CHAPTER IV

Controlled Trandermal Iontophoresis of Sulfosalicylic Acid from Polypyrrole/Poly(acrylic acid) Hydrogel

Phithupha Chansai[a], Anuvat Sirivat[a,*],

Datchanee Chotpattananont[b], Kwanchanok Viravaidhaya[c]

[a]Conductive and Electroactive Polymer Research Unit

The Petroleum and Petrochemical College, Chulalongkorn University,

[b]Industrial Chemistry, Chiangmai University

[c]King Mongkut Institute of Technology, Thonburi

Abstract

Transdermal drug delivery system is a system that delivers a drug into a body at a desired site and rate. The conductive polymer-hydrogel blend between polypyrrole (PPy) doped with an anionic drug and poly(acrylic acid) (PAA) were developed as a matrix/carrier for the transdermal drug delivery in which the characteristic releases depend on the electrical field applied. The PAA films and their blend films were prepared by solution casting using ethylene glycol dimethacrylate (EGDMA) as a crosslinking agent. A mechanical blending of PPy particles and PAA matrix was then carried out. The thermal properties were investigated by means of the thermogravimetric analysis and differential scanning calorimeter analysis. Moreover, an electrical conductivity of the polypyrrole and drug-loaded polypyrrole was measured by using a two-point probe meter. The drug diffusions of blended PPy/PAA hydrogels and the non-blended ones were determined by using a modified Franz-diffusion cell with an acetate buffer, pH 5.5, at 37 ^{0}C, for a period of 48

hours in order to investigate the effects of crosslinking ratio and electric field strength. Amounts of the released drug were measured by UV-Visible spectrophotometry. The diffusion coefficient of the drug was calculated through the Higuchi equation, with and without an electric field and at various crosslinking ratios. The diffusion coefficient decreases with the crosslinking ratio with and without the conductive polymer. The diffusion coefficients are greater at the applied electric field of 1.0 V by an order of magnitude relative to those without electric field.

Keywords: Poly (acrylic acid) hydrogels; Polypyrrole; Sulfosalicylic acid; Diffusion coefficient; Electrically controlled drug release

1. Introduction

Drug release is the process of introducing a drug into the body at the appropriate part of the body, during a desired period and for a specific amount. 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 is generally not preferred due to 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 crosslinked polymer network that is insoluble in water but holding a large amount of water in its interspaces of the network. Some hydrogels can change volume, volume phase transition, in response to minute environmental

stimuli, such as solvent, temperature, pH, ionic concentration, electric field, and light irradiation [1]. Hydrogel networks formed from poly(acrylic acid) (PAA) have the ability to absorb many times their weight in water and are the basis of a class of materials called super absorbents. These polymers are used in many applications including diapers and personal hygiene products, ion exchange resins, membranes for hemodialysis and ultrafiltration, and controlled release devices [2]. Moreover PAA is widely used in pharmaceutical since its pH dependent swelling behavior. The applications of PAA in pharmaceutical are used in sustained release of drugs in ocular, nasal, buccal, gastro-intestinal, epidermal and transdermal drug delivery. PAA becomes ionized above its pK_a value (4.7). The ethylene glycol dimethacrylate (EGDMA) is generally used as a cross-linking agent.

Conductive polymer is composed of conjugated polymer chain with π-electrons delocalized along the backbone contribute to electrical conductivity. Because of the special properties, it is used in a controlled drug delivery system. Polypyrrole (PPy) is one of conductive polymers which have received great attention since it exhibits high electron conductivity, good environmental stability, easy to synthesis, and it processes excellent thermal and electron properties. PPy is normally polymerized by either an electrochemical or chemical method [3]. PPy that is synthesized either chemically or electrochemically is insoluble and infusible due to the strong inter- and intra-molecular interactions and cross-linking [4]. 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, so the solubility is increased. From this reason, blend films of conductive

polymer and hydrogel have been utilized and investigated in the controlled drug release.

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. The electrical properties, morphology, swelling, diffusion and drug releasing rates will be investigated and reported.

2. Materials and methods

2.1. Materials

2.1.1 Polypyrrole synthesis

In the polymerization process of polypyrrole, these chemicals were used: pyrrole (Fluka) as a monomer, ammoniumpersulfate (MERCK) as an oxidant, 5-sulfosalicylic acid (Fluka) as a dopant. Methanol (AR grade, Fluka), Acetone (AR grade, Fluka), and distilled water were used as solvents.

2.1.2 Polypyrrole /Poly(acrylic acid) blend film preparation

Acrylic acid (Aldrich) was used as the polymer matrices. 5-sulfosalicylic acid (Fluka), a model drug, was used in the symptomatic management of painful and inflammatory conditions. Ethylene glycol dimethacrylate, EGDMA (Aldrich) was used as the crosslinking agent. Sodium acetate (Ajax Chemicals,

Australia) and glacial acetic acid (Fluka) were of analytical reagent grade and used without further purification.

2.2 Method

2.2.1 Preparation of Drug-Loaded Poly(acrylic acid) Films [5]

We mixed distilled acrylic acid (AA) and water in a 1:1 ratio. Ethylene glycol dimethacrylate used as crosslinking agent, was added to the solutions at various amounts of 0-2.5% and thoroughly mixed. A quantity of 1% azoisobuthylonitrile (AIBN) was added to initiate the reaction. The model drug was added into the PAA solution under constant stirring for 1 hour. Their solutions were cast on a mold (diameter 9 cm) and dried in a vacuum oven at 60 °C for 12 hours.

2.2.2 Preparation of Polypyrrole [6]

Pyrrole monomer was dried with CaH_2 at the ratio of 100 g of CaH_2 per litre of pyrrole for 24 hours and purified by distillating pyrrole under the reduced pressure before use. The doped polypyrrole (PPy) with various dopant anions was chemically synthesized by the *in situ* doped, oxidative coupling polymerization [6]. 0.3 mole of dried pyrrole monomer and 0.15 mole of 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 maintained at 0 °C. Reaction was carried out for approximately 40 hours 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 was repeated again followed by filtering and drying in a vacuum oven at 25 °C for 24 hours. Polypyrrole powder synthesized was then stored in a desiccators. For synthesizing the undoped polypyrrole, the procedure was the same as that of the doped polypyrroles except that dopant was not added into the mixture.

2.2.3 *Preparation of Polypyrrole/Poly(acrylic acid) Blend Films*

The polypyrrole powder dried at room temperature for 12 hours prior to using. The blends were prepared by mechanical blending of doped synthesized polypyrrole. 0.3 g of polypyrrole and acrylic solution were mixed and the mixture was mechanically stirred for 3 hours to disperse the particles. The mixture was cast on the mold (diameter 9 cm) and specimens were dried in a vacuum oven at 60 °C for 12 hours.

2.3 Characterizations

The FTIR spectrometer (Bruker, Equinox 55/FRA 1065) was used to identify the functional group of synthesized PPy and doped PPy. An ATR-FTIR spectrometer was used to investigate interaction between the drug and the blend films, an optical grade KBr (Carlo Erba Reagent) was used as the background material. A thermal gravimetric analyzer (TG-DTA, Perkin Elmer) was used to investigate thermal behavior of the PPy, the doped PPy, the drug, PAA hydrogel, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend films at the temperature scan from 30

to 600 °C and a heating rate of 10 °C/min under nitrogen atmosphere. The samples were weighed in the range of 10-15 mg and loaded into a platinum pan. DSC thermogram (equilibrated with an indium standard; each sample weighed 3–5 mg) was obtained during heating from 25 to 350 °C at a heating rate of 10 °C/min under nitrogen purge (60 ml/min). A particle size analyzer (Malvern Instruments Ltd., Masterizer X) was used to determine particle sizes of polypyrrole. The lenses used in this experiment were 45 mm. The sample was placed in a sample cell across a laser beam. This instrument measured the average particle size and the standard size distribution.The morphology of doped PPy was examined using a scanning electron microscope or SEM (JEOL, model JSM-5200) at magnifications of x3500 and x1500. A UV-VIS spectrophotometer (PERKIN ELMER, Lambda 10) was used to determine the spectra of the model drug at wavelength 298 nm in order to obtain the calibration curve for the amounts of drug released. The specific conductivity values of the undoped and the doped PPy were measured by a custom-built two point probe (Keithley, Model 6517A).

The swelling studies of poly(acrylic acid) hydrogels were analyzed immediately after the crosslinking process. To determine the equilibrium swelling ratio, Q, a sample of the hydrogel (1 cm^2 square) was cut and weighed in air and heptane (a non-solvent). The sample was placed in a stainless steel mesh basket which was suspended with heptane. The sample was then placed in the buffer solutions at 37 °C for 5 days to allow swelling towards equilibrium, and was weighed in air and heptane again. Before weighting, the sample was blotted with tissue paper to remove residue surface water. Finally, the sample was dried at 25 °C in a vacuum for 5 days. Once again it was weighed in air and heptane. The

equilibrium swelling ratio and the polymer volume fraction in the relaxed and swollen states are calculated using the weights measured.

The membranes are prepared and their polymer volume fraction in the relaxed state is calculated using Eq. (4). After each membrane has swollen to equilibrium at 37 °C, the polymer volume fraction of the swollen polymer is calculated using Eq. (5):

$$\upsilon_{2,r} = \frac{Vd}{Vr} \tag{4}$$

$$\upsilon_{2,s} = \frac{Vd}{Vs} \tag{5}$$

where V_d is the volumes of the polymer sample in the dry states, V_r is the volumes of the polymer sample in the relaxed states, V_s is the volumes of the polymer sample in the swollen states, $\upsilon_{2,r}$ is the polymer volume fractions of the relaxed polymer gel and $\upsilon_{2,s}$ is the polymer volume fractions of the swollen polymer gel.

The volumes of the polymer sample in the dry, relaxed, and swollen states are calculated using Eq. (6) - (8) respectively:

$$V_d = \frac{W_{a,d} - W_{h,d}}{\rho_h} \tag{6}$$

$$V_r = \frac{W_{a,r} - W_{h,r}}{\rho_h} \tag{7}$$

$$V_s = \frac{W_{a,s} - W_{h,s}}{\rho_h} \tag{8}$$

where $W_{a,d}$, $W_{h,d}$ is the weights of the dry polymer in air and heptane, $W_{a,r}$, $W_{h,r}$ is the weights of the relaxed polymer in air and heptane, $W_{a,s}$, $W_{a,s}$ is the weights of the swollen polymer in air and heptane, and ρ_h is the density of heptane.

The swelling ratio (Q) is determined from the weight measurements using Eq. (9):

$$Q = \frac{1}{v_{2,s}} \tag{9}$$

The molecular weight between cross-links, $\overline{M}_c$, is calculated from the swelling data using Eq. (10):

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{\frac{\bar{v}}{\bar{V}_1}[\ln(1 - v_{2,s}) + v_{2,s} + \chi v_{2,s}^2]}{\bar{v}_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \frac{1}{2}\left(\frac{v_{2,s}}{v_{2,r}}\right)\right]} \tag{10}$$

where $\overline{M}_n$ is the number-average molecular weight of the polymer before cross-linking (75000), $\bar{v}$ 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), x is the Flory interaction parameter of PAA (0.5) and the dissociation constant is pKa = 4.7.

In general, the presence of PAA leads to a more open network structure and result to higher $\overline{M}_c$ values. The hydrogel mesh size, ξ, is calculated using Eq. (11) [5]:

$$\xi = v_{2,s}^{-1/3}\left[C_n\left(\frac{2\bar{M}_c}{\bar{M}_r}\right)\right]^{1/2} \tag{11}$$

where C_n is the Flory characteristic ratio for PAA (= 6.7).

The crosslinking density of the hydrogel was calculated using Eq (12):

$$\rho_x = \frac{1}{v\bar{M}_c} \tag{12}$$

The degree of swelling and weight loss of PAA films were measured in acetate buffer solution at 37 ^{0}C for 5 days according to the following equations [7]:

$$\text{Degree of swelling (\%)} = \frac{M - M_d}{M_d} \times 100 \qquad (13)$$

and

$$\text{Weight loss (\%)} = \frac{M_i - M_d}{M_i} \times 100 \qquad (14)$$

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

2.4. Drug release experiments

2.4.1. Preparation of Acetate Buffer

Acetate buffer was chosen to simulate human skin pH condition of 5.5. To prepare 1000 ml of the acetate buffer solution, 150 g of sodium acetate was dissolved in distilled water. 15 ml of glacial acetic acid was then added very slowly into the aqueous sodium acetate solution.

2.4.2. Spectrophotometric Analysis of Model Drug

The UV/Visible spectrophotometer (Shimadzu, UV-2550) was used to determine the maximum spectra of the model drug. The characteristic peak at 298 nm was observed. The absorbance value at the maximum wavelength of model drug

was read and the amount of drug release was calculated from the calibration curve at various model drug concentrations.

2.4.3. Actual Drug Content

The actual amount of drug in the drug-loaded PAA hydrogel (circular disc about 2.5 cm in diameter) and the doped PPy were measured by dissolving the sample in 5 ml of dimethylsulfoxide (DMSO) and then 0.1 ml of the solution was added into 0.4 ml of DMSO. The drug solution was measured for the amount of drug by using the UV-Visible spectrophotometer at a wavelength of 298 nm.

2.4.4. Diffusion studies

Diffusion studies are carried out using the modified franz diffusion cells for in vivo studies. The modified franz diffusion cell is a vertical 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 maintained at 37 °C by a circulating water bath. The polypyrrole/poly(acrylic acid) blend film filled with drug was placed over the net on the receptor half and pressing the drug with the electric potential passing the membrane into the buffer. In the study of effect of crosslinking ratio, a unit of drug-loaded PAA hydrogel of various crosslinking ratios (0, 0.25, 0.5, 0.75, 1, 1.25, 2.0 and 2.5) was placed over the net on the receptor compartment. To apply an electric field, the copper plate was used to distribute the electrical potential (E = 1.0 V) to over all position of the hydrogel. The UV-Visible spectrophotometer was used to

measure the absorbance of the samples taken from the receptor half-cell. Samples were collected from the receptor half-cell at every hour and using a calibration curve derived from known concentrations of the drug solutions, the concentration of each sample taken from the receptor half-cell could be determined.

3. Results and discussion

3.1. Characterization

3.1.1. Fourier transforms infrared spectroscopy (FTIR)

The absorption infrared spectra of PAA hydrogel loaded with 0.1 g of sulfosalicylic acid is shown in comparison with those of PPy, a drug load-PPy, a PAA hydrogel, a drug-load PAA hydrogel, a drug-load PPy/PAA blend film, and sulfosalicylic acid as in Figure 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 [8 and 9]. 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 pyrrole ring [10-13]. After polypyrrole is doped with 5-sulfosalicylic acid, the peak at 3426 cm^{-1} disappears. The band at 1181 cm^{-1} and 590 cm^{-1} represent the S=O and the S-O stretching vibrations of sulfonate anions which are compensated with the positive charges in the polypyrrole chains [14 and 15].

In pure PAA, the drug-load PAA, and the drug-load PPy/PAA blend film, we observe a broad region around 3000 to 3600 cm^{-1} assigned to the OH

stretching and the C=O stretching, and CO^{-} due to intermolecular hydrogen bonding within this same region [16]. The peak at 1705 cm^{-1} represents the C=O stratching in pure PAA but becomes evident at 1698 cm^{-1} and 1701 cm^{-1} in the drug-load PAA hydrogel and drug-load PPy/PAA blend film, respectively.

For pure SSA, two peaks at 1038 cm^{-1} and at around 670 cm^{-1} can be assigned to the sulfonate groups (SO^{3-}) stretching [17]. For the drug-loaded PAA hydrogel and the drug-load PPy/PAA blend film, the sulfonate groups (SO^{3-}) stretching is increased and has a gradual shift of OH stretching around 3000 to 3600 cm^{-1}. These results indicate the H-bonding between the sulfonate groups of sulfosalicylic acid with the hydroxyl group of PAA hydrogel [18] and amine group of PPy.

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

Figure 2 shows DSC thermograms of pure PAA, pure SSA, the drug-loaded PAA hydrogel, PPy, the doped PPy and the drug-load 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 bonded to the polymer backbone for pure PAA, pure PPy, the dopped PPy, the drug-loaded PAA hydrogel, and the drug-loaded PPy/PAA blend film, respectively [19]. The DSC thermograms for pure PAA and the drug exhibit a melting temperature at 312.1 and 165.5 °C, respectively. For pure PPy, the thermogram exhibits a board 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. The

possible reason for the peak shift is the interaction between polymer and drug molecule since SSA can form H-bonding with the hydroxyl group of PAA [7] and the electrostatic interaction between SSA and PPy [20].

Figure 3 shows the TGA thermograms for pure PAA and the drug-loaded PAA hydrogels, the drug-load PPy/PAA blend film, pure SSA, PPy and doped PPy. There are three transitions for undoped and doped polypyrrole. The first transition (45-65 °C) refers to the losses of organic solvent and water. The second transition (100-130 °C) refers to the PPy side chain degradation, and the third transition (215-235 °C) refers to the PPy backbone degradation. The TGA results of PPy and doped PPy show that doped PPy has higher thermal stability, because after doping the degradation temperature of sulfuric acid doped PPy is higher than that of undoped PPy.

For pure PAA, pure SSA, the drug-load PAA hydrogel, and the drug-load PPy/PAA blend film, there are 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 [21]. The third decomposition stage in range of 240-370 °C has been described as the degradation of residual polymer. The TGA results demonstrate that new structure is formed in the drug-load PAA hydrogel and doped PPy.

3.1.3 Conductivity meansurement of PPy and doped PPy

The specific conductivity which is the inversion from specific resistivity (ρ) of undoped PPy and doped PPy with 5-sulfosalicylic acid pellets were measured by using the two-point probe meter. From the geometric correction factor (K) = 6.22 x 10^{-4}, the specific conductivity of undoped PPy is 1.149 S/cm with a standard deviation of 0.039 S/cm. The electrical conductivity of undoped PPy is rather high due to APS, the oxidant used in the polymerization process, produced HSO_4^- which also acted as a dopant. For doped PPy the specific conductivity increases as the doping level is increased, as shown in table 1. The increase in electrical conductivity can be attributed to the increases in the number of charge carriers, the degree of crystallinity and the charge mobility [3].

3.1.4 A particle size analyzer of PPy and doped PPy

The mean particle diameter of PPy was determined by Particle Size Analyzer (PSA) to be approximately 18.57 μm for undoped polypyrrole and 19.71 μm for doped polypyrrole with standard deviations of 0.29 and 0.04 μm, respectively.

3.1.5 Scanning Electron Micrograph of PPy and doped PPy

Figure 4 shows the morphology of PPy and doped PPy powder with 5-sulfosalicylic acid at magnifications x1500 and x3500. The morphologies of PPy powder and doped PPy powder at various doping levels are not different.

3.1.6 Swelling behavior of drug-loaded PAA hydrogel

The PAA hydrogels were prepared by varying the crosslinking ratio through the amount of ethylene glycol dimethacrylate used. The effect of this variable on swelling behavior, the molecular weight between crosslinks, the mesh size and the drug diffusion ability are determined.

Figure 5 shows the degree of swelling and the weight loss of PAA hydrogels at various crosslinking ratios after 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 crosslinking ratio because the lower crosslinked hydrogel has a longer PAA strand between crosslinks or a looser network. It can swell appreciably and their pore size is larger as determined by using the equilibrium swelling theory as developed by Peppas [16]. The swelling data are used to evaluate the crosslinked structure of these hydrogels. The molecular weight between crosslinks, the mesh size and the crosslinking density are parameters used for characterizing the porous structure of hydrogel for drug delivery system. These values of each hydrogel matrix are determined using the equilibrium swelling theory developed by Peppas [16]. Table 2 shows the molecular weight between crosslinks, the mesh size and the crosslinking density of each PAA hydrogel at various crosslinking ratios with and without electric field. An increase in the crosslinking agent EGDMA decreases the molecular weight between crosslinks, $\overline{M}_c$, which in turn results in a smaller network mesh size, ξ [22]. The mesh sizes of hydrogels vary between 103.92 and 478.9 Å under no current and between 132.67 and 516.02 Å under applied current. Thus the comparison of mesh size values between the system

with electric field and without electric field suggests that the electric field has a small effect on the PAA structure.

3.2. Release kinetics of model drug

3.2.1 Determination of actual drug content

The actual amount of drug was measured by using the UV/Visible spectrophotometer at a wavelength of 298 nm. The actual amounts of drug present in the samples are 6.10, 6.29, 6.43, 6.63, 6.66, 6.72, 6.99 and 7.79 for crosslinking 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} is reported as the percentage of the initial content of drug loaded in PAA solution.

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

For the studies of sulfosalicylic acid transport mechanism from the PAA hydrogels, the power law model is used to fit the experimental data. This model is described by the Ritger-Peppas equation [23]:

$$\frac{M_t}{M_\infty} = kt^n \qquad (15)$$

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

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

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \qquad (16)$$

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 are calculated from the slopes of plots of drug accumulation vs. square root of time according to Higuchi's equation [24]:

$$Q = 2C_0 (Dt/\pi)^{1/2} \qquad (17)$$

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.

Effect of crosslinking ratio at electric field strength of 0 and 1 V

The amounts of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at time t vs. t and $t^{1/2}$ at various crosslinking ratios in an absence of electric field during 48 hours are illustrated in Figures 6 and 7, respectively. The amount of released drug gradually increases with time and then reaches an equilibrium value, while the plots of the amount of drug released as a function of square root of time show a linear relationship. The amount of released drug increases with decreasing crosslinking ratio due to the larger pore size of the lesser crosslinked hydrogel [22]. The degree of swelling of PAA hydrogel decreases with increasing ethylene glycol dimethacrylate concentrations in the hydrogels. With increasing crosslinking agent, the crosslink reaction of hydroxyl groups in

poly(acrylic acid) with aldehyde groups in ethylene glycol dimethacrylate to form ether linkage is amplified [25].

From a plot of $\ln(M_t/M_\infty)$ versus ln(t), the scaling exponent n was determined from equation 1 as 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 total period is nearly controlled by the Fickian 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 figure 7). Figure 8 shows the diffusion coefficients of sulfosalicylic acid from poly(acrylic acid) hydrogels and polypyrrole/poly(acrylic acid) blend films vs. crosslinking ratios and mesh size at electric field strength of 0 and 1 V at 37 ^{0}C. The diffusion coefficient of sulfosalicylic acid increases with decreasing crosslinking ratio due to the larger pore size or lower crosslinking ratio resulting in an easier drug diffuse. As the electric field is applied the diffusion coefficient increases due to the electrostatic force from electrical current driving the charged drug, sulfosalicylic acid [26], to the oppositely charged electrode [27]. The diffusion coefficients of drug from PAA hydrogels and PPy/PAA blend films are larger at lower the ratio of drug size and mesh size (a_d/ξ). 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 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 applied electric field strength of 1 V. Peppas and Wright (1995) 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 at pH 3 are 4.53×10^{-6}, and 3.19×10^{-6} cm^2/s, respectively. The diffusion coefficient of myoglobin at pH 3 was undetermined due to the extremely high value of partition coefficient , indicating an excessive binding in the membrane. The diffusion coefficients of theophylline, vitamin B_{12} and myoglobin through PAA membranes at pH 6 are 5.98×10^{-6}, 3.57×10^{-6}, and 1.60×10^{-8} cm^2/s, respectively. 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} is governed by the drug molecules diffusing through the membranes as driven by the osmotic pressure but the apparent diffusion of sulfosalicylic acid obtained in our experiments is governed by the drug molecules diffusing out of the membranes through the concentration gradient effect in the absence of electric field and the electrophoresis of the anionic drug under applied electric field. 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 [5].

Figure 9 shows the log-log plot of diffusion coefficients of sulfosalicylic acid from poly(acrylic acid) hydrogels vs. drug size/mesh size of

hydrogel at electric field strengths of 0 and 1 V at 37 ^{0}C. From these results, the scaling exponent m was determined from the following equation:

$$D = D_0(a/\xi)^{-m} \quad (18)$$

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

The scaling exponent *m* value for the SSA to diffuse through the PAA hydrogel under electric field strength of 0 and 1 V and the SSA to diffuse through the PPy/PAA blend film under electric field strength of 1 V are 0.48, 0.49 and 3.61, respectively. D_0 values are 2.33 x 10^{-9}, 2.09 x 10^{-9} and 2.97 x 10^{-13} cm^2/s, respectively.

4. Conclusions

We prepared the sulfosalicylic acid-loaded poly(acrylic acid) hydrogels at various crosslinking ratios to study the release mechanism and the diffusion coefficient of the drug from poly(acrylic acid) hydrogels with and without electric field. Moreover, the drug-load polypyrrole/poly(acrylic acid) blend films were prepared at various crosslinking ratios to compare the release mechanism and the diffusion coefficient with drug-loaded poly(acrylic acid) hydrogels. Each hydrogel was characterized the swelling ability and mesh size. The degree of swelling, the weight loss, and the mesh size were increase with decreasing of crosslinking ratio. The diffusion coefficients of drug from PAA hydrogel and PPy/PAA blend film increase with decreasing of crosslinking ratio due to larger mesh or pore size of hydrogel. Under applyied electric field, the diffusion coefficient of the drug from

PAA hydrogel increases under applied electric field strength due to the electrostatic force from electrical current is driving the charged drug to the oppositely charged electrode. Moreover, the diffusion coefficient of drug from PPy/PAA blend film is higher than PAA the diffusion coefficient of drug from hydrogel, so the conductive polymer is an effective in promoting the transport of SSA.

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Table 1 Determination the specific conductivity (S/cm) of PPy and doped PPy with 5-sulfosodiumsalicylic acid

Sample	Specific conductivity (S/cm)	SD (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

Table 2 The molecular weight between crosslinks, mesh size and crosslinking density of PAA hydrogels at various crosslinking ratios with and without the electric field

		E = 0 V				E = 1 V				
Sample	Crosslinking ratio	Number-average molecular weight between crosslinks, M_c (g/mol)	Mesh size ξ (A^0)	Crosslinking density (mol/cm^3)	a/ξ	Current (μA)	Number-average molecular weight between crosslinks, M_c (g/mol)	Mesh size ξ (A^0)	Crosslinking 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

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

Sample	Crosslinking ratio, X	Electric field strength (V)	Current (μA)	Diffusional exponent (n)	Kinetic constant (K)(hr^{-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_1Ppy+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_1.5Ppy+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 solute 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	-	Uncrosslink
			395.05	1.41E-08	37	5.5	-	Crosslinking ratio = 3.64E-03
			276.8	1.21E-08	37	5.5	-	Crosslinking ratio = 7.27E-03
			137.85	8.47E-09	37	5.5	-	Crosslinking ratio = 1.45E-02
			490.73	4.92E-08	37	5.5	1	Uncrosslink
			410.87	1.86E-08	37	5.5	1	Crosslinking ratio = 3.64E-03
			308.45	1.51E-08	37	5.5	1	Crosslinking ratio = 7.27E-03
			140.02	1.18E-08	37	5.5	1	Crosslinking ratio = 1.45E-02
Theophylline[5]	180	-	398	4.53E-06	37	3	-	
			589	5.98E-06	37	6	-	
Vitamin B_{12}[5]	1355	-	398	3.19E-06	37	3	-	
			589	3.57E-06	37	6	-	
Myoglobin[5]	17200	-	589	1.60E-08	37	6	-	

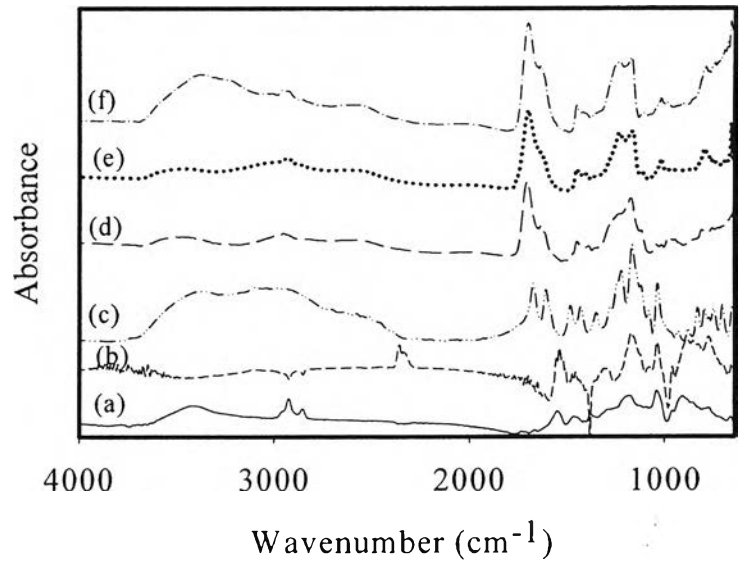


Figure 1 Absorption infrared spectra of: (a) the PPy powder; (b) the PPy doped with SSA; (c) the SSA powder; (d) the PAA hydrogel; (e) the SSA-loaded PAA hydrogel; and (f) the SSA-loaded PPy/PAA blend film.

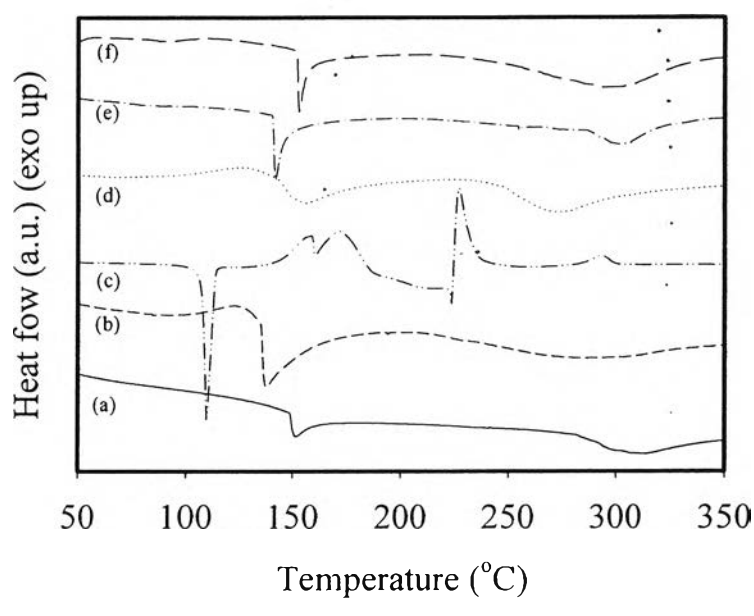


Figure 2 The DSC thermograms of: (a) the pure PAA hydrogel; (b) the pure PPy; (c) the model drug; (d) the drug-loaded PPy; (e) the drug-loaded PAA hydrogel; and (f) the drug-loaded PPy/PAA blend film.

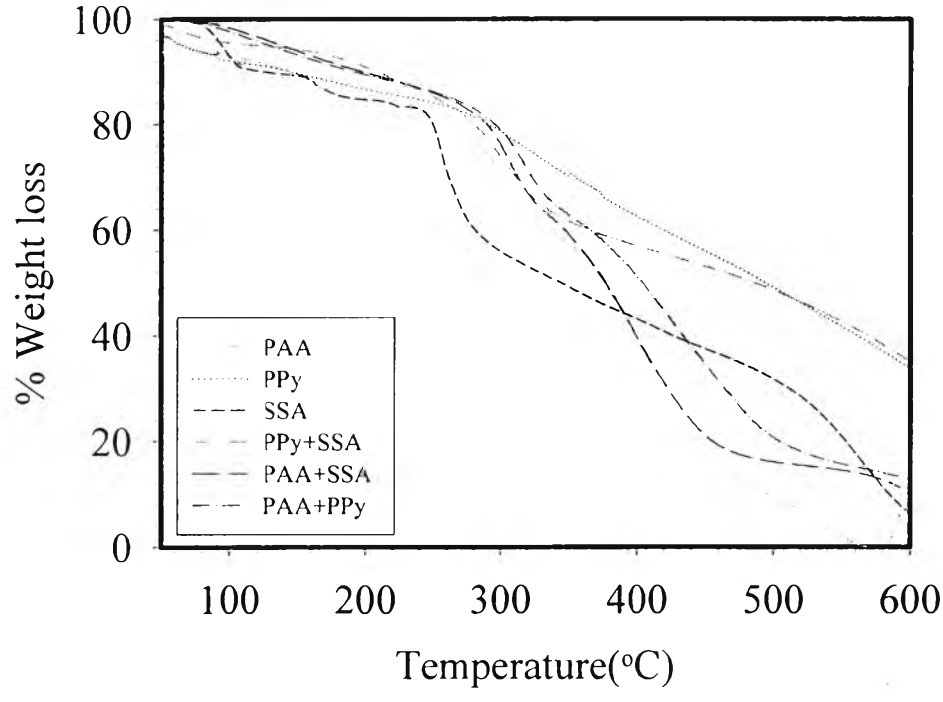


Figure 3 The TGA thermograms of: the pure PAA hydrogel; the drug-loaded PAA hydrogel; the drug-loaded PPy/PAA blend film; the pure model drug; the pure PPy; and the drug-loaded PPy.

(a) **(b)** **(c)**

Figure 4 The morphology of polypyrrole powder and doped polypyrrole powder with 5-sulfosalicylic acid at magnification x3500 of: (a) PPy powder; (b) 1:1; and (c) 1:50.

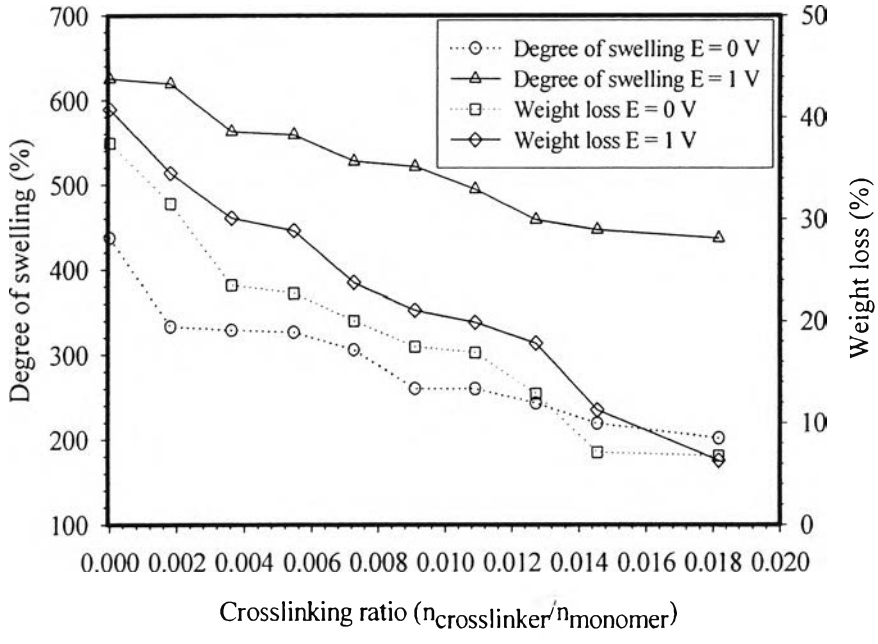


Figure 5 Degree of swelling (%) and weight loss (%) of poly(acrylic acid) hydrogels at various crosslinking ratios at 37 ^{0}C after 5 days.

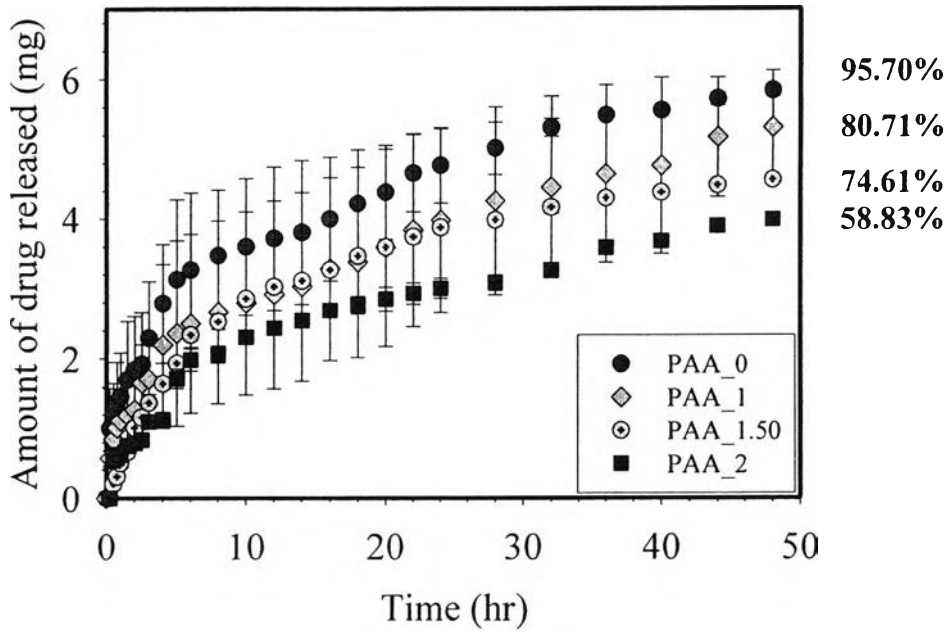


Figure 6 Amount of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at various crosslink ratios, E = 0 V, pH 5.5, 37 ^{0}C, n = # samples =2 vs. time.

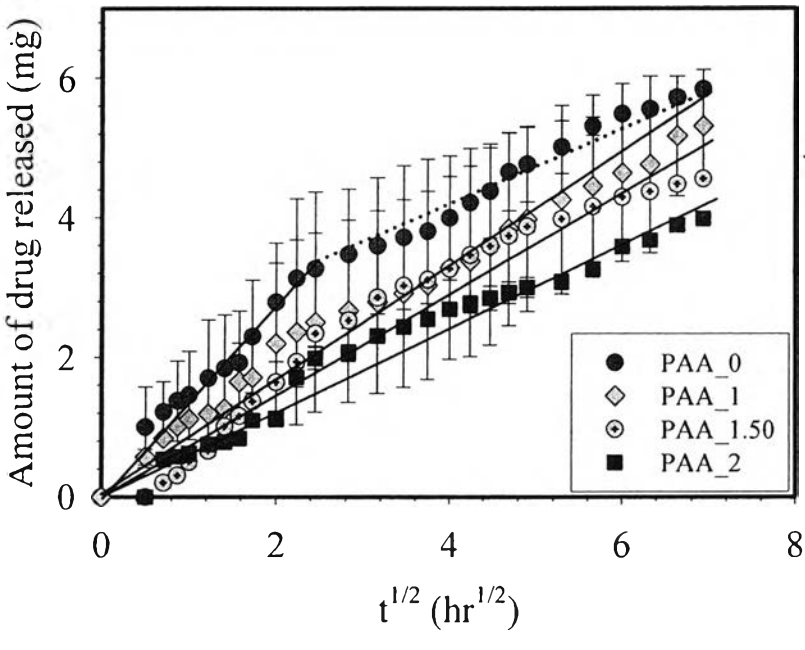
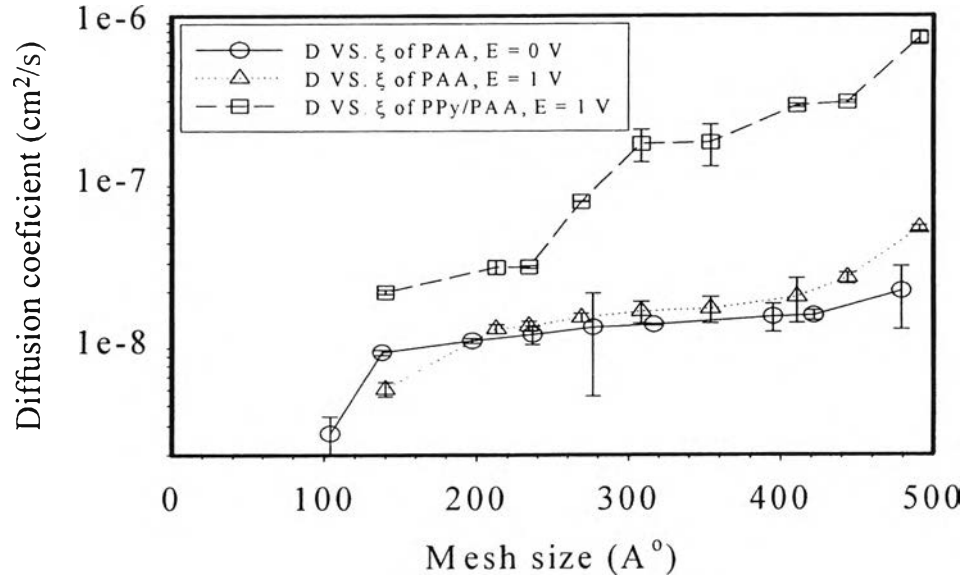
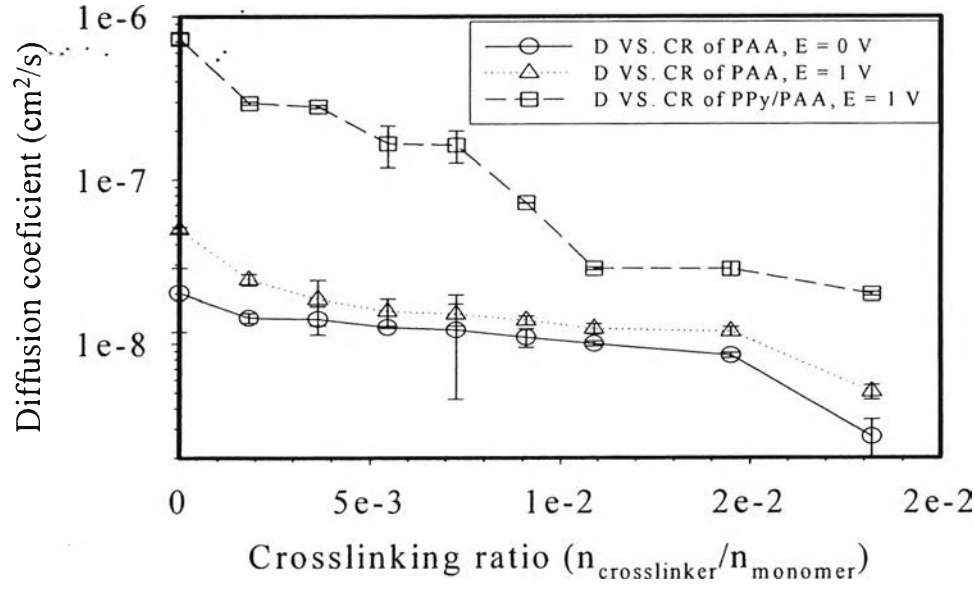


Figure 7 Amount of sulfosalicylic acid released from sulfosalicylic acid-loaded poly(acrylic acid) hydrogel at various crosslink ratios, E = 0 V, pH 5.5, 37 ^{0}C, n = # samples =2 vs. $t^{1/2}$.



(a)



(b)

Figure 8 The diffusion coefficients of SSA from PAA hydrogels and PPy/PAA blend films vs. (a) crosslinking ratios and (b) mesh size (Å), (ξ), at electric field strengths of 0 and 1 V and at 37 ^{0}C.

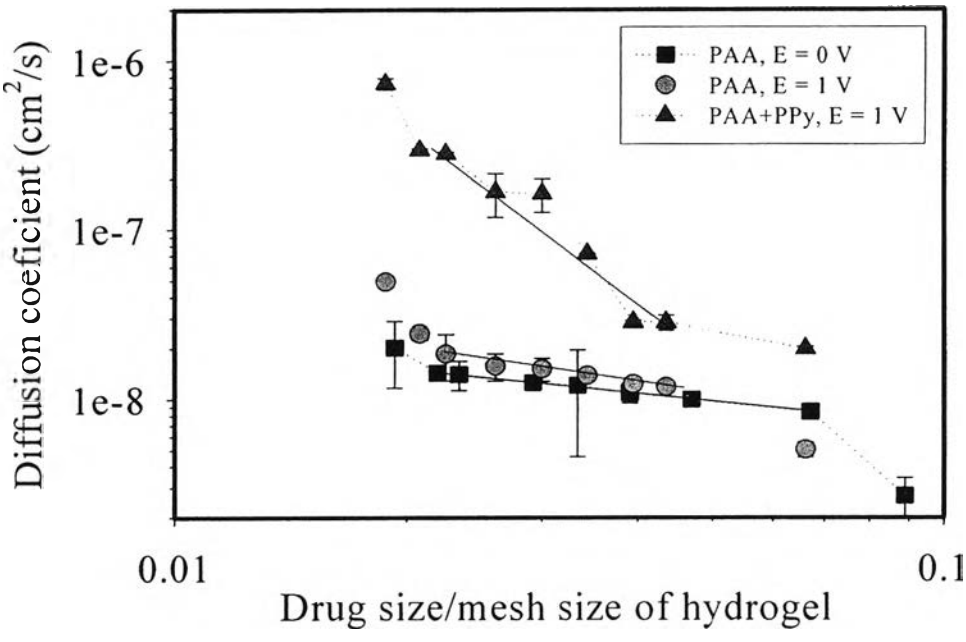


Figure 9 The log-log plot of diffusion coefficients of SSA from PAA hydrogels and PPy/PAA blend films vs. drug size/mesh size of hydrogel at electric field strengths of 0 and 1 V at 37 ^{0}C.