CHAPTER II

LITERATURE REVIEW

2.1 Electrospinning

2.1.1 History of electrospinning

In 1882, Lord Raleigh [1] studied the condition of instability in electrically charged liquid droplets. He showed that when the electrostatic force overcomes the surface tension that acts in the opposite direction of the electrostatic force, liquid is thrown out in the form of fine jets.

In 1934, Formhals [2] was granted the first patent detailing an apparatus and a process for producing polymer fibers by using electrostatic force. Cellulose acetate was used as the model polymer in his patent. Fibers were formed between two electrodes that are in opposite polarities. One electrode was placed into the polymer solution, and another was attached to a conductive collector. The applied potential depended on the properties of solution such as molecular weight of the polymer and viscosity of the solution. The small opening used as the spinneret was constructed by drilling a fine hole in a metal alloy.

In 1964, Doyle et al. [3] observed that when the electrical force tended to a critical limit, solvent molecules evaporated from a charged droplet. The disintegration of the droplet caused an increase in surface charge density. After that, the ejection of many smaller charged droplets are observed.

In 1969, Taylor [4] studied the disintegration of water droplets deformed by an electrostatic field. He demonstrated that an interface between fluids could exist in equilibrium in an electrostatic field. At the onset of the instability, the droplet elongates to form a conical shape called Taylor's cone of which the semi-vertical angle was shown to be 49.3°.

In 1971, Buamgarten [5] was successful in producing acrylic microfibers by the electrostatic spinning process. Dimethyl formamide was used as the solvent. The obtained fiber diameters were in the range of 0.05 to 1.1 microns based on the applied potentials in the range of 5 to 20 kV. The relationships between fiber diameter, fiber jet, solution viscosity, solution feed rate and surrounding gas were observed. He found that fiber diameter increased when the solution viscosity increased. The effect of solution flow rate on fiber diameters was very small, and the effect of surrounding gas depended on the humidity.

The effects of solution viscosity, charge density carried by the jet, and solution surface tension on the formation bead-on-string morphology were investigated by Fong and coworkers [6]. Beads and beaded fibers were less likely to be formed in fibers spun from highly viscous solutions and in jets with high net charge density. Increasing net charge density favored the formation of smaller fibers. Decreasing the surface tension coefficient of the solution favored the formation of larger fibers.

Deitzel and coworkers [7] studied the effects of applied potential and solution concentration on morphology of electrospun poly(ethylene oxide) fibers. They found that the applied potential correlated strongly with the formation of beaded fibers. Changes in solution concentration contributed mostly to the diameters of the obtained fibers, with the fiber diameters increasing with increasing solution concentration following a power law relationship. In addition, electrospinning from solutions of high concentration produced fibers having a bimodal distribution of the diameters.

2.1.2 Experimental setup

Electrospinning of polymer solutions or melts can be carried out either horizontally or vertically, depending on the direction of normal line between the tip of the nozzle and the collective screen. The reservoir can be anything from a pipette to a syringe. In the case of glass pipette, the high potentials were supplied directly to the solutions or the melts through a metal electrode which was submerged in the solutions or the melts directly [8]. On the other hand, when a syringe was used as the reservoir, the high potentials can be applied directly to the solutions or melts through a metal needle by attaching with the metal electrode [9].

Conductive screens from a metal foil or sieve of different geometry have been used as targets to receive the charged jets which converted into fibers after enough solidification. Warner et al. [10] introduced a rotating device to collect the electrospun fibers which could turn the electrospun fibers into yarns as a continuous process.

2.1.3 Polymer Types

It has been reported in the open literature that more than 50 different polymers have been successfully spun into ultrafine fibers. The obtained fibers were reported to range between less than 3 nanometers to over 1 micrometer in diameter. Even though almost all of the reports in the open literature focussed on electrospinning of polymer solutions, electrospinning of polymer melts has also been achieved [11]. Common textile polymers such as nylons, high performance polymers such as polyimide, and biopolymers such as DNA have been electrospun [12,13]. Moreover, liquid crystalline polymers such as polyaramid and conductive polymers such as polyaniline have also been reported as successful.

2.1.4 Charged Jet Pathway

Originally, the mechanism for the fiber formation in the electrospinning process could be divided into four different regions as shown in Figure 1. The jet emerges from the charged surface at the base region, travels through the jet region, divides into many fibers in the splaying region, and stops in the collecting region. It should be noted that, at present, the splitting of the charged jet into small jets was disproved to be the major mode in the thinning down on the charged jet.

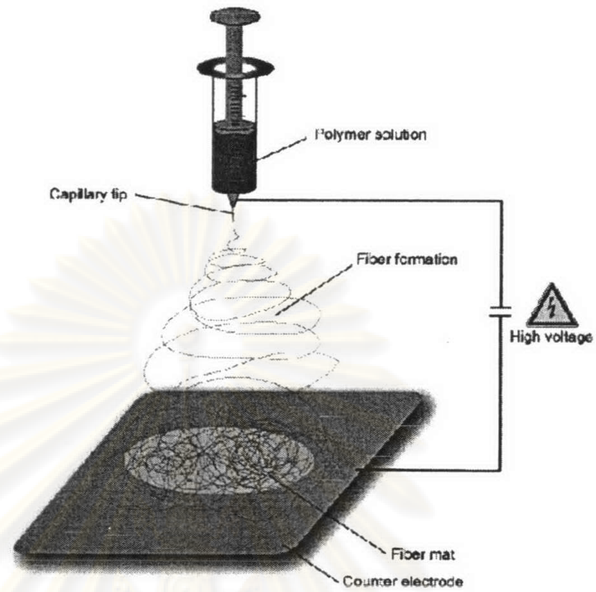

Figure 1 Schematic drawing of an electrospinning set-up

After observation of the jet formation through a high-speed digital video system of up to 2000 frames per second with a time resolution of approximately 0.0125 ms, the proposed mechanism for the fiber formation is different from the previously proposed mechanism. After a charged jet is ejected from the droplet of conical shape, it flows continuously under the influence of the electrostatic field. There are two kinds of electrostatic forces acting on a jet segment. One is from the external field that reacts with charges present in a jet segment and the other from the Coulombic repulsion between adjacent charges of similar polarity. The first force is responsible in carrying the charged jet towards the conductive collector and the second is responsible for the stretching of the charged jet. The Coulombic repulsion can also cause different types of instability such as bending and splitting instability.

The jet followed a bending, winding, spiraling and looping path in three dimensions. The jet in each loop grew longer and thinner as the loop diameter increased, a direct result of the longer path length. After some time, segment of a loop suddenly developed a new bending instability, but at a smaller scale than that of the first one. Each cycle of bending instability can be described in three steps.

Step 1: A smooth segment that was straight or slightly curved suddenly developed an array of bends.

Step 2: The segment of the jet in each bend elongated and the array of bends became a series of spiraling loops with growing diameters.

Step 3: As the perimeter of the loops increased, the cross-sectional diameter of the jet forming the loop grew smaller; the conditions of the first step were established on a smaller scale, and the next cycle of bending instability began.

This cycle of instability was observed to repeat in a smaller scale. It was inferred that a larger number of cycles occurred resulted in a decrease in the jet diameters, hence a decrease in the diameter of the obtained fibers. The fluid jet solidifies as it dries and the electrospun nanofibers are collected some distance below the envelope cone [14].

In electrically driven bending instability, alternatively referred to as whipping instability, the jet rotates in a conical region, whose vertex is the end of the straight jet. The other end of the jet, which is highly stretched and reduced in diameter, is deposited on the collector as a result of the fast bending instability motions [15].

By applying a secondary external field of the same polarity as the surface charge on the jet, it is possible to limit or eliminate the bending instability. This mechanism allows for greater control over the deposition of electrospun fibers on a surface and for collection of electrospun fibers in other forms besides non-woven mats.

Another instability of the charged jet is the splitting instability. It occurs when the surface charge density increases as the solvent evaporates or as the decrease in the jet diameter. The elongation of the jet can reduce charge per unit surface area since elongation increases the surface of a particular mass. The charged jet can reduce its charge per unit surface area by ejecting a smaller jet from the surface of the primary jet, or by splitting apart to form two smaller jets. This type of instability was originally thought as the main contributor to the decrease in the fibers diameter (see Figure 1 in the spraying region).

2.1.5 Microstructure and morphology

The microstructure and morphology of electrospun fibers have been investigated through scanning electron microscope (SEM), differential scanning calorimeter (DSC), synchrotron wide-angle X-ray diffraction/small angle X-ray scattering [16], atomic force microscope [17], transmission electron microscope, and wide-angle X-ray scattering [18].

2.1.6 Applications

Due to the high surface area to volume ratio, high porosity, and light weight of the electrospun fibrous webs, a number of applications has been sought out.

Filtration application

Filtration is a necessary process in various engineering applications. Fibrous materials used as filter media provide advantages of high filtration efficiency and low air resistance [19]. Since filtration efficiency, which is closely related to the fineness of the fibers, is one of the most concerns for achieving the best performance, it is realized that electrospun fibers have high potential to be used as filter media, a directly result of the fineness of the fibers obtained. More importantly, both the size of the fibers and the porosity of the electrospun webs can be tailored with ease, thus high efficiency fibrous filter media can be developed using the electrospinning technique.

Biomedical application

Almost all of the human tissues and organs have fibrous network to provide mechanical integrity to them. These tissues and organs are, for examples, bone, dentin, collagen, cartilage, and skin. Due to the similarity in the structure, electrospun fibers are easily found to be prospective materials to be used as templates for tissue scaffolding applications, controlled release fibers for wound dressing, pharmaceutical, and cosmetic applications. For the treatment of injured or defective tissues or organs, biocompatible materials are designed and fabricated to form structure that mimic the structure and biological functions of extracellular matrix (ECM). Human cells can attach and organize well around the fibers that are smaller them. As a result, nanometer or sub-micrometer fibrous scaffolds could be suitable template for cell seeding, migrating, and proliferating. Polymer nanofibers can also be used for treatment of wounds or burns of a human skin, functioned as haemostatic devices with unique characteristic. Biodegradable polymer can be directly spun onto the injured skin. These fibrous materials can facilitate wound healing by encouraging skin growth without the formation of scar tissue. It has been reported that scaffolds having high surface area to mass ratio (ranging from 5 to 100 m^2/g) is efficient for fluid absorption and dermal delivery [11].

Electrospun polymer fibers have also been explored for cosmetic applications as a skin-care mask for skin treatment or promoting skin healing. These skin masks with high surface area can speed up the rate of effective agent transfer to the skin for the fullest potential of the additive [20].

<u>Protective clothing application</u>

The protective clothing in military is expected to help maximize survivability, sustainability, and combat effectiveness of a soldier against nuclear, biological, and chemical warfare. Light weight and breathable fabric, which is permeable to both air and water vapor, insoluble in all solvents and highly reactive with nerve gases and other hazard chemical agents, is required. Electrospinning results in nanofibers being laid down in layers that have high porosity, but very small pore size providing good resistance to the penetration of chemically-harmful agents.

<u>Other applications</u>

Other prospective uses for nanofibers are in areas such as electronic, composite reinforcement, and advanced space technology [9, 14, 21, 22].

2.2 <u>Drug delivery system</u>

Kenawy et al. [23] used electrospun fibers as drug delivery carriers. Tetracycline hydrochloride was used as the model drug. Poly(lactic acid) (PLA), poly(ethylene-co-vinyl acetate) (PEVA), and a blend of the two polymers were spun from their solutions in chloroform with addition of a small amount of methanol used to dissolve the drug. The release of tetracycline hydrochloride was detected by ultraviolet visible spectroscopy. The release profiles showed that the percentage of drug released from as-spun PLA fiber was a sudden release due to the aggregation of drug on the surface of the fibers. When comparing electrospun fibers and cast films which were prepared from the same solutions, the percentage of drug release from electrospun fibers were much greater than from cast films. The maximum of drug release from cast films was about 5% to less than 25%, comparing to about 30 to 60% from electrospun fibers.

Zeng et al. [24] studied the influences of surfactant and medical drug on the diametral size and uniformity of electrospun poly(L-lactic acid) (PLLA) fibers. The significant improvement of uniformity was observed. They observed that drug was incorporated in the as-spun fibers obtained. The incorporated proteinase K was released from the as-spun fibers following the zeroth order releasing kinetic as a result of the degradation of PLLA.

In order to electrospin pharmaceutical compositions, Ignatious [25]used surfactants to lower the viscosity and surface tension of the formulation. The surfactants were added on a weight by weight basis to the compositions. Suitably, about 10% of surfactants was added, with the preferred amount being about 5% or less. The higher amounts could adversely affect the quality of the electrospun fibers. Another pharmaceutically acceptable excipients may be added to the electrospinning compositions. These excipients may be generally classified as absorption enhancers, additional surfactants, flavoring agents, dye, and etc.

The chemical composition such as polymers or blends of polymers, the fiber diameter, the electrospun morphology and the porosity of the non-woven fibers can be controlled to provide selectable performance criteria for the electrospun fibers being produced. These fibers can also contain a different drug or different concentration of drug. Such fibers offer unique treatment options with combinations of drug and release profile. In one embodiment, the methods of the invention can provide a plurality of different layers. The layers can have the same or different chemical compositions, fiber diameters, morphology, and porosity [26].

Currently available polymers for controlled release can be classified into four major categories:

(1) Diffusion-controlled systems

Diffusion-controlled systems involve two types: reservoir and matrix. A reservoir is generally consists of a drug core in a powder or liquid form. A layer of non-biodegradable polymeric material, through which the drug slowly diffuses, surrounds the core. The properties of the drug and the polymer govern the diffusion rate of the drug and its release rate into the bloodstream. In the reservoir type, a problem that can, however, occur if the reservoir membrane was ruptured accidentally, causing a large amount of drug being released into the bloodstream in a sudden, which is known as drug dumping. In the matrix type, the drug is uniformly distributed throughout the polymer matrix and is released from the matrix at a uniform rate as drug particles dislodge from the polymer network. In this kind of system, there is no danger from drug dumping.

(2) Solvent-activated systems

Solvent-activated system has two types: osmotically-controlled and swelling-controlled systems. In the osmotically controlled system, osmotic pressure tends to decrease the concentration gradient between two sides. The inward movement of fluid forces the dissolved drug out of the device through a small orifice. In the swelling-controlled systems, the polymer holds a large quantity of water without dissolving. The system consists of hydrophilic macromolecules cross-linked to form a three dimensional network. Their permeable rate of solute depends on the polymer swelling rate.

(3) Chemically-controlled systems

Chemically controlled systems have two classes: pendant chain and biodegradable system. A pendant chain is one in which the drug molecule is chemically linked to the backbone of the polymer. The presence of enzyme and the mechanism of the body caused the drug be released at a controlled rate. In biodegradable system, the controlled release of drug depends on decomposition of the polymer. The drug is dispersed uniformly throughout the polymer and is slowly released when the polymer is disintegrated. These two types of systems contain biodegradable polymers which do not need to be removed after the drug was completely dispensed. As a result, biodegradable polymers are likely to increase more than any other type of polymers in the future.

(4) Magnetically controlled systems.

Selective targeting of antitumor agents, while minimizing toxic effects, has been a major concern for cancer chemotherapy. An example of magnetically-responsive drug carrier systems is composed of albumin and magnetic microspheres. Their magnetic characteristic and microspheres are capable of using with a wide variety of drugs. Two major advantages of these carrier systems over other drug delivery systems are its high efficiency for *in vivo* targeting and its controllable release of drug at the microvascular level [27].

Shiraishi et al. [28] studied the effects of molecular weights of chitosan hydrolysates on the release and absorption rates of indomethacin from gel beads. The release rates of indomethacin decreased with increasing molecular weight and indomethacin content. Moreover, the release of indomethacin depended upon the dispersion of indomethacin solid particles in the beads, as well as the porosity, tortuosity and surface area of the matrix.

Indomethacin was used as a model drug for studying controlled release of three types of methacrylic-based copolymers in this present work. Indomethacin is a non-stroidal anti-inflammatory agent used in the symptomatic management of painful and inflammatory conditions. It is used in musculoskeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis, and acute gouty arthritis. It may also be used for mild to moderate pain conditions such as dysmenorrhoea. The most frequent adverse effects are gastro-intestinal and central nervous system disturbances. The chemical structure of indomethacin is shown below [29].

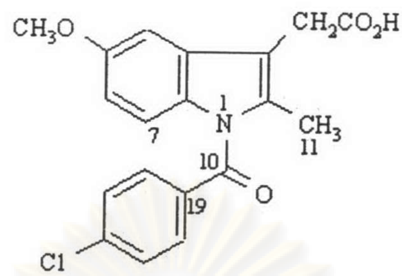

Figure 2 Chemical structure of indomethacin