# Definition and Uses of Biocompatibility in Different Fields

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Using the term “biomaterial” is more logical when referring to healthcare-related materials. This includes materials used to fabricate various medical tools and devices, such as those used in implants and surgery procedures. Therefore, for a material to be referred to as a “biomaterial”, it must follow the definition assigned by the National Institute of Health Consensus Development Conference of November 1982, which states that “any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system that treats, augments, or replaces any tissue, organ, or function of the body”.

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## 1. History of Biocompatibility

Materials have been used to promote human health throughout history, with evidence extending back thousands of years before the common era. For example, the ancient Egyptians utilized copper and gold to make dental fillings, while the Romans used ivory to replace teeth. More advanced surgical procedure concepts have been developed since the nineteenth and twentieth centuries, which have improved numerous individuals’ lives, resulting in the necessity for various biomaterials for medical applications, such as devices, implants, sutures, and prosthetic devices. It is worth noting that cellulose nitrate, while not commonly used in modern medical implants, has historical significance in the development of implant materials. Its use in industries like photography and film provided valuable insights into the properties of polymers and their potential applications in the medical field. The knowledge gained from working with cellulose nitrate contributed to advancements and breakthroughs in developing materials used in medical implants [1].

The journey of understanding biomaterials and the concept of biocompatibility has been extensive. One example can be traced back to the late 1800s; a European specialist in Chicago endeavored to spare the life of a severely burned child by employing a unique approach to biocompatibility. The specialist transplanted skin from a living sheep onto the girl’s body, but unfortunately, she passed after some time. Despite the unsuccessful outcome, the specialist observed that the skin folds demonstrated the capability to nourish the child’s body, revealing the potential of the field of biocompatibility [2].

Another historical milestone was the effective utilization of celluloid to cure cranial anomalies, documented in a groundbreaking publication published in 1891. This transparent flammable plastic material played a significant role in inspiring professionals to utilize it in medical applications. This tremendous breakthrough in medical science cleared the path for the further research and development of implantable materials. This has resulted in modern medical implants comprising various materials, such as metals, ceramics, and polymers. These materials have been deliberately engineered to become biocompatible, enabling them to interact with human tissues safely and effectively without causing injury or unintended responses. The continuous development of novel materials and technology offers immense promise for the future of medical implants, potentially improving and saving countless lives [1].

Ilya Ilyich Metchnikoff, a prominent scientist credited with the discovery of macrophages and pioneering research on the destiny of implanted materials in live soft tissue, conducted a significant study on this subject in 1884. Metchnikoff’s groundbreaking investigation shed light on the biological mechanisms underlying the interaction between implanted materials and living tissue, significantly advancing understanding in the field. His pivotal contributions have had a lasting impact on the scientific community and continue to shape contemporary research in this area. Metchnikoff’s observation on Starfish larvae proved his hypothesis about the biological process of a specific type of cells in the human body attacking any foreign body. These cells are now known as Macrophages. Metchnikoff stated that “I hypothesized that if my presumption was correct, a thorn introduced into the body of a starfish larva, devoid of blood vessels and nervous system, would have to be rapidly encircled by the motile cells, similarly to what happens to a human finger with a splinter.” This quote is an insightful explanation of his understanding of the topic, which triggered further research in this area [3].

Several surgeons experimented with prosthetic materials in the early 1900s. For example, the German physician Themistocles Glück used ivory and nickel-plated metal to create a hip prosthesis as early as 1891. The Czech surgeon Vitezlav Chlumsky also evaluated diverse types of joint interposition material over time but without understanding the toxicological or biocompatibility concerns. None of these trials would likely have been successful because of the lack of knowledge at the time about how implants should be designed and constructed [2].

A significant advancement in biocompatibility occurred with the discovery of ancient human bones in the state of Washington, estimated to be around 8000 years old. Upon examination, the remains revealed evidence of a spear wound and subsequent infection in the human pelvis. Remarkably, because of the absence of modern medical interventions during that era, the individual could have lived a long time before dying. Thus, scientists studied and analyzed the collagenous capsule surrounding the spear tip. This helped researchers to learn more about how ancient people treated injuries and understand their methods for healing them. In a separate discovery in 1931, a Mayan lady's skull was discovered with three seashell dental implants. A radiological examination later revealed that these dental prostheses had been seamlessly integrated into the woman's jawbone (osseointegrated). This shows that seashells were used as early as 600 BCE to replace teeth in humans [2].

In the realm of surgical advancements, the 1930s witnessed the introduction of glass balls for breast augmentation (mammoplasty) to enhance surgical outcomes. Moreover, an array of materials, including wood, leather, gold, rubber, magnesium, zinc, waxes, and plastics, were also experimented with during this era for similar purposes. During the same period, significant breakthroughs emerged with the commercial production of synthetic plastics, namely polyethylene and poly (methyl methacrylate) (PMMA), which found their application in surgical procedures. PMMA's utility in cranioplasty was explored in scholarly discussions throughout the 1930s and 1940s. Dr. J. Bing's influential research paper focused on PMMA's behavior during surgery, offering a comprehensive understanding of its reactions. This pivotal article provided an exhaustive account of the potential side effects and risks associated with employing PMMA in skull reconstruction procedures [1].

During the 1940s, a breakthrough occurred in ophthalmology when British ophthalmologist Harold Ridley recognized the distressing eye injuries sustained by pilots due to shards of glass from broken windshields. To ease their pain and discomfort, Ridley investigated the suitability of poly (methyl methacrylate) (PMMA) for developing an intraocular lens (IOL)—the pioneering artificial lens implanted in humans. The belief in PMMA's biocompatibility fueled its potential as a safe implant material. Ridley's research supported this notion, as there have been no reported cases of adverse effects from PMMA lenses over fifty years later. Notably, the terms "biomaterial" and "biocompatibility" acquired prominence in scientific literature only in the late 1960s, when researchers delved into the compatibility of various materials with each other [2].

## 2. Long-Term Implants

The last decade saw a rise in long-term implant usage due to population growth, demand, and technology. In 2012, the number of Braenemark System implants administered worldwide was 7 million, and an additional million spinal rod implementations were conducted up to 2000 [4]. Long-term implants may include cardiovascular implants, intraocular lenses, orthopedics, and dental implants.

### 2.1. Cardiovascular Implants

The mortality rate associated with cardiovascular diseases continues to be the highest in the world. In recent years, coronary artery disease (CAD) has caused a significant number of deaths in the country. Depending on the severity of the condition, it is possible to choose from a wide range of blood vessel therapies. An example of this is to insert a stent, performing an angioplasty, and, in cases of severe and widespread blocks (greater than 70%), performing a bypass graft operation [5].

#### Artificial Heart Valves

Heart valve implants are required because of the important function of the four heart valves in the cardiovascular system. With each cardiac contraction, these valves work together to guarantee the unidirectional flow of blood. Disorders can harm the heart valves, causing issues like stenosis or regurgitation. Valve failures can happen because of disease or birth defects. Faulty valves can cause serious health issues like stroke and heart failure if left untreated.

The synthetic materials used in a mechanical heart valve, like metal and synthetic polymers, are vital for cardiac surgery. There are two types of blood flow in artificial heart valves: central and lateral. A mechanical valve can be classified

structurally into cage, spherical, disc, double lobe, and other categories [6].

Because of their restricted biocompatibility, as evidenced by its inclination for blood clots to develop on its metal surfaces [7], patients typically have blood haemolysis, coagulation, and the requirement for anticoagulant medication. Because of their stability, heart surgeons frequently use them. Mechanical valves have three common elements: locking element, cover, and valve base.

For young people with a long-life expectancy who need a valve for a long time, the best choice is a mechanical valve. On the other hand, elderly patients with a limited life expectancy are better suited for tissue valves, which are made from biological tissues like the pericardium of pigs or cows. Patients who obtain tissue valves are less likely to need lifelong blood-thinning medication. This advantage arises from the lower risk of blood clots associated with tissue valves. However, one drawback to tissue valves is their tendency to deteriorate over time, as they are not as durable as mechanical valves. This could cause the need for a secondary or subsequent operation to replace the valve.

**Stents**

In cases of blood artery stenosis, cardiovascular stents are utilized to enhance blood flow. Angioplasty inserts coil-shaped stents into arteries to widen them. Stents are classified into two types: self-expanding stents composed of shape memory alloys such as Nitinol and stents placed in a catheter with a balloon made of 316L stainless steel. Stents can be categorized into four structural classes: mesh stents, tubular stents, ganglion-shaped stents, and annular coil stents. It is a critical characteristic of all stents that they suppress blood clot formation as they pass over their surface. It is important to avoid the formation of blood clots at the site of implantation, as this may cause arterial blockage. To prevent blood clotting, stents are coated with calcium phosphate or carbon. Resistance to blood pressure changes, a small diameter, flexibility, consistent cross-section under stress, high fatigue strength, clear route maintenance, compatibility with the body, resistance to infection, availability, and ease of implantation are all important concerns for stents [6].

## 2.2. Intraocular Lenses

Intraocular lenses (IOLs) are a prime example of long-term implanted devices specifically designed to aid human vision and are implanted inside the human eye. Thus, IOLs' materials must be physically compatible with the incubating tissue. In addition, it must have a high resistance to degradation to function in the long term [8].

The variations in materials utilized in these devices are attributed to the need for various chemical structures or surface properties to meet mechanical and physical properties such as flexibility, inertness, and regulating surface hydrophobicity/hydrophilicity [9]. Hydrophilicity refers to a material's affinity towards water and the ability to maximize water contact [10]. Managing these properties is crucial for ensuring clinical usage and achieving the desired functionality [8]. Silicone stands out as a prominent example of a flexible material. Its malleability makes it an excellent choice for IOLs, as it maintains chemical stability and offers various mechanical properties. The biocompatibility of IOLs plays a crucial role in their overall implantation success [9].

## 2.3. Orthopedics

Long-term orthopedic implants are another example of long-term implants. Materials for such applications must exhibit a remarkable resistance to corrosion and wear. In addition to their physical attributes, their chemical stability and appropriate microstructural properties are crucial considerations for orthopedic applications.

Ceramics, which are inorganic and nonmetallic materials, offer a diverse range of features suitable for various applications, particularly in hip and knee repairs, such as ceramics comprising a cobalt–chrome (Co-Cr) metal alloy.

Several orthopedic materials, such as polymers, resorbable materials, and metallic materials, have been utilized. Polymers, including acrylic resins, polyethylene, and others, are known for their structural stability, cost-effectiveness, and relative biocompatibility. This class of materials is suitable for anchoring or prosthesis applications and devices.

Resorbable biodegradable materials are a class of materials that serve therapeutic purposes, such as bone substitutes and fracture healing, for example, polyglycolide (PGA) and polylactide (PLA).

Metallic materials are known for their excellent mechanical properties and are commonly utilized in prosthetic stems and total joint replacements. Stainless steel (316L) and titanium-based alloys are among the materials employed in this category [11].

**Total Joint Replacement**

Total joint replacement involves using materials specifically selected with enhanced mechanical properties, such as creep strength or resistance to continuous deformation under sustained loading. This relates to the “Measurement of a materials’ ability to withstand sustained loading without significant continuous deformation” [12]. These materials also aim to minimize deterioration caused by corrosion and wear. In this context, the primary aim is to create a biomechanical environment that reduces disruption to the homeostatic balance in the bone and surrounding tissues. Biocompatible material requirements for this application can be extended to include how rapid the surrounding bone’s acceptance rate is for the replacement and the surrounding tissue’s prompt response to corrosion and wear debris of the replacement. Titanium and cobalt-chromium-based alloys have emerged as nearly ideal combinations of mechanical characteristics and metallic components for total joint replacement [8].

In total hip replacements, cement is used to secure the implantation components. However, due to a modulus mismatch, loosening can occur at the interface between the cement and bone. To address this, PMMA fixation allows patients to bear weight immediately after surgery. Surface properties, mechanical behavior, and osteocompatibility are all integral aspects of biocompatibility that require thorough investigation to develop novel bone biomaterials [13].

**Spinal Implants**

Spinal surgery has a long history, dating back to Jules Gerin’s initial efforts in repairing scoliosis in 1839. The understanding of the spine has improved, altering surgical techniques and instruments. Spinal implants must be biostable and biocompatible. The materials for these implants are chosen based on stiffness and brittleness. Other important biomechanical factors include stiffness, fatigue, and the strain ratio. Common spinal implant materials are stainless steel, titanium, cobalt-chrome, nitinol, tantalum, and polyether-ketone. These materials are found to meet the requirements for spinal implants and especially the biocompatibility requirements.

The current generation of implants is typically constructed using a combination of cobalt-chromium molybdenum and ultrahigh molecular weight polyethylene to provide the necessary strength and durability. Additionally, a rough titanium surface coating is applied to stimulate bone formation, promoting the integration of the implant with the surrounding bone tissue. This alloy coating is a crucial element in ensuring the implant’s long-term success, which also falls into the concept of biocompatibility [14].

## 2.4. Dentistry and Prosthetic Implants

The oral cavity, which serves as the site of long-term implantation and restoration procedures, poses unique challenges in terms of biocompatibility due to specific characteristics and processes occurring within it. These include the constant exposure of teeth to substances like saliva, bacteria, and food, which significantly influence the requirements for biocompatibility. Additionally, the oral cavity’s continuous exposure also leads to tissue instability and variations in temperature, pH levels, and other environmental aspects [15].

Biomaterials must meet several parameters beyond the basic physical and chemical standards to be deemed biocompatible for dental usage. They need to demonstrate durability and viability in aquatic settings. Moreover, while selecting dental filling materials, it is essential to consider the expected and potential adverse effects associated with their use [15]. However, adverse reactions can also affect dental personnel who handle certain materials, such as rubber products. After years of exposure to methacrylate-based materials, dental professionals have reported issues like dry, peeling, or cracking skin and generalized neuropathy [16].

**Dental Implants**

Dental implant materials must exhibit exceptional mechanical durability to endure the substantial stresses to which teeth are regularly subjected. Teeth experience the highest compressive stress within the body due to significant pressures concentrated on a small surface area. Therefore, the selected materials must have the capacity to withstand constant high-value compressive forces and additional forces during activities like shear and torque [17].

Historically, dental implants were categorized into two main types based on location and function: subperiosteal and endosseous tooth implants [17]. For these implants to be long-lasting and stable, they must establish a suitable connection with the surrounding tissues through osseointegration [18]. Osseointegration refers to the direct anatomical and functional integration between living bone and the surface of the load-bearing implant. It ensures implant stability and long-term therapeutic success. The process begins with the interlocking of the alveolar bone with the implant body and progresses through ongoing bone apposition and transformation towards the implant, ultimately leading to a biological attachment. This complex procedure profoundly influences bone development and preservation at the implant surface [19].

### Endosseous Tooth Implants

Long-term dental implants can replace missing teeth when the natural tooth root is not viable. These implants are made from biomaterials introduced into the jawbone, creating a junction site between the material and the surrounding environment [18]. The ideal choice for a tooth replacement is a dental implant that closely mimics a natural tooth, although alternative options, such as dentures or false teeth, often lack stability and aesthetic appeal, making them a partial solution for patients [17].

An endosseous implant is a dental implant that is anchored in the jawbone. It is implanted into the jawbone and allowed to heal before an artificial tooth or crown is attached. This type of implant, known as an endosteal implant, closely resembles a natural tooth root [20]. Endosseous implants come in various designs, like self-tapping screws, a spiral screw-vent, and a blade-vent, to ensure immediate stabilization and enduring fixation. After approximately 14 months of rigid fixation, an appropriate crown is attached. Some implant systems involve burying the implant root in the extraction site, installing a post through a punctured hole in the gum tissue, and then creating the crown. However, despite the complex design, the success rate of this system is not higher than for other implants, such as blade-vents. Dental implants remain a popular choice [17].

Titanium and zirconia are two common materials used in dental implants. Titanium is a biocompatible metal known for its strength, light weight, and corrosion resistance. Zirconia is a biocompatible ceramic that is a good match for natural teeth color. Both materials are well tolerated by the body and can integrate with the surrounding bone tissue through osseointegration, which is essential for implant stability and long-term effectiveness. However, certain limitations exist with pure titanium implants, especially for small diameter and single-tooth implants, as they may be prone to fatigue fractures. To overcome these challenges, modifications have been made to these materials to meet the required characteristics for dental implants. For instance, the investigation of binary titanium zirconium alloys has shown promise in addressing the issues associated with small diameter implants [21].

### Subperiosteal and Staple/Transosteal Implants

The second type of long-term dental implant is known as the “subperiosteal” implant. This name indicates that the foundation or frame of the implant is positioned beneath the gum line [22]. These implants addressed weak support in certain patients, aiming to provide enhanced support for dentures or other types of bridge treatments placed on top of these implants [17].

Titanium alloys are considered the gold standard for dental implant materials due to their excellent mechanical properties and high biocompatibility with the surrounding environment. However, there are cases where patients require additional support for implants or bridges, particularly in severe maxillary atrophy. Maxillary atrophy is significant bone resorption, sometimes accompanied by maxillary sinus expansion, resulting in inadequate ridge height, width, or both [23]. This poses challenges for conventional implants without needing bone graft surgery and alveolar reconstruction. In such cases, subperiosteal implants offer a viable alternative independent of the maxillary bone [24].

Metals like stainless steel, Co-Cr alloy, and Ti alloy are commonly used for subperiosteal implants due to their ease of manufacturing in standard dental laboratories [17].

### Dental Restoration

Biocompatibility principles are also applied in dental restoration, which involves repairing the teeth affected by decay or cavities [15]. The materials used in dental restoration are known as restorative materials. Most of these materials are not directly set in contact with the surrounding tissues, except for certain materials like dentin and enamel [25].

### Amalgam

Amalgam and composite materials are widely used in dental repairs. Amalgam fillings, composed of liquid mercury, silver, and other metals like copper and zinc, have been utilized for many years due to their affordability, durability, and ease of placement [25]. However, concerns have been raised regarding the potential toxicity of amalgam fillings, since they contain mercury as about half of their components, which is responsible for their silver appearance. Mercury vapor, known for its high volatility, can be released in small amounts from hardened fillings due to stress and tension during activities like eating and brushing [15]. Amalgam restorations have the potential to cause delayed hypersensitivity reactions, and regular exposure to mercury in these restorations may increase the risk of oral lichenoid diseases. Dental professionals working with amalgam are at risk of exposure to inorganic mercury, leading to higher urinary mercury levels and suspected signs of mercury poisoning. However, there is no significant association between urine mercury levels and self-reported memory

problems. Studies have shown that occupational exposure to mercury vapor in dental offices does not damage white blood cells genetically [26].

**Resin-Based Composites**

Resin-based composites (RBCs) are a relatively recent development in restorative dentistry. These materials effectively fill cavities, especially for front teeth. They closely match the original tooth color, resulting in a pleasing appearance. RBCs comprise a combination of ceramics and polymers, with Bisphenol A (BPA) used as a component synthesizer. Using BPA and other potentially hazardous components as monomers has raised concerns regarding RBCs. However, extensive research has been conducted to investigate the harmful effects of these materials. BPA and other toxic materials were less harmful when placed in dentin. Dentin tubules are small hollow tubes or canals that allow heat, cold, and various foods to trigger the nerves and cells inside the tooth, leading to sensitivity when the protective enamel coating wears away [26]. Ongoing research is being conducted to explore this topic further [15].

### 2.5. Biocompatible Alloys

An alloy is a substance formed by combining two or more elements, often metals, either in the form of a compound or a mixture. It is important to note that, in the case of steel, which is an alloy, carbon, a nonmetal, plays a significant role. These materials are engineered to become what is known as a biocompatible alloy [27]. Biocompatible alloys are carefully designed to coexist harmoniously within the human body, ensuring they do not provoke adverse reactions or toxic responses upon introduction. These substances must exhibit excellent corrosion resistance to withstand challenging physiological conditions, preventing any tendency for deterioration over extended periods. Additionally, they must possess the necessary mechanical strength to withstand physiological loads and pressures, avoiding the risk of fracture or distortion. A crucial requirement for biocompatible alloys is their ability to promote the integration of the implant with the adjacent bone tissue, facilitating proper recovery and ensuring long-term structural stability [28]. Biocompatible alloys find a wide range of applications in the field of biomedicine, including orthopedics, dental implants, cardiovascular devices, and surgical instruments. Titanium and its alloys are among the most well-known materials used in the orthopedic and orthodontic fields. This is primarily due to their high biocompatibility, good corrosion resistance, and excellent mechanical properties, including low density and low Young's modulus. Titanium also demonstrates bioactive behavior, significantly enhancing the quality and longevity of implant use. This behavior is attributed to the gradual formation of a titanium hydrated oxide layer on the implant's surface, facilitating the incorporation of calcium and phosphorus [29]. The new trends in alloys for biomedical applications include 3D printing techniques or additive manufacturing where, for example, powder bed fusion (PBF) is used to process enabled beta-titanium (β-Ti) alloys that have an increasing interest to tackle what is known as "stress shielding", a phenomenon caused by a mismatch in a modulus between the implanted and the natural bones. The β-Ti alloys are promising due to their mechanical strength (lower elastic modulus) [30].

## 3. Short-Term Implants

Short-term implants are temporary, such as drug delivery systems, tissue contact parts, and orthopedic implants.

### 3.1. Biodegradable Implanted Systems

Biodegradable implants are a type of material used in various devices that deteriorate. While typical devices prioritize stability, these systems can fail and be purged from the body. Therefore, selecting suitable materials for biodegradable implants is crucial to ensure they fulfill their function without causing harm [8].

Suture materials play a vital role in wound repair by providing support to healing tissues. However, there is no perfect suture material. Various factors need to be considered when choosing sutures, including tensile strength, tissue absorption, diameter, knot strength, security, coefficient of friction, plasticity and elasticity, handling, memory, tissue reactivity, capillarity, fluid absorption, and ease of removal. Sutures can be classified as absorbable or nonabsorbable. Commercially available absorbable sutures include polyglycolic acid, gut, polydioxanone, poliglecaprone, polyglycolide-trimethylene carbonate, polyglactin 910, and caprosyn. Nonabsorbable sutures include materials such as silk, braided polyester, polypropylene, nylon, stainless steel, and polybutester. There are also absorbable and nonabsorbable barbed sutures available [31].

One traditional example of a suture material is catgut, a protein fiber derived from the small intestines of animals such as sheep or oxen, which has long been used in surgical procedures. Despite its significant disadvantages, such as poor repeatability and aggressive tissue reaction, catgut was the sole recognized material for these types of devices for many

years [32]. One of the most significant concerns with catgut is that it stiffens after drying, making it difficult to deal with. That it is derived from animals has raised ethical and health concerns [8].

Despite these drawbacks, recent developments have shown promising applications of catgut in implanted neurological devices and systems, particularly in sutures. Neurosurgeons have discovered that cat sutures, though initially challenging to work with, can be modified to possess characteristics that aid the surgical process. This has led to the increased use of catgut sutures in neurosurgery, potentially improving patient outcomes and reducing recovery times. Ongoing research aims to further explore the properties of catgut and develop new methods for their use, potentially finding applications in other medical fields. While catgut has limitations, its unique properties and potential benefits make it an area of focus for research and development in the medical field [33].

Biodegradable implant materials can undergo spontaneous disintegration, absorption, digestion, or expulsion within the human body, eliminating the need for subsequent implant removal surgeries once the surgical site has healed. However, these materials may have limitations if not modified. Many biodegradable materials, often polymers, lack the mechanical strength required to withstand the weight and pressure of the body, making them unsuitable for load-bearing applications. The choice of material is crucial in the development of these systems. For example, magnesium alloys have been explored as an alternative to temporary metallic orthopedic implants due to their acceptable mechanical properties. Magnesium alloys exhibit compatibility with human bone, providing comparable load-bearing capacity and stress distribution. However, their susceptibility to corrosion poses challenges that need to be addressed for their future successful use [33][34].

### 3.2. Drug Delivery Systems

In the category of short-term implants, drug delivery systems play a significant role. It is essential to consider the influence of medications on the biocompatibility of these systems, especially when formulations involve a stationary depot. This is particularly relevant for long-acting local anesthetics. Various approaches have been employed to achieve the continuous release of medications like bupivacaine, including the use of polymeric particles, spray-dried lipid-protein-sugar particles, liposomes, cross-linked hyaluronic acid gels, and polysaccharide rheological blends. These delivery strategies typically result in minimal or no tissue damage and varying degrees of inflammation when unloaded. However, when loaded with bupivacaine, these systems might cause muscle injury to different extents. Therefore, in developing drug delivery systems, a thorough study of the medication and delivery method and their interaction is necessary to ensure optimal biocompatibility and minimize the risk of unwanted effects. Extensive testing and evaluation through preclinical and clinical trials are crucial to determine the safety and efficacy of these systems before their widespread use [35].

Given the direct interaction of these drug delivery systems with the patient’s body, achieving biocompatibility becomes a critical aim to investigate and enhance. Several examples of chemical and pharmaceutical materials have been used to develop biocompatibility in drug delivery systems. One approach involves modulating the surrounding tissue reactions using anti-inflammatory compounds, which can help reduce inflammation in and around the devices. However, efforts to produce more biocompatible materials have been hindered by a lack of understanding of the complex interactions between materials and tissues. Biocompatibility is not simply a matter of isolated interactions but encompasses various aspects, particularly in drug delivery systems, such as chemical product degradation and interactions with cells. Further research is needed to unravel these material–tissue interactions and determine the most effective strategies for achieving biocompatibility in drug delivery systems [35].

### 3.3. Temporary Orthopedic Implants

Temporary orthopedic implants are commonly used when a patient’s bones are damaged during healing. These implants, including plates, screws, pins, cables, and intramedullary nails, serve a temporary purpose and are only utilized until the bone has healed [36].

Bone is a dynamic tissue capable of regenerating and restoring its biological and mechanical properties after injury. However, certain diseases, disorders, and traumas can cause damage to the skeletal system, leading to fractures and defects that increase the risk of mortality. In some cases, the presence or need for implants can also result in fractures or defects. Therefore, it is crucial to carefully design orthopedic devices to effectively treat skeletal trauma without causing harm to the patient [37].

Temporary orthopedic implants, also known as internal fixations, are relatively straightforward in their components, typically comprising plates of various sizes with holes. These holes are intended for placing screws and pins, which secure the plates to the bone to facilitate proper healing. Using screws and pins as fixations is necessary to withstand

significant load forces and other types of forces [36]. It should be noted that there are different types of internal fixations for temporary orthopedic implants, depending on the location of the fracture or where they are used. For example, internal fixation may involve open reduction with plates and screws in case of a femoral fracture. These implants must be designed with considerations for biocompatibility, mechanical and surface qualities, and chemical and fracture properties. This ensures that the implant closely mimics the biomechanical characteristics of the bone and maintains its integrity for an extended period while integrating with the surrounding tissue as long as needed [37].

Given the skeletal system's inherent capabilities, internal fracture repair biomaterials must withstand recurring stress. Metals, polymers, and ceramics have all been employed as orthopedic biomaterials, but metals are preferred because of their mechanical properties that provide essential stability. Specifically, titanium alloys, cobalt-chrome alloys, and chromium steel are the most commonly used metals, with titanium alloys and electropolished chromium steel being the preferred choices for fracture repair materials. Cobalt-chromium alloys are less used because of their complexity and high manufacturing costs [37].

The primary purpose of these implants is to aid the bone in its healing process, restoring the structural integrity and normal functionality of the injured tissues. Therefore, several factors must be considered during the production of these implant components, including corrosion resistance, wear resistance, mechanical properties, and osseointegration. The most critical factor is the biocompatibility of the material used.

## 4. Tissue Engineering: Advancing Biocompatibility in Regenerative Medicine

Tissue engineering is a rapidly evolving field that combines scaffolds, cells, and physiologically active materials to create functional tissues. The main objective of tissue engineering is to build structures that can heal, sustain, or rejuvenate damaged tissues or organs [14]. As a more practical definition, "Tissue engineering is the creation of new tissue for the therapeutic reconstruction of the human body, by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals" [8].

Considering the fundamental principles of tissue engineering, biocompatibility plays a crucial role. Unlike other fields that focus on stability or specific physical and mechanical functions, tissue engineering requires materials that can activate targeted cellular responses and initiate a cascade of reactions [8]. Therefore, the selection criteria for materials in tissue engineering are contingent upon understanding the target tissue's natural environment and the material's biomimetic properties. One essential component of tissue engineering is the use of scaffolds, which are synthetic three-dimensional (3D) structures made from polymeric materials. These scaffolds provide a multifunctional environment, mimicking the native tissue's properties, cell signaling, and adhesion [38][39]. Electroactive biomaterials, such as polypyrrole, polyaniline, and other polymers, are employed in constructing these scaffolds, mimicking the extracellular matrix (ECM) of muscle cells [38].

Biomaterials used in tissue engineering can be classified into three categories: natural materials, synthetic materials, and hybrid materials, which combine natural and synthetic components. These materials undergo extensive processing and modification to impart functional properties and create porous scaffolds suitable for tissue engineering applications [40]. Resorbable polymers are the primary substrate materials in tissue engineering, while ceramics and metals have limited uses due to their persistence and poor formability. Commonly used polymers include natural protein and polysaccharide gels, resorbable synthetics, cross-linked hydrogels, and fibrous webs. Ceramics may apply to polymer substrates to enhance osteoconductivity. Various fabrication techniques, including traditional methods and rapid prototyping, are employed to create these scaffolds. Custom implants can sometimes be designed using radiographic images of the patient's anatomy [41].

Synthetic tissues should be constructed with cells or components from the same species and tested in the target species. While this approach significantly reduces the risk of immunological reactions, it does not eliminate them entirely. For example, Harriger et al. utilized glutaraldehyde-cross-linked bovine collagen as a scaffold to seed human keratinocytes and fibroblasts, which were subsequently transplanted into athymic mice with full-thickness wounds [40]. Tissue engineering includes in vitro cell production and extracorporeal devices. The overarching goal is to achieve tissue and organ regeneration through innovative approaches [17].

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