FABRICATION OF ELECTROSPUN POLYVINYL ALCOHOL-POLYCAPROLACTONE-NATURAL ANTIBACTERIAL AGENT BLENDED NANOFIBROUS MEMBRANE FOR SKIN TISSUE SCAFFOLD

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ABSTRACT

Bacterial infection can restrict and delay the wound healing process. In this study, three different kinds of natural antibacterial agents (NAA), i.e., chitosan (Cs), epsilon poly-L-lysine (EPL) and curcumin (Cur), were used with a membrane containing polyvinyl alcohol (PVA) and polycaprolactone (PCL), for inhibiting the bacterial growth meanwhile enhancing cell growth. Electrospinning was chosen to fabricate the membrane as this technique produces a nanofibrous membrane that mimics the extracellular matrix (ECM) of human tissue. Moreover, in order to increase the biocompatibility of the membrane, solution formulations containing glacial and 80% (v/v) of acetic acid were introduced to prepare PCL and PVA solutions, respectively, before mixing and adding the NAA. In this study, all electrospun nanofibrous membranes exhibited the chemical functional group of hydrophilic PVA and hydrophobic PCL. The presence of those chemical functional groups in the membranes is essential for achieving ideal scaffold properties. The presence of NAA in the membranes was further confirmed by investigating the presence of nitrogen through carbon, hydrogen, nitrogen and sulphur elemental analysis (CHNS). Overall, all electrospun nanofibrous membranes have tiny fibre diameter (92-176 nm), high porosity (77-89%), surface with hydrophilic property (0-27°), moderate body fluid uptake (209-329%) and controllable degradation rate. Although the water vapour transmission rate in the range of 1435 to 1620 g/m^2/day was relatively lower than the recommended value, this did not restrict them to act as a barrier to prevent excessive water loss during wound healing. The antibacterial studies indicated that the electropun membrane containing NAA inhibited the growth of *S. aureus* and *E. coli*. Among them, electropun PVA*-PCL-EPL showed almost 99.9% of bacterial reduction after 1 h of treatment. Finally, the *in vitro* and *in vivo* studies were also conducted to confirm the effectiveness of the electrospun nanofibrous membrane in wound healing. In conclusion, all electrospun nanofibrous membranes containing PVA, PCL and NAA could be applied as a scaffold for skin tissue regeneration.

ABSTRAK

Jangkitan bakteria boleh menyekat dan melambatkan proses penyembuhan luka. Dalam kajian ini, tiga jenis agen antibakteria semula jadi (NAA), iaitu kitosan (Cs), epsilon poli-L-lisin (EPL) dan kurkumin (Cur) telah digunakan bersama membran yang mengandungi alkohol polivinil (PVA) dan polikaprolakton (PCL), untuk menghalang pertumbuhan bakteria sementara itu meningkatkan pertumbuhan sel. Teknik elektrospinning telah digunakan untuk membuat membran kerana teknik ini menghasilkan membran nanogentian yang menyerupai matriks ekstraselular (ECM) tisu manusia. Lebih-lebih lagi, untuk meningkatkan biokompatibiliti membran, formulasi larutan yang masing-masing mengandungi asid asetik glasier dan 80% (v/v) diperkenalkan untuk menyediakan larutan PCL dan PVA, sebelum dicampurkan dan ditambahkan dengan NAA. Dalam kajian ini, semua membran nanogentian elektrospun menunjukkan kumpulan berfungsi kimia PVA yang hidrofilik dan PCL yang hidrofobik. Kehadiran kumpulan berfungsi kimia tersebut di dalam membran amat penting untuk mencapai sifat perancah yang sempurna. Kehadiran NAA di dalam membran disahkan selanjutnya dengan mengkaji kehadiran nitrogen melalui analisis unsur karbon, hidrogen, nitrogen dan sulfur (CHNS). Secara keseluruhan, semua membran nanogentian elektrospun mempunyai diameter gentian yang kecil (92-176 nm), keliangan yang tinggi (77-89%), permukaan dengan sifat hidrofilik (0-27°), pengambilan cecair badan yang sederhana (209-329%) dan kadar biodegredasi yang terkawal. Walaupun kadar penghantaran wap air dalam julat 1435 hingga 1620 g/m^2/hari adalah lebih rendah daripada nilai yang disarankan secara relatif, ia tidak menyekat membran tersebut daripada bertindak sebagai penghalang untuk mencegah kehilangan air yang berlebihan semasa penyembuhan luka. Kajian antibakteria menunjukkan bahawa membran elektropun yang mengandungi NAA merencatkan pertumbuhan *S. aureus* dan *E. coli*. Antaranya, elektropun PVA*-PCL-EPL menunjukkan pengurangan bakteria sebanyak hampir 99.9% setelah 1 jam rawatan. Akhirnya, kajian *in vitro* dan *in vivo* telah juga dijalankan untuk mengesahkan keberkesanan membran nanogentian elektrospun dalam penyembuhan luka. Kesimpulannya, semua membran nanogentian elektrospun yang mengandungi PVA, PCL dan NAA boleh digunakan sebagai perancah untuk pertumbuhan semula tisu kulit.

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LIST OF ABBREVIATIONS

ATR-FTIR	-	Attenuated Total Reflectance - Fourier-Transform Infrared Spectroscopy
BDT	-	Broth dilution test
CHNS	-	Carbon, Hydrogen, Nitrogen, and Sulphur Elemental Analyser
Cs	-	Chitosan
Cur	-	Curcumin
DDT	-	Disc diffusion test
DSC	-	Differential Scanning Calorimetry
E. coli	-	*Escherichia coli*
ECM	-	Extracellular matrix
EPL	-	Epsilon poly-L-lysine
FESEM	-	Field Emission Scanning Electron Microscope
FWHM	-	Full Width at Half Maximum
NAA	-	Natural antibacterial agent
PCL	-	Polycaprolactone
PVA	-	Polyvinyl alcohol
PVA	-	Polyvinyl alcohol (average Mw: 15 kDa)
PVA*	-	Polyvinyl alcohol (average Mw: 85-124 kDa)
S. aureus	-	*Staphylococcus aureus*
WVTR	-	Water vapour transmission rate
XPS	-	X-ray Photoelectron Spectroscopy
XRD	-	X-ray Diffraction
Mw	-	Molecular weight
UV	-	Ultraviolet light
Ag NP	-	Silver nanoparticle

LIST OF SYMBOLS

V	-	Voltage supply
f	-	Feed rate
r^2	-	Correlation coefficient
d	-	Distance between feeding unit to collector

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CHAPTER 1

INTRODUCTION

1.1 Problem Background

Globally, acute and chronic wounds such as burns and diabetic ulcers impact a remarkable financial burden to patients and the healthcare systems (Homaeigohar and Boccaccini, 2020). For instance, in Europe, up to € 2–2.5 billion has been spent annually for almost 450,000 lower limb amputations due to the inefficient treatment of diabetic foot ulcer. The statistic for the US also stated that almost 6.5 million patients whose annual treatment cost are as much as $ 25 billion. In the case of acute wounds, trauma induced wounds costs $ 670 billion annually for health care and disability in America. Therefore, to circumvent such a costly burden, extensive research in progress to develop technologies able to treat wounds effectively in less expensive approach and in a short time.

Over the past few decades, researchers have found that the utility of polymeric membrane, in particularly nanofibrous membrane as drug delivery carrier for the application of wound treatment is more effective than other dosage form. This is because the nanofibrous membranes use less drug dosage to provide similar biological performance that subsequently able to enhance material bioavailability (Ghosal et al., 2018). Since the nanofibrous membrane allows drugs to be absorbed directly into the systemic circulation, it may also prevent hepatic first pass metabolism. The first hepatic pass metabolism is a drug metabolism process in whichthe concentration of a drug is greatly diminished before it enters the systemic circulation, particularly when given orally. There are many methods could be used to produce the nanofibrous membranes such as phase separation, self-assembly, drawing, template synthesis and electrospinning (Pilehvar-Soltanahmadi et al., 2018).

Electrospinning is a spinning process that utilises electrostatic forces to generate continuous ultrafine fibres. It has been recognised as one of the mosteffective techniques for manufacturing fibres with tiny diameter (from micrometre to nanometer), an incredibly long length, a large surface area and often complicated pore structures (Clanek et al., 2012; Xie et al., 2020). To date, the study of using electrospinning to produce wound dressing has received much attention because it is more reproducible and scale-controllable than other conventional technique of fibrous membrane fabrication. Besides, the resembled structural and physical properties of electrospun nanofibrous membranes with the extracellular matrix (ECM) of the membrane is believed can enhance cellular attachment and proliferation that subsequently accelerate wound healing process (Rodríguez-Tobías, et al., 2019, Xie et al., 2020). As a matter of fact, the application of electrospun nanofibrous membran for acute and cronic wound can be further enhanced by designinig it in such a way that can heal the wound and degrade itself after wound healing. This kind of membrane is like an artificial skin and denoted as skin tissue regeneration scaffold. The benefit of skin tissue regeneration scaffold is it can eliminate the removing process of wound dressing after treamtment. The removing process of wound dressing can cause secondary damage to new skin tissue. However, the study of the fabrication of electrospun nanofibrous membrane for skin tissue regeneration scaffold is still very limited.

The idea of combining polyvinyl alcohol (PVA) and polycaprolactone (PCL) in the production of electrospun nanofibrous membranes for wound treatment, as a matter of fact, have been introduced long time ago. It is because using only one polymer to produce electrospun nanofibrous membrane accompanies many limitations, due to the nature of the material, that subsequenty puncture its advantages towards ideal wound healing material. For example, PVA, a hydrophilic polymer that able to enhance cell attachment and proliferation, has a drawback of unstable in aqueous system and weak tensile strength (Paipitak et al., 2011; Mohseni et al., 2019; Mahmud et al., 2020; Sapalidis, 2020). On the other hand, PCL, a hydrophobic polymer with long degradation rate and strong mechanical strength, is lack of bioactive site (Ferreira et al., 2014). Thus, the combination of PVA and PCL is believed could inherit advantages from both polymers with minimum limitations for skin tissue regeneration scaffold. Many researches also indicated that membranes in which composed of natural and synthetic polymers as well as hybrid blends of two polymers exhibit a better biocompatibility, low immunogenicity and a better clinical functionality (Sedghi and Shaabani, 2016).

Recently, the study of using electrospinning to produce skin tissueregeneration scaffold or wound dressing with antibacterial activity has received a lot of attention because bacterial infection delays wound healing and even endangers patient life. Thus, this project proposed the utilization of natural antibacterial agents (NAA), i.e. chitosan, epsilon poly-L-lysine and curcumin, to enhance the antibacterial activity of the electrospun nanofibrous scaffold. Chitosan (Cs) is a naturally occurring polysaccharide that can be extracted from shellfish such as shrimp, lobster and crabs. Due to its excellent biocompatibility, biodegradable properties and non-toxicity (Paipitak et al., 2011; Shalumon et al., 2011; Wang et al., 2020), Cs is one of most popular natural antibacterial agents used for the fabrication of electrospun nanofibrous membrane with antibacterial activity. Epsilon poly-L- lysine (EPL) is a natural antibacterial protein that widely used in food additive as food preservative (Mercer et al., 2017). It can be considered as a promising candidateto enhance the antibacterial activity of an electropsun nanofibrous membrane because can denature the growth of both gram positive and negative bacteria. Curcumin (Cur) is a yellow-coloured, low molecular weight natural polyphenol(Mahmud et al., 2020). It is a natural antibacterial agent derived from the rhizome ofthe plant *Curcuma longa*. In South Asia, Cur has been widely used as a spice and traditional medicine for a long time. Research has proven that this natural material is suitable for wound treatment because it is biocompatible, biodegradable, antibacterial, antifungal and anti-inflammatory.

In this research, PVA and PCL were blended and transferred into a nanofibrous membrane via electrospinning. NAA such as Cs, EPL, and Cur were also applied to the membrane since both polymers had little antibacterial activity.The fabricated membranes containing PVA, PCL and NAA were expected to promote cell proliferation and inhibite bacterial growth during wound healing.

1.2 Problem Statement

The idea of using electrospinning to produce nanofibrous membrane containing PVA, PCL and Cs for wound treatment has been proposed since decades. However, due to the hydrophilicity of PVA and Cs and the hydrophobicity of PCL, their composite polymer solution formulation cannnt be achieved easily. In 2014, Gholipour-Kanani successfully fabricated electrospun PVA-PCL-Cs nanofibrous membrane but they used a lot of solvent during solution formation. Due to the excessive solvent used, it not only caused a chemical waste but also gave negative effect on membrane. For example, the membrane did not inherit the antibacterial activity of Cs and degraded quickly in aqueous medium. Mouro and Gouveis (2019) also successfully produced the electrospun PVA-PCL-Cs nanofibrous membrane but the solution formulation involved toxic organic solvent, i.e. chloroform and dimethylformamide, that may increased the cytotoxicity of the product.

To date, treatments that have been used to treat acute and chronic wound include tissue culture and skin grafting. In tissue culture, the tissue of specific cell is cultured in a suitable medium prior to the treatment of wound. The drawbacks of the treatment are slow cell tissue culturing and poor cell tissue growing that eventually reduces its effectiveness (Chio and Agrawal, 2010). Skin grafting, on the other hand, is a type of graft surgery involving the transplantation of skin tissue. The limitation of the skin grafting is the lack of genetically identical tissue supply and the risk of graft rejection when non-genetically identical tissue was used. Besides, they possessa risk of disease transmission and post-surgical adhesion. Due to the problem of post-surgical adhesion, patients have to go through a second surgery after grafting, andthis subsequently induces scar tissue formation and bacterial infection. (Kumbar et al., 2008, Bakhsheshi-Rad et al., 2019)

Bacterial infection is another head-aching medical issue that delay wound healing process and may even elevate patient morbidity and fatality (Bakhsheshi-Rad et al., 2019). Thus, different kinds of antibacterial agents such as silver nanoparticles and antibiotic have been introduced to confer the antibacterial activity to the electrospun nanofibrous membrane for wound treatment. Nonetheless, the usage of those antibacterial agents is not recommended because silver nanoparticles is believed can affect patient heath in long term (Liu et al., 2015; Rodríguez-Tobías et al., 2014, Zheng et al., 2019) while the over usage of antibiotic caused the existing ofantibiotic-resistance bacteria (Maharjan et al., 2017, Zheng et al., 2019).

As a result, this research proposed using electrospinning to produce nanofibrous membranes as skin tissue scaffolds with antibacterial activity for wound healing. The membranes constitute PVA, PCL and various types of NAA suchas Cs, EPL and Cur. Acetic acid was used as a potential solvent for solution formulation. As one of common solvent used in biomedical application (Pilejuar-Soltanahmadi et al., 2018), the application of acetic acid in solution formulation is believed can decrease the cytotoxicity and increase biocompatibility of the product.

1.3 Research Objectives

The objectives of the research are as follow:

(a) To formulate solvent systems based on acetic acid and water for the fabrication of electrospun PVA-PCL and PVA-PCL-NAA nanofibrous membranes.

(b) To characterize and evaluate the scaffold's performance of the electrospun PVA-PCL and PVA-PCL-NAA nanofibrous membranes.

(c) To assess the antibacterial activity and biocompatibility of the electrospun nanofibrous membranes.

(d) To investigate the *in vivo* skin irritant or corrosive and wound healing activity of the electrospun nanofibrous membranes using mice wound model system.

1.4 Scope of Study

The study began by searching a suitable solvent or solvent system for the preparation of PVA solution and PCL solution with different molecular weight. In this research, PVA and PCL with two different molecular weights, i.e. 15 and 85-124kDa as well as 16 and 80 kDa, respectively were studied. Casting method was conducted to study the film formation of the polymers. Only polymer with good film formation was selected to produce PVA-PCL and PVA-PCL-NAA nanofibrous membranes through electrospinning.

Three different kinds of NAA were used in this study, i.e. Cs, EPL and Cur. The formulated solution was electrospun into nanofibre and their antibacterial activity was investigated qualitatively using disc diffusion methods (DDT). Electrospun nanofibrous membranes with excellent antibacterial activity were selected and proceed with following characterization and testing.

The selected scaffolds were characterized by Attenuated Total Reflectance - Fourier-Transform Infrared Spectroscopy (ATR-FTIR), Carbon, Hydrogen, Nitrogen, and Sulphur Elemental Analyser (CHNS), X-ray Photoelectron Spectroscopy (XPS), Field Emission Scanning Electron Microscope (FESEM), Liquid Displacement Method, Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Contact Angle Measurement. These characterizations were crucial to confirm the chemical and physical properties of the fabricated electrospun nanofibrous membranes. After that, the scaffold's performance of fabricated electrospun nanofibrous membranes was evaluated by investigating their body fluid uptake, water vapour transmission rate (WVTR), *in vitro* degradation, mechanical property, and *in vitro* NAA releasing profile.

Finally, broth dilution test (BDT) was conducted to study the antibacterial activity of electrospun nanofibous membranes quantitatively. *In vitro* and *in vivo* studies were also carried out to study comprehensively the biocompatibility and wound healing efficiency of the fabricated electrospun nanofibrous membranes.

1.5 Significance of Study

Skin tissue regeneration is critical in treating patients with skin injury; however, its limitation always restricts to the compatibility of the type of material used to replace the extensive skin loss. In this research, electrospinning was used to produce PVA-PCL nanofibrous membrane for wound treatment. Although the idea of combining the PVA and PCL into one membrane was proposed long time ago, their solution formulation for electrospinning have always punctured their effectiveness toward ideal skin tissue regeneration scaffold. Thus, in order to address the issue, a novel solution formulation that using water and acetic acid was proposed.Acetic acid is one of the common solvents used in biomedical application (Pilehvar- Soltanahmadi et al., 2018).

The solution formulation also opened a possibility of adding different type of natural antibacterial agents into the electrospun PVA-PCL nanofibrous membranes. Bacterial infection often occurred during wound treatment. Therefore, this research intended to produce skin tissue regeneration scaffold with antibacterial activity. Different types of NAA such as Cs, EPL and Cur were added into the membrane through single-syringed electrospinning technique. Characterization and scaffold evaluation results show that the electrospun PVA-PCL nanofibrous membranes with different types of NAA have good physiochemical and mechanical property toward ideal skin regeneration scaffold. Besides, based on experiments of antibacterial, *in vitro* and *in vivo* studies, all fabricated electrospun nanofibous membranes that combining PVA/PVA*, PCL and NAA (Cs, EPL and Cur) possessed excellent biocompatible property that not only can inhibit the growth of bacteria but also accelerate the cell proliferation and wound healing. As a result, this research successfully produced different kinds of electrospun PVA-PCL-NAA membranes that can be used as skin tissue regeneration scaffolds with antibacterial activity for wound treatment.

1.6 Limitation of Study

There are two limitations in the research. At first, the study only focused on the fabrication of electrospun PVA-PCL-NAA nanofibous membranes using singe-syringed electrospinning. However, the fabrication can also be conducted using duel-syringed electrospinning and coaxial electrospinning. Those techniques allow more than one type of NAA added in the membranes. Secondly, the *in vivo* study conducted in the research focused only on cut wound. In fact, wound can also occur due to burn.

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