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Controlled transdermal iontophoresis of sulfosalicylic acid from polypyrrole/poly(acrylic acid) hydrogel

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ABSTRACT

A conductive polymer–hydrogel blend between sulfosalicylic acid-doped polypyrrole (PPy) and poly(acrylic acid) (PAA) was used as a carrier/matrix for the transdermal drug delivery under applied electrical field. PAA films and the blend films were prepared by solution casting with ethylene glycol dimethacrylate (EGDMA) as a cross-linking agent, followed by the blending of PPy particles and the PAA matrix. The effects of cross-linking ratio and electric field strength on the diffusion of the drug from PAA and PPy/PAA hydrogels were investigated using a modified Franz-diffusion cell with an acetate buffer of pH 5.5 and at 37 °C, for a period of 48 h. The diffusion coefficient of the drug is calculated using the Higuchi equation, with and without an electric field, at various cross-linking ratios. The drug diffusion coefficient decreases with increasing drug size/mesh size ratio, irrespective of the presence of the conductive polymer as the drug carrier. The diffusion coefficient, at the applied electric field of 1.0 V, becomes larger by an order of magnitude relative to those without the electric field.

1. Introduction

Drug delivery is the process of introducing a drug into a body during a desired period and at a specific rate. It is imperative that the drug concentration in the blood be maintained at a level that provides maximum therapeutic benefit. There are three main categories of controlled-release drug delivery systems: intravenous, transdermal, and oral systems. The oral route has certain disadvantages: poor absorption, drug degradation, and bioavailability. Thus transdermal drug delivery is an especially attractive alternative, because it is usually easy to apply, safe, and painless.

A hydrogel is a cross-linked polymer network that is insoluble in water but holds a large amount of water in its interspaces of the network (Dai et al., 2006). Hydrogel networks of poly(acrylic acid) (PAA) have the ability to absorb water many times their weight and are known as super absorbents. The polymers are used in many applications: diapers and personal hygiene products, ion exchange resins, membranes for hemodialysis and ultrafiltration, and controlled release devices (Elliott et al., 2004). Moreover, PAA is widely used in pharmaceutical processes due to its pH dependent swelling behavior. The pharmaceutical applications of PAA are in the sustained release of drugs in ocular, nasal, buccal, gastrointestinal, epidermal and transdermal drug delivery. PAA becomes ionized above pK_a value of 4.7. The ethylene glycol dimethacrylate (EGDMA) is generally used as a cross-linking agent.

Conductive polymer is one of a conjugated polymer chain with π-electrons delocalized along the backbone which contribute to electrical conductivity. Polypyrrole (PPy) is one of the conductive polymers which has received great attention since it exhibits high electrical conductivity, good environmental stability, easy to synthesis, and it possesses excellent thermal and electrical properties. PPy is normally polymerized by either an electrochemical or chemical method (Soontornworajit et al., 2007). PPy synthesized either chemically or electrochemically is insoluble due to the strong inter- and intra-molecular interactions and cross-linking (Krings et al., 1993). Thereby the insoluble nature of PPy has limited its applications. The incorporation of a large-sized protonic acid as a dopant into the polymer reduces the inter- and intra-molecular interactions, resulting in an increase in its solubility.

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). Thus, the blends of a conductive polymer and a hydrogel are an attractive alternative. Small et al. (1997) prepared conducting polymer–hydrogel blends based on polypyrrole–polyacrylamide hydrogel (Ppy–PAAM) and studied the controlled release behavior of these blends. The gel was cast in an appropriate gel-cell

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before electro-polymerization to form blends. Electro-release of calcon from the Ppy/calcon-PAG blends was faster and occurred at a greater extent than that of the Ppy/calcon film due to the high water content of hydrogel which allowed the ion movement to induce more efficient electrochemical release (Small et al., 1997).

In this work, polypyrrole/poly(acrylic acid) blend film is prepared by the chemical synthesis using 5-sulfosalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), as a model anion drug as well as as a dopant. The electrical properties, morphology, swelling, diffusion and drug releasing characteristics are investigated and reported here.

2. Materials and methodology

2.1. Materials

In the polypyrrole polymerization, the following chemicals were used: pyrrole (Fluka) as a monomer, ammonium persulfate (MERCK) as an oxidant, 5-sulfosalicylic acid (Fluka) as a dopant. Methanol (Fluka, AR grade), acetone (Fluka, AR grade), and distilled water were used as solvents.

Acrylic acid (Aldrich) was used as the polymer matrix. 5-Sulfosalicylic acid (Fluka), generally used in the symptomatic management of painful and inflammatory conditions, was a model drug. Ethylene glycol dimethacrylate, EGDMA (Aldrich), was used as a cross-linking agent. Sodium acetate (Ajax Chemicals, Australia, AR grade) and glacial acetic acid (Fluka, AR grade) were used without further purification.

2.2. Method

2.2.1. Preparation of drug-loaded poly(acrylic acid) films

Acrylic acid (AA) and distilled water were mixed at a 1:1 ratio by weight. Ethylene glycol dimethacrylate, the cross-linking agent, was then added to the solutions at various amounts between 0 and 2.5 wt% and thoroughly mixed. 1 wt% of azoisobuthylonitrile (AIBN) was added to initiate the reaction (Peppas and Wright, 1996). The model drug (10 mg) was added into the PAA solutions under constant stirring for 1 h. The solutions were cast on a mold (9 cm diameter) and dried in a vacuum oven at 60 °C for 12 h. The samples were used to characterize the release profile without additional washing of the gels.

2.2.2. Synthesis of polypyrrole

Pyrrole monomer was dried with CaH_2 at the ratio of 100 g of CaH_2 per 1 l of pyrrole for 24 h, and then purified by distillating pyrrole under the reduced pressure prior to use. Doped polypyrrole (PPy) at various dopant anions was chemically synthesized by the *in situ* doped oxidative coupling polymerization (Prissanaroon et al., 2000). 0.3 mol of dried pyrrole monomer and 0.15 mol of the model drug were dissolved in 500 ml of distilled water. The mixture was stirred vigorously for 15 min at 0 °C in an ice bath. 0.06 mol of ammonium persulfate (APS) in 100 ml distilled water was slowly added to the mixture solution at a rate of 5 ml/min and the temperature was maintained at 0 °C. Reaction was carried out for approximately 40 h and then terminated by pouring 20 ml of methanol into the mixture. The resultant black polypyrrole powder was filtered and washed sequentially with 50 ml of distilled water, 50 ml of methanol, and 50 ml of acetone. The washing procedure described above was repeated, followed by filtering and drying in a vacuum oven at 25 °C for 24 h. Freshly synthesized polypyrrole powder was then stored in a desiccator. To synthesize the undoped polypyrrole, the procedure was the same as that of the doped polypyrroles except for the addition of the dopant into the mixture.

2.2.3. Preparation of polypyrrole/poly(acrylic acid) blend films

Polypyrrole powder was dried at room temperature for 12 h. 0.3 g of the doped polypyrrole powder was dispersed in the acrylic solution, and the mixture was stirred for 3 h. The mixture was cast on the mold (9 cm diameter) and the specimens were dried in a vacuum oven at 60 °C for 12 h.

2.3. Characterizations

An attenuated total reflection Fourier transform infrared spectrometer (ATR-FTIR spectrometer, Bruker, Equinox 55/FRA 1065) was used to identify the functional group of the synthesized PPy and the interaction between the drug and the blend films. The optical grade KBr (Carlo Erba Reagent) was used as a background material. A thermal gravimetric analyzer (TG-DTA, PerkinElmer) was used to investigate the thermal behavior of the undoped PPy, the doped PPy, the model drug, the PAA hydrogel, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend films, at the temperature range between 30 and 600 °C and at the heating rate of 10 °C/min under nitrogen atmosphere. The samples were weighed in between 10 and 15 mg and loaded into platinum pans. DSC thermograms (equilibrated with an indium standard with each sample weight between 3 and 5 mg) were obtained between 25 and 350 °C at a heating rate of 10 °C/min under nitrogen purge (60 ml/min) without a pre-heat treatment. A particle size analyzer (Malvern Instruments Ltd., Masterizer X) was used to determine the polypyrrole particle sizes and the size distribution. The morphology of doped PPy was examined using a scanning electron microscope or SEM (JEOL, model JSM-5200) at the magnifications of 3500× and 1500×. A UV–vis spectrophotometer (PerkinElmer, Lambda 10) was used to determine the concentration of the model drug at the wavelength 298 nm. The specific electrical conductivity values of the undoped and the doped PPy were measured by a custom-built two point probe (Keithley, Model 6517A).

Swelling studies of poly(acrylic acid) hydrogels were carried out immediately after the cross-linking process. The degree of swelling and the weight loss of PAA films were determined from the submersion in the acetate buffer solution at 37 °C for 5 days (Peppas and Wright, 1996):

$$\text{degree of swelling}\,(\%) = \frac{M - M_\text{d}}{M_\text{d}} \times 100 \tag{1}$$

and

$$\text{weight loss}\,(\%) = \frac{M_\text{i} - M_\text{d}}{M_\text{i}} \times 100 \tag{2}$$

where M is the weight of each sample after submersion in the acetate buffer solution, M_d is the weight of the sample after submission for 24 h and after removing the solvent (through vacuum oven) and, M_i is the initial weight of the sample.

To determine the equilibrium swelling ratio, a sample of the hydrogel (1 cm^2 square) was cut and weighed in the air and heptane (a non-solvent). The sample was placed in a stainless steel mesh basket suspended in heptane. The sample was then placed in the acetate buffer solution at 37 °C for 5 days to obtain the equilibrium swelling state, then it was weighed in the air and heptane again. Finally, the sample was dried at 25 °C in a vacuum for 5 days, and it was weighed in the air and heptanes.

The molecular weight between cross-links, $\overline{M}_\text{c}$, is calculated from the swelling data as follows:

$$\frac{1}{\bar{M}_\text{c}} = \frac{2}{\bar{M}_\text{n}} - \frac{\bar{\nu}/\bar{V}_1[\ln(1-\nu_{2,\text{s}}) + \nu_{2,\text{s}} + \chi(\nu_{2,\text{s}})^2]}{\nu_{2,\text{r}}[(\nu_{2,\text{s}}/\nu_{2,\text{r}})^{1/3} - (1/2)(\nu_{2,\text{s}}/\nu_{2,\text{r}})]} \tag{3}$$

where $\overline{M}_n$ is the number-average molecular weight of the polymer before cross-linking (75,000), $\bar{\nu}$ is the specific volume of PAA (0.951 cm^3/g), $\overline{V}_1$ is the molar volume of water (18.1 cm^3/mol), $\nu_{2,\text{r}}$

is the polymer volume fraction in the gel in the relaxed state, $\nu_{2,s}$ is the polymer volume fraction in the gel in the swollen state, and x is the Flory interaction parameter of PAA (=0.5), and the dissociation constant pK_a is 4.7.

The hydrogel mesh size, ξ, is calculated using Eq. (4):

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

where C_n is the Flory characteristic ratio for PAA (=6.7), and M_r is the molecular weight of the repeating unit of PAA.

The cross-linking density of the hydrogel is calculated using the following equation:

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

2.4. Drug release experiments

2.4.1. Spectrophotometric analysis of model drug

A UV–visible spectrophotometer (Shimadzu, UV-2550) was used to determine the UV spectra of the model drug. The characteristic peak of the model drug occurs at 298 nm. The absorbance at this wavelength was used to determine the amount of drug released from the predetermined calibration curve.

2.4.2. Actual drug content

The actual amounts of the drug in the drug-loaded PAA hydrogel (circular disc about 2.5 cm in diameter) and the drug-doped PPy (0.6 mg) were measured by dissolving the samples (the drug-loaded PAA hydrogel and the drug-doped PPy) in 5 ml of dimethylsulfoxide (DMSO), and 0.1 ml of the solution was added to an 8 ml of acetate buffer solution. The drug concentration was measured using the UV–visible spectrophotometer at the wavelength of 298 nm.

2.4.3. Diffusion studies

Diffusion studies were carried out using the modified Franz diffusion cells for the in vitro studies. The modified Franz diffusion cell is a vertical transparent diffusion cell, consisting of two half-cells. The first half-cell is the donor half which is exposed to room temperature (25 °C). Another half-cell is the receptor half which is exposed to 3 ml acetate buffer (pH 5.5 and ionic strength of 0.001225 M) and maintained at 37 °C by a circulating water bath. The polypyrrole/poly(acrylic acid) blend film filled with drug was placed over a porous screen on the receptor half. Electric potential was applied through a thin copper electrode, the attached membrane, the acetate buffer, and a needle electrode. The drug-loaded PAA hydrogels at cross-linking ratios of 0, 0.25, 0.5, 0.75, 1, 1.25, 2.0 and 2.5 were used to investigate the drug release profile. The total diffusion period investigated was 48 h, 0.3 ml of the buffer solution was withdrawn and an equal amount of fresh buffer solution was added to the cell. The UV–visible spectrophotometer was used to measure the absorbance of the samples to determine the model drug concentrations and, hence, the amounts of drug released.

3. Results and discussion

3.1. Characterization

3.1.1. Fourier transform infrared spectroscopy (FTIR)

The absorption infrared spectra of PAA hydrogel loaded with 0.1 g of sulfosalicylic acid, PPy, a drug-loaded PPy, a PAA hydrogel, a drug-loaded PAA hydrogel, a drug-loaded PPy/PAA blend film, and sulfosalicylic acid are shown in Fig. 1. The absorption infrared spectrum of PPy shows a peak at 1280 cm^{-1} and a broad region at 3426 cm^{-1} which can be assigned to the stretching vibration and the bending vibration of N–H bond, respectively (Kang and Geckeler, 2000; Tian and Zerbi, 1989). The peaks at 3000–2800 cm^{-1} represent the aliphatic C–H bonds and the peaks at 1543 and 1465 cm^{-1} can be identified as the asymmetric and the symmetric C=C/C–C stretching vibrations in the pyrrole ring (Khatua and Hsieh, 1997; Rosner and Rubner, 1994; Wadhwa et al., 2006; Toshima and Ihata, 1996). After polypyrrole is doped with 5-sulfosalicylic acid, the peak at 3426 cm^{-1} disappears. The bands at 1181 and 590 cm^{-1} represent the S=O and the S–O stretching vibrations of sulfonate anions which compensate the positive charges in the polypyrrole chains (Gassner et al., 1997; Pouchert, 1997).

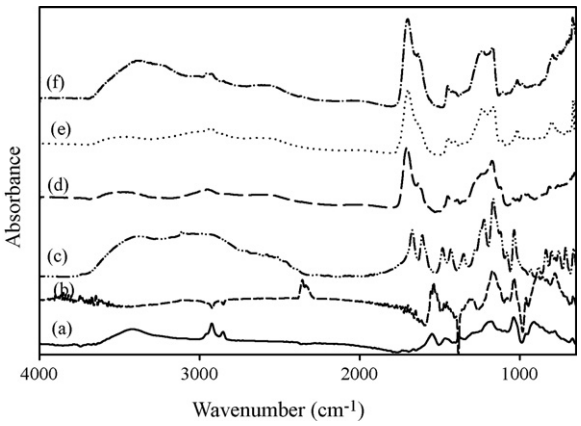

Fig. 1. Absorption infrared spectra of: (a) the PPy powder; (b) the PPy doped with SSA; (c) the SSA powder; (d) the PAA hydrogel; (e) the SSA-loaded PAA hydrogel; and (f) the SSA-loaded PPy/PAA blend film.

For pure PAA, the drug-loaded PAA, and the drug-loaded PPy/PAA blend film, a broad region observed around 3000–3600 cm^{-1} can be assigned to the OH stretching, the C=O stretching, and the CO^- stretching, due to the intermolecular hydrogen bonding within this region (Peppas and Wright, 1998). The peak at 1705 cm^{-1} represents the C=O stretching in pure PAA but shifts to 1698 and 1701 cm^{-1} in the drug-loaded PAA hydrogel and the drug-loaded PPy/PAA blend film, respectively.

For pure SSA, two peaks at 1038 cm^{-1} and at around 670 cm^{-1} belong to the sulfonate groups (SO^{3-}) stretching (Weast and Astle, 1978). For the drug-loaded PAA hydrogel and the drug-loaded PPy/PAA blend film, the sulfonate groups (SO^{3-}) stretching is intensified and the OH stretching peak has a slight shift between 3000 and 3600 cm^{-1}. These results suggest the H-bonding between the sulfonate groups of sulfosalicylic acid with the hydroxyl group of PAA hydrogel (Wu et al., 2006) and the amine group of PPy.

3.1.2. Thermal properties of PPy, doped PPy, and drug-loaded PPy/PAA blend film

Fig. 2 shows DSC thermograms of pure PAA, pure SSA, the drug-loaded PAA hydrogel, PPy, the doped PPy and the drug-loaded PPy/PAA blend film. Endothermic transitions at 151.5, 138.3, 156.0, 142.1 and 153.2 °C can be related to the evaporation of the polymer backbones of pure PAA, pure PPy, the dopped PPy, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend film, respectively (Nateghi and Borhani, 2008). The DSC thermograms for pure PAA and the drug exhibit the melting temperatures at 312.1 and 165.5 °C, respectively. For pure PPy, the thermogram exhibits a broad transition at around 286.3 °C. The melting temperatures (T_m) of dopped PPy, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend film shift to about 274.3, 306.5 and 294 °C, respectively. A possible reason for the peak shifts is the interaction between the polymer and the drug molecule, since SSA can form the H-bonding with the hydroxyl group of PAA (Small et al., 1997)

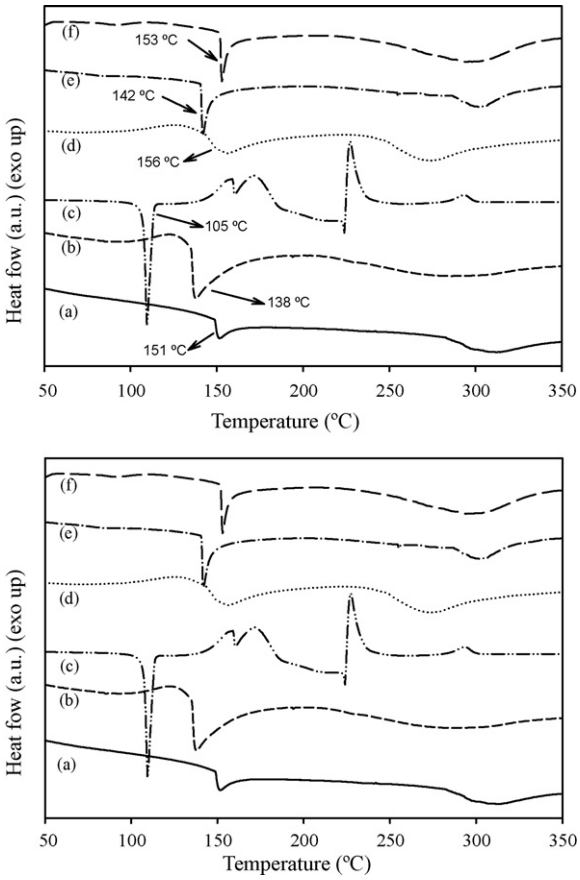

Fig. 2. DSC thermograms of: (a) the pure PAA hydrogel; (b) the pure PPy; (c) the model drug; (d) the drug-loaded PPy; (e) the drug-loaded PAA hydrogel; and (f) the drug-loaded PPy/PAA blend film.

and the electrostatic interaction between SSA and PPy (Xue and Yin, 2006).

Fig. 3 shows the TGA thermograms for pure PAA and the drug-loaded PAA hydrogels, the drug-loaded PPy/PAA blend film, pure SSA, PPy and doped PPy. For the undoped PPY and the doped PPy, there are three transitions. The first transition (45–65 °C) can be referred to the losses of the organic solvent and water. The second transition (100–130 °C) corresponds to the PPy side chain degradation, and the third transition (215–235 °C) identifies the PPy backbone degradation. The TGA results of PPy and doped PPy show that the doped PPy has higher thermal stability; after doping the

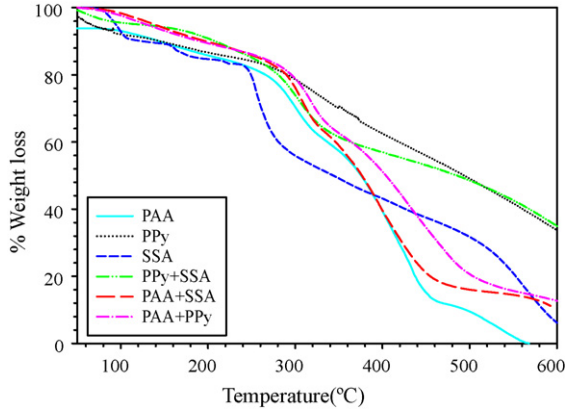

Fig. 3. TGA thermograms of: the PAA hydrogel; the drug-loaded PAA hydrogel; the drug-loaded PPy/PAA blend film; the model drug; PPy; and the drug-loaded PPy.

Table 1
Specific electrical conductivity (S/cm) of undoped PPy and the 5-sulfosodiumsalicylic acid-doped PPy.

Sample	Specific electrical conductivity (S/cm)	Std (S/cm)
PPy	1.149	0.039
PPy:SSA = 1:1	1.154	0.04
PPy:SSA = 1:5	2.072	0.038
PPy:SSA = 1:10	3.312	0.093
PPy:SSA = 1:50	51.836	1.605

degradation temperature of sulfuric acid-doped PPy is higher than that of the undoped PPy. Similarly, pure PAA, pure SSA, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend also show three transitions. The first transition occurs in the temperature range of about 50–90 °C corresponding to the evaporation of water. The second transition covering the temperature range of 150–290 °C is due to the decomposition of the sulfonic functional groups of SSA and the dehydration and the decarboxylation of PAA, leading to the formation of inter- and intra-molecular anhydride (Tanodekaew et al., 2004). The third decomposition stage in the range of 240–370 °C has been described as the degradation of residual polymer.

3.1.3. Electrical conductivity measurement of PPy and doped PPy

The specific conductivity which is the inverse of specific resistivity (ρ) of the undoped PPy and doped PPy with 5-sulfosalicylic acid in the form of pellets were measured using the two-point probe meter. Using the calibrated geometric correction factor (K) of 6.22×10^{-4}, the specific electrical conductivity of the undoped PPy is 1.149 S/cm with a standard deviation of 0.039 S/cm. The electrical conductivity of the undoped PPy is rather high due to APS, the oxidant used in the polymerization process, which produces HSO_4^- acting as a dopant. For the doped PPy, the specific electrical conductivity increases with the doping level, as shown in Table 1. The increase in electrical conductivity can be attributed to the increase in the number of charge carriers, the degree of crystallinity, and the charge mobility (Soontornworajit et al., 2007).

3.1.4. A particle size analyzer of PPy and doped PPy

The mean particle diameter of PPy was determined by the particle size analyzer (PSA) to be approximately 18.57 ± 0.29 and 19.71 ± 0.04 μm for undoped and doped PPy, respectively. This shows that doping has no effect on the particle size.

3.1.5. Scanning electron micrograph of PPy and doped PPy

Fig. 4 shows the morphology of the undoped PPy and the doped PPy powders at magnifications 1500× and 3500×. The morphologies of the undoped PPy powder and the doped PPy powder at various doping levels are not distinguishable. However, the sulfosalicylic acid-doped PPy appears to be more agglomerated than the drug-free PPy due to the electrostatic interaction between the particles.

3.1.6. Swelling behavior of drug-loaded PAA hydrogel

The PAA hydrogels were prepared at various cross-linking ratios using different amounts of ethylene glycol dimethacrylate. The effects of the cross-linking ratios on the swelling behavior, the molecular weight between crosslinks, the mesh size, and the drug diffusion behavior are determined.

Fig. 5 shows the degree of swelling and the weight loss of PAA hydrogels at various cross-linking ratios after an immersion in acetate buffer solution at 37 °C for 5 days. The data show that the degree of swelling and the weight loss increase with decreasing cross-linking ratio. Since the lower cross-linked hydrogel has a longer PAA strand between crosslinks or a looser network, it can swell appreciably more, enlarging the pore size as determined by

Fig. 4. The morphology of polypyrrole powder and the 5-sulfosalicylic acid-doped polypyrrole powder at the magnification 3500×: (a) PPy powder; (b) PPy:SSA = 1:1; and (c) PPy:SSA = 1:50.

using the equilibrium swelling theory developed by Peppas and Wright (1998). The swelling data are used to evaluate the structure of these hydrogels. The molecular weight between crosslinks, the mesh size, and the cross-linking density are the main parameters used for characterizing the porous structure of hydrogel for drug delivery and can be determined using the equilibrium swelling theory developed by Peppas and Wright (1998). Table 2 shows the molecular weights between crosslinks, the mesh size, and the cross-linking density of each PAA hydrogel at various cross-linking ratios with and without electric field. An increase in the cross-linking agent EGDMA decreases the molecular weight between crosslinks, $\overline{M}_c$, which in turn results in a smaller network mesh size, ξ (Serra et al., 2006). The mesh sizes of hydrogels vary between 103.92 and 478.9 Å under no electric field applied and between 132.67 and 516.02 Å under electric field applied. Thus the comparison of mesh size values between the system with electric field and without electric field suggests that the electric field has a measurable effect on the PAA structure. The electro-induced gel swelling can be explained by the electrically induced ionization of a hydrogel. When an electric field is applied to an aqueous medium, the positive ions (H^+) in aqueous medium migrate toward the cathode side. H^+ ions penetrate into the hydrogel on their way to the cathode side. This induces the ionization of the hydrogel and causes the gel on the cathode side to swell as the ionized groups become hydrated (Murdan, 2003).

3.2. Release kinetics of the model drug

3.2.1. Determination of actual drug content

The actual amounts of drug were measured using the UV–visible spectrophotometer at the wavelength of 298 nm. The actual amounts of drug present are 6.10, 6.29, 6.43, 6.63, 6.66, 6.72, 6.99 and 7.79 for the samples with the cross-linking ratios of 1.82×10^{-3}, 3.64×10^{-3}, 5.45×10^{-3}, 7.27×10^{-3}, 9.09×10^{-3}, 1.09×10^{-2}, 1.45×10^{-2} and 1.82×10^{-2}, respectively.

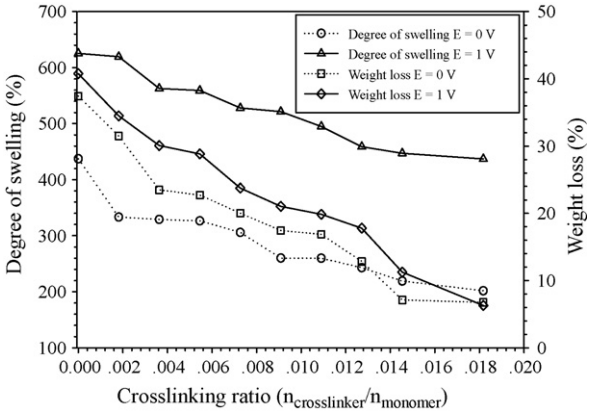

Fig. 5. Degree of swelling (%) and weight loss (%) of poly(acrylic acid) hydrogels of various cross-linking ratios at 37 °C after 5 days.

3.2.2. Release kinetics of model drug from drug-loaded PAA hydrogel and drug-loaded PPy/PAA blend film

For the study of sulfosalicylic acid transport characteristics from the PAA hydrogels, the power law model is used to fit the experimental data. This model is described by the Ritger–Peppas equation (Venkatesh et al., 1992):

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

where M_t/M_∞ is the fractional drug released, k is a kinetic constant, t is the release time, and n is the scaling exponent that can be related to the drug transport mechanisms.

For a thin hydrogel film, when $n = 0.5$, the drug release mechanism is the Fickian diffusion:

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

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 PAA hydrogels can be calculated from the slopes of plots of drug accumulation versus square root of time according to Higuchi's 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, C_0 is the initial drug concentration in the hydrogel, and D is the diffusion coefficient of a drug.

3.2.3. Effect of cross-linking ratio at electric field strengths of 0 and 1 V

The amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at time t and $t^{1/2}$ of various cross-linking ratios in an absence of electric field during the first 48 h are illustrated in Fig. 6(a) and (b), respectively. The amount of released drug gradually increases with time and then reaches equilibrium, while the plots of the amount of drug released as a function of square root of time show a linear relationship. The amount of sulfosalicylic acid released is reported here as the percentage of the actual amount of sulfosalicylic acid present in the PAA hydrogel sample. The percentage of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel are 84.96%, 70.70%, 64.61% and 57.10% for PAA_0, PAA_1, PAA_1.50 and PAA_2, respectively. The amount of released drug increases with decreasing cross-linking ratio, evidently due to the larger pore size of the lesser cross-linked hydrogel (Nateghi and Borhani, 2008). The degree of swelling of PAA hydrogel decreases with increasing ethylene glycol dimethacrylate concentrations in the hydrogels. With increasing cross-linking agent, the cross-link reaction of hydroxyl

Table 2
The molecular weights between crosslinks, the mesh sizes, and cross-linking densities of PAA hydrogels of various cross-linking ratios with and without electric field applied.

Sample	Cross-linking ratio	$E = 0$ V				$E = 1$ V				
		Number-average molecular weight between crosslinks, M_c (g/mol)	Mesh size, ξ (Å)	Cross-linking density (mol/cm^3)	a/ξ	Current (μA)	Number-average molecular weight between crosslinks, M_c (g/mol)	Mesh size, ξ (Å)	Cross-linking density (mol/cm^3)	a/ξ
PAA_0	0	3.74E+04	478.90	503.58	1.93E−02	1.00	3.74E+04	4.91E+02	5.16E+02	1.88E−02
PAA_0.25	1.82E−03	3.72E+04	421.73	421.73	2.19E−02	2.00	3.73E+04	4.44E+02	4.67E+02	2.08E−02
PAA_0.5	3.64E−03	3.69E+04	395.05	395.05	2.34E−02	2.00	3.72E+04	4.11E+02	4.32E+02	2.25E−02
PAA_0.75	5.45E−03	3.47E+04	316.71	316.71	2.92E−02	2.50	3.63E+04	3.54E+02	3.72E+02	2.61E−02
PAA_1	7.27E−03	3.16E+04	276.80	291.07	3.34E−02	3.50	3.40E+04	3.08E+02	3.24E+02	3.00E−02
PAA_1.25	9.09E−03	2.68E+04	236.63	248.83	3.91E−02	2.50	3.05E+04	2.69E+02	2.83E+02	3.44E−02
PAA_1.5	1.09E−02	2.14E+04	197.21	207.37	4.69E−02	1.00	2.63E+04	2.34E+02	2.46E+02	3.95E−02
PAA_1.75	1.27E−02	1.63E+04	162.53	170.90	5.69E−02	1.00	2.32E+04	2.13E+02	2.24E+02	4.35E−02
PAA_2	1.45E−02	1.28E+04	137.85	144.95	6.71E−02	3.00	1.30E+04	1.40E+02	1.47E+02	6.61E−02
PAA_2.5	1.82E−02	7.83E+03	103.92	109.28	8.90E−02	3.50	1.09E+04	1.26E+02	1.33E+02	7.33E−02

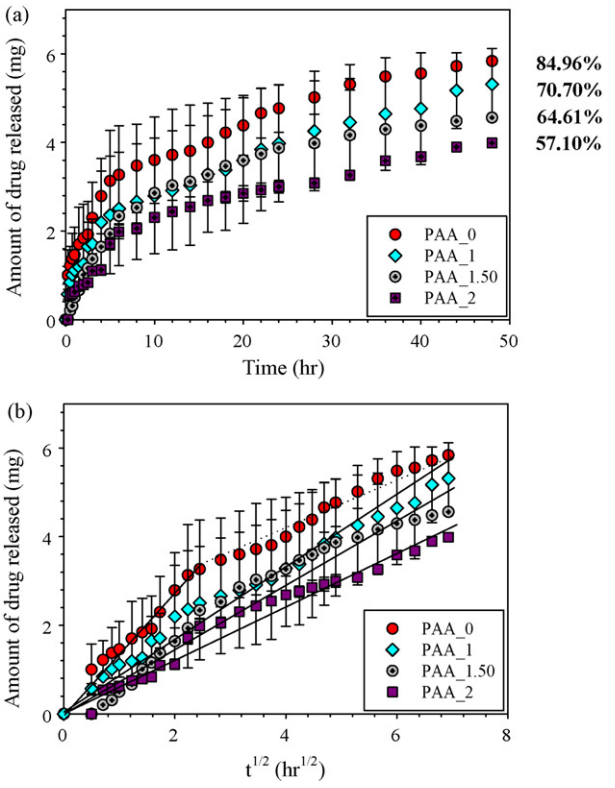

Fig. 6. Amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogels of various cross-linking ratios versus: (a) t and (b) $t^{1/2}$ at $E = 0$ V, pH 5.5, 37 °C, and # samples used 2 ($n = 2$).

groups in poly(acrylic acid) with aldehyde groups in ethylene glycol dimethacrylate to form ether linkage is amplified (Serra et al., 2006).

Fig. 7(a) and (b) shows the amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at time t and $t^{1/2}$ of the samples of various cross-linking ratios at an electric field strength of 1 V. Each sample was attached to the negatively charged electrode (cathode). Similar to the previous finding, the amount of released drug gradually increases with time and then reaches an equilibrium value. Nonetheless, the linear relationship exists between the amount of drug release and the square root of time. The amount of released drug also increases with decreasing cross-linking ratio due to the larger pore size of the lesser cross-linked hydrogel. The amount of sulfosalicylic acid released can be reported here as the percentage of the actual amount of sulfosalicylic acid present in the PAA hydrogel sample. The percentage of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at an electric field strength of 1 V are 96.27%, 78.69%, 65.57% and 44.95% for PAA_0, PAA_1, PAA_1.50 and PAA_2.5, respectively. The amount of SA released at a given cross-linking ratio is greater when the electric field strength of 1 V was applied. The primary driving force is the higher 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 PAA hydrogel mesh size (Niamlang and Sirivat, 2009). Table 2 shows that for the PAA_0 hydrogel, the mesh size increases from 4.78×10^2 to 4.91×10^2 Å as the electrical voltage is increased from 0 to 1 V.

From a plot of $\ln(M_t/M_\infty)$ versus $\ln(t)$, the scaling exponent n was determined from Eq. (1) and shown in Table 3. The n value of uncrosslinked PAA hydrogel without electric field is near the Fickian exponent value of $n = 0.5$. Thus, the sulfosalicylic acid release during the initial period is mainly controlled by the Fickian

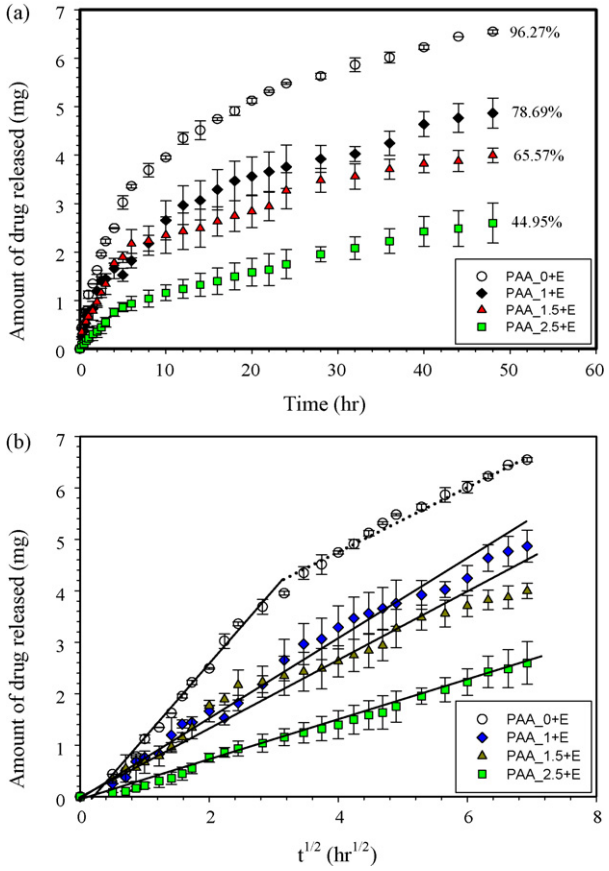

Fig. 7. Amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogels of various cross-linking ratios versus: (a) t and (b) $t^{1/2}$ at E = 1 V, pH 5.5, 37 °C, and # samples used 2 (n = 2).

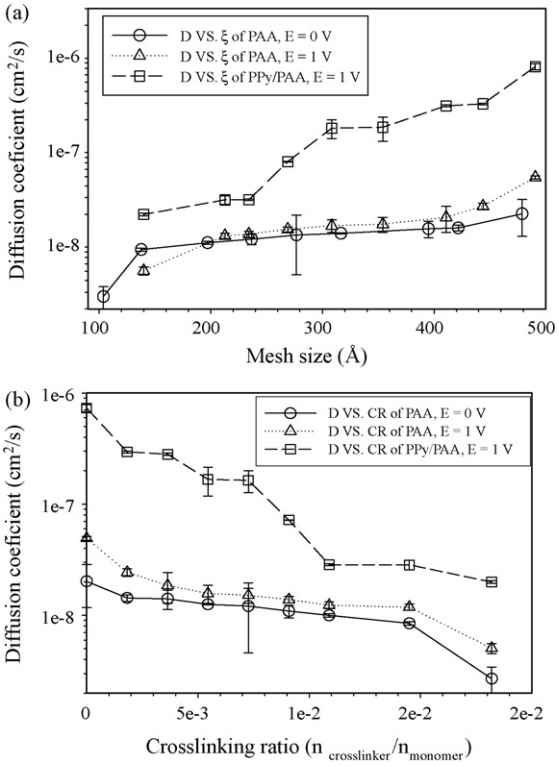

Fig. 8. The diffusion coefficients of SSA from PAA hydrogels and PPy/PAA blend films versus: (a) cross-linking ratios and (b) mesh size (Å), ξ, at electric field strengths of 0 and 1 V and at 37 °C (n = 2).

diffusion mechanism and the change in their structure has an effect on the mechanism of release.

The diffusion coefficients of each system are calculated from the slopes of these plots using the Higuchi's equation (see Fig. 6b).

Fig. 8 shows the diffusion coefficients of sulfosalicylic acid from poly(acrylic acid) hydrogels and polypyrrole/poly(acrylic acid) blend films versus cross-linking ratios and mesh size at the electric field strengths of 0 and 1 V, and at 37 °C. The dif-

Table 3
Release kinetic parameters and the linear regression values obtained from fitting the drug release experimental data to the Ritger–Peppas model.

Sample	Cross-linking ratio, X	Electric field strength (V)	Current (μA)	Diffusional exponent (n)	Kinetic constant (k_H)(h^{-n})	r^2
PAA_0	0.00	0	–	0.352	0.311	0.989
PAA_0.25	1.82E−03	0	–	0.539	0.150	0.984
PAA_0.5	3.64E−03	0	–	0.644	0.109	0.966
PAA_0.75	5.45E−03	0	–	0.609	0.117	0.962
PAA_1	7.27E−03	0	–	0.408	0.218	0.991
PAA_1.25	9.09E−03	0	–	0.495	0.170	0.957
PAA_1.5	1.09E−02	0	–	0.568	0.137	0.943
PAA_2	1.45E−02	0	–	0.438	0.159	0.969
PAA_2.5	1.82E−02	0	–	0.662	0.045	0.982
PAA_0 + E	0.00	1	1.00	0.505	0.226	0.969
PAA_0.25 + E	1.82E−03	1	2.00	0.613	0.140	0.987
PAA_0.5 + E	3.64E−03	1	2.00	0.775	0.076	0.967
PAA_0.75 + E	5.45E−03	1	2.50	0.369	0.240	0.978
PAA_1 + E	7.27E−03	1	3.50	0.543	0.145	0.970
PAA_1.25 + E	9.09E−03	1	2.50	0.708	0.088	0.961
PAA_1.5 + E	1.09E−02	1	1.00	0.477	0.154	0.971
PAA_2 + E	1.45E−02	1	3.00	0.598	0.118	0.960
PAA_2.5+E	1.82E−02	1	3.50	0.557	0.089	0.937
PAA_0 + Ppy + E	0.00	1	3.50	0.412	0.316	0.804
PAA_0.25/Ppy+E	1.82E−03	1	3.50	0.393	0.320	0.952
PAA_0.5/Ppy + E	3.64E−03	1	2.50	0.308	0.355	0.901
PAA_0.75/Ppy + E	5.45E−03	1	2.50	0.615	0.134	0.925
PAA_1/Ppy + E	7.27E−03	1	3.50	0.644	0.124	0.928
PAA_1.25/Ppy + E	9.09E−03	1	2.50	0.511	0.178	0.948
PAA_1.5/Ppy + E	1.09E−02	1	1.00	0.383	0.244	0.986
PAA_2/Ppy + E	1.45E−02	1	1.00	0.710	0.099	0.917
PAA_2.5/Ppy + E	1.82E−02	1	1.00	0.801	0.064	0.855

Table 4
The diffusion coefficients of the drug from PAA hydrogels at various conditions.

Solute	M_w	Drug size (Å)	Mesh size, ξ(Å)	D (cm^2/s)	T (°C)	pH	E (V)	Remarks
Sulfosalicylic acid	254	9.25	478.9	2.02E−08	37	5.5	–	Uncrosslinked
			395.05	1.41E−08	37	5.5	–	Cross-linking ratio = 3.64E−03
			276.8	1.21E−08	37	5.5	–	Cross-linking ratio = 7.27E−03
			137.85	8.47E−09	37	5.5	–	Cross-linking ratio = 1.45E−02
			490.73	4.92E−08	37	5.5	1	Uncrosslinked
			410.87	1.86E−08	37	5.5	1	Cross-linking ratio = 3.64E−03
			308.45	1.51E−08	37	5.5	1	Cross-linking ratio = 7.27E−03
			140.02	1.18E−08	37	5.5	1	Cross-linking ratio = 1.45E−02
Theophylline[a]	180	–	398	4.53E−06	37	3	–	
			589	5.98E−06	37	6	–	
Vitamin B_{12}[a]	1,355	–	398	3.19E−06	37	3	–	
			589	3.57E−06	37	6	–	
Myoglobin[a]	17,200	–	589	1.60E−08	37	6	–	

[a] Peppas and Wright (1996).

fusion coefficient of sulfosalicylic acid increases with decreasing cross-linking ratio due to the larger pore size or the lower cross-linking ratio. As the electric field is applied the diffusion coefficient increases due to the electrostatic force from electrical field driving the charged drug, sulfosalicylic acid (Kantaria et al., 1999), to the oppositely charged electrode (Massoumi and Entezmi, 2001). The diffusion coefficients of the solute from PAA hydrogels at various conditions are shown in Table 4. The diffusion coefficients of sulfosalicylic acid from PAA hydrogels vary between 3.22×10^{-9} and 2.02×10^{-8} cm^2/s in the absence of electric field and between 5.06×10^{-9} and 4.92×10^{-8} cm^2/s under an applied electric field strength of 1 V. For PPy/PAA blend films, the diffusion coefficients of sulfosalicylic acid vary between 1.97×10^{-8} and 7.30×10^{-7} cm^2/s under an applied electric field strength of 1 V.

Peppas and Wright (1996) studied the diffusion coefficients of theophylline, vitamin B_{12}, and myoglobin through PAA membranes at pH of 3 and 6. The diffusion coefficients of theophylline and vitamin B_{12} through PAA membranes are higher than the diffusion coefficients of sulfosalicylic acid from PAA hydrogels since the diffusion coefficients of theophylline and vitamin B_{12} are governed by the drug molecules diffusing through the membranes as driven by the osmotic pressure. On the other hand, the apparent diffusion of sulfosalicylic acid obtained in this experiment 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. For the diffusion coefficients of myoglobin, it is lower than the diffusion coefficients of sulfosalicylic acid from PAA hydrogels since the size of myoglobin is large. 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 (Peppas and Wright, 1996; Sumonman et al., 2009).

Fig. 9 shows the log–log plot of diffusion coefficients of sulfosalicylic acid from poly(acrylic acid) hydrogels versus drug size/mesh size of hydrogels at electric field strengths of 0 and 1 V at 37 °C. From the data, the scaling exponent m was determined from the following equation:

$$D = D_0 \left(\frac{a}{\xi}\right)^{-m} \quad (9)$$

where D is the diffusion coefficient of the drug, D_0 is the initial diffusion coefficient, a is the drug size, ξ is the mesh size of hydrogel, and m is the scaling exponent.

The scaling exponent m value for the SSA to diffuse through the PAA hydrogel under the electric field strengths of 0 and 1 V

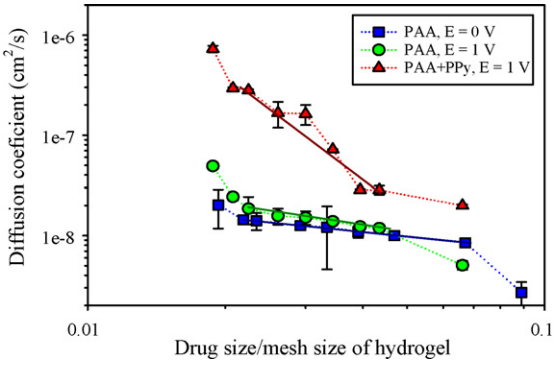

Fig. 9. The diffusion coefficients of SSA from PAA hydrogels and PPy/PAA blend films versus drug size/mesh size of hydrogels at electric field strengths of 0 and 1 V at 37 °C (n = 2).

and the SSA to diffuse through the PPy/PAA blend film under the electric field strength of 1 V are 0.48, 0.49 and 3.61, respectively. D_0 values are 2.33×10^{-9}, 2.09×10^{-9} and 2.97×10^{-13} cm^2/s, respectively.

4. Conclusions

In this work, the sulfosalicylic acid-loaded poly(acrylic acid) hydrogels of various cross-linking ratios was prepared to study the release mechanism and the diffusion coefficient of the drug from poly(acrylic acid) hydrogels with and without applied electric field. Moreover, the drug-loaded polypyrrole/poly(acrylic acid) blend films were also prepared at various cross-linking ratios to compare the release mechanism and the diffusion coefficient with those of the drug-loaded poly(acrylic acid) hydrogels. Each hydrogel was characterized for its swelling ability and mesh size. The degree of swelling, the weight loss, and the mesh size increase monotonically with decreasing cross-linking ratio. The diffusion coefficients of the drug from the PAA hydrogel and the PPy/PAA blend film increase with decreasing cross-linking ratio due to larger mesh or pore size of hydrogel. Under applied electric field, the diffusion coefficient of the drug from the PAA hydrogel increases with increasing applied electric field strength due to the electrostatic force from electrical potential driving the charged drug to the oppositely charged electrode. Moreover, the diffusion coefficient of the drug from PPy/PAA blend film is higher than that of the pristine PAA hydrogel. It can be concluded that, by varying the cross-linking 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 a desired level. Consequently, the conductive polymer is an attractive and effective host in promoting the transport of SSA through the PAA matrix.

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References

A-sasutjarit, R., Sirivat, A., Vayumhasuwan, P., 2005. Viscoelastic properties of carbopol 940 gels and their relationships to piroxicam diffusion coefficients in gel bases. Pharm. Res. 22, 2134–2140.

Dai, H., Chen, Q., Qin, H., Guan, Y., Shaen, D., Hua, Y., Tang, Y., Xu, J., 2006. A temperature-responsive copolymer hydrogel in controlled drug delivery. Macromolecules 39, 6584–6589.

Elliott, J.E., Macdonald, M., Nie, J., Bowman, C.N., 2004. Structure and swelling of poly(acrylic acid) hydrogels: effect of pH, ionic strength, and dilution on the crosslinked polymer structure. Polymer 45, 1503–1510.

Gassner, F., Graf, S., Merz, A., 1997. On the physical properties of conducting poly(3,4-dimethoxypyrrole) films. Synth. Met. 87, 75–79.

Kang, H.C., Geckeler, K.E., 2000. Enhanced electrical conductivity of polypyrrole prepared by chemical oxidative polymerization: effect of the preparation technique and polymer additive. Polymer 41, 6931–6934.

Kantaria, S., Rees, G.D., Lawrence, M.J., 1999. Gelatin stabilized microemulsion-based organogels: rheology and application in iontophoretic transdermal drug delivery. J. Control. Release 60, 355–365.

Khatua, S., Hsieh, Y., 1997. Chlorine degradation of polyether-based polyurethane. J. Polym. Sci. Polym. Chem. 35, 3263–3273.

Krings, L.H.M., Havinga, E.E., Donkers, J.J.T.M., Vork, F.T.A., 1993. The application of polypyrrole as counter electrode in electrolytic capacitors. Synth. Met. 54, 453–460.

Lira, L.M., Torresi, C., 2005. Conducting polymer–hydrogel composites for electrochemical release devices: synthesis and characterization of semi-interpenetrating polyaniline–polyacrylamide network. Electrochem. Commun. 7, 717–723.

Massoumi, B., Entezmi, A., 2001. Controlled release of sulfosalicylic acid during electrochemical switching of conducting polymer bilayer. Eur. Polym. J. 37, 1015–1020.

Murdan, S., 2003. Electro-responsive drug delivery from hydrogels. J. Control. Release 92, 1–17.

Nateghi, M.R., Borhani, M., 2008. Preparation, characterization and application of polyanthranilic acid-co-pyrrole. React. Funct. Polym. 68, 153–160.

Niamlang, S., Sirivat, A., 2009. Electrically controlled release of salicylic acid from poly(p-phenylene vinylene)/polyacrylamide hydrogels. Int. J. Pharm. 371, 126–133.

Peppas, N.A., Wright, S.L., 1998. Drug diffusion and binding in ionizable interpenetrating networks from poly(vinyl alcohol) and poly(acrylic acid). Eur. J. Pharm. Biopharm. 46, 15–29.

Peppas, N.A., Wright, S.L., 1996. Solute diffusion in poly(vinyl alcohol)/poly(acrylic acid) interpenetrating networks. Macromolecules 29, 8798–8804.

Pouchert, C.J., 1997. The Aldrich Library of FT-IR Spectra. Aldrich Chemical Company, Milwaukee.

Prissanaroon, W., Ruangchuay, L., Sirivat, A., Schwank, J., 2000. Electrical conductivity response of dodecylbenzene sulfonic acid-doped polypyrrole films to SO_2-N_2 mixtures. Synth. Met. 114, 65–72.

Rosner, R.B., Rubner, M.F., 1994. Solid-state polymerization polypyrrole within a Langmuir-Blodgett film of ferric stearate. Chem. Mater. 6, 581–586.

Serra, L., Domenech, J., Peppas, N.A., 2006. Drug transport mechanisms and release kinetics from molecularly designed poly(acrylic acid-g-ethylene glycol) hydrogels. Biomaterials 27, 5440–5451.

Small, C.J., Too, C.O., Wallace, G.G., 1997. Responsive conducting polymer–hydrogel composites. Polym. Gels Netw. 5, 251–265.

Soontornworajit, B., Wannatong, L., Hiamtup, P., Niamlang, S., Chotpattananont, D., Sirivat, A., Schwank, J., 2007. Induced interaction between polypyrrole and SO_2 via molecular sieve 13×. Mater. Sci. Eng. B 136, 78–86.

Tanodekaew, S., Prasitsilp, M., Swasdison, S., Thavornyutikarn, B., Pothsree, T., Pateepasen, R., 2004. Preparation of acrylic acid grafted chitin for wound dressing application. Biomaterials 25, 1453–1460.

Tian, B., Zerbi, G., 1989. Structure, lattice dynamics and spectra of pristine and doped polypyrrole. Synth. Met. 28, 1–6.

Toshima, N., Ihata, O., 1996. Catalytic synthesis of conductive polypyrrole using iron (III) catalyst and molecular oxygen. Synth. Met. 79, 165–172.

Venkatesh, S., Hodgin, L., Hanson, P., Suryanarayanan, R., 1992. In vitro release kinetics of salicylic acid from hydrogel patch formulations. J. Control. Release 18, 13–18.

Wadhwa, R., Lagenaur, C.F., Cui, X.T., 2006. Electrochemically controlled release of dexamethasone from conducting polymer polypyrrole coated electrode. J. Control. Release 110, 531–541.

Weast, R.C., Astle, M.J., 1978. CRC Handbook of Chemistry and Physics, 59th ed. CRC Press, Inc., Boca Raton, FL.

Wu, C.S., Lin, F.Y., Chen, C.Y., Chu, P.P., 2006. A polyvinyl alcohol/p-sulfonate phenolic resin composite proton conducting membrane. J. Power Sources 160, 1204–1210.

Xue, S., Yin, G., 2006. Proton exchange membranes based on modified sulfonated poly(ether ether ketone) membranes with chemically in situ polymerized polypyrrole. Electrochim. Acta 52, 847–853.