# BLOOD COMPATIBILITY ASSESSMENT OF METALLOCENE POLYETHYLENE FOLLOWING NITRIC ACID TREATMENT

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*I dedicate this thesis to my beloved family:*

*My dearest parents, Mr. Vellayappan, Mrs. Meenakshi & fiancée Dr.Kamala.*

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# ABSTRACT

Metallocene polyethylene (mPE) has been known for its excellent physical and mechanical properties, but its poor hemocompatibility limits its clinical application. Objective of this study was to analyze the physicochemical properties and blood compatibility of mPE following nitric acid ($HNO_3$) treatment. Characterization tests were performed using 3D Hirox, SEM, AFM, contact angle and FTIR. Blood compatibility of the sample was studied by conducting blood coagulation assays; hemolysis assay, PT, APTT, platelet adhesion and protein adsorption test. Result shows that the contact angle of the mPE treated with $HNO_3$ decreased from 86º to 69.7º. Surface of the mPE and the $HNO_3$ treated mPE investigated with FTIR revealed no major changes in its functional groups. 3D Hirox digital microscopy, SEM and AFM images show increased porosity and surface roughness. The protein adsorption studies show that the adsorbed albumin increased and adsorbed fibrinogen decreased in 60 minutes $HNO_3$ treated sample. Blood coagulation assays prothrombin time (PT) and activated partial thromboplastin time (APTT) were delayed significantly ($P < 0.05$) for the 60 minutes $HNO_3$ treated sample. Hemolysis assay and platelet adhesion of the treated surface resulted in reduced lysis of red blood cells and platelet adherence indicating improved hemocompatibility of $HNO_3$ treated mPE. To determine that $HNO_3$ does not deteriorate elastic modulus of mPE, the elastic modulus, tensile strength and tensile strength at break of mPE and $HNO_3$ treated mPE was compared and the result shows that $HNO_3$ treatment does not deteriorate the mechanical properties of mPE. To conclude, the overall observation suggests that the novel $HNO_3$ treated mPE may hold great potential to be exploited for various temporary blood contacting devices like catheters, endoscopy tip and etc.

# ABSTRAK

Metallocene polietilena (mPE) lebih dikenali dengan sifat-sifat fizikal dan mekanikal yang mengagumkan, namun masalah keserasian dengan darah menghadkan aplikasi klinikal bahan ini. Objektif kajian ini adalah untuk menganalisis sifat-sifat fizikokimia dan keserasian darah mPE selepas rawatan asid nitrik ($HNO_3$). Ujian pencirian telah dilakukan dengan menggunakan 3D Hirox, SEM, AFM , sudut kenalan dan FTIR. Keserasian darah sampel telah dikaji dengan cerakin pembekuan darah seperti cerakin hemolisis, PT, APTT, bilangan platelet melekat dan ujian penyerapan protein. Sudut sentuhan bagi mPE yang ditindakbalaskan dengan $HNO_3$ telah menurun daripada 86º kepada 69.7º. Analisis FTIR menunjukkan tiada sebarang perbezaan yang ketara dari segi kumpulan berfungsi antara mPE dan mPE yang ditidakbalaskan dengan $HNO_3$. Imej pada mikroskop digital 3D Hirox, SEM dan AFM telah menunjukkan peningkatan dari segi saiz liang dan kekasaran permukaan. Kajian penyerapan protein menunjukkan bahawa serapan albumin meningkat manakala penyerapan fibrinogen menurun bagi mPE yang ditindakbalaskan dengan $HNO_3$ selama 60 minit. Masa bagi cerakin pembekuan darah bagi prothrombin (PT) dan separa tromboplastin yang diaktifkan (APTT) mempunyai perbezaan yang ketara ($P < 0.05$) untuk mPE yang ditindakbalaskan dengan $HNO_3$. Cerakin hemolisis dan lekatan platelet untuk permukaan yang ditindakbalas mengurangkan lisis sel-sel darah merah dan pematuhan platelet menunjukkan sifat keserasian dengan darah yang baik untuk mPE yang ditindakbalaskan dengan $HNO_3$. Tiada perubahan dari segi sifat-sifat mekanik; elastik modulus dan kekuatan tegangan tercatat antara sampel mPE sebelum atau selepas ditidakbalaskan dengan $HNO_3$. Oleh itu, analisis keseluruhan menunjukkan bahawa mPE yang ditindakbalaskan dengan $HNO_3$ mempunyai kebarangkalian yang positif untuk diaplikasikan sebagai peranti sementara yang bersentuhan dengan darah seperti kateter, tip endoskopi dan lain-lain lagi.

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| | | |
|---|---|---|
| AFM | - | Atomic force microscopy |
| APTT | - | Activated partial thromboplastin time |
| ATR-FTIR | - | Attenuated total reflectance Fourier transformed infrared spectroscopy |
| BHV | - | Bioprosthetic heart valves |
| BMS | - | Bare-metal stents |
| DES | - | Drug-eluting stents |
| Fg | - | Fibrinogen |
| HA | - | Haemolysis assay |
| HCL | - | Hydrochloric acid |
| HI | - | Hemolytic index |
| $HNO_3$ | - | Nitric acid |
| IH | - | Intimal hyperplasia |
| ISR | - | In-stent restenosis |
| MHV | - | Mechanical heart valves |
| mPE | - | Metallocene polyethylene |
| NaOH | - | Sodium hydroxide |
| PANCMA | - | Poly(acrylonitrile-co-maleic acid)s |
| PCL | - | Poly-3-caprolactone |

| | | |
|---|---|---|
| PES | - | Polyethersulfone |
| PRP | - | Platelet rich plasma |
| PT | - | Prothrombin time |
| PTFE | - | Polytetrafluoroethylene |
| PU | - | Polyurethane |
| PVA | - | Poly vinyl alcohol |
| PVC | - | Poly vinyl chloride |
| RBC | - | Red blood cells |
| SD | - | Standard deviation |
| SEM | - | Scanning electron microscopy |
| ST | - | Stent thrombosis |
| SWCNT | - | Single-walled carbon nanotubes |
| THF | - | Tetrahydrofuran |
| VAD | - | Ventricular assist devices |
| vWF | - | Von willebrand factor |
| BCA | - | Bicinchoninic acid assay |

# LIST OF SYMBOLS

| | | |
|---|---|---|
| $cm^{-1}$ | - | Per centimetre |
| mm-$^{1}$ | - | Per millimetre |
| $cm^2$ | - | Square centimetre |
| g/mol | - | Grams per mole |
| Hz | - | Hertz |
| MPa | - | Megapascal |
| mL | - | Millilitre |
| M | - | Molar |
| nm | - | Nanometre |
| mm | - | Millimeter |
| Ra | - | Average roughness |
| W | - | Watt |
| N | - | Newton |
| w/v | - | Weight per volume |
| $\mu$L | - | Microlitre |
| $\mu$m | - | Micrometre |
| $\mu^2$ | - | Micrometre square |
| $^{o}$C | - | Degree celsius |
| % | - | Percentage |
| ± | - | Plus-minus sign |

# LIST OF APPENDICES

# CHAPTER 1

# INTRODUCTION

## 1.1 Background

Materials which have been playing a vital role in replacing and mirroring the functions of various organs in human system [1] are collectively known as biomaterials. Biomaterial is the combination of substances originating from natural, inorganic or organic materials. These materials are biocompatible exactly or partially when it comes in contact with the body during the healing time. They involve complete or part of a living organism or biomedical device which perform, augments or replaces any natural functions. Biomaterials are commonly used in various medical devices and systems like synthetic skin [2], drug delivery systems [3], tissue cultures [4], hybrid organs [5], synthetic blood vessels [6], artificial heart valves, cardiac pacemakers [7], screws, plates, wires and pins for bone treatments, total artificial joint implants, skull reconstruction [8], dental and maxillofacial applications [9].

Biomaterials broadly fall into the four main types namely metals, ceramics, polymers and biological substances [10]. Metals have unique atomic structure which confers them characteristic strength and properties which enable them specifically for load-bearing applications like orthopaedics. However, the corrosion associated with the use of metals limits their utility. Ceramics have evolved as better biomaterials because of their bio-inertness and compatibility. However, due to brittleness and low impact strength [11], ceramics are losing popularity. Polymers have widespread applications in the field of biomaterials. Properties of polymers are dependent on the unit macromolecule present in the long chain of the polymer.

Among all four types, the polymers have widespread application in the field of biomaterials because of excellent physico-chemical and mechanical properties. Moreover, polymers can be feasibly molded into desired shapes with desired mechanical characteristics. The most important application of polymers is cardiovascular based implants [7] and blood contacting devices [1]. The use of polymers in medical application ranges from vascular grafts, stents, prosthetic heart valves, catheters, heart assist devices, hemodialyser.

Modern revolution in polymer technology like metallocene single-site catalyst introduced a new class of polyolefins with improved performance properties like enhanced toughness, sealability, clarity, and elasticity [12]. The metallocene consists of two cyclopentadienyl anions (Cp,) which are bound to a metal center (M) [12] which has an oxidation state II, thereby resulting in a general formula $M(C_5H_5)_2$. One among the polymers developed through metallocene technology is metallocene polyethylene (mPE). mPE typically finds applications in disposable bags, storage bottles, blood bags, and syringe tubes. Even though mPE has outstanding permeability to oxygen and acts as a barrier towards ammonia and water, mPE lacks blood compatibility [13] to be used for blood contacting biomedical implants.

Biocompatibility is a prime factor which determines the quality of a biomaterial and its application in various arenas. There are different definitions for biocompatibility. It may be defined as the ability of the material to perform at a specific body site with an appropriate host reaction. Biocompatibility may also be defined as the ability of a biomaterial to perform its desired function with respect to a medical therapy, without eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response to that specific situation and optimizing the clinically relevant performance of that therapy [14].

Biocompatibility has been mentioned in many works with increasing interest in evaluating the characteristics of medical materials and devices and also the responses caused by its components. The ideal pattern for determining these properties has not yet been determined; but, various methods have been suggested for this purpose. Biocompatibility encompasses many aspects of the material, including its physical, mechanical and chemical properties, and potential cytotoxic, mutagenic and allergenic effects [15], so that no significant injuries or toxic effects on the biological function of cells and individuals arise. Until the biocompatibility of a material is proven, it must be subjected to various studies ranging from in vitro assays to clinical trials, involving distinct areas such as pharmaceutics, biology, chemistry and toxicology to justify its use as a biomaterial.

The term biocompatibility has been defined by consensus, but not blood compatibility. The interactions between blood and a surface depend on the blood composition, the blood flow and the surface of the material defined by its physicochemical feature. The design of bloodcompatible materials is clearly a challenge to increase success in all medical devices that come in contact with blood and to answer unsolved problems in vascular reconstruction.

To explain blood compatibility from a different perspective, consider a material that is not blood compatible, i.e. a thrombogenic material. Such material would produce specific adverse reactions when placed in contact with blood: formation of clot or thrombus composed of various blood elements; shedding or nucleation of emboli (detached thrombus); the destruction of circulating blood components and activation of the complement system and other immunologic pathways [10]. Thus, we can define blood compatibility as the ability of the material to work in a particular place without eliciting any of the above mentioned blood related complications. Indeed, biocompatibility of blood contacting devices relates mainly to the thrombotic response induced by the materials.

Several distinct but interrelated thrombotic and antithrombotic systems exist to prevent the formation of intravascular clots expected in response to vascular trauma. Haemostasis is the sum of these mechanisms and serves to limit blood loss following injury. Once regulation is initiated, these same mechanisms combine first to localize the clot at the site of injury, then to terminate coagulation and finally to remove the clot once it has served its purpose. These haemostatic mechanisms include platelet activation, coagulation, fibrinolysis and local vascular effects. Blood clotting, platelet adhesion and giant cell formations are major problems associated with blood clotting devices. These problems frequently arise in cardiovascular implants since the material is always in contact with blood and its components [7].

The hypothesis of this thesis was that the $HNO_3$ treatment on mPE may improve the blood compatibility of the mPE polymer, to be utilized for different temporary blood contacting devices application like endscope tip, catheters and etc. The rationale for this hypothesis was that, when the mPE surface is subjected to $HNO_3$ treatment it was expected to etch the mPE surface which may improve the wetabbility or hydrophilicity of mPE. It may be expected that improved hydrophilicity may alter the protein adsorption and blood coagulation time resulting in enhanced blood compatibility. Besides that, it is also hypothesized that the $HNO_3$ treatment on mPE will not affect the mechanical strength of mPE.

## 1.2 Statement of Problem

Although mPE has excellent physico-chemical and mechanical properties, it fails as a promising biomaterial because of its poor blood compatibility. Biocompatibility is a vital factor which determines the quality of a biomaterial and its application in various arenas. It may be defined as the ability of the material to perform at a specific region with the appropriate host reaction. The events occur when the blood comes in contact with the implant is collectively called as blood mediated reactions or blood compatibility. Whenever the blood comes in contact with the implants (biomaterial) it will lead to following complications:

1. Blood components interaction with surfaces resulting in protein and water adsorption.
2. Blood cells interfere with the surface of biomaterial.
3. These actions lead to the hemostasis and coagulation.

To solve these issues, different surface modification techniques have been studied yet most of them are complex and limited to certain family of polymers. In recent times, millions of dollars was invested in advanced biomaterial research which includes discovery of new alternatives. However, in order to cater the high demand, more research needs to be encouraged to enhance the properties of the existing medical materials using feasible, eco-friendly and affordable modification technique. Hence, nitric acid surface modification technique on mPE was performed for improving its blood compatibility and it is the research gaph which will be addressed in this research.

## 1.3 Objectives

This research was carried out to determine the potential of nitric acid ($HNO_3$) treated metallocene polyethylene (mPE) as a biomaterial, for blood contacting device application. The following are the objectives of this study:

1. To investigate the physico-chemical changes induced on the surface of the mPE after $HNO_3$ treatment.

2. To determine the changes in the blood compatibility of the mPE subjected to acid treatment.

## 1.4 Scope of Study

This study consists of two parts. The first part of the study is focused mainly on the sample preparation, optimization of the nitric acid treatment on the mPE, and the characterization of mPE and $HNO_3$ treated mPE surfaces. Various methods were utilized; contact angle, attenuated total reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR), 3D Hirox digital microscopy, scanning electron microscopy (SEM), and atomic force microscopy (AFM) for the determination of the surface characteristic of the mPE and $HNO_3$ treated sample. To examine whether the $HNO_3$ treatment affect the tensile strength, elastic modulus and break strength of mPE, mechanical testing of mPE and $HNO_3$ treated mPE was compared.

In the second part, blood coagulation assays were carried out. The reason for this step is to ascertain the thromboresistance property of mPE and $HNO_3$ treated mPE surfaces when they are utilized as biomaterials, particularly for blood contacting devices. The blood coagulation assays like prothrombin test (PT), activated partial thromboplastin time (APTT), hemolysis assay (HA), and platelet adherence test is performed to investigate the blood compatibility of the mPE and $HNO_3$ treated mPE. Protein adsorption assay was carried out for determining the specific proteins albumin and fibrinogen adsorption on mPE and $HNO_3$ treated mPE. The mPE and the $HNO_3$ treated mPE blood compatibility results were compared with the conventional blood contacting materials for positioning this research with related studies in this field.

## 1.5 Significance of Study

The result of this study will provide an account on the improved blood compatibility of mPE by nitric acid treatment. In addition to that, the effect of the $HNO_3$ on the mPE polymer which was performed for the first time may kindle the enthusiasm of the other researchers to further explore the alternative acids available, to enhance the blood compatibility of polymers. Besides that, as nitric acid is low in cost, a cost effective method for the blood compatibility enhancement of polymers can be introduced.

## 1.6 Thesis outline

This thesis is divided into five chapters. In Chapter 1, a brief explanation about the biomaterials and the research background of this study is given. Further, the objectives of this study have been presented in the context of solving the clinical complications mentioned. Finally, the importance of the proposed method and its influence in encouraging future researches is also projected.

In Chapter 2, a brief explanation about polymers and the problems observed during its contact with biological environment is summarized. In addition, the importance of surface modification techniques in solving those issues and some of the previous researches reported in that viewpoint is also discussed.

In Chapter 3, the research methodology and characterization studies followed in this research are given in detail. The discussions mainly cover the particulars, procedures and the need for characterization studies.

In Chapter 4, the results obtained from characterization and blood compatibility studies have been discussed and compared with the previous study's results. This section is the heart of the thesis, since it evidently reflects the achievement and the effectiveness of proposed idea.

In Chapter 5, a short summary of the whole work and its effectiveness in approaching blood compatibility problems are projected. Moreover, some suggestion about future research in the proposed perspective is also presented.

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