CHAPTER IV

DRUG-LOADED ELECTROSPUN MATS OF POLY(VINYL ALCOHOL) FIBERS AND THEIR RELEASE CHARACTERISTICS OF FOUR MODEL DRUGS

4.1 Abstract

Mats of PVA nanofibers were successfully prepared by the electrospinning process and were developed as carriers of drugs for a transdermal drug delivery system. Four types of non-steroidal anti-inflammatory drug with varying water solubility property, i.e. sodium salicylate (freely soluble in water), diclofenac sodium (sparingly soluble in water), naproxen (NAP), and indomethacin (IND) (both insoluble in water), were selected as model drugs. The morphological appearance of the drug-loaded electrospun PVA mats depended on the nature of the model drugs. The ^{1}H-nuclear magnetic resonance results confirmed that the electrospinning process did not affect the chemical integrity of the drugs. Thermal properties of the drug-loaded electrospun PVA mats were analysed by differential scanning calorimetry and thermogravimetric analysis. The molecular weight of the model drugs played a major role on both the rate and the total amount of drugs released from the as-prepared drug-loaded electrospun PVA mats, with the rate and the total amount of the drugs released decreasing with increasing molecular weight of the drugs. Lastly, the drug-loaded electrospun PVA mats exhibited much better release characteristics of the model drugs than drug-loaded as-cast films.

4.2 Introduction

In recent years, electrospinning process has attracted a great deal of attention due to its ability to produce ultrafine fibers with diameters in the range of nanometers to sub-micrometers and high surface area to volume or mass ratios (Lu, 2001; Doshi, 1995). The principle of electrospinning process is to use electrostatic force as the main driving force for fiber formation (Zhang, 2005; Shim, 2001; Theron, 2004). Morphology of the as-spun fibers depends on a number of parameters such as solution concentration, solution conductivity, applied electrostatic field strength, collection distance, and collection time (Shim, 2001; Ding, 2002). Among others, some potential uses of electrospun fibers in medicine are, for examples, immobilization of enzyme (Wu, 2005), tissue engineering scaffolds (Choi, 2004; Kim, 2004), and DNA (Luu, 2003) and drug delivery systems (Kenawy, 2002; Zong, 2002; Zeng, 2003; Verreck, 2003; Verreck, 2003). One of the obvious advantage of the electrospinning process over the conventional film-casting technique is the highly porous structure of electrospun fiber mats which exhibit much greater surface area that assumingly could allow drug molecules to diffuse out from the matrix much more conveniently (Kenawy, 2002; Zong, 2002).

The electrospun fibers from a good number of polymers have been developed as the matrix for drug delivery system. Poly(lactic acid) (PLA) and poly(ethylene-co-vinyl acetate) (PEVA) were successfully electrospun in the presence of tetracycline hydrochloride (an antibiotic drug) as a model drug by Kenawy et al. (Kenawy, 2002). The total percentage of tetracycline released from the as-cast films was lower than that from the as-spun fiber mats due to the much lower surface area. Zong et al. (Zong, 2002) also used PLA as the matrix and used mefoxin (an antibiotic drug) as the model drug. They arrived at a similar finding to that observed by Kenawy et al. (Kenawy, 2002). For poorly water-soluble drugs, such as itraconazole (an anti-fungal drug) and ketanserin (a drug for ischemic acute renal failure), polyurethane, a non-biodegradable polymer, was used as the matrix (Verreck, 2003). They concluded that the release of poorly water-soluble drugs could be achieved using a water-insoluble polymer and the rate of release could be tailored by varying the drug to polymer ratio (Verreck, 2003). To our knowledge,

electrospinning of a hydrogel polymer for transdermal drug delivery system (TDDS) has not yet been thoroughly investigated. It is therefore the main objective of the present contribution to explore the possibilty of using a hydrogel polymer as a drug carrier.

Hydrogels are polymeric materials that do not dissolve in water at physiological temperature and pH, but are able to swell considerably in an aqueous medium, and widely used as controlled release carriers of drugs and protein because of their good tissue compatibility, easy manipulation under swelling condition, and solute permeability (Kim, 1992; Kim, 2003). One of the most popular hydrogel polymers is poly(vinyl alcohol) (PVA). PVA is a hydrophilic, semi-crystalline polymer with good chemical and thermal stability (Koski, 2004). PVA is interesting here because of its biocompatibility, non-toxicity, good water permeability, and, particularly, excellent electro-spinnability. Over the past few years, many researchers have investigated various parameters affecting morphology of electrospun PVA fibers, e.g. solution concentration, solution flow rate, degree of hydrolysis, applied electrical potential, collection distance, ionic salt addition (Zhang, 2005), molecular weight of PVA (Koski, 2004), and pH (Son, 2005). It is therefore very interesting to explore the use of electrospun PVA fibers as carriers for TDDS. TDDS exhibits great potentials in avoiding hepatic first pass metabolism, maintaining constant blood levels for a longer period of time, decreasing side effects, and improving compliance (Kshirsagar, 2000).

In the present contribution, mats of PVA nanofibers were prepared by electrospinning and these electrospun fiber mats were used as carriers of drugs for TDDS. Four types of non-steroidal, anti-inflammatory drugs of varying water solubility property, i.e. sodium salicylate (SS) (freely soluble in water), diclofenac sodium (DS) (sparingly soluble in water), naproxen (NAP), and indomethacin (IND) (both insoluble in water), were incorporated in the as-spun PVA mats. Morphology and thermal property of neat and drug-loaded as-spun mats, chemical integrity of drugs within the drug-loaded as-spun mats, swelling and weight loss behavior of neat and drug-loaded as-spun mats in an aqueous medium, and release characteristics of drugs from drug-loaded as-spun mats were investigated. Two types of release study, i.e. total immersion and transdermal diffusion through a pig skin, were carried out.

4.3 Experimental

4.3.1 Materials

Poly(vinyl alcohol) (PVA) (degree of polymerization ≈1600 and degree of hydrolysis ≈97.5 to 99.5 mol%) was supplied from Fluka (Switzerland). Sodium salicylate (SS) was purchased from Carlo Erba (Italy). Diclofenac sodium (DS) was purchased from Tangyin Yongqi Chemical Industry (China). Naproxen (NAP) and indomethacin (IND) were donated from Pharmasant Laboratories (Thailand). These drugs are used in the symptomatic management of painful and inflammatory conditions. The chemical structures of these model drugs are shown in Figure 4.1. Sodium acetate (Ajax Chemicals, Australia) and glacial acetic acid (Carlo Erba, Italy) were of analytical reagent grade and used without further purification.

4.3.2 Preparation of neat and drug-loaded as-spun PVA mats and as-cast PVA films

A weighed amount of PVA powder was dissolved in distilled water at 80 °C for 3 h to prepare a PVA solution at a fixed concentration of 10% w/v. After the solution was cooled down to room temperature, four different types of model drug were individually added into the PVA solution under constant stirring for 4 h. The drugs were loaded at either 10 or 20 wt% (based on the weight of PVA powder). Prior to electrospinning, the as-prepared solutions were measured for their viscosity, surface tension, and conductivity using a programmable viscometer (Brookfield, DV III), a drop-shape analyzer (KRU" SS, K10T), and a conductivity meter (Orion, 160), respectively. All the tests were carried out at 25 °C and an average value for each solution was calculated from at least three measurements.

Electrospinning of the as-prepared solutions was carried out by connecting the emitting electrode of positive polarity from a high-voltage DC power supply (D-ES30PN/M692, Gamma High Voltage Research, USA) to the solutions contained in a standard 50 ml syringe, the open end of which was attached with a gauge 20 flat-tipped stainless steel needle (outer diameter = 0.91 mm), used as a nozzle, and the grounding electrode to a home-made rotatingmetal drum, used as the fiber-collecting device. The electrostatic field strength was fixed at 15 kV/15 cm. For

morphological study, the collection time was about 5 min, while, for the rest of the experiments, the collection time was about 24 h. The drum (outer diameter = 15 cm) rotated at a speed of about 50–65 rpm. The feed rate of the solutions was controlled to about 1 ml h^{-1} using a syringe pump. The drug-loaded PVA films were prepared by solution-casting technique from a PVA solution having a concentration of 7% w/v. The thickness of both the electrospun mats (for the mats that were electrospun for about 24 h) and the as-cast films was controlled between 20 and 30 μm.

4.3.3 Characterization of neat and drug-loaded as-spun PVA mats and as-cast PVA films

The morphological appearance of both neat and drug-loaded electrospun mats was observed by a scanning electron microscope (SEM; JEOL JSM-5200). The electrospun mats were sputtered with a thin layer of gold prior to SEM observation. Based on these SEM images, the average diameter of the as-spun fibers and average size of the beads (if any) could be measured. The results were reported as average values from as least 100 measurements. The average number of beads per unit area (i.e. the bead density) of the beaded fibers was calculated from measurements on SEM images of 3500 magnification.

A ^{1}H-nuclear magnetic resonance spectrometer (^{1}HNMR; Bruker DRX400) was used to investigate the chemical integrity of the model drugs in the drug-loaded as-spun PVA mats (each sample weighed 2–3 mg), using deuterated dimethylsulfoxide (dDMSO) as solvent. A differential scanning calorimeter (DSC; Mettler Toledo 822e/400) and a thermogravimetric/differential thermal analyzer (TG/DTA; Perkin Elmer Pyris Diamond) were used to investigate thermal behavior of the PVA matrix, the drugs, and the drug-loaded as-spun PVA mats. The DSC thermogram (equilibrated with an indium standard; each sample weighed 3–5 mg) was obtained during heating from 25 to 350 °C at a rate of 10 °C min^{-1} under nitrogen purge (60 ml min^{-1}), while the TGA thermogram was obtained during heating from 30 to 600 °C at a rate of 10 °C min−1 under nitrogen purge (200 ml min^{-1}).

The degree of swelling and weight loss of both neat and drug-loaded electrospun PVA mats were measured in an acetate buffer solution (see below for the

preparation of the acetate buffer) at 37 °C for 24 h according to the following equations:

$$\text{Degree of swelling } (\%) = \frac{M - M_d}{M_d} \times 100, \quad (4.1)$$

and

$$\text{Weight loss } (\%) = \frac{M_i - M_d - M_r}{M_i - M_r} \times 100, \quad (4.2)$$

where M is the weight of each sample after submersion in the buffer solution for 24 h, M_d is the weight of the sample after submersion in the buffer solution for 24 h in its dry state, M_i is the initial weight of the sample in its dry state, and M_r is the weight of a model drug that was released from the sample.

4.3.4 Release of model drugs from drug-loaded as-spun PVA mats and as-cast PVA films

4.3.4.1 Preparation of acetate buffer

Acetate buffer was chosen to simulate human skin pH condition of 5.5. To prepare 1000 ml of the acetate buffer solution, 150 g of sodium acetate was dissolved in about 250 ml of distilled water. Exactly 15 ml of glacial acetic acid was then added very slowly into the aqueous sodium acetate solution. Finally, distilled water was then added into the solution up to the final volume.

4.3.4.2 Actual drug content

The actual amount of drugs in the drug-loaded electrospun PVA mats and as-cast PVA films (circular disc about 2.8 cm in diameter) was quantified by dissolving the mats in 4 ml of dimethylsulfoxide (DMSO). After that, 0.5 ml of the solution was pipetted and added into 8 ml of the acetate buffer solution. Each drug-containing dilute solution was measured for the amount of drug using a UV-spectrophotometer (Perkin Elmer, Lambda 10) at a wavelength of 296, 282, 272, and 321 for SS, DS, NAP, and IND, respectively. These wavelength values correspond to the maximum wavelength (λmax) for each drug; however, for DS, we used the λmax for diclofenac. The amount of drugs originally present in the as-spun PVA mats and the as cast PVA films was back-calculated from the obtained data against a predetermined calibration curve for each model drug. The presence of DMSO in the dilute solution was proved to have no effect on the UV absorbance at

the wavelengths investigated. The results were reported as averages from at least five measurements.

4.3.4.3 Drug-release assay.

To study the release characteristics of drugs from drug-loaded electrospun PVA mats and as-cast PVA films, two types of release, i.e. total immersion and transdermal diffusion through a pig skin, were carried out. The study of the release characteristics of the drugs through a pig skin was carried out with an aim at resembling the actual release through a human skin. In the case of the total immersion technique, drug-loaded as-spun PVA mats or as-cast PVA films (circular disc about 2.8 cm in diameter) were immersed in 40 ml of the acetate buffer solution at 37 °C. At a specified immersion period ranging between 0 and 24 h (1440 min), 0.5 ml of the buffer solution was taken out. In the case of the transdermal diffusion through a pig skin technique, drug-loaded as-spun PVA mats or as-cast PVA films were placed on a fresh piece of pig skin (abdomen; epidermal hair, subcutaneous fat, and underlying tissues removed; final thickness = 1–1.5 mm) which, in turn, was placed on top of the acetate buffer solution on a modified Franz diffusion cell. At a specified diffusion period ranging between 0 and 24 h (1440 min), 0.3 ml of the buffer solution was taken out and an equal amount of fresh buffer solution was added into the cell to assure a good contact between the buffer solution and the skin. The amount of drugs in the withdrawn solutions was determined using the UV spectrophotometer at the same wavelengths previously mentioned against the predetermined calibration curve for each model drug. These data were carefully calculated to determine the accumulative amount of drugs released from the samples at each specified immersion or diffusion period. The experiments were carried out in triplicate and the results were reported as average values. It should be noted that, for the transdermal diffusion through a pig skin technique, a blank test on fresh pig skins was performed and the results confirmed that no soluble extracts from the pig skins.

4.4 Results and Discussion

4.4.1 Morphology of neat and drug-loaded as-spun PVA mats

The as-prepared 10% w/v PVA solution in distilled water was electrospun under an electrical potential of 15 kV applied over a collection distance of 15 cm (i.e. the electrostatic field strength of 15 kV/15 cm). Figure 4.2 shows a selected SEM image of the as-spun PVA fibers. Clearly, crosssectionally round fibers with smooth surface were obtained. The average diameter of these fibers was about 130 nm. Based on the good quality of the obtained as-spun fibers, 10% w/v PVA solution was used as the base solution into which the four different model drugs were individually added. After complete dissolution/dispersion of the model drugs, the resulting solutions were measured for their viscosity, conductivity, and surface tension, as summarized in Table 4.1. These solutions were later electrospun, and selected SEM images of the drug-loaded as-spun PVA fibers are shown in Table 4.2, while quantitative information of the fibers is reported in Table 4.3.

Based on the information summarized in Tables 4.2 and 4.3, it is obvious that the addition of the drugs within the PVA solution affected the morphological appearance and size of the resulting fibers. For PVA solutions loaded with 10 and 20 wt% of sodium salicylate (SS), both the viscosity and the surface tension of the solutions decreased slightly, while the conductivity increased markedly (about 3 and 6 times, respectively), from those of the neat PVA solution with increasing SS loading. The increase in the conductivity was due to the ionization of the sodium carboxylate group upon the dissolution of SS in water. Electrospinning of SS containing PVA solutions resulted in the formation of beaded fibers. Beaded fibers were also observed when small molecules of drug (Zhang, 2005) or enzyme (Wu, 2005) were added into a spinning solution. The considerable increase in the conductivity resulted in a marked increase in both the Coulombic repulsion and the electrostatic forces. The Coulombic repulsion works to stretch the charged jet, while the electrostatic force carries the jet to the target. Without a careful control of the feed rate, the increased electrostatic force could overcome the increased Coulombic repulsion, leading to the formation of fibers of larger diameters (Wutthicharoenmongkol, 2005). In this case, the feed rate of the solutions was

carefully controlled; both the increase in the conductivity and the slight decrease in the viscosity could be responsible for the observed decrease in the average diameter of the as-spun fibers (see Table 4.3), while the considerable increase in the conductivity could be responsible for the observed increase in the bead density (see Tables 4.2 and 4.3).

For PVA solutions loaded with 10 and 20 wt% of diclofenac sodium (DS), the viscosity increased, while the surface tension decreased, from those of the neat PVA solution with increasing DS content. Like SS, the conductivity of the DS-containing PVA solutions increased significantly (about 2 and 3 times, respectively) with increasing DS content. The presence of the ionizable sodium carboxylate group in the DS molecule should be the reason for the observed increase in the conductivity of the resulting solutions. Electrospinning of DS-containing PVA solutions also resulted in the formation of beaded fibers. Normally, the decreased surface tension favoured the formation of bead-free fibers (Doshi, 1995; Fong, 1999), but the significant increase in the conductivity could override the effect from the decrease in the surface tension, which could destabilize the jet, and beaded fibers would result. Like SS, the significant increase in the conductivity, despite the slight increase in the viscosity, of the solutions should be the reason for the observed decrease in the average fiber diameters (see Table 4.3), while the significant increase in the conductivity and the decrease in the surface tension should be responsible for the significant increase in the bead density (see Tables 4.2 and 4.3). However, one cannot be certain at this point about the reason for the observed greater number of beads found for DS-loaded PVA fiber mats in comparison with that found for the SS loaded counterpart, despite the fact that the conductivity of the PVA solutions containing DS was lower than that of the PVA solutions containing SS (see Table 4.1).

For PVA solutions loaded with 10 and 20 wt% of indomethacin (IND), the viscosity was found to increase from that of the neat PVA solution with increasing IND content, while both the conductivity and the surface tension were essentially unaffected. A similar behavior was also observed for PVA solutions loaded with 10 and 20 wt% of naproxen (NAP) in that the viscosity was found to increase from that of the neat PVA solution with increasing NAP content, while both

the conductivity and the surface tension were little affected. Since IND and NAP were both insoluble in water, their presence should only contribute to the increase in the viscosity of the resulting solutions. Electrospinning of the PVA solutions containing these drugs resulted in beaded fibers with much less amount of beads per unit area, when compared with the as-spun fibers obtained from the solutions containing SS and DS. While IND-containing PVA solutions produced as-spun fibers with diameters larger than those of the as-spun fibers from the neat PVA solution, NAP-containing PVA solutions produced as-spun fibers of similar diameters to those of the as-spun fibers from the neat solution (see Tables 4.2 and 4.3). While the observed increase in the diameters of IND-loaded as-spun PVA fibers should be due to the increase in the viscosity of the IND containing PVA solutions in comparison with that of the neat PVA solution, it is uncertain at this point why the diameters of NAP-loaded as-spun PVA fibers were not affected by the increase in the viscosity of the NAP-containing PVA solutions.

Further observation of the SEM images of the drug-loaded as-spun PVA fibers revealed no presence of the drug crystals or other kinds of drug aggregates on the surface of the fibers, despite the fact that IND and NAP are both insoluble in water. This is a very important observation, since it implies that the drugs were perfectly included within the electrospun fibers. A similar observation has also been reported in the literature (Zeng, 2003). The PVA solutions containing 20 wt% of the model drugs were electrospun to produce drug-loaded as-spun PVA fibers for further investigation.

4.4.2 Chemical integrity of drugs in drug-loaded as-spun PVA mats

Due to the application of a high electrical potential to the drug-containing PVA solutions during the electrospinning, it is questionable whether the chemical integrity of the drugs would be intact after such a treatment. In order to verify that, drug-loaded as-spun PVA mats were dissolved in dDMSO and the resulting drug-containing solutions were investigated by 1H-NMR. A solution of neat as-spun PVA mat in dDMSO was used as an internal control. All of the ^{1}H-NMR spectra along with the chemical structures of the model drugs are illustrated in figure 4.3. Based on the obtained results, the chemical integrity of all the model drugs was unquestionably sustained after the electrospinning process. ^{1}H-NMR was

also used to verify the integrity of cefoxitin sodium after being released from a medicated poly(lactic-*co*-glycolide) (PLGA) fiber mat (Kim, 2004), while it was used as a means for estimating bovine serum albumin (BSA) loading in poly(ethylene glycol) (PEG)/polycaprolactone (PCL) core/shell nanofibrous scaffolds (Jiang, 2005)

4.4.3 Thermal properties of neat and drug-loaded as-spun PVA mats

Figure 4.4 shows DSC thermograms for neat and drug-loaded electrospun PVA mats. The DSC thermogram for neat as-spun PVA mat exhibited a loss of moisture coupled with a glass transition over a temperature range of about 40 to 120 °C, a melting range from about 205 to 235 °C, and possibly a thermal degradation range from about 250 to 350 °C. All of the drug loaded as-spun PVA mats exhibited a loss of moisture coupled with a glass transition over about the same temperature range as that of the neat as-spun PVA mat, while their melting and thermal degradation ranges were different from those of the neat PVA mat. Specifically, the melting peak temperature (*T*m) of the drug-loaded as-spun PVA mats decreased from that of the neat as-spun PVA mat (i.e. about 227.2 °C) to about 203.4, 221.4, 216.9, and 218.4 °C for the as-spun PVA mats containing SS, DS, NAP, and IND, respectively (see figure 4.4).

Clearly, the melting behavior of PVA was least affected by the presence of DS, followed by those of IND, NAP, and SS, respectively. It is known that PVA is a semicrystalline polymer which exhibits a strong intermolecular interaction through hydrogen bonding (H-bonding) between the hydroxyl groups (Hidalgo, 1999). Among the four model drugs, only SS and DS had the potential to form H-bonding with the hydroxyl groups of the PVA molecules. Due to its small molecular size and its complete solubility in water, the presence of SS could affect the molecular packing of PVA molecules and this was reflected in the observed lowest *T*m value and the observed small melting endotherm of the SS-loaded as-spun PVA mat (see figure 4.4(a)). In contrast, the observed highest *T*m value and the rather large melting endotherm of the DS-loaded as-spun PVA mat (see figure 4.4(b)) suggested that H-bonding between the amino group of the drug and the hydroxyl groups of the PVA molecules was less likely to be formed, possibly a result of the steric hindrance effect. In the case of as-spun PVA mats loaded with NAP and

IND, two separate T_m values corresponding to those of the drugs and the PVA matrix were clearly observed (see figures 4.4(c) and (d)). A similar behavior was also reported for as-cast poly(vinyl pyrrolidone) film loaded with NAP (Bettinetti, 1991). That the observed T_m values of the PVA matrix in both NAP- and IND-loaded as-spun PVA mats were not much different from that of the neat as-spun PVA mat implied that no particular interaction between the drugs and the PVA matrix was present.

Based on the DSC thermograms shown in figure 4.4, the presence of SS and DS seemed to expedite, while the presence of NAP and IND seemed to delay, the thermal degradation of the PVA matrix. To ascertain whether the above statement was true, a careful thermal degradation analysis for both neat and drug-loaded as-spun PVA mats was necessary. Figure 4.5 illustrates TGA thermograms for neat and drug-loaded electrospun PVA mats. For the neat as-spun PVA mat, three steps of weight loss were observed. The first covered the temperature range of about 30 to 100 °C, corresponding to the loss of moisture, while the second and the third covered the temperature ranges of about 220 to 340 °C and about 260 to 500 °C, corresponding to the thermal degradation of PVA. The TGA result correlated well with the DSC result. With regards to the TGA thermograms of the four model drugs, SS exhibited two steps of weight loss covering the temperature ranges of about 250 to 300 °C and about 350 to 520 °C (see figure 4.5(a)); DS exhibited two major steps of weight loss covering the temperature ranges of about 40 to 70 °C and about 280 to 400 °C (see figure 4.5(b)); NAP exhibited one step of weight loss covering the temperature range of about 200 to 320 °C (see figure 4.5(c)); and IND exhibited one step of weight loss covering the temperature range of about 220 to 400 °C (see figure 4.5(d)). Based on these TGA results, an endotherm (about 270 to 310 °C) observed in the DSC thermogram of SS (see figure 4.4(a)) was attributed to the thermal degradation of SS. The DSC thermogram of DS exhibited double endotherms covering the temperature range of about 30 to 90 °C (see figure 4.4(b)), likely a result of a kind of phase transition coupled with a loss of moisture, and a series of an endotherm and an exotherm covering the temperature range of about 270 to 330 °C (see figure 4.4(b)), likely a result of the thermal degradation of DS coupled with a kind of high temperature phase transition of the degradation products. Both NAP and

IND exhibited a melting endotherm followed by thermal degradation (see figures 4.4(c), (d), 4.5(c) and (d)).

With regards to the thermal degradation of drug-loaded as-spun PVA mats, the TGA results confirmed that these drug-loaded PVA fiber mats also exhibited two steps of weight loss. In order to illustrate the effect of the model drugs on thermal degradation of the PVA matrix, the peak temperatures of the derivative TGA curves (results not shown) corresponding to the two stages of weight loss were discussed. For the neat as-spun PVA mat, these maximum temperatures were about 280 and 430 °C (see figure 4.5). For drug-loaded as-spun PVA mats, these temperatures were about 250 and 430 °C for the mat containing SS, about 230 and 430 °C for the mat containing DS, about 350 and 430 °C for the mat containing NAP, and about 340 and 430 °C for the mat containing IND, respectively (see figure 4.5). These temperatures corresponded with the degradation peak temperatures observed in the DSC thermograms, i.e. about 255 °C for the mat containing SS, about 240 °C for the mat containing DS, about 335 °C for the mat containing NAP, and340 °C for the mat containing IND, respectively (see figure 4.4). These results confirmed the aforementioned statement that the presence of SS and DS seemed to expedite, while the presence of NAP and IND seemed to delay, the thermal degradation of the PVA matrix.

4.4.4 Swelling behavior of neat and drug-loaded as-spun PVA mats and as-cast PVA films

Figure 4.6 shows the degree of swelling and weight loss of neat and drug-loaded as-spun PVA mats and as-cast PVA films after immersion in an acetate buffer solution at 37 °C for 24 h. In all of the sample types investigated, both the degree of swelling and the weight loss of the as-spun PVA mats were greater than those of the as-cast PVA films, a result of the highly porous nature of the electrospun mats. Based on figure 4.6(a), the as-cast PVA films loaded with SS and IND exhibited a slightly lower, while the films loaded with DS and NAP showed a greater, degree of swelling than that of the neat PVA film.

On the other hand, the as-spun PVA films loaded with SS and DS showed a slightly lower degree of swelling than, while the films loaded with IND and NAP exhibited comparable values to, that of the neat PVA film. Based on figure

4.6(b), only the as-cast PVA film loaded with DS showed a greater weight loss than that of the neat PVA film, while all of the drug-loaded as-spun PVA mats exhibited a greater weight loss than that of the neat as-spun PVA mat. Both the degree of swelling and the weight loss of these samples are discussed along with the results on the release characteristics of the model drugs from these samples in the following section.

4.4.5 Release of model drugs from drug-loaded as-spun PVA mats and as-cast PVA films

Prior to investigating the release characteristics of the model drugs from both the drug-loaded as-spun PVA mats and as-cast PVA films, the actual amount of the model drugs within these samples needs to be measured. The actual amount of drugs in the drug-loaded electrospun PVA mats and as-cast PVA films (circular disc about 2.8 cm in diameter) was quantified by dissolving the mats in 4 ml of dimethylsulfoxide (DMSO). After that, 0.5 ml of the solution was pipetted and added into 8 ml of the acetate buffer solution. Each drug-containing dilute solution was measured for the amount of drug using a UV-spectrophotometer (Perkin Elmer, Lambda 10) at a wavelength of 296, 282, 272, and 321 for SS, DS, NAP, and IND, respectively. These wavelength values correspond to the maximum wavelength (λ_{max}) for each drug; however, for DS, we used the λ_{max} for diclofenac. The amount of drugs originally present in the as-spun PVA mats and the as-cast PVA films was back-calculated from the obtained data against a predetermined calibration curve for each model drug. The presence of DMSO in the dilute solution was proved to have no effect on the UV absorbance at the wavelengths investigated. The results were reported as averages from at least 5 measurements.

Table 4.4 summarizes the actual amount of the drugs present in these samples (reported as the percentage of the initial content of drugs loaded in both the spinning and casting solutions, i.e. 20 wt% based on the weight of PVA powder). For drug-loaded as-spun PVA mats, the actual amount of the drugs present in these samples ranged between about 81 and 98%, while, for the drug-loaded as-cast PVA films, it ranged between about 92 and 104%. Ideally, the actual amount of the drugs present in the drug-loaded as-cast PVA films should be 100%. The discrepancy from

ideality should be due to the inhomogeneity of the drug content in different areas of the film samples, despite careful preparation of the casting solutions.

To study the release characteristics of drugs from drug-loaded electrospun PVA mats and as-cast PVA films, two types of release, i.e. total immersion and transdermal diffusion through a pig skin, were carried out. In case of the total immersion technique, drug-loaded as-spun PVA mats or as-cast PVA films (circular disc about 2.8 cm in diameter) were immersed in 40 ml of the acetate buffer solution at 37°C. At a specified immersion period ranging between 0 and 24 hr (1440 min), 0.5 ml of the buffer solution was taken out. In case of the transdermal diffusion through a pig skin technique, drug-loaded as-spun PVA mats or as-cast PVA films were placed on a fresh piece of pig skin (abdomen; epidermal hair, subcutaneous fat, and underlying tissues removed; final thickness = 1 to 1.5 mm) which, in turn, was place on top of the acetate buffer solution on a modified Franz diffusion cell. At a specified diffusion period ranging between 0 and 24 hr (1440 min), 0.3 ml of the buffer solution was taken out and an equal amount of fresh buffer solution was added into the cell to assure a good contact between the buffer solution and the skin. The amount of drugs in the withdrawn solutions was determined using the UV-spectrophotometer at the same wavelengths previously mentioned against the predetermined calibration curve for each model drug. These data were carefully calculated to determine the accumulative amount of drugs released from the samples at each specified immersion or diffusion period. The experiments were carried out in triplicate and the results were reported as average values. It should be noted that, for the transdermal diffusion through a pig skin technique, a blank test on fresh pig skins was performed and the results confirmed that no soluble extracts from the pig skins would adversely affect the experimental results.

The release characteristics of the model drugs from the drug-loaded as-spun PVA mats and as-cast PVA films were carried out by the total immersion and the transdermal diffusion through a pig skin method. Both experiments were carried out using acetate buffer as the transfer medium at a controlled temperature of 37 ◦C. The accumulative amount of drugs released (reported as the percentage of the actual amount of drugs present in the drug-loaded samples) from the drug-loaded

samples based on the total immersion method is shown in figure 4.7 and that based on the transdermal diffusion through a pig skin method is shown in figure 4.8.

In the total immersion method, it is obvious that both SS-loaded as-spun PVA mat and as-cast PVA film exhibited a burst release characteristic,most likely a result of the high solubility of SS in the medium. Noticably, for a given immersion time, the amount of SS released from the as-spun PVA mat was greater than that from the as-cast PVA film, a result of the highly porous nature of the mat that contributed to the observed high susceptivity to swelling in an aqueous medium (see figure 4.6(a)). It is known that, for a drug delivery system, one of the factors controlling the release of a drug is the swelling behavior of the hydrogel carrier (Rujiravanit, 2003). As soon as the PVA matrix began to swell, molecules of SS drug were solvated and practically leached out from the matrix very rapidly. Another contributing factor was the dissolution of the PVA mechanism for the burst release of SS included the swelling and the partial dissolution of the PVA matrix and the high solubility of the drug within the test medium. Very recently, Zeng *et al* (Zeng, 2005) studied the release characteristic of BSA from electrospun BSA-loaded PVA mat and found that BSA was burst released from as-spun PVA/BSA fibers during the first 2 h and the dissolution of PVA fibers was a factor contributing to the release characteristic of the fibers. It should be noted that the much longer release of BSA in comparison with the four model drugs from PVA fibers could be due to the much greater molecular weight of BSA (i.e. about 66 kDa) in comparison with the four drugs investigated here.

For the samples loaded with other model drugs, the accumulative release of the drugs increased monotonically with immersion time and levelled off at long immersion times. Interestingly, at a short immersion time (i.e. about 40 minfor samples loaded with NAP and about 60 min for samples loaded with DS and IND), the amount of the drugs released from DS-, NAP- and IND-loaded as-cast PVA films was greater than that from the corresponding as-spun PVA mats, but this became lower at a longer immersion time (see figure 4.7(b)). This crossover in the accumulative release of the drugs was not observed in the samples loaded with SS, as stated earlier. Figure 4.9 illustrates selected SEM images of neat and drug-loaded as-cast PVA films. Based on these images, traces of drug aggregates were present in the

PVA films containing DS, NAP, and IND. No such traces were found in the PVA film containing SS (result not shown), nor in all of the drug-loaded as-spun PVA mats (see Table 4.2). The presence of the drug aggregates could be the main reason that the release of these drugs from the as-cast PVA films was much faster initially, but, over a longer immersion period, the release of the drugs from the as-cast PVA films was much slower, most likely a result of the observed lower degree of swelling and weight loss of the films in comparison with those of the as-spun mats (see figure 4.6).

Based on the results shown in figure 4.7(a), the total amount of the drugs released from the drug-loaded as-cast PVA films (at 24 h) was about 96, 76, 38, and 30% for the films loaded with SS, NAP, DS, and IND, respectively, while that released from the drug-loaded as-spun PVA mats was about 98, 97, 76 and 42% for the mats loaded with NAP, SS, DS, and IND, respectively. Based on the chemical structure of these model drugs shown in figure 2.5, the molecular weight of these drugs can be ranked from the lowest to the highest in the following order: SS (160.1 gmol−1) < NAP (230.3 gmol−1) < DS (318.1 gmol−1) < IND (357.8 gmol−1). Evidently, the total amount of the drugs released from the drug-loaded samples decreased with increasing molecular weight of the drugs, despite the marked difference in the solubility of the drugs within the test medium. Intuitively, the initial slope of the accumulative release profiles shown in figure 4.7 represents the rate of the drugs released from the samples. Clearly, the rate of the drugs released from the drug-loaded samples was also a decreasing function of the molecular weight of the drugs. Rujiravanit *et al* (Rujiravanit, 2003) reported that both the rate and the total amount of drug release depended mainly on the molecular weight of the drug. Despite the apparent correlation between the release characteristics and the molecular weight of these drugs, we believe that interaction between the drug and the matrix molecules is a very important factor, but detailed physico-chemical analysis is needed, and this is a subject for further investigation.

In the transdermal diffusion through a pig skin method (see figure 4.8), the amount of the drugs released from the drug-loaded samples increased monotonically with diffusion time, but the rate of the drugs released was much less when compared with that in the total immersion method. This is not surprising since

the transport of the drugs through the pig skin is the rate-determining step for both cases. Specifically, the total amount of the drugs released from the drug-loaded as-cast PVA films (at 24 h) was about 40, 15, 7, and 3% for the films loaded with SS, NAP, DS, and IND, respectively, while that released from the drug-loaded as-spun PVA mats was about 60, 33, 19, and 5% for the mats loaded with SS, NAP, DS, and IND, respectively. Evidently, all of the drug-loaded as-spun PVA mats exhibited much greater release of the model drugs when compared with the drug-loaded as-cast PVA films, and the molecular weight of the drugs was, again, the apparent factor controlling both the rate and the total amount of the drugs released.

4.4.6 Release kinetics of model drugs from drug-loaded as-spun PVA mats and as-cast PVA films

The release kinetics of drugs from a carrier is often characterized using an equation of the following form (Ritger, 1987; Peppas, 1993):

$$\frac{M_t}{M_\infty} = kt^n, \text{ for } \frac{M_t}{M_\infty} < 0.6, \tag{4.3}$$

where M_t is the accumulative amount of drugs released at an arbitrary time t, M_∞ is the accumulation amount of drugs released at an infinite time, n is an exponent characterizing the mechanism with which the release kinetics can be described, and k is the rate of release of the drugs that incorporates physical characteristics of the matrix/drug system as well as some physical contributions from the measurement methods (namely in the case of the transdermal diffusion through a pig skin method which involves the diffusion of the drugs through a pig skin).

For n = 0.5, the release mechanism can be described as Fickian diffusion (Verreck, 2003). For Fickian diffusion, a straight line is expected when the fractional accumulative amount of drug released (i.e. $Mt/M\infty$) is plotted as a function of $t0.5$. Indeed, the results from the transdermal diffusion through a pig skin method for both the drug-loaded as-spun PVA mats and the as-cast PVA films could be described with such an equation, indicating the Fickian diffusion type of the release mechanism of these drugs. The results from such analyses (i.e. parameter k and r 2, which signifies the goodness of the fit) are summarized in Table 4.5. Apparently, the rate parameter k for all of the drug-loaded as-spun PVA mats ranged between 0.018

and 0.027 min−0.5, while that for all of the drug-loaded as-cast PVA films ranged between 0.019 and 0.027 min−0.5.

4.5 Conclusions

Drug-loaded poly(vinyl alcohol) (PVA) electrospun mats were successfully prepared by an electrospinning technique. The morphology of the electrospun mats depended on the properties of the drug-containing PVA solutions which, in turn, were affected by the type of the model drugs. The application of a high electrical potential to the drug-containing solutions did not affect the chemical integrity of the drugs. The presence of sodium salicylate (SS) affected the molecular packing of the PVA matrix, possibly through the formation of hydrogen bonding between the drug and the PVA molecules. For other model drugs, no particular interaction between the drugs and the PVA matrix was present. Interestingly, the presence of SS and diclofenac sodium (DS) seemed to expedite, while the presence of naproxen (NAP) and indomethacin (IND) seemed to delay, the thermal degradation of the PVA matrix.

Both the degree of swelling and the weight loss of the electrospun PVA mats were greater than those of the as-cast PVA films, due largely to the highly porous nature of the electrospun mats. The release characteristics of the model drugs from both the as-spun PVA mats and the as-cast PVA films were investigated using two methods: (1) total immersion and (2) transdermal diffusion through a pig skin. In the total immersion method, both as-spun PVA mats and as-cast PVA films containing SS exhibited a burst release of the drug, and, for a given immersion time, the amount of SS released from the as-spun PVA mat was greater than that from the as-cast PVA film. For the samples loaded with DS, NAP, and IND, the accumulative release of the drugs increased monotonically with immersion time and levelled off at long immersion times. Interestingly, a crossover in the accumulative release of the drugs was observed, in that the accumulative amount of the drugs released from the drug-loaded as-spun PVA mats only become greater than that from the drug-loaded as-cast PVA films at a long immersion time. In the transdermal diffusion through a pig skin method, both the rate and the total amount of the drugs released were much lower when compared with those in the total immersion method, indicating that the

transport of the drugs through the pig skin was the rate-determining step. Lastly, both the rate and the total amount of the drugs released were a decreasing function of the molecular weight of the model drugs, despite the different solubility of the drugs within the medium solution.

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Table 4.1 Some properties of neat and drug-containing PVA solutions

Type of PVA solution	Viscosity (mPa·s)	Conductivity (mS/cm)	Surface tension (mN/m)
Neat	502 ± 1.5	1.07 ± 0.00	61.7 ± 0.12
with 10 wt.% sodium salicylate (SS)	499 ± 0.6	3.89 ± 0.01	61.0 ± 0.09
with 20 wt.% sodium salicylate (SS)	485 ± 0.6	6.49 ± 0.01	58.6 ± 0.20
with 10 wt.% diclofenac sodium (DS)	519 ± 1.0	2.18 ± 0.01	54.1 ± 0.23
with 20 wt.% diclofenac sodium (DS)	529 ± 0.6	3.11 ± 0.01	51.6 ± 0.22
with 10 wt.% naproxen (NAP)	525 ± 0.6	1.04 ± 0.00	59.2 ± 0.39
with 20 wt.% naproxen (NAP)	544 ± 0.6	1.03 ± 0.01	59.7 ± 0.25
with 10 wt.% indomethacin (IND)	516 ± 1.5	1.09 ± 0.00	60.8 ± 0.21
with 20 wt.% indomethacin (IND)	525 ± 1.0	1.07 ± 0.00	60.0 ± 0.20

Table 4.2 Selected scanning electron micrographs (10,000x) of drug-loaded as-spun PVA mats from 10% w/v PVA solutions loaded with a model drug at either 10 or 20% by weight of PVA. The electrostatic field strength was 15 kV/15 cm and the collection time was 5 min

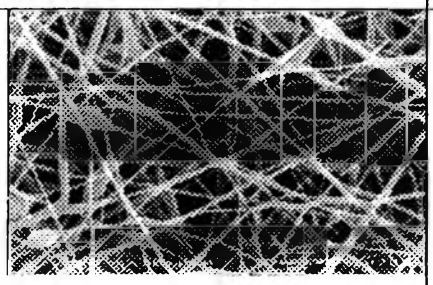
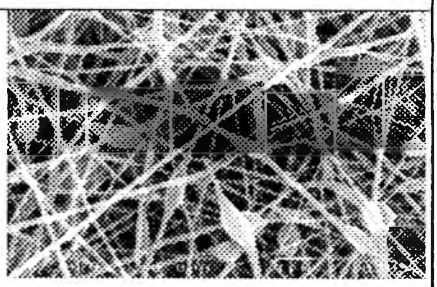
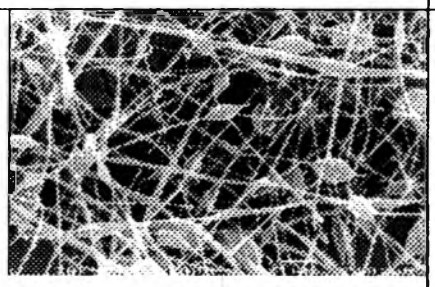
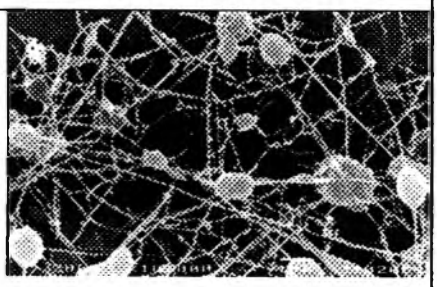
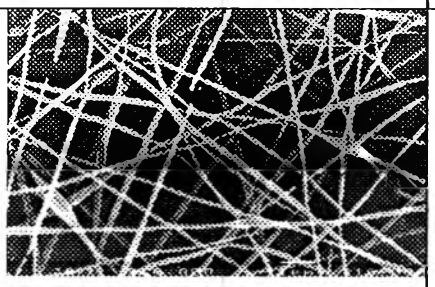
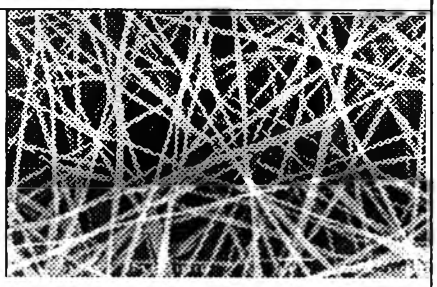
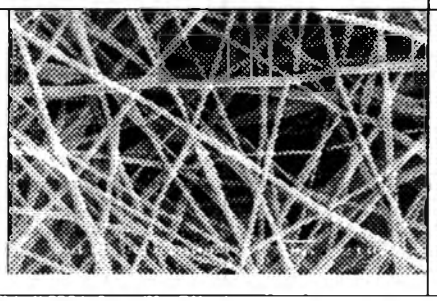
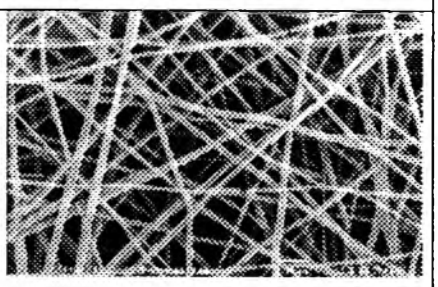
Type of model drug	Initial drug content in 10% w/v PVA solution	
	10% by weight of PVA	20% by weight of PVA
Sodium salicylate (SS)		
Diclofenac sodium (DS)		
Naproxen (NAP)		
Indomethacin (IND)		

Table 4.3 Fiber diameter, bead density and bead diameter of PVA electrospun mats with and without drugs added

Type of electrospun PVA mats	Fiber diameter (nm)	Bead density (#bead/mm^2)	Bead diameter (nm)
Neat	129.1 ± 23.0	-	-
with 10 wt.% sodium salicylate (SS)	111.5 ± 29.2	1.44×10^5	211 - 1690
with 20 wt.% sodium salicylate (SS)	107.8 ± 34.8	1.90×10^5	197 - 2080
with 10 wt.% diclofenac sodium (DS)	106.1 ± 25.5	3.41×10^5	206 - 1590
with 20 wt.% diclofenac sodium (DS)	104.7 ± 26.1	3.40×10^5	210 - 1750
with 10 wt.% naproxen (NAP)	124.3 ± 32.4	5.84×10^4	206 - 1050
with 20 wt.% naproxen (NAP)	127.4 ± 32.6	8.29×10^4	229 - 1510
with 10 wt.% indomethacin (IND)	153.1 ± 39.8	2.92×10^4	299 - 603
with 20 wt.% indomethacin (IND)	165.7 ± 39.0	4.08×10^4	301 - 876

Table 4.4 Actual amount of model drugs within drug-loaded electrospun PVA mats and as-cast PVA films. The original amount of the model drugs loaded in the spinning and the casting solutions was 20% based on the weight of PVA

Type of drug	Actual amount of drug based on the original amount of the drug loaded (%)	
	Drug-loaded electrospun PVA mats	Drug-loaded as-cast PVA films
Sodium salicylate	81.2 ± 1.26	92.9 ± 2.45
Diclofenac sodium	98.3 ± 1.87	97.1 ± 2.52
Naproxen	96.2 ± 2.33	103.5 ± 4.75
Indomethacin	86.1 ± 3.19	91.9 ± 5.49

Table 4.5 Analyzes of the release kinetics of the model drugs from drug-loaded as-spun PVA mats and as-cast PVA films based on the Fickian diffusion type of release mechanism. The experimental results were based on the transdermal diffusion through a pig skin method

Type of sample	Rate parameter k ($s^{-0.5}$)	r^2
Drug-loaded as-spun PVA mats		
with 20 wt.% sodium salicylate (SS)	0.027	0.97
with 20 wt.% diclofenac sodium (DS)	0.026	0.97
with 20 wt.% naproxen (NAP)	0.021	0.97
with 20 wt.% indomethacin (IND)	0.018	0.95
Drug-loaded as-cast PVA films		
with 20 wt.% sodium salicylate (SS)	0.027	0.97
with 20 wt.% diclofenac sodium (DS)	0.027	0.97
with 20 wt.% naproxen (NAP)	0.023	0.97
with 20 wt.% indomethacin (IND)	0.019	0.99

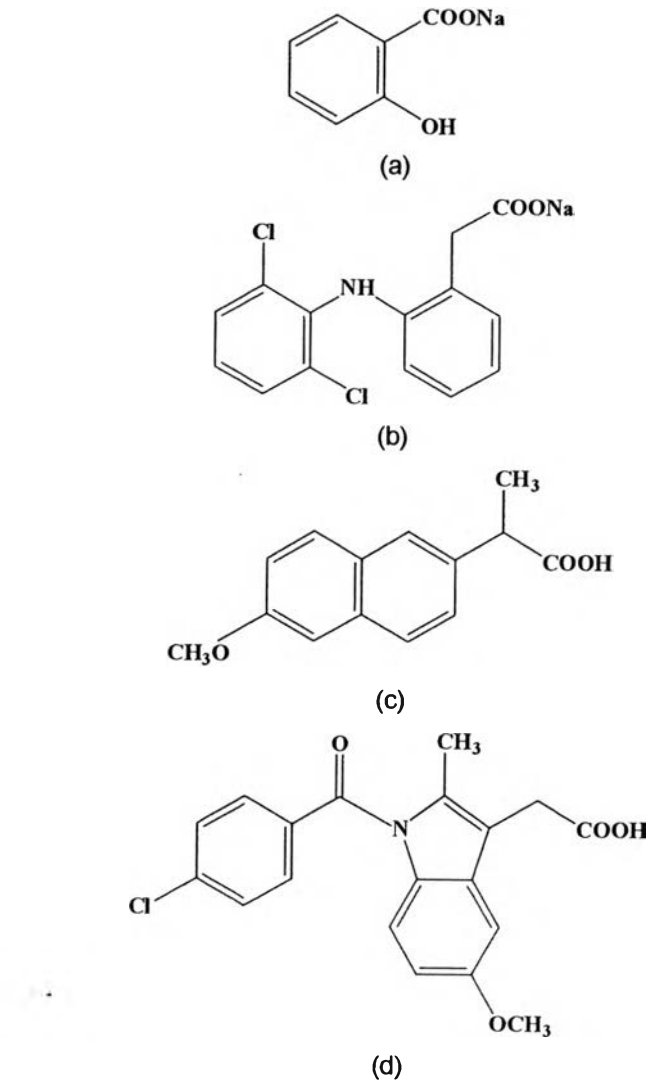


Figure 4.1 Chemical structure of (a) sodium salicylate (SS), (b) diclofenac sodium (DS), (c) naproxen (Nap), and (d) indomethacin (Ind).

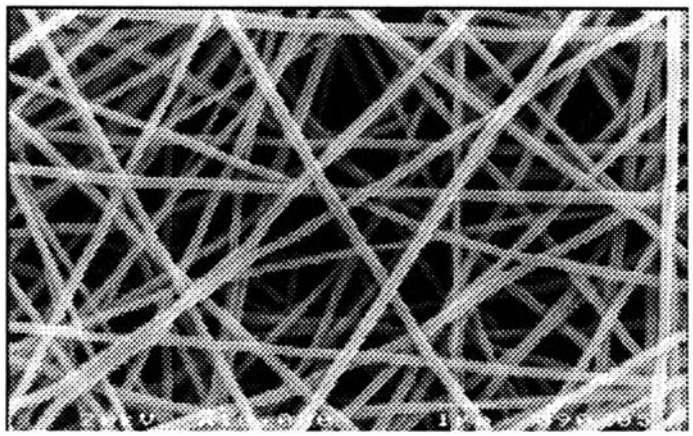


Figure 4.2 Selected scanning electron micrograph (10,000) of electrospun mat from 10% w/v PVA solution. The electrostatic field strength was 15 kV/15 cm and the collection time was 5 min.

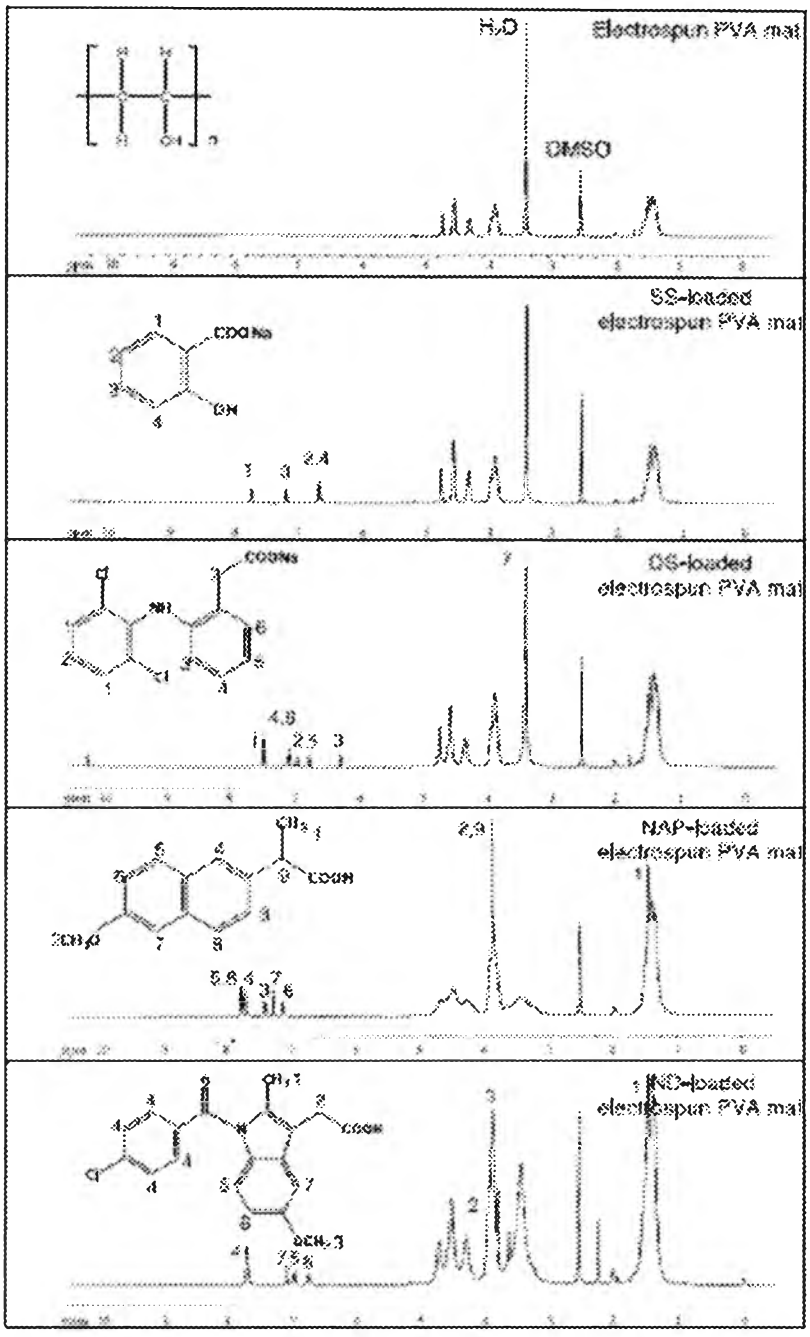


Figure 4.3 ^{1}H-nuclear magnetic resonance spectra of neat and drug-loaded electrospun PVA mats after dissolution in deuterated dimethylsulfoxide.

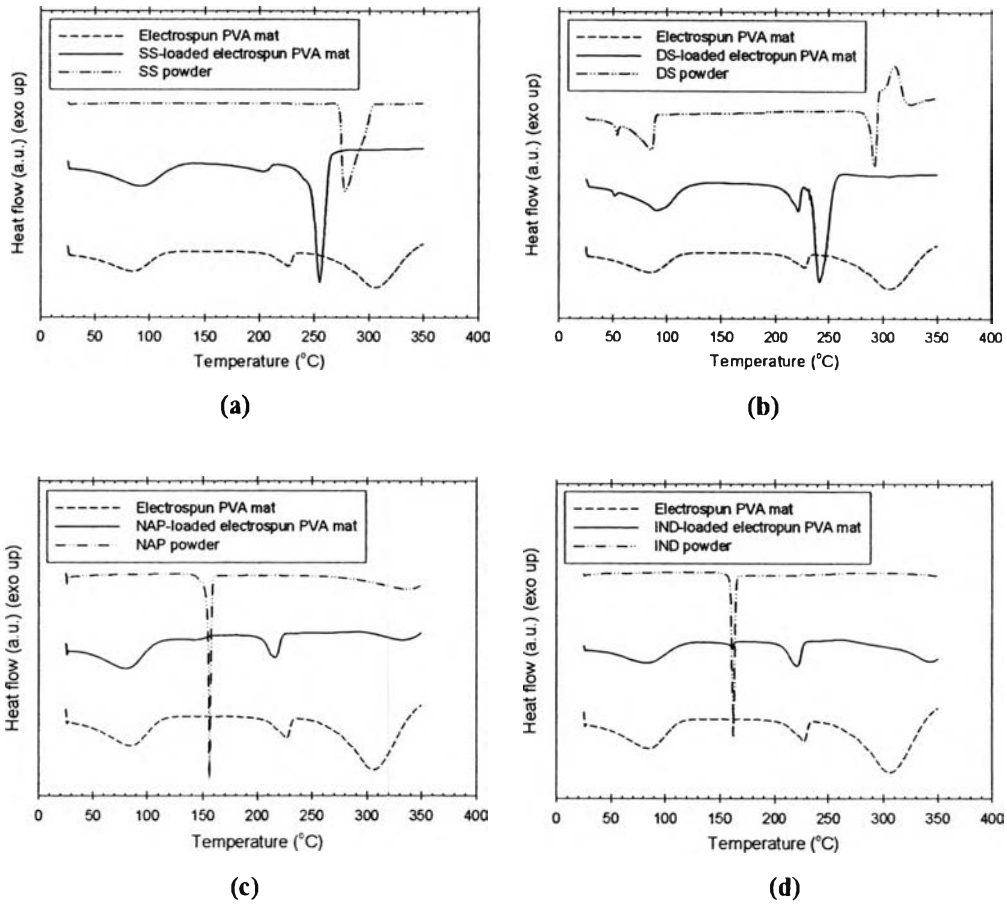


Figure 4.4 Differential scanning calorimetric thermograms of neat electrospun PVA mat, pure model drugs of (a) sodium salicylate (SS), (b) diclofenac sodium (DS), (c) naproxen (NAP), and (d) indomethacin (IND), and corresponding drug-load electrospun PVA mats.

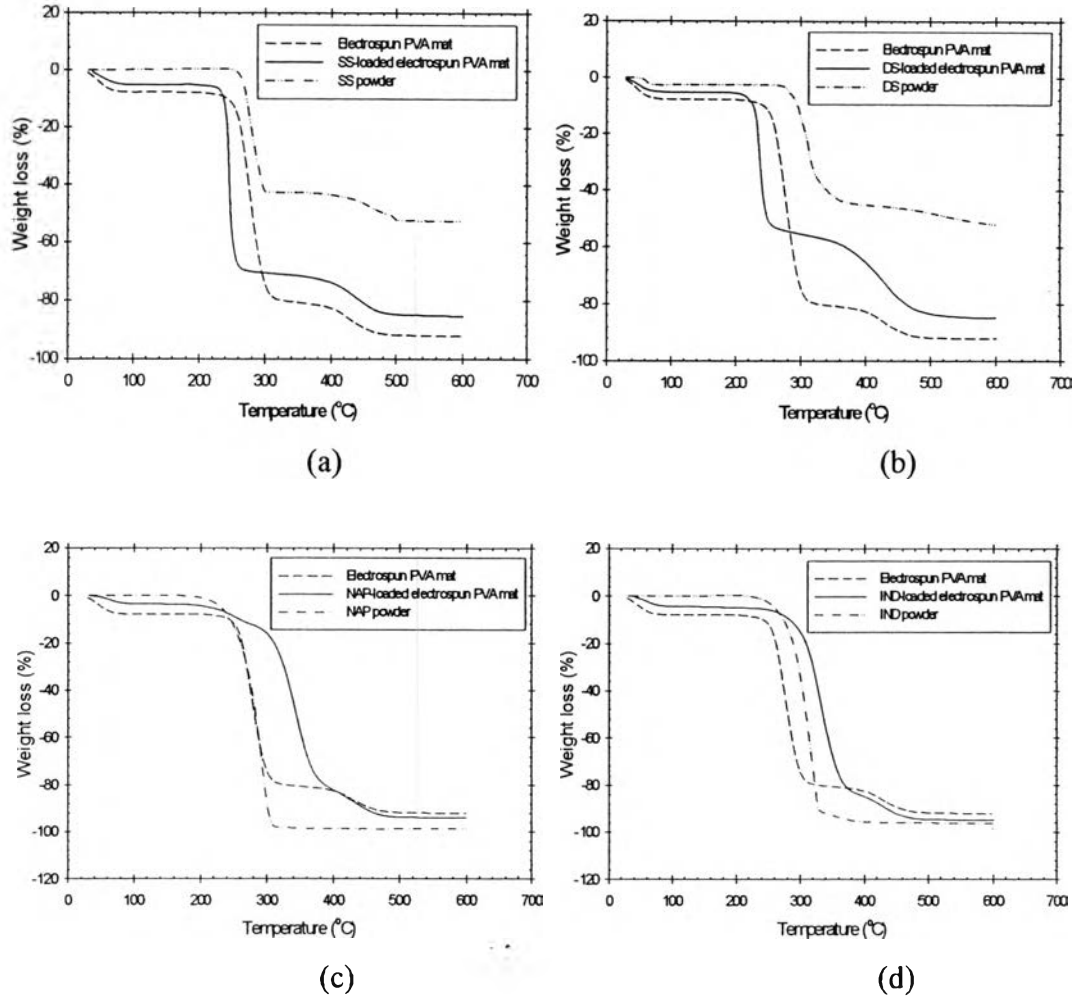
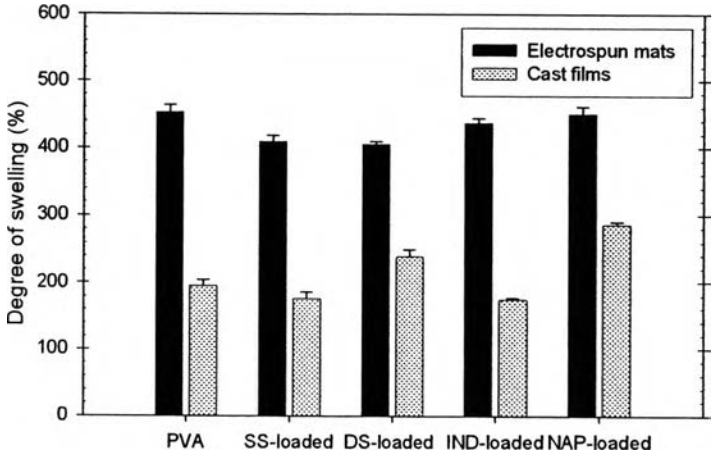
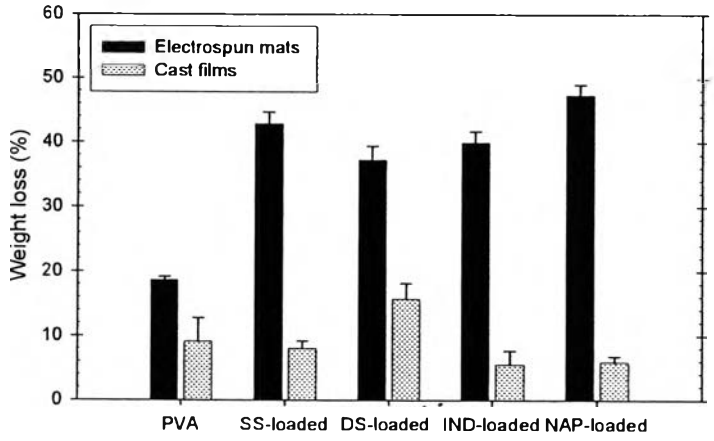


Figure 4.5 Thermogravimetric analytical thermograms of neat electrospun PVA mat, pure model drugs of (a) sodium salicylate (SS), (b) diclofenac sodium (DS), (c) naproxen (NAP), and (d) indomethacin (IND), and corresponding drug-load electrospun PVA mats.

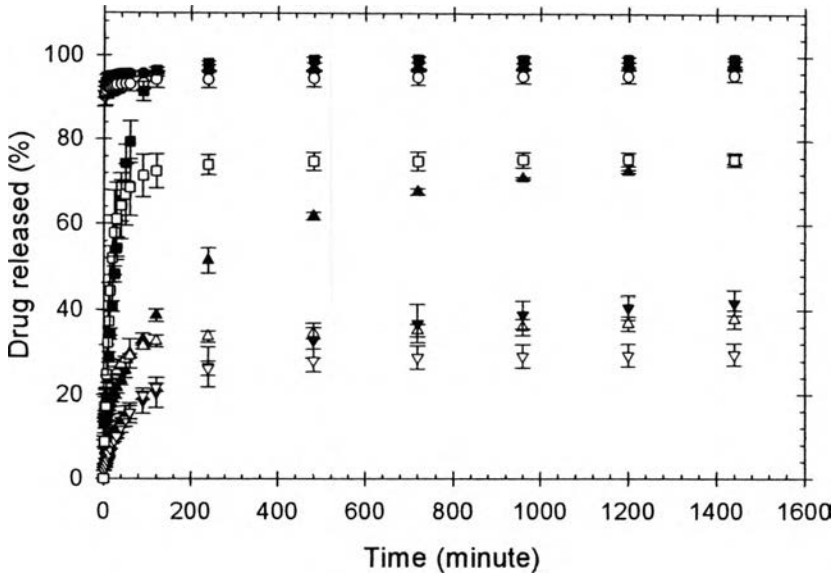


(a)

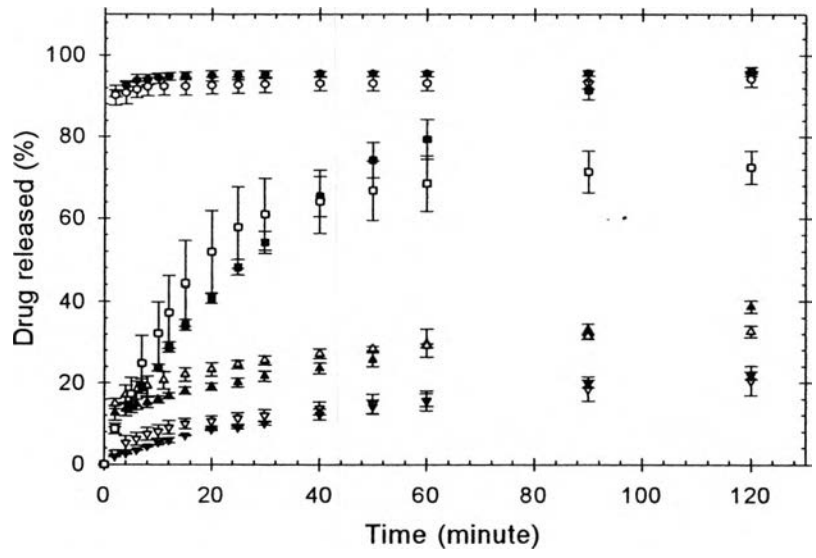


(b)

Figure 4.6 (a) Degree of swelling (%) and (b) weight loss (%) of neat and drug-loaded electrospun PVA mats and as-cast PVA films.



(a)



(b)

Figure 4.7 Profile of (●) sodium salicylate, (▲) diclofenac sodium, (▼) indomethacin, and (■) naproxen drugs released from drug-loaded electrospun PVA mats (closed symbols) and as-cast PVA films (open symbols) by total immersion technique during (a) 0 – 1440 min and (b) 0 – 120 min.

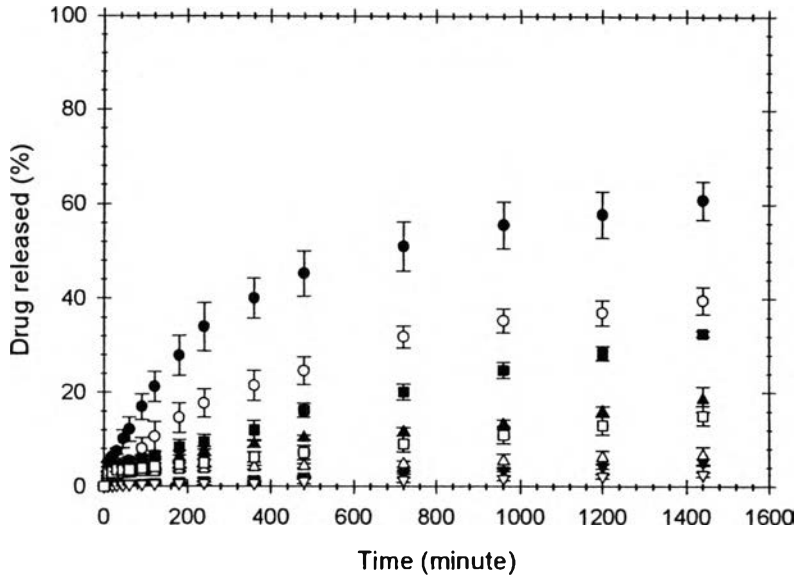


Figure 4.8 Profile of (●) sodium salicylate, (▲) diclofenac sodium, (▼) indomethacin, and (■) naproxen drugs released from drug-loaded electrospun PVA mats (closed symbols) and as-cast PVA films (open symbols) by transdermal diffusion through a pig skin technique during 0 – 1440 min.

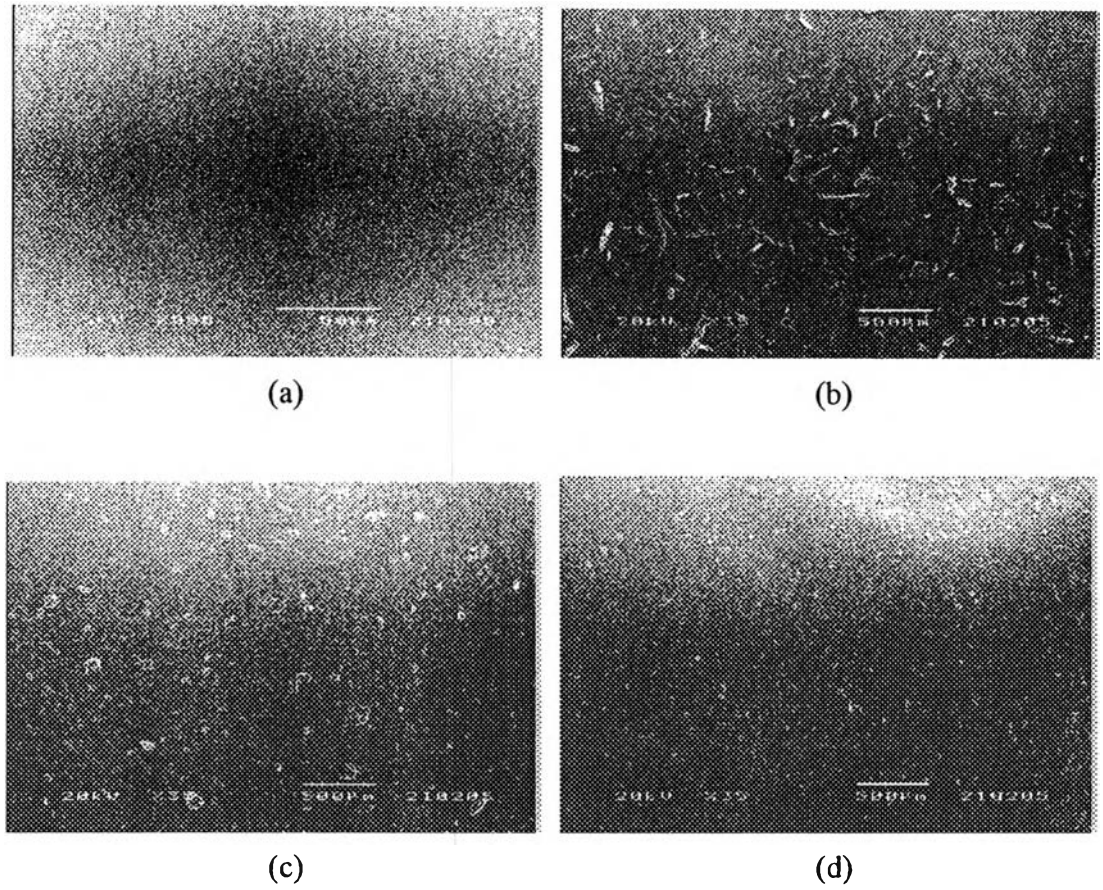


Figure 4.9 Selected scanning electron micrographs of (a) neat as-cast PVA film, (b) DS-loaded as-cast PVA film, (c) NAP-loaded as-cast PVA film, and (d) IND-loaded as-cast PVA film.