THE STUDY CHARACTERISTICS OF ELECTROSPINNING NANOFIBERS IN POLYETYHLENE OXIDE (PEO) FOR CONTROLLED RELEASED AND TARGET DELIVERY

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LIST OF ABBREVIATIONS

C	Carbon
DMF	Dimethyl formamide
DNA	Deoxyribosenucleic Acid
EDX-SEM	Energy Dispersion X-ray Scanning Electron Microscope
Etc	Et cetera
FE-SEM	Field Emission Scanning Electron Microscope
K	Potassium
MW	Molecular Weight
Na	Sodium
PEO	Poly-ethylene Oxide
Re	Reynolds' Number
S	Sulphur
Si	Silicone

LIST OF SYMBOLS

%	Percentage
µ	Micro
cp	Centipoises
G	Gauge
g	Gram
h	hour
k	kilo
K_m	Martin's constant
m	Meter
ml	Milliliter
mm	Millimeter
mol	Molar
MPa	Mega Pascal
nm	Nanometer
RPM	Revolution Per Minutes
s	Second
S	Siemens (unit of conductivity)
V	Voltage
v/v	Volume per volume
w/v	Weight per volume

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ABSTRACT

Nanofibers that develop by using electrospinning technique are a common study field nowadays. There are few advantages of using this technique in producing nanofibers such as in drug delivery and controlled released system, pharmaceuticals products, biotechnological purposes and etc. By using this technique in producing nanofibers, ethanol was chosen to be the solvent instead of water in producing nanofibers. The type of solvent and polymer are believe affecting the morphological structure of the nanofibers and thus the drug delivery system. The configuration of the electrospinning was kept constant in every test run and only the solvent concentration and molecular weight of the polymer were manipulated. This is to check in what conditions will the nanofibers having the best morphology, tensile strength and distribution of fibers. Ethanol is very suitable in producing good nanofibers. However the percentage concentration of ethanol should be check in order to avoid the protein embedded in the nanofibers denature. Stable protein is selected to be used in the nanofibers in avoiding deformation of drugs if to be used commercially.

ABSTRAK

Nanofiber telah dibangunkan dengan menggunakan teknik *electrospinning* adalah suatu bidang kajian yang biasa dijalankan pada masa sekarang. Tedapat beberapa kelebihan dalam menggunakan teknik ini dalam penghasilan nanofibers seperti sistem penyampaian ubat dan pelepasan terkawal, produk farmaseutikal, tujuan bioteknologi dan sebagainya. Dengan menggunakan teknik ini dalam menghasilkan nanofibers, etanol telah dipilh sebagai pelarut dan bukannya air dalam penghasilan nanofibers. Jenis pelarut dan polimer dipercayai mempengaruhi struktur morfologi nanofibers tersebut dan juga sistem penyampaian ubat. Konfigurasi kepada electrospinning telah dimalarkan dalam setiap percubaandan hanya kepekatan pelarut dan juga berat molekul kepada polimer telah dimanipulasi. Hal ini bertujuan untuk memeriksa dalam keadaan apa nanofibers akan berkeadaan terbaik dari segi kekuatan tegangan dan pengedaran fiber-fiber. Etanol adalah sagat sesuai dalam menghasilkan nanofibers yang baik. Walaubagaimanapun,peratusan kepekatan kepada etanol seharunysa diperiksa dalam usaha mengelak protin yang terkandung di dalam nanofibers rosak. Protin yang stabil dipilih untuk digunakan dalam nanofibers bagi mengelakkan diformasi kepada ubatan jika ingin digunakan bagi tujuan komersial.

CHAPTER 1

INTRODUCTION

1.1 Review of Research

Today research of the used of electrospinning in producing electrospun nanofiber have widely known all over the world. It built the interest among researchers to develop many things based on this technology. There are many kinds of nanofibers can be made for the applications such as energy storage, health care, biotechnology, environmental, engineering and defense and security (Ramakrisnan, 2006). There are plenty of advantages of using electrospun nanofibers as a product of various study fields. Target delivery system and also controlled release of drug system was develop from the technology of electrospninng. According to Su Yan *et al.* (2009), electrospinning technology is simple and versatile method to prepare ultrathin fibers from polymer solutions or melts. The ultrathin fibers indicates that nanofibers able to produce a highly pourous mesh and have a large surface area that can improve the performance and functions of the nanofibers itself (Ramakrishna, 2006).

Dehai Liang (2007) has describe that electrospinning is one of the method and technology that can produce non-woven fibrous articles with diameters of fiber ranging from tens of nanometers to microns that are before is hardly produce using a conventional non-woven fiber fabrication techniques. There are several other techniques that can be use to produce nanofibers from the high-volume production such as melt fibrillation, island-in-sea, and gas jet techniques, to highly precise techniques such as nanolithography and self-assembly (Ramakrishna, 2006). This techniques is use to produce various kinds of nanofibers according to the functionality and characteristics of the nanofibers. Nanotechnology as a delivery tool that has a very promising application in drug delivery because of the advantages it offers in enhancing the drug transport across the biological barriers and it delivers drug in a controlled and targeted manner to selective organs.

Electrospinning is the simplest method in generating nanoscale fibers. According to Liang *et al.* (2007), Electrospinning system consist of three major parts which are high voltage power supply, a spinneret and a grounded collecting plate that is usually either a metal screen, plate or rotating mandrel. In order to produce a better fabricated nanofiber, few parameters should be considered in the system when the solution was injected from the electrospinning. The use of nanofibers today was not just limited to certain field of study and moreover the usage of electrospun nanofibrous scaffolds for medical applications has attracted a great deal of attention in the past several years (Liang *et al*, 2007).

Electrospun nanofibrous for target delivery can be said as a transport system chained with the loading of drug onto the nanofibers to deliver it for selected organs. There are certain characteristics that are required in a successful application to a specific target. The nanofibrous scaffolds must exhibit the optimal physical and biological properties closely (Liang *et al*, 2007).

Coaxial nanofiber is one type of structure that is commonly used by using electrospinning. Therapeutic drugs is encapsulated in the nanofibers that have the effect of healing that mainly used for the study of controlled release and targeted delivery. Due to their unique feature such as high surface-to-volume ratio, morphological design flexibility and extracellular matrices structure like, nanofibers are used as scaffolds for drug delivery and tissue engineering. Due to the flexibility in material selection a few drugs can be delivered including antibiotics, anticancer drugs, proteins and DNA. Coaxial nanofibers posses drugs which encapsulated on the nanofibers in the core solution which would be delivered through biological barriers in a controlled manner.

1.2 Research Background

Drug delivery system using coaxial nanofibers by electrospinning is not a new thing nowadays. The technology has started few decades ago by many researchers. The process of using electrostatic forces to form synthetic fibers has been develop for over 100 years ago (Travis. J, 2010). This process brings towards the development and improvement of electrospinning which utilizes a high voltage source to inject charge of a certain polarity inti a polymer solution.

The history of drug delivery from using conventional way can be seen from the story of Edward Jenner which the Jenner's injection of smallpox vaccine into patients to prevent the deadly disease in Europe and America, which medicine has made great stride towards disease control and prevention (Abishek Sigh, 2000). The responsible of controlling and preventing disease has come to a new evolution in very specific ways.

The researches of drug delivery and controlled release have been studied by many scientists. The use of electrospun nanofibers which fabricated coaxially was already done, however the optimization of this fabrication is not merely an interest of many researchers. According to Kim (2007), electrospun ultrafine nanofibers have been explored during past several years as a potential biomedical device including tissue engineering scaffolds, wound dressing materials and drug delivery carriers. The advancement of the technology have offers more widely application of nanofibers for delivering various bioactive material such as antibiotics, anti tumour agents, proteins and plasmid DNA.

Process of electrospinning has been known for almost 70 years and the first patent was issued to Formhals in 1934. The topic of nanofibers and electrospinning has become the interest for the past few years back. It was develop more later on the few years later and in early 1990s, Reneker and Chun, who revived interest in this technology shown the possibility of the technology in a wide range polymer solutions. (Frenot and Chronakis, 2003). It is found that electrospinning is a method that applicable in wide range of polymers that replaced the conventional ways of spinning of polymers such as polyolefine, polymides, polyester, aramide, arcrylic as well as polymers like proteins, DNA, polypeptides or other polymers that are electric conducting and photonic polymers. This shows that the technology develop as today researchers improving the application of nanofibers in the biomedical and tissue engineer aspects.

1.3 Problem Statement

Developing nanofibers using electrospinning has improved from time to time. There are developments of coaxial electrospun nanofibers that uses core and shell model that have very wide advantages toward the development tissue engineering and controlled release. The previous study shows the nanofibers was not deposited uniformly at the ground collector of electrospinning process due to the presence of distilled water in core solutions. Therefore in this research, the study of PEO replacing the distilled water in the core solution will be carried out by observing the morphological differences of the electrospun nanofibers and also determining the effect of ethanol towards the viscosity of solution and the structure of the electrospun nanofibers by using different molecular weight of PEO (MW: 400000, 900000 g/mol).

1.4 Research Objectives

The Objective of this research are as follow:

1.4.1 To study the comparison of polyethylene oxide (PEO) of different molecular weight towards structure of nanofibers using electrospinning.

1.4.2 To identify the effect of water/ethanol solvent towards the viscosity and conductivity of solution for electrospun nanofibers

1.4.3 To investigate morphology analysis of nanofibers by using Field Emission Electron Scanning Microscope (FE-SEM) and Energy Dispersion X-ray Scanning Electron Microscope (EDX-SEM)

1.4.4 To study the effect of different diameter of needle of electrospinning towards the structure of nanofibers.

1.5 Research Scope

The scopes of this study are:

1.5.1 To understand the basic principle and configurations of electrospinning process and the ambient condition of producing nanofibers by using PEO as the nanofibers.

1.5.2 To study the different effect of solution when distilled water used and water/ethanol solution used towards the viscosity and conductivity of solution as well as the relationship to the structure of nanofibers.

1.5.3 To study the clear difference between morphology of nanofibers that used distilled water and ethanol solution and PEO as electrospun nanofibers solution.

1.5.4 To study the effect different size of needle used in the electrospinning process towards the diameter of the electrospun nanofibers.

CHAPTER 2

LITERATURE REVIEW

2.1 Electrospinning Process and Applications

According to Su Yan *et al*. (2009), Electrospinning is a simple and versatile technique to prepare ultrathin fibers from polymer solutions or melts. Electrospinning is a method of producing thin fibrous scaffolds that is ranged between nano to microns of meter. Many researcher agreed on electrospinning as a lesimple and versatile technique in producing fibers meshes in a nanoscale and it has a special characteristics. Fibers produced using this techniques usually have diameters in the order of a few micrometers down to tens nanometers (Travis, 2006). This technique was claimed by Travis that it is an ideal technique in producing materials of biological size scale and the interest on this method of electrospinning was develop for the application of tissue engineering and drug delivery.

In the process of electrospinning a fibrous non-woven mats can be develop easily because of the function of this techniques is very flexible and there are few processing parameters that can affect the properties of the generated fibers. In the early years of development of electrospinning techniques, there are few difficulties relating to a few of these parameters that preventing from emerging as a feasible method to spin a small-diameter polymer fiber (Travis, 2006). The suitable and efficient instruments for the electrospinning itself was not develop until in 1934, when Formhals patented a process and an apparatus that was using electrical charges to spin the synthetic fibers, then the electrospinning technique was truly surface as a valid technique for spinning small-diamters fibers (Formhals, 1934).

There are plenty of advantages in using electrospinning techniques as a process of producing meshes of fibers. According to Su Yan *et al*. (2009), the polymer nanofibers that produce by electrospinning posses numbers of speciality and extraordinary properties including small diameters and the concomitant large specific surface areas, a high degree of structural perfection and the resultant superior mechanical properties. Furthermore, electrospun polymer nanofibers can be used in many biological applications especially stated by Travis (2006) that it was ideally used in tissue engineering and target delivery system. Liang *et al.* (2007) stated the agreement upon the statement that for electospun nanofibrous scaffolds in biomedical applications, the physical and biological properties, such as hydrophilllicity, mechanical modulus, and strength, biodegradability, biocompatibility, and specific cell interactions, are largely determined by the materials' chemical compositions. This few characteristics make the electrospun nanofibers as a very efficient in the application of biological studies, biomedical studies and also tissue engineering.

2.2 Drug Delivery Technology

These few decades have show the development in the technology of pharmaceutical was advancing and more research was done in finding the most efficient ways for human systems to accept drugs. According to Ping Chen *et al*. (2010), there are large groups of researches have been done in order to develop more efficient release systems, decrease side effects and improve selective toxicities against cancer cell. There are not only drugs concerning anti-cancer but there are also numerous researchers that investigating the controlled release of various drugs for repairing wound or broken tissue. Research shows that a suitable controlled release system is important to improve both safety and efficacy of cancer chemotherapy (Chen *et al*., 2010). Therefore it can be said, controlled release and target drug delivery system is important in maintaining the safety and ensuring the efficiency of drugs transport across biological barriers is in optimal condition.

As discussed before, electrospinning technique offers a very flexible in selecting materials for the drug delivery applications. It is either biodegradable or non-degradable materials that can be use to control the drug delivery by diffusion alone or diffusion and scaffold degradation. There are numbers of drugs that can be delivered via this technique such as antibiotics, anticancer drugs, proteins and also DNA. According to Travis (2008), there a few different drug loading method that can be produce by various electrospinning techniques such as coatings, embedded drug and encapsulated drug (coaxial and emulsion electrospinning).

In most research done, it was found that material that can undergo biodegradation is more likely to be used in drug delivery system due to the fact that they eliminate the need for explanation. Travis (2008) stated more to this matter that, in general, it is desirable to design a drug delivery device that gives controlled release agent. However, this may come difficult if the material begins degrading as the drug is being release. The other concern about factor that affects the release profile of drugs is the structure and the fabrication of the nanofibers. Coaxial nanofiber is most common structure that chosen by most researchers because of its special characteristics. Electrospun nanofiber meets both requirement of barrier function and drug delivery that necessary to prevent the abdominal adhesion (Travis, 2008). The requirements that were stated are the ability to fabricate scaffolds containing pores on the nanometer size scale that can brings either limit or eliminate cell migration, scaffolds with inherently high surface area which allows for high drug loadings and the ability to overcome mass transfer limitations associated with the other polymeric systems.

2.3 Solution of Polyethylene Oxide (PEO) for Electrospun Nanofibers

Polyethylene Oxide (PEO) is a polymer that is the addition of polyethylene oxide with water that usually designated by a number roughly corresponding to molecular weight. PEO has a high molecular weight than any other polymer and thus giving the supporting characteristics. In this research, PEO is used as core solution of the electrospun nanofibers for the study of morphology of the nanofibers. In a research by Chen *et al*. (2011), the effect of PEO to the phase change of nanofibers can be manipulated by changing the composition of PEO in the nanofibers and the morphology of nanofibers will be changed according to the level composition of the core solution. This will determine the optimal fabrication of nanofibers that using PEO as a core solution.

According to Frenot and Chronakis (2003), they stated that the morphology of electrospun fibers is strongly correlated with viscosity, equivalent concentration and temperature. This parameter will affect the fabrication of nanofibers when the study of morphology will be done using FE-SEM and EDX-SEM. These parameters are the important advantage from the aspect of industrial application since high temperature makes electrospinning process quickly (Frenot and Chronakis, 2003). PEO have these advantages as the PEO was electrospun with nanofibers it have a good capability to regulate their interior temperature as the ambient temperature alters (Chen *et al*., 2011). Therefore, PEO can be very suitable and promising for the process of electrospinning as a core solution.

If discuss in the aspects of tensile strength, electrospun nanofibers tensile properties are depends to several factors. For an instance, tensile strength of electrospun nanofibers will be affected by the fibers alignment, the testing direction, the electrospinning solution concentration, the fibers component and etc (Chen *et al*., 2011). In a study shows that when PEO was used as a core solution in a nanofiber, the tensile ultimate strength and ultimate strain will be increase when the composition (%) of PEO solution is increase (Chen *et al*., 2011). Thus it shows that PEO give a mechanical support and tensile strength compared to the distilled water that used in the previous study. However, this statement will be proven again and the optimal condition of these drug delivery electrospun coaxial nanofibers in this study.

Different molecular weight of PEO will result in the different characteristics of nanofibers. Certain molecular weight of PEO will give the best characteristic of nanofibers as well as in the drug delivery system itself. According to Hill *et al*. (2008), electrospun nanofibers from PEO/water solutions containing various PEO concentrations, it is found that solutions that contains the viscosity less than 800 centipoises (cp) will broke up into droplets upon electrospinning while solutions with viscosity greater than 4000 cp were too thick to electrospun. Therefore, the selection of molecular weight of PEO will effect in the viscosity of the PEO solution when it will be electrospun. Higher viscosity of PEO solution will bring the problem to the electrospinning process itself. Thus testing the selection of molecular weight of PEO for the best formation characteristics of nanofibers will be tested in this experiment.

2.4 Effect of viscosity and conductivity towards structure of nanofibers

In electrospinning process, viscosity of the solution that would be electrospun is highly contribute to the structure of nanofibers that will develop. According to Feng *et al*. (1999), viscosity of a solution can be affected by the varying the concentration of polymer. By varying the polymer concentration we can controlled the viscosity of the solution so that the formation of beads in the nanofibers can be minimized. There are various factor that affects the formation of beads in electrospun nanofibers such as viscosity, net charge density carried by the electrospinning jet and surface tension of the solutions (Feng *et al.*, 1999). Higher viscosity will leads to the formation of fibers without beads. However, higher net charge density is not only leads to formation of fibers without beads, it is also helps in the formation of lower diameter fibers. In the Table 2.1 shows the preparation and characterisation of the solutions with PEO.

Table 2.1 The preparation and characterization of the solutions (Adapted from Feng *et al.*, 1999)

Sample number	PEO (g)	Water (g)	Ethanol (g)	NaCl (g)	Solution viscosity (Centipoise)	Solution surface tension (mN/m)	Solution resistivity (Ω m)
1	1.00	100			13	77.8	306
2	1.50	100			32	76.4	295
3	2.00	100			74	76.0	254
4	2.50	100			160	78.6	234
5	3.00	100			289	77.6	221
6	3.50	100			527	77.0	212
7	4.00	100			1250	76.6	204
8	4.50	100			1835	76.2	195
A	3.00	97		0.0015	375	76.2	83.4
B	3.00	97		0.0060	392	74.8	47.4
C	3.00	97		0.030	432	75.0	16.7
D	3.00	97		0.150	431	76.0	3.61
E	3.00	97		0.30	387	74.2	1.90
F	3.00	97		1.50	362	76.4	0.462
I	3.00	97	0		402	75.8	110
II	3.00	92	5		504	68.9	130
III	3.00	87	10		623	63.1	180
IV	3.00	77	20		889	59.3	269
V	3.00	67	30		1129	54.7	333
VI	3.00	57	40		1179	50.5	386

(Source: Feng *et al.*, 1999)

The main focus of the study is to fabricate the best structure of electrospinning nanofibers by using PEO. Ethanol was used as a solvent and compared to PEO that dissolve in distilled water. Ethanol was believed as a poor solvent among the researchers and it will cause the increases of viscosity of solution. According to Torres *et al* (2002), when PEO dissolve in the ethanol which was a poorer solvent it should cause a coil contraction which will prevent the interaction among the coils and thus reduced the solution intrinsic viscosity and its zero-shear viscosity. The intrinsic viscosity is directly related to the solubility of solvent which is the interaction of PEO and the solvent. When a PEO is less soluble to the solvent it