Chapter 2
Implantable Medical Devices

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Abbreviations

MEMS	Microelectromechanical systems
NEMS	Nano-electromechanical systems
PCL	Polycaprolactone
PET	Polyethylene terephthalate
PGA	Polyglycolic acid
PLA	Polylactic acid
PU	Polyurethane
PTFE	Poly(tetrafluoroethylene)
PMMA	Polymethylmethacrylate
UHMWPE	Ultrahigh molecular weight polyethylene

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2.1 Introduction

Each year millions of patients improve their quality of life through surgical procedures that involve implanted medical devices. The term implant is used for devices that replace or act as a fraction of or the whole biological structure. Currently, implants are being used in many different parts of the body for various applications such as orthopaedics, pacemakers, cardiovascular stents, defibrillators, neural prosthetics or drug delivery system [1]. Concurrent with the increased life span in today's world, the number of age-related diseases has also increased. Hence, the need for new treatments, implants, prostheses and long-term pharmaceutical usage as well as the need for prolonging the life span of the current techniques has increased [2]. Joint diseases represent one of the examples of changing needs in the medical treatment: Today's estimates show that 90 % of the population over the age of 40 suffers from a degenerative joint disease [3]. In 2000, the number of total hip replacements operation was about 152,000 which represents a 33 % increase from the number of operations in 1990 and also represents about half of the estimated number of operations by 2030 [4]. Cardiovascular diseases are another example. Over the last two decades, coronary stents have become a new standard in angioplasty procedure. In 2004, the number of implanted drug-eluting stents alone exceeded two million [5]. In-stent restenosis is a consequence almost entirely of tissue hyperplasia, occurring principally around the points where the stent struts impinge upon the artery wall. Less common, but troublesome when it occurs, is subacute thrombosis, a complication not quite eliminated by modern stent deployment techniques and antiplatelet agents. By carrying a coating or drug targeted at the thrombotic or hyperplastic responses occurring locally, drug-eluting stents present a solution to the above problems [6].

2.2 Classes of Implantable Medical Devices

The regulatory authorities recognise different classes of medical devices, based on their design complexity, their use characteristics and their potential for harm if misused. Each country or region defines these categories in different ways. The authorities also recognise that some devices are provided in combination with drugs, and regulation of these combination products takes this factor into consideration. The FDA classification of medical devices is based upon the level of control required to assure safety and effectiveness of the device [7]. The classification procedures are described in the Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860).

Class I devices are subject to the least regulatory control "general controls". Class I devices are not intended for use in supporting or sustaining life or to be of substantial importance in preventing impairment to human health, and they may not present a potential unreasonable risk of illness or injury. Examples of class I devices include

elastic bandages, examination gloves and hand-held surgical instruments. *Class II* devices are those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. In addition to complying with general controls, class II devices are also subject to special controls. A few class II devices are exempt from the premarket notification. Special controls may include special labelling requirements, mandatory performance standards and postmarket surveillance. Examples of class II devices include powered wheelchairs, infusion pumps and surgical drapes. *Class III* device is one for which insufficient information exists to assure safety and effectiveness solely through the general or special controls sufficient for class I or class II devices. Such a device needs premarket approval, a scientific review to ensure the device's safety and effectiveness, in addition to the general controls of class I. Class III devices are usually those that support or sustain human life and are of substantial importance in preventing impairment of human health or those which present a potential, unreasonable risk of illness or injury. Examples of class III devices include implantable pacemaker, pulse generators, HIV diagnostic tests, automated external defibrillators and endosseous implants. Most of the devices discussed in this chapter will belong to class III. These are mostly implants in the orthopaedic, dental, ophthalmic and cardiovascular fields as well as soft tissue implants such as implants used in plastic surgery. Implants without bioactive coatings intended to secure teeth or prostheses to the maxillary or mandibular bones, and implants intended to be placed in teeth such as bridges, crowns, dental filling materials and dental alloys belong to class II [8].

Based on the purpose for which they are using, these implantable devices are broadly divided into three classes: cardiovascular implants, orthopaedic implants and implants for other use. Various subcategories under these classes are given in Table 2.1.

2.2.1 Cardiovascular Implants

Cardiovascular implants have strong potential to reduce the overall treatment cost for heart disease and at the same time contribute significantly to improved quality of life. Pacing devices will realise the greatest sales gains, largely due to growth in cardiac resynchronisation therapy. A focus on developing new generations of pacing devices that reduce mortality and improve patient outcomes has resulted in greater pricing flexibility in an increasingly cost-conscious health-care environment. Demand for cardiovascular stents and related devices will be similar to that of demand for pacing devices. The fastest growth will be in structural implants, as technological advances in heart valves, ventricular assist devices and implantable monitors will encourage greater use.

Cardiovascular disease broadly covers a range of conditions affecting both the heart and the blood vessels. Polymer-coated and polymer-based cardiovascular implants are essential constituents of modern medicine and will proceed to gain importance with the demographic changes toward a society of increasing

Table 2.1 Classification of implantable medical devices

Orthopaedic implants	Cardiovascular implants	Other medical implants
Reconstructive joint replacements[a] • Knee replacements • Hip replacement implants • Other reconstructive joint replacements – Shoulder implants – Elbow implants – Ankle implants – Joint replacements	Pacing devices[b] • Cardiac resynchronisation therapy devices • Implantable cardioverter-defibrillators • Implantable cardiac pacemakers • Pacing accessories—pacing leads, pacing batteries	Otolaryngeal implants[b,c] • Cochlear implants • Airway and oesophageal stents • Cosmetic implants—breast implants Ophthalmic implants[b] • Intraocular lenses • Glaucoma and other lenses Neurostimulators[b]
Spinal implants[a] • Thoracolumbar implants • Intervertebral spacers • Motion preservation devices • Cervical implants • Implantable spinal stimulators	Cardiac stents and related implants[b,c] • Coronary stents—drug-eluting stents, bare-metal coronary stents • Stent-related implants – Synthetic grafts—vascular grafts, peripheral grafts – Vena cava filters	Gastroenterological implants[b] • Gastric bands • Biliary stents • Urological implants
Orthobiologics[b] • Hyaluronic acid • Bone substitutes • Bone growth factors • Bone cement	Structural cardiac implants[a] • Heart valves and accessories • Tissue heart valves • Ventricular assist devices • Implantable heart monitors – Insertable loop recorders – Implantable hemodynamic monitors	Gynaecological devices[b] • Soft tissue repair • Intrauterine devices
Trauma implants[b] • Internal fixation devices • Craniomaxillofacial implants • Implantable trauma stimulators		Drug implants[c] • Hormonal implants • Brachytherapy products • Implantable drug pumps

[a]Structural and mechanical support
[b]Functional support
[c]Localised drug delivery

age-related morbidity. Based on the experiences with implants such as coronary or peripheral stents, which are presently widely used in clinical medicine, several properties of the next generation of cardiovascular implants have been envisioned that could be fulfilled by multifunctional polymers. The challenge is to combine tailored mechanical properties and rapid endothelialisation with controlled drug release in order to modulate environmental cells and tissue. Additionally, degradability and sensitivity to external stimuli are useful in several applications. A critical function in terms of clinical complications is the haemocompatibility. The design of devices with improved haemocompatibility requires advanced in vitro test setups as discussed in depth in this article. Finally, degradable, multifunctional shape-memory polymers are introduced as a promising family of functional polymers that fulfil several requirements of modern implants and are of high relevance for

cardiovascular application (e.g. stent technology). Such multifunctional polymers are a technology platform for future cardiovascular implants enabling induced auto-regeneration in regenerative therapies [9]. Shape-memory materials have been proposed for cardiovascular stents due to their self-expansion ability. The most ideal way to anchor a stent is using self-expansion in the range of body temperature. Ajili et al., for the first time, report the use of polyurethane/polycaprolactone (PU/PCL) blend as a proposed material for shape-memory stents. The results showed that the blend supported cell adhesion and proliferation, which indicated good biocompatibility, and the results suggested that this blend might be a potential material as a stent implant [10]. Multifunctional shape-memory polymers are highlighted as a class of materials that combine biocompatibility and the capability for stimuli-induced active movements for anchoring of implants with a controlled degradation and drug release profile to enable a functional regeneration of the tissue at the application site. The challenge is to combine tailored mechanical properties and rapid endothelialisation with controlled drug release in order to modulate environmental cells and tissue. Additionally, degradability and sensitivity to external stimuli are useful in several applications [11]. Current cardiovascular therapies are limited by the loss of endothelium, restenosis and thrombosis. Andukuri et al. reported biomimetic hybrid nanomatrix that combined the unique properties of electrospun PCL nanofibres with self-assembled peptide amphiphiles. Results indicate that this hybrid nanomatrix has great potential application in cardiovascular implants [12].

2.2.2 Orthopaedic Implants

Orthopaedic implants will remain the largest implantable device segment in market value. Gains will also reflect the growing prevalence of degenerative musculoskeletal disorders and lifestyle changes that place people at risk for sports and exercise injuries. At the same time, as products become more durable and long-lived, demand will increasingly come from an enlarged patient base for new surgeries rather than for replacements. Also challenging this segment over the long term will be advances in pharmaceutical alternatives to treat arthritic conditions. However, the segment will benefit from a strong base of insurance approvals for orthopaedic implants, as well as a stable and well-funded medical delivery system and product designs that allow for less invasive surgeries.

One of the most prominent application areas for biomaterials is for orthopaedic implant devices. Both osteoarthritis and rheumatoid arthritis affect the structure of freely movable (synovial) joints, such as the hip, knee, shoulder, ankle and elbow. The pain in such joints, particularly weight-bearing joints such as the hip and knee, can be considerable, and the effects on ambulatory function quite devastating. It has been possible to replace these joints with prostheses since the advent of anaesthesia, antisepsis and antibiotics and the relief of pain and restoration of mobility is well known to hundreds of thousands of patients [13].

Total joint replacement is widely regarded as the major achievement in orthopaedic surgery in the twentieth century. Arthroplasty, or the creation of a new joint, is the name given to the surgical treatment of degenerate joints aimed at the relief of pain and the restoration of movement. This has been achieved by excision, interposition and replacement arthroplasty and by techniques that have been developed over approximately 180 years. In a total knee arthroplasty, the diseased cartilage surfaces of the lower femur (thighbone), the tibia (shinbone) and the patella (kneecap) are replaced by a prosthesis made of metal alloys and polymeric materials. Most of the other structures of the knee, such as the connecting ligaments, remain intact [3].

2.2.3 Other Implants

Evolution of cochlear implant technology resulted in enhanced hearing, speech and cost-effectiveness for children. Binaural cochlear implantation has been used in children. Development of perimodiolar electrodes, implantable microphones and rechargeable batteries promise fully implanted devices in future [14].

Intraocular sustained drug release using implantable devices has been investigated to treat vitreoretinal diseases. Possible targeted diseases include those in which repeated intraocular injections are effective (cytomegalovirus retinitis, uveitis), diseases requiring surgery (proliferative vitreoretinopathy) and chronic diseases (macular oedema, retinitis pigmentosa). Hydrophobic or hydrophilic polymers shaped into a sheet, disc, rod, plug or a larger device can be implanted into the subretinal space, intrascleral space, vitreous space or peribulbar space or at the pars plana [15].

Solid biocompatible implantable devices for sustained or controlled intravitreal drug delivery to the posterior segment of the eye have been developed employing diverse approaches and include osmotic mini-pumps, nonbioerodible and bioerodible drug-loaded pellets, configured capillary fibres, biodegradable scleral plugs, scleral discs, polymeric matrices and scaffolds of various geometries providing unique mechanisms of drug release for the delivery of drugs to the posterior segment of the eye [16].

2.3 Materials Used for Medical Devices

In general, most of the materials used for implants or devices can be divided into the following categories: metals, polymers and ceramics. Metals are based on the metallic bond, ceramics are based on ionic bonds, and polymers are based on covalent bonds; and each of these categories contains many subdivisions. The metallic materials include pure metals and alloys; ceramics include glasses, glass–ceramics and carbons; and the polymers include thermosets, thermoplastics, elastomers and textiles. As biomaterials science emerged, the conventional view of materials, as being

tangible pieces of substances from which useful objects were made, prevailed [17]. The best performance of the vast majority of implantable devices is achieved when the biomaterials used in their construction are chemically and biologically inert; no biological, let alone pharmacological, activity should be sought in these devices. However, at least in theory, there are some exceptions, with the intention of either promoting some biological activity such as bone regeneration or minimising undesirable activity such as infection or blood clotting. Some materials are used with the express intention of delivering some biologically or pharmacologically active agent to the patient; the concept of drug delivery devices is of course well known [18].

2.3.1 Metals

As a class of materials, metals are the most widely used for load-bearing implants. These range from simple wires and screws to fracture fixation plates and total joint prostheses (artificial joints) for the hips, knees, shoulders, ankles and so on. In addition to orthopaedics, metallic implants are used in maxillofacial surgery and cardiovascular surgery and as dental materials. Although many metals and alloys are used for medical device applications, the most commonly employed are stainless steels [19, 20], cobalt-base alloys, commercially pure titanium and titanium alloys and some other metals [21]. Various properties of these metallic implant materials are listed in Table 2.2.

Stainless steels are iron-base alloys, and stainless characteristics are achieved through the formation of an invisible and adherent chromium-rich oxide surface film. This passive film serves as a barrier to corrosion processes in alloy systems that would otherwise experience very high corrosion rates and has the ability of self-healing, when damaged, as chromium in the steel reacts with oxygen and moisture in the environment to reform the protective oxide layer. Based on the characteristic crystallographic structure/microstructures of the alloys, stainless steels are classified into four classes: martensitic, ferritic, austenitic and duplex (austenitic plus ferritic). Stainless steels are used extensively for fracture fixation devices. Compared to the other metals used in orthopaedics, stainless steels exhibit a moderate to high elastic modulus and tensile strength. Additionally, these steels possess good ductility, which allows them to be cold worked. Stainless steels are fairly biocompatible although they never appear to fully integrate with bone or soft tissue. For instance, if stainless steel is placed in close proximity of bone in the body, a thin layer of fibrous tissue will intervene between the bone and metal at the microscopic level. This phenomenon is not conducive to the use of stainless steels in applications where the success of the implant is dependent on its close integration with tissue [22].

Cobalt–chromium alloys are highly corrosion resistant. Compared to stainless steel, they exhibit higher elastic modulus, strength and hardness, but they have relatively low ductility and are difficult to machine. Commonly used cobalt alloys are Co-28Cr-6Mo casting alloy, Co-20Cr-15W-10Ni wrought alloy, Co-28Cr-6Mo thermomechanically processed alloy and Co-35Ni-20Cr-10Mo wrought alloy.

Table 2.2 Comparison of some of the characteristics and mechanical properties of metallic implant materials [22]

	Stainless steels	Cobalt-base alloys	Ti and Ti-base alloys
Grade	Austenitic stainless steel	Cobalt–chromium alloy	α–β alloy
Composition	Fe Cr (17–20) Ni (12–14) Mo (2–4)	Co Cr (19–30) Mo (0–10) Ni (0–37)	Ti Al (6) V (4) Nb (7)
Young's modulus (GPa)	200	230	106
Tensile strength (MPa)	540–1,000	900–1,540	900
Advantages	Cost, availability, processing	Wear resistance, corrosion resistance, fatigue strength	Biocompatibility, corrosion, minimum modulus, fatigue strength
Disadvantages	Long-term behaviour, high modulus	High modulus, biocompatibility	Lower wear resistance, low shear strength
Uses	Temporary devices (fracture plates, screws, hip nails); used for total hip replacement	Dentistry castings, prostheses stems, load-bearing components in total joint replacement	Used in THRs with modular femoral heads; long-term permanent devices (nails, pacemakers)

They possess adequate fatigue properties to serve as artificial joints or total joint prostheses and are used extensively for this purpose.

Commercially pure titanium is well known for its excellent corrosion resistance. Various grades of unalloyed titanium are available with oxygen and iron as primary variants. Biomedical applications for commercially pure titanium grades include pacemaker cases, housings for ventricular assist devices, implantable infusion drug pumps, dental implants, maxillofacial and craniofacial implants and screws and staples for spinal surgery. Superior biocompatibility, enhanced corrosion resistance and lower modulus are some of the attractive properties of titanium-base alloys as biomaterials. Based upon their microstructure after processing, titanium-base alloys are divided into four classes: α, near α, α–β and β. Femoral hip stems, fracture fixation plates, spinal components, fasteners, intramedullary nails and screws are some of the biomedical applications of these alloys [23].

Among the various refractory metals, niobium, molybdenum and tungsten are used as alloying elements in stainless steels, cobalt-base alloys and titanium-base alloys [24]. Tantalum has excellent resistance to corrosion and also offers intrinsic fabrication advantages. Apart from the alloying additive, commercially pure tantalum is fabricated into various medical devices such as foils and sheets for nerve anastomoses, clips for ligation of vessels and staples for abdominal surgery and as pliable sheets and plates for cranioplasty and reconstructive surgery [25].

Table 2.3 Polymers used for implantable devices [26]

Polymers	Applications
Poly(tetrafluoroethylene)	Oxygenator membrane, vascular graft, catheter coating, soft tissue augmentation, vascular prostheses
Poly(dimethylsiloxane)	Oxygenator membrane, tubing, shunt
Polypropylene	Heart valve structures, sutures
Poly(ethylene terephthalate)	Vascular grafts and prosthesis, shunt, sutures
Polyamides (nylons)	Hemodialysis membrane
Poly(ether urethane) (e.g. Pellethane)	Percutaneous leads, catheters, tubings, intra-aortic balloons
Poly(ether urethane urea) (e.g. Biomer)	Artificial heart components, heart valve
Low- and high-density polyethylene	Tubing; knee, hip, shoulder joints
Polysulfones	Artificial heart components, heart valve
Polyvinylchloride	Tubing, blood bags
Poly(2-hydroxyethylmethacrylate)	Catheter coating
Polymethylmethacrylate	Dental restorations, intraocular lenses, joint replacement, e.g. bone cements
Polyamides	Sutures
Polyesters	Vascular prostheses, drug delivery systems like drug-eluting stents, sutures
Silicone	Soft tissue replacement, ophthalmology, finger joint
Hydrogels	Ophthalmology, drug delivery systems
Acrylic, nylon	Tracheal tube

2.3.2 Polymers

Polymeric materials are rapidly replacing other material classes such as metals, alloys and ceramics for use as biomaterials because of their versatility. Their applications range from facial prostheses to tracheal tubes, from kidney and liver parts to heart components and from dentures to hip and knee joints. Various polymers used for implantable medical devices are listed in Table 2.3.

Polymeric materials are generally classified into three different classes depending on their source: natural polymers, obtained from natural sources including both plant and animal origin; synthetic polymers, based on totally synthetic sources; and bio-inspired polymers which comprise materials synthesised to mimic a naturally occurring polymer, but not necessarily identical to it. Natural polymers suffer from various disadvantages such as possibility of antigenicity, possibility of microbial contamination and source-to-source variability of properties. Hence, synthetic polymers have been the material of choice for implants because of their ease of production, availability and versatility of manipulation [27]. Bio-inspired polymers promise innovative materials that have the potential to functionally replace diseased or unavailable cell components, such as the extracellular matrix, which plays a structural role in many organs and tissues [28].

2.3.2.1 Non-biodegradable Polymers

Ultrahigh molecular weight polyethylene (UHMWPE) was the first polymeric material, used in medicine since the 1960s. UHMWPE is highly resistant to corrosive chemicals and has extremely low moisture absorption, very low coefficient of friction, characteristic of self-lubrication and high resistance to abrasion. UHMWPE emerged as a bearing material in many joint replacement devices. Tibial bearings in knee arthroplasties and acetabular bearings in hip arthroplasties are the most common uses of UHMWPE. Recently, it has been found that generation of particulate debris from the articulating surface of this polymer is associated with osteolysis and loosening of implants. Research has been carried out to address these problems and highly cross-linked UHMWPE materials are clinically introduced. Another important medical advancement for UHMWPE in the past decade has been the increase in use of fibres for sutures, where maximum strength and minimum weight are required [25].

Polymethylmethacrylate (PMMA) is used extensively as bone cement, which is primarily used to support the stems of total joint prostheses in the medullary cavity of the bone. The primary purpose of the material is to fill the space between the prostheses and bone to achieve more uniform stress distribution, and bone cements do not serve as adhesives. PMMA is also used for replacement intraocular lenses in the eye when the original lens is removed in the treatment of cataracts. PMMA microspheres injected under the skin reduce wrinkles or scars permanently. Polyetheretherketone, a thermoplastic polymer, is used as biomaterials for trauma, orthopaedic and spinal implants [21].

The use of polyethylene terephthalate (PET) in medical devices has endured for more than 50 years. Current medical applications of PET include implantable sutures, surgical mesh, vascular grafts, sewing cuffs for heart valves and components for percutaneous access devices. The notable biological characteristics of PET are biostability, promotion of tissue ingrowth, a well-characterised fibrotic response and a long history of human implantation [29].

2.3.2.2 Biodegradable Polymers

For most applications, biodegradable materials offer advantages over other materials. The degradable nature of these materials allows for temporospatial clearance of the material from the body, enabling the surrounding and/or ingrowth tissue to autonomously restore its function over time after having benefited from the implant. Synthetic biodegradable polymers offer the ability to control surface as well as mechanical properties and degradation kinetics [28].

There are four major degradation mechanisms for polymers used in biomedical devices: hydrolysis (reaction with water in tissues), oxidation (due to oxidants produced by tissues), enzymatic degradation and physical degradation (e.g. water swelling and mechanical loading and wearing). Hydrolysis has been studied extensively, especially for biodegradable polymers. Polyesters, polyorthoesters, polyanhydrides, polycarbonates and polyamides are some of the polymers that are

degraded by hydrolysis. Degradation of polyurethane material through oxidation is observed in an implantable electrical insulation lead. Biological defence action is also responsible for oxidative degradation, in which inflammatory cells generate oxidative agents that diffuse into polymeric implants and degrade them. Enzymatic degradation is also due to a defensive action against implanted foreign materials. Collagens, polysaccharides (hyaluronic acids), some polyesters (e.g. polyhydroxyalkanoate, PHA), synthetic polycarbonates and proteins are mainly degraded due to this type of reactions. Physical degradation is mostly due to mechanical friction associated with motion under pressure, for example, the wearing of acetabular cups of total hip replacements. Water swelling is another mechanism. This can be a problem if swollen polymers have significant changes in glass transition temperature, geometry and mechanical properties such that the normal functions of the materials are affected [30].

Potentially, devices made from bioresorbable polymers can overcome problems associated with metal implants like stress protection, potential for corrosion, wear and debris formation as well as the necessity of implant removal. Resorbable polymers have proven to be good materials for a range of devices in trauma surgery [31]. Among resorbable polymers for implants, polyhydroxy acids occupy the main position. These are mainly poly(L-lactide), poly(glycolide) and/or copolymers based on L-lactide, L/DL-lactide, DL-lactide, glycolide, trimethylene carbonate and caprolactone. These polymers are well known for their good biocompatibility, with their degradation products being eliminated from the body by metabolic pathways. Many reports have shown that the different PLA-based substrates do not present toxicity since the cells were found to differentiate over the different polymers, as demonstrated by the production of extracellular matrix components by various cell types [32].

Polymers prepared from glycolic acid and lactic acids have found a multitude of uses in the medical industry, beginning with biodegradable sutures first approved in the 1960s. Since that time other medical devices, based on lactic and glycolic acid, as well as other materials, including poly(dioxanone), poly(trimethylene carbonate) copolymers and PCL homopolymers and copolymers, have been accepted for use as medical devices. In addition to these approved devices, a great deal of research continues on polyanhydrides, polyorthoesters and other materials [33].

Collagen has received increasing attention over the last years due to its excellent biocompatibility, degradation into physiological end products and suitable interaction with cells and other macromolecules [34]. Resorbable forms of collagen have been used for closure of grafts and extraction sites. Collagen-based membranes also have been used in periodontal and implant therapy as barriers to prevent epithelial migration and allow cells with regenerative capacity to repopulate the defect area [35]. Tissue-based collagen devices are mostly used for cardiovascular applications in the form of heart valves, vascular prostheses [36].

Polymer coatings such as silicone rubber, PTFE, Parylene and epoxy were used to encapsulate the implantable devices. However, these materials are biocompatible; they have limited abilities to protect the device from water ingress. Polyether-based polyurethane elastomers are currently used in a variety of blood- and tissue-contacting devices in biomedical applications due to their biocompatibility

and stability in biological environment together with their superior processability. Despite their excellent mechanical properties and biocompatibility, the chemical structure and morphology of polyurethanes make them relatively permeable to gases and water [37].

2.3.3 Ceramics and Composites

Restorative materials in dentistry such as crowns, cements and dentures are made up of ceramic materials. The poor fracture toughness of ceramics severely limits their use for load-bearing applications. They are generally used to replace or fix hard connective tissue, such as the bone [22]. The bone itself is a composite, comprising an organic phase and a ceramic phase. This ceramic phase is predominantly calcium hydroxyapatite with a Ca/P ratio of 1.67. Thus, synthetic calcium hydroxyapatite is a good candidate for a successful biomaterial. Several dental and orthopaedic metal implants are coated with hydroxyapatite to ensure long-term fixation in bone [21]. Zirconium dioxide or zirconia ceramics (ZrO_2), a bioinert nonresorbable metal oxide, is being recognised for its high strength, toughness and surface finish. It is used to manufacture femoral heads for total hip replacements and this material is potentially suitable for the highly loaded environments found in joint replacement. A ceramic that is used in load-bearing applications is high-purity alumina. It is used as the bearing surface in total hip prostheses. The material is characterised by its excellent biocompatibility and high strength, hardness and fracture resistance. A class of glassy bioactive ceramics upon implantation undergo a modification of their surface and form a layer of a very bioactive form of hydroxyapatite. As new bone is formed in opposition to this layer, it forms a very strong bond such that the mechanical integrity of the bond can exceed that of bone. Widescale use of these materials has been limited due to their brittle nature [25].

The most successful composite biomaterials are used in the field of dentistry as restorative materials or dental cements. Although carbon–carbon and carbon-reinforced polymer composites are of great interest for bone repair and joint replacement because of their low elastic modulus levels, these materials have not displayed a combination of mechanical and biological properties appropriate to these applications. Composite materials are, however, used extensively for prosthetic limbs, where their combination of low density/weight and high strength makes them ideal materials for such applications.

2.3.4 Drugs and Other Biomolecules

The coated implant can be viewed as a drug/medical device combination product which represents an emerging new trend in therapeutics. Combination products facilitating localised drug delivery have already been used in a variety of applications from cardiovascular diseases to diabetes. Drug and device combinations can

be designed to increase the performance and life time of currently used implants resulting in improved patient life quality [38]. Drug-coated implants function as a semipermeable compartment that holds the drug while permitting passage of preferred molecules in a controlled manner. Drug-eluting stents are good examples of such devices [4, 39, 40].

Various immunosuppressive drugs (sirolimus, everolimus, tacrolimus, ABT-578), antiproliferative drugs (paclitaxel, actinomycin, angiopeptin, etc.), antimigratory drugs (batimastat) and gene therapeutic reagents (antisense and siRNA, vascular endothelial growth factor, endothelial nitric oxide synthase (eNOS and related genes)) have been combined with stents and investigated for their local release and antirestenotic effects. FDA's approval of Cordis' CYPHER™ sirolimus-eluting stent (2003) opened the gate for adapting new technology combining both device and pharmaceutical designs [41].

2.4 Requirements of Implantable Devices

2.4.1 Mechanical Properties

Elasticity, yield strength, ductility, toughness, creep, ultimate strength, fatigue strength, hardness and wear resistance are some of the important mechanical properties of materials used in implantable medical devices.

2.4.1.1 Yield Strength

The yield strength determines the load-bearing capability of the implant. For example, in the case of TJR surgeries where a high load-bearing capability of the implant is essential, one ideally needs an appropriately high yield strength value of the alloy. Thus, the orthopaedic alloys should have a sufficiently high yield strength value with adequate ductility (defined by percentage elongation or percentage reduction of area in a standard tensile test) [42].

2.4.1.2 Elastic Modulus

There is always a concern for the relatively higher modulus of the implant compared to that of the bone (_10–40 GPa, or 1.5–6 _106 psi) [3]. Long-term experiences indicate that insufficient load transfer from the artificial implant to the adjacent remodelling bone may result in bone reabsorption and eventual loosening of the prosthetic device [43]. It has been seen that when the tensile/compressive load or the bending moment to which the living bone is exposed is reduced, decreased bone thickness, bone mass loss and increased osteoporosis occur. This is termed the stress shielding effect, caused by the difference in flexibility and

stiffness, which is partly dependent on the elastic moduli difference between the natural bone and the implant material [44]. Any reduction in the stiffness of the implant by using a lower-modulus material would definitely enhance the stress redistribution to the adjacent bone tissues, thus minimising stress shielding and eventually prolonging the device lifetime [3].

2.4.1.3 Fatigue

Variable fatigue resistance of the metallic implants is also a cause of concern while developing an alloy. The orthopaedic implants undergo cyclic loading during body motion, resulting in alternating plastic deformation of microscopically small zones of stress concentration produced by notches and microstructural inhomogeneities. Standard fatigue tests include tension/compression, bending, torsion and rotation-bending fatigue testing [3].

2.4.2 Corrosion and Biocompatibility

Degree of success of an implant is determined by reactions at the interface between an implant and the environment of the body. In the case of orthopaedic implants, one of the potentially important aspects of this interfacial reaction concerns metallic corrosion. The metals and alloys used as surgical implants achieve passivity by the presence of a protective surface passive film. This film inhibits corrosion and keeps current flow and the release of corrosion products at a very low level, i.e. all the implantable materials undergo corrosion at some finite rate due to complex corrosive environment of the body, while in use [45].

Metallic implant degradation results from both electrochemical dissolution and wear but most frequently occurs through a synergistic combination of the two [46]. Electrochemical corrosion processes include both generalised dissolution uniformly affecting an entire surface and localised areas of a component [47]. Locally these areas tend to be at both identifiable areas relatively shielded from the environment (e.g. crevice corrosion) and at random sites on the surface (e.g. pitting corrosion). In the past, these electrochemical and other mechanical processes have interacted to cause premature structural failure and accelerated metal release (e.g. stress corrosion cracking, corrosion fatigue and fretting corrosion) [48].

The only way to reduce the corrosion of surgical implants is selecting an appropriate alloy with improved surface properties by addition of alloying elements, which improve the nature, composition and stability of the passive film; homogenisation treatment to dissolve the second-phase precipitates; production of cleaner varieties of steels using advanced steel-making processes in order to have control over inclusions; avoiding improper heat treatment; and fabrication in order to eliminate the formation of second phases especially at grain boundaries. Also, the nature, composition and chemical stability of passive films with superior corrosion

resistance can be produced through surface treatment by ion beams. Many of the cases of corrosion could be avoided by improvements in materials selection, implant design, quality control, materials handling and education [45].

According to Williams in 2008, biocompatibility refers to the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy but generating the most appropriate beneficial cellular or tissue response in that specific situation and optimising the clinically relevant performance of that therapy [49]. Biocompatibility studies on an implantable device require complex experiments both in vitro and in vivo in order to test the local and systemic effects of the material on culture cells, tissue sections and the whole body [50].

In vitro assessment of tissue compatibility usually involves performing cell cultures for a wide variety of materials used in medical devices. Direct contact, agar diffusion and elution are the three different cell culture assays used for in vitro study. In all the tests, experimental variables such as cell type (usually L-929 mouse fibroblast), number of cells, duration of exposure and test sample size are kept constant [51]. Positive and negative controls are often used during the assay test to determine the viability of the test. In all cases, the amount of affected or dead cells in each assay provides a measure of the cytotoxicity and biocompatibility of the biomaterials. Cell adhesion, cell spreading, cell migration, cell proliferation and cell function are some of the key parameters that can be investigated individually in these assays [52]. In vivo assessment of tissue compatibility tests are performed to determine the biocompatibility of a prosthetic device and also to assess whether the device is performing according to expectations without causing harm to the patient. Some tests, such as toxicity, carcinogenicity, sensitisation and irritation, determine if the leachable products of the medical device affect the tissues near or far from the implant site. Other tests, such as implantation and biodegradation, study the post-surgery changes in the implant material itself and their ensuing effect on the body. For conducting the actual in vivo tests, animal models (sheep, pig, rat) are usually selected after weighing the advantages and disadvantages for human clinical applications [42].

2.4.3 Sterilisation

Infection is a major problem associated with implantable devices, and a further complication is that organisms of relatively low virulence are frequently found to be pathogenic when they contaminate the bioimplant. Further, little is known about the effect of a prosthetic device on either the host immune response or the inflammatory action of the tissue with which the prosthesis interfaces [53]. Composition of the device and its function, the location, the length of time the device is in place and the underlying condition of the patient are some of the factors affecting the pathogenesis of such infections and the relative rate of infection [54]. The same implant located in different body areas can be associated with different flora, potentially

Table 2.4 Different methods used for sterilisation of implantable medical devices [53]

Method	Principle	Advantages	Disadvantages
Steam sterilisation	Saturated steam in the range of 121–134 °C	Sterilises penetrable materials and exposable surfaces	Microcavitation in case of hydrophilic polymers Altered biocompatibility of heparinised surfaces
Dry heat sterilisation	Carried out in electrically heated ovens at 160–180 °C	Ability to penetrate solids Lack of corrosion in case of non-stainless steel metals	Rubbers, plastic, etc. do not withstand high temperature
Ethylene oxide	Biocidal activity is achieved at 30 % humidity, 45 °C temperature levels with >450 mg/l gas concentration	Suitable for heat-sensitive implants	EO residues after sterilisation cause: Anaphylactoid reactions in dialysis patients Serious tissue reactions in pump oxygenators Mutagenicity and carcinogenicity
Radiation sterilisation	Primary biocidal action is via aqueous free radical formation following the primary physical interaction of the ionising radiation with the biological material	High-energy irradiation sterilisation	Degradation and/or cross-linking of polymers Gas evolution and free radical formation from polymers

different host defence mechanisms and other alterations in milieu that may alter the potential development of prosthesis-associated infection. Implants can also alter the host immune response, through alterations of phagocytic capacity, inflammatory response or immunoglobulin synthesis [55]. Sterilisation of implantable devices is carried out to eliminate infecting microorganisms upon the device. Various sterilisation procedures used for implants are listed in Table 2.4 along with their advantages and disadvantages.

2.5 Applications

2.5.1 Drug Delivery and Scaffolds

One of the fastest growing areas for implant applications is for devices for controlled and targeted delivery of drugs. Combinations of drug and device are predicated on the principle of local controlled drug delivery from an implanted

prosthetic device whose primary purpose is functional or structural replacement of host tissue. Optimal dual functions (i.e. drug release and prosthetic performance) are ideally coordinated and designed to work in tandem. Hence, drug release properties from the device are not simply adjunct to device implantation and must be thoroughly understood. Drug release strategies from implantable devices are frequently considered to address thrombosis, osteomyelitis, periodontitis, biomedical device-related infections and other microbial pathologies or inflammatory complications [41].

Currently, there are various methods available and being used for drug–implant combinations. While polymeric coatings are one of the best recognised techniques, depending on the application, there are other methods currently available and nanoporous coatings are one of them. The nanoporous ceramic templates can be fabricated directly on the currently available implants or stents [4]. Drug loading for the nanoporous templates generally is performed through capillary action by either immersing the templates in the concentrated drug solution or dropping the solution slowly on the template surfaces [56]. Different techniques have been used to increase and accelerate the intake of the drug, including surface enhancement, sonication or solution aids [57]. One of the unique features of these nanoporous coatings is the ability to precisely control the surface properties. By varying the pore size, distribution and density, drug loading and release can be altered. Surface charges of these pores can also be modified to hydrophobic or hydrophilic to accommodate variety of drug molecules. Additionally, through suitable surface modification the release kinetics of the drug molecules can be altered [4].

Many exciting new opportunities exist in the application of microfabricated drug delivery devices to medicine and biology. Microfabricated devices are poised to revolutionise drug delivery. They offer new methods to deliver compounds in a targeted manner, at the desired rate, and are compact to allow minimally invasive placement [58]. Micro- and nano-electromechanical systems (MEMS or NEMS)-based polymeric and electromechanical delivery devices create totally new drug delivery paradigms. MEMS technology has been used to construct microreservoirs, micropumps, nanoporous membranes, nanoparticles, valves, sensors and other structures using biocompatible materials appropriate for drug administration [59]. Using NEMS, complex mechanical nanostructures can be built with lateral dimensions as small as tens of nanometers. By incorporating transducers, control and measurement functions can be built into these systems [60]. A biodegradable polymer chip version of an implantable multireservoir drug delivery device incorporates an array of reservoirs capped with resorbable membranes that may differ from other membranes in the array by thickness or chemical composition. The interior of each reservoir contains drug formulation(s). An advantage of biodegradable polymer-based systems compared to microchip-based systems is the elimination of a requirement for a second surgery to remove the device. In addition, the lack of electronics reduces any size restrictions in terms of device manufacture. Such systems are simpler but will not deliver reservoir contents with as much precision as the analogous microelectronic devices [61].

Drug-eluting stents are among the most widely known combination products. Micromachining technology allowed bare-metal stents to be manufactured that had the physical capability of propping open occluded vessels. Coating the stent with a drug-containing polymer resulted in combination products featuring localised drug release capability in addition to the mechanical action of the stent. Next-generation drug-eluting stents incorporate reservoir-based drug containment on the stent surface, with release properties determined by polymer composition and layer thickness [62].

In case of orthopaedic device-based drug delivery, osteo-inductive molecules as well as biologically derived growth factors, anti-osteoporotic agents and osteosynthetic genetic materials (DNA, siRNA) to bone injury sites are successfully delivered [63]. Osteo-precursor cell-based local delivery is reported for bone engineering [64]. These biotechnology approaches seek to accelerate and enhance bone defect healing and bone-implant stabilisation through local release of cells and mitogenic and morphogenic agents. One commonly used infection management method with orthopaedic implants utilises antibiotics loaded into clinically ubiquitous bone cement, polymethylmethacrylate beads. These non-biodegradable polymer cements have been employed clinically to prevent or treat osteomyelitis in various forms [65].

One of the key components in successful tissue engineering is the production of the correct scaffold using biomaterials. An ideal scaffold should provide cells not only with a structural framework but also with the appropriate mechanical and biochemical conditions so that these cells can proliferate and produce extracellular matrix to form tissue. Areas of research in tissue engineering include the repair or regeneration of the skin, blood vessels, nerves, liver, bone and articular cartilage. PLA and PGA are prime candidates for such scaffolds because they are biocompatible, provide the appropriate mechanical environment, can be easily fabricated and, moreover, are biodegradable. Collagen sponges are also under investigation [21]. Various FDA-approved implantable devices are listed in Table 2.5.

2.5.2 Structural and Mechanical Support

Currently, one of the main achievements in the field of arthroplasty is total joint replacement, where the entire load-bearing joint (mainly in the knee, hip or shoulder) is replaced surgically by ceramic, metal or polymeric artificial materials. Bone replacement, fracture fixation, dental implants, dental restorations, bone plates and orthodontic wires are some of the medical devices that provide structural and mechanical support (Table 2.6).

Table 2.5 FDA-approved implantable medical devices intended for localised drug delivery and functional support

S.No.	Device	Polymer/drug	Purpose/use	Manufacturer	References
1.	PROMUS® Element™ Plus	Everolimus-eluting platinum chromium stent	Coronary stent	Boston Scientific Corporation	[66]
2.	OVATION Abdominal Stent Graft System	The main portion of the graft is made of a plastic tube supported partially by polymer-filled rings and partially by a metallic stent	Used to treat abdominal aortic aneurysms during endovascular repair	Trivascular, Inc.	[67]
3.	LeGoo®	Thermosensitive polymer (poloxamer)	Injected into a blood vessel to temporarily plug a blood vessel and stop blood flow	Pluromed, Inc.	[68]
4.	Propel	The implant contains the active ingredient mometasone furoate, a steroid which suppresses inflammation in the area around the implant	Temporary, self-absorbing implant designed to keep the spaces within and around the sinuses open following sinus surgery	Intersect ENT	[69]
5.	ION™ Paclitaxel-Eluting Coronary Stent System	Expandable, stainless steel tube with paclitaxel contained within a thin polymer coating surface	Paclitaxel-Eluting Coronary Stent	Boston Scientific Corporation	[70]
6.	Gel-One®	Hyaluronate hydrogel produced from chicken combs, in a phosphate-buffered saline solution	Treatment of osteoarthritis	Seikagaku Corporation	[71]
7.	Synvisc-One (hylan GF-20)	Elastoviscous high molecular weight fluid containing hylan polymers	Treatment of osteoarthritis	Genzyme Biosurgery	[72]
8.	Medtronic® Attain StarFix™	Surgically implanted insulated wire that is designed to be used as a part of a biventricular pacemaker system	The other end of the lead connects to an implanted biventricular pacemaker or implantable cardioverter-defibrillator, so signals and electrical impulses can be sent between that device and the left ventricle	Medtronic, Inc.	[73]
9.	Epicel® cultured epidermal autograft (CEA)	Sheets of autologous keratinocytes (skin cells)	Cultured epidermal autografts, or skin grafts, used to replace the epidermal or top layer of skin on severely burned patients	Genzyme Biosurgery	[74]

(continued)

Table 2.5 (continued)

S.No.	Device	Polymer/drug	Purpose/use	Manufacturer	References
10.	INFUSE® Bone Graft	INFUSE® Bone Graft is used to fill space where the bone is needed in order to place endosseous dental implants	Endosseous dental implants are inserted in the jaw and have an exposed head that can be used to secure dental devices like a crown, fixed bridge or dentures	Medtronic Sofamor Danek	[75]
11.	Onyx® Liquid Embolic System (LES)	The Onyx® LES is an artificial material used to block blood flow in the treatment of malformed blood vessels in the brain	This material is used to block the flow of blood before surgical treatment of the malformed vessels	Micro Therapeutics, Inc.	[76]
12.	Endologix PowerLink® System	Y-shaped stent graft made out of a fabric tube of synthetic material called ePTFE	Endovascular graft and used to treat an abdominal aortic aneurysm during a surgical procedure called endovascular repair	Endologix, Inc.	[77]
13.	Nuflexxa™ (Sodium Hyaluronate)	1 % sodium hyaluronate solution	Injected into knee joints to treat pain from osteoarthritis of the knee	Savient Pharmaceuticals, Inc.	[78]

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm286493.htm

Table 2.6 FDA-approved implantable medical devices used for structural and mechanical support

S.No.	Device	Polymer	Purpose/use	Manufacturer	References
1.	Belotero Balance	Hyaluronic acid gel	Injected into facial tissue to smooth wrinkles and folds	Merz Pharmaceuticals	[79]
2.	Edwards SAPIEN Transcatheter Heart Valve	Cow tissue attached to a stainless steel mesh frame with a polyester wrap	Heart valve	Edwards Lifesciences	[80]
3.	Restylane® Injectable Gel	Restylane is a transparent hyaluronic acid gel	Injected into a patient's lips to increase their size	Aesthetics Holdings, Inc	[81]
4.	EUFLEXXA®	Hyaluronate hydrogel in a phosphate-buffered saline solution	Used to relieve pain in the knee due to osteoarthritis	Ferring Pharmaceuticals, Inc.	[82]
5.	St. Jude Medical® Trifecta™ Valve	The valve leaflets are manufactured using bovine pericardial tissue. A polyester-covered titanium stent supports the bovine pericardial tissue	The Trifecta valve is a three-leaflet stented pericardial valve designed for supra-annular placement in the aortic position	St. Jude Medical	[83]
6.	ProGEL™ Pleural Air Leak Sealant	Made of human serum albumin and a polyethylene glycol (PEG) cross-linker that forms a clear flexible gel on mixing	Surgical sealant, sprayed or "painted" on the lung tissue. The ProGEL™ forms on the lung tissue by chemical reaction	NeoMend, Inc.	[84]
7.	Gel-One®	Hyaluronate hydrogel produced from chicken combs, in a phosphate-buffered saline solution	Treatment of osteoarthritis	Seikagaku Corporation	[71]
8.	Sculptra Aesthetic	Sculptra Aesthetic is an implant of poly-L-lactic acid (PLLA) microparticles	It is injected into the facial tissue to correct shallow to deep smile lines (nasolabial fold), contour deficiencies and other facial wrinkles	Sanofi-Aventis U.S.	[85]

(continued)

Table 2.6 (continued)

S.No.	Device	Polymer	Purpose/use	Manufacturer	References
9.	EVOLENCE® Collagen Filler	Collagen Filler	Injected into the inner layers of facial skin (mid to deep dermis) in order to correct moderate to deep facial wrinkles and folds	ColBar LifeScience Ltd.	[86]
10.	Mitroflow Aortic Pericardial Heart Valve	Consists of a single piece of bovine pericardium that is preserved with glutaraldehyde and sewn onto a polyester covered polymer stent	The Mitroflow Aortic Pericardial Heart Valve is intended for the replacement of diseased, damaged or malfunctioning native or prosthetic aortic valves	CarboMedics, Inc.	[87]
11.	Cosmetic Tissue Augmentation Product	Cosmetic Tissue Augmentation Product (CTA) is a transparent hyaluronic acid gel with 0.3 % lidocaine that is injected into facial tissue	CTA works by temporarily adding volume to facial tissue and restoring a smoother appearance to the face	Anika Therapeutics, Inc.	[88]
12.	Radiesse	Radiesse is an injectable calcium hydroxyapatite implant in the form of a gel	Radiesse works by temporarily adding volume to facial tissue and restoring a smoother appearance to the face	BioForm Medical, Inc.	[89]
13.	Inamed® Silicone-Filled Breast Implants	Implant is a silicone shell filled with silicone gel	The breast implant is surgically implanted either under breast tissue or under the chest muscle	Allergan	[90]
14.	ArteFill®	Contains small polymethylmethacrylate beads, collagen and lidocaine	Filler that is injected into the nasolabial folds around the mouth to smooth these wrinkles	Artes Medical, Inc.	[91]
15.	Juvederm Gel Implants	Hyaluronic acid gel	Injected into the middle layer of skin (mid to deep dermis) to temporarily correct moderate to severe facial wrinkles and folds	Inamed Corporation	[92]

http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm286493.htm

2.6 Conclusion

Medical devices are now a pervasive part of modern medical care. The medical development in terms of implantable devices has brought about the robust change in the life of the people (as offered by the cosmetic treatment, dentist, face and cardiology devices). Medical devices have extended the ability of physicians to diagnose and treat diseases, making great contributions to health and quality of life. The approach to quality of devices has depended largely on regulation. The critical nature of medical devices has caused them to come under stringent regulations. Clearance to market devices in the USA is granted only after the Food and Drug Administration (FDA) has determined through its classification and review procedure that there is reasonable assurance of the safety and effectiveness of the device. Such regulatory requirements are necessary and appropriate. A rigorous but responsive and responsible regulatory process helps to ensure that new medical technologies represent the state of the art, have the real potential to do good as demonstrated in scientifically grounded studies and reach patients promptly. Despite the enormous contribution medical devices have made to the public health, there is a fear of the possibility of liability exposure in the event of device malfunction or failure. Its influence is growing and is having a chilling effect on innovation. It also damages global competitiveness and increases health care costs directly and indirectly. Ironically, the shadow of product liability may actually be keeping better performing products from the market rather than being a force for improvement.

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