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International Journal of Pharmaceutics 356 (2008) 1–11
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Electrically controlled release of sulfosalicylic acid from crosslinked poly(vinyl alcohol) hydrogel

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Received 31 August 2007; received in revised form 30 November 2007; accepted 17 December 2007
Available online 24 December 2007

Abstract

Electrically controlled drug delivery using poly(vinyl alcohol) (PVA) hydrogels as the matrix/carriers for a model drug was investigated. 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 from the equilibrium swelling theory as developed by Peppas and Merril, and the latter data were compared with those obtained from scanning electron microscopy. The release mechanisms and the diffusion coefficients of the hydrogels were studied using modified Franz-Diffusion cells in an acetate buffer with pH 5.5 and temperature 37 °C during a period of 48 h, in order to determine the effects of crosslinking ratio, electric field strength, and electrode polarity. The amounts of drug released were analyzed by UV–vis spectrophotometry. The amounts of drug released vary linearly with square root of time. The diffusion coefficients of drug-loaded PVA hydrogels decrease with increasing crosslink ratio. Moreover, the diffusion coefficients of the charged drug in the PVA hydrogels depend critically on the electric field strength between 0 and 5 V as well as on the electrode polarity. Thus, the release rate of sulfosalicylic acid can be altered and controlled precisely through electric field stimulation.

Keywords: Poly(vinyl alcohol) hydrogels; Crosslink; Diffusion coefficient; Electrical control drug release

1. Introduction

Several possible methods of introducing medication into the body are the oral route, the injection, and the transdermal route. However, the conventional oral and injection routes may initially provide the maximum tolerable dose but the dose decreases dramatically over a short time period (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 method are to avoid the first-pass metabolism, to increase compliance, to control plasma levels, and to reduce the overall dosage amount (Xie et al., 2005). However, TDD has been limited to a low amount of drug due to the extremely low drug release rate from the matrix and the low permeability of drug through the skin. In general, precise controls over the drug quantity and the release rate are required in order to optimize the drug therapy. This can be achieved if the drug carrier responds and activates in a reproducible and predictable fashion under an internal or external stimulus such as electric field (Murdan, 2003), pH (Gudeman and Peppas, 1995), and temperature (Xu et al., 2006).

The use of an electric field as an external stimulus is a method that has been successfully employed to enhance the amount of released drug and the precise controls (Chien et al., 1990). There have been several studies on the use of electric current in vivo, through iontophoresis and electroporation mechanisms, for the dermal and the transdermal drug deliveries. Transdermal iontophoresis has been investigated in recent years for the delivery of charged molecules (Chien et al., 1990; Chen and Chen, 1996; Ramanathana and Blockb, 2001; Bose et al., 2001). Bose et al. (2001) studied the release of buprenorphine across human skin via iontophoresis using current density of 0.5 mA/cm^2. They reported that the drug permeation could be significantly enhanced for an ionic drug entrapped in the matrix/carrier.

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doi:10.1016/j.ijpharm.2007.12.023

Hydrogels are hydrophilic three-dimensional networks, held together either by chemical or physical bonds. Interstitial spaces existing within the network allow water molecules to become trapped and immobilized, filling the available free volume (Elvira et al., 2002). Hydrogels have been used as an artificial skin (Young et al., 1998), contact lenses (Brinkman et al., 1991), an interface between bone and implant (Netti et al., 1993), and the matrices in drug delivery systems (Chicq and Peppas, 1986; Karatas and Baykara, 2001; Kim et al., 2003). One of the most well known hydrogels is poly(vinyl alcohol) (PVA). PVA and its copolymers have been employed in various applications in the controlled drug release systems (Ritger and Peppas, 1987; Yeom and Lee, 1996; Li et al., 1998; Taepaiboon et al., 2006) due to their high water content. PVA is hydrophilic and easily swells upon hydration; some commercial grade PVAs have shown volume expansions up to 500% at 37 °C (Morita et al., 2000). PVA is a candidate of the drug matrix in TDD because of its biocompatibility, non-toxicity, good water permeability, and easy manipulation under swelling condition; these characteristics make it ideal for the biomedical uses especially the drug delivery (Kim et al., 2002). PVA hydrogels have been reported to be effective for the releases of both hydrophobic and hydrophilic drugs (Ramanathana and Blockb, 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. We are interested in the effects of matrix crosslinking ratio, electric field strength, and electrode polarity on the drug release characteristics.

2. Materials and methods

2.1. Materials

PVA (Fluka) has the degree of polymerization ≈1600 with M_n = 72,000, and the degree of hydrolysis ≈97.5–99.5 mol% 5-sulfosalicylic acid (Fluka) used as the model drug. Glutaraldehyde (Fluka) with 50% (w/v) in water was used as the crosslinking agent. Sodium acetate (Ajax Chemicals), 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 preparing the second solution, we added 25% (w/v) of glutaraldehyde, 10% sulfuric acid (the catalyst), a 50% methanol (the quencher), and 10% acetic acid (the pH controller), making up a 2:1:2:3 weight ratio solution (Peppas and Wright, 1998). Various amounts of the second solutions were added to the PVA solutions in order to vary X. Each solution was mixed very slowly to prevent the formation of air bubbles. Immediately after mixing the solution, the mixture was cast on a mold (diameter 9 cm, film thickness 0.45–0.50 mm) in a dust-free atmosphere at 60 °C for 3 h and then cooled to room temperature.

2.3. Characterizations

An attenuated total reflection Fourier transform infrared spectrometer (ATR-FTIR; Thermo Nicolet, Nexus 670) was used to investigate the polymer/drug interaction of the drug-loaded PVA hydrogels. The drug-loaded PVA sample (as prepared above) was placed on a crystal sample holder and spectra were taken. A differential scanning calorimeter (DSC; Mettler Toledo, 822e/400) and a thermal gravimetric analyzer (TG-DTA; Perkin-Elmer, Pyris Diamond) was used to investigate the 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 the 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 the heating from 30 to 600 °C at a rate of 10 °C min^{-1} under nitrogen purge (200 ml min^{-1}). The morphology of PVA hydrogel was examined using a scanning electron microscope (SEM; JEOL, JSM-5200). The hydrogel was immersed in distilled water at 37 °C before it was rapidly frozen in liquid nitrogen then dried it in vacuum at −50 °C. After a freeze-dry process, the sample was gold sputtered for 4 min. The sample was scanned at magnifications of 350 and 1500.

The degrees of swelling and the weight losses of PVA hydrogels were measured and determined using an acetate buffer solution at 37 °C during a period of 24 h from the following equations (Taepaiboon et al., 2006):

$$\text{degree of swelling}\,(\%) = \frac{M - M_d}{M_d} \times 100 \quad (1)$$

and

$$\text{weight loss}\,(\%) = \frac{M_i - M_d}{M_i} \times 100 \quad (2)$$

where M is the weight of sample after submersion in the buffer solution for 24 h, M_d is the weight of sample after submersion in the buffer solution for 24 h and after removing the solution (through vacuum oven) or in its dry state, M_i is the initial weight of the sample.

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 weighed in air and heptane. The sample was then placed in distilled water at 37 °C for 5 days to allow it to swell to equilibrium, and weighted in air and heptane. Finally, the sample

was dried at 25 °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 and Wright, 1998).

The molecular weight between crosslinks, M_c, was calculated from the swelling data using Eq. (3) (Peppas and Wright, 1998):

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\overline{\upsilon}/\nu_1[\ln(1-\upsilon_{2,S}) + \upsilon_{2,S} + \chi\upsilon_{2,S}^2]}{\upsilon_{2,r}[(\upsilon_{2,S}/\upsilon_{2,r})^{1/3} - 1/2(\upsilon_{2,S}/\upsilon_{2,r})]} \quad (3)$$

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), ν_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 χ is the Flory polymer–solvent interaction parameter for PVA/water which 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 as follows (Hickey et al., 1995):

$$\xi = \upsilon_{2,s}^{-1/3}\left[C_n\left(\frac{2\bar{M}_c}{\bar{M}_r}\right)\right]^{1/2} l \quad (4)$$

where C_n is the Flory characteristic ratio (8.3), l is the carbon–carbon bond length (1.54 Å), $\bar{M}_r$ is the molecular weight of the repeating unit of polymer, and $\bar{M}_c$ is the molecular weight between crosslinks.

The crosslinking density of the hydrogel was calculated using Eq. (5) (Peppas and Wright, 1996):

$$\rho_x = \frac{1}{\nu\bar{M}_c} \quad (5)$$

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 pigskins from the abdominal part of pig. The skin used in this work was nominally about 1–1.5 mm thick. The whole pigskins 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 determining the maximum absorption wavelength. The characteristic peak was observed. The absorbance value at the maximum wavelength of 298 nm of the model drug was read and the corresponding model drug concentrations were calculated from the calibration curve.

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 determined 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 amount of drug in the buffer solution was measured from the UV/visible spectrophotometer at the wavelength of 298 nm.

2.4.5. Transdermal transport studies

The custom built modified Franz-Diffusion cells were used for the diffusion studies. The diffusion cell consists 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. A drug-loaded PVA hydrogel with a particular crosslinking ratio (0, 0.5, 2.5 or 5.0) was placed between the copper cathode and the pigskin, which was mounted onto the receptor compartment. For the study of effect of electric field, the copper electrode was connected to a power supply, which provided different electrical potentials (V = 0, 0.5, 1.0, 3.0 and 5.0 V) across the hydrogel, the pigskin, and the buffer solution. The drug diffused through the polymer matrix and the pigskin into the solution. A sample of 0.3 ml was withdrawn at various time intervals and simultaneously replaced with equal volume of fresh buffer solution. The drug concentrations in these samples were determined by the UV/visible spectrophotometer at the 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 and those of pristine poly(vinyl alcohol) hydrogel and sulfosalicylic acid powder are shown in Fig. 1. For pure SSA, two peaks at 1036 and 716 cm^{-1} are assigned to the sulfonate group (SO^{3-}) stretching. For pure PVA, we can observe peaks at 1330, 2941 cm^{-1} and a broad region around 3000–3600 cm^{-1}. These characteristic peaks of PVA can be assigned to the CO stretching, the CH_2 stretching, and the OH stretching, respectively. For the drug-loaded PVA hydrogels, the spectra shows that the sulfonate group (SO^{3-}) stretching (1036 cm^{-1}) becomes more evident along with a gradual shift of the OH stretching (3000–3600 cm^{-1}). These results suggest the H-bonding between the sulfonate groups of sulfosalicylic acid and the hydroxyl group of the PVA hydrogel (Wu et al., 2006).

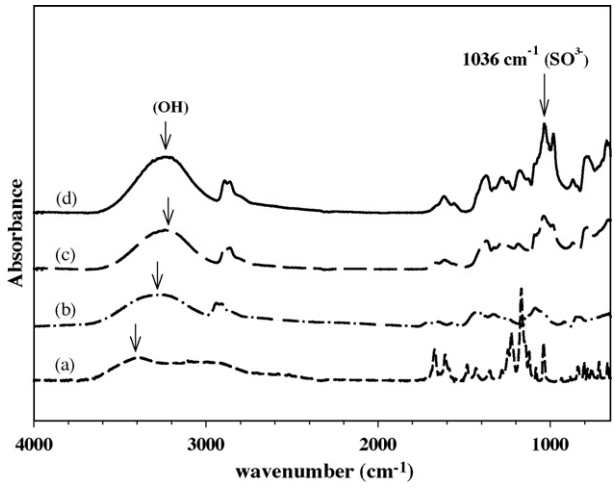

Fig. 1. Absorption infrared spectra of poly(vinyl alcohol) hydrogel loaded with sulfosalicylic acid: (a) SSA powder; (b) pure PVA hydrogel; (c) 10% SSA-loaded PVA hydrogel; (d) 25% SSA-loaded PVA hydrogel.

3.1.2. Thermal properties of drug-loaded PVA hydrogel

Fig. 2 shows DSC thermograms of the drug, pure PVA, and the drug-loaded PVA hydrogel. The DSC thermogram of the SSA drug shows a glass transition at 110 °C, a melting at 165 °C, and a degradation at 210 °C. The DSC thermogram for a pure PVA hydrogel exhibits a gradual loss of moisture over a temperature range between 40 and 120 °C and a glass transition temperature at 110 °C, a melting temperature of 220 °C, and a thermal degradation of 315 °C. For the drug-loaded PVA hydrogel, the thermogram exhibits a loss of moisture coupled with a glass transition at 137 °C, a melting temperature of about 170 °C, and a degradation temperature of 210 °C. The possible cause for the increase in the glass transition temperature for the drug-loaded PVA is the interaction between the polymer and the drug molecule as SSA forms the H-bonding with the hydroxyl group of PVA (Taepaiboon et al., 2006).

Fig. 3 shows the TGA thermograms for the drug, pure PVA, and the drug-loaded PVA hydrogels. Three transitions appear

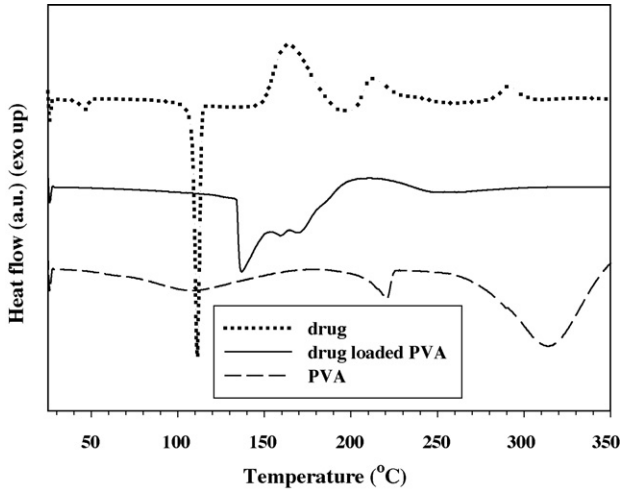

Fig. 2. DSC thermograms of pure PVA hydrogel, drug-loaded PVA hydrogel, and pure model drug.

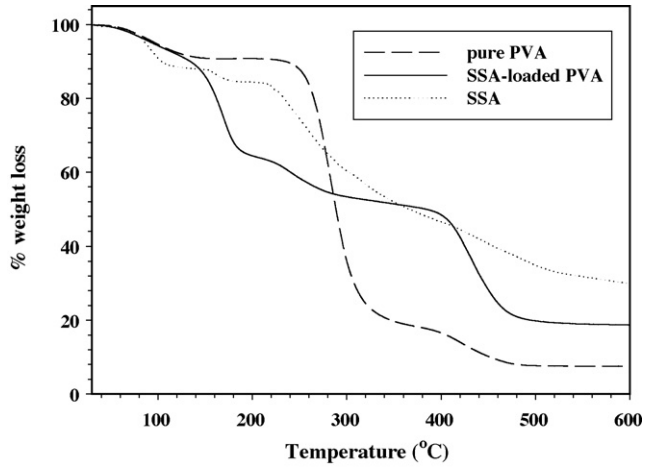

Fig. 3. TGA thermograms of pure PVA hydrogel, drug-loaded PVA hydrogel, and pure model drug.

in the thermogram of the drug. The first transition between 60 and 100 °C refers to the loss of moisture, the second transition at 160 °C is the melting point, and the third transition at 220 °C identifies the degradation of SSA drug. There are three transitions for the pure PVA hydrogel. The first transition occurs in the temperature range of about 50–100 °C, corresponding to the loss of moisture, while the second and the third transitions cover the temperature ranges of 260 and 400 °C, corresponding to the thermal degradation of PVA. The TGA thermogram of drug-loaded PVA hydrogel exhibits four-steps weight loss. The first and gradual transition starting at 60 °C is due to the loss of moisture, and the second transition occurring at 160 °C is the melting point of SSA. The third transition at 230 °C is the thermal degradation of PVA, and lastly the fourth transition at 400 °C also belong to the secondary degradation of PVA. The TGA thermogram results are self-consistent with those of the DSC results. The presence of SSA (drug) appears to expedite the primary thermal degradation of the pure PVA matrix. It is well known that PVA is a semicrystalline polymer which exhibites a strong intermolecular interaction through hydrogen bonding between the hydroxyl group and the ionic drug (Hidalgo et al., 1999; Wu et al., 2006). In summary, the thermal events described support the FTIR results that SSA (drug) interacts with the PVA matrix.

3.1.3. Swelling behavior of drug-loaded PVA hydrogel

The PVA hydrogels were prepared by varying the crosslinking ratio defined as the amount of glutaraldehyde over the amount of PVA used. The effect of the crosslinking ratio on the swelling behavior, the molecular weight between crosslinks, the mesh size, and the drug diffusion characteristics are discussed below.

Fig. 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, and PVA_5.0) after immersions in the acetate buffer solution at 37 °C for 5 days. The results show that the degree of swelling and the weight loss decrease with increasing crosslinking ratio. A lower crosslinked hydrogel has longer PVA strands between crosslinks or a looser network; it

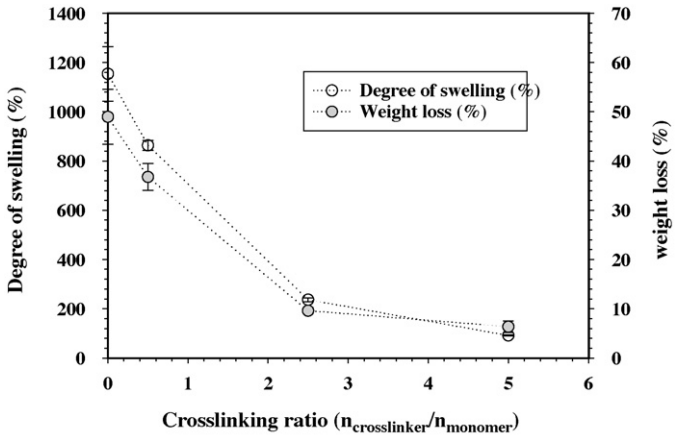

Fig. 4. Degree of swelling (%) and weight loss (%) of poly(vinyl alcohol) hydrogels at various crosslinking ratios (PVA_0, PVA_0.5, PVA_2.5, and PVA_5.0) after immersions in the acetate buffer solution at 37 °C for 5 days; each data point is an average value taken from five samples.

can swell more and its pore size is evidently larger, as shown in the SEM image of PVA hydrogel after swelling (Fig. 5).

The swelling data of Fig. 4 can be used to evaluate the crosslinked structure of these hydrogels. The molecular weight between crosslinks, the mesh size, and the crosslinking density are parameters (Eqs. (3)–(5)) used for characterizing the porous structure of the hydrogel for the drug delivery system. These parameters are determined from the equilibrium swelling theory as developed by Peppas and Wright (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 weights between crosslinks and the mesh size of the PVA hydrogels are larger at lower crosslinking ratios. The mesh size of the hydrogels varies between 36 and 230 Å with no voltage applied, and between 33 and 250 Å with electrical voltage difference of 1 V applied. The corresponding crosslinking density varies between 18.36×10^4 and 0.95×10^4 mol/cm^3 with no voltage applied, and 22.36×10^4 and 0.83×10^4 mol/cm^3 with electrical voltage difference of 1 V applied. Thus, the comparison of the mesh size values between the system with electric field and without electric field suggests that the electric field has no apparent effect on the PVA structure.

The morphologies of hydrogels with and without electric field are shown in SEM micrographs of Figs. 5–7. Fig. 5a–c shows the morphologies of PVA of various crosslinking ratios after swelling without electric field. The pictures clearly show that the typical porous structures are present and that the corresponding pore sizes are larger at lower crosslinking ratios. Fig. 6a–c shows the corresponding morphologies of PVA without crosslinking after swelling under electric field strengths of 0, 1, and 5 V, respectively. Evidently, the pore sizes without electric field are nearly the same as those under electric field. Fig. 7a–c shows the corresponding morphologies of the crosslinked PVA_2.5 after swelling and under electric field strengths of 0, 1, and 5 V, respectively. Finer and slightly smaller pore sizes are visibly present without electric field relative to those of the PVA under electric field.

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 into the PVA solution. The actual amount of drug present in the sample is about 93.1 ± 5.8%. To study sulfosalicylic acid

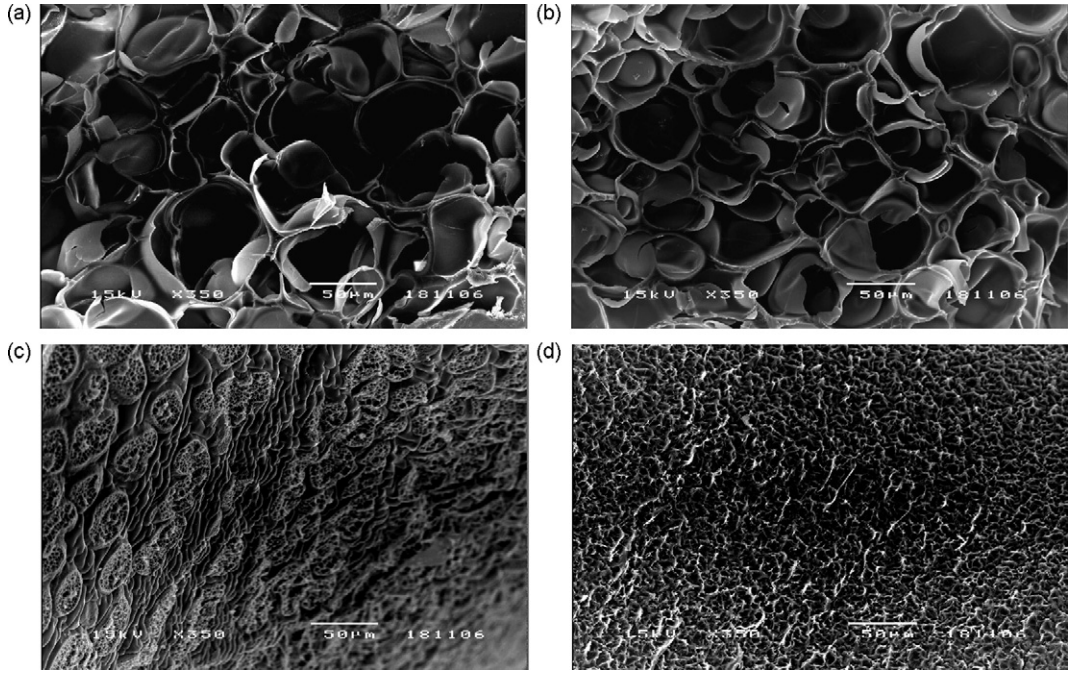

Fig. 5. The morphology of poly(vinyl alcohol) after swelling: (a) PVA_0; (b) PVA_0.5; (c) PVA_2.5; (d) PVA_ 5.0 at magnification of 350.

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 (Å)		Crosslinking density (mol/cm^3 × 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

transport mechanism from the PVA hydrogels, various diffusion models are considered to fit the experimental data.

The model is described by the Ritger–Peppas equation (Venkatesh et al., 1992):

$$\frac{M_t}{M_\infty} = k_1 t^n \tag{6}$$

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

In particular, the Higuchi's equation (Serra et al., 2006) is described by the Fickian diffusion of the drug:

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \tag{7}$$

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 the Higuchi equation (A-sasutjarit et al., 2005):

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \tag{8}$$

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 apparent diffusion coefficient of a drug. We may note the apparent diffusion coefficients obtained from Eqs. (7) and (8) are valid over an initial period of time and based on Fick's laws.

3.2.1. *Effect of crosslinking ratio*

The amounts of sulfosalicylic acid released from the sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogels at various crosslinking ratios (PVA_0, PVA_0.5, PVA_2.5, and PVA_5.0) vs. t and $t^{1/2}$ in the absence of electric field during 48 h are illus-

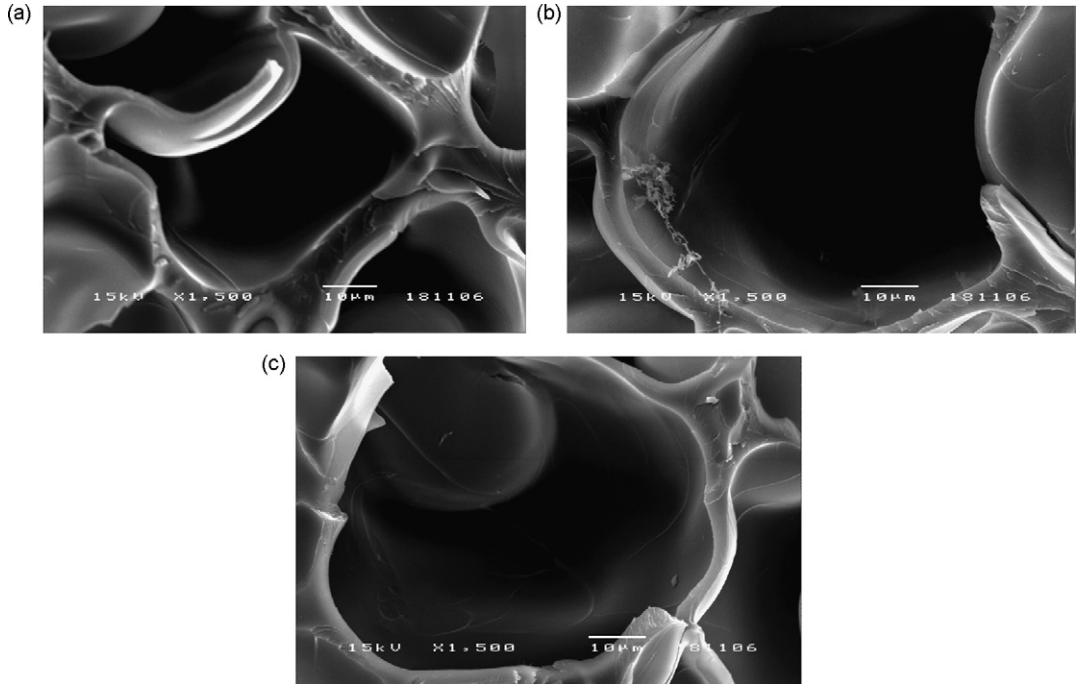

Fig. 6. The morphology of poly(vinyl alcohol) (PVA_0) after swelling under electric field strength of: (a) 0 V; (b) 1.0 V; (d) 5 V at magnification of 1500.

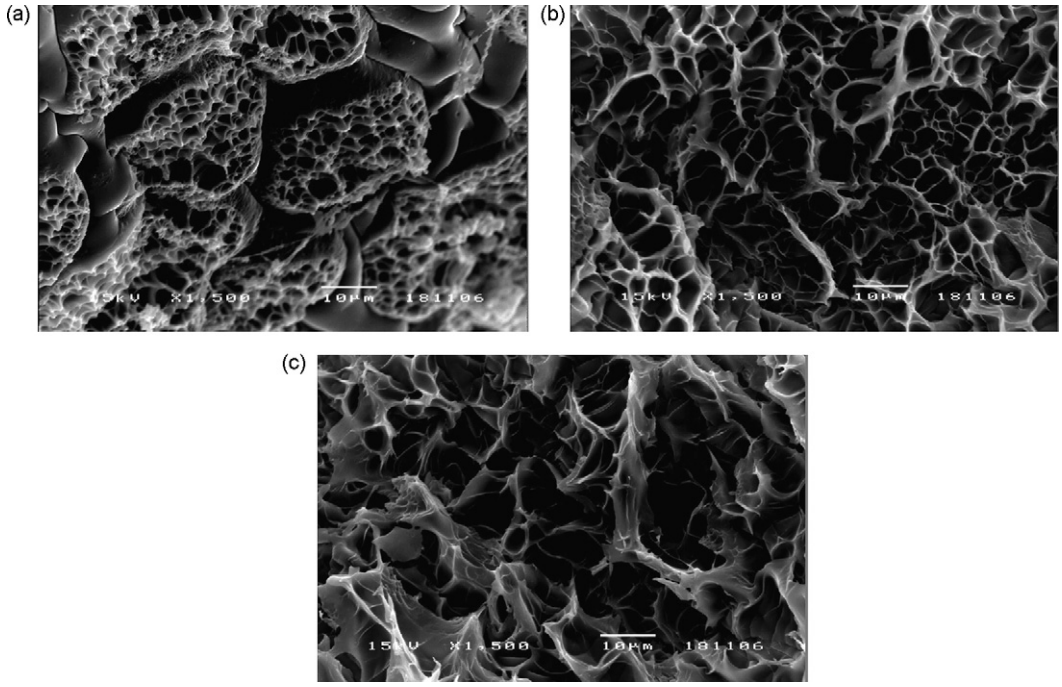

Fig. 7. The morphology of poly(vinyl alcohol) (PVA_2.5) after swelling under electric field strength of: (a) 0 V; (b) 1.0 V; (d) 5 V at magnification of 1500.

trated in Figs. 8 and 9, respectively. The amounts of drug released gradually increase with time and then reach equilibrium values. The plots of the amounts of drug released as functions of square root of time show a linear relationship over a limited period of time. The amount of drug released at a particular time t increases with decreasing crosslinking ratio due to a larger pore size which contributes to the observed susceptibility to swelling in aqueous medium (see Fig. 4). The degree of swelling of drug-loaded PVA hydrogel decreases with increasing crosslinking agent or glutaraldehyde concentration in the hydrogels. With increasing crosslinking agent, the crosslink reaction forming the ether linkages between the hydroxyl groups in poly(vinyl alcohol) with the aldehyde groups in glutaraldehyde is amplified (Yeom and Lee, 1996).

From the data of Fig. 8 and a plot of $\ln(M_t/M_\infty)$ vs. $\ln(t)$ over the total experimental period of 48 h, the scaling exponent n of Eq. (6) was determined and is tabulated in Table 2. The n value of uncrosslinked PVA hydrogel without electric field is 0.58, close the Fickian exponent value of $n = 0.5$. Thus, the amount of sulfosalicylic acid released from the uncrosslimked PVA matrix is predominantly controlled by the Fickian diffusion mechanism. For crosslinked PVA without electric field, the scaling exponent n increases with crosslinking ratio, from 0.58, 0.72, 0.77, to 0.82 for PVA hydrogels with crosslinking ratios of

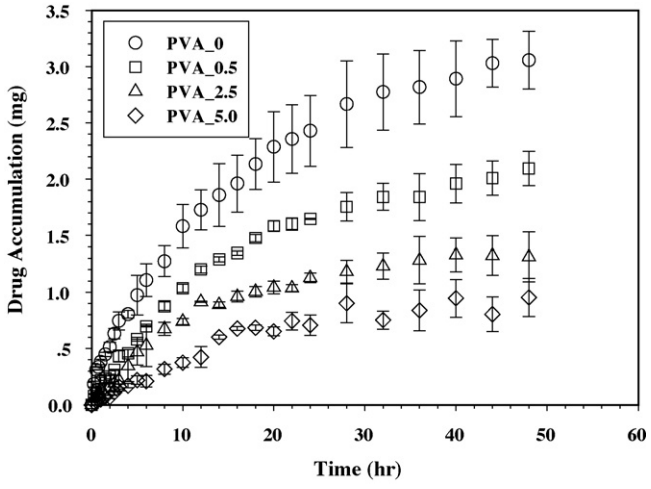

Fig. 8. Amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel vs. time at various crosslink ratios, $E = 0$ V, pH 5.5, 37 °C, each data point is an average value from two samples.

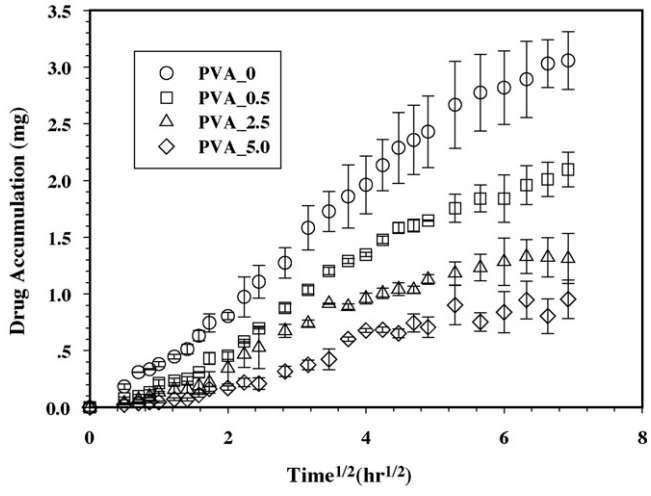

Fig. 9. Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel vs. $t^{1/2}$ at various crosslink ratios, $E = 0$ V, pH 5.5, 37 °C, each data point is an average value from two samples.

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

Sample	Crosslinking ratio	Diffusional scaling exponent (n)		Kinetic constant (k_H)(h^{-n})		r^2	
		$E=0$ 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

0, 0.5, 2.5, and 5, respectively. Therefore, the drug release, without electric field on, deviates further from the Fickian diffusion towards the anomalous case as crosslinking ratio is increased. With electric field on at 1 V, the scaling exponent n increases from 0.63, 0.83, 0.93, and 0.93, respectively. Thus, the effect of crosslinking drives away the drug release mechanism from the Fickian diffusion towards the anomalous case, with or without electric field on. As tabulated in Table 2, the effect of electric field is to increase slightly the scaling exponent n for a given PVA matrix.

The diffusion coefficients of each system are calculated from the slopes of the plots in Fig. 9 over a limited period of time using the Higuchi's equation (Eq. (8)). Fig. 10 shows the diffusion coefficients of sulfosalicylic acid from the poly(vinyl alcohol) hydrogels vs. crosslinking ratio and the mesh size at electric field strengths of 0 and 1 V at 37 °C. Sulfosalicylic acid diffusion coefficients in each system can be ranked in the following order: PVA_0 > PVA_0.5 > PVA_2.5 > PVA_5.0. The diffusion coefficient of sulfosalicylic acid from PVA hydrogel increases with decreasing crosslinking ratio due to the larger pore size (Dai and Barbari, 1999). For a given crosslinking ratio or mesh size, the diffusion coefficient is higher under electric field. This is a direct result of the electrostatic force driving the negatively charged drug, sulfosalicylic acid (Massoumi and Entezmi, 2001) towards the oppositely charged electrode (Jensen et al., 2002). Table 3 shows the ratio of the drug size over the mesh size (a/ξ) and the diffusion coefficients of drug from the PVA hydrogels at various conditions. The diffusion coefficients of drug from PVA hydrogels are larger at lower ratios between drug size and mesh size (a/ξ). The diffusion coefficients of sulfosalicylic acid from the PVA hydrogels vary between 2.76×10^{-10} and 2.08×10^{-9} cm^2/s under zero electric field and between 1.97×10^{-9} and 7.42×10^{-9} cm^2/s under applied electric field of 1 V. Hickey and Peppas (1997) studied the dif-

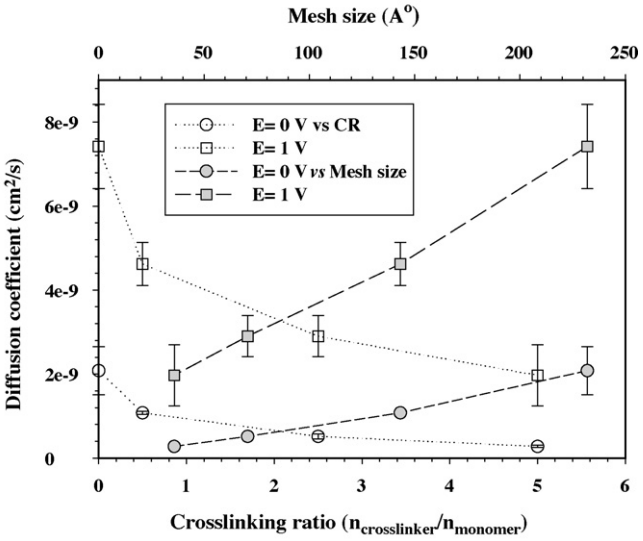

Fig. 10. Diffusion coefficient of sulfosalicylic acid from poly(vinyl alcohol) hydrogels vs. crosslinking ratio and mesh size at electric field strengths of 0 and 1 V, pH 5.5, 37 °C, each data point is an average value from two samples.

Table 3
The ratio of drug size and mesh size (a/ξ) and the diffusion coefficients of the drug from PVA hydrogels at various conditions

Solute			PVA mesh size, ξ (Å)	a/ξ	Diffusion coefficient (cm^2/s)	Condition			
	M_w	Size, a (Å)				T (°C)	pH	E	
Sulfosalicylic acid	254	9.25	232	0.04	2.08×10^{-9}	37	5.5	–	Uncrosslink
			143	0.06	1.08×10^{-9}	37	5.5	–	Crosslinking ratio = 0.5
			71	0.13	5.13×10^{-10}	37	5.5	–	Crosslinking ratio = 2.5
			36	0.26	2.76×10^{-10}	37	5.5	–	Crosslinking ratio = 5.0
			250	0.04	7.42×10^{-9}	37	5.5	1	Uncrosslink
			150	0.06	4.62×10^{-9}	37	5.5	1	Crosslinking ratio = 0.5
			85	0.11	2.90×10^{-9}	37	5.5	1	Crosslinking ratio = 2.5
			33	0.28	1.97×10^{-9}	37	5.5	1	Crosslinking ratio = 5.0
Theophylline[a]	180	3.7	195	0.02	3.07×10^{-7}	25	7	–	10 wt.% PVA, freezing-20/2, thawing 25/5, no. 3
			71.7	0.05	1.33×10^{-7}	25	7	–	15 wt.% PVA, freezing-20/9, thawing 25/3, no. 4
FITC-dextran[a]	4400	16.5	195	0.08	5.28×10^{-8}	25	7	–	10 wt.% PVA, freezing-20/2, thawing 25/5, no. 3
			71.7	0.23	1.70×10^{-8}	25	7	–	15 wt.% PVA, freezing-20/9, thawing 25/3, no. 5

Diffusion coefficient of SSA in water at 37 °C is 7.67×10^{-3} cm^2/s.
[a] Hickey and Peppas (1997).

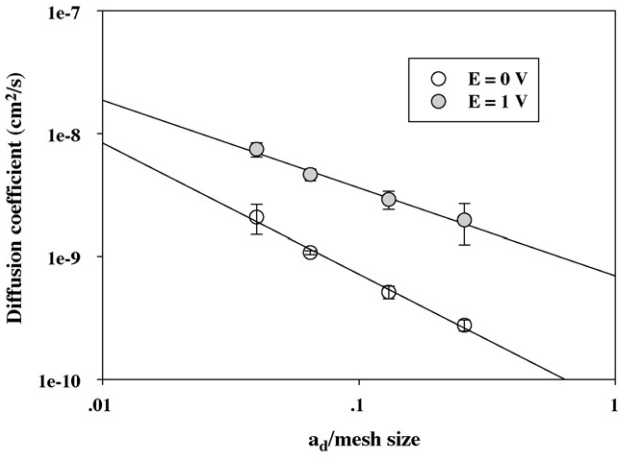

Fig. 11. Diffusion coefficient of sulfosalicylic acid poly(vinyl alcohol) hydrogels vs. drug size/mesh size of hydrogels at electric field strengths of 0 and 1 V, pH 5.5, 37 °C, each data point is an average value from two samples.

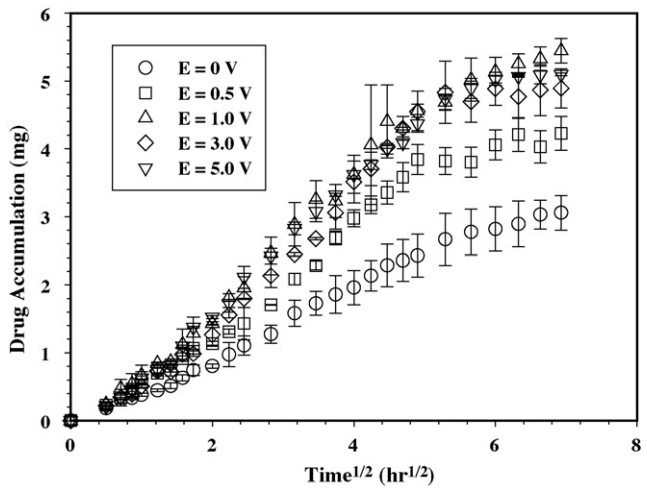

Fig. 12. Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel at time t vs. $t^{1/2}$ at various electric field strength, crosslinking ratio = 0, pH 5.5, 37 °C, each data point is an average value from two samples.

fusion coefficients of theophylline and FITC-dextran through PVA membranes. The diffusion coefficients of theophylline and FITC-dextran through PVA membranes are 3.07×10^{-7} and 5.28×10^{-8} cm^2/s, respectively. Based on these data, the diffusion coefficients of theophylline and FITC-dextran through PVA membranes are higher than the diffusion coefficients of sulfosalicylic acid from PVA hydrogels. The diffusion of theophylline and FITC-dextran is governed by the drug molecules diffusing through the membranes as driven by the osmotic pressure. The apparent diffusion of sulfosalicylic acid obtained in our experiments is governed by the drug molecules diffusing out of the membranes through the concentration gradient effect in the absence of electric field and the electrophoresis of the anionic drug under applied electric field. Thus the diffusion coefficient of the drug in our transdermal delivery system depends on many factors: the chemical composition of the drug; the drug molecular weight, the size of the drug; the polymer matrix; the drug–matrix interaction; and the experimental set up. The appropriate theory for the calculating the drug release with multiple driving forces is available (Kok et al., 2000).

Fig. 11 shows the log–log plot of diffusion coefficients of sulfosalicylic acid from the poly(vinyl alcohol) hydrogels vs. drug size/mesh size ratio of the hydrogels at electric field strengths of 0 and 1 V at 37 °C. From this figure, the diffusion coefficient obeys the scaling behavior:

$$D = D_0 \left(\frac{a}{\xi} \right)^{-m} \tag{4}$$

where D is the diffusion coefficient of the drug; D_0 is the diffusion coefficient in the limit of $a = \xi$, a is the size of drug; ξ is the mesh size of the 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 pigskin under electric field strengths of 0 and 1 V are 1.07 and 0.71, respectively. D_0 values are 6.17×10^{-11} and 6.92×10^{-10} cm^2/s, respectively. We may note that the diffusion coefficient here belongs to the drug permeation through the PVA matrix and the pigskin into the buffer solution, with and without the additional driving force from the electric field.

3.2.2. *Effect of electric field strength*

Fig. 12 shows the amounts of sulfosalicylic acid released from the sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogels with crosslinking ratio of 0 vs. $t^{1/2}$ under various electric field strengths. Here the samples were attached to the negatively charged electrode (cathode). From Fig. 12, it is evident that the amount of released drug and the diffusion coefficients increase with increasing electric field strength. A higher electric field strength induces a higher electrostatic force which drives the negatively charged drug through the polymer matrix (Kantaria et al., 1999). It is known that the mass of drug delivered across the skin is proportional to the applied current and duration of current application (Sage and Riviere, 1992). In addition, the electric field may and can create the transient micropores in the liophilic stratum corneum in the pigskin allowing an easier transport of the drug through the pathways (Weaver et al., 1999). Fig. 13 shows the diffusion coefficient of sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogels with crosslinking ratio of 0 vs. electric field strength as determined from the data of Fig. 12 using Eq. (8).

The diffusion coefficient increase from 2×10^{-9} to 7.5×10^{-9} cm^2/s as electric field increase from 0 to 1 V. Beyond electric field of 1 V, it decreases towards a constant value of 7×10^{-9} cm^2/s.

3.2.3. *Effect of electrode polarity*

Fig. 14 shows the amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel with crosslinking ratio 0 vs. $t^{1/2}$ under the negatively charged electrode (anode in donor), and the positively charged electrode (cathode in donor), and under no current system delivery over a period of 48 h. The amount of drug released and the corresponding diffusion coefficient tabulated in Table 4 under cathode

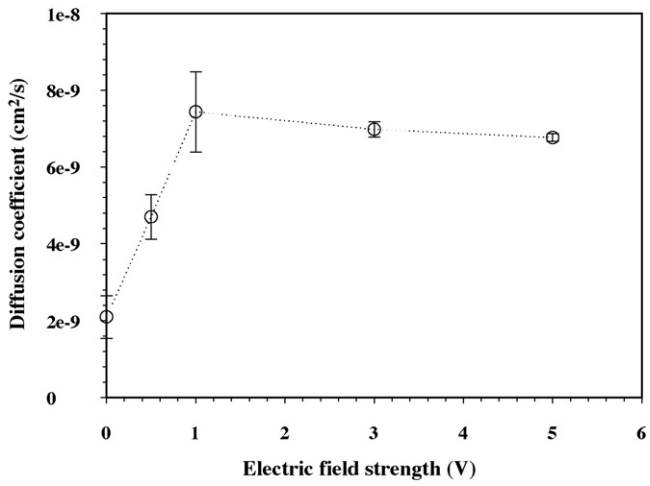

Fig. 13. Diffusion coefficients of sulfosalicylic acid from poly(vinyl alcohol) hydrogel vs. electric field strength at crosslinking ratio of 0, pH 5.5, 37 °C, each data point is an average value from two samples.

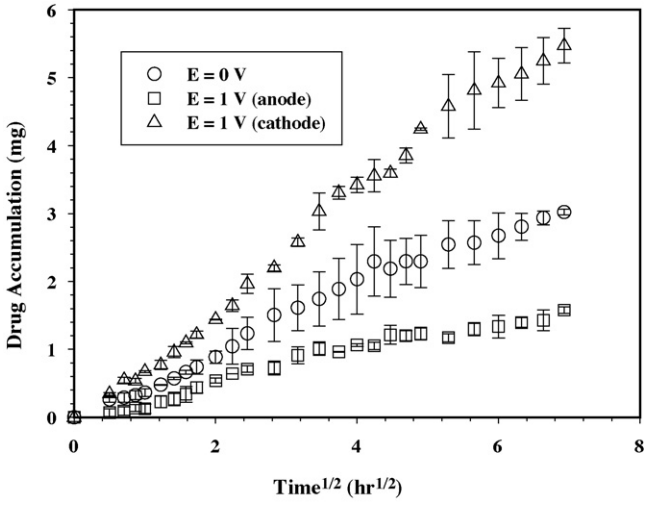

Fig. 14. Amounts of sulfosalicylic acid release from sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogel vs. $t^{1/2}$ with the samples attached to the anode or the cathode, crosslinking ratio of 0, pH 5.5, 37 °C, each data point is an average value from two samples.

are higher than those under zero electric field and under anode. This is a direct result of the electrorepulsion between the negatively charged drug and negatively charged electrode driving the charged drug through the polymer matrix and the pigskin into the buffer solution (Green, 1996). Passive delivery (with no electric field) results in a lower permeation. With the same electric field and under anode, the amount of drug released and the diffusion coefficient are lowest amongst the three cases, since the positively charged electrode tends to retard the drug diffusion through the PVA matrix and the pigskin. Sulfosalicylic acid is a model drug with a negative charge at pH 5.5 and this study establishes that its release rate can be altered to be higher and lower than that under no electric field.

Table 4
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	S.D.
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

4. Conclusions

The sulfosalicylic acid-loaded poly(vinyl alcohol) hydrogels were prepared at various crosslinking ratios to evaluate the diffusion coefficient and to study the release mechanism of the model drug from poly(vinyl alcohol) hydrogels with and without electric field. Each hydrogel was characterized for its mesh size and its swelling ability. The degree of swelling, the weight loss, and the mesh size of PVA hydrogels decrease with increasing crosslinking ratio. The diffusion coefficients were measured as functions of crosslinking ratio, the mesh size, electric field strength, and the electrode polarity. For the effect of crosslinking ratio, the diffusion coefficient of the drug from PVA hydrogel increases with decreasing crosslinking ratio because of a larger mesh or pore size. For the effect of electric field strength, the diffusion coefficient of drug from PVA hydrogel increases with increasing electric field strength due to a higher electrostatic force driving the negatively charged drug through the polymer matrix and the pigskin. For the effect of electrode polarity, the diffusion coefficient of drug under cathode is apparently higher than those under anode and under no current due to the electrorepulsion between the negatively charged drug and the negatively charged electrode. It is possible to conclude that by varying crosslinking density, the electric field, or by changing the electrode polarity, we can control and modulate the drug release rate.

Acknowledgements

The authors would like to acknowledge the financial supports from the Conductive and Electroactive Polymers Research Unit and KFAS of Chulalongkorn University, the Petroleum Petrochemical and Advanced Materials Consortium, Royal Thai Government (Budget of Fiscal Year 2550), and the Thailand Research Fund (TRF-BRG).

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