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Polymer Electrospun Nanofibers For Tissue Engineering Application: A Review

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***Abstract*— This paper reviews recent research in the fields of blending natural polymers and synthetic polymer focusing on electrospinning technique for application of tissue engineering. Suitability of developed new synthetic material promotes new live saving potential for patient. Previous research shows that Polycaprolactone (PCL) and Polylactic acid (PLA) have excellent biodegradability and biocompatibility for tissue engineering. However, the lacks of mechanical strength and elasticity makes this polymer unsuitable for engineering vascular scaffolds. Polyurethane has a potential application in tissue engineering. Many researchers actively conduct experiment based on this elastiomer due to its good mechanical testing and elasticity. This review provides information on current research that is useful for the specific application.**

Keywords*— *Electrospinning, tissue engineering, polymer, Taylor cone.

I. Introduction

Electrospinning is one of the most interesting working techniques which is first patented in 1934 by Anton Formals for the fabrication of fine mess nanofibers [1]. A lot of people working in this area due to some exotic characteristic appear from the fabricated fibers, such as, high surface area per volume ratio, superior mechanical properties compare to bulk size and also can form micro to nanofibers. In this review, we will discuss the electrospinning technique that revolutionized from core shell to different morphology such as hollow fiber or porous fiber, and some of biodegradable polymers that mostly used by researcher related to tissue culture application [2][3].

II. Electrospinning Method

A. *Principle of electrospinning*

Electrospinning process, which is a relatively simple and low cost technique and instrumentation, can fabricate continuous non-woven polymer with various porosity, with a diameter ranging from micrometers to ten of nanometers. The fiber that is produced by this technique is useful for cell culturing because it has a similar characteristic with extra cellular matrix (ECM). Traditionally, cells grow in vitro in the form of two dimensional shape (2D) and get impose of unnatural geometric and also provide mechanical constraints to cell [4]. By using the fiber that is quite similar with ECM, it provides a change for the environment of the cell and consequently gives significant differences in its geometry and formation of chemical signal. Therefore, electrospinning is a technique that is useful for cell culture application [5]. **Figure 1a** shows the important part of electrospinning device that is useful for tissue engineering and other possible applications such as filtration media, drug delivery [6], solar cell and even chemical sensor.

There are three theory of electrospinning which is the theory on the fluid charging [7], the theory on liquid droplet under high voltage or also known as the Taylor cone theory and the theory on the jet in flight – Instability theory [8]. High voltage was connected to end tips of needle consequently high electrostatics fields applied. Free electrons, ions, and ion pairs were generated as charge charier because of the ion mobility and produce double layer. In the present of flow, ions will be convicted away from electrodes and replenish of double layers and this process is referred to as the theory of fluid charging [7]. When increase of electrostatics force, hemispherical surface of liquid occurred at the end of capillary extend and hold out toward then produce conical shapes known as Taylor cone with the half angle 49.3° [9] . Taylor demonstrates the shape cone in the theoretical is just before jet formation within the electrospraying process [10]. **Figure 1b** shows the conical droplet on tips of needle that produce Taylor Cone. Taylor's derivation according to two assumptions which is the surface of cone is an equipotential surface and the cone must exist in steady state equilibrium.

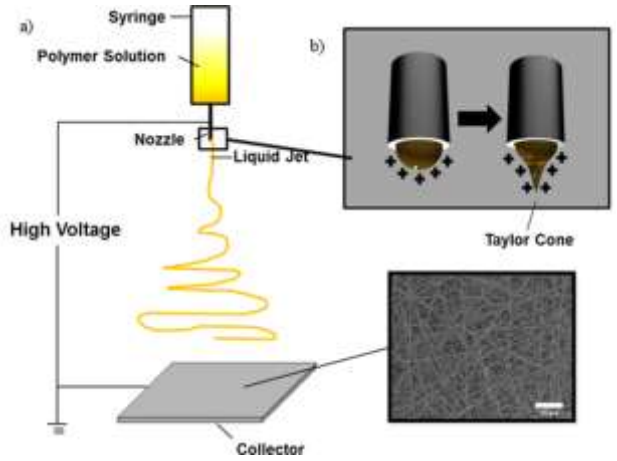

Figure 1: a) Electrospinning instrument consist of three parts, high voltage, spinneret and collector. b) Taylor cone produce in tips of needle.

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When the Taylor's cone forms at the end of capillary, the strand of polymer undergoes instability and continuous tinning liquid jet can be observed. Instability theory applied and according to these phenomena, a lot of works are carried out to explain this theory[11]. Therefore, researchers are trying to manipulate factor that is affecting this electrospinning process in order to manipulate its fibers condition. There are several factors that control the electrospinning process [12]. It comes from ambient parameters, motion of the grounded target, polymer solution flow rate and also distance between spinneret and collectors [13].

B. *Electrospinning Technique*

Electrospinning instrument consists of three main parts which is high voltage, spinneret and collectors. Changes in spinneret and collectors types can control the fibers morphology[14]. **Figure 2a** shows schematic illustration of the three channel tube systems. Three metallic capillaries that are attach in the plastic syringe and arranged at three vertexes with equilateral triangle. Two homogenous liquids fed separately into inner and outer capillaries with suitable flow. Polyvinyl Pyrrolidone (PVP) was mixed with Titanium isopropoxide ($Ti(OiPr)_4$ in ethanol and put in outer capillary whereas paraffin oil is chosen as inner liquid [15]. As the result of SEM, three channel tube systems will produce looks like hollow tube with three vacuums with average diameter distribution of 2.3$^{\mu}$m.

The formation of nanowire-in-microtube structure using electrospinning technique shows in **Figure 2b**. The advancement of this approach is by adding extra middle fluids in between core and shells tube in comparison with the conventional co-axial electrospinning [16]. After that the middle layer needs to effectively remove. The average diameter of wires and middle channel is 284 and 667 nm respectively and the wall thickness is 177 nm. Proper speeding rate of middle fluid is very important because if the rate is too slow, middle fluid sheet will be too thin to separate the inner and outer layer. By increasing the flow rate of liquid, the diameter of fibers enlarges.

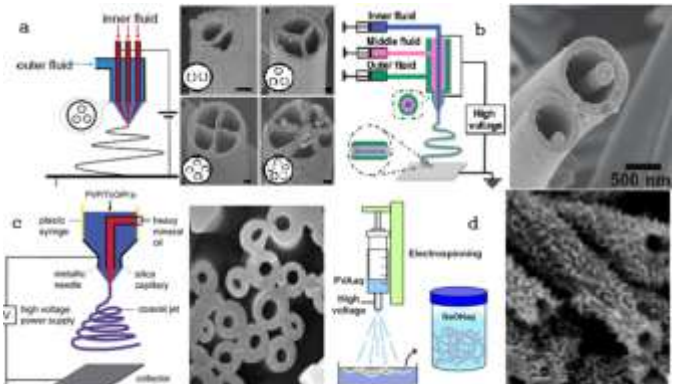

Figure 2: Electrospinning process using different types of spinneret a) Setup for multifluid electrospinning. b) Nanowire-in-microtube structure core/shell fibers. c) Formation of hollow fibers. d) Formation of hollow fibers with surface nanostructure.

The technique that is used to produce hollow fibers with smooth outer structure is shows in **Figure 2c** by using the conventional co-axial technique [17]. Zhang and team have conducted this method of experiment using Polyacrylonitrile (PAN) in DMF as outer layer and PVP as inner layer. Their objective of study is to determine the parameter that affects the hollow fiber such as flow rate, voltage and distance. As the result, fiber thickness will be increased by increasing feed rate. High voltage application is the best way to reduce size of diameter, however, it needs to be controlled at acertain range. If continuously apply the voltage, diameter distribution and continuity of fiber become worsen. The best voltage according to this research is about 15kv. Distance also contributes to the effect of electrospinnig process by increasing the distance between 10 to 25cm, making the solvent volatilized fully and polymer dried well [18].

Hollow fiber with surface nanostructure shows in **Figure 2d.** The procedure to prepare these type of fibers is by co-axial electrospin of polyvinyl alcohol (PVA) direct to solution of titanium tetraisopropoxide (TTIP) in hexane at the ground. Then wash with hexane, undergo alkaline treatment of NaOH, immerse in HCl, dry and lastly calcine at 773K for 2 hour [19]. This technique suitable to be applied for improvement photocatalytic activity compare to tissue culture.

III. Polymer

There are various types of natural polymer that is widely used in biomedical application and tissue engineering. It is easier to use synthetic polymer because it can be processed to a wide range of shapes whereas natural polymer with several shapes is not easy to be obtained. For example, when the natural polymer is exposed to high temperature it can destroy its native structure. In order to promote improvement in morphology and property, researcher doing mixing with two or three polymer between natural and synthetic called as bio-artificial or biosynthetic polymeric materials [20].

A. *Natural polymer*

There are various types of natural polymer that is widely used in biomedical application. It can be from sources of animals' body and also can be a group derived from plants. Natural polymer comes from animal such as chitin [21], chitosan [22], collagen [23], silk [24] and elastin [25]. Starch [26], pectin [27] and cellulose [28] are the examples of natural polymer derived from plants.

Chitosan is polysaccharide that is produced from deacetylation of chitin. Resource of chitin is from crustacean shells, crabs, shrimps, yeast, fungi or insects that are abundant in Malaysia. This biopolymer attracts enormous attention due to its unique properties such as high antibacterial activities against Gram-positives bacterial Staphylococcus Aureus and Gram-negatives bacterial Escherichia coli [29]. They mixed quaternized chitosan and PVP polymer with different molecular weight ratio using electrospinning technique of 0.1mm diameter with 10-40kv and significantly decrease in value average diameters of fibers from 2800 to 1500 nm on increasing the polyelectrolyte content. It is expected to be useful for wound dressing application. According to Flory-Huggins theory,

chitosan can be immisible and compatible due to its ability to form hydrogen bonding between mixing polymers [22].

B. *Synthetic polymer*

There are various synthetic polymers that are biodegradable and biocompatible for cell growth in tissue engineering. However some of them have a limitation and need to be improved in order to be used for implantation. Here, we will discuss some polymers that are commonly use such as Polycaprolactone (PCL) [30], *Poly Glycolic acid (*PGA) [20], Poly Lactic acids (PLA) [31], Polyurethanes (PU) [32] and Polyvinyl pyrrolidone (PVP) [33]

1. Polycaprolactone

PCL is biodegradable and biocompatible polyesters that has a low melting point around 60°C [34]. Analysis on thermal showing glass transition temperature for PCL is about −60 °C. According to research team from Institute of Biomedical Engineering China, they conducted long-term in vivo degradation, adsorption and excretion study done on PCL and concluded that PCL degrades completely in three years to four years without material accumulation in any part of body organ [35]. This shows the compatibility of PCL-based polymer and non-toxicity to animal body. PCL has limitation due to its mechanical endurance [36], surface morphology, high phobicity and biocompatibility. Therefore, researcher usually blend PCL with other natural polymer or synthetic polymer to overcome this problems [34].

In order to overcome the limitation of low degradation rate and improve hydrophobicity of PCL for better morphology for cell attachment, team research Italy blending PCL with water soluble polymer Poly (N-vinyl-2-pyrrolidone) PVP [37]. Then they culture adipose derived stem cells isolated from green fluorescent protein (GFP) mice. As the result, PCL and PVP blending morphology elongated cell decrease with increasing PVP content, show changes in cytoskeletal give affect for cell response which strongly influence by chemical composition and morphology.

PCL porous scaffolds or fiber scaffolds promote low value of tensile strength and elastic modulus, which has tensile strength of 25-43 MPa and elastic modulus around 330-360 MPa [38]. This value must be modified to meet requirement of specific cell culture for example for artery nanofiber application. Iwasaki and team produce three layer robust consist of PCL nanofibers which cell seeded with smooth muscle cell for artery application. In their research-engineered vessel they produce equivalent mechanical strength with native arteries however ultimate modulus and elastin modulus is slightly higher from natives arteries [39].

2. Polyurethane

PU is anelastomer derived from a group of polyesters. Since its invention during the 1940s, PU has been used in a wide range of items, from baby toys, tissue engineering, airplane wings also body, and it continues to be adapted for contemporary technology. This new synthetic polyurethane is resilient, flexible and durable manufactured material and having good mechanical strength [40].

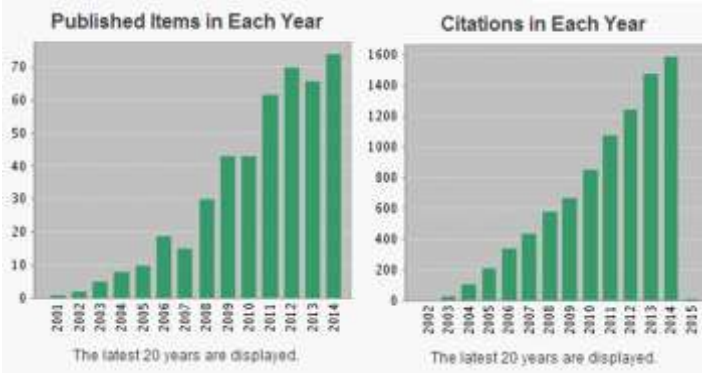

Figure 3: Result from web of science: searching for keywords of "polyurethane and electrospinning" which means the number of published and citation increase in each year.

This polymer consists of three different monomers: hard domain, chain extender and soft domain. It is flexible at physiologic temperature at soft domain and hard domain can impart strength. Previous study of Bergmeister and team synthesized thermoplastic polymer by combining polytetrahydrofuran with hexamethylene diisocyanate in dimethylformamide under argon atmosphere, with tin(II)-2-ethyl-hexanoateas catalyst[41]. The result from their study shows thermoplastic Polyurethane graft performs excellent in vivo for long term vascular graft trial in rodents [32]. Synthetic polymer also shows increasing endothelial cell proliferation in vitro ($p<0.001$). However some researchers who have conduct research on isocyanides shows that this compound maybe carcinogenic and gives adverse health effect such as lung problem and skin irritation.

Publish paper and citation numbers of polyurethane electrospinning fibers in webs of science shows in **Figure 3**. Electrospinning related to PU increase year by years due to its unique characteristics that can be applied in various application fields including tissue engineering fields [42].

3) Polyvinyl Pyrrolidone

PVP is a hydrophilic compound that is easily dissolve in water and various organic compounds. PVP polymer is also known as biocompatible, nontoxic and can form hydrogen bonding interaction when it is blended with other polymer [43]. Pure PVP exhibit smaller fiber distribution and uniform size distribution around 0.95 µm using with 1mm needle diameters, 10 cm working distance and 3-20kv supply voltage [37].

C. *Dissolution*

Different polymers can be dissolved in different types of solvent. **Table 1** shows the solubility of polymer for electrospinning process. The best solvent for electrospinning technique must be easily evaporated during jet flow to get the thinning and fine fibers from microfiber up to nanofibers [44].

Table 1: The solubility of the polymer fabricated nanofiber by using electrospinning techniques.

Summary of dissolution solvent		
Polymer	***Solvent***	***References***
PET	HFIP	[45]
PCL	Acetic Acid Chloroform DCM:DMF (9/1)	[36] [30] [46]
PU	Chloroform: DMF (2:1), HFP	[42] [32]
PVP	Water, various organic solvent, ethanol	[47]
PVA	HFIP, water, DMF	[45],[48]
PLA	Chloroform, DMF	[30][49]
PGA	HFIP	[20]

*HFP: 1,1,1,3,3,3-Hexaflouro-2-propanol, DMF=N,N-dimethylformamide,, HFIP=Hexaflouroisopropanol, DCM=dichloro methane

IV. CONCLUSION

Biodegradable polymers have potential application in tissue engineering application. However some of these synthetic polymers must undergo research improvement to change its mechanical properties, degradable rate and also their biocompatibility. Polyurethane has received recent attention for formation of degradable polymer due to its great achievement in mechanical testing and cell proliferation.

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