CHAPTER II
THEORITICAL BACKGROUND AND LITERATURE SURVEYS

2.1 Theoretical Background

2.1.1 Electrospinning

Electrospinning is a fiber spinning technique that produces polymer fibers of nanometer to micrometer range in diameters. In the electrospinning process, a polymer solution held by its surface tension at the end of a capillary tube is subjected to an electric field. Charge is induced on the liquid surface by an electric field. Mutual charge repulsion causes a force directly opposite to the surface tension. As the intensity of the electric field is increased, the hemispherical surface of the solution at the tip of the capillary tube elongates to form a conical shape known as the Taylor cone. When the electric field reaches a critical value at which the repulsive electric force overcomes the surface tension force, a charged jet of the solution is ejected from the tip of the Taylor cone. Since this jet is charged, its trajectory can be controlled by an electric field. As the jet travels in air, the solvent evaporates, leaving behind a charged polymer fiber which lays itself randomly on a collecting metal screen. Thus, continuous fibers are laid to form a non-woven fabric (Doshi, 1995).

The formation of fibers from this spinning process can be divided into two parts:

2.1.1.1 The initiation of the jet

Before the electric field is applied to the polymer solutions, and when the capillary tube are in a vertical position and carries a drop at the tip of nozzle, the relation between the surface tension and the height of the column of liquid under equilibrium conditions is given by

$$2\gamma(1/R + 1/r) = \rho gh \qquad (1)$$

where γ is the surface tension of the liquid of density ρ, h is the height of the column of liquid above the lowest surface of the drop, R is the radius of curvature of the liquid at the upper liquid surface and r is the radius of curvature of the liquid at the lower surface of the liquid (Michelson, 1990).

Consider a droplet of polymer solutions that is applied to a high electric field. Charges that flow onto liquid surface repel each other. The repulsion forces are opposed to the forces from surface tension. The polymer droplet becomes unstable when the charge distributed on the surface overcome the surface tension. The conditions that are necessary for a charged surface to become unstable are described by considering the equilibrium equation,

$$V_* = (4\pi r\gamma)^{1/2} \qquad (2)$$

where V_* is the critical potential, r is the droplet radius, and γ is the surface tension of the solutions (Koombhongse, 2001). For the droplets subjects to a higher potential, $V > V_*$, the droplet elongates into a cone-like shape that was described mathematically by Taylor and often referred to as a Taylor cone (Taylor, 1969).

As the potential is increased, which obtain the maximum instability of the liquid surface, a jet of liquid ejected from the tip of the cone. Taylor showed that the critical voltage V_c (expressed in kilovolts) at which the maximum instability develops is given by

$$V_c^2 = 4H^2/L^2\,(\ln 2L/R - 1.5)(0.117\pi R\gamma) \qquad (3)$$

where H is the distance between the electrodes, L and R are the length and radius of the capillary, respectively, and γ is the surface tension.

2.1.1.2 The continuous flow of the jet

The mechanism of the appearance of a stable electrospinning jet is evidently established by the observation of the jet formation through the high speed electronic camera which recorded up to 2000 frames per second with a time resolution of approximately 0.0125 ms (Reneker, 2000).

There are two kinds of electrical forces that act on the jet: the external field that tries to pull the jet toward collector and the self-repulsion between the charges carried by adjacent segments of the jet that try to push each other apart. The self-repulsion can also cause different types instability such as bending instability and splitting instability.

In bending instability, or 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 whipping motions (Shin, 2001).

After some time, segment of a loop suddenly developed a new bending instability, but at a smaller scale than the first. Each cycle of bending instability can be described in three steps (Reneker, 2000).

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 for step (1) were established on a smaller scale, and the next cycle of bending instability began.

The schematic drawing of the electrospinning process is shown in figure 2.1.

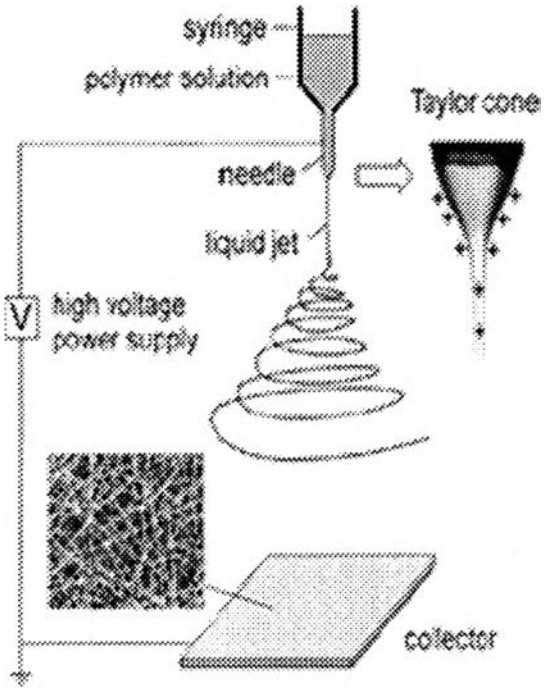


Figure 2.1 Schematic drawing of the electrospinning process (Dan, 2004).

The other instability of the charged jet is the splitting instability. It occurs when the charge density of the charged jet increases as the solvent evaporates. 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 (Koombhongse, 2001).

2.1.1.3 Applications of electrospun fibers

Due to the high surface area to volume ratio, high porosity, and light weight of the electrospun fibrous mats, a number of applications have been sought out (Jayaraman, 2004).

2.1.1.3.1 Filters

Filtration is a necessary process in various engineering applications. Filtration efficiency or capture efficiency of filter media has been shown to be inversely proportional to the diameters of the fibers in filters. Because of the very high surface area-to-volume ratio and the resulting high surface

cohesion of nanofibers, tiny particles on the order of less than 0.5 □m are easily trapped in the nanofiber mats.

2.1.1.3.2 Scaffolds for tissue engineering

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 similarity in the structure, electrospun fibers are easily found to be prospective materials to be used as templates for tissue scaffold applications, controlled release fibers for would 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 fivers that are smaller them. As a result, nanometer or sub- micrometer fibrous scaffolds could be suitable template for cell seeding, migrating, and proliferating. 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 (Haung, 2003).

2.1.1.3.3 Protective Clothing

Protective clothing for military personnel is expected to help maximize the survivability, sustainability, and combat effectiveness of soldiers against extreme weather conditions, ballistics, and nuclear, biological, and chemical warfare. So a lightweight, breathable fabric, permeable to both air and water vapor, insoluble in all solvents, and highly reactive to chemical agents, is desirable. Polymer nanofibers had been developed for various protective clothing applications. It was found that compared with conventional textiles, electrospun nanofiber mats provide minimum impedance to moisture vapor diffusion and maximum efficiency in trapping aerosol particles.

2.1.1.3.4 Reinforcement in Composite Materials

Publications on nanofiber-reinforced composite materials are limited in the literature because of the difficulty of producing these fibers. However, their higher surface-to-volume ratio may improved the interlaminar toughness and interfacial adhesion in nanofiber-reinforced composites.

2.1.1.3.5 Sensors

Polymer nanofibers have been used in the development of functional sensors possessing high sensitivity due to the high surface area of nanofibers. Polymer used in this applications were poly(lactic acid-*co*-glycolic acid) and poly(acrylic acid)-poly(pyrene methanol).

2.1.1.3.6 Drug Delivery System

Controlled delivery systems are used to improve therapeutic efficiency and safety of drugs by delivering them a rate dictated by the need of the physiological environment over a period of treatment to the site of action (Kenawy, 2002). A wide variety of polymeric materials, either biodegradable or non-biodegradable buy biocompatible, can be used as delivery matrices, for example; poly(lactide-co-glycolide) (PLGA) (Kim, 2004), poly(L-lactic acid)(PLLA) fibers (Zeng, 2003), Hydroxypropyl methylcellulose (HPMC) (Verreck, 2003) and poly (ethylene-co-vinylacetate) (PEVA) (Kenawy, 2002). The advantages of the electrospun fibers over the convention cast film are the electrospun fiber has higher surface area and high porosity than film resulting in minimization of the initial burst release of drug and higher amount of drug release was obtained. Moreover, the electrospinnning process is the better alternative compare to the melt processing which is especially important for heat-sensitive drugs.

2.1.2 Drug Delivery System

There are three primary mechanisms by which active agents can be released from a delivery system: diffusion, degradation, and swelling followed by diffusion. (Peppas, 1997). Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the polymer that forms the controlled-release device. The diffusion can occur on a macroscopic scale—as through pores in the polymer matrix—or on a molecular level, by passing between polymer chains. Examples of diffusion-release systems are shown in Figures 2.2 and 2.3. In Figure 2.2, a polymer and active agent have been mixed to form a homogeneous system, also referred to as a matrix system. Diffusion occurs when the drug passes from the polymer matrix into the external environment. As the release continues, its rate normally decreases with this type of

system, since the active agent has a progressively longer distance to travel and therefore requires a longer diffusion time to release.

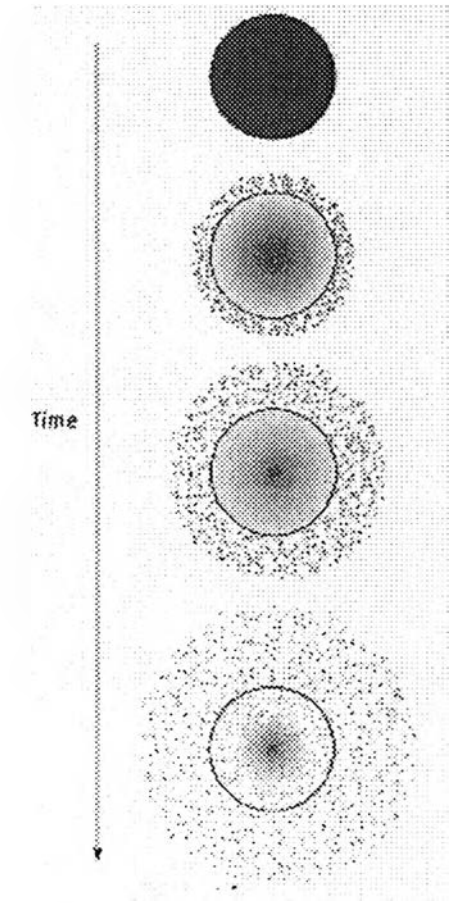


Figure 2.2 Drug delivery from a typical matrix drug delivery system.

For the reservoir systems shown in Figures 2.3a and 2.3b, the drug delivery rate can remain fairly constant. In this design, a reservoir—whether solid drug, dilute solution, or highly concentrated drug solution within a polymer matrix—is surrounded by a film or membrane of a rate-controlling material. The only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Since this polymer coating is essentially uniform and of a nonchanging thickness, the diffusion rate of the active agent can be kept fairly stable throughout the lifetime of the delivery system. The system shown in Figure 2.3a is representative of an implantable or oral reservoir delivery system, whereas the

system shown in Figure 2.3b illustrates a transdermal drug delivery system, in which only one side of the device will actually be delivering the drug.

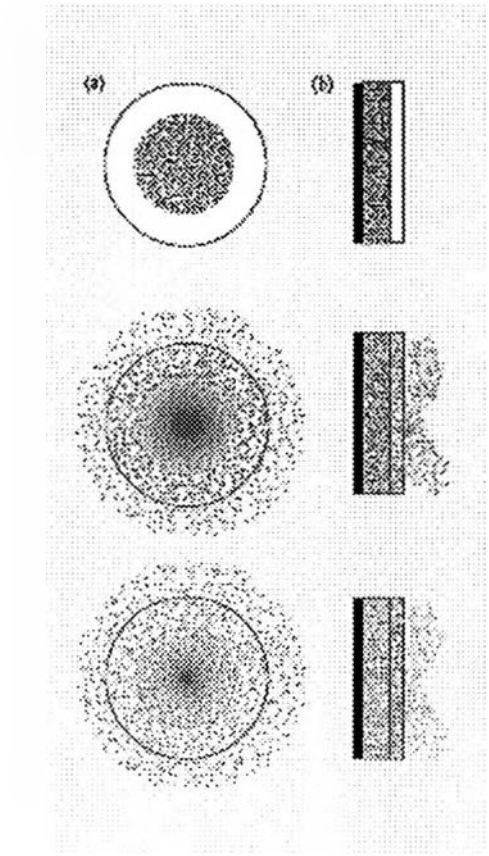


Figure 2.3 Drug delivery from typical reservoir devices: (a) implantable or oral systems, and (b) transdermal systems.

Once the active agent has been released into the external environment, one might assume that any structural control over drug delivery has been relinquished. However, this is not always the case. For transdermal drug delivery, the penetration of the drug through the skin constitutes an additional series of diffusional and active transport steps, as shown schematically in Figure 2.4.

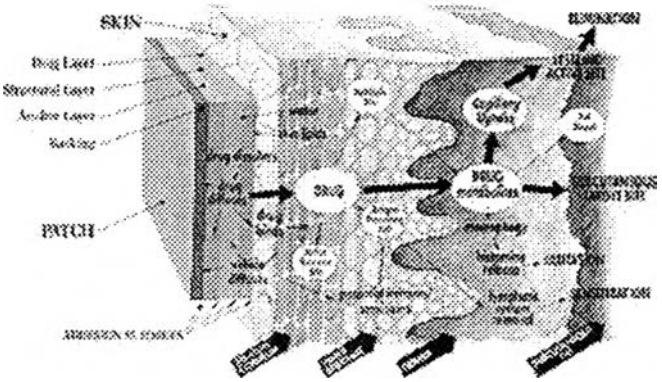


Figure 2.4 Transport processes in transdermal drug delivery (Ishihara, 1983).

For the diffusion-controlled systems described thus far, the drug delivery device is fundamentally stable in the biological environment and does not change its size either through swelling or degradation. In these systems, the combinations of polymer matrices and bioactive agents chosen must allow for the drug to diffuse through the pores or macromolecular structure of the polymer upon introduction of the delivery system into the biological environment without inducing any change in the polymer itself.

2.1.3 Polymeric materials

2.1.3.1 Poly(vinyl alcohol)

Poly(vinyl alcohol) (PVA), a water-soluble polyhydroxy synthetic polymer, is the largest volume synthetic resin produced in the world. It has been used since the early 1930s in a wide range of industrial, commercial, medical and food applications because of its excellent chemical resistance, physical properties, and complete biodegradability (Martien, 1986; DeMerlis, 2003; Koski, 2004) PVA is frequently used in biomedical applications such as implants (Juang, 1996), soft contact lenses (Hyon, 1994), artificial organs (Chen, 1994) and protein immobilization (Kobayashi, 1991; Uhlich, 1999). Beside its hydrophilic character, PVA forms hydrogels that are widely used in pharmaceutics as drug delivery matrix (Seabra, 2003; Kenawy, 2007; Yang, 2007). Such hydrogels are biocompatible, nontoxic and are characterized by a high degree of swelling.

General chemical and physical properties of PVA are summarized in Table 2.1. It is known that, the physical characteristics of PVA are dependent on its method of preparation from the hydrolysis, or partial hydrolysis, of polyvinyl acetate (Finch, 1992). PVA is generally classified into two groups, (a) partially hydrolyzed, and (b) fully hydrolyzed.

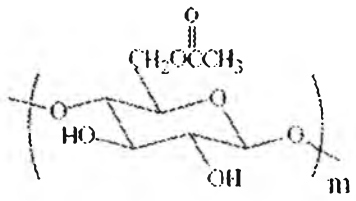
Table 2.1 General chemical, physical, and thermal properties of polyvinyl alcohol (DeMerlis, 2003; Finch, 1992)

Identity/Properties	**Details**
Structure formula	$(\text{-}CH_2CHOH\text{-})_n\text{-}(\text{-}CH_2CHOCOCH_3\text{-})_m$
Empirical formula	$(C_2H_4O)_n(C_4H_6O_2)_m$
Physical appearance	Odorless, white to cream-colored granular powder
Specific gravity	1.19-1.31
Solubility	Insoluble in aliphatic and aromatic hydrocarbons, esters, ketones, and oils; water soluble
Glass transition temperature (°C)	85 for 98-99% hydrolyzed 58 for 87-89% hydrolyzed
Melting temperature (°C)	230 for 98-99% hydrolyzed 180 for 87-89% hydrolyzed

2.1.3.2 Cellulose acetate

Cellulose acetate (CA) is the acetate ester of cellulose, the primary structural component of the cell wall of green plants and is one of the most common biopolymers on earth (Anonymous, 2006). CA is prepared from cellulose by a solution process employing sulfuric acid as the catalyst with acetic anhydride in an acetic acid solvent. The acetylation reaction is heterogeneous and topochemical (Mark, 1985). General properties of CA are shown in Table 2.2.

Table 2.2 General properties of cellulose acetate (40.4% acetyl content) (Mark, 1985)

Properties	Details
Chemical structure	
Melting point (°C)	306
Char point (°C)	315
Density (g/ml)	1.28
Tensile strength (MPa)	71.6

The properties of cellulose acetate are affected by the number of acetyl groups per anhydroglucose unit of cellulose and the degree of polymerization. Fewer acetyl group per anhydroglucose unit (increased hydroxyl content) increase the solubility in polar solvent and decrease moisture resistance (Mark, 1985).

Solubility characteristics of cellulose acetates with various acetyl contents are given in Table 2.3.

Table 2.3 Solubility characteristics of cellulose acetate (Mark, 1985)

Acetyl, %	Soluble in	Insoluble in
43.0-44.8	Dichloromethane	Acetone
37-42	Acetone	dichloromethane
24-32	2-methoxymethanol	Acetone
15-20	Water	2-methoxymethanol
<13	None of the above	All of the above

Cellulose acetate is used in textile fibers, plastics, film, sheeting and lacquers. In biomedical application, cellulose acetate had been used as a semipermeable coating on tablets (Makhija, 2003; Lu, 2003), especially on osmotic pump-type tablets and implants, which allows for controlled, extended release of actives (Santus, 1995).

2.1.4 Anti-inflammatory drugs and vitamins

Four different types of anti-inflammatory drugs used in this work. The chemical structures of model drugs and vitamins were shown in Figure 2.5.

2.1.4.1 Sodium Salicylate

Sodium salicylate, non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as analgesic or antipyretic agents for the clinical treatment of inflammatory diseases. Most NSAIDs exhibit an inhibitory effect on cyclo-oxygenases, which catalyze the biosynthesis of prostaglandins and thromboxane from arachidonic acid (Yamagichi, 2006).

2.1.4.2 Diclofenac sodium

Diclofenac sodium, monosodium{2-[(2,6dichloroanilino)phenyl acetate, is a potent analgesic, non-steroidal anti-inflammatory drug [NSAID]. It is used in inflammatory and painful diseases of rheumatic and non-rheumatic origin (Moser, 1990). Its pharmacological effects are thought to be related to the inhibition of the conversion of arachidonic acid to prostal-glandins, which are the mediators of the inflammatory processes (Kenawi, 2005).

2.1.4.3 Indomethacin

Indomethacin (INM) [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid] is an indole derivative, known for its antipyretic and analgesic action (Day, 1987). It is a nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis and a potent inhibitor of cyclooxygenase, reducing prostaglandia synthesis, relieving pain and reducing temperature in febrific patients. The antipyretic effect is due to a resetting of the hypothalamic temperature-regulating center, whereas the anti-inflammatory and analgesic effects are due to inhibition of prostaglandin synthesis. Therapeutically, INM is indicated to control pain and inflammation (Zhang, 2006).

2.1.4.4 Naproxen

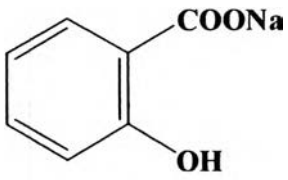
Naproxen [(+)-2-(6-methoxy-2-naphthyl) propionic acid], a non-steroidal anti-inflammatory drug, is widely used to moderate pain relief in the treatment of many diseases, such as rheumatoid arthritis, osteoarthritis, degenerative joint disease, ankylosing spondylitis, acute gout and primary dismenorrea (Boynton, 1988). The major clinical application on NSAIDs is their action as anti-inflammatory agents in muscle skeletal diseases (Okulik, 2006).

2.1.4.4 Vitamin E or α-tocopherol (Vit-E)

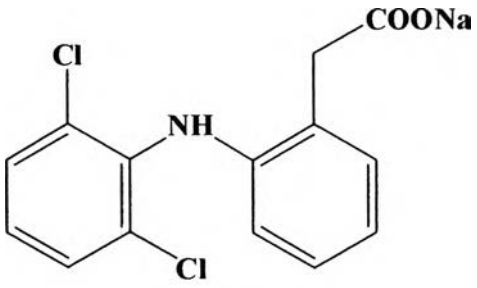
Vit-E, also a lipid-soluble vitamin, is known for its potent antioxidant ability, owing to the presence of a hydroxyl group on its chromanol ring which can readily donate a proton to reduce free radicals (viz. free radicals can cause cell damage that may contribute to the development of cardiovascular disease and cancer) (Anonymous, 2006; Wolf, 1998; Shapiro, 2001; Lin, 2003).

2.1.4.5 All-tran retinoic acid or vitamin A acid (Retin-A)

Retin-A, a naturally-occurring derivative of vitamin A, is a lipid-soluble substance, known to be used for the treatment of acute promyelocytic leukemia, acne, and other skin disorders, and it is believed to help slow skin aging, remove wrinkles, or reduce hyper-pigmentation due to photo-aging (Anonymous, 2006;Cho,2005)



(a)



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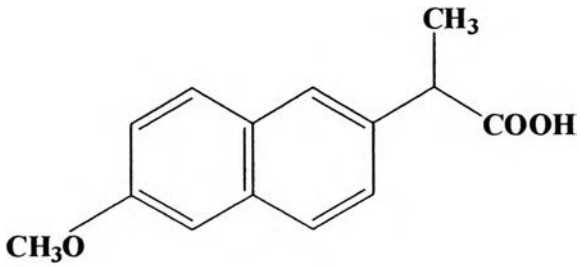

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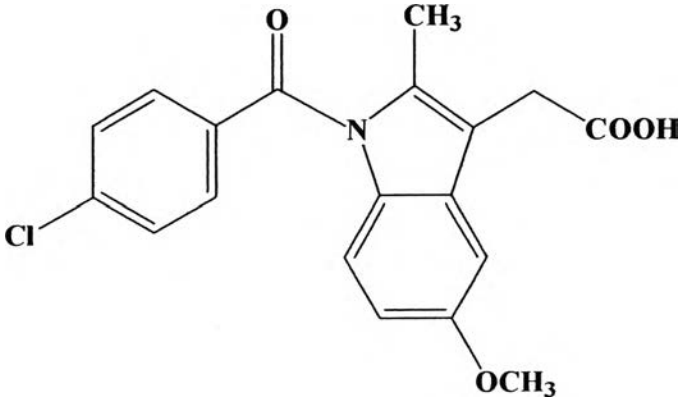

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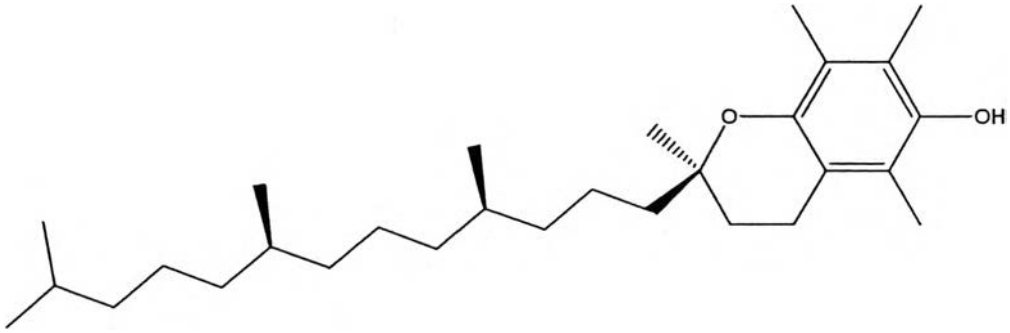
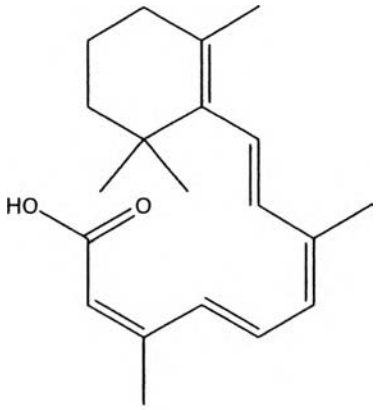


(e)



(f)

Figure 2.5 Chemical structures of (a) sodium salicylate (SS), (b) diclofenac sodium (DS), (c) naproxen (Nap), (d) indomethacin (Ind), (e) vitamin E or α-tocopherol (Vit-E) and (f) all-tran retinoic acid or vitamin A acid (Retin-A).

2.2 Literature surveys

2.2.1 Poly(vinyl alcohol)

2.2.1.1 Electrospinning of Poly(vinyl alcohol)

There are many researchers reported that PVA was successfully fabricated into ultrafine fibers by electrospinning. The electrospun PVA fibers were used in several applications.

Nanoscale poly(vinyl alcohol) fiber (100-500 nm) aggregates were prepared with an electrospinning technique by Ding *et al.* (2002). The concentration of PVA (Mw=65000; 96% hydrolyzed) solution tested ranged from 8 to 16 wt%. And the PVA solution was adjusted to pH value of 2-3 with phosphoric

acid. The voltage was 7 to 19 kV, and distance was 6 to 14 cm. At 10 wt% of PVA solution, PVA fibers with average diameters of about 280 nm were produced. They also studied a chemical crosslinking method used to crosslink the PVA fiber aggregates. Glyoxal as crosslinking agent was added to the PVA solution before electrospinning. The resulted showed that the crosslinked PVA fiber aggregated had better antiwater solubility and mechanical properties than the noncrosslinked PVA fiber aggregates.

Electrospinning and stabilization of fully hydrolyzed poly(vinyl alcohol) fibers was studied by Yao *et al.* (2003). Fully (99+%) hydrolyzed poly(vinyl alcohol) (Mw =115000 g/mol) was electrospun from water using Triton X-100 surfactant to lower the surface tension. The diameter of the electrospun PVA fibers ranged from 100-700 nm. Importantly, the electrospun PVA fibers can be stabilized against disintegration in water by a simple soak in methanol. It was concluded that methanol treatment increased the degree of crystallinity of the PVA fibers, thereby increasing the number of physical crosslinks responsible for fiber stabilization in water. In addition, the mechanical strength of the mats was also increased after treatment with methanol.

In 2004, Koski *et al.* studied the effect of molecular weight on fibrous PVA produced by electrospinning. They reported that the molecular weight of PVA and the solution concentration had a significant effect on the structure of the electrospun fibers. At each Mw, there is a minimum concentration needed to stabilize the fibrous structure and maximum concentration where the solution cannot be electrospun. Fibrous structures were generally obtained at $[\eta]C > 5$, where $[\eta]$ is the intrinsic viscosity and C is the concentration. Typical fiber diameters were between 250 nm and 2 μm. The fiber diameter increases with Mw.

In 2005, Zhang *et al.* studied the morphology of electrospun poly(vinyl alcohol) mats. The concentration of aqueous PVA (degree of polymerization of 1700 ± 50 and DH values from 80%-99%) solution used in this study was 6-8% w/v. The results showed that, when PVA with higher DH of 98% was used, tip-target distance exhibited no significant effect on the fiber morphology, however the morphological structure can be slightly changed by changing the solution flow rate. At high voltage above 10 kV, electrospun PVA fibers exhibited a

broad diameter distribution. With increasing solution concentration, the morphology was changed from beaded fiber to uniform fiber and the average fiber diameter could be increased from 87 ± 14 nm to 246 ± 50 nm. When the DH value of PVA was increased from 80%-99%, the morphology of electrospun PVA fiber was changed from ribbon-like fibers to uniform fibers and then to beaded fibers.

The effect of pH on electrospinning of poly(vinyl alcohol) was investigated by Son *et al.* (2005). PVA (Mw = 78000; hydrolysis 99.7%) solutions (7 wt.%) at various pH values from 2.0 to 12.9 were electrospun in order to study the effect of pH on the morphology and diameter of electrospun PVA. The average diameter of electrospun PVA fibers at pH 7.2 was 290 nm. Electrospun PVA fibers became straighter and finer with increasing pH under basic conditions, whereas the electrospinning of PVA solution was not continuous and PVA fibers with bead-on-string structures were obtained due to the protonation of PVA under acidic conditions.

In 2005, Wu *et al.* prepared nanofibrous PVA membranes by electrospinning and used these membranes for immobilization of enzymes cellulase (Wu, 2005). PVA (degree of polymerization = 1750; DH = 98%) and cellulase were dissolved together in an acetic acid buffer pH 4.6 and electrospun (applied voltage = 10 kV) into nanofibers with diameter of 200 nm. The nanofibrous membranes were crosslinked by glutaraldehyde vapor and examined catalytic efficiency for biotransformations.

2.2.1.2 Crosslinking of PVA

It is well-known that PVA can be chemically cross-linked with a variety of aldehydes, such as glutaraldehyde and glyoxal (Tomihata; 1997). The reaction is due to the formation of acetal bridges between the hydroxyl groups in PVA and the aldehyde molecules.

In 2002, Ding *et al.* prepared crosslinked PVA fiber aggregates by the electrospinning process. A 10 wt% PVA solution was used. Glyoxal and phosphoric acid were added in the PVA solution. The weight percent of glyoxal to PVA ranged from 0 to 10 wt%. The average fiber diameter was about 280 nm. After electrospinning, the curing process was needed for activation of glyoxal by heating sample at 120 °C for 5 min. The primary factor that affected the crosslinking

density was the amount of the chemical crosslinking agent. Their results showed that the properly crosslinked PVA fiber aggregates had better antiwater solubility and mechanical properties than the noncrosslinked PVA fiber aggregates.

Nanofibrous substrate was prepared by electrospinning of PVA followed by chemical crosslinking with glutaraldehyde in acetone by Wang *et al.* (2005). The chemical crosslinking was done by immersion of electrospun PVA substrate in a given concentration of GA (0-60 mM) and 0.01 N HCl in acetone solution for 24 h. The resulting crosslinked PVA substrates showed excellent water resistance and good mechanical properties.

In 2000, Mandal *et al.* developed a swelling controlled release delivery system for miconazole. Miconazole nitrate, a fungicidal, is effective for the local treatment of vaginitis. An aqueous solution of 15% w/w poly(vinyl alcohol) was mixed with a specific amount of miconazole powder. The resultant mixture was cross-linked by freeze±thawing. The effect of the number of freeze±thawing cycles was studied at four levels. The results showed that the release profiles up to 108 h were independent of the number of freeze±thawing cycles.

2.2.1.3 PVA used in drug delivery system

In 1998, Li *et al.* successfully prepared the PVA hydrogel nanoparticles by using a water-in-oil emulsion technology plus cyclic freezing-thawing process and used it for protein/peptide drug delivery. Bovine serum albumin (BSA), as a model protein drug, was incorporated into the PVA hydrogel nanoparticles. The results showed that protein drug loading efficiency in PVA hydrogel nanoparticles is 96.2 ± 3.8% and BSA was stable during preparation of the PVA hydrogel nanoparticles. It was observed that the BSA release followed a diffusion-controlled mechanism. For in vitro release studies, the BSA released from the nanoparticles can be prolonged to 30 h.

Poly(vinyl alcohol) and poly(vinyl pyrrolidone) (PVP) blended films for local nitric oxide release were prepared by Seabra *et al.* (2003). The nitric oxide (NO) donor S-nitrosoglutathione (GSNO) was incorporated in solid polymeric films of PVA, PVP and blended PVA/PVP. These solid matrices imposed a great stabilization effect on the GSNO decomposition, allowing the storage and handling of the formulations and their use for the local release of NO. Kinetic data of

the solid PVA/PVP films in dry conditions and immersed in PBS solution, had shown that they had potential for local applications where either free NO can be released in prolonged period of time or GSNO can be rapidly diffused to tissues.

Kenawy *et al.* (2007) developed new systems for the delivery of ketoprofen as non-steroidal anti-inflammatory drug (NSAID). Electrospun fibers from partially and fully hydrolyzed poly(vinyl alcohol) (PVA) were developed as drug delivery system. Electrospun PVA fibers were stabilized against disintegration in water by treatment with alcohol such as methanol. The release of ketoprofen from the electrospun fibers was determined by UV spectrophotometer at the body temperature (37 °C) and at the room temperature (20 °C). The results showed that upon the treatment of electrospun PVA with alcohol, the burst release was eliminated. The release rates varied according to the degree of hydrolysis of the PVA. Moreover, Methanol treated mats and films showed a lower release than untreated ones.

In 2007, Yang *et al.* studied Gelatin/PVA bicomponent nanofibers via electrospinning, and they investigated its control release of Raspberry ketone (RK). They reported that the RK loaded GEL/PVA electrospinning nanofibers should have potential application in controlled drug delivery based on the following observations: (1) The addition of PVA helped to enhance both the tensile strength and elongation at break of the membrane and (2) the RK release rate could be tailored by changing the content of RK in GEL/PVA matrix, the ratio of GEL and PVA, and the crosslinking time by glutaraldehyde vapor.

2.2.2 Cellulose acetate

2.2.2.1 Electrospinning of cellulose acetate

Liu *et al.* (2002) investigated three solvents for electrospinning cellulose acetate, which is, acetone, acetic acid, and dimethylacetamide (DMAc). Their results showed that none of these solvents alone can produce fibers. An improvement in the electrospinning of CA was achieved when 2:1 v/v acetone/dimethylacetamide (DMAc) was used as the solvent system. This mixture allowed the resulting CA solutions with concentration in the range of 12.5-20 wt.% to be continuously spun into fibers with diameters ranging between ~100 nm and ~1 μm.

In 2004, Son *et al.* successfully electrospun ultrafine fibers of CA by using a mixture of acetone/water with the water content in the range of 10-15 wt.%. Moreover, they found that the electrospinning of a CA solution in acetone/water in an acidic condition produced larger fibers, while that of the solution in a basic condition produced much finer ones.

In 2005, Ma *et al.* has prepared the affinity CA fibrous membranes from 0.16 g ml^{-1} CA (acetyl content = 40%; M_w = 29 000 Da) solution in 3:1:1 v/v/v acetone/DMF/TFE by electrospinning (applied electrical potential = 25 kV; collection distance = 15 cm; polarity of emitting electrode = positive; solution flow rate = 4 ml h^{-1}). The diameter of electrospun fibers was ranging from ~200 nm to ~1 μm. The membranes were subsequently heat-treated at 208°C for 1 h and later treated in 0.1M NaOH solution in 4:1 v/v water/ethanol for 24 h to obtain regenerated cellulose (RC) membranes. Cibacron Blue F3GA, a sulfonated triazine dye, was then covalently coupled onto the surface of RC membranes. The capture capacity of the membranes towards bovine serum albumin (BSA) was reported to be 13 mg g^{-1}.

Son *et al.* (2004, 2006) prepared the antimicrobial CA fibrous membranes from 10 wt.% CA (acetyl content = 39.8%; M_w = 30 000 Da) solution in 80:20 w/w acetone/water containing $AgNO_3$ in the amount of 0.01-0.5% (based on the weight of CA) by electrospinning (applied electrical potential = 17 kV; collection distance = 10 cm; polarity of emitting electrode = positive; solution flow rate = 3 ml h^{-1}). Ag+ ions were photoreduced into Ag nanoparticles, an active antimicrobial agent, by irradiating the as-spun fibers (average diameters = 610-1910 nm) with UV light (the maximum wavelength = 245 or 365 nm) that resulted in the Ag nanoparticles with the average diameters ranging between 3 and 21 nm.

Electrospun bioscaffolds that mimic the topology of extracellular matrix from CA had been studied by Han *et al.* (2006). They used different concentration of CA solutions and processing parameters in order to produce three different layers of the scaffolds. The structure of the fibrous layer consists of uniformsized fibers with an average diameter of 1.7 ± 0.1 μm. The cell-type layer's pore sizes vary widely-the smallest being 11.8 μm and the largest 72 μm

(average pore size estimated to be 36.6 μm). The dense bottom level has a thickness of 2.0 μm.

2.2.2.2 *CA used in drug delivery systerm*

Cellulose acetate membranes for transdermal delivery of scopolamine base were studied by Wang et al. (2002). The cellulose acetate membranes were cast with acetone as a solvent at 22 and 40 °C. Polyethylene glycol (PEG, MW 600) was used as a pore-forming agent. The in vitro release rates of scopolamine base as a model drug through the membranes were evaluated in phosphate buffer solution (PBS, pH 7.4) at 32 °C. They found that both PEG content and fabrication temperature affected on the properties of resultant membranes. The structure of membranes fabricated at 40 °C are more homogeneous and denser. The permeation rate of scopolamine base through the membranes fabricated at 40 °C with 10% and 20% PEG is constant over 3 days in vitro. PEG content should be optimized to yield membranes with good mechanical properties and provide a linear release profile of a drug.

In 2006, Zhou et al. prepared chitosan/cellulose acetate multimicrospheres (CCAM) loaded with different model drugs via the method of w/o/w emulsion. Model drugs with different hydrophilicity were selected to investigate the delivery system, such as hydrophilic ranitidine hydrochloride (RT), amphoteric acetaminophen (ACP) and hydrophobic 6-mercaptopurine (6-MP). The results showed that with the increasing of hydrophobicity of drug, the holes in the appearance of microspheres became smaller and the loading efficiency increased. The CCAM system had good effect on the controlled release in vitro of all model drugs of different hydrophobicity. However, the release rate was affected by the hydrophobicity of model drug. It became slower with the increasing of hydrophobicity of drugs. The highest release rate was almost 60% during 48 h which was for the hydrophilic drug of RT and the release rate of hydrophobic drug (6-MP) was not more than 30% in the same time.

The interplay of phase inversion and membrane formation in the drug release characteristics of a cellulose acetate (CA) membrane-based delivery system was examined by Ma *et al* (2007). Drug encapsulated films were cast from

solutions of naproxen (drug), CA (polymer), acetone (solvent), and water (nonsolvent). The rate of drug release was controlled by the CA membrane morphologies formed during the film casting process. The burst release effect for the high DL films can be avoided by controlling the interplay of phase inversion, drug crystallization, and membrane formation. Morphology control allows higher drug loads without bursting. They also reported that the drug release followed a diffusion-controlled, non-zero order release mechanism.

2.2.3 Electrospun fibers used in drug delivery system

Electrospun fiber mats were explored a drug delivery vehicles using tetracycline hydrochloride as a model drug (Kenawy, 2002). The mats were made either from poly (ethylene-co-vinylacetate) (PEVA), poly(lactic acid) (PLA) and their blend. Electrospinning was carried out using 14% w/v solution of PEVA, PLA and a 50/50 blend in chloroform. The concentration of tetracycline hydrochloride was 5 wt%. It was found that release of tetracycline hydrochloride from electrospun mats of PEVA, PLA and 50/50 PLA/PEVA gave relatively smooth release of drug over about 5 days. Moreover, electrospun PEVA showed a higher release rate than the mats derived from blend or PLA. For comparison purpose, cast film with equal amount of drug were prepared and tested. The results showed that the total percent released from the cast film were lower than that of the electrospun mats, as would be expected due to the much lower surface area of film samples.

Hydroxypropyl methylcellulose (HPMC), a water-soluble polymer, was selected to electrospun in the presence of itraconazole (poorly water-soluble drug) by Verreck *et al.* (2003). When a 40:60, itraconazole:HPMC ratio was used, the diameter of obtained fiber was about 1-4 □m (applied voltage =16 kV) and 300-500 nm (applied voltage =24 kV). They concluded that there were a number of potential applications of electrospun fibers in drug delivery based on the following observations: 1) complete release of highly poorly water-soluble drugs can be achieved and 2) the rate of drug release can be tailored by a variety of parameters: for example, the drug/polymer ratio and the diameter of electrospun fibers.

In 2003, Zeng *et al.* studied the influences of surfactants and medical drugs on the diameter size and uniformity of electrospun poly(L-lactic acid)(PLLA) fibers. PLLA was dissolved in mixture of chloroform and acetone (2:1 v/v) and yield

3.9 wt% of PLLA in solution. Rifampin (a drug for tuberculosis) was added in the PLLA solution as a model drug (5-100 wt% of polymer). Addition of three kinds of surfactants (anionic, cationic and nonionic) can reduce the diameter size and distribution of electrospun fibers. Electrospun fibers containing various percents of rifampin were prepared and the drug was capsulated inside fibers. Along with degradation of the fibers (in the presence of proteinase K), the drug was released constantly. No burst release was observed.

The successful incorporation and sustained release of a hydrophilic antibiotic drug (Mefoxin®, cefoxitin sodium) from electrospun poly(lactide-co-glycolide) (PLGA)-based nanofibrous scaffolds without the loss of structure and bioactivity was demonstrated by Kim *et al.* (2004). When cefoxitin sodium was added, the morphology of electrospun PLGA/PLA/PEG-b-PLA scaffolds changed from bead-and-string to a completely fibrous structure. In addition, the average fiber diameter and the fiber diameter distribution decreased from 360 ± 220 nm (without drug) to 260 ± 90 (with 5 wt% of drug). The introduction of PEG-b-PLA block copolymer in the polymer matrix reduced the cumulative amount of the released drug at earlier time points and sustained the drug release profile to longer time (up to 1 week). The released cefoxitin sodium from electrospun scaffolds was found to be structurally intact as well as effective in its ability to inhibit *S. aureus* bacteria growth.

Controlled release of heparin from poly(e-caprolactone) electrospun fibers was studied by Van *et al.* (2006). Heparin was incorporated into electrospun poly(e-caprolactone) (PCL) fiber mats for assessment as a controlled delivery device. Fibers with smooth surfaces and no bead defects could be spun from polymer solutions with 8%w/v PCL in 7:3 dichloromethane:methanol. A significant decrease in fiber diameter was observed with increasing heparin concentration. Assessment of drug loading and imaging of fluorescently labeled heparin showed homogenous distribution of heparin throughout the fiber mats. A total of approximately half of the encapsulated heparin was released by diffusional control from the heparin/PCL fibers after 14 days. The fibers did not induce an inflammatory response in macrophage cells in vitro and the released heparin was effective in preventing the proliferation of

VSMCs in culture. These results suggest that electrospun PCL fibers are a promising candidate for delivery of heparin to the site of vascular injury.