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Electrically controlled release of salicylic acid from poly(p-phenylene vinylene)/polyacrylamide hydrogels

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ABSTRACT

The apparent diffusion coefficients, D_{app}, and the release mechanisms of salicylic acid from salicylic acid-loaded polyacrylamide hydrogels, SA-loaded PAAM, and salicylic acid-doped poly(phenylene vinylene)/polyacrylamide hydrogels, SA-doped PPV/PAAM, were investigated. In the absence of an electric field, the diffusion of SA from the SA-doped PPV/PAAM is delayed in the first 3 h due to the ionic interaction between the anionic drug (SA anion) and the PPV. Beyond this period, SA is dissolved in and can diffuse into the buffer solution through the PAAM matrix. The D_{app} of the SA-doped PPV/PAAM is higher than that of the SA-loaded PAAM, and the former increases with increasing electric field strength due to combined mechanisms: the expansion of PPV chains inside the hydrogel; the reduction reaction under a negative potential driving the anionic SA through the PAAM matrix; and the expansion of the matrix pore. The D_{app} of SA from the SA-loaded PAAM and the SA-doped PPV/PAAM apparently obey the scaling behavior: $D_{app}/D_0 = (drug\ size/pore\ size)^m$ with the scaling exponent m equal to 0.50 at 0.1 V for both SA-loaded PAAM and SA-doped PPV/PAAM. Thus, the presence of the conductive polymer and the applied electric field can be combined to control the drug release rate at an optimal desired level.

1. Introduction

Conducting polymers and hydrogels are macromolecular systems, which possess special and important characteristics, making them suitable for a wide range of practical applications (Small et al., 1997). The electrical properties of conducting polymers make them suitable for devices driven by an external electric signal, such as a potential or current (Kim et al., 2000a,b). On the other hand, hydrogels, consisting of tri-dimensional structures formed by crosslinking hydrophilic polymeric chains, possess the ability to swell in solution in response to the chemical nature of the media, the pH, the ionic strength, the electric field, and the temperature (Tao et al., 2005).

Hydrogels and conductive polymers are also called "smart materials" due to their abilities to change their volume or to release substances under external stimuli. Recently, the diffusion and release of a solute from these polymeric systems has emerged as an important issue for the potential application of using the polymeric systems as a controlled drug delivery system (Tao et al., 2005). In fact, both systems, hydrogels and conductive polymers, have been investigated as suitable candidates in controlled drug release applications. However, the conductive polymer system has certain limitations: only charged drugs can be released by the electrochemical control; large drugs, even though charged, cannot be easily released through the conducting polymer network with limited pore size; and, the ionic exchange that takes place between the drug and the electrolyte media, independent of the oxidation state of the polymer, diminishes the capacity of an electrochemical control (Zinger and Miller, 1984). In typical drug delivery systems, hydrogels have played a more accepted role than the conducting polymers; but they often have slow response, which limits their ability to deliver the stimuli efficiently throughout the gel (Lira and Torresi, 2005). A novel blend consisting of a conductive polymer and a hydrogel is thus expected to fulfil the important requisites of the ideal drug release device: the possibility of switching on/off and the precise control of the release rate as functions of the applied potential.

In this study, poly(p-phenylene vinylene), or PPV, is selected as the conductive polymer because of its unique properties: nonlinear optical properties, electroluminescence, and high electrical conductivity upon doping (Cakmak et al., 2004). These characteristics are desirable properties for a new class of controlled-release devices when subjecting them to an electric field (Kim et al., 2000a,b; Kontturi et al., 1998). Polyacrylamide is chosen as the hydrogel matrix because of its non-toxicity, high water absorbency, and electro-responsive properties. The objectives of this work are to

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investigate a combined conductive/hydrogel system as a controlled drug release device, and to study the physiochemical phenomena that are involved in the electrical controlled release of a salicylic acid-doped poly(p-phenylene vinylene)/polyacrylamide hydrogel system. In this work reports the effects of the matrix pore size and the electric field strength on the drug release profile and the drug release kinetics of salicylic acid-doped poly(p-phenylene vinylene) in the polyacrylamide hydrogel system.

2. Experimental

2.1. Materials

Salicylic acid, SA (AR grade, Fluka), was used as the model drug. Acrylamide, AAM (AR grade, Fluka, China), N,N′ methylenebisacrylamide, N,N′-MBA (AR grade, Fluka, Netherlands), tetramethylenediamine, TEMED (AR grade, Fisher Scientific, United Kingdom), and ammonium peroxodisulfate (AR grade, Fluka, Switzerland) were used as the monomer, the crosslinker, the catalyst, and the initiator, respectively. Sodium acetate (AR grade, Ajax Chemicals, Australia) and glacial acetic acid (AR grade, Mallinckrodt Chemicals, USA) were used without further purification. α,α′-dichloro-p-xylene and tetrahydrothiophene, THT (AR grade, Aldrich, Japan), were used to synthesize the poly(p-phenylene vinylene). Acetone and methanol (AR grade, Merck, Germany) were used as received.

2.2. Synthesis of poly(p-phenylene vinylene)

The PPV was synthesized via the polyelectrolyte precursor according to the method of Burn et al. (1992). To a suspension of 10 g of α,α′-dichloro-p-xylene in 150 mL of methanol, 15 mL of tetrahydrothiophene, THT, was added. The resulting mixture was heated in a 50 °C oil bath overnight, and 250 mL of acetone was added to precipitate the salt p-phenylene dimethylene bis tetramethylene sulfonium chloride. The mixture was stirred in an ice bath for 0.5 h before filtration. The white solid salt obtained was washed with acetone and dried under vacuum at room temperature until two sequential weighings were the same. The yield was 85% (Burn et al., 1992). One gram of the washed and dried salt was dissolved in 7.5 cm^3 methanol, cooled to 0 °C, and added to 6.3 cm^3 aqueous sodium hydroxide (0.4 M). After 120 min, 1 cm^3 of hydrochloric acid (0.4 M) was added to the solution to stop the reaction. The 14.8 cm^3 solution was then dialyzed against a water–ethanol mixture (1:1, 3 × 1000 cm^3) for 3 days. After cooling, the aqueous solution of poly[(p-phenylene) bis(tetrahydrothiophenechloride)] was poured into a glass dish and allowed to evaporate at room temperature under atmospheric conditions for a duration of 24 h. The obtained yellow–green precursor films were heated to and kept at 200 °C for 16 h in a vacuum oven to yield PPV film. The obtained PPV films were grounded in a jar mill for 2 days.

2.3. Preparation of salicylic acid-doped poly(p-phenylene vinylene) (SA-doped PPV)

The salicylic acid-doped poly(p-phenylene vinylene) was prepared by the acid-assisted redox doping reaction, as illustrated in Eq. (1):

$$[\mathrm{PPV}] \times n + \mathrm{HX} \times n + \mathrm{H_2O_2} \times \frac{n}{2} \rightarrow [\mathrm{PPV^+X^-}] \times n + \mathrm{H_2O} \times n \qquad (1)$$

In this reaction, hydrogen peroxide (H_2O_2) was chosen as the oxidant; [PPV] represents a repeating unit of the conjugated PPV polymer, and HX symbolizes the functionalized salicylic acid. n is the number of moles of these substances (Sanden, 1997). One gram of PPV was stirred with 100 mL of SA solution (0.0125 M) and 50 mL of H_2O_2 for 24 h. SA-doped PPV particles were filtered and vacuum dried for 24 h.

2.4. Preparation of salicylic acid-loaded polyacrylamide hydrogel (SA-loaded PAAM hydrogel)

SA-loaded PAAM hydrogels, 0.2% w/w (based on the weight of the acrylamide monomer), were prepared by the free-radical polymerization of 2.32 g of acrylamide in an aqueous solution of salicylic acid (0.0125 M), with N, N′-MBA as the crosslinker (Lira and Torresi, 2005). Ammonium persulfate and TEMED were used as the initiator and the accelerator, respectively. To study the effect of crosslinking ratio on the release of SA from the SA-loaded PAAM hydrogels, gels at various crosslink ratios (mol_{MBA}:mol_{AAM}; 0.002, 0.005, 0.010, 0.016, and 0.024) were prepared using various amounts of N,N′-MBA. Before gelation (typically after 10 min of mixing the reagents at 27 °C), the pre-gel solution was cast in a mold (diameter 8 cm, thickness 0.5 mm). After gelation, each PAAM hydrogel was cut into a disk shape (diameter ≈18 mm, thickness ≈0.5 mm).

2.5. Preparation of salicylic acid-doped poly(p-phenylene vinylene)/polyacrylamide hydrogel (SA-doped PPV-loaded PAAM hydrogel)

The SA-doped PPV/PAAM hydrogels were prepared by the free-radical polymerization of 2.32 g of acrylamide in an aqueous solution with 7.5 mg of SA-doped PPV, N,N′ MBA, and ammonium persulfate and TEMED, and then were cast in a mold, as previously described in the preparation of the SA-loaded PAAM hydrogels.

2.6. Characterization

2.6.1. SA-doped PPV characterization

Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Bruker, Equinox 55/FRA 1065X) operated in the transmission mode with 32 scans and a resolution of ±4 cm^{-1} covering a wavenumber range of 4000–400 cm^{-1} using a deuterated triglycine sulfate detector. Optical grade KBr (Carlo Erba Reagent) was used as the background material. The synthesized PPV was intimately mixed with dried KBr at a ratio of 1:20 PPV:KBr and was compressed into a disc. Scanning electron micrographs of the PPV particles were taken (JEOL, JSM-5200-2AE) using an acceleration voltage of 20 kV and a magnification of 350. TGA thermograms of the SA, PPV, and SA-doped PPV were recorded (Dupont, TGA 2950) to determine their thermal behavior. The 2–4 mg samples were accurately weighed in a platinum pan. The measurements were done under N_2 atmosphere at 30–600 °C at a heating rate of 10 °C/min. A particle sizer (Malvern, Master-sizer X) was used to obtain the PPV particle size distribution and the mean sizes.

2.6.2. PAAM characterization

The mesh size, ξ, the molecular weight between crosslinks, M_c, and the crosslinking density, ρ, of the crosslinked PAAM hydrogel, were determined by equilibrium swelling analysis (Lira and Torresi, 2005). Each hydrogel sample (1 cm^2 square) was cut immediately after crosslinking and was weighed in air and heptane (a non-solvent). The particular sample was then placed in deionized water at 37 °C for 5 days to allow it to swell under an electric field strength of 0–0.1 V was applied to reach the equilibrium size, and the sample was then weighed again in air and heptane. Finally, the sample was dried for 5 days at room temperature and weighed in air and heptane. The average molecular weight between crosslinks of the PAAM gel, M_c, was determined from the swelling data using

Eq. (2), as given by Peppas and Wright (1996):

$$\frac{1}{M_c} = \frac{2}{M_n} - \frac{\frac{\bar{v}}{V_1}\left[\ln(1-v_{2,s}) + v_{2,s} + \chi_1 {v_{2,s}}^2\right]}{v_{2,r}\left(\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right)} \quad (2)$$

where M_n is the number-average molecular weight of the polymer before crosslinking (determined by using an Ubelodde tube at ~36,400 g/mol), $\bar{v}$ is the specific volume of PAAM (0.741 mL/g), and $\overline{V_1}$ is the molar volume of water (18.1 mL/mol). $v_{2,r}$ is the polymer volume fraction in the gel in the relaxed state, $v_{2,s}$ is the polymer volume fraction in the gel in the swollen state, and χ is the interaction parameter of PAAM-water, 0.48 (Peppas and Wright, 1996).

The hydrogel mesh size, ξ, was calculated from the following equation:

$$\xi = (v_{2,s}^{-1/3})\left[C_n\left(\frac{2M_c}{M_r}\right)\right]^{1/2} l \quad (3)$$

where C_n is the Flory characteristic ratio for PAAM (8.8), M_r is the molecular weight of the repeating unit, and l is the carbon–carbon bond length (=1.54 Å).

The crosslinking density of the hydrogel was calculated using Eq. (4) (Peppas and Wright, 1996):

$$\rho x = \frac{1}{vM_c} \quad (4)$$

2.7. Release of SA from SA-loaded PAAM hydrogel and SA-doped PPV/PAAM hydrogel

2.7.1. Preparation of buffer solution

To prepare 1000 mL of an acetate buffer solution at a pH of 5.5, 15 mL of glacial acetic acid and 150 g of sodium acetate were added to distilled water in a volumetric flask with a total volume of 1000 mL.

2.7.2. Spectrophotometric analysis of the model drug

A UV/visible spectrophotometer (Shimadzu, UV-2550) was used to determine the spectrum peak of the model drug. The model drug, in an aqueous solution, was prepared; and the characteristic peak was observed to be at a wavelength of 296 nm. The peak intensity was read corresponding to a particular model drug concentration and the process was repeated at different concentrations to obtain the calibration curve.

2.7.3. Actual amount of drug

The actual amount of SA in the SA-loaded PAAM (circular disc ~1.8 cm in diameter, thickness ~0.5 mm) and SA-doped PPV (0.6 g) was determined by dissolving the sample in 4 mL of dimethyl sulfoxide (DMSO), and 0.5 mL of the solution was added to an 8 mL acetate buffer solution. The drug amount in the solution was measured using a UV/Visible spectrophotometer at a wavelength of 296 nm and a predetermined calibration curve. The data is reported here as an average value taken from at least three measurements of three samples.

2.7.4. Drug release studies

The diffusion through a nylon net (mesh size = 2.25 mm^2) was carried out in order to study the release characteristics of the drug from a SA-loaded PAAM hydrogel and SA-doped PPV/PAAM hydrogel. A net was placed on top of the acetate buffer solution on a custom built, modified Franz diffusion cell. The area available for permeation was 2.51 cm^2. The nylon net was allowed to come into contact with the acetate buffer (pH 5.5, ionic strength of 0.001225 M) in the receptor chamber; the buffer was magnetically stirred throughout the experiment period (48 h) at a thermostatically maintained temperature (37 ± 2 °C). The SA-loaded PAAM and SA-doped PPV/PAAM hydrogel with particular crosslinking ratios (mol_{MBA}:mol_{AAM} = 0.002, 0.005, 0.016, or 0.024) were placed between the copper cathode and the net, and the assembly was mounted onto the receptor compartment. To study the effect of electric field strength on the release of the SA from the SA-loaded PAAM and SA-doped PPV/PAAM hydrogels, the cathode electrode (copper) was connected to a power supply (KETHLEY 1100 V Source Meter), which provided various electrical voltages (V = 0, 0.01, 0.03, 0.05, 0.07, 0.09, and 0.1 V) across the hydrogel, the nylon net, and the buffer solution. The anode electrode pin was positioned in the buffer solution. The total duration of the constant electric field strength applied to the experimental setup was ~48 h. The donor and receiver compartments were kept in contact by wrapping a parafilm around the junction. The total diffusion period investigated was 48 h; 0.3 mL of the buffer solution was withdrawn and an equal amount of the fresh buffer solution was added to the cell every 15 min during the first hour to ensure good contact between the buffer solution and the PAAM matrix at all times. The drug amount in the withdrawn solution sample was determined using a UV spectrophotometer at 296 nm. The experiments were carried out in triplicate and the data were reported as average values.

3. Results and discussion

3.1. Characterization

3.1.1. SA-doped PPV characterization

The PPV particle diameter is 46 μm with a standard deviation of ~4 μm, as measured by the particle analyzer. The particle microstructure was observed by a scanning electron microscope (SEM). Fig. 1 shows the PPV particles and salicylic acid-doped PPV particles; their shapes are quite irregular. However, salicylic

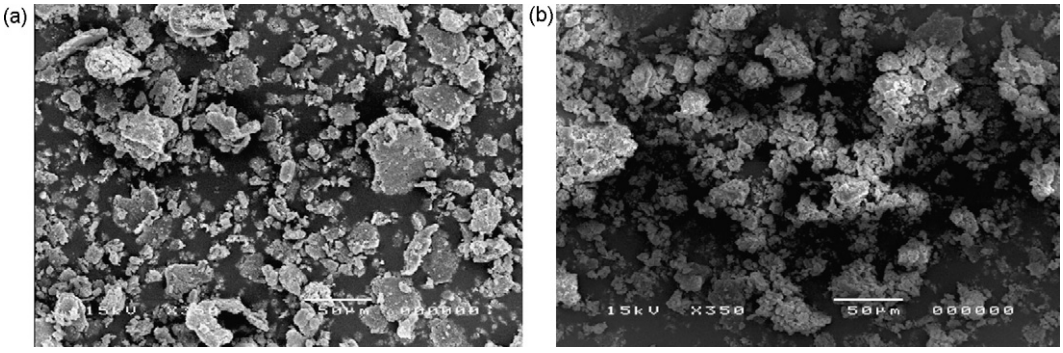


Fig. 1. Morphology of (a) poly(phenylene vinylene), PPV; and, (b) salicylic acid-doped poly(phenylene vinylene), SA-doped PPV, at a magnification of 350.

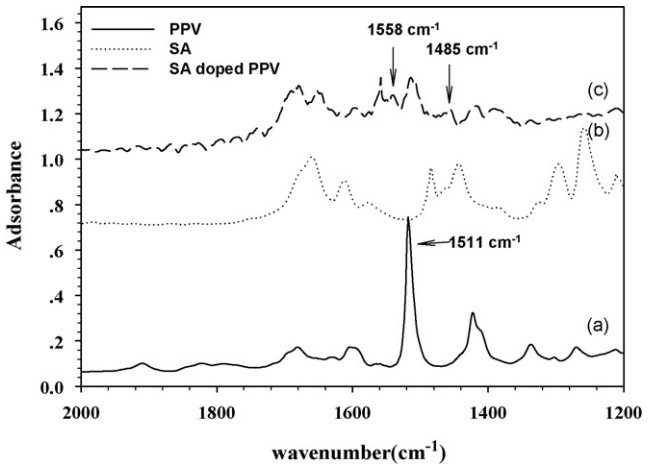


Fig. 2. Absorption infrared spectra of (a) poly(phenylene vinylene), PPV; (b) salicylic acid, SA; and, (c) salicylic acid-doped poly(phenylene vinylene), SA-doped PPV.

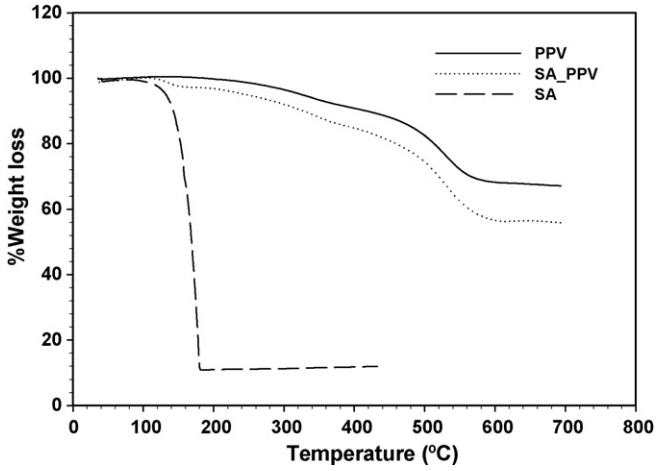


Fig. 3. Thermogravimetric thermograms of poly(phenylene vinylene), PPV; salicylic acid, SA; and salicylic acid-doped poly(phenylene vinylene), SA-doped PPV (sample weights are ~2–4 mg).

acid-doped PPV appears to be more agglomerated than the drug-free PPV due to the electrostatic interaction between the particles.

Fig. 2 shows the FTIR spectra of synthesized PPV, salicylic acid, and salicylic acid-doped PPV. The synthesized PPV FTIR spectra indicate distinct adsorption peaks at 3022, 550, 830, and 1511 cm^{-1}. They represent the trans vinylene C–H stretching mode, the phenylene out-of-plane ring bending, the p-phenylene ring C–H out-of-plane bending, and the C–C ring stretching, respectively (Burn et al., 1992). The FTIR spectrum of the salicylic acid-doped PPV shows new bands at 1558, 1485, 1316, 1280, 1150, and 876 cm^{-1}. The emergence of these new bands in the spectra is due to the formation of the quinoid structures, which are result of the symmetrical breaking of the polymeric chain. Although the formation of the quinoid structure occurs for the doping agent used, certain FTIR peaks (3022, 550, 830, and 1511 cm^{-1}) remain after the doping process, which could be associated with the benzoid structure (undoped PPV). Therefore, even after the extensive oxidation process, only partial oxidation of the polymer takes place, and the two structures coexist.

Fig. 3 shows the TGA thermograms of synthesized PPV, salicylic acid-doped PPV, and salicylic acid. The synthesized PPV thermogram shows only a single degradation step at 450–550 °C, corresponding to the degradation reaction of the PPV main chain (Cirpan et al., 2003). The salicylic acid-doped PPV thermogram shows a two-step weight loss. The first step, 130–180 °C, is due to the loss of the counterion belonging to the dopant. The second step, 480–580 °C, is due to the degradation of the polymer. The TGA results of the PPV and the doped PPV show that the doped PPV has a higher thermal stability; after doping, the degradation temperature of the salicylic acid-doped PPV is higher than that of the pure PPV (drug-free PPV).

3.1.2. PAAM characterization

PAAM was chemically polymerized through the free radicalization and subsequent crosslinking at 27 °C (Fernandez et al., 2005). The molecular weight between crosslinks, the mesh size, and the crosslinking density are parameters (Eqs. (2)–(4)) used in characterizing the porous hydrogel structure. These parameters are determined from the equilibrium swelling analysis carried out in distilled water at 37 °C, as described previously by Peppas and Wright (1996). Table 1 gives the molecular weights between crosslinks, M_c, the mesh size, ξ, and the crosslinking density for each hydrogel in terms of crosslinking ratio, with and without an applied electric field. The data clearly indicate that as the crosslinking ratio decreases, the mesh size and the molecular weight between crosslinks increase. As the amount of crosslinking agent decreases, the spacing between the crosslinks becomes wider and the strand becomes longer. The mesh sizes of the hydrogels are between 57 and 252 Å at an electric field strength of 0 V, and between 119 and 348 Å at an electric field strength of 0.1 V. Thus, the increase in the mesh size of the PAAM with electric field suggests that the PAAM structure is electroactive. This phenomenon of electro-induced gel swelling rarely occurs relative to that of gel deswelling (Murdan, 2003). In this work, the electro-induced gel swelling can be explained by the electrically induced ionization of the amide groups in the PAAM hydrogels. When an electric field is applied to an aqueous medium, the positive ions (H^+) in the aqueous medium migrate toward the cathode side. H^+ ions penetrate the PAAM hydrogels on their way to the cathode. This induces the ionization of the amide groups in the PAAM hydrogels and causes the gels to swell as the ionized groups become hydrated (Murdan, 2003).

3.2. Release characteristics of SA from SA-loaded PAAM hydrogel and SA-doped PPV/PAAM hydrogel

The actual amount of drug contained within the SA-loaded PAAM hydrogel sample was determined and is reported as the percentage of the drug amount initially loaded into each PAAM sample (~0.938 mg of SA). The actual amounts of SA remaining in the samples after gelation are about 95.1 ± 3.5%, as tabulated in Table 2.

The amount of SA in the SA-doped PPV was determined and is reported as the percentage of the SA amount in the SA-doped PPV (~1.400 mg of SA/mg of PPV). The amount of SA present in the SA-doped PPV samples is about 57.1 ± 4.7%, after the doping process. The actual amount of SA within the SA-doped PPV/PAAM hydrogel sample is reported as the percentage of the SA amount present relative to the amount loaded into the SA-doped PPV/PAAM samples (~0.96820 mg of SA). The actual SA amounts remaining in the samples after gelation are about 93.5 ± 5.7%, as tabulated in Table 2.

3.2.1. Effect of matrix mesh size

The release characteristics of SA from the SA-loaded PAAM and the SA-doped PPV/PAAM, pertaining to the diffusion from the hydrogel matrix, were investigated next. The experiments were carried out using an acetate buffer as the transfer medium at the physiological temperature of 37 °C, both in the absence of an electric field and under an applied electric field. The amounts of SA released from the SA-loaded PAAM hydrogels of various crosslink-

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

Sample	Crosslinking ratio, X (mol_{MBA}/mol_{AAM})	Number-average molecular weight between crosslinks, M_c (g/mol)		Mesh size ξ (Å)		Crosslinking density ($mol/cm^3 \times 10^4$)	
		$E = 0$ V	$E = 0.1$ V	$E = 0$ V	$E = 0.1$ V	$E = 0$ V	$E = 0.1$ V
PAAM_0.002	0.002	8293 ± 339	33398 ± 3693	252 ± 7	348 ± 7	1.63 ± 0.07	0.41 ± 0.04
PAAM_0.005	0.005	4318 ± 21	34294 ± 397	158 ± 14	304 ± 5	3.13 ± 0.02	0.42 ± 0.01
PAAM_0.010	0.010	4050 ± 43	24031 ± 3823	128 ± 2	227 ± 16	3.33 ± 0.04	0.57 ± 0.09
PAAM_0.016	0.016	2700 ± 332	18196 ± 1058	85 ± 2	177 ± 5	5.04 ± 0.62	0.74 ± 0.04
PAAM_0.024	0.024	1555 ± 277	8752 ± 1903	57 ± 5	119 ± 4	8.82 ± 1.57	1.58 ± 0.34

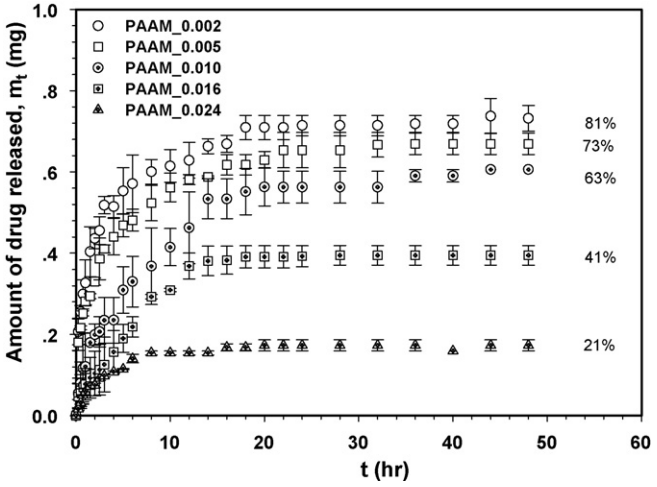


Fig. 4. Amounts of SA released from SA-loaded PAAM hydrogels at time t (h) at various crosslinking ratios, $E = 0$ V, pH 5.5, and at 37 °C.

ing ratios (PAAM_0.002, PAAM_0.005, PAAM_0.010, PAAM_0.016, and PAAM_0.024) in the absence of an electric field during a 48 h period are shown as functions of time in Fig. 4. The amounts of SA released ($C_6H_4(OH)CO_2H \Leftrightarrow C_6H_4(O^-)CO_2H + H^+$, SA dissociation in a buffer solution) from all systems of the SA-loaded PAAM hydrogels increase very rapidly over the first 6 h; after this period they increase gradually until reaching equilibrium. The amount of salicylic released can be reported here as the percentage of the actual amounts of SA present in the PAAM sample (~0.89 mg of SA). The percentages of SA released from the SA-loaded PAAM are 81, 73, 63, 41, and 21% for PAAM_0.002, PAAM_0.005, PAAM_0.010, PAAM_0.016, and PAAM_0.024, respectively. Thus, a larger pore size

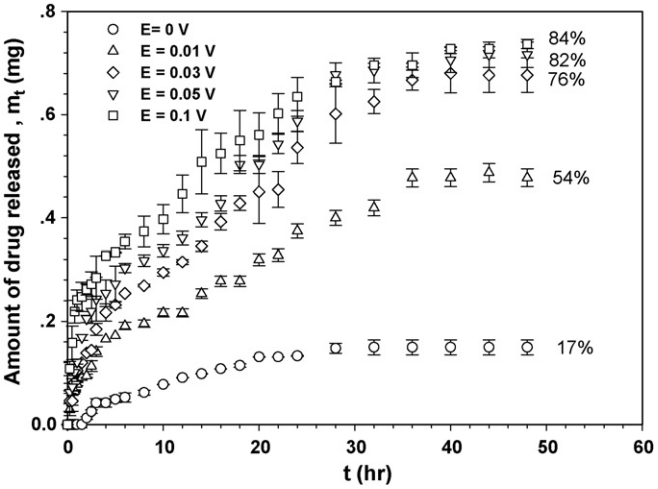


Fig. 5. Amounts of SA released from SA-PPV/PAAM hydrogels at time t (h) at various electric field strengths, pH of 5.5, and at 37 °C.

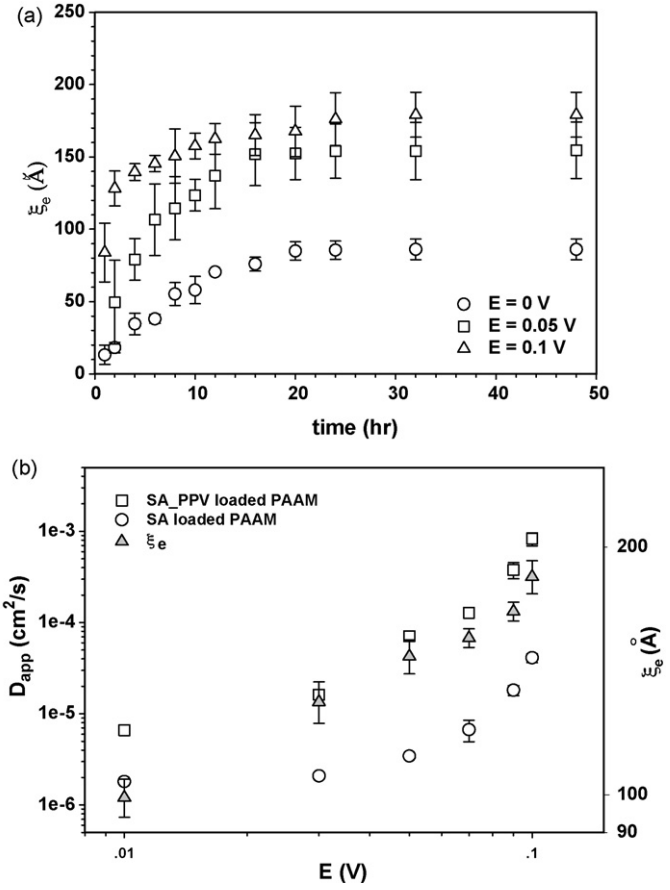


Fig. 6. Effect of electric field strength on, (a) mesh size of PAAM hydrogel, and (b) the apparent diffusion coefficient (D_{app}) of SA from SA-doped PPV/PAAM hydrogels and SA-loaded PAAM hydrogels at pH 5.5, and at 37 °C.

hydrogel releases a greater amount of SA. Moreover, the amount of SA released from the SA-loaded PAAM is higher at any given time for a hydrogel with a larger pore size.

3.2.2. Effect of electric field strength

The release characteristics of SA from the pure PAAM system is expected to be dependent on the applied electric field strength and the duration of the electric field applied (Sage and Riviere, 1992). The amount of SA released at a given time is clearly greater at a higher electric field strength. The driving force is the higher

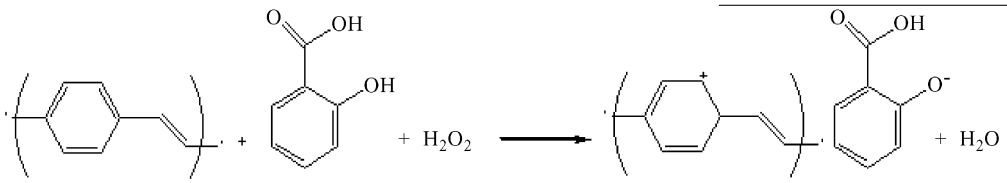
Table 2
Actual amounts of salicylic acid in PAAM and PPV/PAAM.

Sample	Amount of loaded drug (mg)	Actual amount of salicylic acid (drug amount initially loaded into sample, %)
PAAM	0.935	95.1 ± 3.5
PPV/PAAM	0.968	93.5 ± 5.7

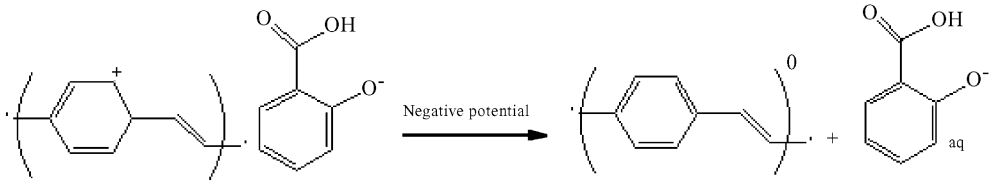
electrostatic force pushing the negatively charged drug through the polymer matrix (Murdan, 2003; Kantaria et al., 1999). The second driving force possibly comes from the expansion of the PAAM hydrogel mesh size. Table 1 shows that for the PAAM_0.002 hydrogel, the mesh size increases from 252 to 348 Å as electrical voltage is increased from 0 to 0.1 V.

Fig. 5 shows the amounts of SA released from the SA-doped PPV/PAAM versus time at various electric field strengths, 0–0.1 V. Each sample was attached to the negatively charged electrode (cathode). As seen in Fig. 5, in the absence of an electric field, the SA molecules are not released from the SA-doped PPV/PAAM during the first 3 h. Beyond that period, the amount released gradually increases until reaching equilibrium. It is clear that the amount of SA released from the SA-doped PPV/PAAM is greater at a higher electric field strength due to the stronger reduction reaction of the SA-doped PPV. As the PPV is reduced, the PPV chains also expand and generate a larger free volume in the hydrogel, which facilitates the diffusion of SA through the PAAM matrix (Lira and Torresi, 2005). The second driving force comes from the electrostatic force between the negative charge and the cathode electrode (Murdan, 2003; Kantaria et al., 1999). The third driving force originates from the direct expansion of the PAAM hydrogel pore size due to the electric field.

The SA-doped PPV was successfully prepared by the acid-assisted redox doping reaction:



It is well-known that the drug counter ions ($C_7H_5O_3^-$) that are incorporated into the conductive polymers during the doping process can be released upon the application of a negative potential by the reduction reaction according to:



Li et al. (2005) studied the release of heparin from polypyrrole-poly(vinylalcohol) under electric field stimulation. They found that under the action of an electric field (1.0 mA), the amount of released heparin was nearly three times higher than that without an electric field. Several factors are involved: the electrophoresis of the charged drug, the change in pH due to H^+ migration towards the cathode, the expansion of mesh size, and the reduction reaction of the drug-doped conductive polymer.

Lira and Torresi (2005) studied the release of safranin dye from a semi-interpenetrating polyaniline-polyacrylamide (PANI-PAAM) network when an electric field was applied. Under the electric field (−0.1 V), the amount of released safranin was higher than that without an electric field. As PANI chains are reduced, they create a larger free volume in the hydrogel, which facilitates the diffusion of safranin.

3.2.3. Release kinetics

In order to study the SA transport mechanism from the PAAM or PPV/PAAM hydrogels, various diffusion models can be used to analyze the experimental data. The amount of drug released from a hydrogel at time t (M_t), with respect to the total amount of drug released (M_∞), can be expressed in terms of a power law of time, as follows:

$$\frac{M_t}{M_\infty} = kt^n, \tag{5}$$

where n is the diffusion scaling exponent. The value of n determines the dependence of the release rate on time that can be related to the drug transport mechanism. The drug transport mechanisms can be identified as Fickian, non-Fickian (anomalous), linear (zero order), and super case II transport when n is equal to 0.5, $0.5 < n < 1.0$, 1.0, and $n > 1.0$, respectively (Korsmeyer et al., 1983).

From our data (Figs. 4 and 5), $\ln(M_t/M_\infty)$ are plotted versus $\ln(t)$ in order to determine the scaling exponent n as shown in Eq. (5). For the crosslinked PAAM without an applied electric field, the scaling exponent n varies from 0.47, 0.50, 0.55, 0.58 to 0.60 for the PAAM hydrogels with the crosslinking ratios of 0.002, 0.005, 0.010, 0.016, and 0.024, respectively. For SA-doped PPV/PAAM at various electric field strengths, the scaling exponents n are 0.58, 0.53, 0.48, 0.41 to 0.34 at electric field strengths of 0, 0.01, 0.05, 0.07, and 0.1 V, respectively. The n values of both SA-loaded PAAM hydrogel and SA-doped PPV/PAAM vary between 0.34 and 0.60, values that are close to the Fickian exponent value of $n = 0.5$. Thus, the amounts of SA released from both SA-loaded PAAM hydrogel and SA-doped PPV/PAAM can be considered to be dominantly controlled by the Fickian diffusion mechanism.

In particular, Higuchi's equation (Korsmeyer et al., 1983) is associated with the Fickian diffusion of the drug:

$$\frac{M_t}{M_\infty} = k_H t^{0.5}, \tag{6}$$

where M_t/M_∞ is the fractional drug released, k_H is Higuchi's kinetic constant, and t is the release time.

The kinetic constant k_H of Eq. (5) decreases from 0.37, 0.31, 0.19, 0.20 to 0.14 (h^{-n}) for PAAM hydrogels with the crosslinking ratios of 0.002, 0.005, 0.010, 0.016, and 0.024, respectively. The release rate is thus slower in a sample with a higher crosslinking ratio, apparently due to the smaller pore size (Sairam et al., 2006), as also shown in Table 1. In addition, the smaller % swelling may further hinder the amount of salicylic acid released from the hydrogel.

For SA-doped PPV-loaded PAAM, the kinetic constant k_H increases from 0.012, 0.089, 0.103, 0.171 to 0.268 (h^{-n}) at electric field strengths of 0, 0.01, 0.05, 0.07, and 0.1 V, respectively. The release rate is accelerated under an applied electric field because of the reduction reaction of SA-doped PPV under an electric field, the electrophoresis effect driving SA, and the expansion of the mesh size, as previously discussed.

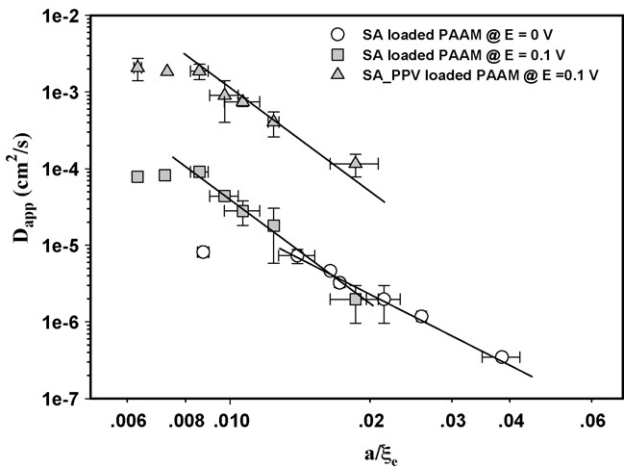


Fig. 7. Apparent diffusion coefficient, D_{app}, of SA from SA-loaded PAAM hydrogels and SA-doped PPV/PAAM hydrogels versus drug size/mesh size of the hydrogel at electric field strengths of 0 and 0.1 V, pH 5.5, and at 37 °C.

The apparent diffusion coefficients, D_{app}, of SA from the SA-loaded PAAM hydrogels and SA-doped PPV/PAAM hydrogels through the nylon net can be influenced by the physical characteristics of the matrix/drug system, as well as by some physical contributions from the experimental procedures. Each D_{app} value is calculated from the slope of the amount of released drug versus the square root of time during the initial period, according to Higuchi's equation (Ferreira et al., 2001):

$$Q = 2C_0\left(D_{app}\frac{t}{\pi}\right)^{1/2}, \tag{7}$$

where Q is the amount of drug released per unit area, C_0 is the initial drug concentration in the gel, and D_{app} is the apparent diffusion coefficient of a diffusant (Ferreira et al., 2001). It should be note that D_{app} values obtained from Eq. (7) and referred to in Eq. (8) are valid over an initial period of time and based on Fick's laws.

Fig. 6(a) shows the plot between the mesh size (ξ_e, Å) at various electric field strengths versus time (t, h). In each electric field strength, the mesh size gradually increases in the first 6 h and reaches an equilibrium value. At any given time, the mesh size increases with electric field strength due to the stronger electrically induced ionization of the amide groups in the PAAM hydrogels.

Fig. 6(b) shows the equilibrium mesh size, ξ_e (right axis), versus electric field strength (0–0.1 V) for the hydrogel at a crosslinking ratio of 0.016. The equilibrium mesh size, ξ_e, increases non-linearly with electric field strength. Fig. 6(b) also shows D_{app} of SA from the SA-loaded PAAM and SA-doped PPV/PAAM hydrogels, at a crosslinking ratio of 0.016, versus electric field strength (0–0.1 V), at 37 °C. D_{app} values were determined from the data of Figs. 4 and 5 through Eq. (7). The D_{app} values of SA from the SA-loaded PAAM and the SA-doped PPV/PAAM also show a non-linear dependence on electric field strength and increase monotonically with increasing electric field strength. D_{app} of SA from the SA-doped PPV/PAAM is clearly greater than D_{app} of SA from the SA-loaded PAAM by one order of magnitude due to the reduction reaction of PPV, the electrophoretic force, and the expansion of PAAM's pore size. In general, we may conclude that the diffusion coefficient of a drug in a transdermal delivery system depends on several factors: the chemical composition of the drug, the molecular weight of the drug, and the size of the drug, the polymer matrix, the drug-matrix interaction, presence of conductive polymer, and the experimental set up.

Fig. 7 shows the plot of D_{app} of SA from the SA-loaded PAAM hydrogel and the SA-doped PPV/PAAM hydrogel versus the drug size/mesh size ratio (a/ξ_e) at electric field strengths of 0 and 0.1 V, and at 37 °C. Here, ξ_e is the mesh size of the hydrogel under a particular electric field strength (values are tabulated in Table 1). The D_{app} in each case generally decreases with a/ξ_e or with increasing crosslink ratio due to the reduction of the matrix mesh size (Ferreira et al., 2001).

For the SA-loaded PAAM hydrogels, two changes occur as an electric field is applied. First, the D_{app} of each hydrogel of a given crosslinking ratio increases by nearly a factor of two as an electric field of 0.1 V is applied, corresponding to a vertical shift on the log-log plot of Fig. 7. Secondly, D_{app} versus the drug size/mesh size ratio (a/ξ_e) shifts to the left on the log–log plot due to increases in the mesh size ξ_e under an electric field.

The D_{app} of SA released from the SA-doped PPV/PAAM hydrogels versus the drug size/mesh size ratio (a/ξ_e) is similar to that of the SA-loaded PAAM hydrogels, except the former is greater by an order of magnitude. The diffusion coefficients of the three systems shown in Fig. 7 follow the scaling behavior as follows:

$$D_{app} = D_0\left(\frac{a}{\xi_e}\right)^{-m} \tag{8}$$

where D_{app} is the apparent diffusion coefficient of the drug, D_0 is the diffusion coefficient as the drug size approaches the mesh size, a is the size of the drug, ξ_e is the mesh size of the hydrogel, and m is the scaling exponent. The scaling exponent m value for the SA diffusion through the polyacrylamide matrix under electric field strengths of 0 and 0.1 V are 0.35 and 0.50, respectively. Corresponding D_0 values are 1.42×10^{-10} and 8.71×10^{-11} cm^2/s, respectively. For the SA-doped PPV/PAAM hydrogel, the scaling exponent m value at electric field strengths of 0.1 V is 0.50, and the corresponding D_0 values is 3.05×10^{-11} cm^2/s. Thus, under electric field, the scaling exponent is about 0.5, regardless of the way the drug is loaded.

Juntanon et al. (2008), studied the diffusion coefficients of sulfosalicylic acid from poly(vinyl alcohol), PVA hydrogels through pigskin at electric field strengths of 0 and 1 V and 37 °C. Their results showed that the diffusion coefficients obey the scaling behavior as shown in Eq. (8). 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. The diffusion coefficient 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.

In summary, the SA released from the SA-loaded PAAM hydrogel and the SA-doped PPV/PAAM are controlled by the Fickian diffusion mechanism. For the SA-loaded PAAM system, changes in the PAAM structure and the matrix pore size, and in the SA/PAAM interaction through an electric field evidently are responsible for the difference in the diffusion scaling exponent m under an electric field. The presence of PPV does not affect the diffusion scaling exponent m under electric field.

3.2.4. Effect of electrode polarity

Fig. 8 shows the amounts of SA released from the SA-doped PPV/PAAM hydrogel with a crosslinking ratio of 0.016 versus t (h) under a negatively charged electrode (cathode in donor), and a positively charged electrode (anode in donor), and under no current system delivery, over a period of 48 h. The amount of drug released under the cathode is higher than those under zero electric field and under the anode. This is a direct result of the reduction reaction of the SA-doped PPV under negative potential, the electrorepulsion between the negatively charged drug and the negatively charged electrode driving the charged drug through the polymer matrix into the buffer solution (Green, 1996). Passive delivery (with no electric

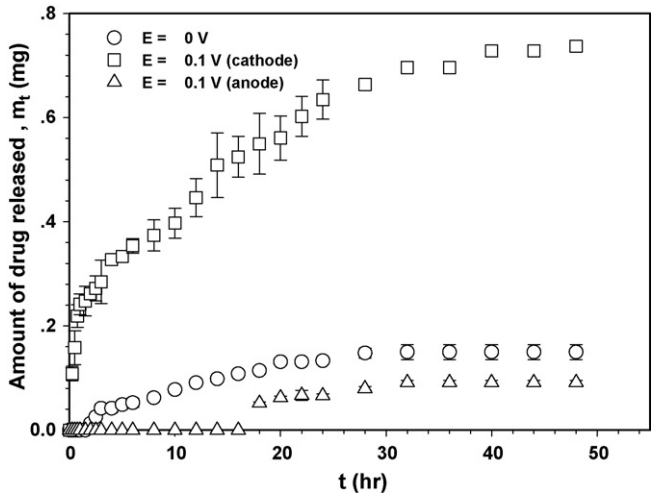


Fig. 8. Amounts of SA released from SA_PPV loaded PAAM hydrogels at time t versus t (h) with the anode and cathode as the driving electrodes, at pH of 5.5, and at 37 °C.

field) results in a lower permeation. With the same electric field and under the anode, the amount of drug released and the diffusion coefficient are lowest among the three cases. The drug starts to be released after 16 h, since the positively charged electrode retards the reduction reaction of the SA-doped PPV and the SA diffusion through the PAAM matrix. Salicylic acid is a model drug with a negative charge at pH 5.5, and this study clearly establishes that its release rate can be altered to be higher and lower than that with no electric field.

4. Conclusion

The SA-loaded PAAM and SA-doped PPV/PAAM hydrogels were prepared by varying the crosslinking ratio to study the release mechanism and the apparent diffusion coefficient, D_{app}, of the model drug from drug-loaded PAAM and drug-doped conductive polymer/PAAM with and without an electric field. In the absence of an electric field, the model drug SA is not released from SA-doped PPV/PAAM hydrogel in the first 3 h period, and then it is released until reaching an equilibrium value. The lack of drug release in the first period originates from the ionic interaction between the conductive polymer and its counter ion (PPV/drug ion). After this first period, the drug anion can diffuse through the PAAM matrix. For the effect of crosslinking ratio, D_{app} of both the SA-loaded PAAM and the SA-doped PPV/PAAM hydrogel systems decreases with increasing crosslink ratio due to the larger mesh size with the lower crosslinking ratio. For the effect of electric field strength, the D_{app} of both the SA-loaded PAAM and the SA-doped PPV/PAAM hydrogel systems increases with increasing electric field strength. The increase in D_{app} at low electric field strength is due to the electrophoresis effect driving the SA and the expansion of the mesh size. The D_{app} of the SA-doped PPV/PAAM hydrogel system is larger than the D_{app} of the SA-loaded PAAM by one order of magnitude, due mainly to the reduction reaction of the SA-doped PPV, where the negative potential accelerates the SA diffusion from the PAAM matrix. It is possible to conclude that, by varying the crosslinking density, the electric field strength, the drug size, the hydrogel matrix mesh size, the drug-matrix interaction, and the presence of a conductive polymer, the drug release rate can be controlled towards an optimal desired level.

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