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AN OVERVIEW OF POLYMER BIOMEDICAL MATERIALS USED IN CARDIOLOGY

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ABSTRACT

Cardiology disorders have been reported to be the leading cause of fatalities in modern countries accounting to the highest percentage of the health budget. The highly increasing number of hospitalization related to cardiology disorders has given rise to various approaches like medical and surgical interventions. Even though these methods have proved beneficial there's still high rate of death associated to the disorder. The scarcity of donors and donor complication related to surgery have paved was for alternative treatment and research like the use of biomedical implants to overcome certain anomalies. Significant advances in material science, engineering and biotechnology have enabled the possibility to use biomedical implants in the human body. The rise in the demand for biomedical implants has sparked of research in the biomedical material field in order to find a "perfect" biomedical material for medical implants. These studies show that these materials are a specific group of materials that are characterized by different material composition, chemical structure and mechanical, chemical and biological properties. In this review we highlight the most common polymer biomedical materials used in cardiology with reference to biocompatibility.

KEYWORDS: Biomedical materials, medical implants, biocompatibility, polymers, cardiology.

INTRODUCTION

Cardiology disorders have been reported to be the leading cause of fatalities in modern countries like the USA which annually incurs over US$200 billion in healthcare costs.[1] Due to the increasing number of hospitalization related to cardiology disorders various approaches like medical and surgical interventions have come up. Although modern interventions are effective in treating a variety of cardiology disorders there is still a high fatality rate. Therefore patients tend to opt for organ transplantation which also has its associated drawback such as immunogenic complications, donor pool limitations, technical requirements, and high financial costs.[2] This has paved was for alternative treatment and research like the use of biomedical implants to overcome certain anomalies and the scarcity for donor organs. Significant advances in material science, engineering and biotechnology have enabled the possibility to use biomedical implants in the human body such as defibrillators and pacemakers.[3] The interest in biomedical implant materials has sky rocketed during the past decade along with the huge demand for better biomedical materials to replace the available traditional implants.[4] The cardiovascular system comprises of the heart and all the blood vessels therefore biomedical implant materials may contact blood (both arterial and venous), vascular endothelial cells, fibroblasts, and myocardium, as well as a number of other cells and cellular matrix material that make up all biological tissue. This review article highlights different polymers in biomedical implant materials used in cardiology and also discusses biocompatibility criteria.

A biomaterial is any material aside from a drug or a blend of materials, synthetic or natural in origin that can be used for any given period of time either as a section or as a whole part of a system and its aimed at treatment, augmentation, tissue or organ replacement or aid in body functions as described by the National Institutes of Health (NIH) Consensus Development Conference on the Clinical Applications of Biomaterials in the United States comprehensively.[5]

There are a variety of major criteria considered when choosing a biomedical implant material on implants such as; material choice and its application, material effect on the living body and surroundings after it is implanted, bioavailability hypotheses, tissue reaction mechanisms, biophysical, biochemical and biomechanical hypotheses once it is implanted, corrosion,

abrasion and degradation capacity, material surface layering mechanism etc. Biomedical implant materials are ought to play more complex, lengthy roles in tissues therefore personalizing and maximizing the material-tissue interface is important in order to ascertain the best long term clinical outcomes. Cardiovascular biomaterials may contact blood vascular endothelial cells, fibroblasts, and myocardium, as well as a number of other cells and a cellular matrix material that make up all biological tissue. Biomaterials can be categorized into two main categories; synthetic such as polymers, ceramics and metals whereas natural biomedical materials include allogeneic sources, xenogeneic sources and autogenic sources.[6] The demand and preference for inert biomedical materials has risen in medical applications since they have reduced material-biological tissue reactions once implanted. However, newer studies have sparked interest in the merits of interactive biomaterials for expanding treatment like drug delivery for therapeutics or stem cell transplants for tissue repair and regeneration. For years, studies have been performed about the properties of biomedical polymer materials that could be successfully implanted into the human body. These studies have shown the various advantages of polymers in material composition, chemical and biological properties, chemical structure etc. The major feature of all the polymers biomaterials is their biocompatibility factor.

Polymers

Polymers are defined as organic materials that consist of several different or similar, straight monomers attached to macromolecules with a higher molecular weight. Polymer material features include: low density, low stiffness, creep resistance, low mechanical strength and thermal conductivity, good insulation properties (electrical and thermal), resistance to weathering and chemicals and ease of shaping. Basing upon of their medical use, polymeric biomedical implant materials are grouped into two: synthetic and natural polymers.

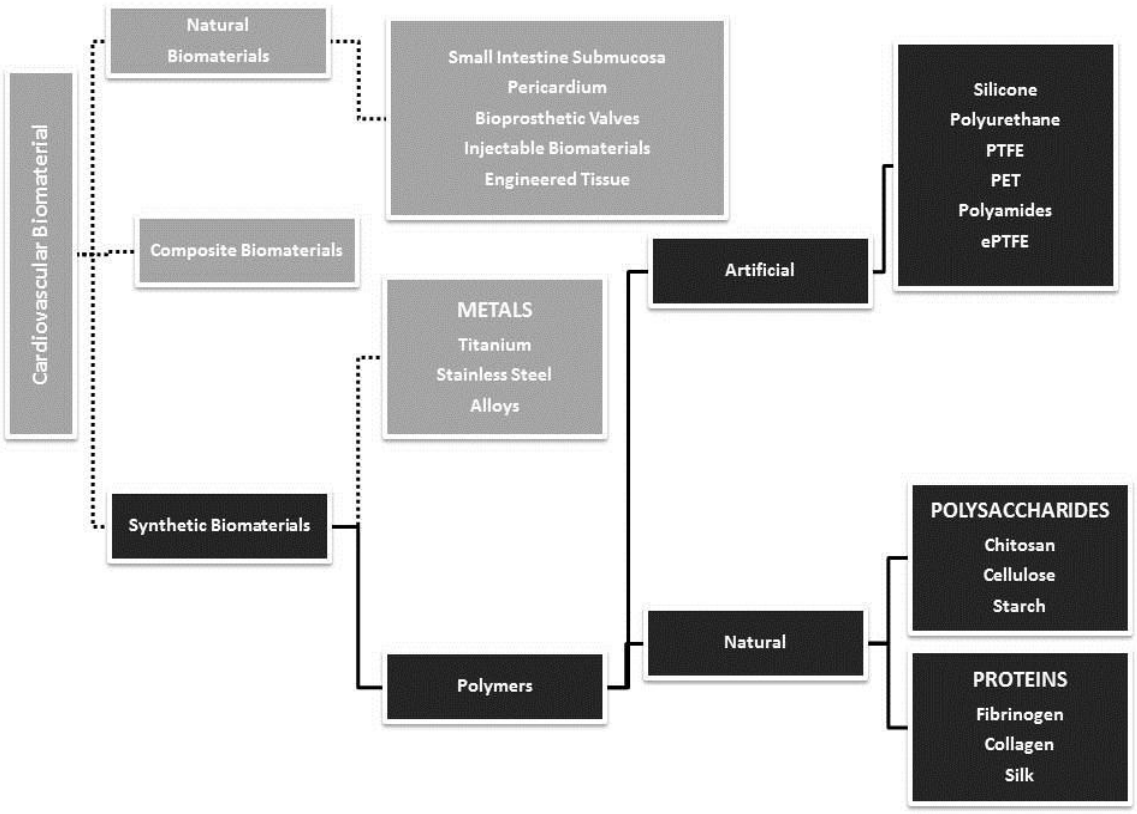

Fig 1: Summary of biomaterials currently used in cardiovascular applications with emphasis on polymer biomedical materials.

Synthetic Polymers

Polytetrafluoroethylene (PTFE)

PTFE is an exceptionally digestible thermoplastic polymer with a wide range of medical applications such as manufacture of urological catheters, vascular prostheses, and in cardiology as a biomaterial for artificial heart valves. Not only does PTFE have good biocompatibility but also high impact resistance to chemicals, microorganisms and fungi. It doesn't cause allergic reactions, non-toxic and physiologically inert thereby substantially accelerating the healing process of pierced bodies. The PTFE textile graft is no longer commercially available because of its handling characteristics. The material was deemed not good enough as its counterpart the polyester textile graft because commercially available PTFE fibers were larger in diameter than polyester fibers. However, polyester and PTFE textiles, as well as expanded PTFE, are available as flat sheets. The textile materials are available as knits, weaves, and felts. These materials are used for patches and suture buttresses.

Expanded polytetrafluoroethylene (ePTFE)

ePTFE is composed of a fluorocarbon polymer, formed into sheets by extrusion. This material is manufactured by Gore Medical and it's commercially known as Gore-tex®. Expanded PTFE is formed by compressing PTFE with a carrier medium and extruding the mixture. It is used to manufacture cardiovascular products for general cardiac reconstruction, vascular grafts and pediatric shunts. Its chemical composition promotes low thrombogenicity, lower rates of restenosis and hemostasis, less calcification and biochemically inert properties.[7–9] In addition, ePTFE has been shown to have high resistance to allergic reaction and inflammation and has even been used for covering implantable devices to minimize inflammation.[8,10] However, owing to the fact that ePTFE is a synthetic material it is capable eliciting a negative immune response and thrombosis.

Polyethylene terephthalate (PET)

This is a chemically inert thermoplastic polymer produced by Maquet Cardiovascular and commercially known as Dacron®. It can be produced into various types, and it is usually applied in cardiology as vascular grafts in the knitted or woven or knitted forms. The difference between the forms is in the pore size to reduce blood leakage. PET grafts properties like reduced blood loss and antibiotic effect are further elevated through coatings such as albumin or collagen to prevent graft infection.[11] PET grafts have also been found to promote endothelialization by recruiting endothelial cells to the graft's luminal surface, with no calcification or tissue overgrowth. Collagen and glycosaminoglycan deposits have also been found in implanted grafts and circumferential mechanical properties show little degradation over time.[12] Like ePTFE, PET also has the disadvantage of being a synthetic material and can therefore cause a foreign body reaction with increased chance of thrombus formation.

Polyurethane (PU)

Polyurethanes are a class of polymers obtained through the reaction of an isocyanate group with a hydroxyl group to produce foam. They can alternatively be manufactured into a harder thermoplastic form which is then used in medical applications. The thermoplastic form contains higher elastic property and strength, transparency and its microbial resistance characteristic and pliability is ideal for avoiding infection, and improved handling characteristics respectively. Although durable, they lack flexibility. In order to overcome this drawback, products made of PU like pacing leads are manufactured with the option of a PU–

silicone copolymer in order to take advantage of silicone's flexibility thereby increasing the overall flexibility. The probability for thrombosis of PU is similar to other materials such as PTFE.[13] One of the disadvantages of PU cardiovascular implants is the material's tendency to oxidize and degrade in vivo, creating problems after implantation. Modifications to the material have been effective, as it has been shown that chemically coating the surface with an antioxidant aids in reducing oxidation.[14] In vitro biocompatibility test have shown that a variety of cell types have good proliferation ability on the PU surface. These cell types include fibroblasts, epithelial, and endothelial cells.[15] Current studies on PU design have put emphasis on production of biodegradable Pus. These are designed with the intention to act as temporary healing agents thereby promoting tissue repair.[16] Cardiac patches with thinner film patterns have also been designed from high elastic Pus. These play a supportive role in cardiomyocyte attachment and growth.[17] They have further been used in designing of a variety of small diameter vascular conduits with 2-methacryloyloxyethyl phosphorylcholine thereby enhancing their patency.[18]

Polyamides (PA)

This material is one of the first engineering thermoplastic invented; the aim of the invention was to obtain a "super polyester" fiber that had molecular weight greater than 10,000. It is also commonly referred to as Nylon.

Silicone

Silicones, also scientifically polysiloxanes are general category of synthetic polymers whose backbone is made of repeating silicon to oxygen bonds. They have organic groups (R or R1) like methyl, vinyl or phenyl groups attached to silicone. Due to their unique combination of thermal stability, low risk of unfavorable biological reactions, elastomeric properties and in particular patient comfort, silicones are the materials of choice in many novel and high technology device applications. The most common silicone used is room temperature vulcanizing (RTV) silicone also referred to as polydimethylsiloxane (PDMS).[19] Silicone has been found to have many medical applications due to its unique mechanical properties as well as chemical inertness, low toxicity, long term bio stability and biocompatibility.[20] Moreover it is odorless, tasteless and stainless. Silicones are by far the most widely used biomedical materials among the synthetic group of polymers for biomedical applications. Silicone has a variety of merits in medical application such as; less degradation, it is suitable for autoclaving, minimal deterioration of properties over time, less tissue reaction caused by medical-grade

silicones and its ability to resist against attack by the body and metabolism by other organisms. Silicones are known to impact very minimal response both in and out of the body therefore highly used in medical implants. Silicones have a semi inorganic structure making them difficult to be absorbed by living tissues and moreover they retain their mechanical properties even after implantation into the body.

Natural polymers

Collagen

Collagen is a ubiquitous extracellular matrix protein extracted from different animal species that provides tensile strength to tissues. It is a viscous, inexpensive, nontoxic, non-immunogenic, and biodegradable compound. There about 29 types of collagen identified to date. The most outstanding type is type I collagen because of its quaternary fibrillar structure and its ability to form fibers, both in vivo and in vitro.[21] Even though collagen exhibits proteolytic resistance and tensile mechanical strength, which depends on a highly regulated mechanism of intermolecular crosslinking, involving the formation of covalent bonds from aldehydes produced by the enzymatic action of lysyl oxidase on lysine and hydroxylysine residue[22], its covalent crosslinks are lost and the scaffolds obtained from these extracts exhibit poorer mechanical properties and are subject to enzymatic degradation in vivo during extraction thereby limiting their use in tissue engineering applications.[23] Collagen also exhibits more resilience and reversible deformation which is attributed to its elastic property.[24] It is obtained from animal tissues. The animal tissue is treated and purified using glutaraldehyde (stabilizing agent) in order to overcome degradability. Special precaution and care is observed during the extraction process in order to control the quality, purity and also prevent the transmission of infectious agents.[25] Moreover, the use of stabilizing agents like glutaraldehyde requires optimization to prevent calcification of the tissue after it is implanted.[26] Collagen has been used in cardiac patches derived like bovine pericardium made by CardioCel.[27] These have successfully delivered mesenchymal stem cells in human subjects for cardiac repair.[28] Since 1990, collagen has been in a variety of material and medical implants.[29]

Fibrin

Fibrin is a fibrous protein that has an important role in blood clotting. Fibrin mechanics has become increasingly important in view of extensive new applications of fibrin as a biomaterial. The biomaterial not only has a remarkable rheological feature of extremely high

elasticity and stability despite very low protein content but also good viscosity.[30] Another important mechanical property that is common to many filamentous protein polymers but no other polymers is stiffening occurring in response to shear, tension, or compression.

Fibrin has been made into fibrin gels. These fibrin gel have proved to have good attractive bioactivity and availability as an autologous sources and therefore they have been used for tissue engineering purposes.[31–33] Fibrin is converted from the plasma protein fibrinogen. This process takes place in the presence of activated protease thrombin and calcium. It is the final product in the coagulation pathway. Fibrin gel quality is highly influenced by the initial fibrinogen, thrombin and calcium formula.[33] The mechanical strength and degradation rate of a fibrin gel can be tuned by controlling the polymerization process. One of the most significant attributes of fibrin use is that its precursor soluble fibrinogen can be collected easily from patients' own blood in order to produce fibrin which is used for biomedical engineering purposes.[34] Fibrin hydrogels have also been made from fibrin and they have proved to have great biocompatibility as that of collagen gels. Research and experimental analysis has shown that fibrin scaffolds have a higher viability with promotion of proliferation and migration.[35] Fibrin has been used to make fibrin based heart valve scaffolds which are prepared by the use of an injection molding technique.[36] The biggest drawback to fibrin is its low mechanical strength therefore fibrin based scaffolds have a very poor mechanical strength making them unsuitable for direct implantation. Like other reported hydrogels, fibrin also exhibits shrinkage which is due to cell mediated contractile forces.

Silk

Silk is also a protein-based material that is mainly produced by insects and spiders. Silk fibers to be exact have exhibited extraordinary characteristics, like great strength and extensibility, resulting in a great toughness in combination with good biocompatibility thereby making silk not only a promising candidate for a variety of applications in the biomedical field but also a favorable material for technical applications.[37,38] The most commonly used silk for tissue engineering is obtained from Bombyx mori a type of silkworm.[39] Silk fiber quality and properties entirely depends on the anthropoid's origin and species. B. mori silk fibers consist of a fibroin component that is enveloped in an adhesive sericin coat. Research has shown presence of immunological activation linked to silk sutures with sericin proteins.[40] This sparked off numerous research and experiments aimed at creating medical biomaterials derived from the purified fibroin component. However, further investigation reported that

sericins doesn't cause any FBR (foreign body response), but rather the response is triggered by the combined fibroin–sericin structure.[41] Silk is highly degradable; this is highly by the material properties like fabrication method, location of the implant and beta sheet content. The primary mechanism for silk degradation in vivo is through the actions of proteases, these generally target the areas between beta sheets.[42] Remodeling and degradation will take place in those silk fibroin structures allow the infiltration of immune cells like macrophages.[43] This immunological action is due to activation of the complement cascade by silk fibroin materials, which generally persists through to 14 days post implantation and by 12 weeks no inflammatory cells are present.[44,45] Therefore characteristic properties of silk fibroin materials heavily depend on the processing method, which changes the degree of beta sheet formation, and has implications on degradability of the final product.[46]

Chitin

Chitosan is a linear polymer that naturally occurs only in certain fungi called Mucoraceae.[47] Chitosan is chemically composed of glucosamine and N-acetylglucosamine monomers linked through β- (1−4) glycosidic linkages. Its fully N-acetylated form is called chitin; chitin is derived from the exoskeleton of insects and crustaceans, such as shrimps, lobsters and crabs. The deacetylation of chitin produces the polymer chitosan.[48] Chitosan is widely used in biomedical and pharmaceutical applications, due to its unique combination of nontoxicity, excellent biocompatibility, biodegradability, and antimicrobial and polycationic properties.[49–53] Therefore due to its high biocompatibility and easy control of its physiochemical characteristics make chitosan a highly suitable material for tissue engineering.

Biocompatibility

Biocompatibility is the capability of a biomedical material to execute its intended designated application and not simply exist in an inert state in the tissues elicits a response appropriate for the intended or designated medical application. Biocompatibility testing not only accounts for the impact of the biomedical implant material on blood and tissue but also the impact of the organism on the biomedical material. There are available international standards set for biocompatibility tests and these define a series of tests the selection of which depends on the period the material will interact with the organs, tissue or body. Biocompatibility standards are grouped into short term and long term usage. Any biomedical material with usage duration of less than 30 days is considered as short term use and those that fall above 30 days of usage are considered as long term. There are a variety of other parameters considered

during testing such as; whether the material is internal or external application, blood contact, tissue contact etc. These parameters dictate what tests to be carried on a given material. Biomedical materials undergo so many processes prior to their testing such as contamination due to preparation processes which in turn may affect biocompatibility. Some materials may diffuse from polymers such as plasticizers, solvents, low molecular weight polymers and unreacted monomers or accelerated diffusion due to thermal and cleansing processes. Therefore, biocompatibility testing of biomedical materials is vital before the materials are used in medical implants. Biocompatibility testing involves high costs therefore screening tests that are subsets of the original standard tests have been established and can be used on new materials. Moreover some biomedical materials producers give biocompatibility data of this type. Once the biomedical materials pass the biocompatibility testing, further assessment is then done such as device function etc. The Food and Drug Administration (FDA) has set up guidelines and tests needed for biocompatibility testing and these are provided in the Blue Book Memo. These tests are based on the International Standards Organization (ISO) Document ISO-10993. (Biological evaluation of medical devices). For example genotoxicity, implantation tests, cytotoxicity, subchronic toxicity, sensitization, irritation tests, implantation, and hemocompatibility tests are neded for materials interacting with blood for more than 30 days whereas genotoxicity and subchronic toxicity tests are not needed for materials less than 24 hours. On the other hand carcinogenicity tests and chronic toxicity tests are essential for materials intended for long term medical implants. The American Society for Testing and Materials (ASTM) has also developed biocompatibility testing protocols basing from the ISO standard protocols. These have been grouped into long term, short term and animal studies.

The American Society for Testing and Materials protocols

Long-Term Testing

Biomedical materials intended for long term medical implants or use need to undergo endurance testing. The biomedical material undergoes simple bending or tensile testing, after approval further testing is carried out such as shelf life of the material, processing effects and sterilization. The tests enable the medical implant manufacturer to account for reliability. Different cardiovascular devices like ventricular assist devices, stents, heart valves, grafts etc., have different reliability tests and standards developed to suit their application and purpose. Cardiovascular biomaterials have a tendency to degrade upon storage therefore it’s of utmost importance to carry out long-term shelf life bench testing for these devices. Some of the

factors affecting material shelf life include; temperature, humidity etc., these have been used by test labs for shelf life testing.

Polymers degrade under stress after long term usage thereby affecting material function; therefore polymeric based medical devices need to undergo bio-stability testing. Biodegradation may be due to hydrolytic and enzymatic stability therefore a test procedure that incorporates hydrolytic stability under mimicked physiological stress is required as well as evaluation in animals. Stress may accelerate most of the degradation mechanisms, and biomaterials that are stable under static conditions may fail to perform well when stress is applied such as polyether polyurethane (soft form) undergoes oxidative degradation when stress is applied cause by oxidative enzymes present in biologic systems. Even though some regulatory companies calculate reliability using specific formulas, it is crucial to measure reliability rather than calculate since materials will be used inside the patient. Despite of the difficulties in mimicking the body system like blood or other biological fluids in a long term test set up, substitutes like saline have been found.

Short-Term Testing

Short-term testing procedures include material identification, surface characterization, mechanical properties, etc. Material identification tests categorize the bulk properties of the material depending upon the chemical formula, crystalline percentage, molecular weight, softening point, and degree of cross linkage. Biomedical materials are defined and grouped according to their properties such as composition, grain size, and contamination levels which are a characteristic of metallic materials. On the hand composition, molecular weight, cross linkage, shrinkage temperature, and purity are characteristics of biological materials. The biomedical material surface qualities will highly influence material-tissue reaction. In some cases biomaterial composition on the surface may be different from its bulk composition. Material coats used either intentionally or through contamination also change the material-tissue response. Therefore in order to overcome these drawbacks individual identification tests have been made to detect material coatings in case of contamination. Material surface properties have also been studied and analyzed lie the use of a scanning electron microscope to study and measure the surface roughness. Mechanical qualities of the material determine if a device will suffer an early failure therefore tests such as elastic modulus test and tensile strength test can be used for tensile testing, impact type test for impact loading, and tear test

for tear sensitive biomedical materials like silicone. ASTM has also set up protocols for mechanical tests and for operating test equipment.

Animal Studies

Animal studies differ therefore there aren't a lot of standard protocols these tests. These studies are critical and therefore they are made with consideration of the material or device dimension and function. Two ways are considered while choosing animal study protocol; firstly, using a model of the condition under investigation to study the function and effect of the material or device such as implantation of vascular grafts as alternatives for arterial segments. Secondly, designing a test that shows the functional characteristics of the device but doesn't treat an abnormal condition such as implantation of left ventricular assist devices in normal animals. Here the device effects on blood and tissues would be monitored and the effect of the biological environment surrounding the device monitored and recorded. This will reveal the functional property of the device or material and its effectiveness in treating a medical condition. Furthermore the it will also test the bio-stability and depending on the length of the experiment it will also test the long-term biocompatibility.

CONCLUSION

Many implantable device manufacturers have been pushed into searching alternative or replacement biomaterials for their devices. This has created high demand for medical biomaterials thereby paving way for more research into biomaterials. The past decade has seen a rise in biomaterial engineering and created a combination of new material from the existing biomedical material with a promise of better biocompatibility. FDA has encourage d biomaterial research by modified its procedures for replacement materials. Replacement materials aren't tested as new materials anymore but rather the materials should only exhibit equivalency to previously used materials. With the growing demand and research for biomaterials more and better biomedical devices would be set up and overcome the challenge of biocompatibility.

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