Design Development and Fabrication of Bileaflet Mechanical Mitral Heart Valve

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September, 2019

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A thesis submitted in partial fulfillment of the requirement for the degree of Masters of Science

In

Biomedical Engineering

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DEDICATION

I dedicate my thesis to my parents and family who have always been my nearest and have been so close to me that I found them with me whenever I needed. It is their unconditional love that motivates me to set higher targets.

*My supervisor, **Dr. Murtaza Najabat Ali**; I will be forever grateful to him for all his valuable time and patience; and for all that he has taught me.*

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ACKNOWLEDGMENTS

All praises to Almighty Allah who guides in darkness and helps in difficulties and all respects for his last Holy prophet Hazrat Muhammad (PBUH) who enabled me to recognize my Creator.

My supervisor Dr Murtaza Najabat Ali for his time and effort in contributing to and shaping my research; and his uncanny problem solving abilities. He has been a brilliant supervisor. My lab fellows Hafsa Inam and Bakhtawar Ghafoor, for his kind guidance and support, throughout my academic period in NUST. A lot of what I have achieved is because of him. My fellow researchers and friends specially Aysha Nauman, Iqra Bashir and Faiza Kulsoom. These people have been a huge support for me throughout my time in NUST, and I am very thankful to them for this. Lastly, I am extremely grateful to my parents and my siblings and my sister Nadra for their endless support, unconditional love and care without which this thesis completion wouldn't have been possible.

Thank you.

Natasha

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List of Abbreviations

PYC	Pyrolytic Carbon
CVD	Chemical Vapor Deposition
PTFE	Polytetrafluoroethylene
PET	Polyethylene terephthalate
CAD	Computer-Aided Design
MHV	Mechanical Heart Valve
SJM	St. Jude Medical
CNC	Computer Numerical Control
SCCM	Standard cubic centimeters per minute
SEM	Scanning electron microscope
FTIR	Fourier-transform infrared spectroscopy
XRD	X-Ray Diffraction
RBCs	Red blood cells
PBS	Phosphate-buffered saline
ETDA	Ethylenediaminetetraacetic acid
UV	Ultraviolet
ASTM	American Society for Testing and Materials

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Abstract

Heart valve problems affect more than 100 million people worldwide. According to statistics around 55% valvular diseases are treated by mechanical prosthesis. The first heart valve replaced model was caged-ball valve, more than 50 models of heart valves designed by different companies. Every design has different aspects like valve geometry, total leaflets, materials used for model manufacturing, coating techniques, and coating materials. Human heart consist of four chambers two atria and two ventricles and these chambers contain four valves mitral valve, tricuspid valve, aortic valve, and pulmonary valve. These heart valves control the blood flow and prevents the back flow of blood from one chamber to another. Congenital defect or any other abnormality of heart valves like stenosis or regurgitation causes severe problem in cardiovascular system and lead to death, so to avoid these problems surgeons repair or replace the heart valve by an artificial prosthesis valve. Depend on the patient need and condition, either replaced from biological or mechanical heart valve. Biological valves are made of living tissues whereas mechanical valves manufactured by the manmade materials or normally called biomaterials which are biocompatible and don’t causes any reaction inside the body when they become in direct contact with blood and living tissues.

Evolution of mechanical valve designs significantly consists of valve geometry and improvement in hemodynamics characteristics. Recently available design provides good hemocompatibility, reduced tissue ingrowth and less thrombotic effect as compare to previous designs. Although due to high shear and stress in blood flow causes blood cells damage and clot formation which will leads to failure of prosthesis. Mechanical Heart valves are manufactured by biomaterials like graphite, pyrolytic carbon (PyC) PTFE, PET, titanium and thus these prosthesis present satisfactory strength, durability and longer lifespan in the body. To improve the wear resistance and strength of graphite these valves further coated with pyrolytic carbon by Chemical Vapor deposition (CVD). CVD is a lengthy process in this process thin layer of pyrolytic carbon deposited by the thermal reaction of gaseous mixture. After Coating samples characacterization have been done to validate coatings.

Keywords: Mechanical heart valve, Hemocompatibility, CVD, Pyrolytic carbon, Graphite, 3D CAD model, Antithrombotic, Hemodynamics, anticoagulation therapy.

Chapter 1 INTRODUCTION

Human heart is a pumping organ which supply oxygenated blood each and every tissue of the body. Heart consist of four chambers and each chamber has one-way flow valve that prevents back flow of blood from one chamber to other. Theses valves further divided into two main categories.

1. Two Atrioventricular valves → Tricuspid valve, Mitral Valve
2. Two Semilunar valves → Pulmonary valve, Aortic valve

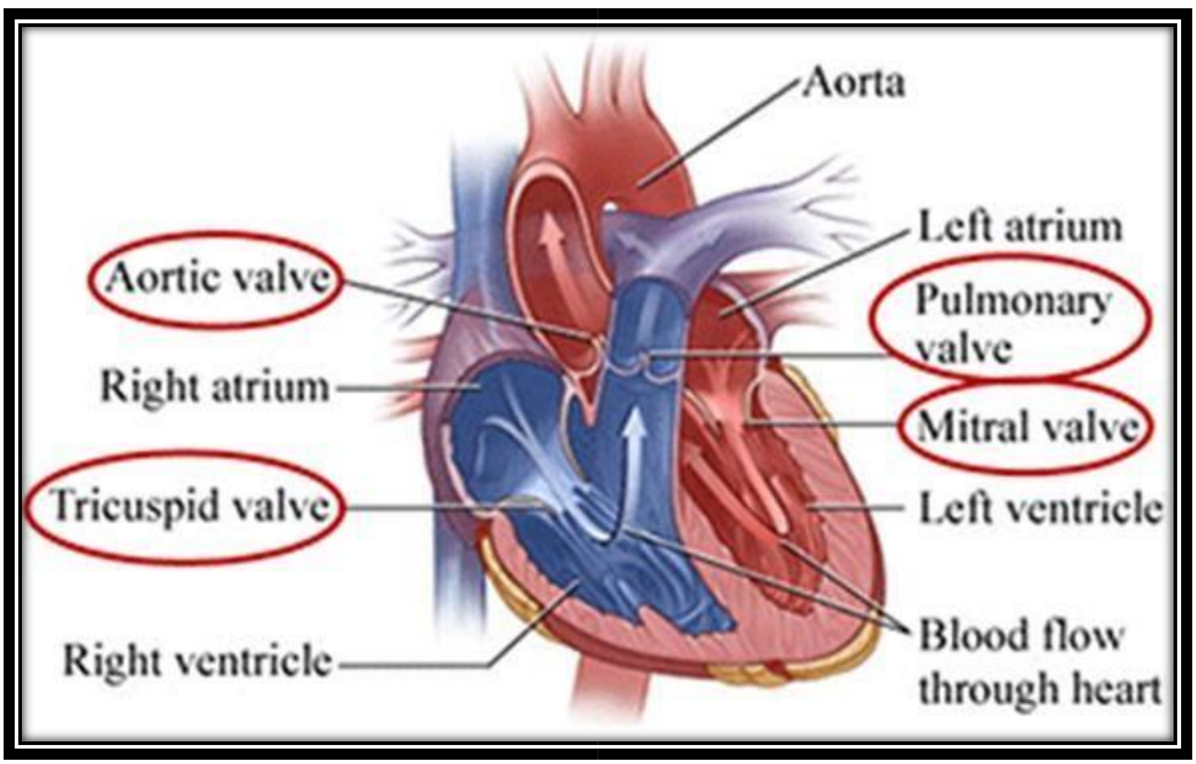


Figure 1Human Heart Valves

1.1 Function of heart valves and their disorders

The most common problems in heart valves are regurgitation, stenosis and atresia in these conditions blood continuously leaked through the valves and mixed from one chamber to other and it will ultimately lead to clot formation at the site of leakage, stroke, heart failure and death.

(Walther et al., 2000)The abnormality may occur in any valve but the most commonly replaced valve is mitral valve each year 40,000 mitral valves replaced. Heart valve prosthesis improves the quality of life when a person is suffering from any valvular disorder. (Nkomo et al., 2006)These valves open and close naturally due to gradient pressure of blood they have only one-way flow.
This thesis based on “the design development and fabrication of bileaflet mechanical mitral valve” as the mitral valve related surgical procedures are most common globally. The mitral valve present on the left side of heart and it is consisting of two cusps it will open when atrial pressure become greater than ventricular pressure and whole blood is flushed out from one chamber to other during each cardiac cycle.(Carapetis, Steer, Mulholland, & Weber, 2005)

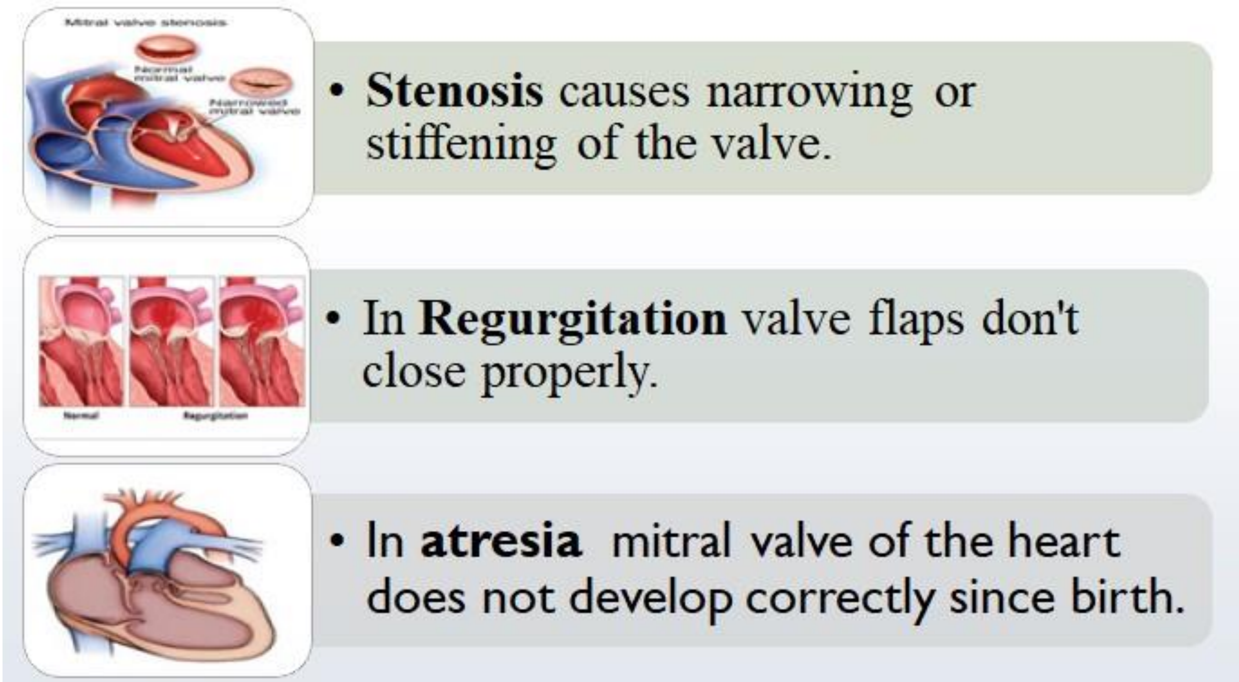


Figure 2Most common problems of mitral valves

1.2 Current heart valve prostheses

There are two types of prostheses currently present in the market. Mechanical and Biological heart valves. Mechanical Heart valves are totally made from man-made materials (commonly called biomaterials) they have long life span as compare to biological valves but they require anticoagulation therapy to prevent abnormalities in blood rheology. (Laczkovics et al., 2001)
Whereas biological valves are manufactured by the living tissues they exhibit good biocompatibility and no need of anticoagulant with these types of valves but they have short life

span. Mechanical valves consist of caged ball valves used in early ninety's and currently bileaflet mechanical valves are implanted which shows improved hemodynamics as compare to caged ball valves. (Vongpatanasin, Hillis, & Lange, 1996)

Multiple designs of mitral valves are made from different biomaterials worldwide and they have variety of important characteristics. Each model shows its unique characteristics on the basis of biocompatibility and their life span in host body. Efficiency of heart valve depends on its model design and material selection for fabrication. (Vongpatanasin et al., 1996)

1.3 Motivations and Objectives

Motivation behind this research is to fabricate mechanical heart valve for MDDC Pakistan. Heart replacement surgeries done in Pakistan but unfortunately there is not a single industry which is working on the heart valve manufacturing that's why surgeons import the different heart valves from foreign that's why it's too much costly. As these heart valves manufactured in our country it will not only reduce the cost also improves the health statistics of our country. And the objectives of this thesis are to design 3D CAD model through Solid Works software. Design reviewed by different simulation and animations on the solid works.

- Making feasibility and manufacturability of bileaflet mechanical mitral valve at Prosthetics and Implantology Lab SMME NUST.
- Selection of appropriate materials for fabrication which doesn't causes any toxic effect on the surroundings and provides good hemocompatibility and improved hemodynamics.
- Fabrication of mechanical valve prototype by machining tools.
- Coatings of Pyrolytic carbon to improve the surface smoothness of material and improvement of hemocompatibilty.

Chapter 2 LITERATURE REVIEW

Heart valve diseases are the most leading cause of death all over the world. More than 100 million people suffering from valvular heart disease worldwide and problem is growing day by day due to high prevalence of rheumatic heart disorders especially in emerging countries. Most of population effected by the degenerative valve diseases, (like regurgitation, stenosis) due to stiffness of leaflets. (Cannegieter, Rosendaal, & Briet, 1994) About 300 to 400000 prosthetic heart valves replaced each year and most of them are mitral replacements. In past 50 years 4 million heart valves replaced. It is life threatening treatment for most of the severe valvular defective patients. (Starr & Edwards, 1961) Mitral valve disease may lead to cause the negative impact on the cardiac output during each cycle of heart beat. Mitral valve defects comprise 2 million disorders caused by mitral regurgitation and 3 million by stenosis of mitral valve. Diseased valve repaired or replaced by the surgeon depend on the condition of patient. Although total replacement of valve takes time, because of different choices available in market and which one is perfect and compatible with body. Prosthetic valve shows tremendous role in saving the life of patient who is suffering from malfunctioning of heart valve. (Vitale et al., 1996)

There are two main types of heart valves present: biological and mechanical. The biological valves are made from living tissues whereas mechanical valves fabricated by the graphite and Dacron and other bio-materials which are biocompatible with living tissues and don’t cause any reaction in body. A mechanical valve shows more durability than biological valve but they are thrombogenic that’s why requiring anticoagulant therapy. However biological valves offer good hemodynamics performance and don’t require extensive anticoagulation therapy but they are less durable according to structural analysis and they remain functional only for five to ten years’ maximum. (Sharif, Pillai, & Caes, 1996)

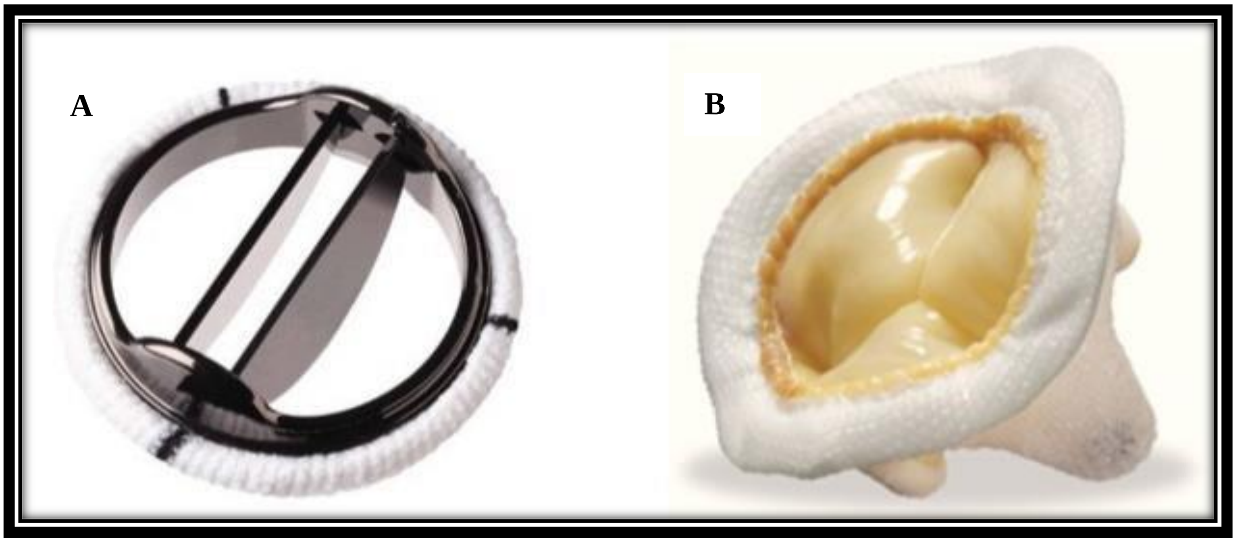


Figure 3Mitral heart valves A. Mechanical B. Biological

In this chapter mainly discussed mechanical mitral valves designs, models their fabrication and coating and mainly focus on the coating materials and hemodynamics performance with different coating materials. We also review antithrombotic effect in mechanical mitral valve. (Cai et al., 2013) The bileaflet heart valve mainly contains a hinge mechanism and two semicircular leaflets. These leaflets retained in orifice by the hinges. Bileaflet heart valves are more protected than other designs as the leaflets barely projected from the valve orifice, even in maximum opening position. Bileaflet heart valve provide good hemodynamics and very low blood cell damage during opening and closing of valve. The mechanical valve hemodynamics or flow rate mainly related with the design and structural mechanics. The design Structures disturb the loading and dynamics of heart valve and material properties determines the durability, biocompatibility and performance of valve in living environment. The flow stimulated by the valve geometry. The geometry components regulate the flow, stress and shear. In bileaflet valve hinges produce section of flow inertia, which leads to thrombosis and causes restrictions in motion of leaflets. (Rashtian et al., 1986)

Mechanical wear and material degradation is generally interconnected, as degradation stimulates the eviction of material due to wear. To improve the biocompatibility, fatigue, wear and tear problem scientists use different coatings on the base material. The external orifice and leaflets of currently available mechanical valves are fabricated by graphite and pyrolytic carbon (PyC).

The surface is coated with thin PyC up to 0.5-1μm thickness by using thermal chemical Vapor Deposition (CVD). Different coating materials use for MHV to decrease friction, wear, thrombogenicity and improve the blood flow across the valve. Whereas external cuff which is commonly called suturing ring made of Dacron materials covers the metals surface in few models there is a tungsten wire wrapped around the orifice to make it radiopaque and visible in fluoroscopy or other imaging procedures to check the localization of valve inside the heart. And suturing ring help the surgeon to suture valve on specific location. (Lund & Bland, 2006)

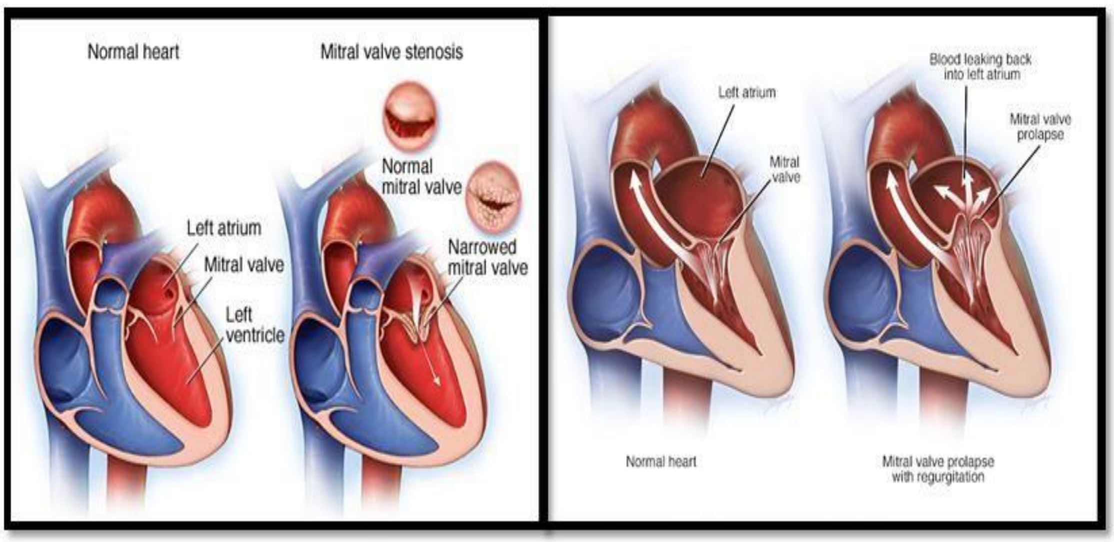


Figure 4 Mitral Valve Stenosis & Regurgitation

2.1Mitral valve Disorders

Mitral valve is located between the left atrium and left ventricle of the heart. Amongst the valvular diseases the most prevalent valvular disorders are mitral valve regurgitation and mitral valve stenosis and sometime congenital defects in mitral valve in which the flaps (leaflets) or valve orifice not properly developed at embryonic stage. (Nkomo et al., 2006) Most of the time people with age above 75 years suffering from mitral regurgitation or stenosis. Mitral valve regurgitation caused by the prolapse of mitral valve, in this situation leaflet bulge back into the left atrium during the contraction of heart muscles. Sometimes leaflets don't close properly which may lead to blood leakage into left atrium which may be fatal if not treated appropriately. Whereas in mitral valve stenosis the leaflets become stiff or thick and this condition causes abnormal valve opening and closing which may lead to disturb the blood flow between left atrium and ventricle. Treatment of these abnormalities depend upon the condition and severity sometimes mitral valve repair whereas in some cases total replacement of mitral valve. Complete valve replacement either biological valve or mechanical valve depend on the age and body compatibility of patient and lifespan of prosthesis being implanted. (Feng, Nakamura, Fujimoto, & Umezu, 2002)

2.2 Comparison of different Mechanical Valve prosthesis

Currently available mechanical heart valves are continuously progressing to achieve the optimal hemodynamics performance immense durability and less anticoagulant required. To avoid abnormal bleeding and clot formation after mechanical valve replacement anticoagulation therapy must needed but in certain amount because these long term anticoagulants causes other side effects as well. (Carapetis et al., 2005)

Consequently, different manufacturer trying to achieve the better hemocompatibility as compare to the residual models. Different materials and coatings are available to achieve this goal and made the prosthesis more compatible with blood and body tissues so patient require less anticoagulant therapy. (Camilleri et al., 2001)

The St. Jude mechanical heart valve represents tremendous hemodynamics, recognized durability and less thrombosis formation with low dosage of anticoagulants as compare to other mechanical valve models. (Puvimanasinghe et al., 2004) Whereas On-X mechanical valves show unique structural features like its internal orifice geometry exhibit low positive pressure drop and leaflet ears extended orifice ear inhibit the tissue growth which maintain the leaflet movement after few years of implantation. Tissue ingrowth around the prosthesis also major cause of valve failure because it will restrict the leaflet movement and leads to abnormal flow between the atria and ventricles. (Ling et al., 1997)

2.3 Different Models with Technical Specifications: [3]

2.3.1 The On-X Mechanical Heart Valve:

Valve Type: Bileaflet heart valve

Available Models: On-X mitral, On-X Aortic, and On-X Conform Swing Ring X valve.

Different Sizes and Dimensions: 23-33mm diameter in Mitral valve, 19-29mm Aortic and the Conform swing ring X valve available in flexible cuff which is adjustable according to annulus of multiple sizes.

Orifice Ring: Orifice made of pure Pyrolytic carbon (On-X carbon) with pyrolytic carbon coating on the surface.

Leaflets: On-X carbon with Pyrolytic carbon coating 20% tungsten to make it radiopaque.

Suturing Ring: Teflon or (PTFE) polytetrafluoroethylene, is used for making the suturing ring. Thin titanium ring placed inside the Teflon to provide structural stability.

Scientific Features: manufactured and sold by MCRI (Medical Carbon Research Institute). (Fig. 3) Entire Series designed for supra-annular sewing ring settlement with intra-annular frame. [51].

Physical Attributes: improved blood flow at the center of valve. MCRI used pure carbon no any alloy added to the base material. The Pyrolytic carbon (PyC) is named On-X carbon by the manufacturer. The On-X carbon increases the material durability and robustness it also reduces thrombogenicity. (Laczkovics et al., 2001)

Radiographic Information: to acquire X-ray visibility the leaflets imbued with 20% tungsten. Titanium another radiopaque material is used inside the suturing ring for x-ray visibility of occlude ring.

Special Aspects: The On-X reported a unique design with improved mechanical and thrombogenic properties as compare to the other designs. Additional significant features of On-X valves comprise the butterfly shape hinges, extended and flared inlet of orifice, delicate and thin leaflets which upgrade the hemodynamics the extended orifice decreases the opening and closing angel of leaflet therefore no regurgitation occurs at the leaflets and impact velocity during closure of valve also reduced. The unique flare design and leaflet guards offers physical obstacle to guard the tissue invasion during leaflet motion. (Birnbaum et al., 2000)

FDA Approved: the clinical trials of On-X valves initiated in 1996 in Germany.

The On-X received approval from market in 2001 for aortic prosthesis and in 2002 for mitral and Conform-X valves. (Mirkhani, Davoudi, Hanafizadeh, Javidi, & Saffarian, 2016)

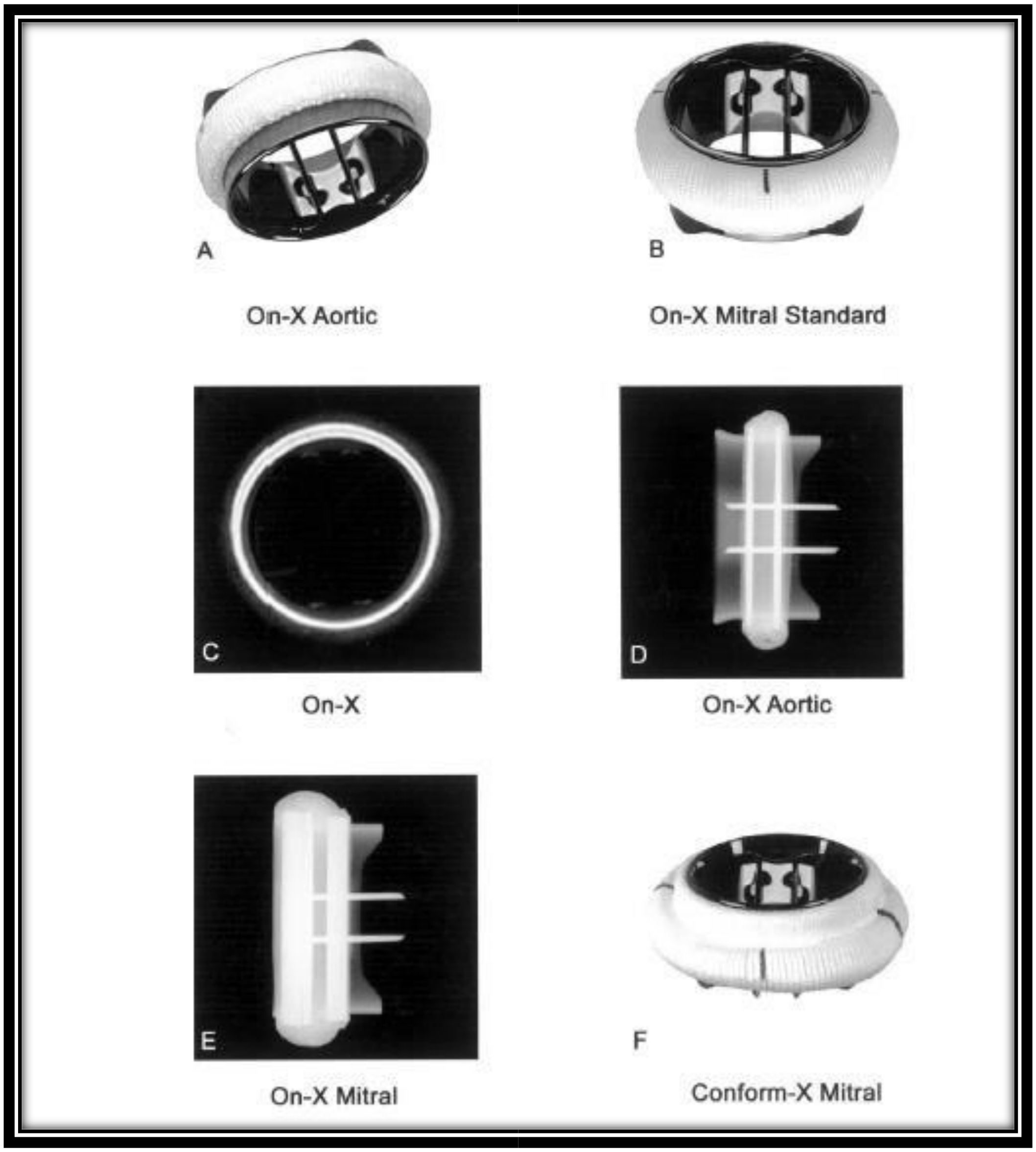


Figure 5 Different models of On-X mechanical heart valves

2.3.2 The St. Jude Medical (SJM) mechanical Heart valve:

Valve Type: Bileaflet mechanical heart valves.

Available models: St. Jude Medical provides multiple models mainly Aortic, Mitral and tricuspid valve. SJM Expanded series consist of SJM Master Series, SJM reagent series and SJM Silzone coated models.

Different Sizes and Dimensions: Mitral valve with diameter of 14.7-26mm, [fig 4] whereas SJM regent and master series available in 17-31 aortic and mitral valves.(Baudet et al., 1995)

Orifice Ring: the occlude ring or orifice made of graphite with PyC coatings.

Leaflets: Graphite substrate used for leaflets then PyC coating and impregnated with 10% tungsten by weight.

Suturing Ring: PET (Polyethylene terephthalate) commonly called Dacron used as suturing ring and it is coated with metallic silver. (Camilleri et al., 2001)

Scientific Features: SJM (St. paul, MN USA) are the manufacturer of all models and sold by the same company. In 1977 SJM bileaflet valves were introduced in market. While HP and Expanded series were introduced in 1996, SJM Silzone was introduced in 1997 and the Master series in 1999.

Physical Attributes: blood flow across all the SJM mechanical valve models is symmetric and approximately no turbulent. The mean pressure gradient in mitral valve is from 1.4 to 7 mmHg, whereas regurgitation volume from 4.3 to 6.4cm3/stroke at mitral position. The configuration of leaflet hinges is butterfly shaped depression with pivot guards which restrict the leaflet motion in certain angels.

Radiographic Information: the outer ring of valve is manufactured by PyC which is X-ray visible in standard model. Leaflets are coated with PyC impregnated tungsten by 10% to make them radiolucent. (Ribeiro et al., 1986)

FDA Approved: All SJM mechanical heart valves models are FDA approved except SJM Silzone. As Silzone coatings models reported different clinical problems and leakage that's why discontinued in January 2000.

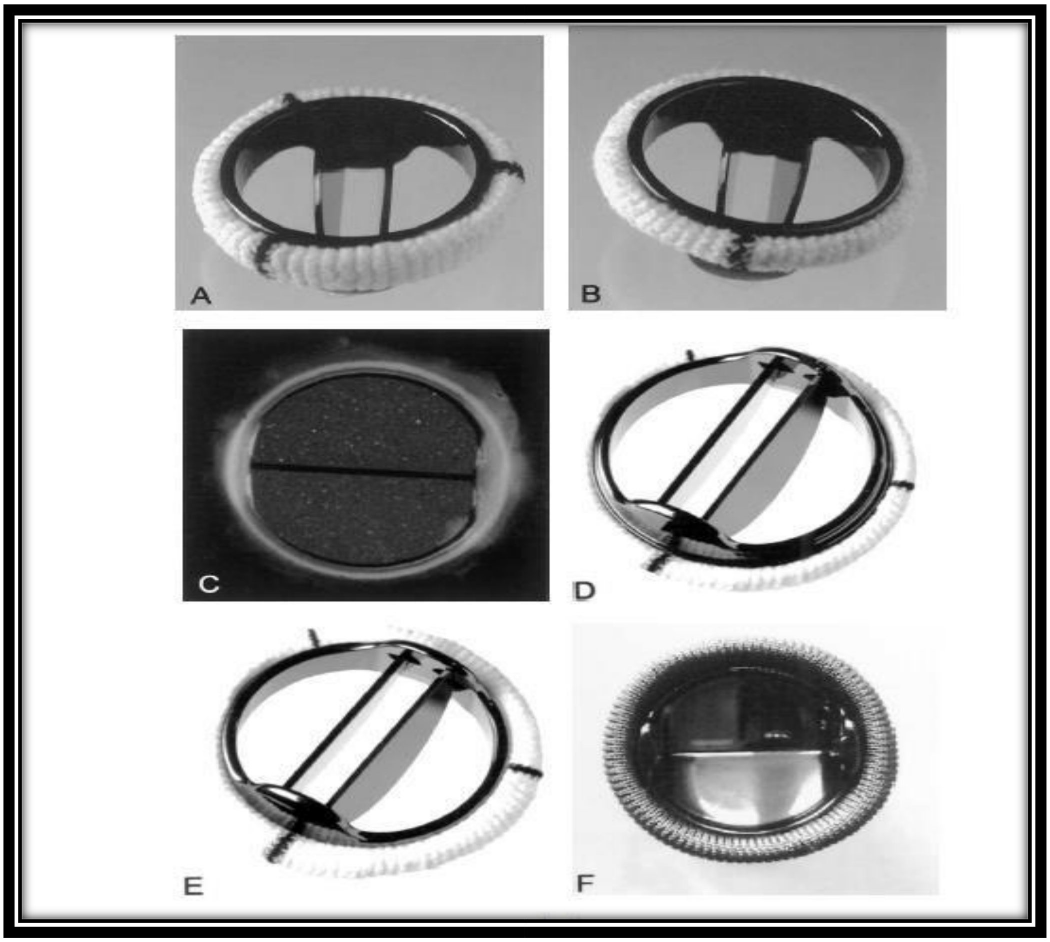


Figure 6 Different models of St. Jude mechanical heart valves

2.3.3 The Advancing the Standard (ATS) Mechanical Heart valve:

Valve Type: bileaflet mechanical valves, Aortic and mitral positions.

Available models: ATS standard series open pivot heart valves and ATS advance performance heart valve series.

Different Sizes and Dimensions: ATS standard series dimension 19-33mm mitral and 19-31mm for aortic position. ATS advance performance series dimension 16-20 mitral and 16-28mm aortic. [42]

Orifice Ring: Occlude ring made of pyrolytic carbon. (Sharif et al., 1996)

Leaflets: graphite substrate with PyC coating and 20% tungsten impregnated in coating.

Suturing Ring: Suturing ring is made by Dacron **(**PET) double velour, which controls the tissue ingrowth. To increase the flexibility of suturing cuff the Dacron filled by Teflon (PTFE). Titanium ring also inserted in Dacron for rotation of cuff.

Scientific Features: manufactured and Sold by the ATS. Two series are available in market Standard series and Advance performance series for the intra-annular and supra-annular positions. (Krian, 1998)

Physical Attributes: ATS medical provide open pivot valves two different series Standard and AP both valves have central blood flow.

Radiographic Information: Due to high contents of tungsten in leaflets coating ATS valve show high X-ray visibility. The titanium rotating ring is also radiopaque which make outer ring radiolucent.

FDA Approved: In May 1992 first clinical trial of ATS valve was approved and then in October 2000 ATS valves received approval by FDA. (Alemu et al., 2010)

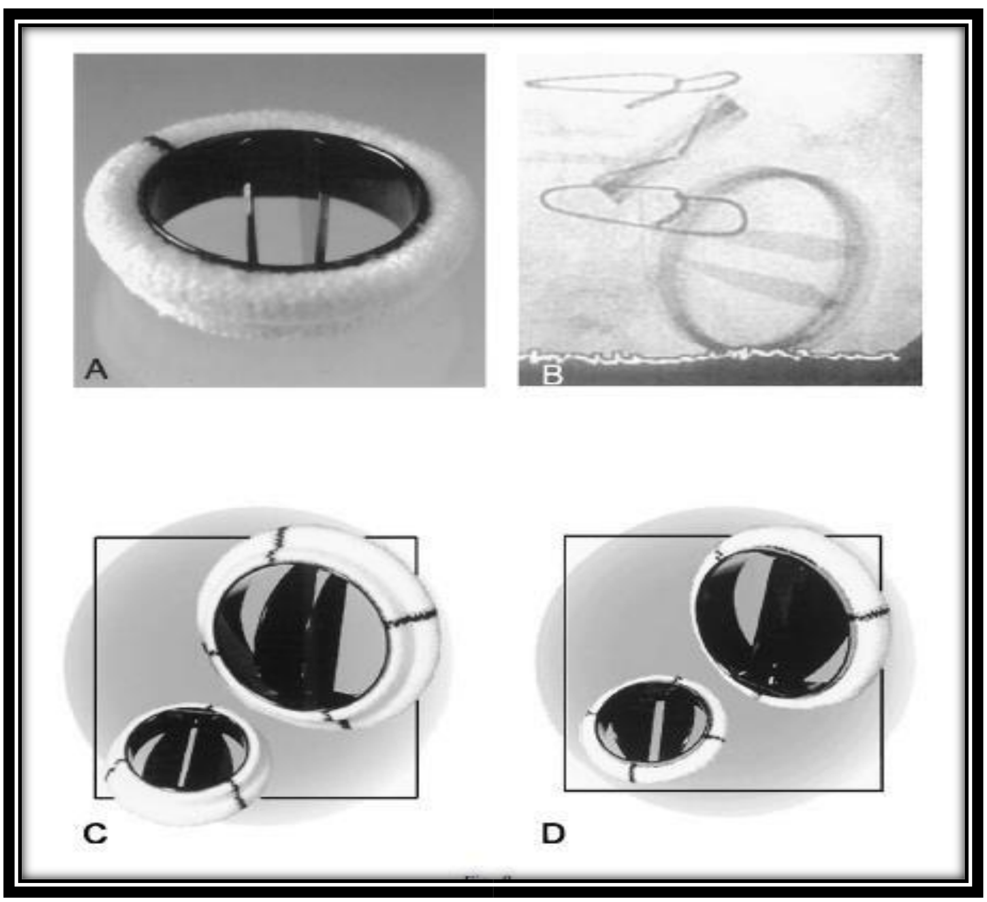


Figure 7Different models of ATS mechanical heart valves

2.3.4 The Medtronic Hall Mechanical Heart Valve:

Valve Type: Both aortic and mitral positions Single leaflet and bileaflet.

Available models:

Different Sizes and Dimensions: Medtronic valves available in diameter of 20-29mm for aortic and 23-31mm for mitral position.

Orifice Ring: Titanium is used by Medtronic Hall for manufacturing of outer ring.

Leaflets: made of pyrolytic carbon (PyC)

Suturing Ring: the suturing ring is made up of knitted Teflon and Dacron material.

Scientific Features: All Medtronic valves are manufactured and sold by Medtronic (USA). (Gott, Alejo, & Cameron, 2003)

Physical Attributes: Medtronic mechanical heart valve models "encourages" central blood flow across the large orifice to annulus ratio and transvalvular gradients are low comparatively. The closed angel for mitral valve is 0 whereas opening angel is 70. (Nitter-Hauge, Abdelnoor, & Svennevig, 1996)

Radiographic Information: the housing ring is made of titanium that's why radiopaque whereas disc or leaflets are made of PyC which is also radiolucent.

FDA Approved: The Medtronic Heart valves are FDA approved. (Butchart, Li, Payne, Buchan, & Grunkemeier, 2001)

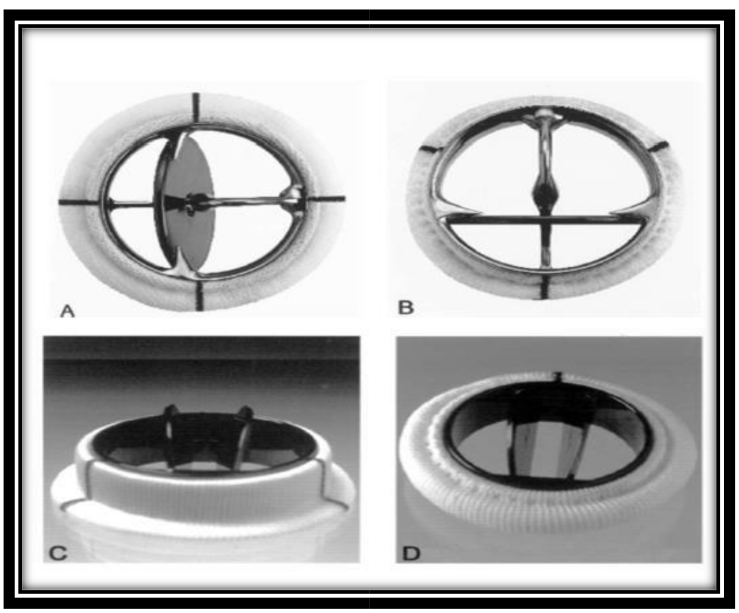


Figure 8 Different models of Medtronic mechanical heart valves

2.4 Discussion

The main advantage of Mechanical Heart Valves as compare to biological or tissue valve is its long life and improved structural reliability. The modern Mechanical Bileaflet Heart valves provide long life with good hemodynamics and biocompatibility with body tissues and blood as well. The structure and unique design of these valves improve the blood flow across the valve and less damage to blood cells during each cardiac cycle. This review paper mainly focused on the materials used for the fabrication of different heart valves and the coating techniques along with the material being coated and its hemocompatibilty. (Yoganathan, He, & Casey Jones, 2004)

The above discussed four different companies of heart Valves are differentiated according to the material being used for the fabrication of orifice and leaflets plus their suturing ring and coatings. The material used in suturing ring is mostly Dacron and Teflon and both materials are antiabsorbent, biocompatible, strong and nonflexible. It surrounds the orifice and provides the site for suturing the heart valve with surrounding tissues. According to the meta-analysis and biological evaluation of Dacron and Teflon proved that there is no strong evidence of priority given to one material over the other both exhibit tremendous performance in different cardiovascular applications and vascular grafts. (Chambers & Ely, 1998)

These heart valves discussed in this review are coated by (CVD) Chemical Vapor Deposition. CVD is the process by which thin films or coatings can be done. In CVD the substrate is placed into the vacuum glass tube and exposed with two or more gases which react with the substrate and produce thin coat onto the substrate according to given conditions. The difference between them is material being coat, coating thickness and precursor gases being used in the reaction. In some cases the CVD equipment and its parameters may be different. (Hauert, 2003)

2.5 Chemical Vapor Deposition (CVD) Method

CVD is the most commonly used technology and in materials sciences it plays vital roles for surface modification and coating of different materials onto the substrate one or more layers of materials coated by this technique. The extensive variety of materials and composites are prepared and deposited onto the substrates by CVD. In the simplest materialization, CVD includes flowing of gases into the vacuum chamber consist of one or multiple preheated substrates, and as a result of chemical reaction thin film deposition on the surface of substrate. (Palatianos et al., 2007)

During this process large amount of heat produced and chemical reaction occur into the vacuum chamber by the precursor gases mixtures and excessive by products are eliminated from the chamber along with the non-reactant gases by proper exhaust system to prevent the contamination into the reaction chamber. The temperature is from 400-1200°C and pressure maintained between 1-5 torr throughout the reaction in case of pyrolytic carbon coating onto graphite substrate. (Hassler, 2012)

CVD has numerous advantages one of them most important advantage is its uniform coating techniques during this process coating done uniformly throughout the substrate and on each side of substrate coating thickness will be same no any difference in thickness present as result of the reaction. Another important factor of this technology is, due to large variation of materials deposition, it is deposited with high rate of purity in the deposited material because during this process impurities removed from the substrates by using precursor gases. And the deposition rate of CVD method is high as compare with other methods like Physical Vapor Deposition (PVD) or magnetron sputtering.

CVD technology categorized according to the following aspects:

I. Substrate precursor gas used during reaction
II. Material applications
III. Equipment used or process (either temperature or pressure based)

Characteristics of Coatings

Typically, the CVD coating comprises:

- Fine grain sizes.
- Resistant.
- Purity.
- Improved strength.
- Surface smoothness.

Materials used for fabrication and coatings of bileaflet Heart Valves:

Among these four different heart valves only Medtronic contain different material in the orifice. The external orifice of Medtronic is fabricated by the titanium due to its strength and ease of fabrication they use titanium and the leaflets of Medtronic manufactured by the pyrolytic carbon. Because pyrolytic carbon represents good hemocompatibility as compare to other biomaterials and the leaflets have maximum contact with blood that's why it will not causes any reaction. And the suturing ring of Medtronic also made from knitted Teflon and Dacron both so its unique feature of Medtronic models over other heart valve models. The orifice doesn't need further coatings but the leaflets further coated with pyrolytic carbon to improve the strength and surface smoothness which will increase the hemocompatibility.(Bajpai & Singh, 2011)

The ATS heart valves models fabricated by using graphite and pyrolytic carbon. Orifice made from graphite and leaflets from pyrolytic carbon and further coated by CVD to improve material hemocompatibility and strength. Radiopacity achieve by adding tungsten in coatings. The suturing ring made of Dacron material. (Dumont et al., 2007)

St Jude manufactured heart valves used graphite for fabrication of orifice and leaflets and further coated with pyrolytic carbon and 10% tungsten is used in coatings for radiopacity. St Jude is considered to be more biocompatible as compare to the Medtronic and Ats heart valves models due to its Pyrolytic coatings and graphite substrate they use 10% tungsten because it will only provide radiopacity so there is no need to add greater percentage of tungsten material because ultimately it will reduce the hemocompatibility of valves. Although the density of graphite St Jude manufacturer used shows less strength and require greater warfarin with these models. (Ely et al., 1998)

On-X heart valves by Cryolife USA are on top priority valve due to its unique design characteristics and density of graphite they using for the fabrication of heart valve models. The On-X heart valve is only mechanical valve model which is clinically proven that they require less anticoagulation as compared to other available models. During prospective clinical trials, On-X heart valves patients with reduce dose of warfarin (anticoagulant) and causes less harmful effects when come in contact with blood. (Wu, Hwang, & Lin, 2002). The Cryolife is the only industry which manufactures On-X mechanical heart valves which are made of pure Pyrolytic Carbon. Its innovative design and progressive material increase the life span of prosthetics in human body without causing harmful effect on the surrounding tissue and blood cells. Surgeons prefer On-X heart valves because of its long life span with good hemocompatibilty and patients with On-X heart valve require less warfarin and short term anticoagulation therapy after implantation. (Schroeter, Kratochvil, & de Oliveira Gomes, 2006).

Significant improvement has been made in manufacturing, design and materials of mechanical heart valves over last 50 years. Although these improvements done after different clinical trials and testing of biomaterials according to the application and media in which implant placed.

Initially material's biocompatibility testing, surface smoothness, hemolytic activity and strength have been checked according to ISO standards. (Wu et al., 2002) Currently available mechanical heart valves cause less toxic effects in blood and shows good biocompatibility with surround heart tissues. The ratio of biocompatibility and hemocompatibility may vary in the above discussed four types of valves based on their biomaterials and coatings. (Tong et al., 2004) On-X by Cryolife is the only commercially available mechanical heart valve which is made of pure pyrolytic carbon and shows less anticoagulation therapy with improved hemodynamics. Pyrolytic carbon exhibit high ratio of biocompatibility and characterize remarkable results in the clinical trials. Scientists and researchers working further improvement of mechanical valves and ultimately, it is feasible that one day they will produce a mechanical heart valve that is free from anticoagulation therapy and patient don't need lifelong anticoagulants. (Camilleri et al., 2001)

Chapter 3 MATERIAL AND METHODS

The first and foremost important task of this research was to design 3D CAD model of bileaflet mechanical mitral valve. For this approach Solid works 2016 software toolkits used. The design inspiration was taken from the literature and reviews taken from the top most cardiologist of Pakistan also discussed this project with Executive director of Rawalpindi Institute of Cardiology. He also suggested to go with the commercially available top priority mechanical heart valve OnX by Cryolife USA. On-X is the only available heart valve which contain pure pyrolytic Carbon and required minimal anticoagulation therapy. Design further approved from the Clinical Center of American heart Poland. After completing the design review and approval 3D model designed by Solid Works. The approach of this thesis is to manufacture a prototype which provide good hemodynamics and require less anticoagulation therapy as well as does not causes toxic effect in human body. Selection of appropriate material, Fabrication and biocompatible coatings are the main challenges faced during the manufacturing of prototype.

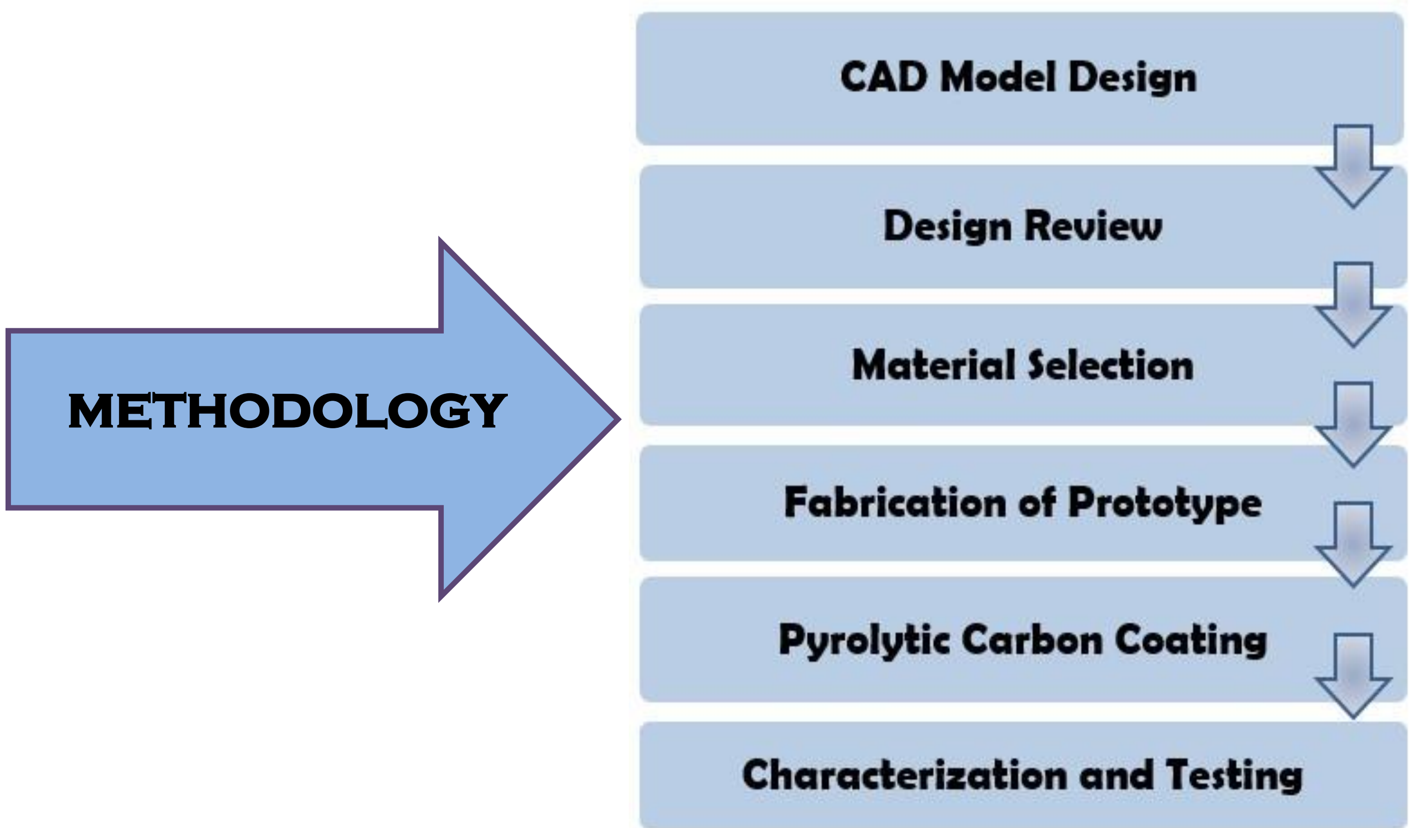


Figure 9 Methodology

3.1 Material Selection

3.1.1 Material Selection Criteria

- Material must be biocompatible.
- Smooth surfaces and non-porous.
- Good hemocompatiblilty and hemodynamics.
- Antithrombotic.

3.1.2 Materials under Consideration

There are different biomaterials used for the fabrication of mechanical heart valves in previous eras. Most of them are Aluminum and its alloys and graphite with different grades and densities. In this research Aluminum and graphite mainly considered for the Fabrication of mitral valve depend upon their pros and cons.

Aluminum	Graphite
Aluminum and its alloys also widely used in biomedical applications.	Graphite and Pyrolytic Carbon considered as ideal material for fabrication of heart valve.
It provides strength and ease of fabrication.	It provides smooth and non-porous surface with good hemodynamics.
It provides smooth surface and good hemodynamics.	It causes less thrombosis.
But it causes toxicity and thrombosis in long term applications.	It exhibits antihemolytic activity when come in contact with blood.
Aluminum oxidize quickly in moist environment.	But its challenging to fabricate graphite through machining due to brittle nature
Leaching is one of major complication with aluminum based implants.	Graphite is little bit porous but the porosity of graphite overcome by Pyrolytic Carbon Coating

Figure 10 Materials under consideration

According to literature graphite is the most suitable material for the fabrication of mitral valve because it shows excellent hemocompatibility when in come in direct contact with blood. Although fabrication through machining tools is difficult due to brittle nature of graphite. There are multiple pros and few cons of graphite given in the table 2.

PROS	CONS
Graphite provide smooth surface with good hemodynamics.	Graphite is difficult to fabricate.
It exhibits excellent hemocompatibility.	It is brittle material.
Graphite is free from leaching, wear and tear issue.	But strength improved with pyrolytic carbon coating.
Less thrombosis occurs in graphite coated with pyrolytic carbon.	Causes much pollution machining tools.

Figure 11 Pros and Cons of Graphite

3.1.3 Short listed Material

After the extensive literature review and experts advise graphite is shortlisted for the fabrication of mitral valve prototype. Graphite with **1.95g/cm3** density is most suitable for cardiovascular implants fabrication. Additional graphite is coated with pyrolytic carbon by Chemical Vapor Deposition (CVD) method. CVD improve the surface smoothness and reduce the pores present in graphite as a result blood compatibility improved.

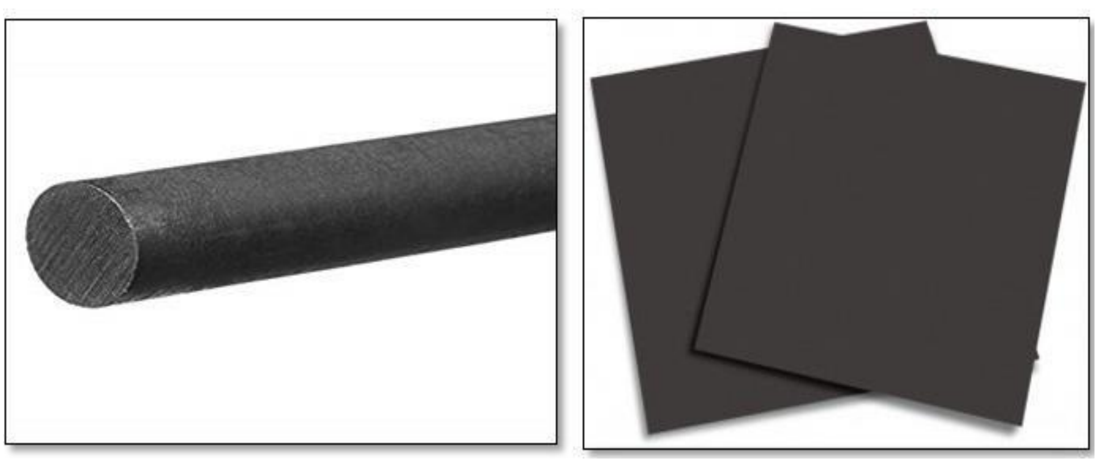


Figure 12 Graphite rod & Sheets

Two different forms of graphite with same density purchased from market for the fabrication of mitral heart valve prototype fabrication. As discussed in earlier chapters' mechanical valve consist of multiple parts like orifice leaflets and suturing cuff so here rod is used for the fabrication of orifice or commonly called outer ring and leaflets which fixed into the orifice small thin structures made from the graphite sheets and then they assemble into one part.

After selection of appropriate material fabrication started by using machining tools. And machining or fabrication of prototype from graphite is done by the 5 Axis CNC (Computer Numeric Control) machine. For CNC fabrication 3D CAD model is designed by using software.

3.2 CAD Model Designing

3D CAD model of mitral valve prepared by Solid Works 2017. Although its complicated design but successfully designed through the different tool kits of Solid works. Model also reviewed from different animations and simulations either working properly or not. In software model leaflet movement is smooth and maximum degree of motion like 0-90-degree motion of leaflet present in this model.

Few images of solid works models are given below

Figure 13 3D CAD model of mitral Valve orifice

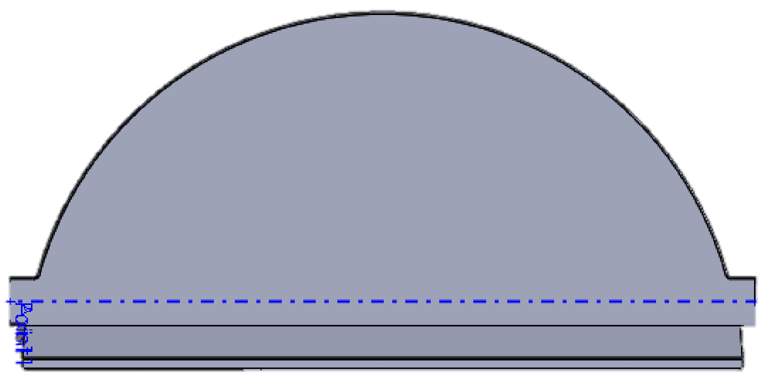


Figure 14 3D CAD Model of Mitral Valve Leaflet

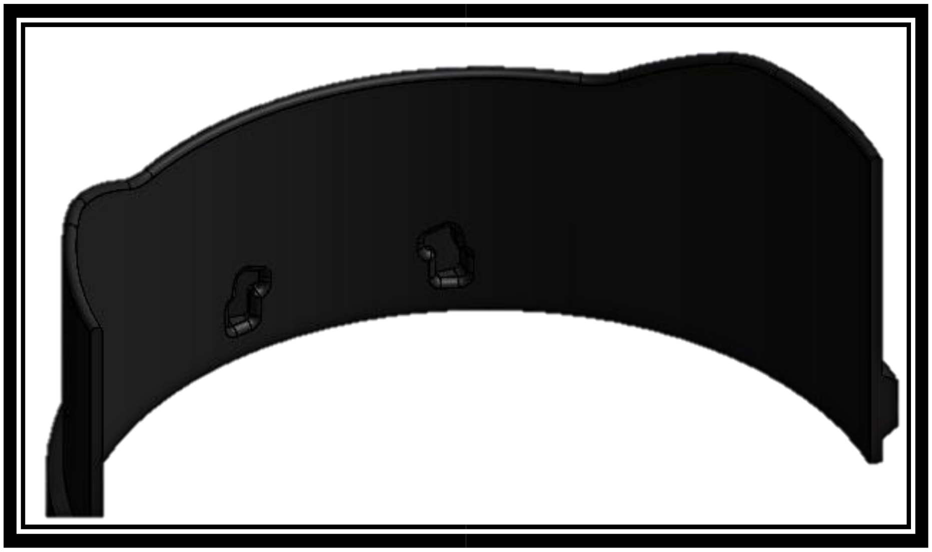


Figure 15 3D CAD Model cut view of orifice

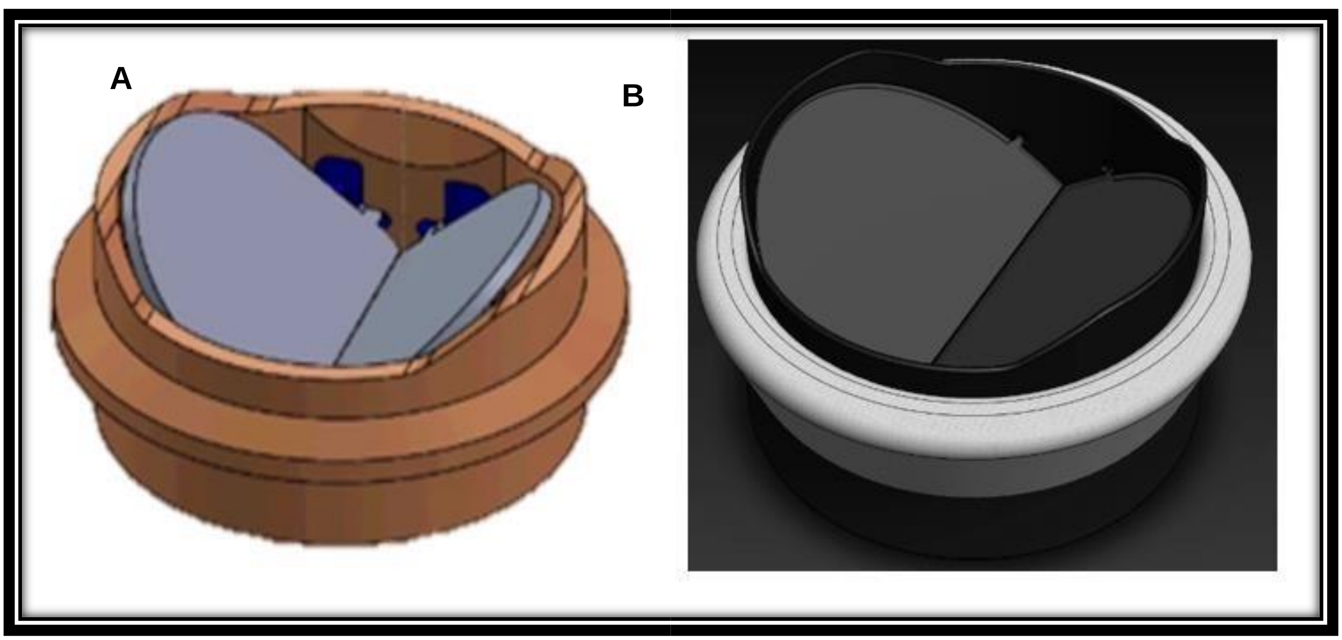


Figure 16 3D CAD model (A) without leaflet and (B) with leaflet

3.2.1 Design Review and Selection

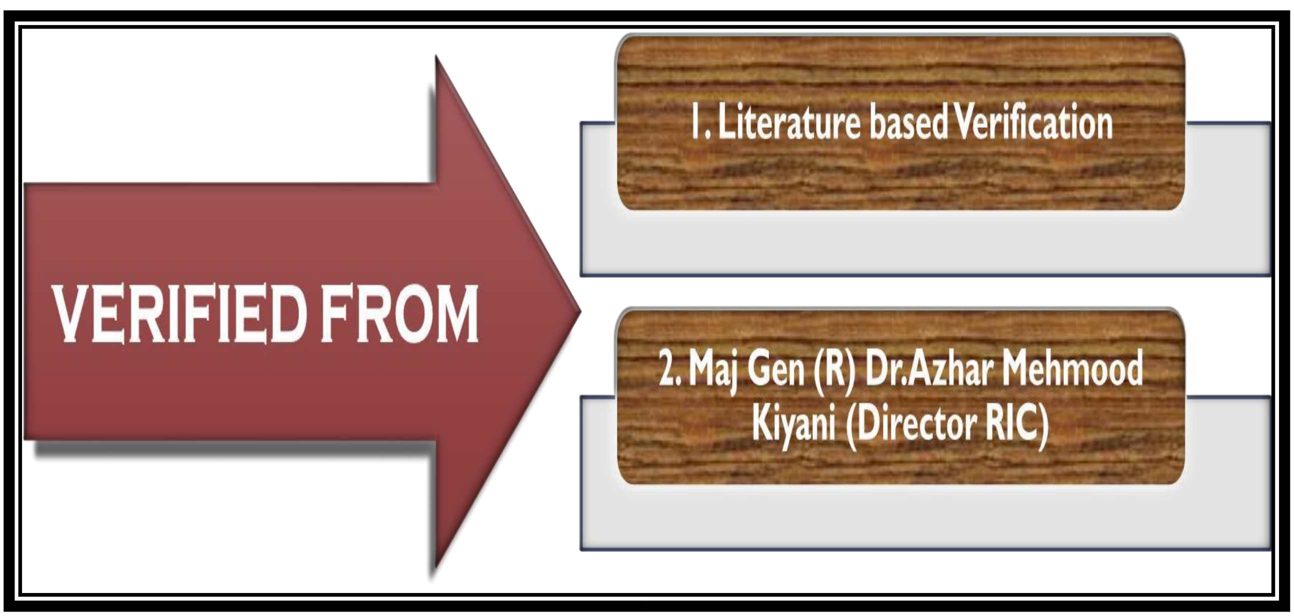
- Collaborations was established for prototype design review with (RIC)Rawalpindi Institute of Cardiology.
- 3D design inspiration was taken from On-X Heart Valve by Cryolife USA.
- On-X design was replicated according to our lab resources.
- On-X is the only commercially available heart valve in which pure Pyrolytic Carbon is present.

Some of the advantages incorporated in our prototype designing which are also present in On-X valve.

I. Long leaflet ear which restrict tissue growth around orifice & leaflet.

II. Maximum degree of leaflet movement.

III. Hinge cavity provide smooth blood flow with minimal clot formation.



3.3 Fabrication

Mitral valve prototype was fabricated by the 5 Axis CNC machine using graphite material.

- Orifice and leaflets are fabricated by using 5 Axis CNC (Computer Numeric Control) machine.
- DELCAM is used to communicate the CAD model with machine.
- CAD file imported into the software of machine then by using multiple cutting and grinding tools final prototype prepared.

Multiple cutting and gridding tools used during the manufacturing of graphite prototype as it is brittle material that's why it is the most challenging phase of project. After so many trials final prototype prepared by the CNC machine.

Figure 17 5-Axis CNC Machine

3.3.1 Specifications of CNC Machine

CNC machine is completely computerized machine which take command from computer generated codes and work on the basis of those commands. In this project 5 axis CNC used for fabrication, 5 axis means machining tools move into five different directions and due to its multi directional tools complex geometries manufacturing can be done easily.

YCM young Chin 5 axis CNC used for the fabrication of mechanical mitral valve prototypes. Specifications of the machines given below.

		TC15(6")	TC15(8")	TC25A(10")
Swing Over Bed	mm	ø450	ø450	ø590
Swing Over Carriage	mm	ø310	ø310	ø440
Max. Turning Diameter	mm	ø250	ø250	ø500
X/Z Axis Travel	mm	150/500	150/500	260/500
Spindle Motor	kW	11	11	15
Spindle Nose		A2-5	A2-6	A2-8
Hole Through(spindle/draw bar)	mm	ø56/ø45	ø62/ø52	ø90/ø78
Spindle Speed (std.)	rpm	50~6000	45~4000	30~3500 (HS)
Spindle Speed (opt.)	rpm	L: 50~288~1535 H: 195~1125~6000	L: 45~192~1025 H: 175~750~4000	30~2100 (HT)
Tail Stock Quill Taper		MT-4	MT-4	MT-5 (opt.)
Turret Capacity (opt.)		8/12T	8/12T	12 (8)T
Machine Weight	kg	3230	3230	4590

Figure 19 Specification of CNC Machine

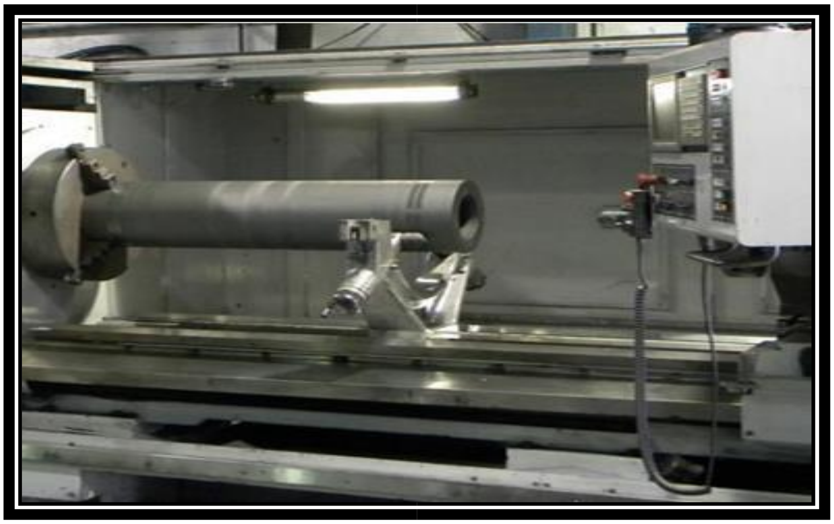


Figure 20 Machining Process of graphite

3.3.2 Fabrication Steps

Mitral valve prototype was prepared by 5 axis CNC using graphite rod and sheets. Complete step by step diagram given bellow.

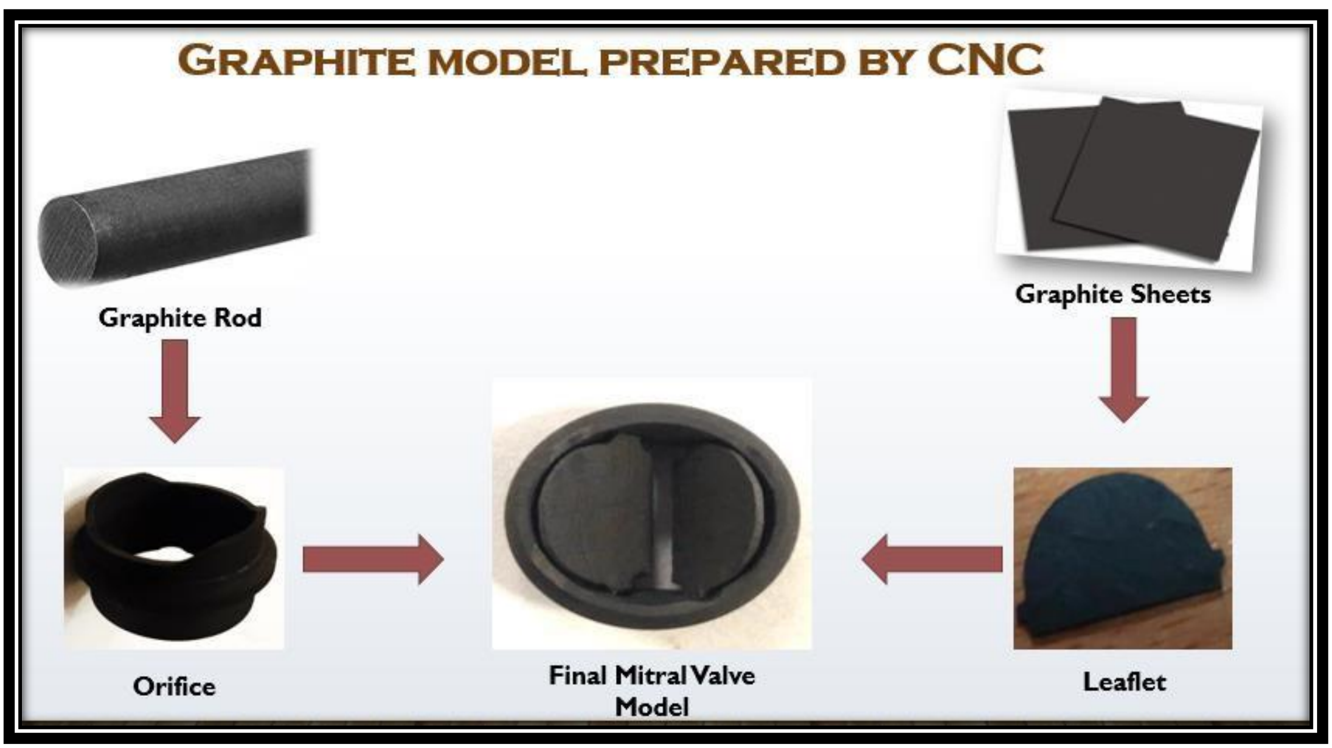


Figure 21 Fabrication steps of Model and Assembly

After fabrication of prototype leaflets assembled into the butterfly shaped hinges engraved in orifice and theses hinges proved smooth blood flow across the orifice and maximum degree of freedom to the leaflets. Leaflets open and close during each cardiac cycle and they provide oneway flow of blood and maximum degree of movement prevent mixing of blood between two chambers. As leaflet open maximum angle is **90**°and maximum blood flow from one chamber to other and in closed position **0**° angle means no blood flow across the leaflets.

3.4 Coating

Coating is the most important task of the research. After manufacturing the whole prototype coatings performed on graphite models for surface smoothness and improvement of hemocompatibility. The coating on graphite was done by the Chemical Vapor Deposition (CVD) method. CVD is a type of chemical reaction in which substrate placed under the closed vacuum chamber and by introducing two or more gaseous mixtures chemical reaction done between the substrate and gases and a thin layer of material deposited onto the surface of substrate. It is very complex and dangerous method because temperature is very high in the chamber and gaseous mixture pressure also maintained throughout the reaction if any mishandling during reaction may causes blast or any other accident which is harmful for the lab environment.

3.4.1 Coating Parameters

The important parameters used during the CVD process are

- Coating thickness---- 0.5µm.
- Deposition rate---- 0.01µ/min.
- Temperature 1000°C. (1)
- Pressure must be between 1-5 torr.
- Flow rate of Argon 999-1000 ------ 50sccm.
- Flow rate of CH_4 & H 1000 ------ 20sccm.
- sccm "standard cubic centimetres per minute"

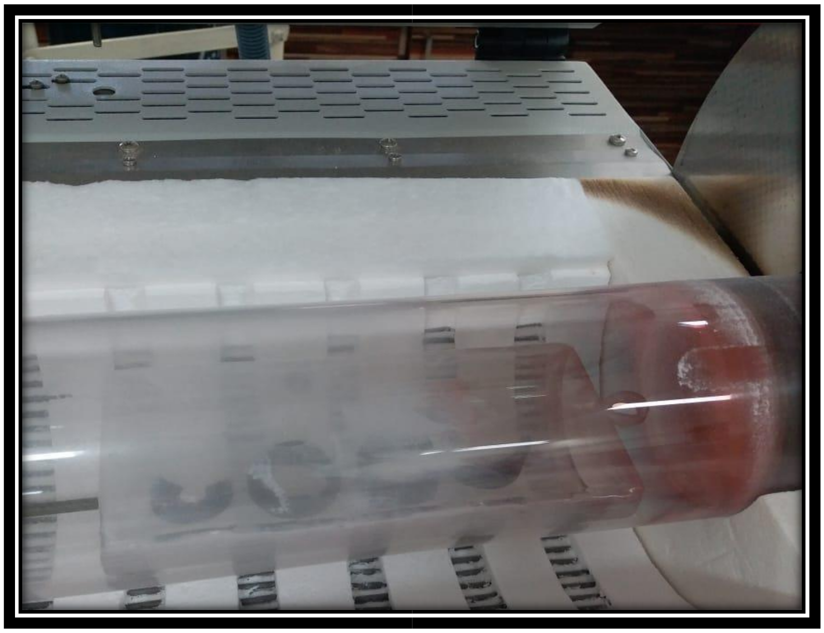


Figure 22 CVD Reaction Chamber

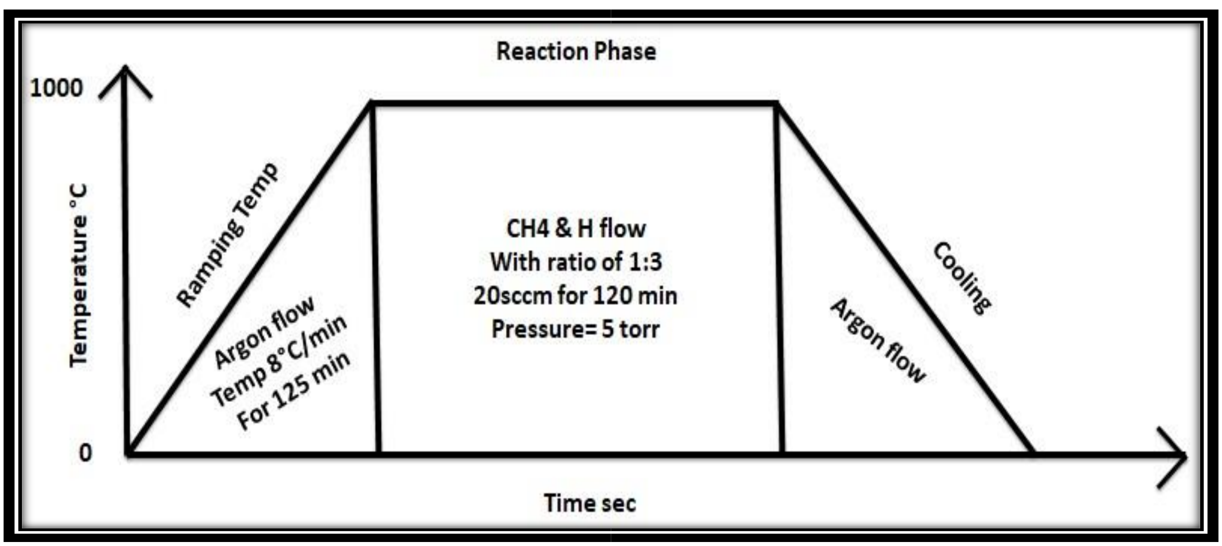


Figure 23 CVD Reaction Phases

Figure 24 CVD Equipment Processing Unit

Figure 25 CVD Equipment Control Unit

3.4.2 Coating process

Pyrolytic carbon coating was done by CVD method in energy system lab of USP-CASEN at NUST. The equipment used for the coating was "**Protherm by NanoVak**" company. This equipment used for the temperature and pressure based coatings. For the mitral valve coating thermal based technique is preferred because it will reduce the reaction time and the graphite surface preparation for coating and contamination removed by using high temperature. The temperature ranges for the chemical reaction set between **800-1000°C.**There are three gases used in the reaction, hydrogen(H), argon(Ar) and methane (CH_4). Ar is used as carrier gas during the chemical reaction. In the first phase of reaction normally this phase is called ramping temperature phase. During ramping phase, the surface of substrate (graphite) is prepared for coatings and the oxygen particles either present on the surface also removed in this phase. The temperature was raised 8°C/min and continuously Ar flow into the reaction chamber and this phase was done in approx. 120-140min. After ramping phase when temperature reached to 1000°C Ar flow stopped. During this phase pressure maintained between 1-5 torr by adjusting the throttle valve. Throttle valve in CVD equipment considered as safety valve by open and close of this valve pressure maintained into the reaction chamber.

When temperature reached up to 1000°C ramping phase is finished and reaction phase started. In reaction phase Ar flow was stopped only $CH_{4,}$ H gas flow into the chamber and their ratio was 1:3 with 20sccm and pressure maintained between 1-5torr this phase consist of the coating thickness in mitral valve coating thickness is 0.5µm so this phase finished in approx. 60-80min. coatings was done during this phase substrate react with the gaseous mixture in presence of high temperature and pressure and as a result thin layer coated onto the graphite which is called pyrolytic carbon because pyrolytic carbon is similar chemical compound only difference of covalent bonding. In reaction phase due to gaseous reaction and temperature the covalent bond squeezed and as a result pyrolytic carbon formed. After coating pores reduced and a shining grey layers produced on the material. After completion of reaction the substrate cooled down at room temperature and this phase is called cooling and during this phase Ar is continuously flow into the chamber with flow rate of 10-20sccm to avoid contamination into the reaction chamber and exhausted out the remaining particles from the reaction chamber. Finally, graphite was coated with pyrolytic carbon and further its coating analysis done by Characterization of materials before and after coating by SEM, FTIR and XRD.

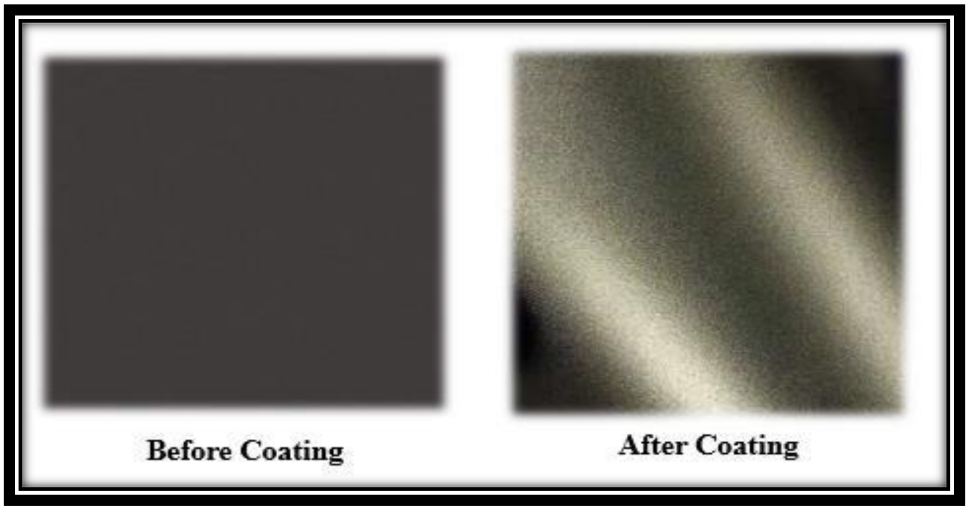


Figure 26 Graphite Surface before and after coating

3.5 Characterization

Characterization have been done for the analysis of materials and further validation of coating also done by the characterization. Like materials morphological and chemical changes verified by the material characterization techniques. Before and after coating how material's surface change, chemical bonding difference between graphite and pyrolytic carbon analysis done by the following techniques.

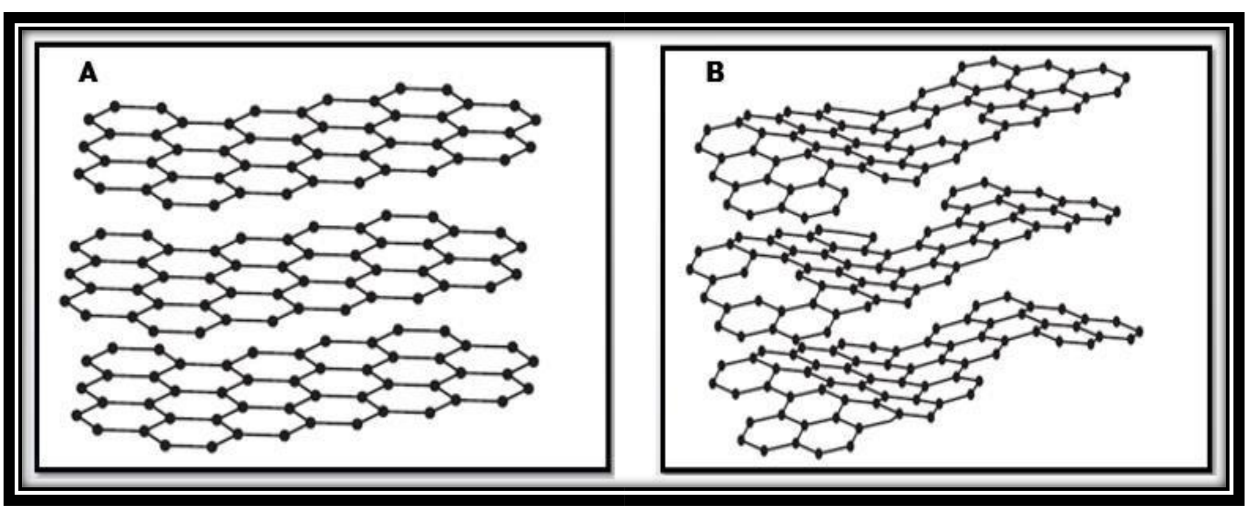


Figure 27 Chemical Structure of (A) Graphite & (B) Pyrolytic Carbon

3.5.1 Scanning Electron Microscopy (SEM) Analysis

SEM is the type of electron microscopy in which surface of materials analyzed by using high electron beam. These electrons interact with the material and produce information regarding surface topography and materials composition. SEM images give details about the surface topography cross sectional views of samples and change in surface area of material also analyzed by this method.

For the analysis of SEM was conducted. VEGA3 TESCAN Analytical scanning electron microscope (JEOL, Tokyo, Japan) was used for the assessment of the surface morphology of the curcumin/PVA mats at an activation voltage of 20 kV.

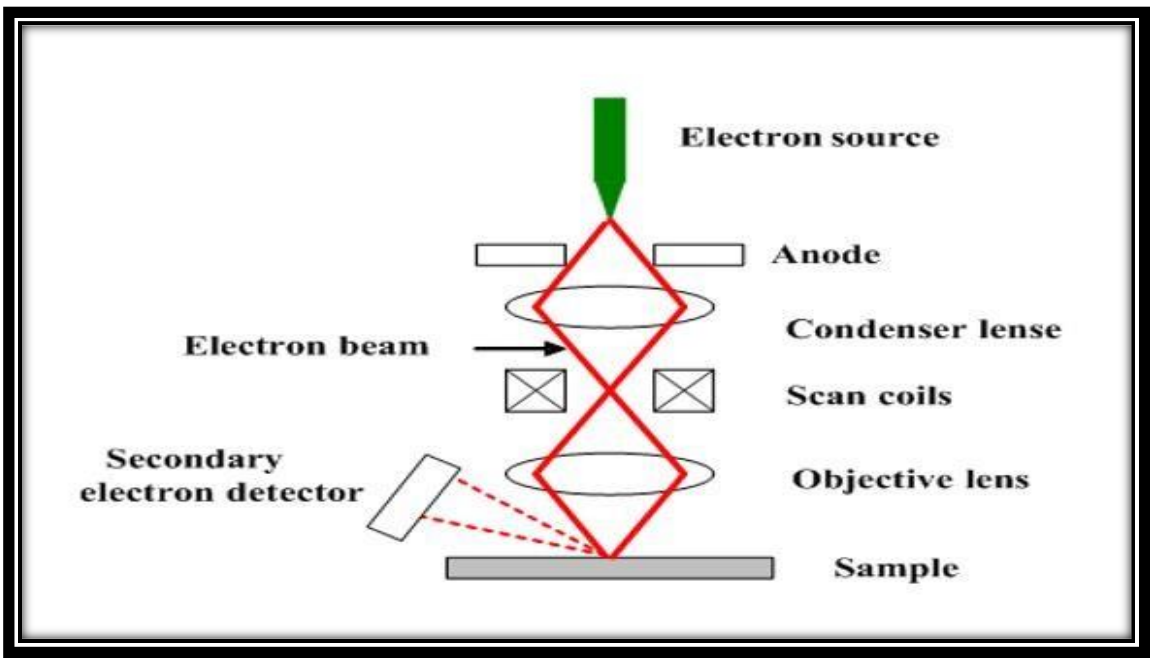


Figure 28 SEM Schematics

3.5.2 Fourier Transform Infrared (FTIR) Spectroscopy

FTIR is characterization technique in which infrared spectrum of absorption or transmission obtained. It is an analytical technique used to find out the organic and inorganic and their chemical properties also analyzed by FTIR spectroscopy.

Fourier transformed infrared (FTIR) spectroscopy was conducted using a Perkin Elmer spectrophotometer of spectrum 100 FTIR for the investigation of the chemical and physical interaction between the carbon atoms present in the graphite and pyrolytic carbon and how they are different from each other. It was carried out at 256 scans with a resolution of 8cm-.

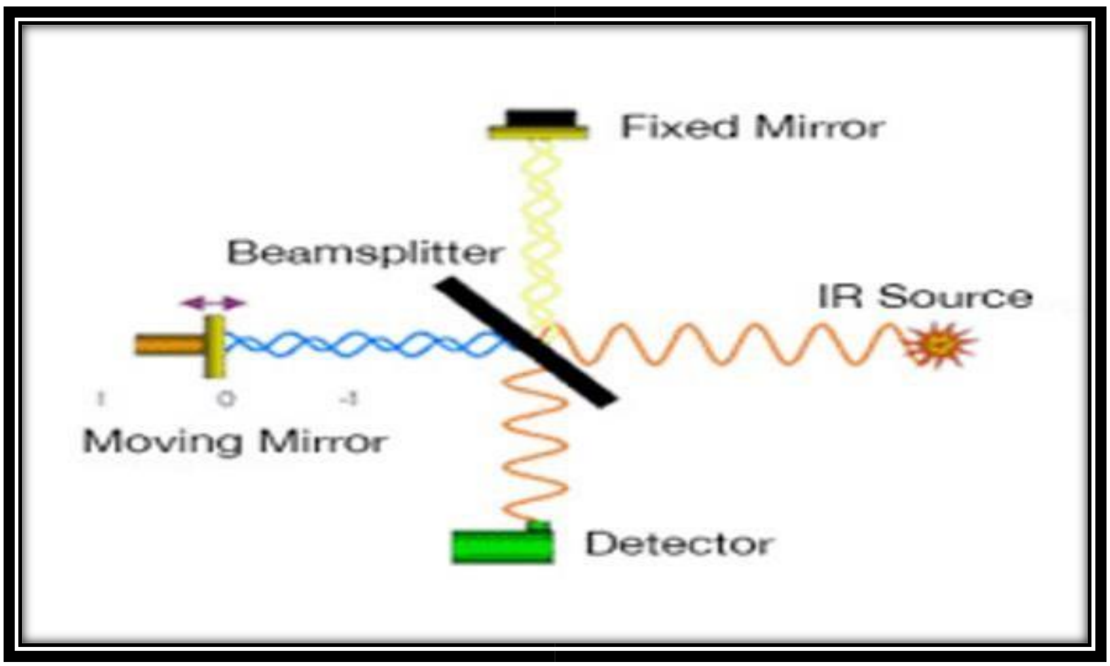


Figure 29 FTIR Schematics

3.5.3 X-rat Diffraction (XRD)

XRD is the analytical method for the investigation of crystalline domains in the chemical compound. By using X-ray beam and detector sample can be analyzed and identify chemical compounds by using the peaks obtained at the output graph.

For the investigation the degree of crystallinity and amorphous domain in the graphite and pyrolytic carbon, x-ray diffraction was performed. X-ray diffraction patterns were obtained over the 2ɵ range of 10-40°.

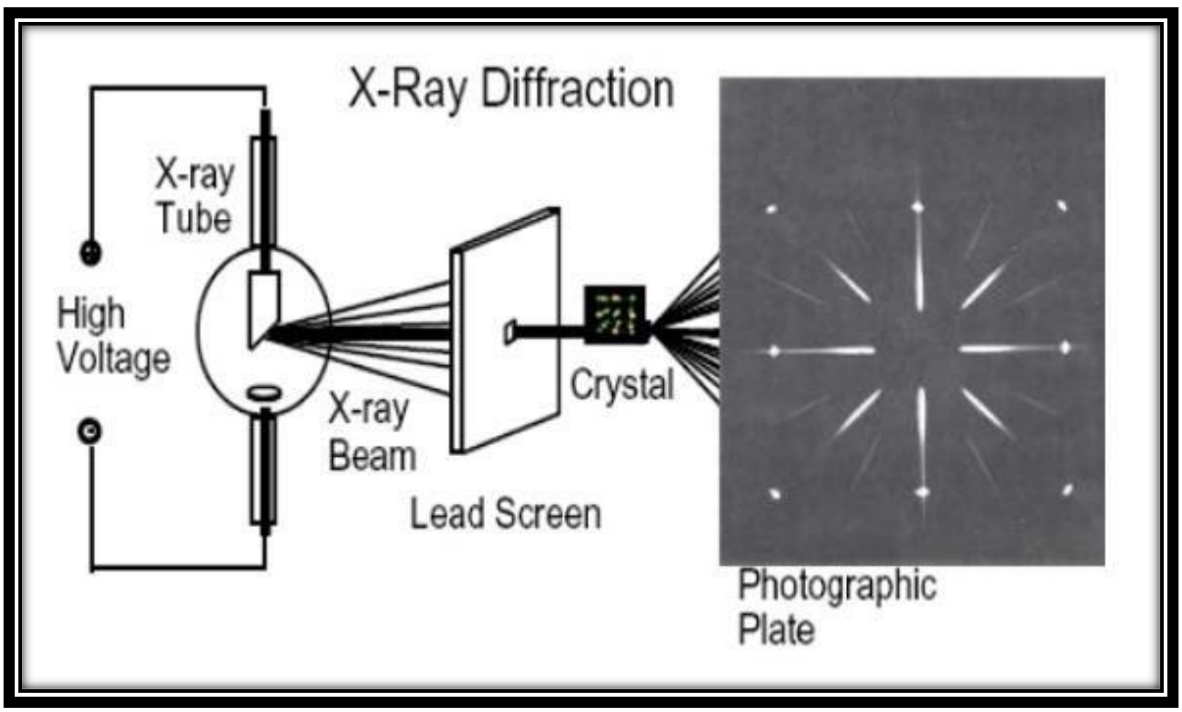


Figure 30 XRD Schematic

Chapter 4 RESULTS AND DISCUSSION

Although mechanical heart valves required so many testing for design and materials validation like mechanical testing, fatigue testing, physical testing, biological testing etc. In this research two types of testing have been done these are on the basis of materials. Testing of mechanical mitral valves consist of two main phases.

1. Characterizations.
2. Hemolytic.

Both testing validate the material characteristics and validation of pyrolytic carbon coatings.

4.1 Characterizations of materials

The materials used for the fabrication of mechanical mitral valve is graphite and further coated with pyrolytic carbon both materials tested to check the materials crystalline domains surface smoothness and chemical structure changes. There are three main process done before and after coatings for validation of materials and their names are

- SEM (scanning electron microscopy).
- FTIR (Fourier transform infra-red spectra).
- XRD (X-ray powder diffraction).

4.1.1 Objectives of Characterization

- Validation of coated material.
- Surface morphology Analysis Porosity Analysis.
- Crystalline domains confirmation.
- Difference between graphite and Pyrolytic carbon bonding.

4.2 Phase-I

In Phase-I characterization was done before and after coating to check the materials characteristics. It was consisting of three tests which discussed earlier and their details and graphical representations given bellow.

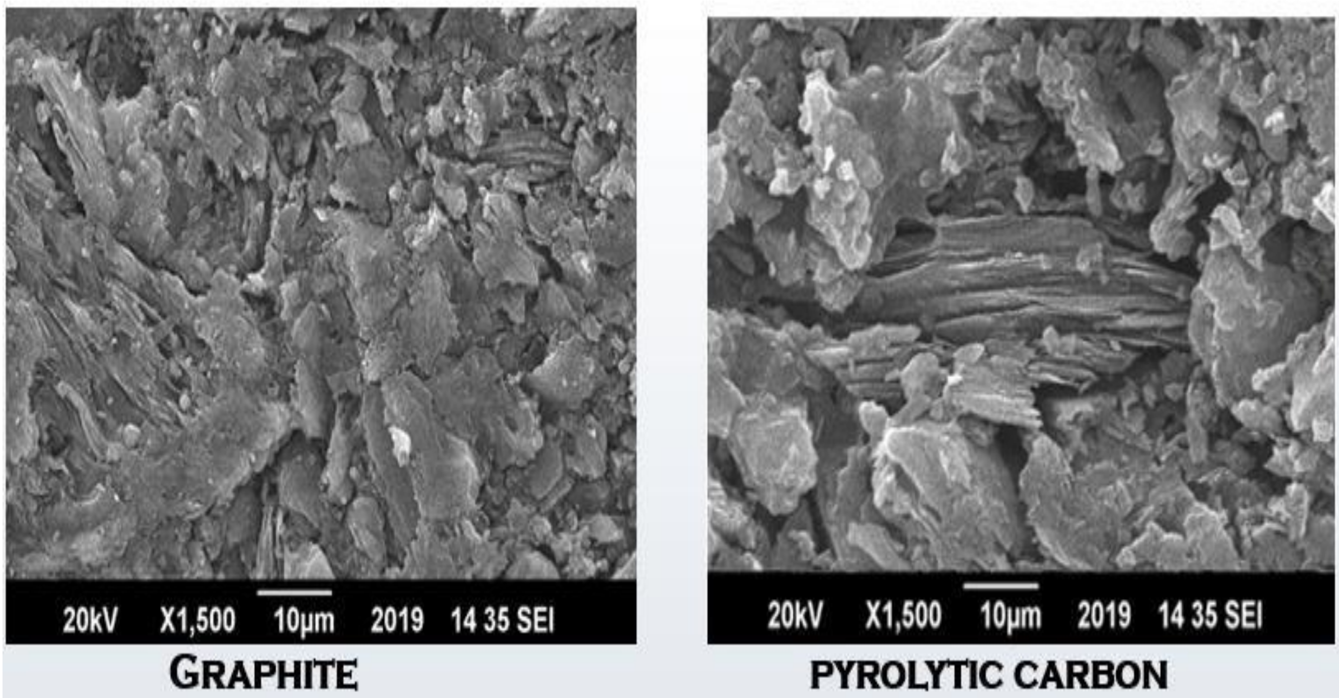


Figure 31 SEM results before and after Coatings

4.2.1 SEM Analysis Results

SEM was done before and after coating and the results are given below.

From the SEM images it has been estimated that there is some change in the surface of material after coating. As clearly seen in the pyrolytic carbon image the surface area reduced it means the contact angle increased and as a result the less adhesion when this material come in contact with liquid or blood. These images are taken at 20Kv voltage and 10micro meter with X1500.

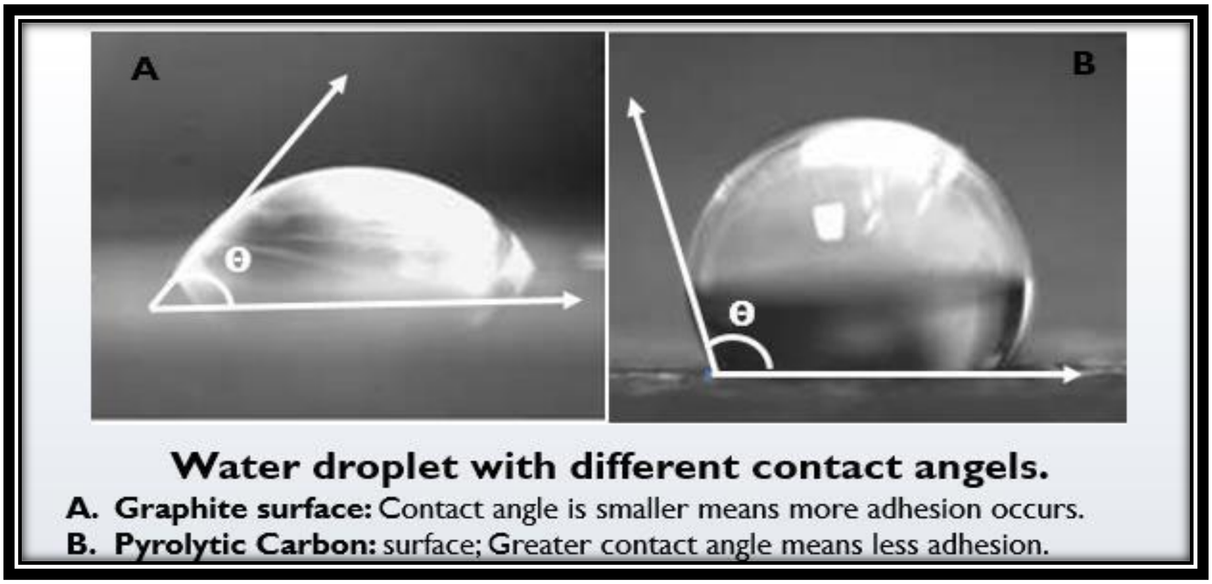


Figure 32 Contact Angle analysis with coated and uncoated surfaces

Graphite surface produce smaller contact angle as it is not perfectly smooth there are some pores present in graphite which causes wettability or decrease the contact angle with water droplet and as result it is stated that graphite provides surface adhesion. Where as in second figure the greater contact angle means more hydrophobic surfaces because pores removed and surface become smoother and causes no adhesion results can be clearly seen in the figure water droplet on the coated surface (pyrolytic carbon). Hence it is proved from the SEM analysis that there is coating present on the graphite surface and changes occur in the chemical bonding of graphite after CVD.

4.2.2 FTIR Results

FTIR Analysis of graphite and pyrolytic carbon also represent, both compounds having same chemical formula that's why in graph same pattern was observed at the FTIR graph. And the % transmittance is change due to change in chemical bonding. Although in both compound there is no other than Carbon and hydrogen so the peaks at different values represent the stretching of bond between C-C at 3418cm-3 and 1632cm-3 shows stretching of bond between C-H. Further rest of peaks at 11.19cm-3 and at 372cm-3.

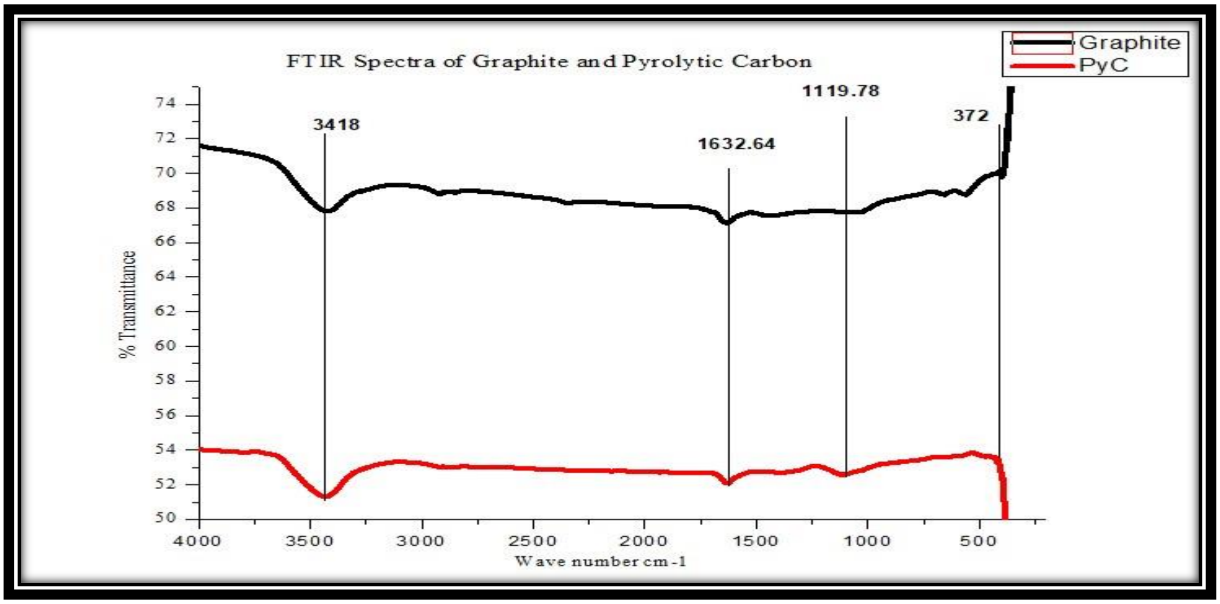


Figure 33 FTIR Analysis Graph

4.2.3 XRD Results

XRD patterns were obtained over the range of 2ɵ 20°-300°. A broad characteristic peak of graphite was observed between 20°-30° due to crystalline nature. Diffraction pattern exhibited single sharp peaks which showed the presence of crystalline domains in graphite **(Figure 33)**. Peak goes up to 1400 means the intensity of X-ray beam in graphite is very high.

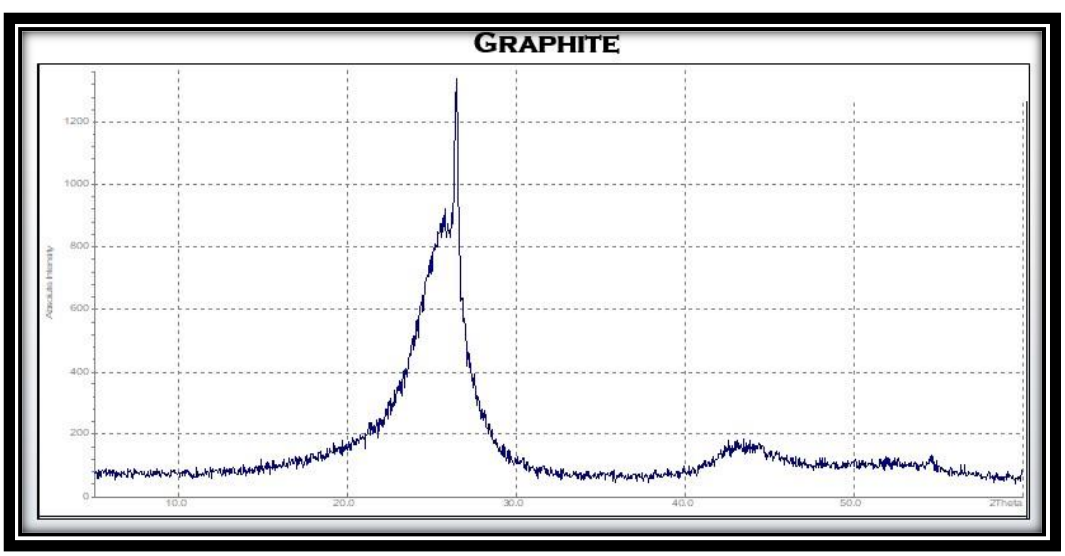


Figure 34 XRD Analysis of Graphite

Whereas in case of pyrolytic carbon XRD patterns were obtained over the range of 2ɵ broad peak was observed between 20°-30°. In pyrolytic carbon peak arise between 20°-30° means at same angle but not too much sharp peak its absolute intensity on y-axis goes up to 450. Peak sharpness reduces due to semi-crystalline structure of pyrolytic carbon and they show the bond squeezed after CVD process.

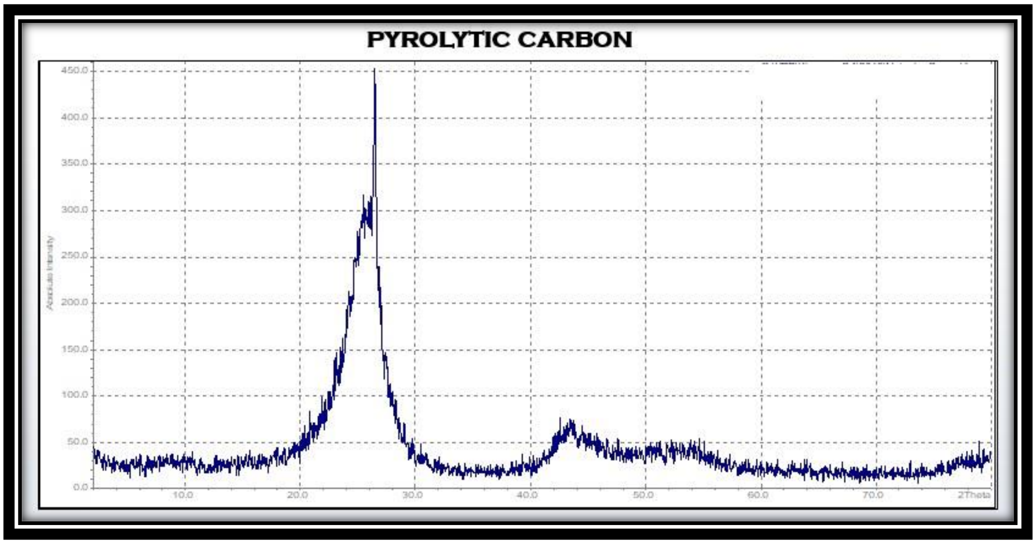


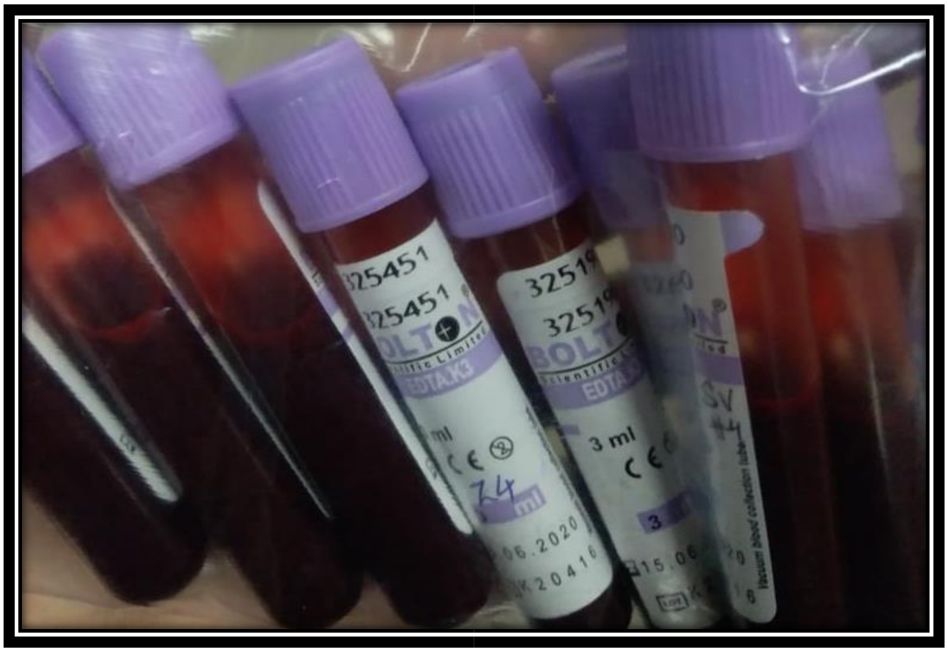
Figure 35 XRD Analysis of Pyrolytic Carbon

4.3 Phase-II

In phase-II hemolytic activity performed with coated and uncoated material to check the hemolysis with the coated and uncoated material.

4.3.1 Hemolysis Testing Protocol

- Hemolysis assay is widely used method to determine the hemocompatibility of blood contacting materials.
- In this research test samples were placed in direct contact with RBCs, to check the effect of graphite material on RBCs.
- The haemolytic activity done with coated and uncoated sample of graphite with positive control (0.5% Triton) and negative control (PBS Solution).
- Samples were analysed in triplicates.



Hemolytic Testing Protocol

For the hemolytic testing first of all 30ml fresh human blood collected in ETDA tube this tube contain anticoagulants which prevents the blood clotting. After taking blood centrifugation have been done with 5000rpm for 5 mints to separate the plasma and blood cells. Plasma removed from the tube and rest of RBCs washed with PBS solution and again centrifuge for removal of remaining plasma from the sample. After that a solution prepared with the PBS and blood cells by the ratio of 1:3 and samples putted into the tubes and incubated at 37 C for three hours. After incubation samples again centrifuge for quantitative analysis by UV to check the hemolysis %age. Whereas qualitative analysis done without centrifuge.

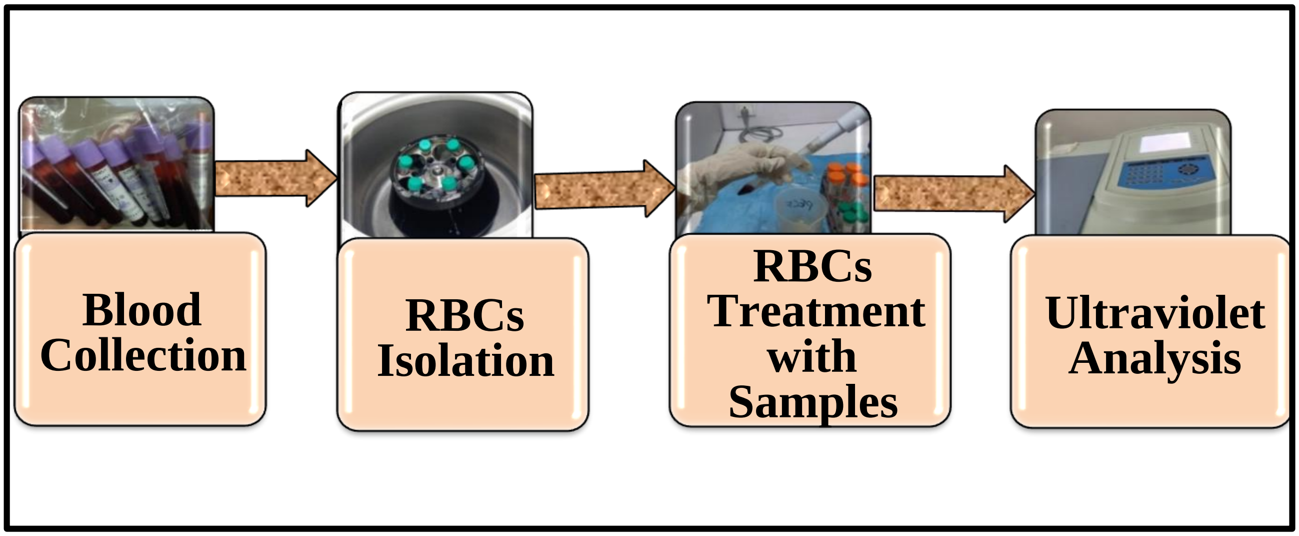


Figure 36 Hemolytic Testing Protocol

There are two methods of analysis

I. Qualitative Analysis.
II. Quantitative Analysis.

During qualitative analysis clearly seen RBCs hemolysis in the positive control sample tube in the form of dark red color. Whereas Quantitative analysis done by UV with 550nm wavelength.

4.3.2 Qualitative Analysis

It gave us results in the form of colors like wise in this study hemolysis occur in the sample clearly seen by naked eyes. Because the sample in which hemolysis occurs show dark red color because of RBCs cell wall ruptured and red color pigment present in human blood spread into the solution and researcher can easily observed the results of hemolysis. In this research hemolysis performed with four types of samples and further they are in triplicates and their details are given below

1. C= Coated sample.
2. UC= Uncoated Sample.
3. -ve Control= PBS Solution.
4. +ve Control= 0.5% Triton.

RBCs hemolysis clearly seen in positive control dark red color solution in figure (37)

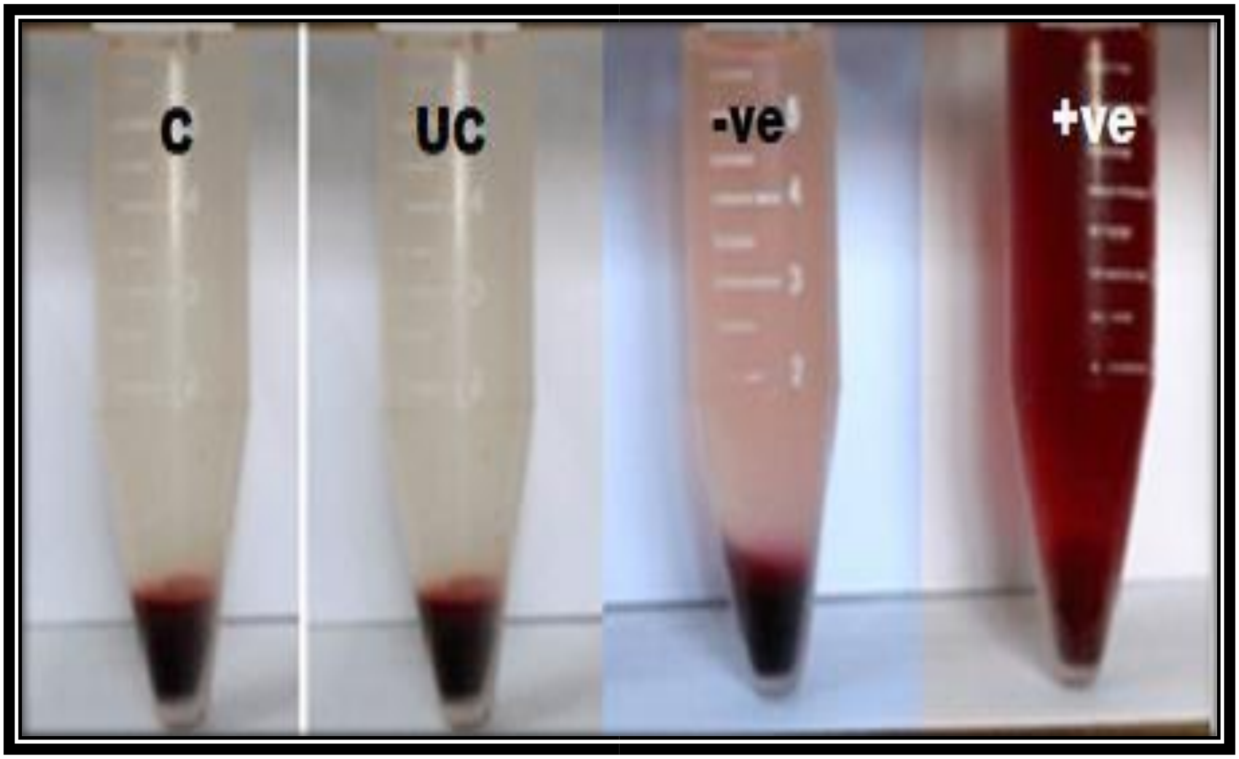


Figure 37 Qualitative Analysis of hemolysis

4.3.3 Quantitative Analysis

Quantitative analysis performed by UV analysis after incubation of sample in direct contact with blood for three hours again centrifuge performed and then rest of solution placed under the UV analysis at 550nm wavelength to check the hemolysis % in the solution. Here 550nm range is set because hemoglobin molecules absorbance range is 520-546nm. After UV analysis the quantitative results shows that there is 98% hemolysis occur in positive samples and test of the samples shows hemolysis less than 2% as seen in the figure (38)

According to ASTM Standard F756 (American Society for Testing & Materials)

- Hemolysis results >5% then material will be considered hemolytic.
- Hemolysis results >2% material will be slightly hemolytic.
- Hemolysis results <2% material will be non-hemolytic.

S #	Samples	% Hemolysis
1	Uncoated (Graphite)	1.407
2	Coated (Pyrolytic Carbon)	0.88
3	Negative Control	0.85
4	Positive Control	9.75

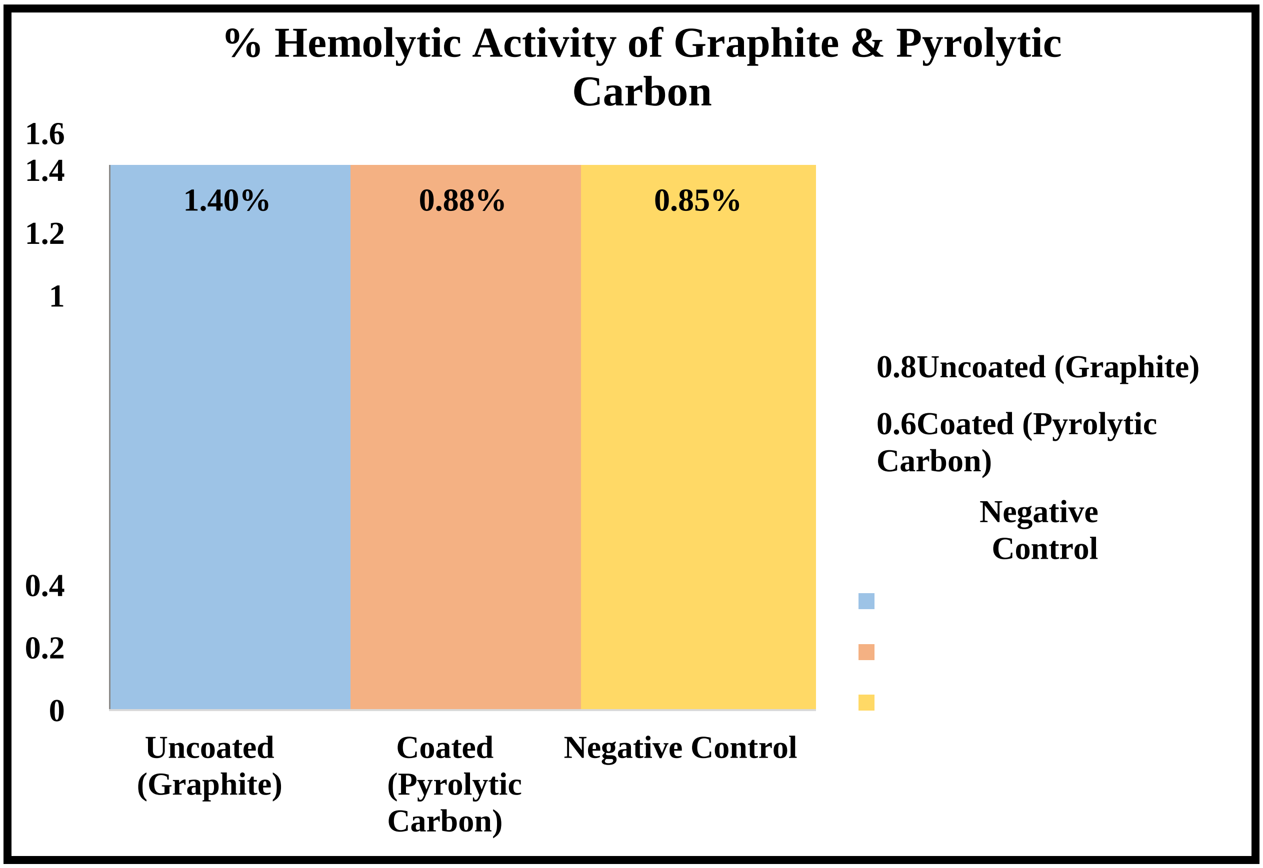


Figure 38 Quantitative Analysis of Hemolysis

Graphite and pyrolytic carbon both are hemocompatible they do not cause haemolysis when directly come in contact with blood. Hence it is proved from this experiment that pyrolytic carbon coating improves the hemocompatibility of graphite.

Chapter 5 CONCLUSION AND FUTURE WORKS

In this research bileaflet mechanical mitral valve prototype was fabricated from the graphite and then coated by pyrolytic carbon which is excellent for the cardiovascular prostheses. The improved software model designed by solid works 2016 tool kits. After considering the previous models problems like in this model long leaflet ear which reduce the tissue growth and provide maximum degree of motion. Butterfly shaped hinges provide good hemodynamics with less damage to RBCs. Graphite after coating of Pyrolytic carbon exhibit better hemodynamics as compare to the other materials. Coating done by the CVD technique which provide strength and surface smoothness to the material, indications to less damage of blood cells and reduced thrombosis due to smooth surface. Although improved blood compatibility and less thrombosis formation with this material. Hence patient with these type of implants required less anticoagulation therapy. Hemolytic activity proved that pyrolytic carbon is antihemolytic material and suitable for cardiovascular implants.

Future Works

Fabrication of Test bench for the mechanical, fatigue and accelerated testing

Two main test bench required for the testing

1. Accelerated testing.
2. Flow pattern analysis.

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