reliability [70]. On the other hand, synthetic polymers are universally accepted endorsed materials for prosthetics, dental surgery, disposable medical items, and medical implants [71]. The biopolymeric are used in several medical applications includes vascular grafts, soft tissue replacements, wound dressing materials, stitching materials, catheters, stents, ligament & tendon repair, and mechanical heart valves [72].

Currently polypropylene, polyethylene, polymethylmethacrylate, Polytetrafluoroethylene, and polyurethane are the most widely used non-degradable synthetic biopolymers in healthcare for exceptional physical-mechanical qualities that resembles with the nature of human soft tissues [73,74]. The biomedical operations of such biopolymers are shown in table 3.

Polymeric biomaterials are superior to metallic or ceramic biomaterials for their simple process of fabrication in various forms like fibre, films, sheets etc. with minimal cost and desired physical and mechanical properties. Considerable drawbacks of such polymers are moisture absorption property and protein in the human body, polymeric surfaces are easily degraded and problematic towards sterilization, contains leachable components, easily go through biodegradation, and prone to wear & tear [75,76].

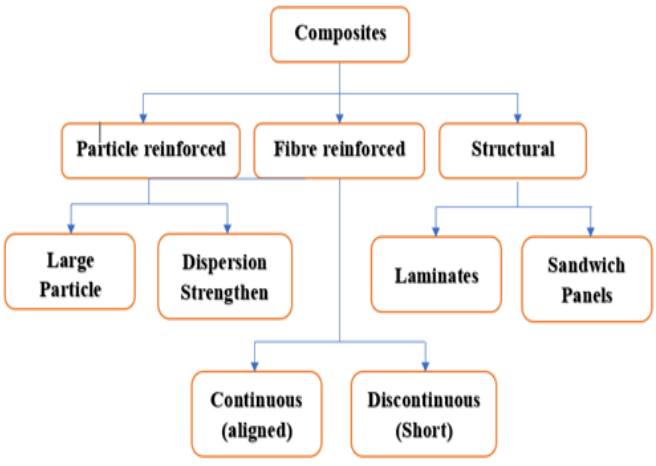

Figure 7: Types of Composites

Composite Biomaterials

The term "biocomposite" refers to the composite employed in biomedical engineering which is combined with two or more materials having distinct composition or phases, morphological, and physical properties [77]. Since bones, teeth, cartilage, tendons, ligaments, skin etc. are of natural composite structures present within the living system, various synthetic biocomposites are developed and subsequently utilized to fabricate prosthesis that able to simulate the tissues by tailoring mechanical behaviour and able to repair and regain the function of such damaged or diseased tissues [78]. Advantages of biocomposites includes good durability, high biocompatibility. moderate resistant against to wear, corrosion, fatigue failure, bio-inert, high fracture toughness. Disadvantages of bio- composites are degradation of interface between components and water absorption property of polymer composite reduces the stiffness of the composite [79]. Composite are universally classified into three different categories based on reinforcements such as i) particle reinforced, ii) fiber-reinforced and iii) structural (figure 7).

Major applications of biocomposites include cardiovascular applications (cardiovascular devices and therapeutic support for heart and blood vessels), dental applications (restorative materials, fixed and removable dental prostheses, dental implants, cranial bone repair), orthopaedic applications (bone fraction fixation devices, joint prostheses, artificial cartilage) as well as used as prosthetic pockets [80].

Based on Tissue Response

The body's immune system is designed in such way that it can easily identify and target the foreign substances, which are placed in the body to restore some function or repair damage tissue by any means and thus they will attack and try to dismantle the substance. In order to prohibit this mechanism, exclusive materials have been developed that do not create any unfavourable response from the host immune system. Therefore, when such advanced material is incorporated within the human body, tissue response instantly to the implant in a several ways based on the nature of biomaterials and the mechanism of tissue/implant interaction is possible depending on the tissue reaction to the implant surface [81]. Normally, three different designated terms bioinert, bioactive, and bioresorbable are specified to classify the biomaterials and explain the tissues responses.

a) Bioinert biomaterials

Bioinert or biologically inert material is a class of biomaterials that has minimal or no interaction with the surrounding tissue and do

not initiate or elicit a response from the host tissue when it implanted within the living system. This type of materials admits the bone and surrounding tissues to regenerate and integrate without creating any adverse tissue response [82]. Generally, a fibrous capsule might cover the bioinert implants after introduced in the biological system and thus its biofunctionality fully dependant on tissue integration through the implant [83]. Examples of such biomaterials include stainless steel, alumina, zirconia and ultra-high molecular weight polyethylene etc. are belongs to the category of biometals, bioceramics and biopolymers. In orthopaedics and dental application, inert biomaterials are integral component of implants, bone grafts, prostheses, and gap fillings due to their osteoconductive and osteogenic properties. These biomaterials can also have utilized in contact lenses, pacemakers, heart valves, orthopaedic devices, and many more.

b) Bioactive biomaterials

Bioactive biomaterial is a kind of material that are easily interact with the biological tissue such as surrounding bone and sometimes with the soft tissues thus avoiding the formation of fibrous tissue layer around the implants [84]. Bioactive biomaterials are fabricated in such way that extort a precise biological response which restricts the formation of fibrous layer. This tissue response occurs through a time dependent kinetic modification of the bioactive surface of the implant, where an ion-exchange reaction takes place between the bioactive implant and surrounding body fluids [85, 86]. As a result, a biologically active carbonate apatite (CHAp) layer is formed over the implant surface which is chemically and crystallographically like the mineral content of bone.

Bioactive biomaterials are either naturally derived such as hyaluronic acid, collagen, gelatine, fibrin, chitosan, silk, alginate, fibrin etc. or man-made synthetic biomaterials includes bioactive-glass, calcium phosphate ceramics, hydrogels etc. These biomaterials have active interaction with the biological environment thus encouraging the biological response as well as promotes the tissue-implant bonding [87]. Bioactive biomaterials have wide range of application in medical device system and also in drug delivery systems. In near future, application of bioactive biomaterials will lie in the fabrication of 3D bioactive & biodegradable scaffold that have both osteogenic and angiogenic features [88].

c) Bioresorbable biomaterials

The term "bioresorbable" materials means biodegradable or naturally absorbing materials that can broke down easily and readily absorbed by the body when such material introduced within the human body to repair or regenerate the damaged tissue [89]. After implantation, such materials will start to dissolve (i.e., degrade) and slowly replaced by growing tissue (resorb) thus there is no need to removed such materials manually. Common examples of these kind of bioresorbable materials include tricalcium phosphate [Ca3(PO4)2], bioactive glass, Polyglycolic acid (PGA), Poly-L-lactic acid (PLLA), polycyanoacrylates, polyanhydrides, polypropylene fumarate, etc. Primary application of these kind of materials are bioresorbable stent, biodegradable suture, guided tissue regeneration, bone grafts etc.

Current Applications of Biomaterials in Medical Practice

Since inception, biomaterials are widely used by doctors, researchers, and bioengineers for different medical applications [90] such as:

- Various medical implants such as cardiovascular implants (artificial heart valves, cardiac stents, and grafts); joints replacing implants (hip prosthesis, knee prosthesis) dental implants etc.
- Arrangements to encourage healing of host tissues such as sutures, Mitchel clips, and staples for wound closing, and dissolvable dressings.
- Regeneration of host tissues using cells and bioactive molecules incorporated scaffolds.
- Probes and nanoparticles to aid in cancer imaging and therapy at the molecular level.
- Biosensors to identify the existence and number of specific substances and to transmit that data. Examples include blood glucose monitoring devices and brain activity sensors.
- Drug-delivery systems that administered drugs to a target disease. For example, drug-eluted vascular stents and implantable chemotherapy wafers for cancer patients.

Recent Trends in Biomaterials Applications

Due to continuous advancements in science and technology for biomaterials development, recently the trends of biomaterials functions have been shifted towards disease treatments such as drug delivery to the targeted cells, cancer immunotherapy, cell regeneration and many more [91,92]. Various types of biomaterials have been used for such applications which includes polymer-based biomaterials, lipid-based biomaterials, and inorganic biomaterials.

Polymer-based biomaterials

Hydrogels are widely accepted polymer-based biomaterials that used in the treatment of several diseases [93]. Two types of hydrogels may exist either naturally or derived synthetically. Chitosan, fibrin, and alginate are well known examples of natural hydrogels, whereas poly (vinyl alcohol) is best example of a synthetic hydrogel [94]. Due to their gelation properties, hydrogels can carry DNAs, mRNA, proteins, and/ or cytokines for specific disease treatments like cancer immunotherapy and chemotherapy [95]. Furthermore, potential of hydrogels in clinical application in curing systemic sclerosis and inflammatory airway disease have been recently investigated and reported.

Micelles are another promising polymer-based biomaterial suitable for drug delivery and cancer immunotherapy. For their amphiphilic nature, micelles can be easily assembled as nanosized particles which can deliver drugs or chemical agent to draining lymph nodes and thus endorse systemic drug administration [96].

A recent experiment reveals that polypeptide-based micelles can regulate the tumour microenvironment and help in inhibiting tumour cell metastasis. In another study, Ren et al. have also investigated that micelles can be covalently bonded with chemically modified short peptide antigens which is suitable for effective drug delivery towards dendritic cells for potent cellular immune responses, therefore implying their potential in anti-cancer vaccine development and encouraging their expedition as a component of cancer immunotherapy [97]. Fascinatingly, micelles can be used as transportation system for ligand delivery along with chemotherapy drugs that has recently grown interest due to substantially increase in selective immunogenic cell death in triple-negative breast cancer, an aggressive and deadly breast cancer type that lacks targeted therapy and has a poor prognosis because of high metastasis.

Lipid-based biomaterials

Liposomes are classic example of lipid-based biomaterials that are highly prosperous and commonly advertised in various types of disease treatments [98]. They are rounded vesicles of phospholipid

bilayers that enclosed different types of therapeutic drugs where hydrophilic drugs are encapsulated within the central aqueous region, and hydrophobic drugs are ensnared within the lipid bilayers which make liposomes an effective biomaterial for several disease treatments [99].

From 1986, several liposome-based materials have been approved and permitted for different medical applications includes chemotherapy drugs delivery for cancer treatments, enveloping deactivated viruses for vaccination purposes, administering antibiotics for antimicrobial therapy, executing analgesic drugs for pain management etc. [100,101]. Moreover, several investigations have shown that liposomes might be useful for cancer immunotherapy as well as nanocarriers of imaging agents for progressing clinical analysis and treatment. 1n 2021, liposome-based mRNA vaccines have been developed by Moderna and Pfizer/BioNTech to combat COVID-19 disease exploring the exceptional capability of liposomes to provide safeguard to mRNAs against degeneration by nucleases in the blood circulation and permit the mRNAs to smoothly invade the cells cytoplasm via endocytosis.

Inorganic Biomaterials

Gold nanoparticles and silica nanoparticles are the advanced inorganic biomaterials that are extensively investigated for disease treatments. Gold nanoparticles has been extensively utilized in disease treatments. According to the investigation of Li et al., the utilization of gold nanorods in photothermal unit in association with chemotherapy augments the efficiency of cancer treatment and modulates the tumour microenvironment [102,103].

Another study in animal model reveals that radioisotope-labeled gold nanoclusters cede for the activation of dendritic cells followed by promoting long-term anti-cancer immunity by eliminating primary tumours and suppressing distant-tumour development [104]. In addition, when gold nanoparticles are coated with cancer-specific T-cell receptors, it will aid in effective imaging. As a result, easy observation of T-cell migration, distribution, and kinetics under imaging is possible in a better way [105].

On the other hand, silica nanoparticles show anti-cancer properties when doped with calcium, magnesium, and zinc particle. These dopants can boost the CD4+ and CD8+ T-cells in the spleen and trigger an anti-cancer immune response [106]. Furthermore, Kakizawa et al. have reveals that amino acid (specific) coated silica nanoparticles when incubated with dendritic cells, then ligands will induce the production of crucial cytokines, such as IL-1 and IFN [107]. Thus, silica nanoparticles might be act as a carrier for cellular immunotherapy. In addition, silica nanoparticles have been widely accepted for formulations of vaccines against bacteria and viruses such as Mycoplasma hyopneumoniae, hepatitis B, and currently, SARS-CoV-2.

Smart biomaterials

The concept of "Smart Biomaterials" was first introduced in 2004 to explain the materials behaviour i.e., degree of interaction with physiological environment which ensuing biological responses to a specific cellular signal. It can also respond to altered physiological parameters & external stimuli and extend to impact many aspects of modern medicine. These materials can promote promising therapies and improve treatment of debilitating diseases [108].

Smart biomaterials have been rapidly emerging since the concept of tissue engineering was prospective for tissue repair and regeneration. Collaborating with human cells, smart biomaterials can play a key role in novel tissue morphogenesis [109]. Various aspects of biomaterials utilized in or being sought for the goal of encouraging bone regeneration, skin graft engineering, and nerve conduits etc. Smart biomaterials promote triggering or stimulating effects on cells and tissues by constructing the material's receptivity to internal or external stimuli or have intelligently tailored properties and functions which can encourage tissue repair and regeneration [110].

The smart material-based path for biomedical applications includes stem cell incorporated smart scaffolds and smart drug delivery systems to augment bone regeneration; smart dental materials to that protect tooth structures by inhibiting acid-producing bacteria; smart polymers to inflect biofilm species away from a pathogenic composition and shift towards a healthy composition; and smart materials to suppress biofilms and avoid drug resistance [111]. Advanced smart biomaterials will bring provocative potential and encouraging opportunity to substantially boost the hard tissue engineering and regenerative medicine effectively.

Future Directions of Biomaterials Research

Biomaterials have made a great impact on medicine but still a number of challenges are there. To address such objection, three captivating technologies were suggesting that determines the future directions for biomaterials on the horizon:

Immuno-modulating biomaterials

Immunomodulation means adjustment in the hosts immune system by some agents that trigger or inhibit its function. So, it is an alteration of the immune response to a desired level. The biomaterials which can cause such changes are known immunomodulating biomaterials that may help to control the widespread chronic autoimmune diseases like type 1 diabetes where the body's defense shatter the insulin-producing â cells in the pancreas [112, 113]. Recently material scientists have developed an injectable, synthetic biomaterial that antipode the type 1 diabetes in non-obese diabetic mice which is a significant step in developing a biodegradable platform to control the effects of the disease [114].

Injectable biomaterials

The applications of injectable biomaterials are increasing day by day for the administering of therapeutic agents like drug, antibiotic, hormones, and proteins. They overture the opportunity to treat a few conditions by delivering medicine to the targeted tissues without consumed by the immune system [115]. Recent advancements of both synthetic and naturally derived injectable biomaterials are so encouraging that in near future injectable biomaterials may be used to treat bone defects, cancer, and heart attacks [116].

Supramolecular biomaterials

Supramolecular biomaterials are a cluster of biomolecules that exceed the capacity limits of individual molecule. It has an exceptional potential for both sensing and responding which makes them ideal materials for correcting injury or disease. Researchers are trying the fabricate much more interesting supramolecular biomaterials that can be easily turned on or off in response to physiological cues or that mimic natural biological signalling [117,118].

Conclusion

Since antiquity, medical materials are mainly applied in healthcare devices but recently their application has expanded substantially trough their degree of sophistication. Currently, in biomaterials research, the need of bioactive & resorbable materials for repair and regeneration of hard tissues are actively sought and bring a considerable interest because biodegradable demeanour permits

the dodging of a subsequent operation to reduce the discomfort and expenditure for patients too. Due to their continuous advancement, modern biomaterials are affluent of message and integrate biologically active components derived from natural source for better performance. In future, biomaterials will play much bigger role in modern medicine and will find accelerated use in a wide variety of non-medical applications through bio-inspired design and fusion of dynamic behaviour.

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