Research Article

Electric Field-Controlled Benzoic Acid and Sulphanilamide Delivery from Poly (Vinyl Alcohol) Hydrogel

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Abstract. The controlled release of benzoic acid (3.31 Å) and sulphanilamide (3.47 Å) from poly(vinyl alcohol), PVA, hydrogels fabricated by solution casting at various cross-linking ratios, were investigated. The PVA hydrogels were characterized in terms of the degree of swelling, the molecular weight between cross-links, and the mesh size. The drug release experiment was carried out using a modified Franz diffusion cell, at a pH value of 5.5 and at temperature of 37°C. The amount of drug release and the diffusion coefficients of the drugs from the PVA hydrogels increased with decreasing cross-linking ratio, as a larger mesh size was obtained with lower cross-linking ratios. With the application of an electric field, the amount of drug release and the diffusion coefficient increased monotonically with increasing electric field strength, since the resultant electrostatic force drove the ionic drugs from the PVA matrix. The drug size, matrix pore size, electrode polarity, and applied electric field were shown to be influential controlling factors for the drug release rate.

KEY WORDS: electrophoresis force; ionic drug delivery; iontophoresis; poly(vinyl alcohol).

INTRODUCTION

A major research area thrust in the transdermal drug delivery (TDD) field has been the development of controlled release systems for drugs and bioactive agents through the skin into the blood system. Many of the delivery systems in use and under development consist of a drug dispersed within a polymeric matrix carrier. The purpose of developing controlled release systems is to successfully deliver a drug at a specified rate in a given time period. TDD is the system that delivers a drug through hydrophobic human skin (stratum corneum) to the blood system. The limitation of an ionic drug, which cannot easily penetrate through the hydrophobic skin, can be overcome by an applying external electric field. When the external electric field is applied to a TDD system, the electrostatic force between the ionic drug and the electrode will drive the ionic drug through the skin. In addition, the electric field can generate a micropathway through the skin (1).

The external electric field TDD method or iontophoresis TDD plays an important role in the TDD industrial sector because it can accurately control the diffusion rate and amount of drug release at a particular therapeutic level by adjusting the electric field strength. There are a number of factors that influence iontophoretic transport: pH of skin, drug concentration in TDD patch, drug characteristics, molecular size of drug, current, voltage, application time, and skin resistance (2).

One of the major types of polymers that has been identified for use in controlled release applications is hydrogels (3). They are cross-linked polymer networks that are generally not soluble; however, they are able to swell in water or biological fluids. Hydrogels can be either natural or synthetic superabsorbent polymers. They have flexibility similar to a natural tissue, due to their significant water content. Therefore, they have been widely used as carriers for drug delivery applications (4,5). Diffusion is the main mechanism for controlling the drug release from a hydrogel-based drug delivery system. The drug release *via* a hydrogel system occurs by diffusion through the macromolecular mesh or through water filled pores (6). Poly(vinyl alcohol), PVA, is a well-defined hydrogel. It is biocompatible, non-toxic, water permeable, and swells easily, all of which can contribute to the application of the matrix in TDD applications (7).

In order to obtain a tailor-made hydrogel system for drug release applications, the fundamental mechanism of drug transport through the hydrogel membranes must be understood completely at certain conditions. In the present work, we investigated the mechanism of drug diffusion through hydrogels as well as the importance of network morphology in controlling the transport of drugs in hydrogels by applying an electric field or not (8,9). The effects of drug size, electric field strength, and matrix pore size on the diffusions of benzoic acid (3.31 Å) and sulphanilamide (3.47 Å) through a poly(vinyl alcohol) hydrogel system are systematically investigated.

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MATERIALS AND METHODS

Materials

Poly (vinyl alcohol), PVA, (degree of polymerization $\approx$ 1,600, degree of hydrolysis $\approx$ 97.5 to 99.5 mol% with M_n = 72,000) was supplied by Fluka, Switzerland. Model drugs, benzoic acid and sulphanilamide, were purchased from Ajax Chemicals, Australia. A cross-linking agent, glutaraldehyde [50% (*w/v*) in water], was obtained from Fluka. Sodium acetate (Ajax Chemicals, Australia), sulfuric acid (Merck, Germany), methanol (BDH, England), and glacial acetic acid (Merck, Germany) were of analytical reagent grade.

Methods

Preparation of Drug-Loaded PVA Hydrogels

To prepare a PVA solution, 10% (*w/v*) of PVA powder was weighed and dissolved in distilled water at 80°C for 3 h. The obtained solution was cooled to room temperature. Subsequently, the model drug (benzoic acid, 3.31 Å or sulphanilamide, 3.47 Å) was added to the PVA solution in the proportion of 1:10 (weight of model drug:weight of PVA powder) followed by a constant stirring for 1 h. For the cross-linked PVA, glutaraldehyde was used as the cross-linking agent to produce various cross-linking ratios. The cross-linking ratio, *X*, was defined as the ratio of moles of the cross-linking agent to moles of the PVA repeating unit. The solution mixtures consisted of 25% (*w/v*) glutaraldehyde, 10% (*w/v*) sulfuric acid as the catalyst, 50% (*w/v*) methanol as the quencher, and 10% (*w/v*) acetic acid as the pH controller, corresponding to the solution weight ratios of 2:1:2:3, respectively, were added to the PVA solutions in order to vary *X*. To prevent the formation of air bubbles, the solution was mixed very slowly. After mixing the solution, the mixture was dry cast on a mold (diameter of 9 cm) directly, then dried in a dust-free atmosphere at 60°C for 3 h, and finally cooled to room temperature (10,11).

Characterization

PVA Hydrogel Charaterization

To investigate the morphology of swollen PVA hydrogels at various cross-linking ratios with and without an electric field, scanning electron micrographs (SEM) of the hydrogels were taken (JEOL, JSM-5200-2A) using an acceleration voltage of 15 kV and a magnification of 350. To study the effect of the electric field on the PVA morphology, the hydrogels were swollen in an acetate buffer of pH 5.5, then attached to a copper electrode. The other electrode was placed elsewhere in the acetate buffer. Samples were prepared from frozen swollen hydrogels with and without an electric field in liquid nitrogen and dried in a vacuum at −50°C (11,12).

To determine the degree of swelling and the weight loss of the PVA hydrogels, experiments were carried out in an acetate buffer solution at 37°C for 5 days, and the degree of swelling and weight loss were calculated using Eqs. 1 and 2, respectively (11):

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

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

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

To determine the molecular weight between cross-links, $\overline{M}_c$, the mesh size, ξ, and the cross-linking density, ρ_x, a PVA film sample was cut after cross-linking. The sample was weighed in air and heptane. Then, the sample was placed in distilled water at 37°C for 5 days to allow it to swell to equilibrium, and was weighed in air and heptane again. Lastly, the sample was dried at 25°C in a vacuum oven for 5 days and was weighed in air and heptane a final time. Three different weights were used to calculate the polymer volume fraction (10).

The value of the molecular weight between cross-links, $\overline{M}_c$, was calculated from the swelling data as in Eq. 3 (10):

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

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

The mesh size of the hydrogel, ξ, describes the linear distance between consecutive cross-links. It indicates the diffusional space available for solute transport and can be calculated by using Eq. 4 (13):

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

where C_n is the Flory characteristic ratio (C_n=8.3), *l* is the carbon–carbon bond length (*l*=1.54 Å), M_r is the molecular weight of the repeating unit of polymer, and $\overline{M}_c$ is the molecular weight between cross-links.

To determine the cross-linking density, ρ_x, of the cross-linked PVA, the value was calculated using Eq. 5 (14):

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

Drug Release Experiments

Preparation of Acetate Buffer

An acetate buffer solution (pH 5.5) was prepared by dissolving 150 g of sodium acetate in distilled water. Glacial acetic acid (15 ml) was added to the aqueous sodium acetate solution, and the total volume was adjusted with distilled water to 1,000 ml (11).

Spectrophotometer Analysis of Model Drug

To determine the maximum spectra of various model drugs, a UV–visible spectrophotometer (Shimadzu, UV-2550) was used to measure the maximum absorption wavelength of the model drugs in the acetate buffer solution pH 5.5. In the present work, benzoic acid and sulphanilamide were used as the model drugs. The characteristic UV absorbance peaks of benzoic acid and sulphanilamide that were used for identifications were at 234 and 260 nm, respectively. The model drug concentrations were calculated from the calibration curves between the UV peaks and the model drug concentration (11).

Transdermal Transport Studies

In this experiment, a custom-made modified Franz diffusion cell was used for the diffusion study (Fig. 1). The diffusion cell was comprised of a donor and a receptor compartment. The donor compartment was exposed to ambient conditions, and the receptor compartment was filled with the acetate buffer solution (pH 5.5) and maintained at 37°C by using a circulating water bath. In the study of effect of the cross-linking ratio, the drug-loaded PVA hydrogels of various cross-linking ratios (0.0, 1.0, 2.0, and 5.0) were mounted in the donor compartment. For the electric field study, a copper electrode was connected to a power supply that provided various electrical potentials (0.0, 1.0, 2.0, 3.0, and 5.0 V). The drugs diffused through the polymer matrix towards the solution. The amounts of drug concentrations were determined by using the UV–visible spectrophotometer at a wavelength of 235 and 260 nm for the benzoic acid and sulphanilamide, respectively (12).

Mathematical Analysis

Mathematical Analysis of the Drug Transport Mechanism

There are several diffusion models that are commonly used to fit the experimental data to investigate the drug transport mechanism of hydrogels:

One model is the Ritger–Peppas equation (15):

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

where M_t/M_α is the fractional drug release, k_1 is a kinetic constant (with units of t^{-n}), t is the release time, and n is the diffusion exponent that is related to the drug transport mechanism. For a thin hydrogel film, when $n=0.5$, the drug release mechanism is known as the Fickian diffusion of case I. When $n=1$, or case II, there is a zero-order release or a linear release. Where n is between 0.5 and 1, it is known as the non-Fickian or the anomalous transport.

For $n=0.5$, the release is described by the Higuchi's equation (16) or the Fickian diffusion:

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

where M_t/M_α is the fractional drug release, k_H is the Higuchi's kinetic constant (with units of t^{-n}), and t is the release time.

The diffusion coefficients of the model drugs, benzoic acid and sulphanilamide from the PVA hydrogels can be calculated from the slopes that were obtained from the plots of drug mass accumulation against the square root of time according to the Higuchi's equation (12,17):

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

where Q is the amount of drug mass released per unit cross-section of the barrier (gram per centimeter square) as a function of time, t (second), M_t is the amount of drug release at time t (gram), A is the diffusion area (centimeter square), C_0 is the initial drug concentration in the hydrogel (gram per centimeter square), and D is the diffusion coefficient of the drug (centimeter square per second).

RESULTS AND DISCUSSION

Characterization

PVA Hydrogel Characterization

PVA hydrogels were prepared at different cross-linking agent concentrations to study the effect of the cross-linking ratio on the swelling behavior, the molecular weight between cross-links, the mesh size, and the drug diffusion characteristics. Figure 2 shows the degree of swelling and the weight loss of PVA hydrogels *versus* cross-linking ratio (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0) after the 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 cross-linking ratios. The lower cross-linked hydrogel tends to create
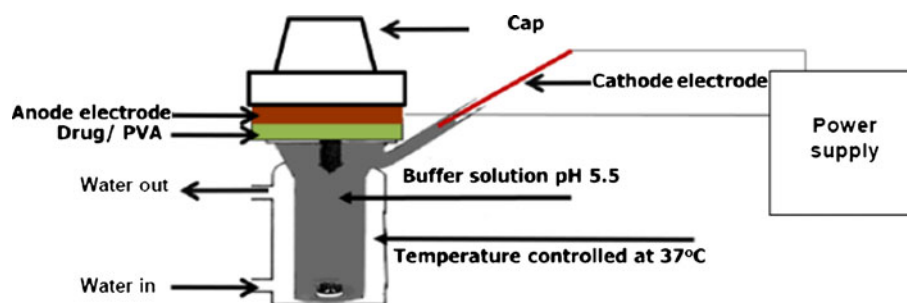
Fig. 1. The experimental set up for drug release characteristics of the drug-loaded PVA hydrogels
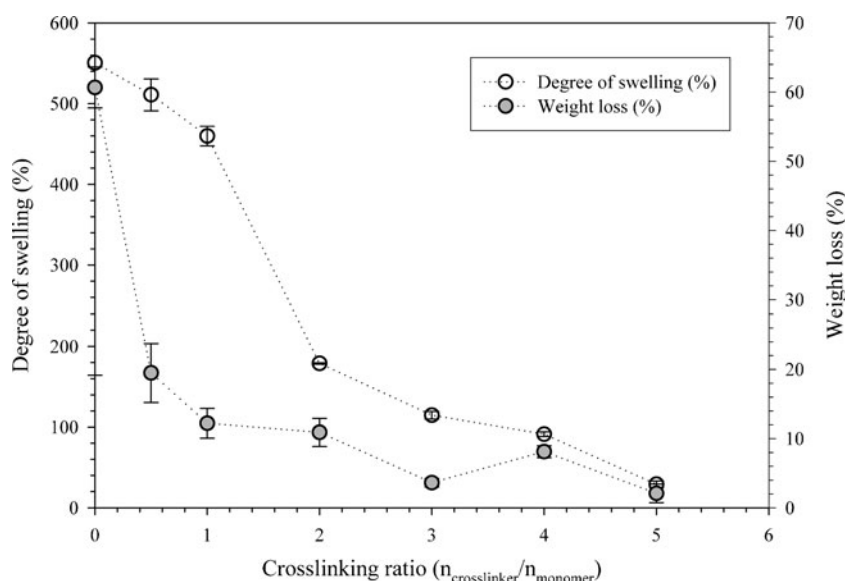
Fig. 2. Degree of swelling (percent) and the weight loss (percent) of PVA hydrogels at various cross-linking ratios (0.0, 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0) after immersion in an acetate buffer solution at 37°C for 5 days

a longer PVA strand between cross-links, thus producing a looser network that contributes to easier water diffusion into the hydrogel. Table I shows that the molecular weight between cross-link, $\overline{M}_c$, and the mesh size, ξ, of PVA hydrogels decreases with increasing crossinking ratios, corresponding to a smaller network mesh size and a less flexible structure, as also shown in SEM micrographs of swollen PVA hydrogels at various cross-linking ratios (Fig. 3). The SEM micrographs confirm the porous structure of the PVA hydrogels (Fig. 3a–d), which is suitable for the TDD application. The mesh sizes of the PVA hydrogels fall into a size range of 30 to 300 Å in the absence of an electric field and between 40 and 330 Å under an applied electric field. The cross-linking density value falls in a range of 20.60×10^4 to 0.70×10^4 mol/cm^3 without electric field strength and is in a range of 14.00×10^4 to 0.60×10^4 mol/cm^3 under an applied electric field, for the PVA hydrogels with the cross-linking ratio varied from 0.0 to 5.0. In comparing of the mesh size values with and without an electric field, it can be seen that the mesh size under applied electric field strength is slightly larger than that without electric field at any given cross-linking ratio (18).

Drug Release Kinetics from Drug-Loaded PVA Hydrogels

Effect of the Cross-Linking Ratio for Drug-Released Characteristics

For the study of PVA hydrogel mesh size on the drug release characteristics, drug-loaded PVA hydrogels were prepared at various cross-linking ratios, as shown in Fig. 3. The amounts of benzoic acid release from the PVA hydrogels are plotted against time (hour) without an electric field, as shown in Fig. 4. The amounts of benzoic acid released from benzoic acid-loaded PVA hydrogels monotonically increase with time until reaching equilibrium. The amount of drug release increases with decreasing cross-linking ratios; this is due to a larger pore size of the PVA hydrogel at a lower cross-linking ratio, which swells in the aqueous medium (11), as shown in Figs. 2 and 3. The release profiles, in Fig. 4, have two distinct periods. In the first period, the scaling exponent *n* value of the uncross-linked PVA hydrogel and the PVA hydrogels, with the cross-linking ratios of 0.5, 1.0, 2.0, and 5.0 without electric field strength varies between 0.35 and 0.61; the latter is close to the Fickian exponent value of *n*=0.5. From the obtained *n* values in the first period, the release mechanism

Table I. Molecular Weight Between Cross-links, Mesh Size, and Cross-Linking Density of PVA Hydrogels at Various Cross-Linking Ratios With and Without Electric Field Strength

| Sample	Cross-linking ratio, *X*	Number-average molecular weight between cross-links, $\overline{M}_c$ (g/mol)		Mesh size, ξ (Å)		Cross-linking density, ρ_x $(mol/cm^3 \times 10^4)$	
		E=0 V	*E*=1.0 V	*E*=0 V	*E*=1.0 V	*E*=0 V	*E*=1.0 V
PVA_0	0	17,400±1,400	19,700±1,800	300±9	330±100	0.70±0.10	0.60±0.30
PVA_0.5	0.5	8,300±600	9,800±700	200±7	200±80	1.60±0.30	1.50±0.30
PVA_1.0	1.0	5,100±500	6,600±100	180±15	200±10	1.90±0.30	1.70±0.40
PVA_2.0	2.0	3,200±300	3,800±700	120±20	170±60	2.70±0.50	2.60±1.40
PVA_3.0	3.0	1,900±400	2,500±800	70±10	90±30	7.00±1.50	5.50±2.00
PVA_4.0	4.0	1,200±300	1,600±300	50±100	60±10	11.40±2.80	8.30±1.60
PVA_5.0	5.0	700±200	800±200	30±7	40±10	20.60±7.80	14.00±4.30
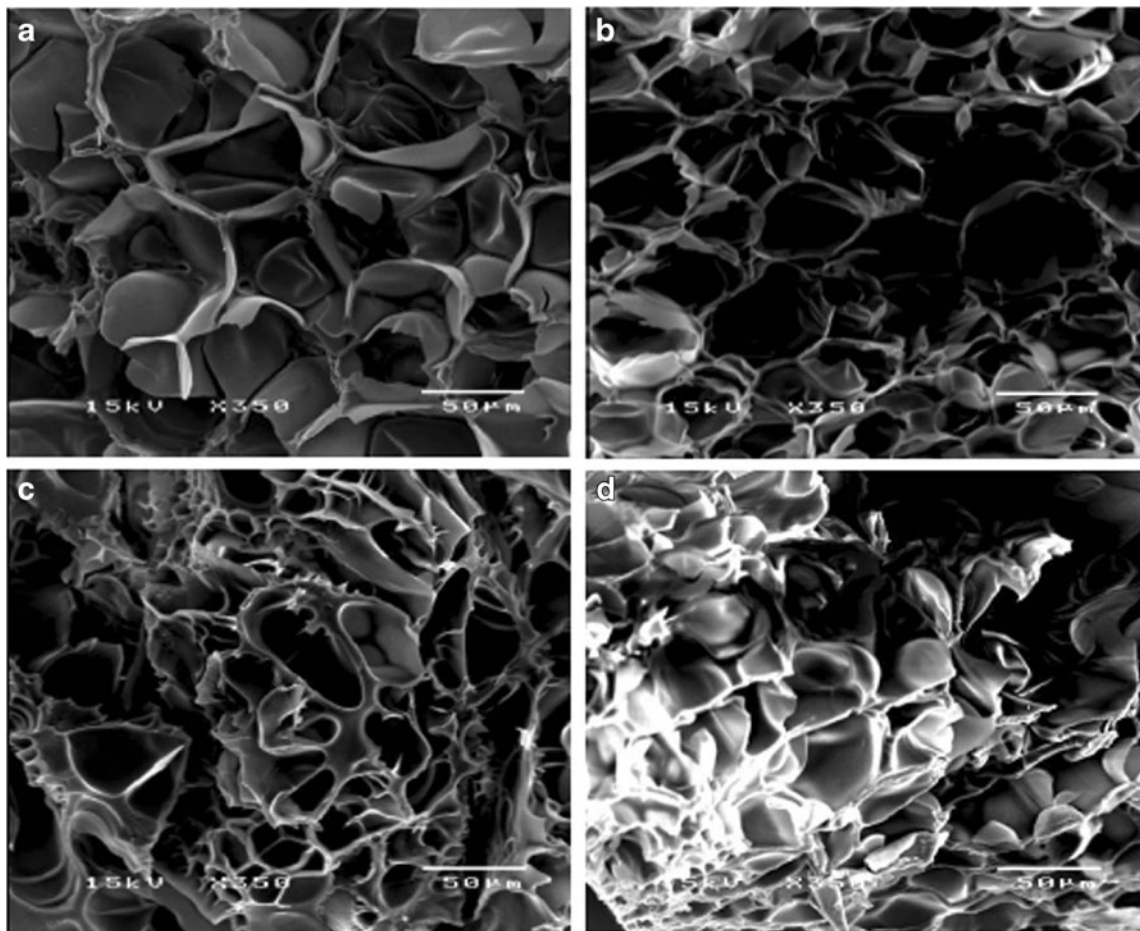
Fig. 3. Morphology of PVA hydrogel samples after swelling: **a** PVA_0; **b** PVA_2; **c** PVA_3; and **d** PVA_4

from the PVA hydrogels is representative of Fickian diffusion. In the second period, swelling of the polymer matrix allows water to dissolve the trapped drug molecules to diffuse outward (19,20).

The scaling exponent n value in the second period varies between 0.10 and 0.19. Table II summarizes the drug release kinetic parameters and the linear regression values. In the first
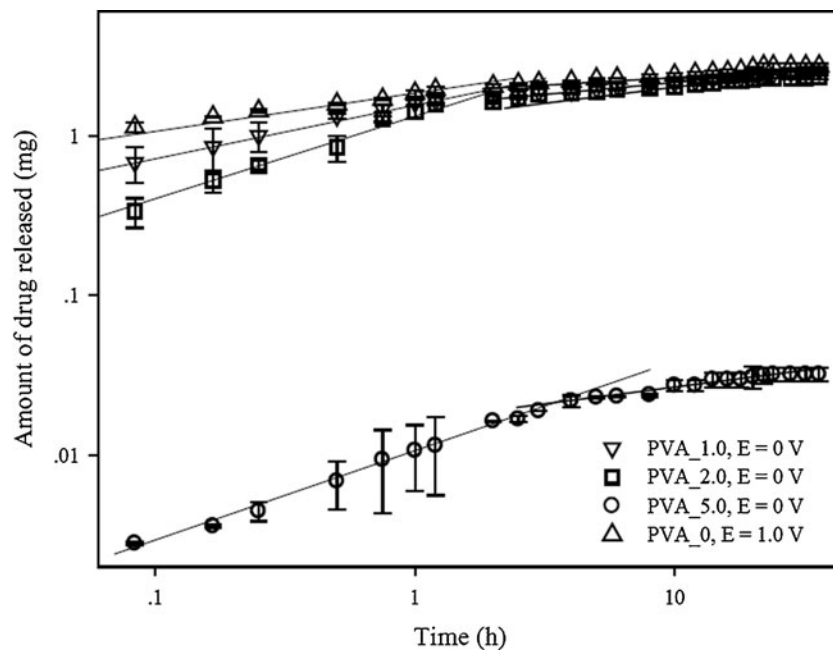

Fig. 4. Amounts of benzoic acid released from the benzoic acid-loaded PVA hydrogels over time, in the absence of electric field and under the electric field of 1.0 V, at pH 5.5, and 37°C

Table II. Release Kinetic Parameters and Linear Regression Values (Obtained from the Benzoic Acid Experimental Data) According to the Ritger–Peppas Model Without Application of an Electric Field

Sample	Cross linking ratio	Diffusional scaling exponent (*n*)		Kinetic constant (k_1)(t^{-n})		R^2	
		n_1	n_2	k_1	k_2	R_1^2	R_2^2
PVA_0	0	0.56	0.11	1.80	4.98	0.9537	0.9656
PVA_0.5	0.5	0.38	0.13	5.42	5.36	0.9971	0.9811
PVA_1.0	1.0	0.35	0.12	5.37	5.43	0.9967	0.9956
PVA_2.0	2.0	0.61	0.10	6.38	5.20	0.9756	0.9840
PVA_5.0	5.0	0.57	0.19	94.73	59.76	0.9920	0.9440

n_1, n_2 are the first period and the second period scaling exponents
k_{H1}, k_{H2} are the first period and the second period pre-factors

period, *n* is close to 0.5. Therefore, the data in the first period can be fitted to the Higuchi's equation (Eq. 7). The diffusion coefficient of each system is then calculated from the slope of the plot of the amount of drug released as a function of the square root of time according to Higuchi's equation (Eq. 8).

Figure 5 shows that the diffusion coefficient of benzoic acid from the PVA hydrogels decreases with increasing cross-linking ratio due to the smalle pore size, resulting in retarded drug diffusion (11,21). The diffusion coefficient decreases from 1.2×10^{-6} to 3.8×10^{-8} cm^2/s as the cross-linking ratio increases from 0.0 to 5.0, in the absence an electric field.

Effect of Electric Field Strength

In the effect of electric field strength study, the drug-loaded PVA hydrogels were prepared without cross-linking. Each drug-loaded PVA hydrogel sample was attached to a negatively charged electrode (cathode). The release kinetic parameters and the linear regression values of the uncross-linked hydrogel under various electric field strengths are tabulated in Table III.

The value of n_1 varies between 0.20 and 0.56 in the first period, the latter value is close to the Fickian diffusion. On the other hand, the n_2 value varies between 0.10 and 0.11 in the second period, implying the anomalous diffusion.

The diffusion coefficient values were obtained by plotting the amounts of benzoic acid released from the benzoic acid-loaded PVA hydrogels *versus* time$^{1/2}$, using Higuchi's equation, (Eq. 8), to calculate the diffusion coefficient value. Figure 6 shows that the diffusion coefficient increases with increasing electric field strength. The diffusion coefficient of PVA hydrogel increases from 1.20×10^{-6} to 6.90×10^{-6} cm^2/s as electric field strength increases from 0.0 to 5.0 V. It saturates at a value of 6.9×10^{-6} at and beyond 3.0 V. The greater electrostatic force is evidently due to the stronger electrical field strength, accelerating the negatively charged drug through the polymer matrix (11,22,23).

Effect of Electrode Polarity

Electrode polarity was next investigated by measuring the amount of benzoic acid released from the benzoic acid-
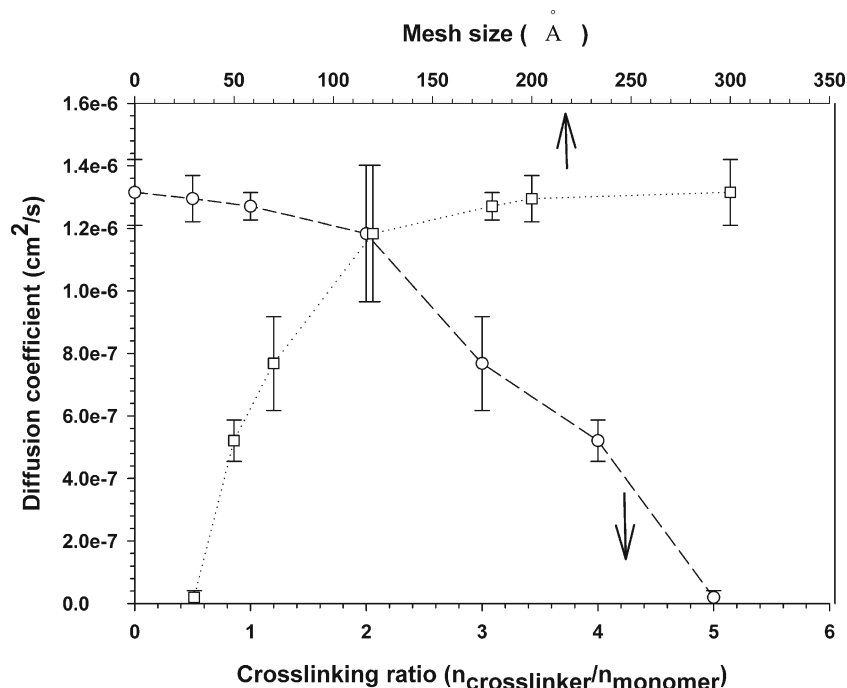

Fig. 5. Diffusion coefficient of benzoic acid from PVA hydrogels in relation to the mesh size and the cross-linking ratio without an electric field, at pH 5.5, and 37°C

Table III. Release Kinetic Parameters and Linear Regression Values Obtained from the Benzoic Acid Experimental Data According to the Ritger–Peppas Model at the Cross-linking Ratio of 0 Under Various Electric Field Strengths

Sample	Cross-linking ratio	E (V)	Diffusional scaling exponent (n)		Kinetic constant (k_1)(t^n)		R^2	
			n_1	n_2	k_1	k_2	$R_1^2 1$	$R_2^2 2$
PVA_0	0	0	0.56	0.11	1.80	4.98	0.9537	0.9656
PVA_0	0	1.0	0.20	0.11	4.05	4.68	0.9896	0.9910
PVA_0	0	2.0	0.38	0.10	3.76	4.60	0.9400	0.9834
PVA_0	0	3.0	0.20	0.10	3.86	4.51	0.9994	0.9835
PVA_0	0	5.0	0.38	0.10	2.87	4.56	0.9615	0.9874

n_1, n_2 are of the first period and the second period
k_{H1}, k_{H2} are of the first period and the second period

loaded PVA hydrogel under the negatively charged electrode (cathode in donor part) and the positively charged electrode (anode in donor part), under no electric current system, as shown in Fig. 7. The amount of drug released under cathode is higher than that under anode in the presence of an electric field at any given time. The electrorepulsion between the negatively charged drug and the negatively charged electrode is clearly the driving force for the charged drug through the polymer matrix (11,24). The amount of drug released under anode is lowest because the model drug, benzoic acid, is negatively charged at pH 5.5, and therefore the positively charged electrode hindered the drug from passing through the PVA matrix into the buffer solution (11).

The diffusion coefficients of the drug in the absence of an electric field, under anode and cathode with an electric field strength of 1.0 V are 1.24×10^{-6}, 3.27×10^{-7}, 4.10×10^{-6} cm^2/s, respectively.

In Fig. 8, the diffusion coefficient follows the scaling behavior as:

$$D = D_0 (a_d / \xi)^{-m} \qquad (9)$$

where D is the apparent diffusion coefficient of the drug, D_0 is the diffusion coefficient as the drug size approaches the mesh size, a_d is the size of the drug, ξ is the mesh size of the hydrogel, and m is the scaling exponent. In addition, this figure shows the comparison of the diffusion coefficients of the PVA hydrogels of various drug sizes; the diffusion coefficient values are tabulated
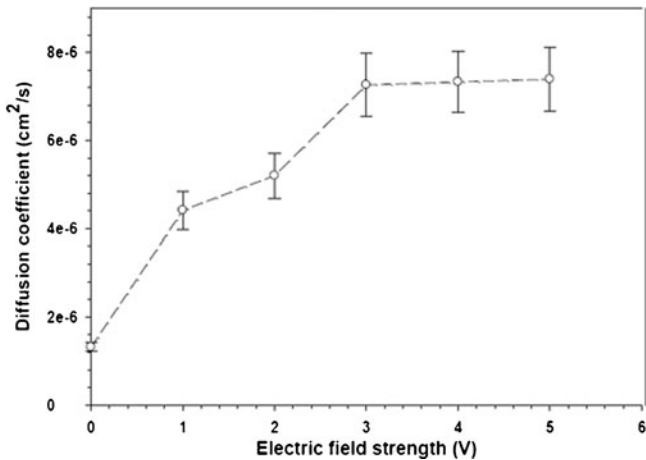
in Table IV. The scaling exponent m values for the model drugs—benzoic acid and sulphanilamide—diffusion through the PVA matrix with and without applied electric field are 1.73 and 0.65, respectively. The diffusion coefficient of benzoic acid–PVA hydrogel and sulphanilamide–PVA hydrogel without electric field stimulation shows two regimes of diffusion characteristics. First, the diffusion coefficient is independent of drug size/mesh size (a_d/ξ is between 0.01 and 0.04) because the mesh size is significantly larger than the drug molecule sizes; benzoic acid size is 3.31 Å and sulphanilamide size is 3.47 Å. In this regime, the diffusion occurs without obstruction, and no difference in the diffusion scaling exponent m under electric field is observed between the two drugs (11,25,26). In the second regime, the diffusion coefficient decreases with increasing a_d/ξ (a_d/ξ is more than 0.04) due to the decrease in the mesh size, which creates obstacles towards diffusion of drug. However, the diffusion coefficient is monotonically enhanced by the electrical stimulation from 1 to 5 V (Fig. 6). This is because the benzoic acid–PVA hydrogels and sulphanilamide–PVA hydrogels are the drug systems in which the anionic drugs are present, adjacent to the cathode; the negatively charged electrode then creates the electro-repulsion force to the negatively charged drug molecules. In the case of sulfosalicylic acid (SSA) (11) as the anioic drug containing in the SSA–PVA hydrogel and under electrical stimulation, 1 V of applied voltage, also promotes a faster diffusion results in a certain range, a_d/ξ. However, the SSA–PVA hydrogel system provides smaller diffusion coefficients than those of

Fig. 6. Diffusion coefficient of benzoic acid-loaded PVA hydrogel in relation to the electric field strength at the uncross-linked hydrogel, at pH 5.5, and 37°C
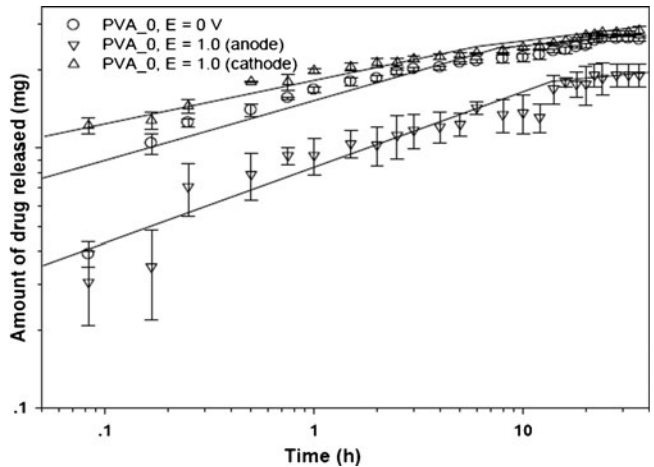

Fig. 7. Amounts of benzoic acid released from the benzoic acid-loaded PVA hydrogel in relation to time with the samples attached to the anode or the cathode, with the uncross-linked hydrogel, at pH 5.5, and 37°C
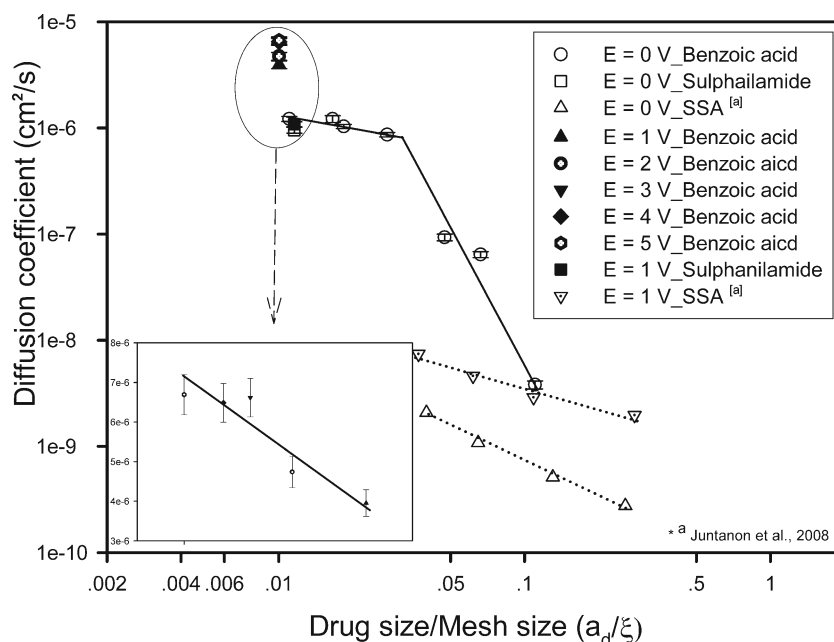
Fig. 8. Diffusion coefficients of drug-loaded PVA hydrogels in relation to drug size/mesh size at the electric field strength between 0.0 and 5.0 V, at pH 5.5, and 37°C

the benzoic acid–PVA hydrogel and the sulphanilamide–PVA hydrogel systems with and without electrical stimulation, at and around $a_d/\xi=0.05$. This may imply that the bulky and steric hindrance effect between the SSA molecule (SSA size is 9.25 Å) and its matrix may be different from the other systems even at the same a_d/ξ.

CONCLUSIONS

Benzoic acid and sulphanilamide-loaded PVA hydrogels were prepared at various cross-linking ratios to study release

mechanism characteristics and to determine the diffusion co-efficient of the model drugs from the PVA hydrogels with and without an electric field. The swelling ability and the mesh size of each PVA hydrogel sample were characterized. The degree of swelling, weight loss, and mesh size of the PVA hydrogels increased with decreasing cross-linking ratios. The amount of drug released and the diffusion coefficients of the drugs from PVA hydrogel increased with a decreasing cross-linking ratio due to the larger mesh size of the hydrogel. The amount of drug released and the diffusion coefficient of the drugs from PVA hydrogel increased monotonically with increasing

Table IV. The Diffusion Coefficient of Drug on PVA Hydrogel at Various Conditions at 37°C, pH 5.5

Solute	M_w	Drug size (Å)	Mesh size, ξ,(Å)	D (cm²/s)	E(V)	Remarks
Benzoic acid	122	3.31	300	1.2408E−06	–	Uncross-link of PVA
			200	1.2396E−06	–	Cross-link ratio=0.5
			180	1.0292E−06	–	Cross-link ratio=1.0
			120	8.7402E−07	–	Cross-link ratio=2.0
			70	9.6301E−08	–	Cross-link ratio=3.0
			50	6.4407E−08	–	Cross-link ratio=4.0
			30	3.8553E−09	–	Cross-link ratio=5.0
			330	4.1036E−06	1.0	Uncross-link of PVA
			355	4.8348E−06	2.0	Uncross-link of PVA
			370	6.7511E−06	3.0	Uncross-link of PVA
			380	6.6611E−06	4.0	Uncross-link of PVA
			395	6.8732E−06	5.0	Uncross-link of PVA
sulphanilamide	172	3.47	300	9.6734E−07	–	Uncross-link of PVA
			330	1.1060E−06	1.0	Uncross-link of PVA
Sulfosalicylic acid (SSA)[a]	254	9.25	232	2.08×10^{-9}	–	Uncross-link of PVA
			143	1.08×10^{-9}	–	PVA_cross-link ratio=0.5
			71	5.13×10^{-10}	–	PVA_cross-link ratio=2.5
			36	2.76×10^{-10}	–	PVA_cross-link ratio=5.0
			250	7.42×10^{-9}	1	Uncross-link of PVA
			150	4.62×10^{-9}	1	PVA_cross-link ratio=0.5
			85	2.90×10^{-9}	1	PVA_cross-link ratio=2.5
			33	1.97×10^{-9}	1	PVA_cross-link ratio=5.0

[a] Juntanon *et al.* [11]

electric field strength. The diffusion coefficient of the drug under cathode is higher than that under anode, and that under the absence of electric field because of the electro-repulsion between the negatively charged drug and the positively charged electrode. The drug size (benzoic acid, 3.31 Å and sulphanilamide, 3.47 Å), matrix pore size, drug–matrix interaction, electrode polarity, and an applied electric field were shown to be important controlling factors for drug release *via* the polymer hydrogels.

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