DUAL-FUNCTIONAL SURFACES OF EVEROLIMUS IMMOBILISED ON BIODEGRADABLE POLY(L-LACTIC ACID)/POLY(D-LACTIC ACID) SCAFFOLD MEDIATED BY POLYDOPAMINE COATING FOR STENT DEVELOPMENT

MOHAMAD AMIN BIN JUMAT

UNIVERSITI TEKNOLOGI MALAYSIA

DUAL-FUNCTIONAL SURFACES OF EVEROLIMUS IMMOBILISED ON BIODEGRADABLE POLY(L-LATIC ACID)/POLY(D-LACTIC ACID) SCAFFOLD MEDIATED BY POLYDOPAMINE COATING FOR STENT DEVELOPMENT

MOHAMAD AMIN BIN JUMAT

A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy

School of Biomedical Engineering and Health Sciences
Faculty of Engineering
Universiti Teknologi Malaysia

FEBRUARY 2022

ACKNOWLEDGEMENT

The deepest thanks to ALLAH (Almighty), Al-Rahman, the most merciful, and the compassionate for uncountable gifts given to me.

First and foremost, I want to thank my main supervisor Dr. Syafiqah Saidin for her guidance and support. It has been an honour to be one of her doctorate students. She has taught me, how good research in biomaterials can be conducted. I appreciate all her contributions, time, ideas and experience. I want to thank her for the pleasant and trusting co-operation until I am able to complete this thesis.

Also, an appreciation to my co-supervisor, Dr. Rania Al-Ashwal for her advice and motivation. I would like to acknowledge the financial support from Zamalah UTM scholarship, which covered me for the whole years of study for the completion of this research project. Special thanks of gratitude to Canada-ASEAN Scholarships and Educational Exchanges for Development (SEED) scholarship from Canadian government who gave me an opportunity and sponsored me to do a short training in Canada.

I would also like to thank all members of Biomedical Science Laboratory who helped and guided me in performing experiments and analyses. A pleasurable thank to my friend, Herman bin Tuminoh for always there, giving me moral support when I felt down. Lastly but not least, I would like to thank my family for all their love and encouragement, especially my parents (Jumat bin Angas and Sajerah binti Bair) who raised me with love and supported me in all my pursuits.

ABSTRACT

Drug-eluting stent (DES) is a promising treatment for atherosclerosis and in-stent restenosis. However, the long-term implantation of DES contributes to late-stent thrombosis due to the rapid release of anti-proliferative drug and delayed endotheliasation. Besides, the presence of anti-proliferative drugs which is typically effective in preventing in-stent restenosis, has also could suspend the healing process by inhibiting the growth of endothelial cells. Everolimus is one of the anti-proliferative drugs used in developing commercial DES. Therefore, this study, aimed at developing a dual-functional surfaces of everolimus immobilised polydopamine (PDA) on poly(l-lactic acid)/poly(d-lactic acid) (PLLA/PDLA) scaffolds. The study, also printed scaffolds with different PLLA and PDLA compositions (100% PLLA, 0% PDLA; 90% PLLA, 10% PDLA; 80% PLLA, 20% PDLA and 70% PLLA, 30% PDLA) using three-dimensional (3D) printer. The study further subjected PLLA/PDLA scaffolds to wettability, mechanical and degradation analyses. The incorporation of PDLA into the blend of PLLA has increased the scaffold hydrophobicity and mechanical properties. Observation on the degraded PLLA/PDLA scaffolds show the capability in retaining its chemical functionalities. Less crack formation, less acidity of the degraded solution, higher percentages of remaining weight, greater average molecular weight and higher crystallinity percentages were recorded on the higher PDLA composition after the degradation analysis. The 80% PLLA and 20% PDLA scaffold blend was selected for further grafting and immobilisation processes due to its wettability, mechanical and degradation properties. The grafted scaffolds with the PDA intermediate layer were partly immobilised with different everolimus concentrations (0.01, 0.05 and 0.10 mM) to form dual-functional surfaces. The study further analyses the dual-functional surfaces of everolimus immobilised PDA using ATR-FTIR, XPS, SEM, AFM, wettability, everolimus quantification, drug release, coating stability, blood compatibility and *in-vitro* endothelial cell analyses. Immobilisation of the everolimus on the PDA layer through O–N and C–O covalent linkages was also determined. The flowery-structured everolimus demonstrated a lower wettability (103.33 ± 7.13°) and higher surface roughness (784.92 ± 21.33 nm) on the greater concentration of everolimus (0.10 mM). A sustainable drug release profile based on the zero-order release profile was acquired for 0.05 mM and 0.10 mM everolimus concentrations. The higher everolimus concentration produced greater contribution on the coating stability. All scaffolds were classified as non-haemolytic with haemolytic index less than 2%. The endothelial cells extensively proliferated on the PDA surface which support scaffold implantation in the abluminal area. Meanwhile, cell growth inhibition was observed on the everolimus surface. Thus, this dual-functional scaffolds are beneficial for DES application in preventing possible complications such as burst drug release, late-stent thrombosis and delayed endotheliasation.

ABSTRAK

Sten pembebasan ubat (DES) adalah satu kaedah rawatan yang memberi harapan untuk aterosklerosis dan pembentukan restenosis dalam sten. Walaubagaimanapun, implantasi DES pada jangka masa panjang telah menyumbang kepada kelewatan trombosis dalam sten disebabkan oleh pembebasan ubat anti-percambahan yang cepat dan pertumbuhan sel endotelial yang lambat. Selain itu, kehadiran ubat anti-percambahan yang berkesan menghalang restenosis dalam sten, juga telah menangguhkan proses penyembuhan dengan merencat pertumbuhan sel endotelial. Everolimus adalah salah satu ubat anti-percambahan yang digunakan dalam penghasilan DES yang dikomersialkan. Oleh itu, kajian ini, bertujuan untuk membangunkan permukaan dwi-fungsi everolimus dinyahgerakkan polidopamin (PDA) dibina di atas perancah poli(asid l-laktik)/poli(asid d-laktik) (PLLA/PDLA). Kajian ini, telah mencetak perancah dengan berbeza komposisi PLLA dan PDLA (100% PLLA, 0% PDLA; 90% PLLA, 10% PDLA; 80% PLLA, 20% PDLA dan 70% PLLA, 30% PDLA) menggunakan pencetak (3D) tiga dimensi. Kajian ini kemudiannya menjadikan perancah PLLA/PDLA kepada analisis kebasahan, mekanikal dan penguraian. Penggabungan PDLA ke dalam campuran PLLA meningkatkan sifat hidrofobik dan sifat mekanikal perancah. Pemerhatian pada perancah PLLA/PDLA yang terurai menunjukkan keupayaan dalam mengekalkan fungsi kimianya. Pembentukan retak yang sedikit, keasidan yang kurang dalam larutan terurai, purata berat molekul yang tinggi dan peratusan habluran yang tinggi dicatatkan pada komposisi PDLA yang lebih tinggi selepas analisis penguraian. Campuran perancah 80% PLLA dan 20% PDLA dipilih untuk proses cantuman dan penyahgerakkan selanjutnya kerana sifat kebasahan, mekanikal dan penguraiannya. Sebahagian dari perencah yang telah dicantumkn dengan lapisan perantara PDA dinyahgerakkan dengan everolimus pada kepekatan yang berbeza (0.01, 0.05 dan 0.10 mM) untuk menghasilkan permukaan dual-fungsi. Kajian selanjutnya menganalisis permukaan dual-fungsi everolimus dinyahgerak PDA menggunakan ATR-FTIR, XPS, SEM, AFM, kebasahan, pengkuantitian everolimus, pembebasan ubat, kestabilan salutan, keserasian darah dan analisis sel endotelial secara *in-vitro*. Penyahgerakkan everolimus berjaya pada lapisan PDA melalui ikatan kovalen O–N dan C–O juga ditentukan. Everolimus berstruktur bunga menunjukkan kebasahan yang lebih rendah (103.33 ± 7.13°) dan kekasaran permukaan (784.92 ± 21.33 nm) yang lebih tinggi pada kepekatan everolimus yang lebih tinggi (0.10 mM). Profil pembebasan ubat yang mampan berdasarkan profil pembebasan tertib sifar telah diperolehi untuk kepekatan everolimus 0.05 mM dan 0.10 mM. Kepekatan everolimus yang lebih tinggi meningkatkan kestabilan salutan. Kesemua perancah dikelaskan sebagai tidak hemolisis berdasarkan hemolitik indek yang kurang 2%. Sel-sel endotelial bercambah secara meluas di permukaan PDA yang menyokong penempelan perancah di kawasan abluminal. Sementara itu, perencatan pertumbuhan sel berlaku pada permukaan everolimus. Oleh itu, keupayaan perancah dual-fungsi ini bermanfaat untuk aplikasi DES dalam mencegah komplikasi yang mugkin akan berlaku seperti pembebasan ubat yang cepat, kelewatan trombosis di dalam sten dan endoteliasasi yang lambat.

TABLE OF CONTENTS

TITLE		PAGE
DECLARATION		**iii**
DEDICATION		**iv**
ACKNOWLEDGEMENT		**v**
ABSTRACT		**vi**
ABSTRAK		**vii**
TABLE OF CONTENTS		**viii**
LIST OF TABLES		**xii**
LIST OF FIGURES		**xiii**
LIST OF ABBREVIATIONS		**xvi**
LIST OF SYMBOLS		**xix**
LIST OF APPENDICES		**xx**
CHAPTER 1	**INTRODUCTION**	**1**
1.1	Background of the Study	1
1.2	Problem Statement	4
1.3	Objective of the Study	6
1.4	Scope of the Study	6
1.5	Significance of the Study	8
CHAPTER 2	**LITERATURE REVIEW**	**9**
2.1	Introduction	9
2.2	Blood Vessel	9
2.2.1	Anatomy and Physiology of Blood Vessel	9
2.2.2	Atherosclerosis	13
2.3	Stent	16
2.3.1	Bare Metal Stent	17
2.3.2	Biodegradable Stent	18
2.3.3	Drug-Eluting Stent	20

2.4 Everolimus 22
2.4.1 Everolimus Properties and Mechanism of Action 22
2.4.2 Everolimus-Eluting Stent 24
2.5 Coating Technique 25
2.6 Polydopamine (PDA) 28
2.6.1 PDA Properties and Structure 28
2.6.2 Molecules Immobilisation on PDA layer 29
2.7 Mathematical Modelling of Drug Release Mechanism 31
2.8 Poly(lactic acid) (PLA) 33
2.8.1 Properties of PLA 33
2.8.2 PLLA and PDLA Stereo-complex 34
2.8.3 Degradation of PLA 36
2.9 Scaffold Fabrication for Biodegradable Polymeric Stent Application 37
2.9.1 Fused Deposition Modeling 3D Printing 37
2.10 Summary 38

CHAPTER 3 RESEARCH METHODOLOGY 41
3.1 Overview 41
3.2 Fabrication of PLLA/PDLA Scaffolds 43
3.2.1 Sample Preparation 43
3.2.1.1 Extrusion of PLLA/PDLA Filaments 43
3.2.1.2 3D Printing of PLLA/PDLA Scaffolds 44
3.2.2 Wettability Test 45
3.2.3 Mechanical Test 45
3.2.4 Degradation Test 46
3.2.4.1 Percentage of Remaining Weight 46
3.2.4.2 Chemical Functionality 47
3.2.4.3 Surface Morphology 47
3.2.4.4 Average Molecular Weight 47
3.2.4.5 Thermal Properties 48

3.3 Everolimus Immobilisation on PLLA/PDLA Scaffolds Mediated with PDA 49
3.3.1 Sample Preparation 49
3.3.1.1 Polydopamine Grafting 49
3.3.1.2 Everolimus Immobilisation 50
3.3.2 Characterisation Analyses 52
3.3.2.1 ATR-FTIR Analysis 52
3.3.2.2 XPS Analysis 52
3.3.2.3 SEM Analysis 52
3.3.2.4 AFM Analysis 53
3.3.3 Wettability Test 53
3.3.4 Quantification of Immobilised Everolimus 53
3.3.5 Everolimus Release Test 54
3.3.5.1 Measurement of Everolimus Release 54
3.3.5.2 Mathematical Modelling of Everolimus Release 54
3.3.6 Stability Test 55
3.3.7 Blood Compatibility Test 55
3.3.7.1 Ethical Approval and Blood Procurement 55
3.3.7.2 Haemolysis Assay 56
3.3.8 *In-vitro* HUVEC Test 56
3.3.8.1 Cell Culture and Maintenance 57
3.3.8.2 Sample Preparation for *In-vitro* Test 58
3.3.8.3 Cell Viability and Proliferation 58
3.3.8.4 Cell Attachment 59
3.4 Statistical Analysis 59

CHAPTER 4 RESULTS AND DISCUSSION 61
4.1 Overview 61
4.2 PLLA/PDLA Scaffolds 61
4.2.1 Wettability Analysis 61
4.2.2 Mechanical Analysis 62

4.2.3 Degradation Analyses 64
4.2.3.1 Chemical Functionality 65
4.2.3.2 Percentage of Remaining Weight 66
4.2.3.3 Average Molecular Weight 66
4.2.3.4 Thermal Properties 68
4.2.3.5 Surface Morphology 69
4.3 Everolimus Immobilisation Mediated with PDA 72
4.3.1 ATR-FTIR Analysis 72
4.3.2 XPS Analysis 74
4.3.3 SEM Analysis 78
4.3.4 AFM Analysis 79
4.4 Wettability Analysis 81
4.5 Quantification of Immobilised Everolimus 82
4.6 Everolimus Release Profile 83
4.7 Stability Analyses 88
4.7.1 ATR-FTIR Analysis 88
4.7.2 SEM Analysis 89
4.8 Blood Compatibility Analysis 90
4.9 *In-Vitro* Human Umbilical Vein Endothelial Cell Analyses 91
4.9.1 Cell Viability and Proliferation 91
4.9.2 Cell Attachment 93
4.10 Summary 95

CHAPTER 5 CONCLUSION AND RECOMMENDATIONS 97
5.1 Conclusion 97
5.2 Future Work and Recommendation 98

REFERENCES 101

LIST OF PUBLICATION 136

LIST OF TABLES

TABLE NO.	TITLE	PAGE
Table 2.1	Common biodegradable polymers for stent development.	20
Table 2.2	Different types of DES [94].	22
Table 2.3	Several available everolimus-eluting stents [114].	25
Table 2.4	Different stent coating techniques	26
Table 2.5	Immobilisation of different types of molecules using PDA layer.	31
Table 3.1	Blended composition of PLLA/PDLA filaments.	44
Table 3.2	Description of fabricated scaffolds.	51
Table 4.1	pH of PBS after 30 and 60 days degradation of PLLA/PDLA scaffolds.	64
Table 4.2	Thermal properties of PLLA/PDLA scaffolds, prior and following degradation test.	70
Table 4.3	Percentage of immobilised everolimus on PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10.	83
Table 4.4	Everolimus release kinetic on PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 based on different mathematical models.	86

LIST OF FIGURES

FIGURE NO.	TITLE	PAGE
Figure 2.1	Arterial and venous systems of human body [52].	10
Figure 2.2	Coronary arteries of the heart [52].	11
Figure 2.3	Anatomy of artery [55].	12
Figure 2.4	Main risk factors of atherosclerosis.	14
Figure 2.5	Stages of atherosclerosis formation: (a) Normal artery structure, (b) initial steps of atherosclerosis, (c) lesion progression involves SMC migration and (d) ultimate formation of atherosclerosis [65].	15
Figure 2.6	Schematic illustration of stent implantation [71].	16
Figure 2.7	316L stainless steel bare metal stent: (A) general photo, (B) SEM photo and (C) SEM photo of strut at higher magnification [74].	17
Figure 2.8	Biodegradable stents that are under development and/or have reached clinical trial phase [81].	19
Figure 2.9	Everolimus chemical structure [107].	23
Figure 2.10	Mechanism action of everolimus [109].	24
Figure 2.11	(a) Mussel attached to glass surface and (b) biodistribution of mussel adhesive protein [140].	29
Figure 2.12	*Mytilus edulis* mussel anatomy and byssus structures [139].	29
Figure 2.13	Polymerisation process of dopamine to PDA [143].	30
Figure 2.14	Chemical structures of (a) PLLA and (b) PDLA [162].	34
Figure 2.15	Chemical orientation of sc-PLA [170].	35
Figure 2.16	Illustration on different stages of PLA based material degradation process [78].	36
Figure 2.17	Schematic diagram of FDM 3D printing [187].	38
Figure 3.1	Flowchart of experimental procedure.	42
Figure 3.2	Schematic illustration of scaffold fabrication process.	43
Figure 3.3	(a) PLLA pellets, (b) PDLA pellets and (c) Noztek Pro desktop extruder	44

Figure 3.4	(a) Cylindrical scaffold design in 3D CAD Solidwork software, (b) Micro+ 3D printer and (c) 3D printed PLLA/PDLA scaffold.	45
Figure 3.5	Degradation test on 3D printed PLLA/PDLA scaffolds in PBS.	46
Figure 3.6	Gel permeation chromatography, GPC (Waters 515 HPLC pump) connected to laser photometer instrument.	48
Figure 3.7	Polydopamine grafting on PLLA/PDLA printed scaffolds.	50
Figure 3.8	Immobilisation of everolimus process.	51
Figure 3.9	Chemical reagents for HUVEC maintenance.	57
Figure 3.10	Schematic illustration of briefly cell culture process.	58
Figure 3.11	Sample preparation for *in-vitro* test.	58
Figure 4.1	Contact angle values on printed PLLA/PDLA scaffolds.	62
Figure 4.2	(a) Compressive strength and (b) stress-strain curve of printed PLLA/PDLA scaffolds.	63
Figure 4.3	ATR-FTIR spectra on PLLA/PDLA scaffolds, before and after degradation test.	65
Figure 4.4	Percentages of remaining weight for PLLA100, PLLA90, PLLA80 and PLLA70 after 30 and 60 days degradation in PBS.	66
Figure 4.5	Average molecular weight of printed and degraded PLLA/PDLA scaffolds.	67
Figure 4.6	DSC second heating curves of printed and degraded PLLA/PDLA scaffolds.	68
Figure 4.7	Surface morphologies of PLLA100, PLLA90, PLLA80 and PLLA70 at (a) 50× magnification, degradation day 0 and (b) 1000× magnification, degradation day 0, 30 and 60.	71
Figure 4.8	ATR-FTIR spectra of PP, PP-EVE, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05, PP-PDA-EVE0.1 and everolimus.	73
Figure 4.9	(a) XPS survey spectra and (b) high resolution spectra of C1s, O1s and N1s on PP, PP-PDA and PP-PDA-EVE surfaces.	76
Figure 4.10	Schematic illustration of possible mechanisms of covalent bonding between PDA and everolimus.	77
Figure 4.11	SEM images of PP, PP-EVE, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 surfaces.	78

Figure 4.12 (a) 3D image of AFM topography and (b) graph of average roughness, R_a on PP, PP-EVE, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 surfaces. 80

Figure 4.13 Contact angle values of PP, PP-EVE, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10. 81

Figure 4.14 Standard curve of everolimus. 82

Figure 4.15 Cumulative percentages of everolimus released for PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10. 84

Figure 4.16 Fitted mathematical model graphs of (a) zero-order, (b) first-order, (c) Higuchi, (d) Hixon-Crowell and (d) Korsmeyer-Peppas model for PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10. 85

Figure 4.17 Schematic illustration of everolimus release on (a) PP-PDA-EVE0.01 and (b) PP-PDA-EVE0.05 as well as PP-PDA-EVE0.10. 87

Figure 4.18 ATR-FTIR spectra of PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 after 28 days immersion stability test. 88

Figure 4.19 SEM images of PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 after 28 days immersion stability test. 89

Figure 4.20 Haemolysis percentages for PP, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10. 91

Figure 4.21 HUVEC viability and proliferation at day 1, 3 and 7 (* indicates $p < 0.05$) of incubation on PP, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 surfaces. 92

Figure 4.22 Morphology of attached HUVEC at day 1 and 7 of incubation on PP, PP-PDA, PP-PDA-EVE0.01, PP-PDA-EVE0.05 and PP-PDA-EVE0.10 surfaces. %CV: percentage of cell viability 94

Figure 4.23 Schematic illustration of dual-functionalised stent implantation inside blood vessel. 95

LIST OF ABBREVIATIONS

3D	-	Three Dimensional
ABS	-	Acrylonitrile Butadiene Styrene
AFM	-	Atomic Force Microscopy
AM	-	Additive Manufacturing
ANOVA	-	Analysis of Variance
ASTM	-	American Society for Testing and Materials
ATR-FTIR	-	Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy
BBE	-	Bovine Brain Extract
CAD	-	Computer-Aided Design
CNTs	-	Carbon Nanotubes
Co-cr	-	Cobalt Chromium
CVD	-	Cardiovascular Disease
DES	-	Drug-Eluting Stent
DMSO	-	Dimethyl Sulfoxide
DOPA	-	3,4-dihydroxyl-L-phenylalanine
DSC	-	Differential Scanning Calorimeter
EBM	-	Endothelial Cell Basal Medium
EC	-	Endothelial Cell
EDTA	-	Ethylenediaminetetraaceticacid
FBS	-	Fetal Bovine Serum
FDA	-	Food And Drug Administration
FDM	-	Fused Deposition Modelling
GPC	-	Gel Permeation Chromatography
hEGF	-	Human Epidermal Growth Factor
HUVEC	-	Human Umbilical Vein Endothelial Cell
ISO	-	International Organization for Standardisation
LDL	-	Low Density Lipoprotein
MAP	-	Mussel Adhesive Protein
MRI	-	Magnetic Resonance Imaging

mTOR	-	Mammalian Target of Rapamycin
MTT	-	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium
NO	-	Nitric Oxide
PBAT	-	Poly(butylene adipate terephthalate)
PBS	-	Phosphate Buffer Saline
PCI	-	Percutaneous Coronary Intervention
PCL	-	Poly(caprolactone)
PDA	-	Polydopamine
PDLA	-	Poly(d-lactic acid)
PLA	-	Poly(lactic acid)
PLGA	-	Poly(lactic-*co*-glycolic acid)
PLLA	-	Poly(l-lactic acid)
PnBMA	-	Poly(n-butyl methacrylate)
PP	-	PLLA/PDLA Scaffold
PP-PDA	-	PP Grafted Polydopamine
PP-PDA-EVEx	-	PP-PDA Immobilised Everolimus at Different Concentrations
PSI	-	Proliferation Signal Inhibitor
Pt-cr	-	Platinum Chromium
PTDC-PC	-	Poly-tyrosine-derived polycarbonater
PTFE	-	Polytetrafluoroethylene
RCA	-	Right Coronary Arteries
SAMs	-	Self-Assembly Monolayer
SC-PLA	-	Stereo-complex Poly(lactic acid)
SD	-	Standard Deviation
SEM	-	Scanning Electron Microscopy
SLA	-	Stereolithography Apparatus
SLS	-	Selective Laser Sintering
SMC	-	Smooth Muscle Cell
SS	-	Stainless Steel
Tris-HCL	-	Tris-Hydrochloride
UV	-	Ultraviolet Visible
VPSEM	-	Variable Pressure Scanning Electron Microscopy

WHO	-	World Health Organisation
XPS	-	X-Ray Photoelectron Spectroscopy

LIST OF SYMBOLS

%	-	Percentage
±	-	Plus Minus
×	-	Times
°	-	Degree
°C	-	Degree Celsius
µL	-	Microlitre
µm	-	Micrometre
eV	-	Electron Volt
g	-	Gram
g/mol	-	Gram per Mole
J/g	-	Joule per Gram
kN	-	Kilo Newton
kV	-	Kilo Volt
L	-	Litre
mg	-	Milligram
mL	-	Millilitre
mm	-	Millimetre
mM	-	Millimolar
MPa	-	Megapascal
nm	-	Nanometre
rpm	-	Revolution per Minute
W	-	Watt
wt%	-	Weight Percent

LIST OF APPENDICES

APPENDIX	TITLE	PAGE
Appendix A	Statistical Analyses	121
Appendix B	Consent Forms for Blood Compatibility Test	124
Appendix C	Statistical Analyses for Haemolysis Assay	132
Appendix D	Statistical Analyses of MTT Assay for HUVEC	133

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Coronary heart disease, stroke, peripheral arterial disease and aortic disease are several abnormalities in the heart and blood vessels which will lead to cardiovascular diseases (CVD) [1]. Deficit in blood flow to the heart cause rapid shortfall of oxygen and nutrients in the cardiac cells, thus promoting ischemia [2]. The prolong deficit blood flow leads to cardiac tissue necrosis and relative circulatory complication [2]. In 2019, approximately 18.6 million of global deaths were caused by CVD that can be associated to a significant narrowing of the artery due to atherosclerosis [3]. Diabetes, smoking habit, obesity and mental stress are among the factors that could trigger atherosclerosis [4]. It is also recognised that endothelial layer damage and inflammatory responses are two cascaded events related to the formation of atherosclerosis [5].

Stent implantation is adopted in the percutaneous coronary intervention treatment (PCI) to treat atherosclerosis [6]. Stent in combination with balloon angioplasty is a prominent treatment for atherosclerosis. It is fabricated in a shape of small tubular wire mesh, intended to open narrowed blood vessel until the vessel remodels into its normal state [6]. During stent implantation, arterial injury followed by a cascade of biological events that resulted in-stent restenosis and neointimal hyperplasia have been reported [7–9]. In-stent restenosis and neointimal hyperplasia are the results of delayed wound healing, smooth muscle cells (SMC) growth and extracellular matrix deposition within the arterial lumen [7,10]. Hence, the incorporation of stent surfaces with specific drugs and biomolecules is crucial to improve the biological and bioactive properties of the stent in preventing in-stent restenosis and neointimal hyperplasia. Drug-eluting stent (DES) is a drug-coated stent which functioned to accommodate drugs and to regulate drug release into surrounding

tissues [11]. Even though DES has the capabilities to prevent in-stent restenosis and neointimal hyperplasia [12], the burst release of drugs has triggered late-stent thrombosis and has suppressed endotheliasation as well as tissue healing following an implantation [13]. Tissues injuries have been reported in the early phase of implantation due to the implementation of several anti-proliferative drugs such as sirolimus, paclitaxel and everolimus [14].

Everolimus is a type of commercial drug that has been widely used in developing DES [15,16]. It is derived synthetically from sirolimus which is classified as an immunosuppressive agent [17]. This drug inhibits kinase, the mammalian target of rapamycin (mTOR) which is identified to have a beneficial effect in preventing atherosclerosis formation [15]. An exposure to everolimus will activate mTOR proliferation signal and induce the generation of cell cycle block in the G1 phase, thus inhibiting cell proliferation [18]. Besides, it could suppress the growth of SMC in preventing in-stent restenosis and neointimal hyperplasia [18]. This drug is beneficial in the atherosclerosis treatment but requires modification in the coating design and technique to provide dual functions of cell suppression in the luminal stent and cell integration in the abluminal stent. A successful implantation should enhance the proliferation of endothelial cells (EC) to accelerate vessel integration and should inhibit the growth of SMC to prevent clot formation [19].

In this study, an immobilisation technique was chosen to immobilise everolimus on scaffold surfaces to prevent burst drug release using the mediation of polydopamine (PDA) layer. This layer can be developed through the surface modification of based-materials with a cross-linker agent [10]. Surface modification with PDA layer has gained interest among researchers due to its ability to form strong chemical linkages on a various types of structures and materials [20,21]. This method is facile, versatile and low cost [20,21]. It has been used to modify various implant medical surfaces to immobilise antibacterial agents, proteins, nanoparticles and biomolecules [22]. There are two active functional groups presented in PDA, catechol and amine groups, which contribute to its ability to bind covalently with a broad range of inorganic, organic and metallic substrates [23,24]. This covalent linkages have motivated the exploration on element release where PDA emerges as a highly

promising candidate to stabilise and sustain the release of immobilised molecules due to its strong chemical linkages [24]. Besides, PDA layer also has assisted cell attachment and adhesion for advance tissues integration [24]. Therefore, in developing dual-functional surfaces coating on stent, PDA is the best candidate to mediate everolimus immobilisation for sustainable cell suppression purpose (luminal stent) and to enhance cell integration (abluminal stent) for vessel remodelling purpose.

In this study, everolimus was immobilised on biodegradable poly(l-lactic acid)/poly(d-lactic acid) (PLLA/PDLA) scaffolds to construct biodegradable polymeric DES. Biodegradable stent is currently attained researcher's attention due to its ability to degrade while allowing tissues regeneration [25]. Biodegradable stent made of metal is mainly being explored due to its mechanical strength to support vessel wall [26]. However, the degradation of metal product may lead to inflammation and late-stent thrombosis [26]. Therefore, much attention has been diverted to biodegradable polymeric stent which does not produce degraded and accumulated metal products in the physiological circulation system [25]. The 3D printing technique is viewed as a promising approach for the fabrication of biodegradable polymeric stents or scaffolds due to its ability to produce complex shape design [27]. It adopts an additive manufacturing (AM) technology which constructs 3D printed objects based on 3D computer-aided design (CAD) models [28]. In the biomedical field, fused deposition modelling (FDM) is frequently utilised for printing 3D structures, attributable to its high adaptability in creating distinctive forms of implant shape [29] and the ability to choose biocompatible filament materials in preventing cytotoxicity response [30]. Therefore, in this study, FDM was used to extrude filaments with different compositions of polylactic acid (PLA) derivatives.

Polylactic acid is an aliphatic polyester that has been classified as one of the most popular biodegradable polymers [31]. The use of PLA in the human body is clinically approved by the Food and Drug Administration (FDA) due to the biocompatibility factor [29]. There are two enantiomers of sc-PLA formation which are poly(l-lactide) (PLLA) and poly(d-lactide) (PDLA) [32,33]. Several research have been conducted to improve the formation, structure, mechanical and degradation properties of PLLA by combining both PLLA and PDLA, to develop sc-PLA [34–37].

The enhanced properties of sc-PLA led to the selection of these polymers as a based-material for the fabrication of biodegradable polymeric DES. In the beginning, PLLA and PDLA were blended at different compositions and 3D printed to form biodegradable scaffolds. The scaffolds were surface grafted with a PDA layer. One side of the scaffolds was immobilised with different concentrations of everolimus to develop a dual-functional surfaces coating for DES application. This dual-functional surfaces coating is proposed to prevent the proliferation of cell growth (luminal surfaces) and to support EC proliferation (abluminal surfaces) while controlling the release of anti-proliferative drugs. Thus, the novelty of the present study lies on the immobilisation of everolimus on PLLA/PDLA 3D printed scaffolds using PDA layer and the dual-functional surfaces coating of PDA and everolimus, to be potentially applied as biodegradable polymeric DES.

1.2 Problem Statement

World Health Organisation (WHO) reported that cardiovascular related diseases are the number one cause of death globally [38]. A total of 75% of the heart attack occurred from plaque rupture of atherosclerosis [39]. Atherosclerosis is being treated with PCI procedures [6]. Previous research focused on bare metal stents for PCI treatment. An early generation of this stent has several drawbacks including in-stent restenosis, stent thrombosis, poor endotheliasation and delayed wound healing that impact the effectiveness of stent implantation [40].

Drug-eluting stent is used to overcome the issues of bare metal stent. However, other complications of delayed endotheliasation and late-stent thrombosis have been reported from DES implantation [41]. The utilisation of polymer coating layer on DESs could trigger an inflammatory and hypersensitivity response which result in cardiac infraction and sudden death [42,43]. Besides, burst or rapid drug release is another DES related drawback which cause deficiencies on the delivery of therapeutic effects at the implanted lesion and impacts on late-stent thrombosis [13]. Thus, DES development with sustain drug release capability to ensure enough drug supplementation along the implantation to prevent late-stent thrombosis is immensely

needed. Sufficient amount of drugs is also needed to promote EC growth and to prevent SMC proliferation where both functions are the main roles of tissues/vascular remodelling [44].

Rapamycin drug such as everolimus has become the subject of interest in developing DES. However, the rapid release of everolimus in some cases due to non-stable coating, cause deficiencies in its therapeutic effectiveness [45]. Moreover, everolimus does not have the ability to selectively inhibit SMC and EC where a successful implantation should inhibit SMC to prevent clot formation and should enhance EC proliferation that can accelerate vessel integration [19]. Therefore, an ideal everolimus DES should has dual functions, to prevent the proliferation of SMC and to support EC proliferation.

Furthermore, a second surgery is mostly needed to remove the metal stent and to treat inflammation [46]. The revolution of biodegradable metal stent gives a promising value to overcome in-stent restenosis and stent thrombosis [47]. However, degradation of the metal products has caused inflammation and accumulation on specific organs that lead to forthcoming diseases [26]. Therefore, the attention on biodegradable metal stent has been diverged, covering the development of biodegradable polymeric stent. However, low mechanical strength and high degradation rate of biodegradable polymeric stent become major limitations for the implementation of polymeric stent to support weaken blood vessel wall [48]. It is crucial to maintain the structural of biodegradable stent at least within 6 months and to ensure element degradation instead of large compounds dissociation [49].

Modifying the polymer stent materials to increase its mechanical strength has drawn a significant challenge [19,48]. In addition, the complex structure of stent calls for a huge exploration on stenting technology to fabricate wire-mesh tubes [50,51].

1.3 Objective of the Study

The aim of this study is to develop dual-functional surfaces coating of PDA and everolimus on biodegradable polymeric materials for DES application. Therefore, the objectives of the study are stated as below:

(a) To fabricate and characterise the effects of different compositions of PDLA and PLLA on the wettability, mechanical and degradation properties of the 3D printed PLLA/PDLA biodegradable polymeric scaffolds.

(b) To assess the capability of PDA to mediate the immobilisation of everolimus on the 3D printed PLLA/PDLA scaffolds at different everolimus concentrations in developing dual-functional surfaces coating through chemical composition, morphology, roughness and wettability analyses.

(c) To determine the everolimus release mechanism and the stability of the dual-functional surfaces coating at different everolimus concentrations through an immersion approach.

(d) To investigate the blood compatibility and the responses of human umbilical vein endothelial cells (HUVEC) on the dual-functional surfaces coating through haemolysis, cytotoxicity, cell proliferation and cell attachment analyses.

1.4 Scope of the Study

In the beginning of the study, different compositions of PLLA and PDLA were blended (PLLA100, PLLA90, PLLA80 and PLLA70) to produce PLLA/PDLA filaments. The extruded filaments were installed into a 3D printer to print PLLA/PDLA scaffolds. The wettability of the printed scaffolds was identified through a contact angle measurement and the mechanical properties were determined through a compression test.

Then, the printed scaffolds were subjected to a degradation test through a static immersion in phosphate buffer saline (PBS) for 30 and 60 days at 37°C to study the degradation behaviour of PLLA/PDLA scaffolds. The pH of the degradation solution and the remaining weight of the degraded scaffolds were recorded. The degraded scaffolds were also subjected to attenuated total reflectance-Fourier transform infrared spectroscopy (ATR-FTIR), scanning electron microscopy (SEM), gel permeation chromatography (GPC) and differential scanning calorimeter (DSC) analyses, respectively, to determine the chemical functionality, morphology, molecular mass and thermal degradation of the scaffolds.

Based on the mechanical and degradation findings, the composition of PLLA80 was selected to further print the 3D PLLA/PDLA scaffolds. The PLLA/PDLA scaffolds were grafted with PDA by immersing the scaffolds in dopamine salt solution (PP-PDA). Different concentrations of everolimus (0.01 mM, 0.05 mM and 0.10 mM) were then immobilised on the PP-PDA scaffolds, partly, and known as PP-PDA-EVE*x* to develop dual-functional surfaces coating. The dual-functional surfaces coating was characterised through ATR-FTIR, X-ray photoelectron spectroscopy (XPS), SEM, atomic force microscopy (AFM) and wettability analyses.

The quantification of immobilised everolimus was performed with ultraviolet-visible (UV) spectrophotometry. The everolimus release and the stability of the dual-functional surfaces coating were assessed through a month immersion approach in deionised water. The release of everolimus profile was determined with UV spectrophotometry and five mathematical models were used to further elaborated the everolimus release mechanism. The stability of the dual-functional surfaces coating was examined under ATR-FTIR and SEM.

The compatibility of the dual-functional surfaces coating towards red blood cells was then investigated through haemolysis assay. *In-vitro* assessments of cytotoxicity and cell proliferation were also performed with HUVEC on the dual-functional surfaces coating using MTT (3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyl tetrazolium) (MTT) assay. The capability of the dual-functional surfaces coating to

inhibit cell attachment was verified on the everolimus surface while the ability of the dual-functional surfaces coating to support HUVEC integration was verified on the PDA surface under VPSEM visualisation.

1.5 Significance of the Study

This study produced dual-functional surfaces coated biodegradable scaffold which has an ability to inhibit cell growth (luminal) on one surface and has capability to support EC growth (abluminal) on another surface. These dual-functionalities are achieved by immobilising everolimus, partly, on biodegradable 3D printed PLLA/PDLA scaffolds mediated with PDA layer. While another part is accommodated with only PDA layer, without the immobilisation of everolimus.

The PDA grafted scaffold surfaces will accelerate endotheliasation process for greater vessel integration (abluminal surface) while overcome the everolimus limitation in selectively inhibiting EC. The release of everolimus will also prevent plaque formation and cell attachment in the luminal structure of stent, thus avoiding in-stent and late-stent thrombosis. Furthermore, the utilisation of PDA to mediate everolimus immobilisation is intended to control and sustain the release of everolimus.

This dual-functionalities biodegradable scaffolds have advance values in DES application as a replacement for bare metal stent, biodegradable metal stent and DES metal stent. It will prevent patients from undergoing a secondary surgery to remove metallic implant and to avoid inflammation caused by the degradation of metal products. The blending of PLLA and PDLA to form sc-PLA could provide an appropriate mechanical strength and degradation properties to biodegradable polymeric scaffolds that can be used in polymeric stent application to support weak blood vessels.

REFERENCES

[1] J.K. Olijhoek, Y. van der Graaf, J.-D. Banga, A. Algra, T.J. Rabelink, F.L.J. Visseren et al., The Metabolic Syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm, Eur. Heart J. 25 (2004), pp. 342–348.

[2] M.A. Pena-Duque, J.L. Romero-ibarra, M.B.A. Gaxiola-mac and E.A. Arias-Sanchez, Coronary Atherosclerosis and Interventional Cardiology, Arch. Med. Res. 46 (2015), pp. 372–378.

[3] Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019., Lancet (London, England) 396 (2020), pp. 1204–1222.

[4] P.K. Shah, Inflammation, infection and atherosclerosis, Trends Cardiovasc. Med. (2019), pp. 1–5.

[5] G.K. Hansson, Inflammation, atherosclerosis, and coronary artery disease., N. Engl. J. Med. 352 (2005), pp. 1685–1695.

[6] J.M. Kim, I. Bae, K.S. Lim, J. Park, D.S. Park, S. Lee et al., A method for coating fucoidan onto bare metal stent and in vivo evaluation, Prog. Org. Coat. (2014), pp. 1–9.

[7] A.C. Newby and A.B. Zaltsman, Molecular mechanisms in intimal hyperplasia, J. Pathol. 190 (2000), pp. 300–309.

[8] N. Kipshidze, G. Dangas, M. Tsapenko, J. Moses, M.B. Leon, M. Kutryk et al., Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions., J. Am. Coll. Cardiol. 44 (2004), pp. 733–739.

[9] J. Torrado, L. Buckley, A. Durán, P. Trujillo, S. Toldo, J. Valle Raleigh et al., Restenosis, Stent Thrombosis, and Bleeding Complications: Navigating Between Scylla and Charybdis, J. Am. Coll. Cardiol. 71 (2018), pp. 1676–1695.

[10] S.M. Kim, K.S. Park, E. Lih, Y.J. Hong, J.H. Kang, I.H. Kim et al., Fabrication and characteristics of dual functionalized vascular stent by spatio-temporal coating, Acta Biomater. 38 (2016), pp. 143–152.

[11] L.A. Alicea, J.I. Aviles, I.A. López, L.E. Mulero and L.A. Sánchez, Mechanics

Biomaterials : Stents, Appl. Eng. Mech. Med. (2004), pp. 1–21.

[12] T. Simard, B. Hibbert, F.D. Ramirez, M. Froeschl, Y.-X. Chen and E.R. O'Brien, The Evolution of Coronary Stents: A Brief Review, Can. J. Cardiol. 30 (2014), pp. 35–45.

[13] A. Tan, Y. Farhatnia, A. De Mel, J. Rajadas, M.S. Alavijeh and A.M. Seifalian, Inception to actualization : Next generation coronary stent coatings incorporating nanotechnology, J. Biotechnol. 164 (2013), pp. 151–170.

[14] T. Watanabe, M. Fujita, M. Awata, O. Iida, S. Okamoto, T. Ishihara et al., Integrity of stent polymer layer after drug-eluting stent implantation: in vivo comparison of sirolimus-, paclitaxel-, zotarolimus- and everolimus-eluting stents., Cardiovasc. Interv. Ther. 29 (2014), pp. 4–10.

[15] J. Hasskarl, Everolimus, Small Mol. Oncol. (2014), pp. 373–392.

[16] L. Jia and R. Hui, Everolimus , a promising medical therapy for coronary heart disease ?, Med. Hypothesis 73 (2009), pp. 153–155.

[17] S. Guethoff, C. Grinninger and I. Kaczmarek, Everolimus : Sidekick against atherosclerosis ?, Atherosclerosis 231 (2013), pp. 28–29.

[18] V.F. Panoulas, I. Mastoris, K. Konstantinou, M. Tespili and A. Ielasi, Everolimus-eluting stent platforms in percutaneous coronary intervention: comparative effectiveness and outcomes., Med. Devices (Auckl). 8 (2015), pp. 317–329.

[19] R. Hou, L. Wu, J. Wang, Z. Yang, Q. Tu, X. Zhang et al., Surface-degradable drug-eluting stent with anticoagulation, antiproliferation, and endothelialization functions, Biomolecules 9 (2019), .

[20] T.S. Sileika, H. Do Kim, P. Maniak and P.B. Messersmith, Antibacterial performance of polydopamine-modified polymer surfaces containing passive and active components, ACS Appl. Mater. Interfaces 3 (2011), pp. 4602–4610.

[21] L. Jia, F. Han, H. Wang, C. Zhu, Q. Guo, J. Li et al., Polydopamine-assisted surface modification for orthopaedic implants, J. Orthop. Transl. 17 (2019), pp. 82–95.

[22] Y. Bin Lee, Y.M. Shin, J. hye Lee, I. Jun, J.K. Kang, J.C. Park et al., Polydopamine-mediated immobilization of multiple bioactive molecules for the development of functional vascular graft materials, Biomaterials 33 (2012), pp. 8343–8352.

[23] H. Lee, S.M. Dellatore, W.M. Miller and P.B. Messersmith, Mussel-Inspired

Surface Chemistry for Multifunctional Coatings, Science (80-.). 318 (2007), pp. 426 LP – 430.

[24] Y.H. Ding, M. Floren and W. Tan, Mussel-inspired polydopamine for bio-surface functionalization, Biosurface and Biotribology 2 (2016), pp. 121–136.

[25] Z. Wang, N. Li, R. Li, Y. Li and L. Ruan, Biodegradable intestinal stents : A review, Prog. Nat. Sci. Mater. Int. 24 (2014), pp. 423–432.

[26] J. Goldman, E.R. Shearier, S. Zhao, R.J. Guillory II, F. Zhao, J. Goldman et al., Biodegradable metals for cardiovascular stents: from clinical concerns to recent Zn - alloys, Adv Heal. Mater 5 (2016), pp. 1121–1140.

[27] A. Guerra, A. Roca and J. de Ciurana, A novel 3D additive manufacturing machine to biodegradable stents, Procedia Manuf. 13 (2017), pp. 718–723.

[28] J. Goole and K. Amighi, 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems, Int. J. Pharm. 499 (2019), pp. 376–394.

[29] D. Singh, A. Babbar, V. Jain, D. Gupta, S. Saxena and V. Dwibedi, Synthesis, characterization, and bioactivity investigation of biomimetic biodegradable PLA scaffold fabricated by fused filament fabrication process, J. Brazilian Soc. Mech. Sci. Eng. 41 (2019), pp. 1–13.

[30] S.M. Oskui, G. Diamante, C. Liao, W. Shi, J. Gan, D. Schlenk et al., Assessing and Reducing the Toxicity of 3D-Printed Parts, Environ. Sci. Technol. Lett. 3 (2016), pp. 1–6.

[31] C. Chen, J. Chueh, H. Tseng, H. Huang and S. Lee, Preparation and characterization of biodegradable PLA polymeric blends, Biomaterials 24 (2003), pp. 1167–1173.

[32] T.M. Quynh, H. Mitomo, N. Nagasawa, Y. Wada, F. Yoshii and M. Tamada, Properties of crosslinked polylactides (PLLA & PDLA) by radiation and its biodegradability, Eur. Polym. J. 43 (2007), pp. 1779–1785.

[33] H. Tsuji, Poly (lactide) stereocomplexes : Formation, structure, properties, degradation and applications, Macromol. Biosci. 5 (2005), pp. 569–597.

[34] D.D.W. Charlesworth, J.A. King, D.M. Miller and C.H. Lim, In vitro flexural properties of hydroxyapatite and self-reinforced poly(L-lactic acid), J. Biomed. Mater. Res. Part A (2006), pp. 9–13.

[35] H. Tsuji, Y. Ikada, S. Hyon, Y. Kimura and T. Kitao, Stereocomplex formation between enantiomeric poly (lactic acid). VIII . Complex fibers spun from mixed solution of poly (D-lactic acid) and poly (L-lactic acid), J. Appl. Polym. Sci. 51

(1994), pp. 337–344.

[36] H. Tsuji, In vitro hydrolysis of blends from enantiomeric poly(lactide)s. Part 4: Well-homo-crystallized blend and nonblended films, Biomaterials 24 (2003), pp. 537–547.

[37] J. Zhang, H. Sato, H. Tsuji, I. Noda and Y. Ozaki, Infrared spectroscopic study of CH3 ... O=C interaction during poly (L-lactide)/ poly (D -lactide) stereocomplex formation, Macromolecules 38 (2005), pp. 1822–1828.

[38] Cardiovascular Diseases. Available at https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1.

[39] R. Pahwa and I. Jialal, Atherosclerosis, StatPearls Publishing, Treasure Island (FL), 2020.

[40] T. Htay and M.W. Liu, Drug-eluting stent : a review and update, Vasc. Health Risk Manag. 1 (2005), pp. 263–276.

[41] F. Bozsak, D. Gonzalez-Rodriguez, Z. Sternberger, P. Belitz, T. Bewley, J.-M. Chomaz et al., Optimization of Drug Delivery by Drug-Eluting Stents, PLoS One 10 (2015), pp. e0130182.

[42] I. Iakovou, L. Ge and A. Colombo, Contemporary stent treatment of coronary bifurcations., J. Am. Coll. Cardiol. 46 (2005), pp. 1446–1455.

[43] J.R. Nebeker, R. Virmani, C.L. Bennett, J.M. Hoffman, M.H. Samore, J. Alvarez et al., Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project., J. Am. Coll. Cardiol. 47 (2006), pp. 175–181.

[44] A. Strohbach and R. Busch, Polymers for Cardiovascular Stent Coatings, Int. J. Polym. Sci. (2015), pp. 1–11.

[45] M. Wu, L. Kleiner, F.W. Tang, S. Hossainy, M.C. Davies and C.J. Roberts, Surface characterization of poly(lactic acid)/everolimus and poly(ethylene vinyl alcohol)/everolimus stents, Drug Deliv. 17 (2010), pp. 376–384.

[46] J. Zheng, L. Liu, Y. Cao, D. Zhang, R. Wang and J. Zhao, Carotid Endarterectomy with Stent Removal in Management of In-stent Restenosis : A Safe , Feasible , and Effective Technique, Eur. J. Vasc. Endovasc. Surg. 47 (2013), pp. 8–12.

[47] J. Foerst, M. Vorpahl, M. Engelhardt, T. Koehler, K. Tiroch and R. Wessely, Evolution of Coronary Stents : From Bare-Metal Stents to Fully Biodegradable , Drug-Eluting Stents, Comb Prod Ther 3 (2013), pp. 9–24.

[48] H.Y. Ang, Y.Y. Huang, S.T. Lim, P. Wong, M. Joner and N. Foin, Mechanical behavior of polymer-based vs . metallic-based bioresorbable stents, J. Thorac. Dis. 9 (2017), pp. S923–S934.

[49] M. Peuster, P. Wohlsein, M. Brügmann, M. Ehlerding, K. Seidler, C. Fink et al., A novel approach to temporary stenting : degradable cardiovascular stents produced from corrodible metal — results 6 – 18 months after implantation into New Zealand white rabbits1. Peuster M, Wohlsein P, Brügmann M, Ehlerding M, Seidler K, Fink C, et al. , Heart 1000 (2001), pp. 563–569.

[50] A. Melocchi, F. Parietti, A. Maroni, A. Foppoli, A. Gazzaniga and L. Zema, Hot-melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling, Int. J. Pharm. 509 (2016), pp. 255–263.

[51] S. Farah, D.G. Anderson and R. Langer, Physical and mechanical properties of PLA, and their functions in widespread applications — A comprehensive review, Adv. Drug Deliv. Rev. 107 (2016), pp. 367–392.

[52] I. Peate, Anatomy and physiology, 8. The circulatory system, Br. J. Healthc. Assist. 12 (2018), pp. 62–67.

[53] I. Peate, The circulatory system, Br. J. Healthc. Assist. 14 (2020), pp. 548–553.

[54] C. Vlachopoulos, M. O'Rourke and W.W. Nichols, McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles, 6th editioCRC Press, 2011.

[55] G.A. Holzapfel, T.C. Gasser and R.W. Ogden, A New Constitutive Framework for Arterial Wall Mechanics and a Comparative Study of Material Models, J. Elast. Phys. Sci. solids 61 (2000), pp. 1–48.

[56] D.K. Molina and V.J.M. DiMaio, Normal organ weights in men: part I-the heart., Am. J. Forensic Med. Pathol. 33 (2012), pp. 362–367.

[57] Anatomy, Thorax, Pericardium. Available at https://www.ncbi.nlm.nih.gov/books/NBK482256/.

[58] A. Saxton, R. Chaudhry and B. Manna, Anatomy, Thorax, Heart Right Coronary Arteries., Treasure Island (FL), 2021, .

[59] T.E. Carew, R. Vaishnav and D.J. Patel, Compressibility of the Arterial Wall, Circ. Res. 23 (1968), pp. 61–68.

[60] A. Ostadfar, Biofluid Mechanics: Principles and Applications, Academic Press, 2016.

[61] F.H. Epstein, Atherosclerosis - An Inflammatory Disease, N. Engl. J. Med.

(1999), pp. 115–126.

[62] V.L. Roger, A.S. Go, D.M. Lloyd-jones, R.J. Adams, J.D. Berry, T.M. Brown et al., Heart Disease and Stroke Statistics — 2011 Update: A Report From the American Heart Association, 2013.

[63] N. Torres, M. Guevara-Cruz, L.A. Velazquez-Villegas and A.R. Tovar, Nutrition and Atherosclerosis, Arch. Med. Res. 46 (2015), pp. 408–426.

[64] R.J. Esper, R.A. Nordaby, J.O. Vilariño, A. Paragano, J.L. Cacharrón and R.A. Machado, Endothelial dysfunction: a comprehensive appraisal., Cardiovasc. Diabetol. 5 (2006), pp. 4.

[65] P. Libby, P.M. Ridker and G.K.. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature 473 (2011), pp. 317–325.

[66] G.H. Tomkin and D. Owens, The chylomicron: relationship to atherosclerosis., Int. J. Vasc. Med. 2012 (2012), pp. 784536.

[67] K. Kim, S. Ivanov and J.W. Williams, Monocyte Recruitment, Specification, and Function in Atherosclerosis, Cells 10 (2021), pp. 1–16.

[68] U. Schönbeck, F. Mach, G.K. Sukhova, C. Murphy, J.Y. Bonnefoy, R.P. Fabunmi et al., Regulation of matrix metalloproteinase expression in human vascular smooth muscle cells by T lymphocytes: a role for CD40 signaling in plaque rupture?, Circ. Res. 81 (1997), pp. 448–454.

[69] B. Dave, Bioresorbable scaffolds: Current evidences in the treatment of coronary artery disease, J. Clin. Diagnostic Res. 10 (2016), pp. 37–48.

[70] I. Neamtu, A.P. Chiriac, A. Diaconu, L.E. Nita, V. Balan and M.T. Nistor, Current concepts on cardiovascular stent devices., Mini Rev. Med. Chem. 14 (2014), pp. 505–536.

[71] How Is Coronary Angioplasty Done?. Available at http://www.nhlbi.nih.gov/%0Ahealth/health-topics/topics/angioplasty/howdone.html.

[72] H.C. Lowe, S.N. Oesterle and L.M. Khachigian, Coronary in-stent restenosis: Current status and future strategies, J. Am. Coll. Cardiol. 39 (2002), pp. 183–193.

[73] A survey of stent designs., Minim. invasive Ther. allied Technol. MITAT Off. J. Soc. Minim. Invasive Ther. 11 (2002), pp. 137–147.

[74] S. Jin, X. Qi, B. Zhang, Z. Sun, B. Zhang, H. Yang et al., Evaluation of promoting effect of a novel Cu-bearing metal stent on endothelialization process

from in vitro and in vivo studies, Sci. Rep. 7 (2017), pp. 1–13.

[75] G. Mani, M.D. Feldman, D. Patel and C.M. Agrawal, Coronary stents: A materials perspective, Biomaterials 28 (2007), pp. 1689–1710.

[76] M. Santos, M.M.M. Bilek and S.G. Wise, Plasma-synthesised carbon-based coatings for cardiovascular applications, Biosurface and Biotribology 1 (2015), pp. 146–160.

[77] Developments in metallic biodegradable stents. 2010.

[78] Y. Onuma and P.W. Serruys, Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization?, Circulation 123 (2011), pp. 779–797.

[79] M. Moravej and D. Mantovani, Biodegradable metals for cardiovascular stent application: Interests and new opportunities, Int. J. Mol. Sci. 12 (2011), pp. 4250–4270.

[80] A.P. Mathew, K. Oksman and M. Sain, Mechanical properties of biodegradable composites from poly lactic acid (PLA) and microcrystalline cellulose (MCC), J. Appl. Polym. Sci. 97 (2005), pp. 2014–2025.

[81] Y. Zhang, C. V Bourantas, V. Farooq, T. Muramatsu, R. Diletti, Y. Onuma et al., Bioresorbable scaffolds in the treatment of coronary artery disease, Med. Devices (Auckl). 6 (2013), pp. 37–48.

[82] R.C. Eberhart, S.-H. Su, K.T. Nguyen, M. Zilberman, L. Tang, K.D. Nelson et al., Review: Bioresorbable polymeric stents: current status and future promise, J. Biomater. Sci. Polym. Ed. 14 (2003), pp. 299–312.

[83] S.A. Park, S.J. Lee, K.S. Lim, I.H. Bae, J.H. Lee, W.D. Kim et al., In vivo evaluation and characterization of a bio-absorbable drug-coated stent fabricated using a 3D-printing system, Mater. Lett. 141 (2015), pp. 355–358.

[84] I. Izsó and L. Asztalos, Development Options for Coronary Stent Coatings, Acta Mater. Transylvanica 3 (2020), pp. 70–75.

[85] H. Tsuji and T. Tsuruno, Accelerated hydrolytic degradation of Poly(l-lactide)/Poly(d-lactide) stereocomplex up to late stage, Polym. Degrad. Stab. 95 (2010), pp. 477–484.

[86] M. Bartkowiak-Jowsa, R. Będziński, B. Szaraniec and J. Chłopek, Mechanical, biological, and microstructural properties of biodegradable models of polymeric stents made of PLLA and alginate fibers., Acta Bioeng. Biomech. 13 (2011), pp. 21–28.

[87] P.J. Gandhi, Z. Venkata and P. Murthy, Investigation of Di ff erent Drug Deposition Techniques on Drug Releasing Properties of Cardiovascular Drug Coated Balloons, Ind. Eng. Chem. Res. 52 (2012), pp. 10800–10823.

[88] C.M. McKittrick, S. Kennedy, K.G. Oldroyd, S. McGinty and C. McCormick, Modelling the Impact of Atherosclerosis on Drug Release and Distribution from Coronary Stents, Ann. Biomed. Eng. 44 (2016), pp. 477–487.

[89] M.-C. Morice, P.W. Serruys, J.E. Sousa, J. Fajadet, E. Ban Hayashi, M. Perin et al., A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization., N. Engl. J. Med. 346 (2002), pp. 1773–1780.

[90] D.J. Kereiakes, I.T. Meredith, S. Windecker, R. Lee Jobe, S.R. Mehta, I.J. Sarembock et al., Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II Randomized Trial., Circ. Cardiovasc. Interv. 8 (2015), .

[91] G.W. Stone, S.G. Ellis, D.A. Cox, J. Hermiller, C. O'Shaughnessy, J.T. Mann et al., One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial., Circulation 109 (2004), pp. 1942–1947.

[92] L. Mauri, J.M. Massaro, S. Jiang, I. Meredith, W. Wijns, J. Fajadet et al., Long-term clinical outcomes with zotarolimus-eluting versus bare-metal coronary stents., JACC. Cardiovasc. Interv. 3 (2010), pp. 1240–1249.

[93] D.E. Kandzari, M.B. Leon, I. Meredith, J. Fajadet, W. Wijns and L. Mauri, Final 5-year outcomes from the Endeavor zotarolimus-eluting stent clinical trial program: comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents., JACC. Cardiovasc. Interv. 6 (2013), pp. 504–512.

[94] I. Rykowska, I. Nowak and R. Nowak, Drug-eluting stents and balloons-materials, structure designs, and coating techniques: A review, Molecules 25 (2020), .

[95] R. Jabara, N. Chronos and K. Robinson, Novel bioabsorbable salicylate-based polymer as a drug-eluting stent coating., Catheter. Cardiovasc. Interv. Off. J. Soc. Card. Angiogr. Interv. 72 (2008), pp. 186–194.

[96] N. Bricout, F. Chai, J. Sobocinski, A. Hertault, W. Laure, A. Ung et al., Immobilisation of an anti-platelet adhesion and anti-thrombotic drug (EP224283) on polydopamine coated vascular stent promoting anti-

thrombogenic properties, Mater. Sci. Eng. C 113 (2020), pp. 110967.

[97] A.I. Sánchez-fructuoso, Everolimus : an update on the mechanism of action , pharmacokinetics and recent clinical trials, Expert Opin. Drug Metab. Toxicol. 4 (2008), pp. 807–819.

[98] J.C. Townsend, P. Rideout and D.H. Steinberg, Everolimus-eluting stents in interventional cardiology, Vasc. Health Risk Manag. 8 (2012), pp. 393–405.

[99] M.B. Atkins, U. Yasothan and P. Kirkpatrick, Everolimus, Nat. Rev. Drug Discov. 8 (2009), pp. 535–536.

[100] R.R. Martee, J. Klicius and S. Galet, Inhibition of the immune response by rapamycin , a new fungal antibiotic, Can. J. Physiol. Pharmacol. 55 (1977), pp. 48–51.

[101] D.P. Houchens, A.A. Ovejera, S.M. Riblet and D.E. Slagel, Human Brain Tumor Xenografts a Chemotherapy Model * in Nude Mice as, Eur. J. Cancer Clin. Oncol. 19 (1983), pp. 799–805.

[102] A.Q.C. Angiography, J.E. Sousa, M.A. Costa, A. Abizaid, A.S. Abizaid, F. Feres et al., Lack of Neointimal Proliferation After Implantation of Sirolimus-Coated Stents in Human Coronary Arteries: A Quantitative Coronary Angiography and Three-DImensional Intravascular Ultrasound Study, Circulation 103 (2001), pp. 192–195.

[103] C. Vezina, A. Kudelski and S.N. Sehgal, Rapamycin (AY-22,989), a New Antifungal Antibiotic. I. Taxonomy of The Producing Streptomycete and Isolation of The active Principle, J. Antibiot. (Tokyo). 28 (1975), pp. 721–726.

[104] S. Faivre, G. Kroemer and E. Raymond, Current development of mTOR inhibitors as anticancer agents, Nat. Rev. Drug Discov. 5 (2006), pp. 671–688.

[105] J. Daemen, P. Wenaweser, K. Tsuchida, L. Abrecht, S. Vaina, C. Morger et al., Early and late coronary stent thrombosis of sirolimus- eluting and paclitaxel-eluting stents in routine clinical practice : data from a large two-institutional cohort study, Lancet 369 (2005), pp. 667–678.

[106] N. Van Boven, S. Windecker, V.A. Umans, R.T. Van Domburg, I. Kardys, K.M. Akkerhuis et al., Stent thrombosis in early-generation drug-eluting stents versus newer-generation everolimus-eluting stent assorted by LVEF, Heart 101 (2015), pp. 50–57.

[107] D.J.A.R. Moes, H. Guchelaar and J.W. De Fijter, Sirolimus and everolimus in kidney transplantation, Drug Discov. Today 20 (2015), .

[108] M. Laplante and D.M. Sabatini, Review mTOR Signaling in Growth Control and Disease, Cell 149 (2012), pp. 274–293.

[109] J. Daemen and P.W. Serruys, Drug-Eluting Stent Update 2007, Circulation 116 (2007), pp. 316–328.

[110] H.A. Lane, J.M. Wood, P.M.J. Mcsheehy, P.R. Allegrini, A. Boulay, J. Brueggen et al., mTOR Inhibitor RAD001 (Everolimus) Has Antiangiogenic/Vascular Properties Distinct from a VEGFR Tyrosine Kinase Inhibitor, Clin. Cancer Res. 15 (2009), pp. 1612–1623.

[111] M. Pan, F. Burzotta, C. Trani, A. Medina, J.S. de Lezo, G. Niccoli et al., Three-year follow -up of patient with bifurcation lesion treated with sirolimus- or everolimus-eluting stents: SEAside and CORpal Cooperative study, Res Esp Cardiol. 67 (2014), pp. 797–803.

[112] C.M. Campos, H.M. Garcia-garcia, T. Muramatsu, D.A. Gonc, Y. Onuma, D. Dudek et al., Impact of the Everolimus-eluting Bioresorbable Scaffold in Coronary Atherosclerosis, Res Esp Cardiol 69 (2016), pp. 109–116.

[113] M. Almalla, J.W. Schröder, V. Pross, E. Stegemann, N. Marx, R. Hoffmann et al., Everolimus-Eluting Versus Paclitaxel-Eluting Stents for Treatment of Bare Metal Stent Restenosis, Am. J. Cardiol. (2010), .

[114] S. Borhani, S. Hassanajili, S.H. Ahmadi Tafti and S. Rabbani, Cardiovascular Stents: Overview, Evolution, and next Generation, Vol. 7, Springer Berlin Heidelberg, 2018.

[115] S. Park, S.H. Bhang, W.-G. La, J. Seo, B.-S. Kim and K. Char, Dual roles of hyaluronic acids in multilayer films capturing nanocarriers for drug-eluting coatings, Biomaterials 33 (2012), pp. 5468–5477.

[116] Y. Wang, W. Zhang, J. Zhang, W. Sun, R. Zhang and H. Gu, Fabrication of a novel polymer-free nanostructured drug-eluting coating for cardiovascular stents., ACS Appl. Mater. Interfaces 5 (2013), pp. 10337–10345.

[117] S. Diaz-Rodriguez, C. Rasser, J. Mesnier, P. Chevallier, R. Gallet, C. Choqueux et al., Coronary stent CD31-mimetic coating favours endothelialization and reduces local inflammation and neointimal development in vivo, Eur. Heart J. 42 (2021), pp. 1760–1769.

[118] A. Gallo and G. Mani, A stent for co-delivering paclitaxel and nitric oxide from abluminal and luminal surfaces: Preparation, surface characterization, and in vitro drug release studies, Appl. Surf. Sci. 279 (2013), pp. 216–232.

[119] J.M. Morais, F. Papadimitrakopoulos and D.J. Burgess, Biomaterials/tissue interactions: possible solutions to overcome foreign body response., AAPS J. 12 (2010), pp. 188–196.

[120] Y. Levy, D. Mandler, J. Weinberger and A.J. Domb, Evaluation of drug-eluting stents' coating durability--clinical and regulatory implications., J. Biomed. Mater. Res. B. Appl. Biomater. 91 (2009), pp. 441–451.

[121] J. Jiang, L. Zhu, L. Zhu, H. Zhang, B. Zhu and Y. Xu, Antifouling and antimicrobial polymer membranes based on bioinspired polydopamine and strong hydrogen-bonded poly(n -vinyl pyrrolidone), ACS Appl. Mater. Interfaces 5 (2013), pp. 12895–12904.

[122] M. Ammam, Electrophoretic deposition under modulated electric fields: a review, RSC Adv. 2 (2012), pp. 7633–7646.

[123] M. Livingston and A. Tan, Coating Techniques and Release Kinetics of Drug-Eluting Stents, J. Med. Device. 10 (2019), pp. 10.1115/1.4031718.

[124] Y. Huang, M. Hao, X. Nian, H. Qiao, X. Zhang, X. Zhang et al., Strontium and copper co-substituted hydroxyapatite-based coatings with improved antibacterial activity and cytocompatibility fabricated by electrodeposition, Ceram. Int. 42 (2016), pp. 11876–11888.

[125] T.M. Bedair, W. Park, B.-J. Park, M.-W. Moon, K.-R. Lee, Y.K. Joung et al., Dual-Layer Coated Drug-Eluting Stents with Improved Degradation Morphology and Controlled Drug Release, Macromol. Res. 26 (2018), pp. 641–649.

[126] M.-C. Chen, H.-F. Liang, Y.-L. Chiu, Y. Chang, H.-J. Wei and H.-W. Sung, A novel drug-eluting stent spray-coated with multi-layers of collagen and sirolimus., J. Control. Release 108 (2005), pp. 178–189.

[127] M. Pagel and A.G. Beck-Sickinger, Multifunctional biomaterial coatings: synthetic challenges and biological activity: , Biol. Chem. 398 (2017), pp. 3–22.

[128] Y. Wang and X. Zhang, Vascular restoration therapy and bioresorbable vascular scaffold, Regen. Biomater. 1 (2014), pp. 49–55.

[129] R. Batul, M. Bhave, P.J. Mahon and A. Yu, Polydopamine Nanosphere with In-situ Loaded Gentamicin and Its Antimicrobial Activity, Molecules 25 (2020), pp. 1–13.

[130] H. Lee, S.. Dellatore, W.. Miller and P.. Messersmith, Mussel-Ispired Surface

Chemistry for Multifunctional coating, Science 318 (2007), pp. 426–430.

[131] C.D. Hodneland, Y.-S. Lee, D.-H. Min and M. Mrksich, Selective immobilization of proteins to self-assembled monolayers presenting active site-directed capture ligands, Proc. Natl. Acad. Sci. U. S. A. 99 (2002), pp. 5048–5052.

[132] R. Langer and D.A. Tirrell, Designing materials for biology and medicine, Nature 428 (2004), pp. 487–492.

[133] G. Wu, P. Li, H. Feng, X. Zhang and P.K. Chu, Engineering and functionalization of biomaterials via surface modi fi cation, J. Mater. Chem. B 3 (2015), pp. 2024–2042.

[134] J. Zhu, Bioactive modification of poly(ethylene glycol) hydrogels for tissue engineering, Biomaterials 31 (2010), pp. 4639–4656.

[135] R.G. Nuzzo, F.A. Fusco and D.L. Allara, Spontaneously organized molecular assemblies. 3. Preparation and properties of solution adsorbed monolayers of organic disulfides on gold surfaces, J. Am. Chem. Soc. 109 (1987), pp. 2358–2368.

[136] S. Saidin, P. Chevallier, M.R. Abdul Kadir, H. Hermawan and D. Mantovani, Polydopamine as an intermediate layer for silver and hydroxyapatite immobilisation on metallic biomaterials surface, Mater. Sci. Eng. C 33 (2013), pp. 4715–4724.

[137] T.S. Natarajan, C.H. Tsai, H.L. Huang, K.S. Ho, I. Lin and Y.F. Wang, Fabrication of polyaniline coated plasma modified polypropylene filter for antibioaerosol application, Aerosol Air Qual. Res. 16 (2016), pp. 1911–1921.

[138] Y. Liu, C. Xu, Y. Gu, X. Shen, Y. Zhang, B. Li et al., Polydopamine-modified poly(L-lactic acid) nanofiber scaffolds immobilized with an osteogenic growth peptide for bone tissue regeneration, RSC Adv. 9 (2019), pp. 11722–11736.

[139] H.G. Silverman and F.F. Roberto, Understanding Marine Mussel Adhesion, Mar. Biotechnol. 9 (2007), pp. 661–681.

[140] H. Lee, N.F. Scherer and P.B. Messersmith, Single-molecule mechanics of mussel adhesion, Proc. Natl. Acad. Sci. 103 (2006), pp. 12999 LP – 13003.

[141] M.J. Harrington, A. Masic, N. Holten-Andersen, J.H. Waite and P. Fratzl, Iron-Clad Fibers: A Metal-Based Biological Strategy for Hard Flexible Coatings, Science (80-.). 328 (2010), pp. 216 LP – 220.

[142] J.H. Waite and X. Qin, Polyphosphoprotein from the adhesive pads of Mytilus

edulis, Biochemistry 40 (2001), pp. 2887–2893.

[143] Y. Hu, W. Dan, S. Xiong, Y. Kang, A. Dhinakar, J. Wu et al., Development of collagen/polydopamine complexed matrix as mechanically enhanced and highly biocompatible semi-natural tissue engineering scaffold, Acta Biomater. 47 (2017), pp. 135–148.

[144] N.M. Daud, N.A. Masri, N.A.N. Nik Malek, S.I. Abd Razak and S. Saidin, Long-term antibacterial and stable chlorhexidine-polydopamine coating on stainless steel 316L, Prog. Org. Coatings 122 (2018), pp. 147–153.

[145] X. Yu, J. Walsh and M. Wei, Covalent immobilization of collagen on titanium through polydopamine coating to improve cellular performances of MC3T3-E1 cells, RSC Adv. 4 (2014), pp. 7185–7192.

[146] Z. Yang, Q. Tu, Y. Zhu, R. Luo, X. Li, Y. Xie et al., Mussel-inspired coating of polydopamine directs endothelial and smooth muscle cell fate for re-endothelialization of vascular devices., Adv. Healthc. Mater. 1 (2012), pp. 548–559.

[147] R. Batul, T. Tamanna, A. Khaliq and A. Yu, Recent progress in the biomedical applications of polydopamine nanostructures, Biomater. Sci. 5 (2017), pp. 1204–1229.

[148] C.H. Yeh, Y.W. Chen, M.Y. Shie and H.Y. Fang, Poly(Dopamine)-assisted immobilization of Xu Duan on 3D printed poly(Lactic Acid) scaffolds to up-regulate osteogenic and angiogenic markers of bone marrow stem cells, Materials (Basel). 8 (2015), pp. 4299–4315.

[149] N. Mohd Daud, I.F. Saeful Bahri, N.A.N. Nik Malek, H. Hermawan and S. Saidin, Immobilization of antibacterial chlorhexidine on stainless steel using crosslinking polydopamine film: Towards infection resistant medical devices, Colloids Surfaces B Biointerfaces 145 (2016), pp. 130–139.

[150] X. Li, Y. Wang, M. Guo, Z. Wang, N. Shao, P. Zhang et al., Degradable Three Dimensional-Printed Polylactic Acid Scaffold with Long-Term Antibacterial Activity, ACS Sustain. Chem. Eng. 6 (2018), pp. 2047–2054.

[151] Y. Zhang, F. Wang, Q. Huang, A.B. Patil, J. Hu, L. Fan et al., Layer-by-layer immobilizing of polydopamine-assisted ε-polylysine and gum Arabic on titanium: Tailoring of antibacterial and osteogenic properties, Mater. Sci. Eng. C 110 (2020), pp. 110690.

[152] T. He, W. Zhu, X. Wang, P. Yu, S. Wang, G. Tan et al., Polydopamine assisted

immobilisation of copper(II) on titanium for antibacterial applications, Mater. Technol. 30 (2015), pp. B68–B72.

[153] N.A. Peppas and B. Narasimhan, Mathematical models in drug delivery: How modeling has shaped the way we design new drug delivery systems, J. Control. Release 190 (2014), pp. 75–81.

[154] J. Siepmann and F. Siepmann, Mathematical modeling of drug dissolution, Int. J. Pharm. 453 (2013), pp. 12–24.

[155] M.L.B.T.-S. to M. the D.R. from P.S. Bruschi, ed., 5 - Mathematical models of drug release, Woodhead Publishing, 2015, pp. 63–86.

[156] M.P. Paarakh, P.A.N.I. Jose, C.M. Setty and G. V Peter, Release Kinetics – Concepts And Applications, Int. J. Pharm. Res. Technol. (2018), pp. 12–20.

[157] B.A. Hadaschik, R.F. Paterson, L. Fazli, K.W. Clinkscales, S.W. Shalaby and B.H. Chew, Investigation of a novel degradable ureteral stent in a porcine model., J. Urol. 180 (2008), pp. 1161–1166.

[158] M.M. Torki, S. Hassanajili and M.M. Jalisi, Design optimizations of PLA stent structure by FEM and investigating its function in a simulated plaque artery, Math. Comput. Simul. 169 (2020), pp. 103–116.

[159] X. Shi, J. Qin, L. Wang, L. Ren, F. Rong, D. Li et al., Introduction of stereocomplex crystallites of PLA for the solid and microcellular poly(lactide)/ poly(butylene adipate-co-terephthalate) blends, R. Soc. Chem. 8 (2018), pp. 11850–11861.

[160] R.P. Babu, K.O. Connor and R. Seeram, Current progress on bio-based polymers and their future trends, Prog. Biomater. 2 (2013), pp. 1–16.

[161] Y. Ikada, K. Jamshidi, Hideto Tsuji and S.-H. Hyon, Stereocomplex Formation between Enantiomeric, Macromolecules 1 (1987), pp. 904–906.

[162] C.M. Chan, L.J. Vandi, S. Pratt, P. Halley, D. Richardson, A. Werker et al., Composites of wood and biodegradable thermoplastics: A review, Polym. Rev. 58 (2018), pp. 444–494.

[163] E.H. Baran and H.Y. Erbil, Surface modification of 3D printed PLA objects by fused deposition modeling : A review, Colloids and interfaces 3 (2019), .

[164] F. Luo, A. Fortenberry, J. Ren and Z. Qiang, Recent Progress in Enhancing Poly (Lactic Acid) Stereocomplex Formation for Material Property Improvement, Front. Chem. 8 (2020), pp. 1–8.

[165] F. Tasaka, Y. Ohya and T. Ouchi, One-Pot Synthesis of Novel Branched

Polylactide Through the Copolymerization of Lactide with Mevalonolactone, Macromol. Rapid Commun. 22 (2001), pp. 820–824.

[166] K. Zhang, A.K. Mohanty and M. Misra, Fully Biodegradable and Biorenewable Ternary Blends from Polylactide , Poly (3-hydroxybutyrate-co-hydroxyvalerate) and Poly (butylene succinate) with Balanced Properties, Appl. Mater. Interfaces 4 (2012), pp. 3091–3101.

[167] Z. Jing, X. Shi, G. Zhang and R. Lei, Investigation of poly (lactide) stereo-complexation between linear poly (L -lactide) and PDLA-PEG-PDLA tri-block copolymer, Polym. Int. 64 (2015), pp. 1399–1407.

[168] X. Shi, G. Zhang, C. Siligardi, G. Ori and A. Lazzeri, Comparison of Precipitated Calcium Carbonate / Polylactic Acid and Halloysite / Polylactic Acid Nanocomposites, J. Nanomater. (2015), pp. 1–11.

[169] Z. Sun, L. Wang, J. Zhou, X. Fan, H. Xie, H. Zhang et al., Influence of Polylactide (PLA) Stereocomplexation on the Microstructure of PLA / PBS Blends and the Cell Morphology of Their Microcellular Foams, Polymers (Basel). 12 (2020), pp. 1–15.

[170] R. Ahmed, Poly (lactic acid) stereocomplex formation in the melt : limitations and prospectives, Eindhoven University of Technology, 2011.

[171] K. Fukushima and Y. Kimura, Stereocomplexed polylactides (Neo-PLA) as high-performance bio-based polymers : their formation , properties , and application, Polym. Int. 55 (2006), pp. 626–642.

[172] H. Tsuji, Y. Ikada, S. Hyon, Y. Kimura and T. Kitao, Stereocomplex Formation Between Enantiomeric Poly (lactic acid). VIII . Complex Fibers Spun from Mixed Solution of Poly (D-lactic acid) and Poly (L-lactic acid), J. Appl. Polym. Sci. 51 (1994), pp. 337–344.

[173] J. Zhang, H. Sato, H. Tsuji, I. Noda and Y. Ozaki, Infrared Spectroscopic Study of CH 3 ,,, O d C Interaction during Poly (L -lactide)/ Poly (D -lactide) Stereocomplex Formation, Macromolecules 38 (2005), pp. 1822–1828.

[174] H. Tsuji, Poly (lactide) Stereocomplexes : Formation , Structure , Properties , Degradation , and Applications, Macromol. Biosci. 5 (2005), pp. 569–597.

[175] X. Zhang, M. Kotaki, S. Okubayashi and S. Sukigara, Effect of electron beam irradiation on the structure and properties of electrospun PLLA and PLLA/PDLA blend nanofibers, Acta Biomater. 6 (2010), pp. 123–129.

[176] D. Kenny and Z.M. Hijazi, Bioresorbable stents for pediatric practice: Where

are we now?, Interv. Cardiol. 7 (2015), pp. 245–255.

[177] Y. Zhu, K. Yang, R. Cheng, Y. Xiang, T. Yuan, Y. Cheng et al., The current status of biodegradable stent to treat benign luminal disease, Mater. Today 20 (2017), pp. 516–529.

[178] D. Brie, P. Penson, M.-C. Serban, P.P. Toth, C. Simonton, P.W. Serruys et al., Bioresorbable scaffold - A magic bullet for the treatment of coronary artery disease?, Int. J. Cardiol. 215 (2016), pp. 47–59.

[179] J. Goole and K. Amighi, 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems, Int. J. Pharm. 499 (2016), pp. 376–394.

[180] L.E. Diment, M.S. Thompson and J.H.M. Bergmann, Clinical efficacy and effectiveness of 3D printing: a systematic review, BMJ Open 7 (2017), pp. e016891.

[181] S.A.M. Tofail, E.P. Koumoulos, A. Bandyopadhyay, S. Bose, L. O'Donoghue and C. Charitidis, Additive manufacturing: scientific and technological challenges, market uptake and opportunities, Mater. Today 21 (2018), pp. 22–37.

[182] P. AU - Chung, J.A. AU - Heller, M. AU - Etemadi, P.E. AU - Ottoson, J.A. AU - Liu, L. AU - Rand et al., Rapid and Low-cost Prototyping of Medical Devices Using 3D Printed Molds for Liquid Injection Molding, JoVE (2014), pp. e51745.

[183] D.K. Tan, M. Maniruzzaman and A. Nokhodchi, Advanced pharmaceutical applications of hot-melt extrusion coupled with fused deposition modelling (FDM) 3D printing for personalised drug delivery, Pharmaceutics 10 (2018), .

[184] A.W. Martinez and E.L. Chaikof, Microfabrication and nanotechnology in stent design, Wiley Interdiscip. Rev. Nanomedicine Nanobiotechnology 3 (2011), pp. 256–268.

[185] J. Gonzalez, J. Rydz, M. Musio, W. Sikorska, A. Hercog and M. Kowalczuk, Three-dimensional printing of PLA and PLA/PHA dumbbell-shaped specimens of crisscross and transverse patterns as promising materials in emerging application areas : Prediction study, Polym. Degrad. Stab. 156 (2018), pp. 100–110.

[186] W. Liu, J. Zhou, Y. Ma, J. Wang and J. Xu, Fabrication of PLA filaments and its printable performance, IOP Conf. Ser. Mater. Sci. Eng. 275 (2017), pp. 1–6.

[187] M.A. Alhnan, T.C. Okwuosa, M. Sadia, K.-W. Wan, W. Ahmed and B. Arafat,

Emergence of 3D Printed Dosage Forms: Opportunities and Challenges, Pharm. Res. 33 (2016), pp. 1817–1832.

[188] A.H. Yusop, M.N. Sarian, F.S. Januddi, Q.U. Ahmed, M.R. Kadir, D. Hartanto et al., Structure, degradation, drug release and mechanical properties relationships of iron-based drug eluting scaffolds: The effects of PLGA, Mater. Des. 160 (2018), pp. 203–217.

[189] F1635-16, Standard test method for in vitro degradation testing of hydrolytically degradable polymer resins and fabricated forms for surgical implants, (2018), pp. 1–7.

[190] G. Sabbatier, A. Larrañaga, A.A. Guay-Bégin, J. Fernandez, F. Diéval, B. Durand et al., Design, degradation mechanism and long-term cytotoxicity of poly(L-lactide) and poly(Lactide-co-ε-Caprolactone) terpolymer film and air-spun nanofiber scaffold, Macromol. Biosci. 15 (2015), pp. 1392–1410.

[191] M.A. Jumat, P. Chevallier, D. Mantovani, F. Copes, S.I.A. Razak and S. Saidin, Three-dimensional printed biodegradable poly(l-lactic acid)/(poly(d-lactic acid) scaffold as an intervention of biomedical substitute, Polym. Technol. Mater. 60 (2021), pp. 1005–1015.

[192] S.T. Robinson, Everolimus for the Prevention of Allograft Rejection and Vasculopathy in Cardiac-Transplant Recipients, Surv. Anesthesiol. 48 (2004), pp. 160.

[193] J. Shao, Y. Guo, S. Xiang, D. Zhou, X. Bian, J. Sun et al., The morphology and spherulite growth of PLA stereocomplex in linear and branched PLLA/PDLA blends: Effects of molecular weight and structure, CrystEngComm 18 (2015), pp. 274–282.

[194] B. Yu, Y. Cao, H. Sun and J. Han, The structure and properties of biodegradable PLLA/PDLA for melt-blown nonwovens, J. Polym. Environ. 25 (2017), pp. 510–517.

[195] I. Moreno Gomez, A Phenomenological Mathematical Modelling Framework for the Degradation of Bioresorbable Composites, Springer TSpringer, 2019.

[196] H. Tsuji and K. Ikarashi, In vitro hydrolysis of poly(L-lactide) crystalline residues as extended-chain crystallites: II. Effects of hydrolysis temperature, Biomacromolecules 5 (2004), pp. 1021–1028.

[197] A. Gupta, A.K. Pal, E.M. Woo and V. Katiyar, Effects of amphiphilic chitosan on stereocomplexation and properties of poly(lactic acid) nano-biocomposite,

Sci. Rep. 8 (2018), pp. 1–13.

[198] K. Formela, A. Hejna, J. Haponiuk and A. Tercjak, 8 - In situ processing of biocomposites via reactive extrusion, D.B.T.-B. for H.-P.A. Ray, ed., Woodhead Publishing, 2017, pp. 195–246.

[199] H. Tsuji, K. Tashiro, L. Bouapao and M. Hanesaka, Synchronous and separate homo-crystallization of enantiomeric poly(L-lactic acid)/poly(D -lactic acid) blends, Polymer. 53 (2012), pp. 747–754.

[200] L. Han, P. Pan, G. Shan and Y. Bao, Stereocomplex crystallization of high-molecular-weight poly (L-lactic acid)/poly (D-lactic acid) racemic blends promoted by a selective nucleator, Polymer. 63 (2015), pp. 144–153.

[201] P. Pan, L. Han, J. Bao, Q. Xie, G. Shan and Y. Bao, Competitive stereocomplexation, homocrystallization, and polymorphic crystalline transition in poly(L-lactic acid)/poly(D-lactic acid) racemic blends: Molecular weight effects, J. Phys. Chem. B 119 (2015), pp. 6462–6470.

[202] F. Alexis, Factors affecting the degradation and drug-release mechanism of poly (lactic acid) and poly [(lactic acid)-co-(glycolic acid)], Polym Int 54 (2005), pp. 36–46.

[203] S.P. Lyu and D. Untereker, Degradability of polymers for implantable biomedical devices, Int. J. Mol. Sci. 10 (2009), pp. 4033–4065.

[204] E. El-Khodary, Y. Fukui, M. Yamamoto and H. Yamane, Effect of the melt-mixing condition on the physical property of poly(L-lactic acid)/poly(D-lactic acid) blends, J. Appl. Polym. Sci. (2017), pp. 1–8.

[205] R.Y. Bao, W. Yang, W.R. Jiang, Z.Y. Liu, B.H. Xie, M.B. Yang et al., Stereocomplex formation of high-molecular-weight polylactide: A low temperature approach, Polymer. 53 (2012), pp. 5449–5454.

[206] E. Wojtczak, T. Biedroń and M. Bednarek, Hydrolytic stability of polylactide stereocomplex microparticles containing metal ions, Polym. Bull. 76 (2019), pp. 1135–1149.

[207] H. Tsuji and K. Nakahara, Poly (L -lactide). IX. Hydrolysis in acid media, J. Appl. Polym. Sci. 86 (2002), pp. 186–194.

[208] S.R. Andersson, M. Hakkarainen, S. Inkinen, A. Södergård and A.C. Albertsson, Polylactide Stereocomplexation Leads to Higher Hydrolytic Stability but More Acidic Hydrolysis Product Pattern, Biomacromolecules 11 (2010), pp. 1067–1073.

[209] X.G. Zhao, K.J. Hwang, D. Lee, T. Kim and N. Kim, Enhanced mechanical properties of self-polymerized polydopamine-coated recycled PLA filament used in 3D printing, Appl. Surf. Sci. 441 (2018), pp. 381–387.

[210] N.M. Zain, R. Hussain and M.R.A. Kadir, Surface modification of yttria stabilized zirconia via polydopamine inspired coating for hydroxyapatite biomineralization, Appl. Surf. Sci. 322 (2014), pp. 169–176.

[211] C.T. Kao, C.C. Lin, Y.W. Chen, C.H. Yeh, H.Y. Fang and M.Y. Shie, Poly(dopamine) coating of 3D printed poly(lactic acid) scaffolds for bone tissue engineering, Mater. Sci. Eng. C 56 (2015), pp. 165–173.

[212] X. Sun, L. Cheng, J. Zhao, R. Jin, B. Sun, Y. Shi et al., bFGF-grafted electrospun fibrous scaffolds via poly(dopamine) for skin wound healing, J. Mater. Chem. B 2 (2014), pp. 3636–3645.

[213] F. Podczeck, The Influence of Particle Size Distribution and Surface Roughness of Carrier Particles on the in vitro Properties of Dry Powder Inhalations The In ¯ uence of Particle Size Distribution and Surface Roughness of Carrier Dry Powder Inhalations, Aerosol Sci. Technol. 4 (1999), pp. 301–321.

[214] F.K. Yang and B. Zhao, Adhesion Properties of Self-Polymerized Dopamine Thin Film, Open Surf. Sci. J. 3 (2011), pp. 115–122.

[215] G. Torres-flores, A. Gonzalez-horta, Y.I. Vega-cantu, C. Rodriguez and A. Rodriguez-garcia, Preparation and Characterization of Liposomal Everolimus by Thin-Film Hydration Technique, Adv. Polym. Technol. 2020 (2020), pp. 9.

[216] A. Mirmohseni, J. Hosseini, M. Shojaei and S. Davaran, Design and evaluation of mixed self-assembled monolayers for a potential use in everolimus eluting coronary stents, Colloids Surfaces B Biointerfaces 112 (2013), pp. 330–336.

[217] L.Y. Jun, N.M. Mubarak, L.S. Yon, C.H. Bing, M. Khalid, P. Jagadish et al., Immobilization of Peroxidase on Functionalized MWCNTs-Buckypaper/Polyvinyl alcohol Nanocomposite Membrane, Sci. Rep. 9 (2019), pp. 2215.

[218] J. Wu, N. Wang, L. Wang, H. Dong, Y. Zhao and L. Jiang, Unidirectional water-penetration composite fibrous film via electrospinning, Soft Matter 8 (2012), pp. 5996–5999.

[219] K. Saha, B.S. Butola and M. Joshi, Drug Release Behavior of Polyurethane / Clay Nanocomposite : Film vs . Nanofibrous Web, J. Appl. Polym. Sci. 40824 (2014), pp. 1–9.

[220] M.M. Wan, T.T. Xu, B. Chi, M. Wang, Y. Huang, Q. Wang et al., A Safe and Efficient Strategy for the Rapid Elimination of Blood Lead In Vivo Based on a Capture–Fix–Separate Mechanism, Angew. Chemie Int. Ed. 58 (2019), pp. 10582–10586.

[221] C. Wang, L. Zhang, Y. Fang and W. Sun, Design, Characterization, and 3D Printing of Cardiovascular Stents with Zero Poisson's Ratio in Longitudinal Deformation, Engineering (2020), .

[222] S.K. Jaganathan, M.P. Mani, A.F. Ismail and M. Ayyar, Manufacturing and Characterization of Novel Electrospun Composite Comprising Polyurethane and Mustard Oil Scaffold with Enhanced Blood Compatibility., Polymers (Basel). 9 (2017), .

[223] Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009). .

[224] M.S. Singhvi, S.S. Zinjarde and D. V Gokhale, Polylactic acid: synthesis and biomedical applications, J. Appl. Microbiol. 127 (2019), pp. 1612–1626.

[225] P. Slepička, I. Michaljaničová, N. Slepičková Kasálková, Z. Kolská, S. Rimpelová, T. Ruml et al., Poly-l-lactic acid modified by etching and grafting with gold nanoparticles, J. Mater. Sci. 48 (2013), pp. 5871–5879.

[226] S.H. Ku, J. Ryu, S.K. Hong, H. Lee and C.B. Park, General functionalization route for cell adhesion on non-wetting surfaces, Biomaterials 31 (2010), pp. 2535–2541.

LIST OF PUBLICATION

Jumat, M.A., Chevallier, P., Mantovani, D., Copes, F., Abd. Razak, S.I., and Saidin, S. (2021). Three-dimensional printed biodegradable poly (l-lactic acid)/(poly (d-lactic acid) scaffold as an intervention of biomedical substitute. *Polymer-Plastics Technology and Materials*, 60(9), 1005-1015. (Q3, IF: 2.371)

Saidin, S., **Jumat, M.A.**, Amin, N.A.A.M., and Al-Hammadi, A.S.S. D. (2021). Organic and inorganic antibacterial approaches in combating bacterial infection for biomedical application. *Materials Science and Engineering: C*, 118, 111382. (Q1, IF: 7.328)

Jumat, M.A., Chevallier, P., Mantovani, D., and Saidin, S. (2021). Everolimus immobilisation using polydopamine intermediate layer on poly(l-lactic acid)/poly(d-lactic acid) scaffold for sustainable anti-proliferative drug release. *Progress in Organic Coating*, under review. (Q1, IF: 5.161)

Jumat, M.A., Chevallier, P., Mantovani, D., and Saidin, S. (2021). Blood compatibility and *in-vitro* human umbilical vein endothelial cells evaluation on dual-functional surfaces coating of everolimus-immobilised PDA scaffolds, in preparation.

Jumat, M.A., Zahidin, N.S., Zaini, M.A.A., Fadzil, N.A., Nur, H., and Saidin, S. (2021). Incorporation of *acalypha indica* extract in polyvinyl alcohol hydrogels: physico-chemical, antibacterial and cell compatibility analyses. *Jurnal Teknologi*, 83(2), 57-65. (Indexed by Scopus)

Pupathi, J.S., **Jumat, M.A.**, Zain, N.M., and Saidin, S. (2021). Tailoring The Everolimus Immobilisation Time on Poly(l-lactic acid)/Poly(d-lactic acid) Scaffold for Biodegradable Stent Coating Development. *2021 8th International Conference on Chemical and Material Engineering*, accepted. (Indexed by Scopus).