

SYNTHESIS AND CHARACTERIZATION OF POLY(3,4-ETHYLENEDIOXYTHIOPHENE)-POLY(STYRENESULFONATE) COATED POLYLACTIDE/POLY(3-HYDROXYBUTYRATE-CO-3-HYDROXYVALERATE) ELECTROSPUN MEMBRANES

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*This thesis is dedicated to*

*Dad, Chang Ah Sang,*

*Mum, Yong Yuet Lian,*

*Sister, Janice Chang,*

*Love, Sharon Eng,*

*Project supervisor, Dr. Naznin*

*& all my colleagues and friends.*

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## ABSTRACT

Biomaterials based scaffolds or membranes fabricated from electrospinning with suitable properties are highly desired in tissue engineering. Blending of natural polymer with synthetic polymer allows the modulation of properties to produce membranes for tissue engineering. Recently, conductive polymers have gained great attention in research due to their conductive properties, which can stimulate tissue regeneration. In this study, composite membrane was fabricated by blending a synthetic polymer, polylactic acid (PLA) and a natural polymer, poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) using electrospinning technique. PLA/PHBV electrospun membranes were dipped into PEDOT:PSS solution to prepare conductive membranes. It was observed that electrospinning of 20 % (w/v) PLA/PHBV with the weight ratio of 50:50 in chloroform solvent produced the most uniform fibers with no beads. The coated and uncoated membranes were evaluated using several techniques, including scanning electron microscopy (SEM), field emission scanning electron microscopy (FESEM), water contact angle (WCA), attenuated total reflectance (ATR), and atomic force microscopy (AFM). The measured electrical conductivity of the 30 % PEDOT:PSS coated PLA/PHBV was 1.45  $\mu\text{S}/\text{m}$ . Also, the surface roughness and wettability of the PEDOT:PSS coated PLA/PHBV membranes were greater than the uncoated membranes. Based on the results of the cells viability of human skin fibroblast (HSF) using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, cell attachment and cell proliferation, the conductive PEDOT:PSS-coated PLA/PHBV membranes were found to be more favorable for tissue engineering application than the uncoated membranes. Antibacterial evaluation also showed that tetracycline hydrochloride (TCH)-coated membrane possess antibacterial properties. In conclusion, conductive PEDOT:PSS coated membrane that has the potential to be used in tissue engineering application was successfully fabricated and characterized.

## ABSTRAK

Bahan bio berasaskan perancah atau membran dihasilkan daripada teknik *electrospinning* dengan sifat-sifat yang sesuai adalah sangat dikehendaki dalam bidang kejuruteraan tisu. Penyebatian polimer semula jadi dengan polimer sintetik membolehkan modulasi sifat-sifatnya untuk menghasilkan membran dalam kejuruteraan tisu. Baru-baru ini, polimer konduktif telah mendapat perhatian yang khusus dalam penyelidikan disebabkan sifat konduktif mereka, yang boleh merangsang pertumbuhan semula tisu. Dalam kajian ini, penghasilan membran komposit adalah dengan menggabungkan polimer sintetik, *polylactic acid* (PLA) dan polimer semula jadi, *poly(3-hydroxybutyrate-co-3-hydroxyvalerate)* (PHBV) menggunakan teknik *electrospinning*. Membran PLA/PHBV dicelup ke dalam larutan *poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate)* (PEDOT:PSS) untuk menghasilkan membran konduktif. *Electrospinning* 20 % (w/v) PLA/PHBV dalam nisbah 50:50 menghasilkan serat yang lebih seimbang dan tidak bermanik. Membran bersalut dan membran tidak bersalut tersebut dinilai dengan menggunakan beberapa teknik termasuk mikroskopi pengimbas elektron (SEM), mikroskopi pengimbas elektron pancaran medan (FESEM), sudut kontak air (WCA), pengecilan jumlah pantulan (ATR), dan mikroskopi daya atom (AFM). Kekonduksian elektrik yang diukur untuk 30% PEDOT:PSS bersalut PLA/PHBV ialah  $1.45 \mu\text{S/m}$ . Selain itu, kekasaran permukaan dan kebolehbasaan membran PLA/PHBV bersalut PEDOT:PSS adalah lebih tinggi daripada membran tidak bersalut. Keputusan daripada kebolehhidupan sel HSF menggunakan cerakin MTT, lekatan sel dan proliferasi sel menunjukkan bahawa membran PLA/PHBV bersalut PEDOT:PSS adalah lebih sesuai untuk aplikasi kejuruteraan tisu berbanding membran tidak bersalut. Penilaian antibakteria juga menunjukkan bahawa membran bersalut tetrasiklin hidroklorida (TCH) memiliki sifat-sifat anti-bakteria. Kesimpulannya, membran bersalut PEDOT:PSS yang berpotensi untuk digunakan dalam aplikasi kejuruteraan tisu telah berjaya difabrikasi dan dikarakterisasi.

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**LIST OF ABBREVIATIONS**

AFM	-	Atomic force microscopy
ANOVA	-	Analysis of variance
ATR	-	Attenuated total reflectance
calcein-AM	-	Calcein acetoxymethyl ester
CHA	-	carbonated hydroxyapatite
CMFDA	-	chloromethylfluorescein diacetate
CNT	-	carbon nanotubes
DMEM	-	Dulbecco's Modified Eagle Medium
DMF	-	dimethylformamide
DMSO	-	dimethyl sulfoxide
DNA	-	deoxyribonucleic acid
DSSC	-	dye-sensitized solar cells
ECM	-	extracellular matrix
EDOT	-	ethylenedioxythiophene
EDX	-	Energy dispersive X-ray spectroscopy
EG	-	ethylene glycol
EthD-1	-	Ethidium Homodimer-1
FBS	-	fetal bovine serum
FDA	-	fluorescein diacetate
FESEM	-	Field emission scanning electron microscopy
FPMS	-	flexible pressure mapping system
FTIR	-	Fourier transform infrared spectroscopy
HA	-	Hydroxyapatite
hMSC	-	human mesenchymal stem cells
HSF	-	human skin fibroblast
HV	-	hydroxyvalerate



I	-	iodine
ITO	-	indium tin oxide
L929	-	murine fibroblast cells
LA	-	lactide or lactic acid
MTS	-	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
MTT	-	methylthiazoletetrazolium
NGF	-	neuron growth factor
NSC	-	neural stem cells
ORR	-	oxygen reduction reaction
PAN	-	polyacrylonitrile
PANi	-	polyaniline
PBS	-	phosphate buffer saline
PCL	-	poly(caprolactone)
PDLLA	-	poly(D,L-lactide)
PEDOT	-	Poly(3,4-ethylenedioxythiophene)
PEDOT:PSS	-	Poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate)
PEG	-	polyethylene glycol
PEO	-	poly(ethylene oxide)
PGA	-	polyglycolic acid
PHA	-	Poly(hydroxyalkanoate)
PHB	-	Poly(3-hydroxybutyrate)
PHBV	-	Poly(hydroxybutyrate-co-valerate)
PLA	-	Poly(lactic acid) or poly(lactide)
PLA or PLLA	-	Poly(L-lactic acid)
PLGA	-	Poly(lactic-co-glycolic acid)
PNB	-	pernigraniline base
POC	-	point-of-care
Ppy	-	polypyrrole
PS	-	polystyrene
PSC	-	polymer solar cells
PSS	-	poly(4-styrenesulfonate)

PTh	-	polythiophene
PVA	-	polyvinyl alcohol
PVF2-TrFE	-	poly(vinylidene fluoride-trifluoroethylene)
RGO	-	reduced graphene oxide
RNA	-	Ribonucleic acid
SC	-	spinal cord
SEM	-	Scanning electron microscopy
SPS	-	sodium polystyrene sulfonate
TCH	-	tetracycline hydrochloride
TCP	-	tricalcium phosphates
UV	-	ultraviolet

**LIST OF SYMBOLS**

cm	-	centimetre
cP	-	centipoise
g	-	gram
Gpa	-	GigaPascal
Hz	-	Hertz
kV	-	kiloVolt
k $\Omega$	-	kiloOhm
ml	-	millilitre
mm	-	millimetre
Mpa	-	MegaPascal
nm	-	nanometre
v/v	-	volume per total volume
w/v	-	weight per volume
w/w	-	weight per weight
wt%	-	weight percent
$^{\circ}$ C	-	Degree Celcius
$\mu$ L	-	microlitre
$\mu$ m	-	micrometre
$\mu$ S	-	microSiemens

## CHAPTER 1

### INTRODUCTION

#### 1.1 Research Background

Tissue engineering has emerged as an alternative method to the conventional methods, which include autografts, allografts, and xenografts, to restore and repair tissue functions. It involves the use of biomaterials as scaffold, cells, and bioactive agents to regenerate and restore damaged tissues.

Various techniques can be used to fabricate biodegradable membranes or scaffolds. These include phase separation (Tu *et al.*, 2003b), self-assembly (Lopes and Jaeger, 2001), freeze drying (Sultana, 2014), and electrospinning (Sill and von Recum, 2008). Recently, electrospinning has been widely researched to produce fibrous scaffolds for tissue engineering purposes. Electrospinning can produce micro- and nanometer-sized electrospun fibers with high surface area and high porosity, that can mimic the cellular environment, hence enhancing cell adhesion and attachment (Tong *et al.*, 2010a). Electrospinning process utilizes electric field to create a charged jet of polymer solution (Doshi and Reneker, 1993). When electrical forces in the solution is balanced by surface tension, a Taylor cone will be formed (Taylor, 1969). By increasing the electric field, the electrostatic forces in the solution will become greater than the surface tension, causing the ejection of a charged fiber jet from the apex of the Taylor cone. The charged fiber jet will then accelerate towards the grounded

collector (Hassan *et al.*, 2014). The end product will be the micro- or nano-sized electrospun fibers, also known as electrospun membranes which are collected at the collector (aluminium foil).

Over the past few decades, conductive polymers have been used widely in many applications. They are used in drug delivery system, in the construction of bioactuators, as well as in the tissue engineering field (Ravichandran *et al.*, 2010). Conductive polymers can be synthesised alone, or combined with other polymers to form composites. Besides that, they also can be electrospun into microfibers and nanofibers (Balint *et al.*, 2014). Up to date, there are more than 25 types of conductive polymers (Balint *et al.*, 2014). Also, conductive polymers can be modified to be biodegradable and biocompatible, and these make them very useful in tissue engineering applications.

Biocompatible conductive polymers have been researched and used in various biomedical applications (Guimard *et al.*, 2007). Recently, poly(3,4-ethylenedioxythiophene) (PEDOT), a biocompatible conductive polymer, is being researched, to be used as nanobiointerfaces for medical applications, including controlled release of neuron growth factor (NGF), nucleic acid detection, and guided cell growth (Luo *et al.*, 2008). Currently, PEDOT is used in various fields, such as biotechnology and biomedicine due to its properties of high electrical conductivity and chemical stability (Ravichandran *et al.*, 2010). In order to obtain a water soluble polyelectrolyte system with good film-forming properties, PEDOT is doped with poly(4-styrenesulfonate) (PSS) (Groenendaal *et al.*, 2000). This copolymer has good stability and a moderate band gap in the doping state (Schweizer, 2005).

PEDOT:PSS had received great attention from researchers owing to its electrochemical, thermal, and oxidative stability. These properties allow PEDOT:PSS to be used in wide applications in areas such as flexible electrodes, nanocomposites, electrochromical displays, transistors (Chen *et al.*, 2002; Heuer *et al.*, 2002; Daoud *et al.*, 2005; Reddy *et al.*, 2010). In addition, due to its good oxidative stability, there has been an increased interest in PEDOT for biomedical applications (Owens and

Malliaras, 2010). Positive results had shown that conductive polymer scaffolds made from PEDOT:PSS are structurally suitable for bone tissue engineering (Shahini *et al.*, 2014).

In this study, a novel conductive membrane was fabricated using PEDOT:PSS, PLA and PHBV using an established electrospinning protocol. PLA is a Food and Drug Administration (FDA) approved biodegradable and biocompatible polymer to be used in biomedical applications. Meanwhile, PHBV is biocompatible with blood and tissue (Duan *et al.*, 2010). In addition, PEDOT:PSS can enhance cellular response (Shahini *et al.*, 2014). In this research, the fabrication of PLA/PHBV membrane at different blend ratios was reported. The composition of 50:50 PLA/PHBV was found to be suitable to fabricate beadles and uniform fibers. Next, to render the membrane conductive, it was coated with PEDOT:PSS. The conductive membrane was then characterized using Scanning electron microscopy (SEM), Field emission scanning electron microscopy (FESEM), Energy dispersive X-ray spectroscopy (EDX), Attenuated total reflectance (ATR), contact angle measurements, porosity measurements, Atomic force microscopy (AFM), and electrical resistance and conductivity measurements. The fabricated membranes were also tested for *in vitro* cell cytotoxicity, cell adhesion, and cell proliferation using human skin fibroblast (HSF) cells. Also, tetracycline hydrochloride (TCH) was incorporated to the membranes and tested against *Staphylococcus aureus* (*S. aureus*) (Gram-positive bacteria) and *Escherichia coli* (*E. coli*) (Gram-negative bacteria).

## 1.2 Problem Statement

By using different combinations of biomaterials, cells, and bioactive agents, tissue engineering aims to heal or regenerate injured tissue. Therefore, in this field, it is important to produce a biodegradable scaffold that serves as a temporary and artificial extracellular matrix (ECM) for the growing cell. Also, scaffold serves as a reservoir to deliver bioactive agents to promote regeneration of the injured tissues

(Goh *et al.*, 2013). PHBV is hydrophobic and has a very slow degradation rate, which limit their practical applications. Meanwhile, PLA is a biodegradable and biocompatible polymer and has been approved by the US Food and Drug Administration (FDA) for human use (Marin *et al.*, 2013). By blending PHBV with PLA, its degradation properties will be improved. Studies had shown that the blending of PHBV and PLA improved the biocompatibility and wettability of the electrospun polymer scaffolds compared to the electrospun PLA fibre (Feng *et al.*, 2011).

On the other hand, the conductive nature of the conducting polymer will allow the cells or tissues cultured upon them to be stimulated (Balint *et al.*, 2014). PEDOT:PSS is hydrophilic and possess conductivity properties. Hence, in this research, the conducting polymer, PEDOT:PSS was coated into the PLA/PHBV electrospun membranes to further enhance the surface properties, including conductivity and wettability, of the membranes to be used in tissue engineering applications.

For skin tissue engineering application, scaffolds with antibacterial properties are important to prevent inflammation and infection of wound. Therefore, in this study, the fabricated membranes were loaded with antibacterial agent, TCH which are essential to inhibit bacteria growth on wound prior to skin regeneration.

### **1.3 Objectives**

- i. To fabricate PLA, PHBV and PLA/PHBV membranes using electrospinning technique and, to fabricate conductive membrane by coating PEDOT:PSS on PLA/PHBV membrane.
- ii. To characterize the morphology, chemical, and conductivity properties of the electrospun membranes and PEDOT:PSS coated membrane.

- iii. To evaluate potential use of PLA/PHBV and PEDOT:PSS coated PLA/PHBV membranes in tissue engineering via *in vitro* biological assessment using HSF cells.
- iv. To coat tetracycline hydrochloride (TCH) drug into the fabricated membranes and investigate their antibacterial properties.

#### 1.4 Scope

In this research, PLA, PHBV and PLA/PHBV electrospun membranes were fabricated using electrospinning technique by varying electrospinning parameters (voltage, distance between needle-tip to collector, flow rate). Also, PEDOT:PSS was coated into the optimized PLA/PHBV electrospun membranes. Characterization of both PLA/PHBV and PEDOT:PSS coated PLA/PHBV electrospun membranes were carried out using several techniques. The characterization include fiber morphology (SEM and FESEM), wettability (water contact angle), water uptake, density and porosity measurement, chemical bonding analysis (ATR), surface roughness (AFM), and conductivity test. *In vitro* cell cytotoxicity, cell adhesion and cell proliferation were also studied using human skin fibroblast (HSF). Tetracycline hydrochloride drug was incorporated into PLA/PHBV and PEDOT:PSS coated PLA/PHBV electrospun membranes by dipping method and were tested for antibacterial properties against *S. aureus* (Gram-positive bacteria) and *E. coli* (Gram-negative bacteria).



## 1.5 Significance of Research

In this study, PEDOT:PSS coated PLA/PHBV membranes were fabricated for tissue engineering applicatio. As far as we are concerned, no other research group had fabricated PEDOT:PSS coated electrospun membrane using the similar approach. PEDOT:PSS is hydrophilic and conductive, allowing the coated membranes to be more favorable for cellular adhesion and proliferation. The *in vitro* biological evaluation results of this study demonstrated an increase in human skin fibroblast (HSF) cell adhesion and proliferation on PEDOT:PSS coated membrane compared to the non-coated membrane, providing insight of using different cells and carrying out *in vivo* evaluation in future studies.

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