Toxicologic Pathology, 36:70-80, 2008

ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623307310949

Biocompatibility: Meeting a Key Functional Requirement of Next-Generation Medical Devices

[1]Michael N. Helmus, [2]Donald F. Gibbons, and [3]David Cebon

From [1]Medical Devices, Biomaterials, Drug Delivery, and Nanotechnology, Worcester, Massachusetts, USA; [2]3M Corporation, North Oaks, Minnesota, USA; and [3]Granta Design Limited, Cambridge, United Kingdom.

Abstract

The array of polymeric, biologic, metallic, and ceramic biomaterials will be reviewed with respect to their biocompatibility, which has traditionally been viewed as a requirement to develop a safe medical device. With the emergence of combination products, a paradigm shift is occurring that now requires biocompatibility to be designed into the device. In fact, next-generation medical devices will require enhanced biocompatibility by using, for example, pharmacological agents, bioactive coatings, nano-textures, or hybrid systems containing cells that control biologic interactions to have desirable biologic outcomes. The concept of biocompatibility is moving from a "do no harm" mission (i.e., nontoxic, nonantigenic, nonmutagenic, etc.) to one of doing "good," that is, encouraging positive healing responses. These new devices will promote the formation of normal healthy tissue as well as the integration of the device into adjacent tissue. In some contexts, biocompatibility can become a disruptive technology that can change therapeutic paradigms (e.g., drug-coated stents). New database tools to access biocompatibility data of the materials of construction in existing medical devices will facilitate the use of existing and new biomaterials for new medical device designs.

Keywords: Biomaterial; biocompatibility; bioactive; biostable; biodegradable; drug eluting; implant; database.

Introduction

Materials used in medical devices, particularly in those applications in which the device either contacts or is temporarily inserted or permanently implanted in the body, are typically described as biomaterials and have unique design requirements. The National Institute of Health Consensus Development Conference of November 1982 defined a biomaterial as "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 which treats, augments, or replaces any tissue, organ, or function of the body" (Boretos and Eden, 1984, pp. 27-88, 128-132, 193-253).

The required material properties are determined by the specific device application and the functional life of the device, which ranges from temporary use to permanent implant. Devices can be used in (1) blood-contacting applications such as extracorporeal devices that remove and return blood from the body, devices that are inserted into a blood vessel, or devices that are permanently implanted; (2) soft-tissue device applications, such as soft-tissue augmentation; (3) orthopedic and dental applications for joint, bone, and tooth replacement and repair, (4) specific organ applications (e.g., neural); and (5) scaffolds for tissue engineering for tissue and organ replacement.

Address correspondence to: Michael N. Helmus, PhD, Consultant: Medical Devices, Biomaterials, Drug Delivery, and Nanotechnology, 2 Jamesbury Dr., Worcester, MA 01609; e-mail: Mhelmus571@aol.com.

Abbreviations: Co-Cr-Mo, cobalt-chrome-molybdenum; ISO, International Standards Organization; OCP, FDA's Office of Combination Products; PMMA, polymethylmethacrylate; PTFE, poly(tetrafluoroethylene); PVC, poly(vinyl chloride); SIBS, styrene-isobutylene-styrene triblock copolymer or Poly(Styrene-b-isobutylene-b-styrene); ULTI, ultra low temperature isotropic carbon.

Materials for medical devices can be characterized as synthetic polymers, biodegradable polymers, bioactive materials, natural macromolecules (i.e., biopolymers), metals, carbons, and ceramics (Boretos and Eden, 1984; Helmus and Tweden, 1995; Helmus, 2003). They can be implanted for permanent replacement, as in an artificial heart valve or hip prosthesis, or for temporary use, such as an intravenous catheter or bone plates and rods. The sterilized device, and by default, the materials of which it is constructed, need to meet basic biocompatibility requirements, generally as defined by the ISO 10993 standards, to be nontoxic, nonthrombogenic, noncarcinogenic, nonantigenic, and nonmutagenic (Helmus, 2003). In blood-contacting applications, it must be nonthrombogenic to mitigate complications from thrombi and emboli. Potential complications will vary with a device and its application. Biodegradation and infection become increasingly important in longer term applications such as central venous catheters and permanently implanted devices. Because of the large surface area in extracorporeal circuits, activation of biologic pathways, such as the coagulation, fibrinolytic, and complement pathways, may be magnified. Patients who are treated by extracorporeal methods (e.g., hemodialysis) are repeatedly exposed to leachable plasticizers and sterilant residuals.

Many devices, such as heart valves, artificial hearts, and hip implants are constructed of multiple materials. Joining methods can affect material properties that can reduce strength, fatigue life, and biostability. The material's form and size, how it interfaces with the body, and its required duration of use will determine its required properties. One material property alone is unlikely to lead to a successful and durable device, whereas a lack of a single key property can lead to failure.

Coatings for improved biocompatibility and as carriers for drug delivery have an increasingly important role. Bioactive

materials, which tend to use the nature of natural material or mimic natural materials, have applications in orthopedic implants to enhance bone attachment, antimicrobials to mitigate infection, and antithrombotics to mitigate thrombus. Drug–polymer combinations have been used in drug-eluting stents, heparin-release coatings for catheters, and steroid-releasing electrodes for pacemakers (Helmus and Tweden, 1995; Ranade et al., 2004; Ranade et al., 2005; Stokes, 1987). These drug-eluting devices are representative of combination devices that have the potential to create potent new therapies by using the best properties of drug-device, biologic-device, or drug-biologic combinations. The Food and Drug Administration's Office of Combination Products (OCP) has broad responsibilities covering the regulatory life cycle of these combination products and will determine which Center has primary regulatory responsibility (Helmus, 2007). For example, the drug-eluting stent is primarily regulated by Center for Devices and Radiological Health, but Center for Drug Evaluation and Research has secondary responsibility for the analysis of drug content and compounding and manufacturing requirements.

The phenomena controlling the bioresponse are basically wound healing in the presence of a sterile medical device. The outcome of this healing process can have profound implications on the success of a device and can depend on material properties such as texture, crystallinity, wettability, surface chemistry, cytotoxic leachables, and degradation products (Andrade et al., 1987; Brash, 2000; Helmus and Tweden, 1995). These properties determine primarily the interaction between the materials and proteins in the biological environment, and subsequently, the interactions with the cells and tissues. The biologic response to materials, e.g., inflammation and thromboresistance, is an important consideration in the design of medical devices. Chronic inflammatory responses resulting in a thick fibrous capsule and the persistence of white cells, is undesirable and can lead to damage to surrounding tissue and to failure of the device. Leachables can cause local cytotoxicity and result in inflammation. Hypersensitivity reactions can occur to corrosion products and residual monomers, plasticizers, additives such as antioxidants, and degradation products. Cytotoxic leachables and degradation products, which may exhibit systemic effects if the dose is high, may result from the fabrication and sterilization methods used as well as ambient degradation by processes such as hydrolysis and oxidation over time (Coury et al., 1988; Stokes, 1987; Takahara et al., 1992). Contamination by bacteria, endotoxins (the breakdown products of gram-negative bacteria), and particulate debris can have profound effects on inflammatory responses (Helmus et al., 1986). These responses are generally a matter of handling, processing, and minimizing wear and corrosion in vivo. The lack of bacteriological contamination can be designated as an incoming requirement on materials from a vendor; however, wear and corrosion debris are inherent properties of materials and are a matter for appropriate materials selection.

Biostability refers to the ability of a material to resist biodegradation mechanisms and maintain its properties in situ. Degradation may result from hydrolysis, oxidation, enzyme catalyzed enhancement of hydrolysis, oxidation, lipid absorption, swelling, and calcification. Biomaterials with enhanced compatibility will combine new materials that have negligible leachables and exceptional biostability to mitigate adverse biologic responses to leaching of additives and breakdown products. Styrene-isobutylene-styrene triblock elastomer, used as the carrier for paclitaxel in the drug-eluting stents (Ranade et al., 2004; Ranade et al., 2005), is an example of this type of new-generation material and is described in the last section of this article.

TABLE 1.—International standards for biological evaluation of medical devices.[a]

Reference	Title
ISO 10993-1	Guidance on selection of tests
ISO 10993-2	Animal welfare requirements
ISO 10993-3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity
ISO 10993-4	Selection of tests for interactions with blood
ISO 10993-5	Tests for cytotoxicity: In vitro methods
ISO 10993-6	Tests for local effects after implantation
ISO 10993-7	Ethylene oxide sterilization residuals
ISO 10993-8	Withdrawn: Clinical investigation of medical devices
ISO 10993-9	Evaluation of biodegradation of medical devices
ISO 10993-10	Tests for irritation and sensitization
ISO 10993-11	Tests for systemic toxicity
ISO 10993-12	Sample preparation and reference materials
ISO 10993-13	Identification and quantification of degradation products from polymers
ISO 10993-14	Static test to quantify in vitro degradation of ceramics
ISO 10993-15	Identification and quantification of degradation products from metallic materials used in medical devices
ISO 10993-16	Toxicokinetic study design for degradation products and leachables
ISO 10993-17	Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices
ISO 10993-18	Characterization of materials
ISO 10993-19	Physico-chemical, morphological, and topographical characterization of materials
ISO 10993-20	Principles and methods for immunotoxicology testing of medical devices

[a]Helmus (2003); http://www.iso.org/iso/en/StandardsQueryFormHandler.StandardsQueryFormHandler?scope=CATALOGUE&sortOrder=ISO&committee=ALL&isoDocType=ALL&title=true&keyword=10993

Thromboresistance relates to the tendency of a material to reduce thrombus or emboli formation by formation of platelet-based and/or fibrin-based clots. Thrombi can form a nidus for coagulation, and they can also form a site that is prone to bacterial colonization and infection. Consumption of blood elements may be an indication of microemboli and activation of thrombotic mechanisms and is undesirable. Many bioprostheses, such as the bioprosthetic pericardial heart valve, are considered thromboresistant, whereas mechanical heart valves made from a variety of materials require permanent anticoagulation therapy. The effect of design and materials on thrombosis is difficult to separate in these cases. Materials such as poly(ester) fabrics are moderately thromboresistant but are suitable for their application as vascular grafts larger than 6 mm in diameter. Intimal hyperplastic responses resulting in the excess thickening of vascular tissue limit the use of synthetic small-diameter vascular grafts (Boretos and Eden, 1984) and result in the chronic closure of vessels after angioplasty.

Basic schemes for testing the acceptability of materials in terms of cytotoxicity, hemolysis, and mutagenicity can be

TABLE 2.—Selected examples of materials from Materials for Medical Devices database.[a]

Material Examples	Device Example	ISO 10993 Tests	Biocompatibility Citations for Soft Tissue Response and Blood Compatibility
Synthetic plastic			
Ultra high molecular weight polyethylene	Annuloplasty rings	3, 4, 6, 10, 11	Chowdhury et al. (2004), Takami et al. (1997), Hunter et al. (1995), Richardson et al. (1975)
Synthetic elastomer			
Silicone rubber	Sewing ring component pericardial heart valve	3, 5, 6, 10, 11	Belanger et al. (2000), Harmand and Briquet (1999), Iomhair and Lavelle (1996), McCoy et al. (1989), Mirzadeh et al. (2003), Ertel et al. (1994), Bordenave et al. (1992), Ammar (1984), Van der Giessen et al. (1996), Spilizewski et al. (1987)
Synthetic textile			
Polyethylene terphthalate knitted/woven	Mechanical heart valve	3, 4, 5, 6, 10, 11	Toes (1999), Bonchek et al. (1969), Radomski et al. (1987), Marois et al. (1999), Marois et al. (1996), Urayama et al. (1996), Granström et al. (1986)
Biodegradable			
Polylactic acid	Biodegradable pericardial replacement	3, 4, 5, 6, 10, 11	Nguyen et al. (2003), (Tamai et al. (2000), Kohn et al. (2004), Cutright and Hunsuck (1971), Su et al. (2003)
Tissue derived			
Bovine pericardium	Heart valve	3, 4, 5, 6, 10, 11	Fürst and Banerjee (2005), Chang et al. (2001), Chang et al. (2002), Neuhauser and Oldenburg (2003)
Bioderived			
2-methacryloyloxyethyl phosphorylcholine	Stent coating	3, 4, 5, 6, 7, 10, 11	De et al. (2002), Galli et al. (2001), Rose et al. (2004), Malik et al. (2001), Goreish et al. (2004)
Passive coating			
Butyl methacrylate	Carrier for drug-eluting stent	3, 4, 5, 6, 10, 11	Sousa et al. (2001), Suzuki et al. (2001)
Bioactive			
Surfactant heparin	Annuloplasty rings	3, 4, 5, 6, 7, 10, 11	Tonda et al. (2005), Lazar et al. (1999), Novello et al. (2000), Yang et al. (2005), De Scheerder et al. (1997)
Tissue adhesive			
Albumin	Tissue sealant	3, 5, 6, 10, 11	Skarja et al. (1997), Werthén et al. (2001), Marois et al. (1996)
Metal			
Stainless steel	Endovascular stent	3, 4, 5, 6, 7, 10, 11	Selvaduray and Bueno (2004), Hao et al. (2005b), Wever et al. (1997), Indolfi et al. (2000)
Ceramics and carbon			
Pyrolytic carbon (LTI)	Mechanical heart valve	3, 4, 5, 6, 10, 11	Yannas (2004), Feng and Andrade (1994), Mantero et al. (2002), Yang et al. (1996), Maropis et al. (1977), Antoniucci et al. (2000)
Composites			
Silicone impregnated with barium sulfate	Annuloplasty ring	3, 4, 5, 6, 7, 10, 11	See *silicone rubber* above
Nanotechnology			
Nanostructured copolymer Styrene-isobutylene-styrene (SIBS)	Carrier for drug-eluting stent	3, 4, 5, 6, 10, 11	Gallocher et al. (2006), Silber (2003), Ranade et al. (2004)

Iso = International Standards Organization.
[a]ASM International (2006).

found in the following standards and guidelines: American Society for Testing and Materials (ASTM) F-748 and the International Standards Organization 10993 standards; see Table 1. These documents provide a method of testing by device application (Helmus, 2003).

MEDICAL MATERIALS INFORMATION

Materials can be classified in a variety of different ways. The following, which is suitable for medical devices, sorts by type and application: synthetic polymer, biodegradable materials, tissue-derived materials, bioderived macromolecules, passive surface coatings, bioactive and tissue-adhesive materials, metals, ceramics and glassy carbons, composites, and nano materials. Table 2 gives examples of materials in each category, a medical device in which it is used, a list of ISO 10993 tests that it passed when fabricated as part of that medical device, and literature citations on its blood and soft-tissue compatibility. These data were extracted from ASM International's Materials for Medical Devices Database, Cardiovascular Implant Materials Module (ASM International and Granta Design, 2007).

The database is an extensive resource, containing the engineering and biological performance of materials used in implantable cardiovascular devices as well as information about compatible coatings and drugs, manufacturing processes, and an extensive database of relevant published literature. The data are comprehensively cross-linked and fully traceable to original sources. The database can be used for information retrieval and selection of materials, drugs, and coatings for combination devices.

TABLE 3.—Biocompatibility issues.

	Biomaterial Category									
	Synthetic	Biodegradable	Tissue	Bioderived	Passive Coatings	Bioactive Coatings	Metals and Alloys	Ceramics & Carbons	Composites	Nanomaterials
Biocompatibility										
ADME, biodegradation byproducts, biodeposition		+	+	+		+		+		+
Bioactivity			+	+		+	+	+		+
Biodegradation particulates		+		+		+				
Biodegradation: Effect of infection, acid pH		+	+	+		+				
Biodegradation: Effect of hematoma, basic pH		+	+	+		+				
Calcification	+		+	+		+				
Cell membrane and blood-brain barrier passage										+
Cells viability (cryopreserved allografts)			+							
Corrosion byproducts							+			
Cytotoxic preservatives			+							
Decellularization process			+							
Extractables	+	+	+	+	+	+			+	
Hypersensitivity reactions	+		+	+		+	+		+	
Immune responses			+	+		+				
Infectious contamination: Bacterial, viral, fungal, prion			+	+		+				
Lipid uptake	+		+	+					+	
Matching biomechanics of original tissue			+				+	+	+	
Necrotic cell death/apoptosis										+
Purity				+		+				
Protein adsorption: Hydrophilic	+				+					
Protein adsorption: Hydrophobic	+				+					
Sterilization residuals	+	+	+	+	+	+				
Surface exposure of compounded particles									+	
Uptake in the reticuloendothelial system										+
Thromboresistance			+		+	+		+		
Physical integrity										
Biostability	+		+	+	+	+	+	+	+	
Coating adherence					+	+				
Corrosion: Pitting, fretting, stress							+			
Cross-linking effects on properties			+	+						
Durability	+		+		+	+		+	+	
Fatigue life	+	+					+	+	+	
Fracture toughness	+						+	+	+	
In situ cure time: Bone cements, tissue adhesives	+					+		+	+	
Rate of biodegradation: Surface		+						+		
Rate of biodegradation: Bulk		+	+	+						
Wear	+				+		+	+		

ADME = adsorption, deposition, excretion, and metabolism.

Table 3 summarizes the types of biocompatibility issues that might be a consideration in each category of biomaterials described below. These considerations are general and are influenced by the nature of the material (e.g., biostable vs. biodegradable) and application (e.g., soft-tissue, blood, or hard-tissue applications). The issues highlighted are the ones of particular devices have profound influence on the safety and efficacy of the device and are therefore categorized in this table.

SYNTHETICS

Commonly available synthetic polymers are used in applications such as sutures, housings for extracorporeal devices

devices), vascular grafts, heart-valve stents, abdominal patches, periodontal patches, and low-cost, high-volume tubing, connectors, and bags.

Examples include poly(amides), used as suture materials; poly(vinyl chloride) (PVC),[1] used as tubing and bags for the storage of blood and pharmaceutical products; poly(ethylene terephthalate) textiles, used as large-diameter vascular graft materials and as sewing cuffs on mechanical and biological heart valves; polymethylmethacrylate (PMMA), used as a fixation cement for the orthopedic prosthetics and for housings for extracorporeal devices; and poly(tetrafluoroethylene) (PTFE), used extensively as an expanded membrane material for medium-diameter vascular grafts, abdominal patches, periodontal membranes, and as anterior-cruciate-ligament prostheses (Helmus, 2003). These materials tend to exhibit structural stability, relative biocompatibility, and low cost. Some vendors supply specifically designated biomedical grades. Master files are kept on the material production, and the vendors usually certify the material biocompatibility based on standardized testing that shows that the materials as supplied are noncytotoxic and stable in the biological environment for certain periods of time and under certain conditions. Because of ongoing concerns with medical liability, some materials suppliers have limited the availability of their materials for use in permanent medical devices.

Some of the unique properties of synthetic materials are being used in new-generation devices. Hydrogel coatings, such as poly(ethylene oxide), are used for blood contact because of low levels of protein adsorption and their exceptional lubricity (Helmus and Hubbell, 1993). Poly(ether urea urethanes) are an example of a thermoplastic elastomer with excellent fatigue resistance. This material is used in the pumping bladder of the artificial heart. Highly oriented and highly crystalline poly(ethylene terephthalate) film is used as a balloon in certain angioplasty catheters because of its extraordinary bursting strength (Helmus and Hubbell, 1993). Table 3 summarizes the issues related to synthetic polymers.

Biodegradables

Biodegradable biomaterials are of high interest because of their ability to be absorbed gradually by the body (Kohn et al., 2004). The property of biodegradation in the biological environment makes these materials particularly appropriate for applications that are temporary in nature. These applications would normally require surgical removal.

Biodegradable products must have breakdown products that are nontoxic and eliminated by the body's metabolic pathways. The most widely used biodegradable materials are homopolymers or copolymers of alpha-hydroxy acids, such as lactic and/or glycolic acids (Williams, 1981). These materials can be formulated to degrade with a half-life for mass loss ranging from a few months to a few years. They are widely used as bioresorbable sutures and carriers for drug-eluting stents.

Surface-erodible polymers are hydrophobic and are used to maintain the device's physical strength for longer periods of time or to approach a zero-order release rate of pharmaceutical agents formulated into these surface-erodible polymers (Kohn et al., 2004). Examples include the polyanhydrides and polyorthoesters. Table 3 summarizes the issues related to biodegradables.

Tissue-Derived Materials

Processed tissues of human or nonhuman origin are used for ligaments, arteries, veins, and heart valves. Biodegradation and calcification during a period of 10 to 15 years has been an ongoing issue. Biologically derived materials are particularly susceptible to biodegradation mediated by proteolytic enzymes from plasma or from adherent cells. Calcification, seen particularly in biologically derived materials such as the bioprosthetic heart valve, can lead to stiffening and tearing of the bioprosthetic heart-valve cusps (Levy et al., 2003; Carpentier et al., 2007). Newer multiple-step processes entail treating the tissue to reduce antigenicity and to increase longevity in vivo by enzyme digestion, detergent extraction, and/or cross-linking with glutaraldehyde or other bifunctional agents. Significant efforts in reducing calcification have been demonstrated with ethanol and aluminum chloride treatments (Levy et al., 2003) as well as improvements in both calcification and thromboresistance with surfactant and alcohol treatment (Carpentier et al., 2007). Table 3 summarizes the issues related to tissue-derived materials.

Bioderived Macromolecules

Purified macromolecules are used for cardiovascular and soft-tissue applications. Collagen, both from human and nonhuman sources, is used as a space filler in cosmetic surgery, as a coagulation-inducing material, as a matrix to promote healing, and as a surface-treatment to make textile vascular grafts nonporous. Hyaluronic acid is being used as a coating to increase the lubricity of catheters and as an injectable into joints to reduce inflammation. Phosphorylcholine-derived polymers have been used to produce thromboresistant and biocompatible surfaces (De et al., 2002; Galli et al., 2001; Rose et al., 2004; Malik et al., 2001; Goreish et al., 2004). Human fibrin is used as a sealant and space filler in vascular and plastic surgery. Table 3 summarizes the issues related to bioderived macromolecules.

Passive Surface Modifications and Coatings

Specialized polymer coatings (e.g., silica-free silicones, hydrogels, and fluorocarbons), used to improve biocompatibility, and in many cases, to increase lubricity, are being developed for several cardiovascular applications (Hoffman, 1987). Plasma etching and plasma polymerization have also been used to modify surface properties. For example, the surface modification of vascular graft materials with nonpolymerizing gas plasmas (such as argon, oxygen, or nitrogen plasmas) has been observed to increase wettability and to generally increase the extent of cell attachment to materials. Treatment with a polymerizing gas plasma, such as tetrafluoroethylene, has been used to place a very thin, highly cross-linked polymer overlayer on a variety of base polymer substrates. These processes allow modification of surface properties without changing the bulk physical properties of the materials. Ultra low temperature isotropic (ULTI) carbon is used to modify Dacron polyester

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.