CHAPTER IV

Controlled release of sulfosalicylic acid from poly(vinyl alcohol) hydrogel by electrical stimulation

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Abstract

This study evaluated and characterized the use of poly (vinyl alcohol) (PVA) hydrogels as the matrix/carriers for a drug in the electrically controlled drug delivery system. The drug-loaded PVA hydrogels were prepared by solution-casting using sulfosalicylic acid as the model drug and glutaraldehyde as the crosslinking agent. The average molecular weight between crosslinks, the crosslinking density, and the mesh size of the PVA hydrogels were determined using the equilibrium swelling theory developed by Peppas and Merril, as well as by scanning electron microscopy (SEM). The release mechanisms and the diffusion coefficients of the hydrogels were studied using modified Franz-Diffusion cells in an acetate buffer at pH 5.5 and at a temperature of 37 $^\circ$C for 48 hours, in order to determine the effects of crosslinking ratio, electric field strength and electrode polarity. The amount of released drug was analyzed by UV-Visible spectrophotometry. The plots of the amount of drug released as a function of square root of time show a linear relationship. The diffusion coefficients of drug in PVA hydrogels decrease with increasing crosslink ratio. Moreover, the diffusion coefficients of drug in the PVA hydrogels depend critically on the electric field strength between 0-5 V and the electrode polarity.

1. Introduction

There are several possible routes of introducing controlled release medication into the body such as oral, injection, topical administration, and etc. However, the conventional oral and injection routes of drug administration may provide initially the maximum tolerable dose and the dose decreases dramatically in a short period requiring subsequent administrations (Gil et al., 1996).

One recent effort at eliminating some of the problems of the conventional dosage form is the development of Transdermal Drug Delivery [TDD] without the adverse effects associated with the frequent oral administration (Kim et al., 2006). Advantages of this system are to avoid first-pass metabolism, to increase compliance, to control plasma levels and reduce overall dose (Xie et al., 2005). However, its application has been limited to low amount of drug because of the extremely low amount of released drug from the matrix and low permeability of drug through the skin. Furthermore, precise controls over the drug quantity and timing, are highly desirable in order to optimize drug therapy. This can be achieved if the drug carrier responds in a reproducible and predictable fashion to an internal or external stimulus such electric field (Murdan, 2003), pH (Gudeman et al., 1995) and temperature (Xu et al., 2006).

The use of an electric field as an external stimulus is one such method that has been successfully employed to enhance the amount of released drug and the precise controls through monitoring applied electrical current (Chien et al., 1990). There were many literatures on the use of electric current in vivo, in the form of iontophoresis and electroporation, in the field of the dermal and the transdermal drug delivery. Transdermal iontophoresis has gained increasing recognition in recent years for the delivery of charged molecules (Chien et al., 1990; Chen et al., 1996; Ramanathana et al., 2001; Bose et al., 2001). Bose et al., 2001 studied the release of buprenorphine across human skin via iontophoresis using current density of $0.5mA/cm^2$. They concluded that the drug concentration was significantly enhanced by applied electric current. This system consisted of the electronic controller which provided the electrical current through an ionic drug entrapped in the matrix/carrier.

Hydrogel are hydrophilic natured three-dimensional networks, held together by chemical or physical bonds. If interstitial space exists within the network, water

molecules can become trapped and immobilized, filling the available free volume (Elvira *et al.*, 2002). It can be applied as artificial skin (Young *et al.*, 1998), contact lenses (Brinkman *et al.*, 1991), an interface between bone and implant (Netti *et al.*, 1993) and drug delivery systems (Chicq *et al.*, 1986; Pitt *et al.*, 1992; Karatas *et al.*, 2001; Kim *et al.*, 2003). One of the most popular hydrogel polymers is poly(vinyl alcohol). PVA and its copolymers have found various applications in the controlled drug release (Ritger *et al.*, 1987; Yeom *et al.*, 1996; Li *et al.*, 1998; Taepaiboon *et al.*, 2006) due to their high water content. PVA is hydrophilic and easily swells upon hydration, some grades (based on molecular weight) have shown volume expansion up to 500% at 37 °C (Morita *et al.*, 2000). PVA is interesting here because of its biocompatibility, non-toxicity, good water permeability and easy manipulation under swelling condition, these characteristics make it ideal for biomedical use especially drug delivery system (Kim *et al.*, 2002). PVA hydrogels have been reported to be useful for the release of both hydrophobic and hydrophilic drugs (Ramanathana *et al.*, 2001; Taepaiboon *et al.*, 2006).

In the present contribution, the drug-loaded poly(vinyl alcohol) hydrogels were prepared by solution casting and these hydrogels were used as matrix/carrier of drug for TDD. The sulfosalicylic acid was used as the anionic model drug. The thermal properties, morphology, swelling behavior of the drug-loaded poly(vinyl alcohol) hydrogels and the polymer-drug interaction due to the drug ionic nature were investigated. For the release characteristics of drug from their hydrogels, we were interested in the effects of matrix crosslinking ratio, electric field strength, and electrode polarity.

2. Materials and methods

2.1. Materials

Poly(vinyl alcohol) (PVA) (degree of polymerization ≈ 1600 and degree of hydrolysis ≈ 97.5 to 99.5 mol% with $M_n = 72000$) was supplied from Fluka. 5-sulfosalicylic acid was purchased from Fluka and used as the model drug. Glutaraldehyde (50% in water) was purchased from Fluka and used as the

crosslinking agent. Sodium acetate (Ajax Chemicals, Australia), sulfuric acid (Merck), methanol (Carlo Erba Reagent), and glacial acetic acid (Merck) were of analytical reagent grade and used without further purification.

2.2. Preparation of drug-loaded PVA hydrogels

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, the model drug was loaded at 10 wt% (based on the weight of PVA powder) into the PVA solution under constant stirring for 1 h. In order to crosslink PVA, glutaraldehyde was used as the crosslinking agent at various crosslinking ratios. The crosslinking ratio, X, is defined as the ratio of moles of crosslinking agent to moles of PVA repeating unit. In addition to adding 25% solution of glutaraldehyde, other solutions used were a 10% solution of sulfuric acid (the catalyst), a 50% solution of methanol (the quencher), and a 10% solution of acetic acid (the pH controller). They were added to the PVA solution in a 2: 1: 2: 3 ratio, respectively. The solution was mixed very slowly to prevent the formation of air bubbles (Peppas et al., 1998). Immediately after mixing the solution, the mixture was cast on the mold (diameter 9 cm, film thickness 0.45-0.50 mm) in a dust-free atmosphere at 60 °C for 3h and then cooled to room temperature.

2.3. Characterizations

An ATR-FTIR spectroscopy (Thermo Nicolet) was used to investigate the polymer/drug interaction in the drug-loaded PVA hydrogels. The sample was placed on the crystal and spectra were taken to determine any interactions between the drug and polymer. A differential scanning calorimeter (DSC; Mettler Toledo 822e/400) and a thermal gravimetric analyzer (TG-DTA, Perkin Elmer) were used to investigate thermal behavior of the PVA hydrogel, the drug, and the drug-loaded PVA hydrogel. 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 heating 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 $^{\circ}$C at a rate of 10 $^{\circ}$C min−1 under nitrogen purge (200 ml min−1). The morphology of PVA hydrogel was examined using a scanning electron microscope or SEM (JEOL, model JSM-5200). The hydrogel was immersed in distilled water at 37 $^{\circ}$C before it was rapidly frozen in liquid nitrogen then dried it in vacuum at -50°C. After Freeze-Dry process, the sample was gold sputtered for 4 min. The sample was scanned at magnification of 350x and 1500x.

The degree of swelling and weight loss of PVA hydrogels were measured in acetate buffer solution at 37 $^{\circ}$C for 24 h according to the following equations (Taepaiboon et al., 2006):

$$\text{Degree of swelling (\%)} = \frac{M - M_d}{M_d} \times 100 \tag{1}$$

and

$$\text{Weight loss (\%)} = \frac{M_i - M_d}{M_i} \times 100 \tag{2}$$

where M is the weight of each sample after submersion in the buffer solution, M_d is the weight of sample after submersion in the buffer solution in its dry state, M_i is the initial weight of the sample in its dry state.

To determine the molecular weight between crosslinks, M_c the mesh size, ξ, and the crosslinking density, ρ, a sample of PVA hydrogel was cut immediately after crosslinking. This sample was weighted in air and heptane. The sample was then placed in distilled water at 37 $^{\circ}$C for 5 days to allow it to swell to equilibrium, and weighted in air and heptane. Finally, the sample was dried at 25 $^{\circ}$C in vacuum oven for 5 days. Once again, it was weighted in air and heptane. These weights were used to calculate the polymer volume fraction (Peppas et al., 1998).

The molecular weight between crosslinks, $\bar{M}_c$, was calculated from the swelling data using Eq (3) (Peppas et al., 1998).

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\dfrac{\overline{\upsilon}}{V_1}[\ln(1-\upsilon_{2,s})+\upsilon_{2,s}+\chi\upsilon_{2,s}^{2}]}{\upsilon_{2,r}[(\dfrac{\upsilon_{2,s}}{\upsilon_{2,r}})^{1/3}-\dfrac{1}{2}(\dfrac{\upsilon_{2,s}}{\upsilon_{2,r}})]} \qquad (3)$$

where $\overline{M}_n$ is the number-average molecular weight of the polymer before crosslinking (= 72,000), υ is the specific volume of PVA (= 0.788 cm^3/g), V_1 is the molar volume of the water (= 18.1 cm^3/mol), $\upsilon_{2,r}$ is the volume fraction of the polymer in the relaxed state, $\upsilon_{2,s}$ is the volume fraction of the polymer in the swollen state, and the Flory polymer-solvent interaction parameter, χ for PVA/water is 0.494.

The hydrogel mesh size, ξ, defines the linear distance between consecutive crosslinks. It indicates the diffusional space available for solute transport and can be calculated using Eq (4) (Hickey *et al.*, 1995).

$$\xi = \upsilon_{2,s}^{-1/3}\,[C_n(2\overline{M}_c/\overline{M}_r)]^{1/2}\,l \qquad (4)$$

where C_n is the Flory characteristic ratio (= 8.3), l is the carbon-carbon bond length(= 1.54 A^0), $\overline{M}_r$ is the molecular weight of the repeating unit of polymer, and $\overline{M}_c$ is the molecular weight between crosslinks.

The crosslinking density of the hydrogel was calculated using Eq (5) (Peppas *et al.*, 1996).

$$\rho_x = \frac{1}{v\overline{M}_c} \qquad (5)$$

2.4. Drug release experiments

2.4.1. 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 distilled water. 15 ml of glacial acetic acid was then added very slowly into the aqueous sodium acetate solution.

2.4.2. Skin Preparation

Transdermal diffusion experiments were performed using fresh pig skins from the abdominal part of pig. The skin used in this work was about 1-1.5 mm thick. The whole pig skins were surgically removed and cleaned with sterile normal saline. The subcutaneous fat, tissue, blood vessel, and epidermal hair were carefully removed by blunt section. The skin was free of obvious holes or defects. The full thickness skin was cleaned with saline and finally with distilled water, cut into circular shape, wrapped with an aluminium foil, and stored frozen before use.

2.4.3. Spectrophotometric Analysis of Model Drug

A UV/Visible spectrophotometer (Shimadzu, UV-2550) was used to determine the maximum spectra of model drug. Model drug in aqueous solution was prepared for scanning the maximum absorption wavelength. The characteristic peak was observed. The absorbance value at the maximum wavelength of model drug was read and the correspondent model drug concentrations were calculated from the calibration curve with various model drug concentration.

2.4.4. Actual Drug Content

The actual amount of drug in the drug-loaded PVA film (circular disc about 2.5 cm in diameter) was quantified by dissolving the sample in 4 ml of dimethylsulfoxide (DMSO) and then 0.5 ml of the solution was pipetted and added into 8 ml of the acetate buffer solution. The drug solution was measured for the amount of drug using the UV/Visible spectrophotometer at a wavelength of 298 nm.

2.4.5. Thansdermal Transport Studies

The custom built modified Franz-Diffusion cells were used for the diffusion studies. The diffusion cell consisted of two compartments; a donor compartment, which was exposed to an ambient condition, and a receptor compartment which was filled with the acetate buffer solution pH 5.5 and maintained at 37 °C by a circulating water bath. In the study of effect of crosslinking ratio, a unit of drug-loaded PVA hydrogel with various crosslinking ratios (0, 0.5, 2.5 and 5.0) was placed over the pig skin mounted on the receptor compartment. For the study of effect of electric field,

the copper plate was used to distribute the electrical potential (V= 0, 0.5, 1.0, 3.0 and 5.0 Volt) to over all position of the hydrogel. The drug diffused through the polymer matrix and the pig skin through the solution. A sample of 0.3 ml was withdrawn at various time intervals simultaneously replaced with equal volume of fresh buffer solution. The drug concentrations in these samples were determined by the UV/Visible spectrophotometer at wavelength of 298 nm.

3. Results and discussion

3.1. Characterization

3.1.1. Fourier transform infrared spectroscopy (FTIR)

The absorption infrared spectra of poly(vinyl alcohol) hydrogel loaded with 10 and 25% sulfosalicylic acid is shown in comparison with poly(vinyl alcohol) free hydrogel and sulfosalicylic acid power in Figure 1. In pure PVA, we observed peaks at 1330, 2941 cm^{-1} and a broad region around 3000 to 3600 cm^{-1}. They are characteristic of PVA and have been assigned to the CO stretching, CH_2 stretching and OH stretching, respectively. In pure SSA, two peaks at 1036 and around 716 cm^{-1} have been assigned to sulfonate groups (SO^{3-}) stretching. For drug-loaded PVA hydrogel the sulfonate groups (SO^{3-}) stretching grows and has a gradual shift of OH stretching. These results indicate the H-bonding between the sulfonate groups of sulfosalicylic acid with hydroxyl group of PVA hydrogel (Wu et al., 2006).

3.1.2. Thermal properties of drug-loaded PVA hydrogel

Figure 2 shows DSC thermograms for pure PVA and drug-loaded PVA hydrogel. The DSC thermogram for pure PVA hydrogel exhibits a loss of moisture coupled with a glass transition over a temperature range between 40-120 $^\circ$C, a melting range at 200-225 $^\circ$C and a thermal degradation range between 250-350 $^\circ$C. The drug-loaded PVA hydrogel exhibits a loss of moisture coupled with a glass transition at the same temperature range of the pure PVA hydrogel, while the melting temperature(T_m) of both drug and PVA in drug-loaded samples shift to about 140 $^\circ$C and 170 $^\circ$C, respectively. The possible reason for the peak shifh is the interaction

between polymer and drug molecule since SSA had a potential to form H-bonding with the hydroxyl group of PVA (Taepaiboon et al., 2006).

Figure 3 shows the TGA thermograms for pure PVA and drug-loaded PVA hydrogels. There are three transitions for pure PVA hydrogel and the drug-loaded PVA hydrogel. The first occurs the temperature range of about 50-100 °C, corresponding to the loss of moisture, while the second and the third transitions cover the temperature range of 255 to 320 °C and 400-500 °C, corresponding to the thermal degradation of PVA. The TGA thermogram of drug-loaded PVA hydrogel also exhibits four steps of weight loss. The results show that the presence of SSA (drug) seemed to expedite the thermal degradation of the pure PVA matrix. It is known that PVA is a semicrystalline polymer which exhibites a strong intermolecular interaction through hydrogen bonding between hydroxyl group and ionic drug (Hidalgo *et al.*, 1999; Wu *et al.*, 2006)

3.1.3. Swelling behaviour of drug-loaded PVA hydrogel

The PVA hydrogels were prepared by varying the crosslinking ratio through the amount of glutaraldehyde used. The effect of this variable on swelling behavior, the molecular weight between crosslinks, the mesh size and the drug diffusion ability will be discussed below.

Figure 4 shows the degree of swelling and the weight loss of drug-loaded PVA hydrogels at various crosslinking ratios (PVA_0, PVA_0.5, PVA_2.5, PVA_5.0) after immersion in acetate buffer solution at 37°C for 5 day. The results show that degree of swelling and weight loss increase with decreasing crosslinking ratio because the lower crosslinked hydrogel has a longer PVA strand between crosslinks or a looser network. It can swell appreciably and their pore size are larger as determined by using the equilibrium swelling theory as developed by Peppas (Peppas *et al.*, 1998) and shown in the SEM image of PVA hydrogel after swelling (figure 5).

The swelling data were used to evaluate the crosslinked structure of these hydrogels. The molecular weight between crosslinks, the mesh size and the crosslinking density are parameters used for characterizing the porous structure of hydrogel for drug delivery system. These values of each hydrogel matrix are

determined using the equilibrium swelling theory developed by Peppas (Peppas *et al.*, 1998). Table 1 shows the molecular weight between crosslinks, the mesh size and the crosslinking density of each PVA hydrogel at various crosslinking ratios with and without electric field. The molecular weight between crosslinks and mesh size values of PVA hydrogels are larger at lower crosslinking ratios. The mesh sizes of hydrogels varied between 36 and 230 A° for no current and between 33 and 250 A° for apply current. Thus the comparison of mesh size values between the system with electric field and without electric field suggests that the electric field has no effect on the PVA structure change.

The morphologies of hydrogels with and without electric field are shown in SEM micrographs of figures 5, 6 and 7. The pictures show porous morphology and their pore sizes are larger at lower crosslinking ratios.

3.2. Release kinetics of model drug from drug-loaded PVA hydrogel

Initially, the actual amount of drug within the sample was measured. The actual amount of drug present in the sample is reported as the percentage of the initial content of drug loaded in PVA solution. The actual amount of drug presented in the sample is about 93.1 ± 5.8 %.

In order to study sulfosalicylic acid transport mechanism from the PVA hydrogels, two diffusion models are considered to fit the experimental data.

Model 1 is described by the Ritger-Peppas equation (Venkatesh *et al.*, 1992):

$$\frac{M_t}{M_\infty} = k_1 t^n \tag{1}$$

where M_t/M_∞ is the fractional drug release, k_1 is a kinetic constant and t is the release time and n is the scaling exponent that can be related to the drug transport mechanism. For a thin hydrogel film, when n = 0.5, the drug release mechanism is the Case I or the Fickian diffusion. When n = 1, Case II transport occurs corresponding to the zero-order release. When the value of n is between 0.5 and 1, the anomalous transport is observed.

Model 2 is based on the Higuchi's equation (Serra *et al.*, 2006) and described by the Fickian diffusion of the drug:

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \tag{2}$$

where M_t/M_∞ is the fractional drug release, k_H is a kinetic constant, and t is the release time.

The diffusion coefficients of sulfosalicylic acid from the PVA hydrogels are calculated from the slopes of plots of drug accumulation *vs.* square root of time according to Higuchi's equation (A-sasutjarit *et al.*, 2005):

$$Q = 2C_0 (Dt / \pi)^{1/2} \tag{3}$$

where Q is the amount of material flowing through a unit cross-section of barrier in unit time, t; C_0 is the initial drug concentration in the hydrogel; and D is the diffusion coefficient of a drug.

3.2.1.Effect of crosslinking ratio

The amounts of sulfosalicylic acid released from sulfosalicylic acid- loaded poly(vinyl alcohol) hydrogel at time t vs. t and $t^{1/2}$ at various crosslinking ratios (PVA_0, PVA_0.5, PVA_2.5, PVA_5.0) in an absence of electric field during 48 h are illustrated in Figure 8 and 9 respectively. The amount of released drug gradually increases with time and then reaches an equilibrium value, while the plots of the amount of drug released as a function of square root of time show a linear relationship. The amount of released drug increases with decreasing crosslinking ratio due to the larger pore size of the lesser crosslinked hydrogel which contributes to the observed highly susceptibility to swelling in aqueous medium (see figure 4). The degree of swelling of drug-loaded PVA hydrogel decreases with increasing glutaraldehyde concentrations in the hydrogels. With increasing crosslinking agent, the crosslink reaction of hydroxyl groups in poly(vinyl alcohol) with aldehyde groups in glutaraldehyde to form ether linkage is amplified (Yeom *et al.*, 1996).

The diffusion coefficients of each system are calculated from the slopes of these plots using the Higuchi's equation (see figure 9). Figure 10 shows the diffusion coefficients of sulfosalicylic acid from poly(vinyl alcohol) hydrogels vs. crosslinking ratios and mesh size at electric field strength of 0 and 1 V at 37 ^{0}C. From the data, sulfosalicylic acid diffusion coefficients in each system are ranked in the following

order: PVA_0 > PVA_0.5 > PVA_2.5 > PVA_5.0. We suggest that the diffusion coefficient of sulfosalicylic acid from PVA hydrogel increases with decreasing crosslinking ratio due to the larger pore size or lower crosslinking ratio resulting in an easier drug movement in this pathway. As the electric field is applied the diffusion coefficient increases due to the electrostatic force from electrical current driving the charged drug, sulfosalicylic acid (Massoumi *et al.*, 2001), towards the oppositely charged electrode (Jensen *et al*, 2002). Figure 11 shows the log-log plot of diffusion coefficients of sulfosalicylic acid from poly(vinyl alcohol) hydrogels vs. drug size/mesh size of hydrogel at electric field strengths of 0 and 1 V at 37 ^{0}C. From these results, the scaling exponent m was determined from the following equation;

$$D = D_0 (a/\xi)^{-m} \qquad (4)$$

where D is the diffusion coefficient of a drug; D_0 is the initial diffusion coefficient; a is the size of drug; ξ is the mesh size of hydrogel and m is the scaling exponent. The scaling exponent m value for the sulfosalicylic acid to diffuse through the poly(vinyl alcohol) matrix and the pig skin under electric field strength of 0 and 1 V are 1.07 and 0.71, respectively.

From a plot of ln M_t/M_∞ versus ln(t), the scaling exponent n was determined from equation 1 as shown in table 2. The n value of uncrosslinked PVA hydrogel without electric field is near the Fickian exponent value of n = 0.5. Thus, sulfosalicylic acid release was controlled by the Fickian diffusion mechanism and the change in their structure has an effect on the mechanism of release.

3.2.2. Effect of electric field strength

Figure 12 shows the amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel with crosslinking ratio 0 at time t vs. $t^{1/2}$ at various electric field strengths under the negatively charge electrode (cathode). The data from figures 12 and 13 show that the amount of released drug and the diffusion coefficients increase with increasing electric field strength because a higher electrical current, a higher electrostatic force for driving the charged drug through the polymer matrix (Kantaria *et al.*, 1999) and the electric field may create the transient

micropores in the skin which permit transport of drug across these pathway (Weaver *et al.*, 1999). The mass of drug delivered across the skin is proportional to the applied current and duration of current application (Sage *et al.*, 1992).

3.2.3. Effect of electrode polarity

Figure 14 shows the amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel with crosslinking ratio 0 at time t vs. $t^{1/2}$ under the positive charge electrode (anode in donor), negative charge electrode (cathode in donor) and no current system delivery over 48 h. The diffusion coefficient under cathode is much higher than that under anode and no current (table 3) due to the electrorepulsion between the charged drug and charge electrode driving the charged drug through the polymer matrix and the pig skin into the solution (Green *et al.*, 1996). Passive delivery (no current) results in a low permeation similar to the anodic delivery. Sulfosalicylic acid model drug has negative charge at pH 5.5 and this study establishes that it should be delivered under cathode.

4. Conclusions

The sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogels were prepared varying the crosslinking ratios to study the release mechanism and diffusion coefficient of drug from poly(vinyl alcohol) hydrogels with and without electric field. Each hydrogel was characterized the swelling ability and mesh size. The degree of swelling, the weight loss, and the mesh size of PVA hydrogels increase with decreasing of crosslinking ratio. The diffusion coefficients were studied as a function of crosslinking ratio, mesh size, electric field strength and electrode polarity. For the effect of crosslinking ratio, the diffusion coefficient of drug from PVA hydrogel increase with decreasing of crosslinking ratio due to larger mesh or pore size of hydrogel. For the effect of electric field strength, the diffusion coefficient of drug from PVA hydrogel increases with increasing of electric field strength due to higher force for driving the charged drug through the polymer matrix and the pig skin. For the effect of electrode polarity, the diffusion coefficient of drug under cathode is much higher than that under anode and no current because of the electrorepulsion between charge drug and charge electrode.

It is possible to conclude that the varying crosslinking density, applying the electric field or changing electrode polarity can control and modulate the drug release kinetic.

5. Acknowledgements

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Table 1 The molecular weight between crosslinks, the mesh size, and the crosslinking density of PVA hydrogels at various crosslinking ratios with and without the electric field

Sample	Crosslinking ratio, X	Number-average molecular weight between crosslinks, M_c (g/mol)		Mesh size ξ (A^0)		Crosslinking density (mol/cm^3, x 10^4)	
		E = 0 V	E = 1 V	E = 0 V	E = 1 V	E = 0 V	E = 1 V
PVA_0	0	13464 ± 1733	15400 ± 2100	232 ± 23	250 ± 28	0.95 ± 0.13	0.83 ± 0.11
PVA_0.5	0.5	6484 ± 2069	6800 ± 940	143 ± 31	150 ± 13	1.99 ± 0.57	1.88 ± 0.28
PVA_2.5	2.5	2063 ± 734	2600 ± 750	71 ± 15	85 ± 15	6.26 ± 1.57	4.99 ± 1.34
PVA_5.0	5.0	691 ± 176	570 ± 270	36 ± 6	33 ± 10	18.36 ± 4.29	23.60 ± 8.30

Table 2 Release kinetic parameters and linear regression values obtained from fitting drug release experimental data to the Ritger-Peppas model

Sample	Crosslinking	Diffusional exponent(n)		Kinetic constant (K)(hr^{-n})		r^2	
	ratio	E= 0 V	E= 1 V	E= 0 V	E= 1 V	E= 0 V	E= 1 V
PVA_0	0	0.58	0.63	0.1313	0.1197	0.9903	0.9842
PVA_0.5	0.5	0.72	0.83	0.0954	0.0708	0.9854	0.9831
PVA_2.5	2.5	0.77	0.93	0.1117	0.0549	0.8448	0.9720
PVA_5.0	5	0.82	0.93	0.0672	0.0429	0.8956	0.9466

Table 3 Diffusion coefficients of sulfosalicylic acid in poly(vinyl alcohol) hydrogels under anode and cathode

Electric field strength (V)	Diffusion Coefficient (cm^2/s)			
	1	2	Average	SD
0	2.76E-09	1.357E-09	2.06E-09	9.93E-10
1(anode)	·5.69E-10	5.999E-10	5.84E-10	2.21E-11
1(cathode)	5.57E-09	5.967E-09	5.77E-09	2.79E-10
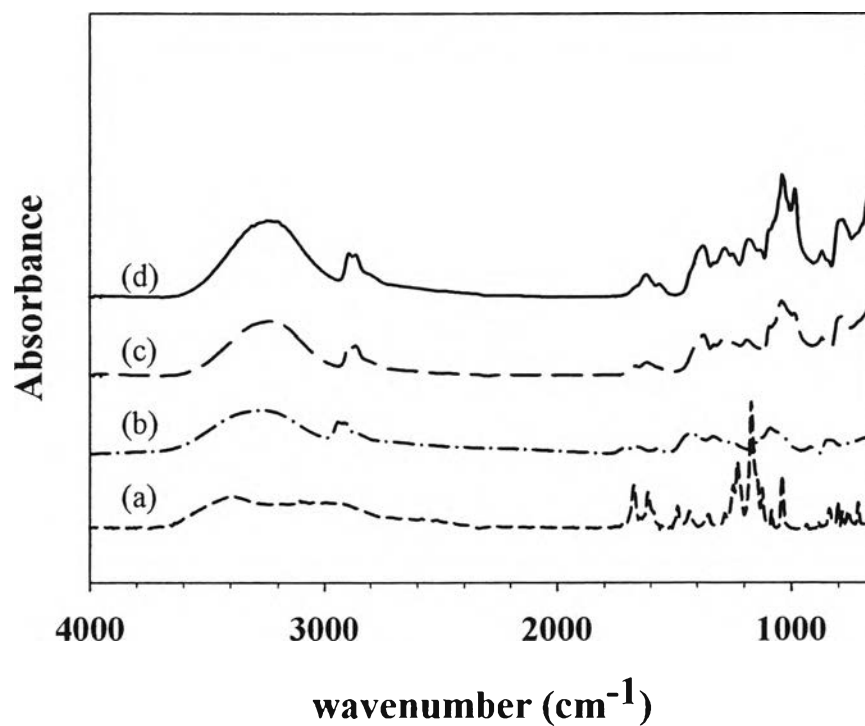
Figure 1 Absorption infrared spectra of poly(vinyl alcohol) hydrogel loaded with sulfosalicylic acid: (a) SSA powder; (b) pure PVA hydrogel; (c) 10%SSA-loaded PVA hydrogel; and (d) 25%SSA-loaded PVA hydrogel.
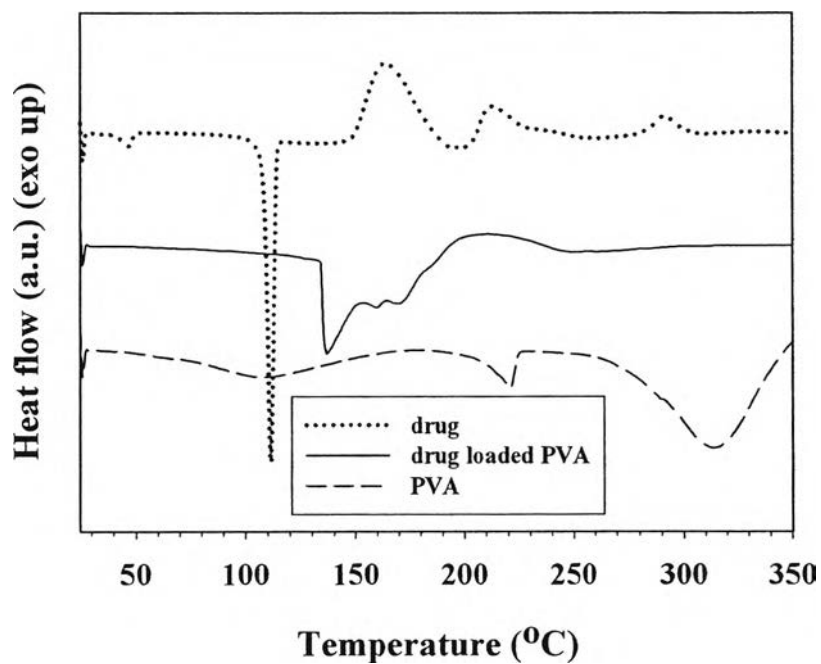
Figure 2 The DSC thermograms of pure PVA hydrogel, drug-loaded PVA hydrogel, and pure model drug.
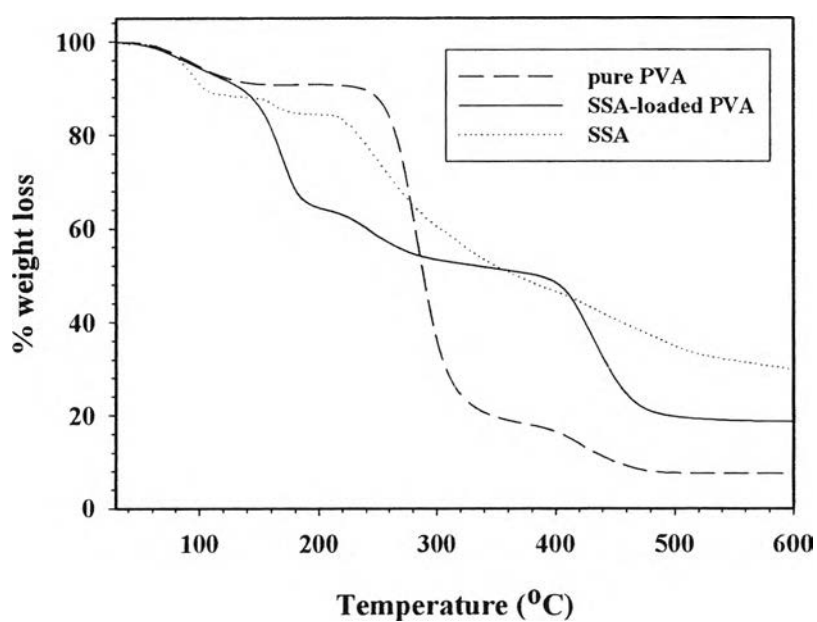
Figure 3 The TGA thermograms of pure PVA hydrogel, drug-loaded PVA hydrogel, and pure model drug.
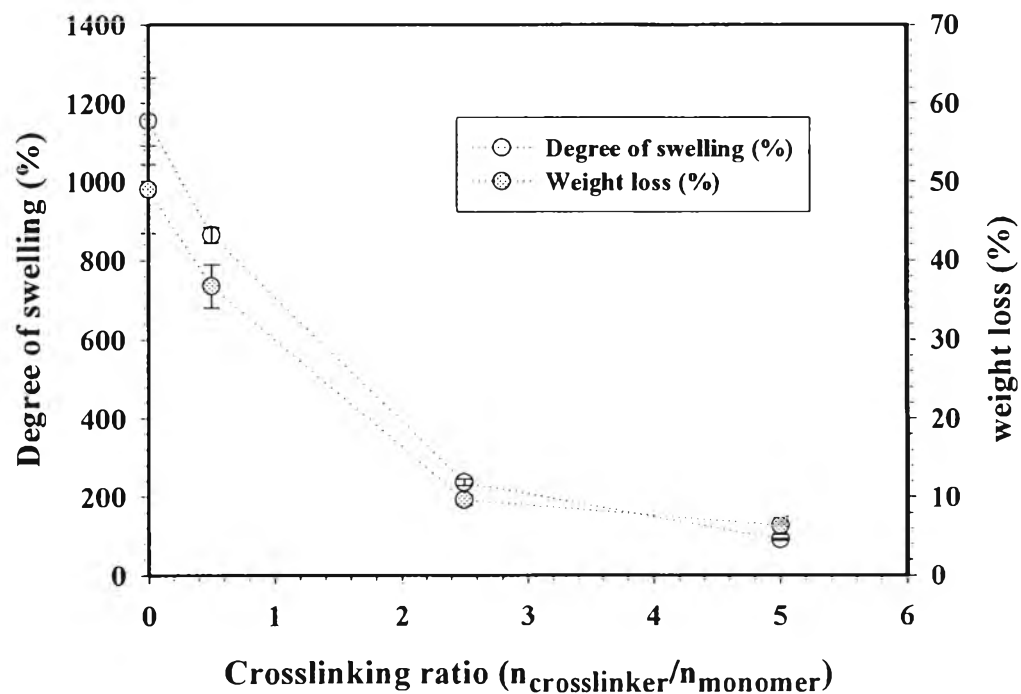
Figure 4 Degree of swelling (%) and weight loss (%) of poly(vinyl alcohol) hydrogels at various crosslinking ratios (PVA_0, PVA_0.5, PVA_2.5 and PVA_5.0) at 37^0C after 5 day, each data point was obtained from 5 samples.
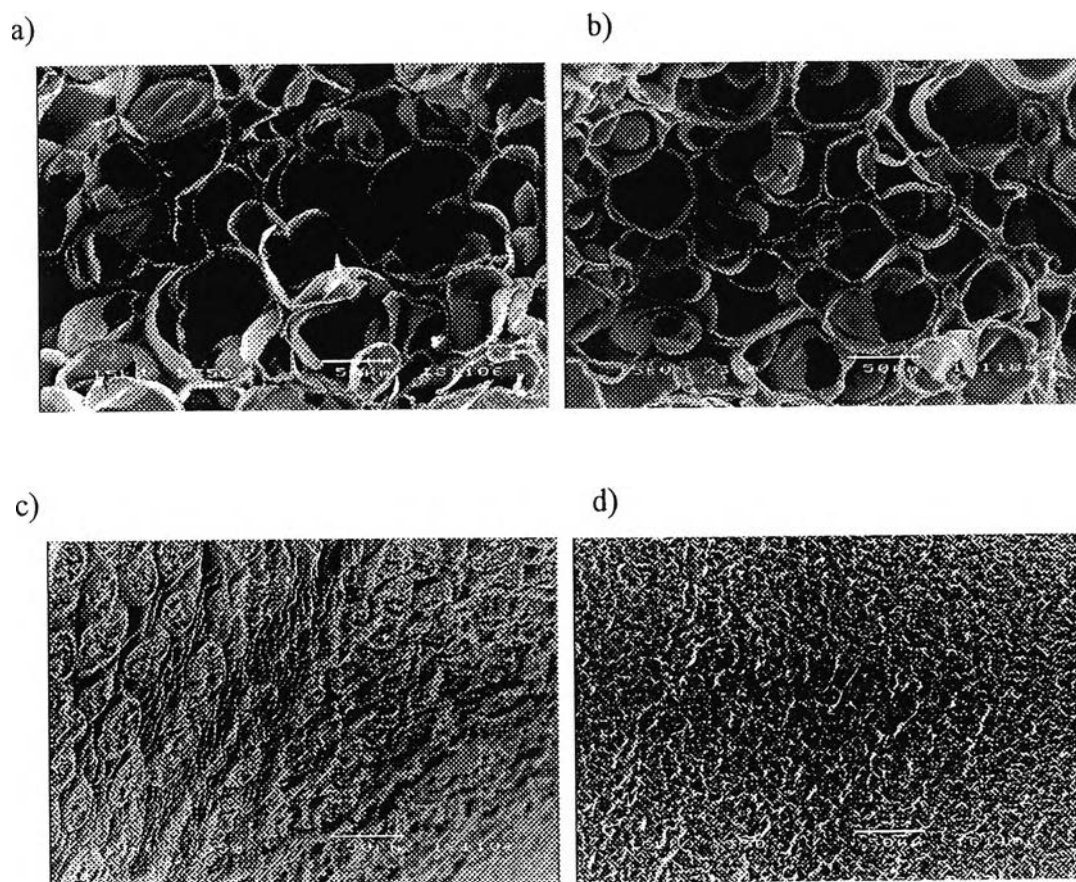
Figure 5 The morphology of poly(vinyl alcohol) after swelling: a) PVA_0; b) PVA_0.5; c) PVA_2.5; and d) PVA_ 5.0 at magnification of 350.
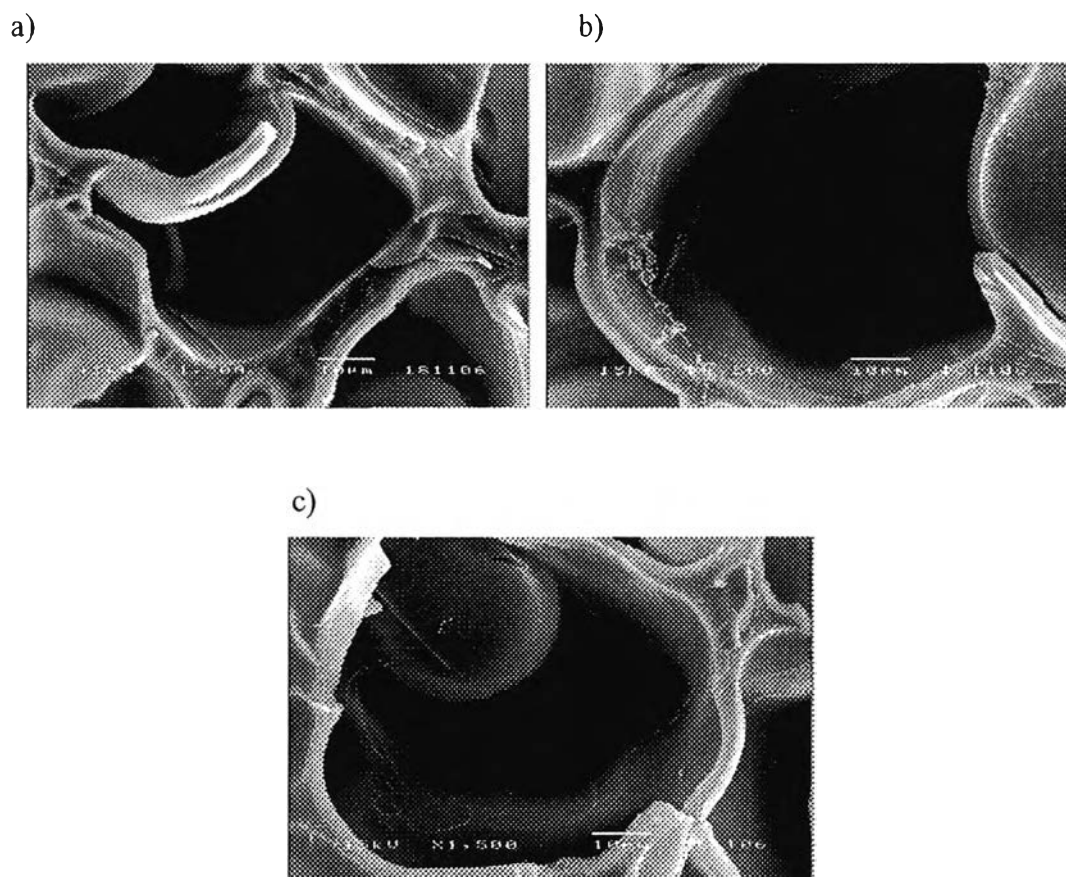
Figure 6 The morphology of poly(vinyl alcohol) (PVA_0) after swelling under electric field strength of: a) 0 V ; b) 1.0 V; and d) 5 V at magnification of 1500.

a)

b)

c)
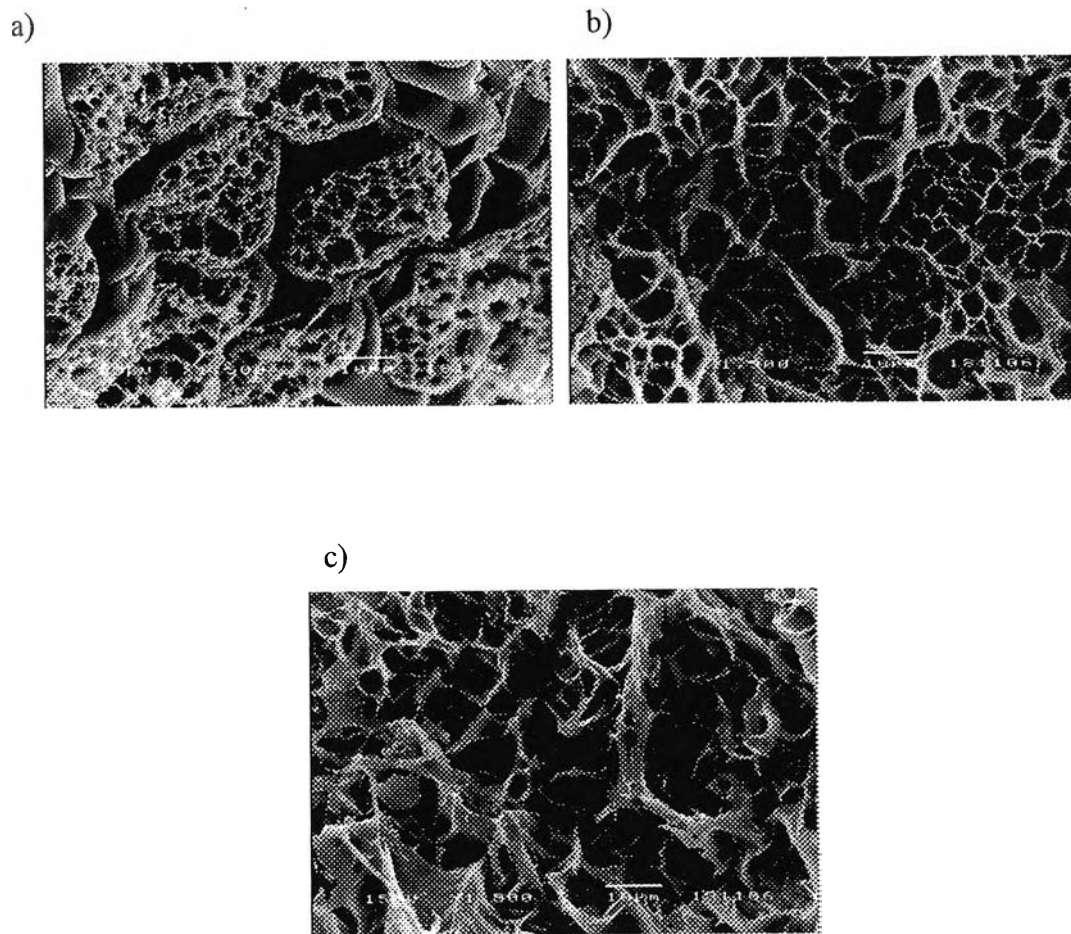
Figure 7 The morphology of poly(vinyl alcohol) (PVA_2.5) after swelling under electric field strength of: a) 0 V ; b) 1.0 V; and d) 5 V at magnification of 1500.
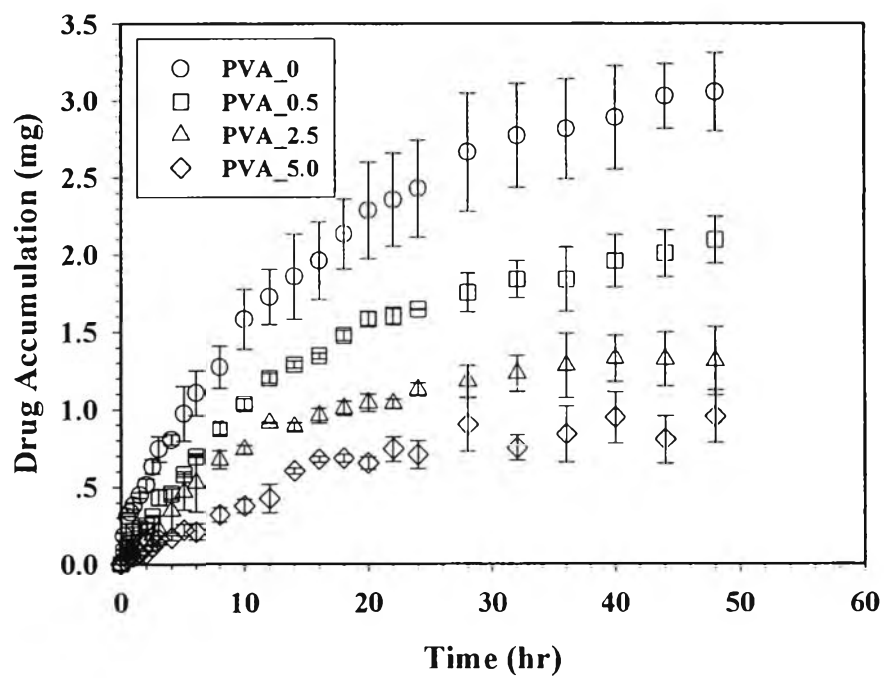
Figure 8 Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel vs. time at various crosslink ratios, E = 0 V, pH 5.5, 37^0C, n = # samples =2.
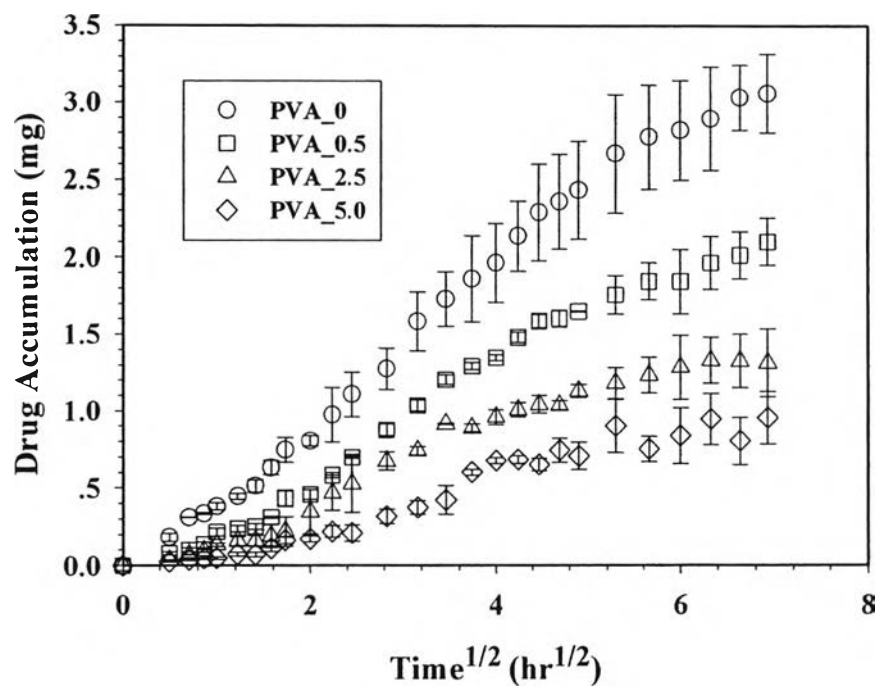
Figure 9 Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel vs. $t^{1/2}$ at various crosslink ratios, $E = 0$ V, pH 5.5, 37^0C, n = # samples =2.
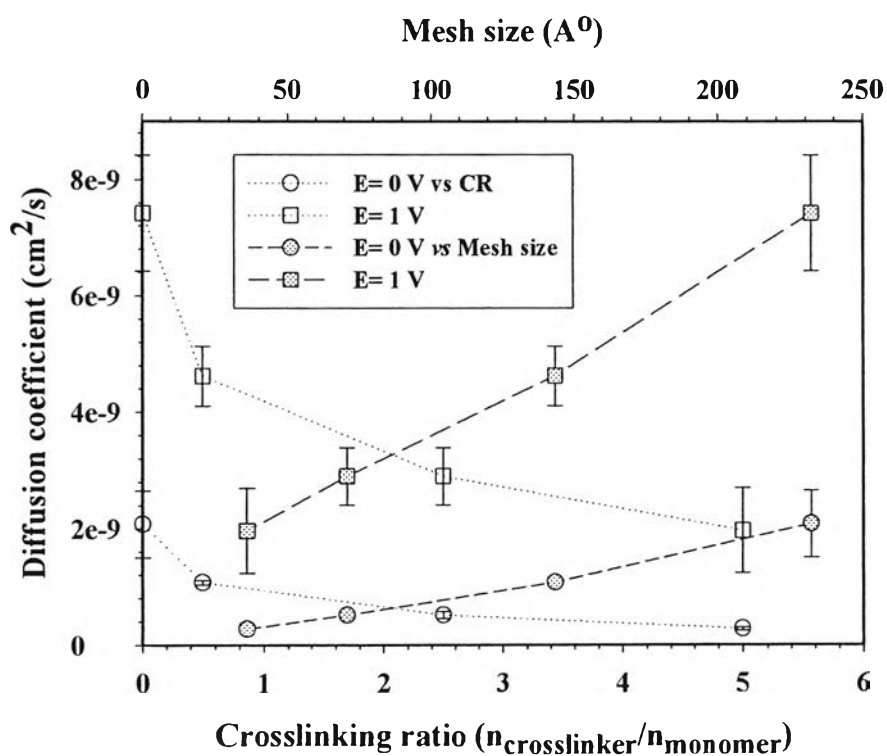
Figure 10 Diffusion coefficient of sulfosalicylic acid from poly(vinyl alcohol) hydrogels vs. crosslinking ratios and Mesh size at electric field strength of 0 and 1 V, pH 5.5, 37 ^{0}C, n = # samples = 2.
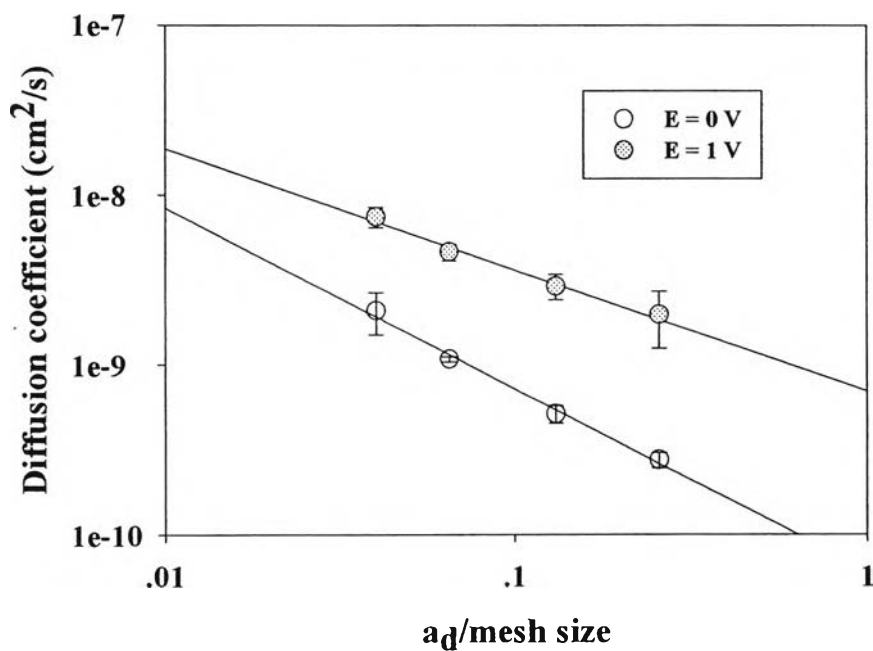
Figure 11 Diffusion coefficient of sulfosalicylic acid poly(vinyl alcohol) hydrogels vs. drug size/mesh size of hydrogel at electric field strength of 0 and 1 V, pH 5.5, 37 ^{0}C, n = # samples = 2.
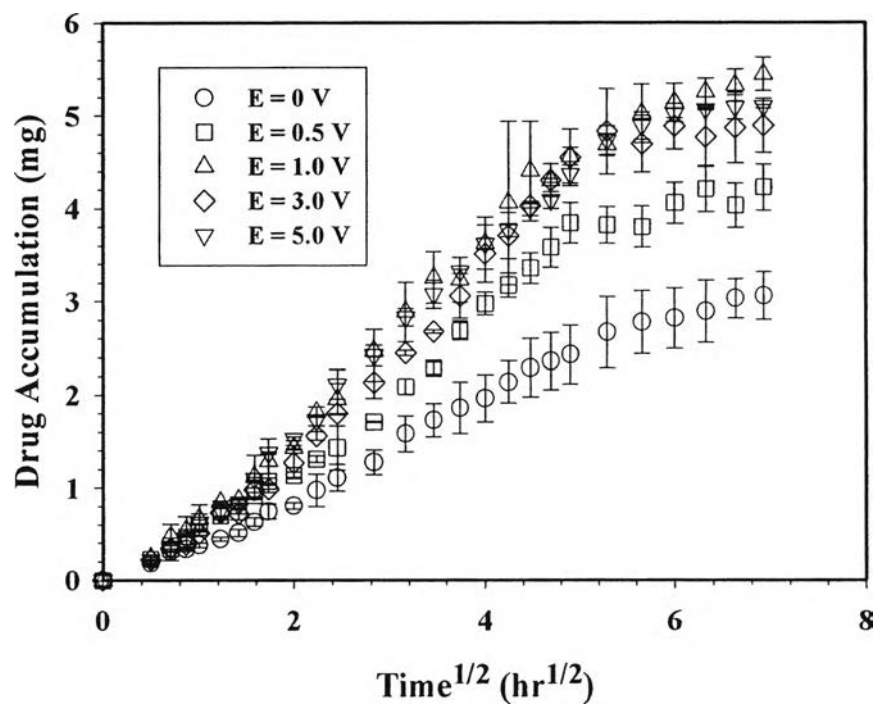
Figure 12 Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel at time t vs. $t^{1/2}$ at various electric field strength, crosslinking ratio = 0 , pH 5.5, 37^0C, n = # samples = 2.
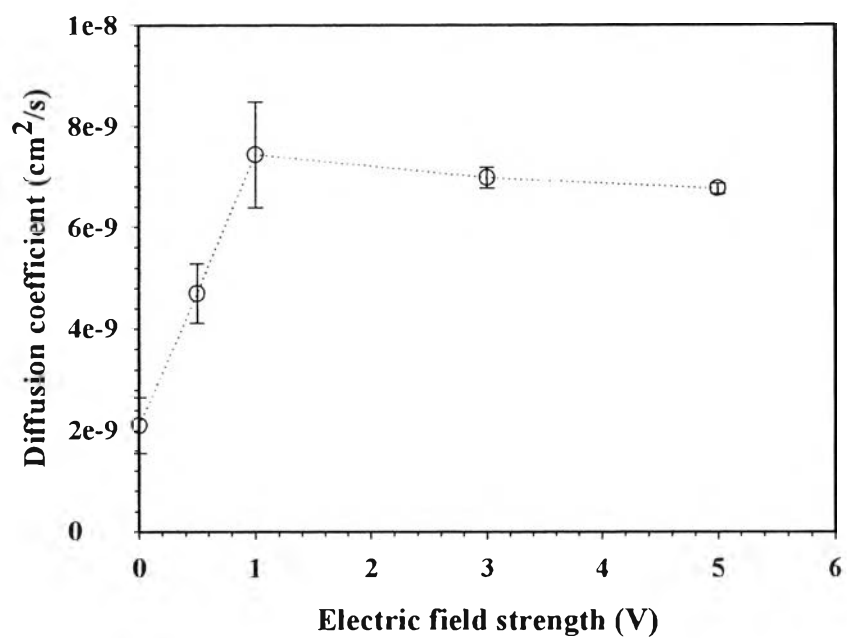
Figure 13 Diffusion coefficient of sulfosalicylic acid from poly(vinyl alcohol) hydrogels vs. electric field strength at crosslinking ratio of 0 , pH 5.5, 37 ^{0}C, n = # samples = 2.
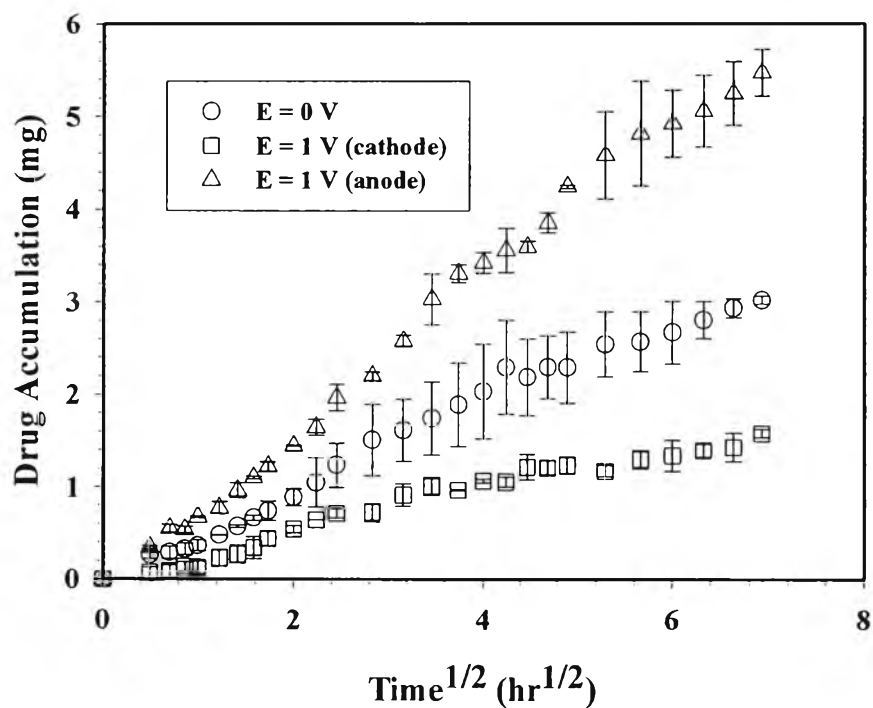
Figure 14 Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel at time t vs. $t^{1/2}$ with applied the anode and cathode, crosslinking ratio = 0 , pH 5.5, 37^0C, n = # samples = 2.