INTRODUCTION

Transdermal drug delivery system (TDDs) is a route for transporting drugs through the skin and into the circulatory system. There are many advantages for using TDDs such as by passing the first pass metabolism, decreasing in concentrations of drug in blood, decreasing side effects, as well as reducing fluctuations of drug in blood. However, the delivery of drugs via the skin is restricted due to lipophilic nature of skin and molecular drug size [1-6]. Iontophoresis is one of the methods used to enhance drug penetration across the skin by applying an electrical potential. This is especially true for both ionized and unionized drugs, including high molecular weight such as peptides, proteins, and oligonucleotides [4-6].

Hydrogel is one class of polymer-based controlled drug release matrices. The physical and chemical crosslinking process can produce a hydrophilic polymer as hydrogel by converting the soluble polymer chains into an insoluble polymer networks [7,8]. Besides exhibiting swelling behavior in water, other environmental conditions may still affect hydrogel volume change: temperature, pH, ionic concentration, solvent composition, and external electrical stimuli [9,10]. However, hydrogel is not an excellent material for response under electrical stimuli due to the relatively low electrical conductivity of the polymer matrix [11].

Stimulus-responsive hydrogels or smart hydrogels can potentially be used for the development of controlled drug release under applied electric field because the change in the structure of the polymer can change the drug release ability in response to the electrical potential. Electrochemically controlled drug release, using a conductive polymer, has been used in drug release systems [12]. A conducting polymer is composed of a conjugated polymer chain which can promote ¶-electron delocalizing along the polymer backbone and contributes to electrical conductivity. Conductive polymers combined with drugs are prepared with ease on conductive substrates to form various patterns and shapes, and drug release is precisely controlled under applied electrical current or potential stimuli [12]. Ge *et al*. prepared a stimuli-responsive material for electrical drug delivery [13]. Poly[(D,L-lactic acid)-co-(glycolic acid)]-b-poly(ethylene oxide)-b-poly[D,L-lactic acid)-co-(glycolic acid)] was used as the hydrogel matrix combined with PPy nanoparticles loaded with

fluroescein or daunorubicin as the model drugs. The chemical synthesis produced negatively charged fluroescein or positively charged daunorubicin incorporated into the PPy nanoparticles. The drugs in PPy nanoparticles were able to prevent the unwanted release from the hydrogel without an applied electric field. Under applied electric field, the fluroescein was released upon reduction, while the oxidation reaction could promote the release of daunorubicin. The amount of drug released increased with increasing electrical potential [13].

In this work, poly(3,4-ethylenedioxythiophene) (PEDOT) was selected as the conductive polymer for a drug substrate and blended with a hydrogel because of high conductivity in the doped state [14]. Alginate (Alg), which has biocompatibility, non-toxicity, and transparency, was used as the hydrogel matrix [15]. The objective of this work was to study the release mechanism of a combined conductive polymer/hydrogel system as PEDOT/alginate (PEDOT/Alg) hydrogel for controlled release of benzoic acid under applied electric field. The release profile and release kinetics of benzoic acid from blend films were investigated based on the effects of the matrix mesh size, PEDOT particle size, and electric field.

LITERATURE SURVEY

Alginate and drug release

Badwan et al. (1985) [16] prepared an alginate bead from calcium ions as a crosslink with sulphamethoxazole as a model drug loading in a calcium-alginate bead. The average diameter of the beads was 1.25 nm and the sulphamethoxazole uptake was about half of the incorporated quantity. The factors that affect to the release rate were studied such as sodium alginate and calcium chloride concentration, pH, hydration, and compression. The results showed that the release did not depend on the sodium alginate concentration, but calcium chloride did affect the release. The release decreased when the calcium chloride concentration was high and the water content was low. Compression of the beads yielded deformed beads with an increase in their release. This system may offer a simple and efficient sustained release preparation.

Stockwell et al. (1986) [17] evaluated a sodium alginate gel system as an orally release drug delivery system with a potential for prolonged stomach residence. Formulations containing sodium alginate, calcium phosphate, sodium bicarbonate, lactose, and drugs such as chlopheniramine, sodium salicylate, or caffeine were investigated. Its ability to undergo a gelatin in acid conditions enabled a gel matrix to be formed. Introduction of an effervescent component in the system produced a buoyant gel and a possible means to prolonging residence time in the stomach. The release rate from systems containing a polyelectrolyte was dependent upon the charge carrier of the drug. The alginate polyion carried a negative charge and could therefore interact with the cationic drug, thereby reducing the release rate. Cross-linking the gel with calcium gave rise to an increase in the release rate.

Yotsuyanagi et al. (1987) [18] fabricated an alginate gelatin by using calcium-induced cross-linking. Alginate gel was in a bead form and was prepared by dropping a sodium-alginate solution into a calcium chloride solution to form Ca^{2+} alginate beads. The possible application of this work was orally-administered drug delivery. Because of the alginate aerogel reswelling properties were susceptible to surrounding pH. The swelling property of a dried gel particle prepared from a fully-cured hydrogel was studied. The particle remained unchanged in distilled water or acidic medium (pH 1.5) but swelled rather rapidly in a phosphate buffer pH 7.0 to a size greater than its

original size, before being dried. Such a pH-sensitive swelling property could be advantageous as an orally-administered drug vehicle, especially when an acid-sensitive drug is incorporated in the gel.

Kim et al. (1992) [19] prepared alginate beads as an oral controlled release system of such macromolecular drugs as vaccines and polypeptide drugs. Calcium ions were used as the cross-linking agent of an alginate bead and blue dextran was the model drug. The release of blue dextran from the alginate bead was considerably affected by the drying time and the blue dextran/sodium alginate ratio. Moreover, the release of blue dextran was constant due to preparative conditions. No significant result depended on other experimental factors such as the sodium alginate and calcium chloride concentrations, curing time, and the drop size. The drug release from alginate beads at pH 6.8 showed a nearly zero-order release rate, which was more than at the pH 1.2 level.

Rubio et al. (1994) [20] loaded acetaminophene as model drug into an alginate sphere formulation. The hydrophilic polymer sodium alginate, which gelled in the presence of cross-linking ions, was used as the matrix for the sphere product. The effect of formulation variables on the release rates of acetaminophene from various systems and the cross-linking agents such as calcium chloride, calcium acetate, and aluminium sulfate were investigated. The resulting small-sized beads, containing a low drug level and prepared with 5% w/v cross-linking material, were of the smallest bead size, but with a faster drug release. The cross-linking materials and the rotational speed of the dissolution apparatus had no effect on the drug release rate from the alginate sphere. The mechanism of drug release from the alginate sphere, containing 20 % w/v acetaminophene and prepared with 5 % w/v cross-link material, offers a potential to control the drug release rates.

Cohen et al. (1997) [21] demonstrated a gel in the eye from an aqueous solution of sodium alginate, without the addition of external calciumion or other bivalent or polyvalent cation. The extent of alginate gelation and consequently the release of pilocarpine, depended on the percent guluronic acid (G) residues in the polymer backbone. Alginate with G contents of more than 65% instantaneously formed gels upon their addition to a stimulated lacrimal fluid. While those having low G contents formed weak gels at a relatively slow rate. Alginate system based on polymer of high

G content was an excellent drug carrier for the prolonged delivery of pilocarpine or other ocular drug.

Aslani et al. (1996) [22] studied the permeability of acetaminophene as a model drug in an alginate gel where the alginate gel film was prepared by cross-linking a sodium alginate film in an aqueous solution of calcium and zinc acetate. They compared the permeability property resulting from the alginate gel crosslinked with Ca^{2+} and Zn^{2+}. Acetaminophene permeability in the alginate gel film decreased with increasing divalent cation concentration and cross-linking time until an apparent optimum was reached. The decrease in permeability was suggested to be due to the increase in the cross-linking in the gel structure. The permeability of acetaminophene in the gel film decreased in this order: alginate gel film > acid exposed alginate gel film > divalent alginate gel film. Dehydration decreased the permeability of acetaminophene in the Ca^{2+}alginate gel film but Zn^{2+} had no significant effect.

Musa et al. (1999) [23] studied the effect of parameters of a drug-loaded crosslinked sodium alginate matrix film and the release rate of a drug from this system. The release rate was influenced by the cross-linking technique used in production of the matrix film; the cross-link type and concentration; drug physico-chemical properties, especially solubility and molecular weight; acidity of the release medium; concentration of the loaded drug in the matrix. Metoclopramide hydrochloride and cisapride as drug release asgents were used to study the effect of the drug type and Ca^{2+}, Ba^{2+}, and Al^{3+} as the cross-linking agents, were used to study the effect of cross-linker type, which affected the film surface morphology and consequently its diffusion properties.

Gonzalez-Rodrigues et al. (2002) [24] prepared alginate/chitosan particles for sodium diclofenac release that were prepared by using Ca^{2+} and Al^{3+} as ionics to form gelation. The ability to release the active substance was examined as a function of some technological parameters and the pH of the dissolution medium. The release of sodium diclofenac was prevented at acidic pH levels, while it was completed in a few minutes when the pH was raised to 6.4 and 7.2. The alginate/chitosan ratio and the nature of the gelifying cations allowed a controlled release rate of the drug.

Kim et al. (2003) [9] developed an alginate hydrogel by combining alginate and poly(diallyldimethylammonium chloride) (PDADMAC) to form an interpenetrated

hydrogel (IPN) and tested electrical responses. The alginate/PDADMAC IPN hydrogel was synthesized using the sequential IPN method. The swelling behavior of the system was studied by an immersion of the gel in an aqueous HCl solution. The swelling ratio decreased with increasing concentrations of the aqueous HCl solution. Under applied electric current, the IPN showed a significant and quick bending toward the cathode with electric current. Whenthe electric stimulus was removed the gel returned to its original position. Therefore, the alginate/PDADMAC IPN hydrogel system could be useful as a drug delivery system.

Moura et al. (2005) [25] developed and studied the compressive stress and the morphology of Ca^{2+} alginate hydrogel IPN with a PNIPAAm network. When hydrogel was prepared by cross-linking sodium alginate with Ca^{2+} inside the PNIPAAm network, the IPN hydrogels displayed two distinct pore morphologies under thermal stimuli. Below 30-35 °C, with the LCST of PNIPAAm in water, IPN hydrogels were highly porous. The pore size of the hydrogels heated above LCST became progressively smaller. The highest gel strength occurred at 40 °C when the hydrogel had the smallest pore size. These hydrogels had a tight structure with a smaller pore size and were stronger when subjected to an unaxial compressive stress.

Pasparakis et al. (2006) [15] investigated the swelling behavior and the release of the antihypertensive drug verapmil hydrochloride from calcium alginate and chitosan treated calcium alginate beads. The swelling of both bead systems were dependent on the presence of a polyelectrolyte complex between alginate and chitosan, the pH of the aqueous media, and the initial physical state of the beads. Verpamil hydrochloride could be encapsuted in calcium-alginate beads. The in-vitro stability of verpamil hydrochloride encapsulating beads, resulted in 70 % drug release from wet and dry calcium alginate beads within 1 and 3 h, respectively. The presence of chitosan was found to significantly retard the release from the wet beads. However, in the dry beads the presence of chitosan had no significant effect on the initial release stage and significantly increased the release in later stages.

Dong et al. (2006) [26] prepared a blend film between alginate and gelatin application for controlled drug release using Ca^{2+} as a cross-linker and ciprofloxacin hydrochloride as the model drug. The film was prepared by a casting/solvent evaporation method. The factors that influenced the drug release from the blend film

included the component ratio of alginate and gelatin; the load amount of ciprofloxacin hydrochloride; pH and ionic strength of the release solution; the thickness of the drug loaded film; and the cross-linking time with Ca^{2+}. The blend with 50 % gelatin content showed the best tensile strength at 102.5 MPa and breaking elongation at 29.4 %. The results of controlled release tests showed that the release rate of the drug decreased with an increase in the proportion of gelatin present in the film and amount of drug loaded in the film. For the sensitivity towards pH and ionic strength of the blend film, the drug release rate at pH 7.4 was faster incomparison to pH 3.6 and was simultaneously accelerated by high ionic strength.

George et al. (2007) [27] designed of a pH-sensitive alginate-guar gum hydrogel crosslinked with glutraldehyde as a controlled protein drug delivery. The crosslinked alginate-guar gum hydrogel prepared by the freeze drying method generated a matrix with high porosity and highly controlled delivery of a protein drug. The beads having an alginate to guar gum ratio of 3:1 showed desirable characteristics like better encapsulation efficiency and more appropriate swelling characteristics at 0.5% (w/v). The proposed freeze-dried alginate-guar gum hydrogel can be considered as a potential candidate for a protein delivery matrix to the intestine via the oral route. The hydrogel released a low amount (~20%) of BSA at pH 1.2 while higher levels of protein release were observed at pH 7.4 (~90% in 10 hr.).

He et al. (2009) [28] investigated a smart polymeric composite carrier consisting of carboxylated chitosan grafted nanoparticles (CCGN) and a bialminated film with a calcium alginate mucoahesive layer and an ethylcellulose backing layer for the oral delivery of peptide drugs. Weight change and swelling rate of the film increased with decreasing ionic strength of the solution. The thermodynamic properties of CCGN and the alginate hydrogel did not change during the formation procedure to the carrier. The pH-sensitive carrier exhibited a high mucoahesive force. In the release stage, nanoparticles and model peptide calcium were both restricted in an acidic environment while a fast and complete release was achieved in a neutral medium. Therefore, this novel carrier would be a promising candidate for a hydrophilic peptide drug via oral administration.

Electrically Stimulated Controlled Release

Miller et al. (1987) [29] prepared and characterized a poly(N-methylpyrrolylium) poly(styrenesulfonate) composite by the anodic polymerization of N-methylpyrrole from an aqueous sodium poly(styrenesulfonate) solution. The polymer was conductive and had electrochemical properties superficially similar to those of poly(N-methylpyrrolylium) perchlorate. The polymer could be reduced at -0.4 V vs. SCE in aqueous NaC1, and it was shown that this process incorporated sodium ions. It was aso shown that reduction of the film in aqueous solutions of dopamine promoted dopamine binding. The bound dopamine could be released by stepping up the polymer film potential to +0.5 V.

The effect of electrical current on solute release of poly(2-acrylamido-2-metbylpropane sulfonic acid-eo-n-butylmethacrylate) [poly(AMPS/BMA)] was studied by Kwon et al. (1991) [30]. Edro-phonium chloride, a positively charged solute, was released in an on-off pattern from a poly(AMPS/BMA) monolithic device with electric stimulus. The on-off release mechanism of the positively charged solute was explained as an ionic exchange between positive solute and hydroxonium ion, followed by the fast release of the exchanged solute from the gel. The fast release was attributed to the electrostatic force, the squeezing effect, and the electro-osmosis of the gel. However, the release of neutral solute hydro-cortisone was controlled by the diffusion mechanism as affected by the swelling and the deswelling of the gel.

Colombo et al. (1996) [31] studied the movement of the penetrated and polymer fronts and the drug dissolution in highly loaded swellable matrix tables. Three boundaries were identified corresponding to swelling, diffusion, and erosion fronts. The kinetics of the drug release depended on the relative movement of the erosion and swelling/diffusion fronts under certain conditions of drug solubility and loading in the matrix.

Ramanthana et al. (2001) [32] studied the electrically modulated drug delivery from the chitosan gels as matrices. Chitosan gels were prepared by the acetylation of chitosan and subsequently hydrated. In the electrification study, variation in mass, surface pH changes, and later, release-time profiles for neutral (hydrocortisone), anionic (benzoic acid), and cationic (lidocaine hydrochloride) drug molecules from hydrated chitosan gels were monitored in response to different milliamperages of

current as a function of time. Hydrated gels had very similar microviscosity while exhibiting different aspects of the gel. The cumulative gel mass loss and rate of gel mass loss increased with an increase in the miliamperage (mA) of the applied current.

Sutani et al. (2002) [33] studied the controlled release of an ionic drug from polyampholyte gel. The use of 2-(Dimethylamino)ethyl methacrylate or methacryloyloxyethyl trimethylammonium chloride as a cationic monomer was copolymerized by UV-VIS with an anionic monomer such as acrylic acid (AAC), into a polyampholyte. The pH and electro-responsive drug release functions content in the ionic copolymer changed to an electro response. The polymer shrank at the on-state of an electric field and swelled at the off-state of an electric field when the copolymer was rich of cationic and anionic compositions. The anion polymer could be used as electro-responsive intelligent materials in a drug delivery system.

Tang et al. (2008) [34] synthesized a polyacylate/polyaniline hybrid by a two-step aqueous polymerization method. An Aniline monomer was absorbed in the network of polyacrylate and followed by a polymerization reaction between the aniline monomers. The hydrogel possessed a conductivity of 2.33 mS/cm. The behavior of conductivity of the hydrogel suggested that the conductivity was due to charge carrier (protons) hopping along the polyaniline chain. The hydrogel had predominant pH and thermo-sensitive swelling properties. The hydrogel showed two sharp water absorbent peaks at pH 4-6 and pH>12. The sensitive temperature of the hydrogel to swelling was about 30 °C. Based on the porous structure, the hydrogel possessed loading and releasing properties. Diffusion exponent η values for the hydrogel between .45 and .89 indicated an anomalous release mechanism.

Juntanon et al. (2008) [35] investigated a controlled drug delivery, with poly(vinyl alcohol) (PVA) hydrogel as the matrix/carrier by applied electrical stimuli. The drug-loaded PVA hydrogels were prepared by a solution-casting method using sulfosalicylic acid as a model drug and glutaraldehyde as the cross-linking agent. The diffusion coefficients were measured as functions of cross-linking ratio, mesh size, electric field strength, and electrode polarity. For the effect of cross-linking ratios, the diffusion coefficient of the drug from PVA hydrogel increased with decreasing cross-linking ratio, for the effect of electric field strength, the diffusion coefficient of the drug in the hydrogels increased with increasing electric field strength. For the effect

of electrode polarity, the diffusion coefficient of the drug under cathode was higher than those under anode and no current.

Niamlang et al. (2009) [36] compared the controlled release of salicylic acid as model drug from salicylic acid-loaded polyacrylamide hydrogels (SA-loaded PAAM), and salicylic acid-doped poly(phenylene viny-lene)/polyacrylamide hydrogels (SA-doped PPV/PAAM). Without an electric field, the diffusion of SA from the SA-doped PPV/PAAM was delayed in the first 3 hours due to the ionic interaction between the anionic drug (SA anion) and the PPV. The D_{app} of the SA-doped PPV/PAAM was higher than that of the SA-loaded PAAM, and the former increased with increasing electric field strength that obeyed the scaling behavior: D_{app}/D_0 = (drug size/pore size)$_m$. The SA-loaded PAAM and SA-doped PPV/PAAM showed the scaling exponent m equal to 0.50 at 0.1 V, respectively. However, the drug release rate depended on the crosslinking density, electric field strength, drug size, hydrogel matrix mesh size, drug-matrix interaction, and the presence of a conductive polymer.

Chanisai et al. (2009) [37] prepared a conductive polymer–hydrogel blend between sulfosalicylic acid-doped polypyrrole (PPy) and poly(acrylic acid) (PAA) as a carrier/matrix for transdermal drug delivery under an applied electrical field. The blend was prepared by solution casting with ethylene glycoldimethacrylate (EGDMA) as the cross-linking agent. The effects of the cross-linking ratio and electric field on the diffusion of the drug from PAA and PPy/PAA hydrogels were investigated using a modified Franz-diffusion cell. The drug diffusion coefficient decreased 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, became larger by an order of magnitude relative to those without the electric field.

EXPERIMENTAL

Materials

Alginic acid sodium salt (Na-Alg) from brown algae, 3,4-ethylenedioxythiophene (EDOT), benzoic acid (BA as anionic drug; 5.58 Å), folic acid (FA as cation drug; 8.31 Å), tannic acid (TA as anionic drug; 36.84 Å), and 2-(*N*-Morpholino) ethanesulfonic acid (MES) monohydrate were purchased from Sigma-Aldrich to act as a matrix, monomer, model drug, and buffer solution, respectively. Calcium chloride dihydrate ($CaCl_2 \cdot H_2O$) was used as a crosslinking agent and purchased from Ajax Finechem. Ammonium peroxydisulfate (APS) was purchased from Qrec and used as an oxidizing initiator. Acetone, methanol, and dimethyl sulfoxide (DMSO) were purchased from Labscan.

Synthesis of benzoic acid-loaded poly(3,4-ethylenedioxythiophene) (BA-loaded PEDOT)

BA-loaded PEDOT was prepared by dropping EDOT monomers into a solution that consisted of APS and BA dissolved in distilled water, then it was stirred for 72 h. The preparation of PEDOT particles without BA was similar to the preparation of BA-loaded PEDOT except that the solution before doping EDOT monomer only consisted of APS. The color of solution transformed from yellow to green, then blue to dark blue during that time. The product was separated from the solution by using centrifugal separation and washed with methanol and acetone solution (methanol: acetone = 20:3). Lastly, the product was dried in a vacuum oven at 60 °C for 24 h. The BA-loaded PEDOT particles, at various doping levels (molar of EDOT:molar of APS), were synthesized by various amounts of APS as noted in the following Table 1:

Table 1 Condition of synthesis BA-loaded PEDOT at 0.15 M of EDOT and 0.45 M of BA

Doping level (molar of EDOT : molar of APS)	APS (M)
1:1	0.15
1:2	0.30
1:3	0.45

Preparation of benzoic acid-loaded poly(3,4-ethylenedioxythiophene)/alginate hydrogel (BA-loaded PEDOT/Alg)

Na-Alg solution with 0.4% w/v was prepared by dissolving Na-Alg powder in distilled water. Then BA-loaded PEDOT powder (25 mg) was added to the Na-Alg solution under constant stirring. In order to crosslink, $CaCl_2$ (moles of $CaCl_2$ of 0.006, 0.010, 0.014, 0.020, 0.026, and 0.030 mol) was added to the solution under constant stirring at various crosslinking ratios (moles of crosslinking agent/moles of uronic acid monomer unit): 0.3, 0.5, 0.7, 1.0, and 1.3. Each solution (10 ml) was cast onto a mold (diameter 5 cm) to control a film thickness and dried at 40 °C for 72 h to obtain the homogeneous BA-loaded PEDOT/Alghydrogel films of various crosslinking ratios with a film thickness of ~0.3 mm [38].

BA-loaded PEDOT characterization

The functional groups of the BA-loaded PEDOT particle were identified using a Fourier-transform infrared spectroscopy (FTIR; Thermo Nicolet, Nexus670). The spectrometer was set up in absorption mode using KBr as the background material with 64 scans, a resolution of ±4 cm^{-1}, and covering the wavenumber range of 400-4000 cm^{-1}.

The thermal behavior of BA-loaded PEDOT particles was examined using a thermogravimatric analyzer (TGA; PerkinElmer, TGA7). An aluminium pan was loaded with samples (5-10 mg). The change of mass was investigated under nitrogen atmosphere from 30 °C to 900 °C at a heating rate of 10 °C/min.

The morphology of BA-loaded PEDOT was studied using a scanning electron microscopy (SEM; Hitachi, S4800) which was operated in an acceleration voltage of 5 kV and a magnification of 100 k.

Electrical conductivity of the BA-loaded PEDOT was measured by using a custom-built two point probe connected with an electrometer (Keithley, Model 6517A), which supplied the voltage and recorded the current. The Van der Pauw method was used to estimate the current to find the linear Ohmic regime. The linear Ohmic regime, which consisted of applied voltage and resultant current, was transformed to the electrical conductivity of BA-loaded PEDOT using Equation 1:

$$\sigma = \frac{1}{\rho} = \frac{1}{R_s \times t} = \frac{I}{K \times V \times t} \quad (1)$$

where σ is the specific conductivity (S/cm), ρ is the specific resistivity (Ω cm), R_s is the sheet resistivity (Ω), I is the measured current (A), K is the geometric correction factor (3.53×10^{-3}), V is the applied voltage (V), and t is the pellet thickness (cm).

PEDOT/Alginate hydrogel (PEDOT/Alg hydrogel) characterization

The molecular weight between crosslinks ($\overline{M}_c$) and the mesh size (ξ) correlates to the release behavior of the drug and the physical properties of hydrogel were determined. A hydrogel sample was immersed in MES buffer solution (pH 5.5) after it was weighed in air and heptane. After the hydrogel sample was swollen to equilibrium for 5 day, it was weighed in air and heptanes again. Lastly the sample was dried at 40 °C in vacuum oven for 5 days, then weighed in air and heptanes one more time. Various weights were used to determine the polymer volume fraction [39].

The $\overline{M}_c$ was calculated by the Flory-Rehner equation as follows in Equation 2 [39,40]:

$$\frac{1}{\overline{M}_c} = \frac{2}{\overline{M}_n} - \frac{\left(\frac{\bar{v}}{V_1}\right)\left[\ln\left(1-v_{2,s}\right) + v_{2,s} + \chi_1\left(v_{2,s}\right)^2\right]}{v_{2,r}\left[\left(v_{2,s}/v_{2,r}\right)^{1/3} - 0.5\left(v_{2,s}/v_{2,r}\right)\right]} \quad (2)$$

where $\overline{M}_n$ is the number averaged molecular weight of the polymer before crosslinking ($\overline{M}_n$ = 450000 g/mol), $\bar{v}$ is the specific volume of Alg ($\bar{v}$ = 0.60 cm^3/g of Alg) [40], V_1 is the molar volume of the water (V_1 = 18 mol/cm^3) [40], $v_{2,r}$ is the volume fraction of the polymer in a relaxed state, $v_{2,s}$ is the volume fraction of the polymer in a swollen state, and the Flory polymer-solvent interaction parameter (χ_1) for Alg is 0.473 [40].

The ξ was determined using Equation 3 [41,42]:

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

where C_n is the Flory characteristic ratio (C_n = 27.33) [41], l is the carbon-carbon bond length of the monomer unit (l = 5.15 Å) [42], M_r is monomer molecular weight (M_r = 198 g/mol) [42], and $\bar{M}_c$ is the molecular weight between crosslinks.

Preparation of MES buffer pH 5.5

A MES buffer solution was selected to simulate human skin. MES solution 0.1 M (at pH 5.5) was prepared and poured into the receptor chamber of a modified Franz-Diffusion cell.

Spectrophotometric analysis of drug

The maximum absorption wavelength of BA was investigated using a UV/Visible spectrophotometer (UV-TECAN infinite M200). The absorbance value at the peak wavelength of BA corresponded to the BA concentration, thus BA calibration curves were created.

Actual drug content

The actual amount of BA in the BA-loaded PEDOT was determined by dissolving the BA-loaded PEDOT (0.6 g) in 4 mL of DMSO. Next, the solution (0.5 mL) of BA-loaded PEDOT in DMSO was added to the MES buffer solution (0.8 mL). The amount of BA in the solution was determined by the UV/Visible spectrum peaks (at the wavelengths of 232 nm), which were associated with the calibration curves in order to determine of the actual drug content.

Drug release studies

Modified Franz-Diffusion cells were used to study the diffusion of BA from BA-loaded PEDOT/Alg hydrogels as shown in Figure 1. A diffusion cell is composed of two component chambers as receptor and donor chambers. The receptor chamber was filled with MES buffer solution (pH 5.5) and kept at 37±2 °C via a circulating water bath. The donor component was exposed to ambient conditions. The BA-loaded

PEDOT/Alg hydrogel sample (thickness ~0.3 ± 0.01 mm) was placed over a nylon net (mesh size = 2.25 mm^2 and thickness ~0.2 mm), which was on top of the receptor chamber. The area available for BA diffusion was 2.51 cm^2. The MES buffer solution was stirred throughout the experiment for 48 h that came into contact in the receptor chamber. An electric field (various electrical voltages of 0, 0.01, 0.05, 0.5, 0.8, and 1.0 V or electric field of 0, 20, 100, 1000, 1600, and 2000 V/m) was applied on the surface of the hydrogel, nylon net, and buffer solution via an aluminum cathode electrode that was connected to a power supply (KEITHLEY 1100 V Source Meter). The diffusion of BA occurred when it passed through the polymer matrix and nylon net into the solution. A sample (0.1 mL) was taken out at specific times and replaced with fresh buffer solution at an equal volume. The drug amount was determined by a UV/Visible spectrophotometer [38].

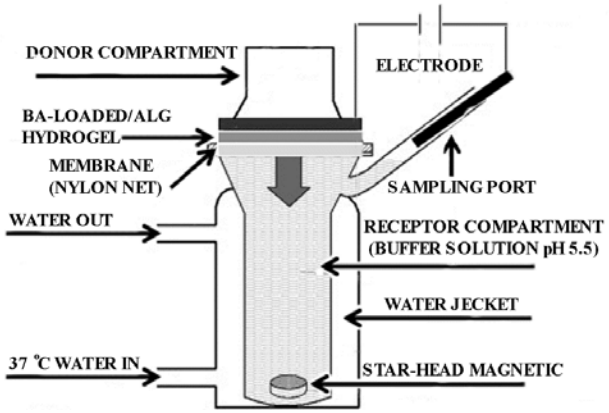

Figure 1 The modified Franz-Diffusion cell experiment set up.

Release characteristics of BA from BA-loaded PEDOT/Alg hydrogel

The release mechanism of BA was studied by the Korsmeyer-Peppas model, as shown in Equation 4 [43,44], which explains the drug release from the polymeric system. The amount of drug released was fitted with the Korsmeyer-Peppas model [43,44], a power law in time:

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

where M_t/M_α is the fraction of the drug released at time *t*, *k* is the kinetic constant (unit of T^{-n}), and *n* is the diffusion scaling exponent for drug release, which is used to characterize different release mechanisms. Furthermore, Higuchi's equation as shown in Equation 5 [44,45] indicates the fraction of drug release from the matrix and is proportional to the square root of time.

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \tag{5}$$

where M_t and M_α are the masses of drug released at the times equal to *t* and infinite time, respectively, and k_H is the Higuchi constant (unit of T^{-n}). The Higuchi equation corresponds to a particular case of Equation 4 when *n* is precisely equal to 0.5. If the Higuchi drug release (i.e., Fickian diffusion) is obeyed, then a plot of M_t/M_α versus $t^{1/2}$ will be a straight line with a slope of k_H.

The diffusion coefficient of the BA from the PEDOT/Alg hydrogels was calculated from a slope of plot between drug accumulation and the square root of time according to the Higuchi equation as in Equation 6 [45,46]:

$$M_t = 2C_o A \left(\frac{Dt}{\pi}\right)^{1/2} \tag{6}$$

where M_t is the amount of drug released (g), *A* is the diffusion area (cm^2), C_o is the initial drug concentration in the hydrogel (g/cm^3), and *D* is the diffusion coefficient of the drug (cm^2/s).

RESULTS AND DISCUSSION

BA-loaded PEDOT characterization

Figure 2a shows the FTIR spectra of BA, PEDOT, and BA-loaded PEDOT. The peaks of BA at 2835 cm^{-1} and 1700 cm^{-1} can be referred to as the O-H and C=O bonds. The benzene ring peak appears at 900-1000 cm^{-1} [47]. For the PEDOT particle synthesized without BA, stretching of quinoidal structure in the thiophene ring and stretching of the thiophene ring are presented as peaks at 1519 cm^{-1} and 1356 cm^{-1}, which originated from the C-C or C=C respectively. The peaks at 1206 cm^{-1} and 1098 cm^{-1} refer to the stretching vibration of the C-O-C bond in the EDOT. The peaks at 980, 843, and 700 cm^{-1} can be referred to as the C-S bond in the thiophene ring [48,49]. The absorption peaks of BA-loaded PEDOT are similar to those of PEDOT except a peak at 1682 cm^{-1} appears, which indicates benzoate anion loaded PEDOT. This peak is referred to as the carboxylate group (COO^-) of BA, which interacts with PEDOT. Furthermore, the thermal stability of BA-loaded PEDOT was examined using TGA. The thermogram is shown in Figure 2b. The decomposition temperature of BA showed up at 135 °C. The PEDOT showed adecomposition temperature of 210 °C as the dopant degradation of SO_4^{-2} from APS, and in the region between 310 °C to 420 °C the polymer backbone degradation occurred [49]. The decomposition temperature of BA-loaded PEDOT shifted to 215 °C for the dopant and 320-460 °C for the polymer backbone. Furthermore, the observed changes in thermal stability were accompanied by increasing char residue, showing that existing BA with PEDOT as BA-loaded PEDOT offered higher thermal resistance. This resulted from the electrostatic interaction between the carboxylate group of BA and the positively charged PEDOT sites as shown by FTIR at 1682 cm^{-1} [50,51].

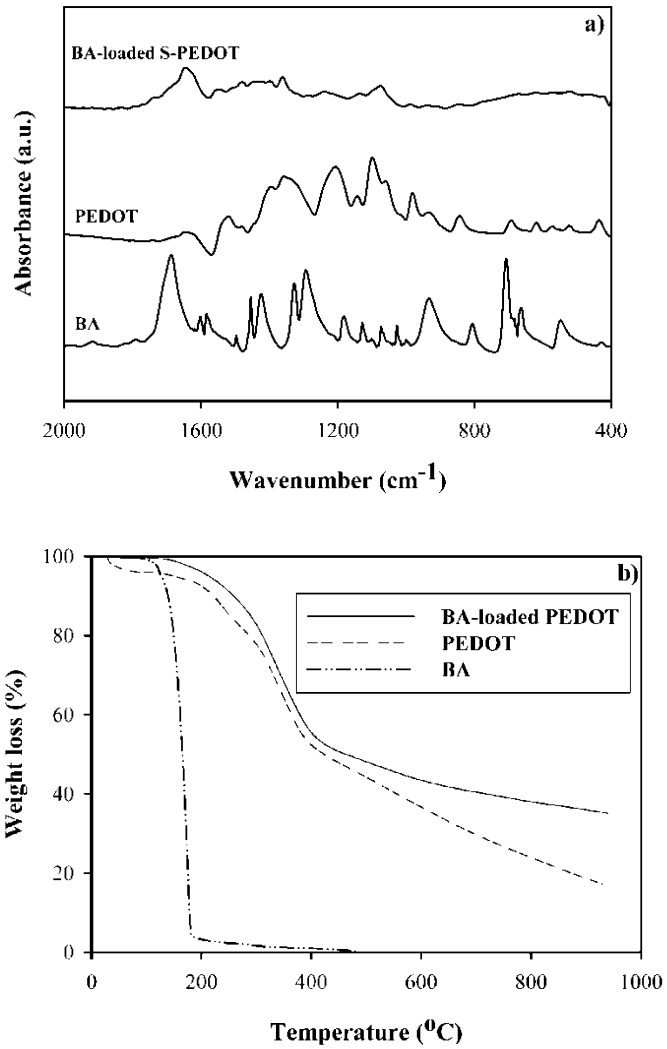

Figure 2 a) Absoption infrared spectra and b) thermogravimetric thermograms of BA, PEDOT, and BA-loaded PEDOT.

The BA-loaded PEDOT nanoparticles at various APS concentrations show various particle sizes and shapes, as shown in Figure 3. The particle sizes of BA-loaded PEDOT are 220 nm irregular shape (L-PEDOT), 71 nm raspberry agglomerate shape (S-PEDOT), and 108 nm coralliform shape (C-PEDOT). They were synthesized by 0.15, 0.30, and 0.45 M of APS concentrations, respectively. The BA-loaded PEDOT particle sizes and shapes vary a great deal with APS concentration, in which it acted as an oxidizing initiator affecting the rate of polymerization and PEDOT polymeric cation amount as shown in Figure 4. In the first step, EDOT is oxidized by

APS to become EDOT cation radical, which forms EDOT dimers via protonation and deprotonation, respectively. The process is duplicated to polymerize and to obtain PEDOT. Finally, the polymerized PEDOT is doped by the counter ions as the benzoate ions [48,52]. The structure was confirmed by FTIR and TGA (Figures 2a and 2b).

A greater amount of PEDOT polymeric cations is due to a higher APS concentration creating a stronger electro-repulsive force between PEDOT polymeric cation radicals, leading to a smaller particle size. On the other hand, a higher APS concentration (> 0.3 M) enhances the sulfate counter anions of APS, which generates the screening effect of the electro-repulsive reaction. This is the cause of the agglomeration of PEDOT particles resulting in a larger particle size as the coralliform shape [48].

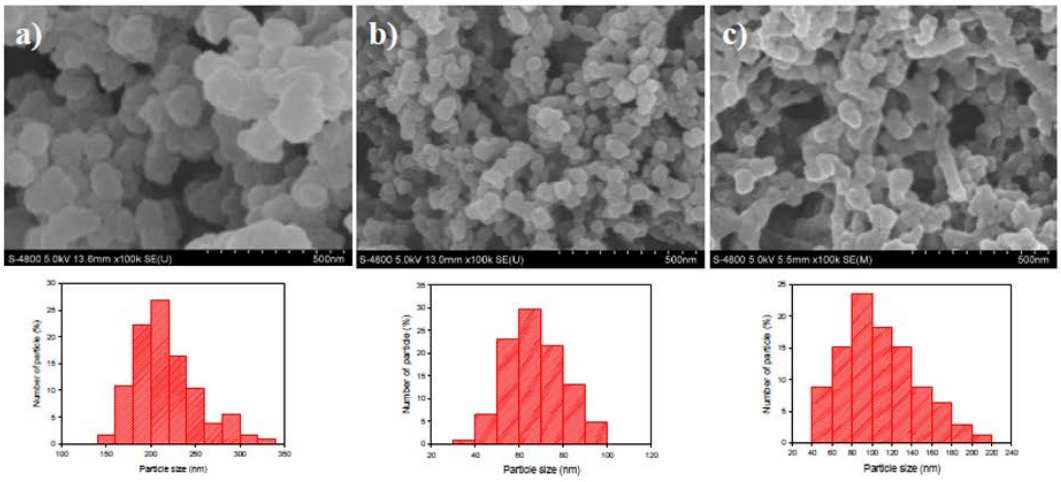

Figure 3 Morphologies and size distributions of BA-loaded PEDOT at various APS concentrations: a) 0.15 M; b) 0.30 M; and c) 0.45 M.

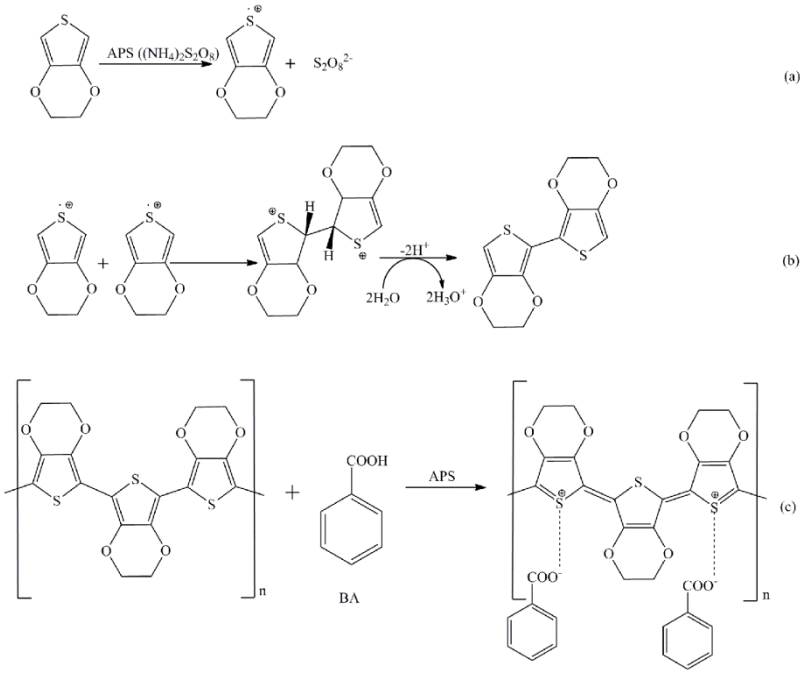

Figure 4 Proposed polymerization mechanism of BA-loaded PEDOT: (a) EDOT as a monomer is oxidized by APS to a cation radical; (b) EDOT cation radicals form dimers that subsequently are deprotonated; and (c) PEDOT polymer is doped by benzoate ion.

Table 2 shows the relationship between electrical conductivity and BA-loaded PEDOT particle size. The electrical conductivity values are 95.64, 10.65, and 2.78 S/cm for BA loaded S-PEDOT, C-PEDOT, and L-PEDOT, respectively. Electrical conductivity increases as the particle size decreases because the smaller particle size has a higher surface area for electron to transfer, and thus higher electrical conductivity [48,49]. Moreover, the electrical conductivity of BA-loaded-C-PEDOT is lower than that of BA-loaded-S-PEDOT because the coralliform shape is a result from PEDOT particles aggregation which possesses a lower surface area and greater free space for electron to transfer, thus reducing electron mobility [48].

Table 2 The particle size and electrical conductivity of BA-loaded PEDOT and actual amount of benzoic acid in PEDOT

Drug-loaded PEDOT	Particle size (nm)	Electrical conductivity (S/cm)
BA-loaded S-PEDOT	71 ± 43	95.64 ± 5.52
BA-loaded C-PEDOT	108 ± 43	10.65 ± 3.86
BA-loaded L-PEDOT	220 ± 37	2.78 ± 4.35

PEDOT/Alg hydrogel characterization

The PEDOT/Alg hydrogels were prepared at various crosslinking ratios (0.3, 0.5, 0.7, 1.0, and 1.3) and various PEDOT particle sizes and shapes (S-PEDOT, C-PEDOT, and L-PEDOT). The $\overline{M}_c$ and ξ of the PEDOT/Alg hydrogels were investigated to characterize the porous structure of the hydrogels with and without applied electric field. The $\overline{M}_c$ and ξ are larger at a lower crosslinking ratio because there is a longer Alg strand between crosslinks and easier more relaxed swelling behavior, which is produced via a lower crosslinker resulting in larger $\overline{M}_c$ and ξ [38]. The $\overline{M}_c$ and ξ without electric field decrease when PEDOT particles are added to the Alg hydrogel in the preparation of the PEDOT/Alg hydrogel because the PEDOT/Alg hydrogel is more rigid than the Alg hydrogel due to the existing PEDOT particles restricting chain movement and relaxation; thus, the PEDOT/Alg hydrogel exhibits less swelling and a smaller mesh size results [52,53]. The ξ of the Alg hydrogel varies between 641 and 3313 Å at an electrical potential of 0 V and between 1277 and 3887 Å at an electrical potential of 1 V as shown in Figure 5. The ξ of PEDOT/Alg hydrogel varies between 171 and 2626 Å at an electrical potential of 0 V and between 1282 and 3930 Å at an electrical potential of 1 V. Thus, ξ under applied electric field is larger than that without electric field applied. The electric field affects Alg chain expansion through the resultant electro-repulsive force between the negatively charged electrode and negatively charged carboxylate group in the Alg structure, so called “electro-induced Alg expansion” [38] as well as the voltage-induced motion of ions and polymer expansion in the previous work [54,55]. The ξ of the PEDOT/Alg hydrogel increases with decreasing PEDOT particle size, due to more free volume for water adsorption.

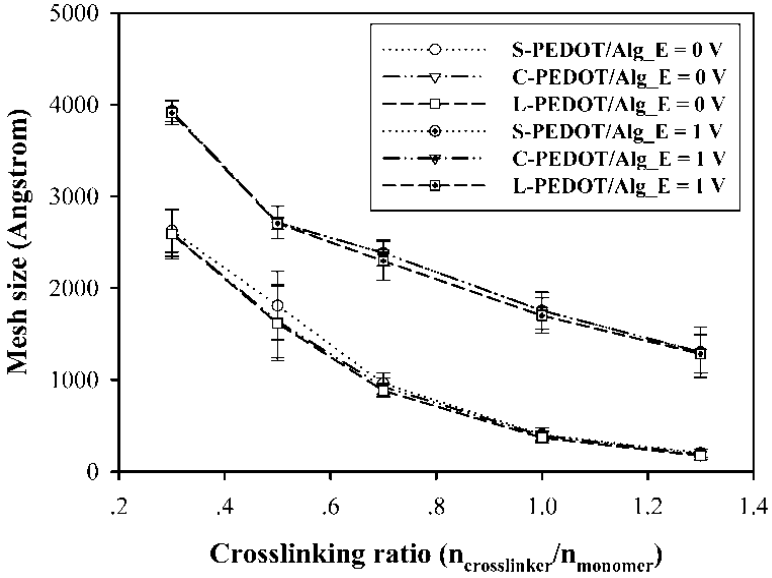

Figure 5 Mesh size of PEDOT/Alg hydrogel at various crosslinking ratios under electrical potential of 0 and 1 V.

Release characteristics of BA from BA-loaded PEDOT/Alg hydrogel

In order to study the release mechanism of BA from the BA-loaded PEDOT/Alg hydrogel, the actual amount of BA within the hydrogel sample was determined as a percentage of the BA amount presents relative to the amount actually loaded in the BA-loaded PEDOT/Alg samples. The actual amounts of BA in the samples were 95.4 ± 5.1, 93.8 ± 7.8, and 94.1 ± 6.3% for the BA-loaded S-PEDOT, C-PEDOT, and L-PEDOT/Alg hydrogels, respectively.

Effect of electrical potential

The release mechanism of BA from the BA-loaded PEDOT/Alg hydrogel was analyzed using the diffusion scaling exponent (*n*) from Equation 4. The *n* value is the slope of the curve of the plot between log (M_t/M_α) and log time, (Figure 6). The *n* values of the BA-loaded PEDOT/Alg hydrogels are tabulated in Tables 3and 4 at electrical potential of 0 V and 1 V, respectively. The *n* values are between 0.41 and 0.58, which are quite close to 0.5 in both cases, thus the release of BA is the diffusion controlled mechanism or the Fickian diffusion [44]. The PEDOT/Alg hydrogels act as

a diffusion barrier, and BA is released mainly by the diffusion mechanism as supported by the swelling behavior [56,57].

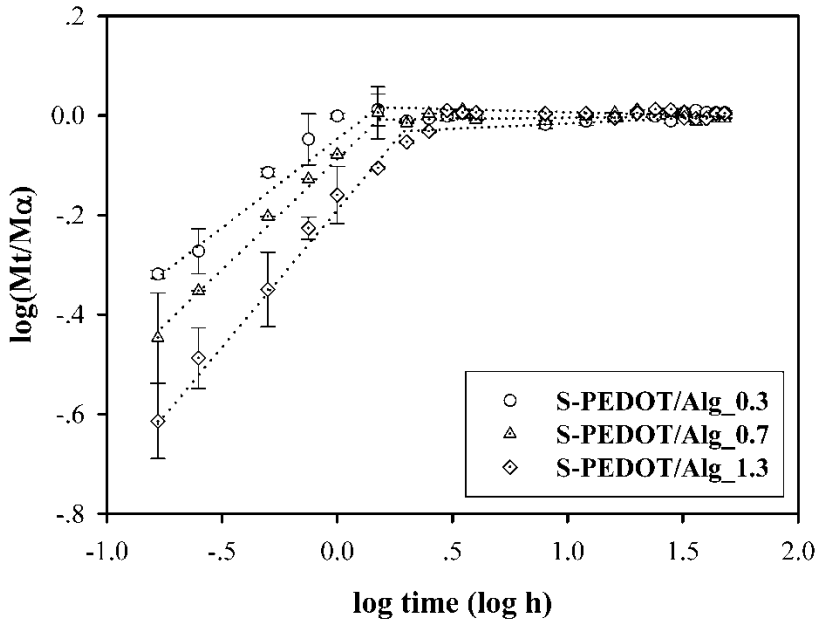

Figure 6 Plot of log M_t/M_α vs. log time of benzoic acid released from variously crosslinked S-PEDOT/Alg hydrogels at electrical potential of 1 V.

Table 3 Release kinetic parameters and the linear regression values obtained from fitting the drug release experimental data

Crosslinking ratio of Ca-Alg	**Release kinetics**								
	S-PEDOT			**C-PEDOT**			**L-PEDOT**		
	n	**$k_H(h^{-n})$**	**r^2**	**n**	**$k_H(h^{-n})$**	**r^2**	**n**	**$k_H(h^{-n})$**	**r^2**
0.3	0.49	0.98	0.9834	0.47	1.09	0.9756	0.48	0.9912	0.9943
0.5	0.48	0.92	0.9922	0.45	1.07	0.9876	0.46	0.9874	0.9874
0.7	0.44	0.86	0.9833	0.42	1.06	0.9833	0.42	0.9718	0.9611
1.0	0.42	0.84	0.9785	0.41	0.98	0.9678	0.41	0.9585	0.9802
1.3	0.42	0.78	0.9876	0.41	0.96	0.9832	0.41	0.9412	0.9798

Table 4 Release kinetic parameters and the linear regression values obtained from fitting the drug release experimental data at an electrical potential of 1 V

Crosslinking ratio of Ca-Alg	Release kinetics								
	S-PEDOT			C-PEDOT			L-PEDOT		
	n	$k_H(h^{-n})$	r^2	n	$k_H(h^{-n})$	r^2	n	$k_H(h^{-n})$	r^2
0.3	0.58	1.00	0.9689	0.59	1.06	0.9698	0.52	0.99	0.9716
0.5	0.56	0.96	0.9461	0.58	1.05	0.9682	0.52	0.98	0.9653
0.7	0.55	0.92	0.9708	0.56	1.02	0.9669	0.52	0.97	0.9527
1.0	0.54	0.88	0.9833	0.55	0.92	0.9947	0.51	0.95	0.9761
1.3	0.50	0.75	0.9288	0.54	0.85	0.9499	0.50	0.82	0.9689

The amount of BA released from the BA-loaded PEDOT/Alg hydrogel increases steadily up to 1 h after that it approaches equilibrium. Plotting the release of BA as a function of square root of time shows a linear relationship in the first 1 h. In Figure 7a, with absence of an electric field, the BA molecules are gradually released from the BA-loaded S-PEDOT/Alg hydrogel until the amount of BA released reaches equilibrium. Moreover, the amount of BA released from the BA-loaded S-PEDOT/Alg hydrogel is higher with an increase in electrical potential (cathode in a donor part represents a negatively charged electrode). The electric field generates the driving force to enhance the BA diffusion from the electro-repulsive force between the negatively charged BA and the negatively charged electrode so called “cathode-BA^- electrorepulsion” as shown in Figure 4b [36,58,59]. In addition, the electric field also creates electro-induced Alg expansion, which produces the expansion of hydrogel matrix, a larger mesh size, and a corresponding increase in the BA diffusion [59]. Lastly, the electrical potential enhances the release of BA as it provides a stronger reduction reaction of the BA-loaded S-PEDOT as shown in Figure 7b. The PEDOT chain in the reduced form is produced and contracted via electron injection under electric field, this causes squeezing BA^- out of neutralized PEDOT with lesser electrostatic binding interaction, inducing higher drug release so called “PEDOT electro-neutralization” [36,60].

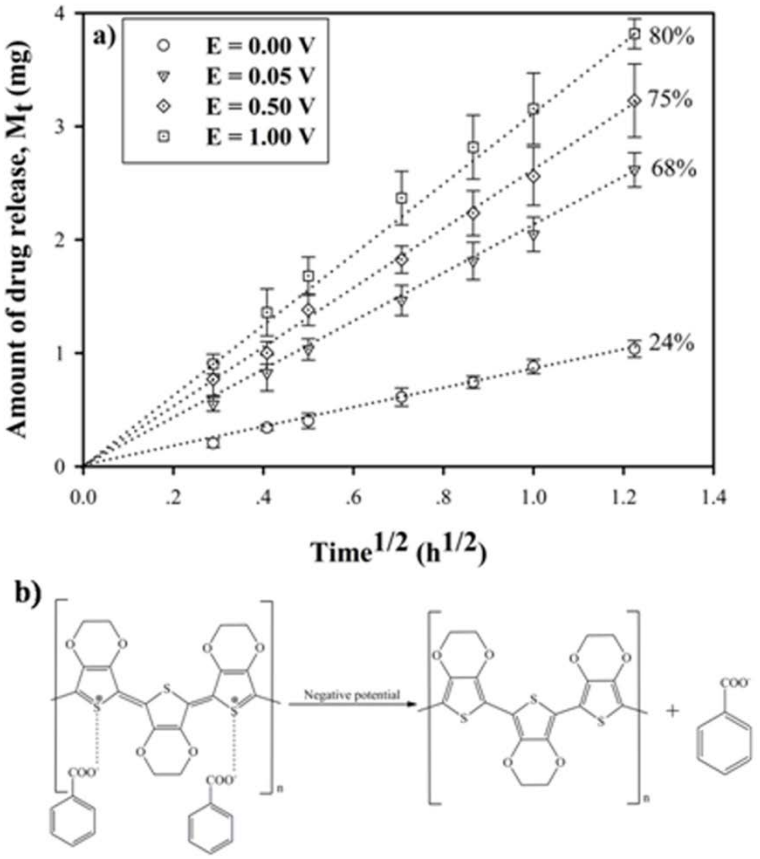

Figure 7 a) Amount of benzoic acid released from S-PEDOT/Alg_0.7 hydrogels at various electrical potentials b) Release reaction of benzoic acid from BA-loaded PEDOT/Alg hydrogel under applied electric field.

The *D* of each system was calculated from the slope of the Higuchi's equation, which is the plot between M_t and $t^{1/2}$. Figure 8 shows the *D* of BA increases with increasing electrical potential (E = 0 - 1 V at the current of 0 - 0.25 μA) under cathode as an electrode (negative charge) in the donor part. Increasing electrical potential produces greater cathode-BA^- electrorepulsion, facilitating the diffusion of BA from the polymer matrix [35,38]. Furthermore, the particle size of PEDOT affects the *D* of BA under applied electric field. The *D* at a given applied electrical potential of BA-loaded S-PEDOT has the highest value, followed by the BA-loaded C-PEDOT, and the BA-loaded L-PEDOT, respectively. The smaller PEDOT particle size exhibits higher electrical conductivity than the larger particle size; this induces electron to transfer more easily as an electric field is applied. Safranin dye was studied for its

release characteristics under applied electric field (E = - 0.1 V) from a semi-interpenetrating polyaniline-polyacrylamide (PANI-PAAM) network by Lira and Torresi [61]. The safranin release under electric field was greater than without an electric field because the reduced PANI chains created more free volume within the hydrogel, therefore, safranin diffusion increased [61]. Furthermore, heparin was investigated for release from polypyrrole-poly(vinylalcohol) with applied electric field (E = 1 mA) by Li *et al* [61]. The amount of heparin released was greater than with no applied electric field. There were several factors in which electric field controls releasing: charged drug electrophoresis reactions, drug doped conductive polymer reduction reactions, mesh size expansion, and increased or decreased pH due to H^+ migration towards the cathode [61].

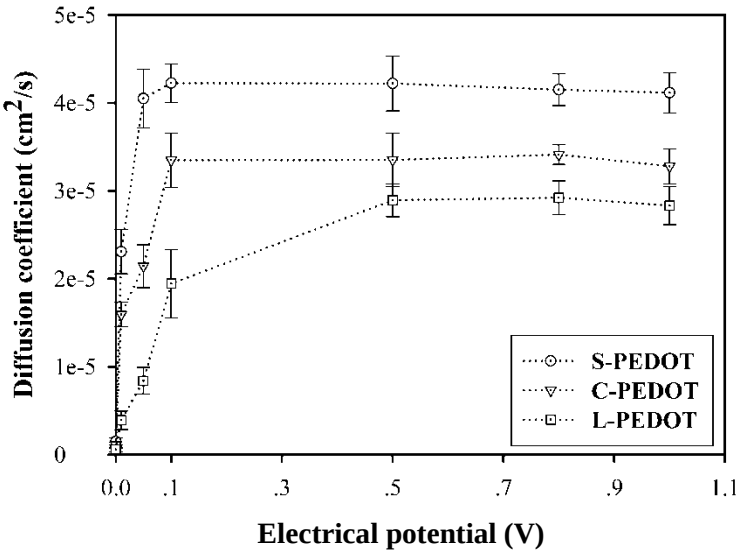

Figure 8 Diffusion coefficient of benzoic acid from PEDOT/Alg_0.7 of various PEDOT particle sizes vs. electrical potential.

Effect of crosslinking ratio

The amount of BA released decreases with increasing crosslinking ratio (as shown in Figure 6) because smaller mesh size at a higher crosslinking ratio results in a smaller pathway for BA to diffuse, so called “mesh size-hindering effect” [38].

In Figure 9, the crosslinking ratio and mesh size at the electrical potentials of 0 and 1 V affect the *D* of BA from the BA-loaded S-PEDOT/Alg hydrogels. The *D* of

BA decreases with increasing crosslinking ratio because the mesh size-hindering effect retards BA diffusion. In addition, the *D* of BA under electric field is higher than that of without electric field because the cathode-BA^- electrorepulsion, electro-induced Alg expansion, and and PEDOT electro-neutralization are created as an electric field is applied [35,36,38,58-60].

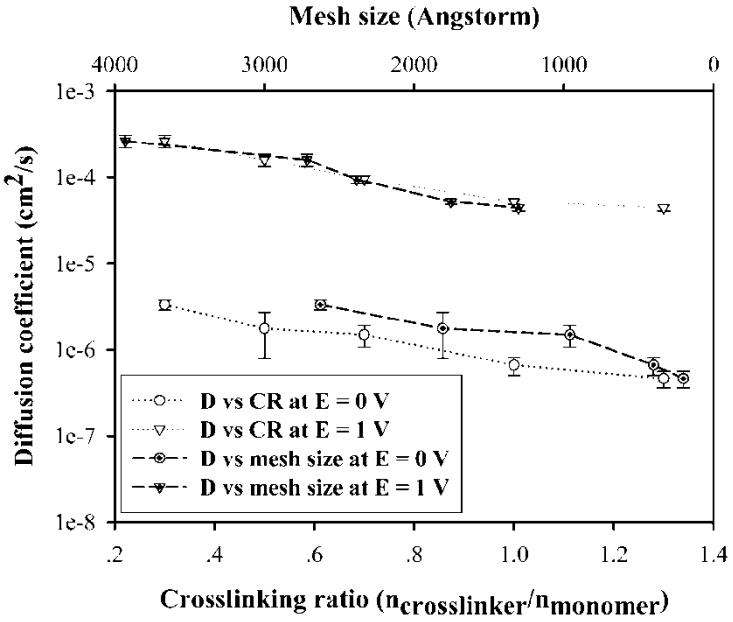

Figure 9 Diffusion coefficient of benzoic acid from S-PEDOT/Alg as a function of crosslinking ratio and mesh size at electrical potential of 0 and 1 V.

Effect of electrode polarity

The amount of BA release and the *D* under cathode are greater than that of no applied electric field, and under anode (positive charge) as electrode in the donor part, as shown in Figure 10. Thus, the electric field under cathode placed on hydrogel generates the cathode-BA^- electrorepulsion, which enhances BA diffusion from the BA-loaded PEDOT/Alg hydrogel. On the other hand, the diffusion of BA is retarded when the anode electrode is placed on the hydrogel because it creates an electro-attractive force between the positively charged electrode and the negatively charged BA resulting in restricted the BA diffusion [35,38].

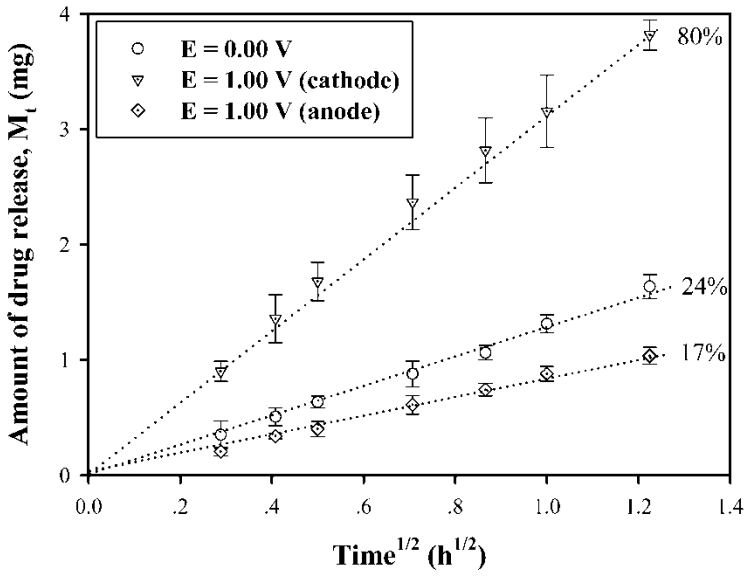

Figure 10 Amounts of benzoic acid released from S-PEDOT/Alg_0.7 hydrogels at electrical potentials of 0 V and 1 V with hydrogel samples attached to anode or cathode.

The log-log plot of the *D* as a function of the ratio of drug size over mesh size of hydrogel under the electrical potentials of 0 and 1 V at 37 °C is shown in Figure 11. The scaling exponent, *m*, can be determined from Equation 7:

$$D = D_0(a_d/\xi)^{-m} \quad (7)$$

where *D* is the diffusion coefficient of the drug; D_0 is the diffusion coefficient at a very small drug size; a_d is the drug size (5.58 Å); ξ is the apparent mesh size of the hydrogel, and *m* is the scaling exponent [35,38].

The *m* values for the BA diffusion through the Alg matrix and the PEDOT/Alg matrix without electric field are 1.06 [38] and 1.95, respectively, and the D_0 values are 2.01×10^{-7} [38] and 1.02×10^{-9} cm^2/s, respectively. The *m* values under applied electric field (E = 1 V) of Alg, S-PEDOT/Alg, C-PEDOT/Alg, and the L-PEDOT/Alg hydrogel are 1.28 [38], 1.13, 1.05, and 1.31, respectively and the D_0 values are 2.08×10^{-6} [38], 1.89×10^{-9}, 1.97×10^{-8}, 6.57×10^{-9} cm^2/s, respectively.

Figures 11a and b show decreasing diffusion when a_d/ξ increases due to the mesh size-hindering effect. In all cases of applied electric field (cathode in the donor part), the D can be divided onto 2 regimes, when a_d/ξ is below and above 2.38×10^{-3}. Below 2.38×10^{-3}, the diffusion is a_d/ξ independent because this a_d/ξ range also provides easy drug penetration. Above 2.38×10^{-3}, D decreases monotonically.

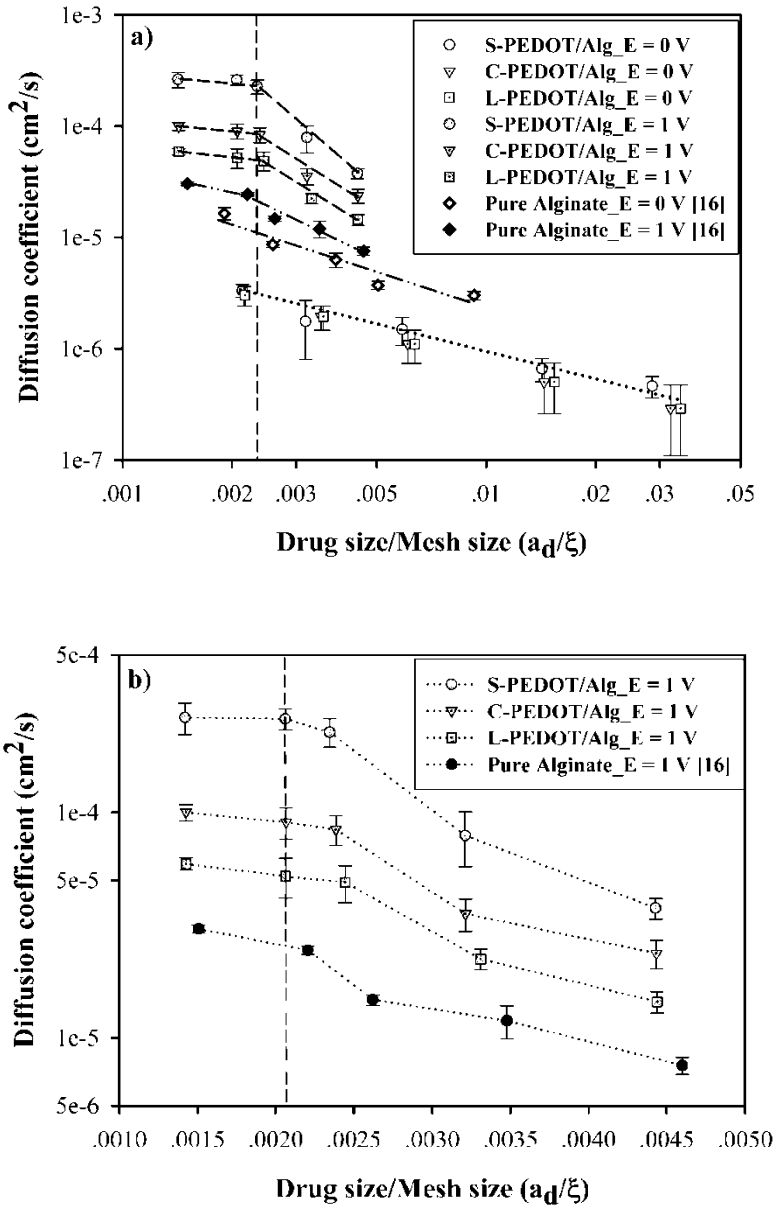

Figure 11 Diffusion coefficient of: a) benzoic acid from alginate and PEDOT/Alg hydrogel at electrical potentials of 0 and 1 V; and b) benzoic acid from PEDOT/Alg hydrogel at electrical potential of 1 V.

Furthermore, Figure 12 shows the comparison of the values of the drug from the Alg, S-PEDOT/Alg, C-PEDOT/Alg, L-PEDOT/Alg, and the polypyrrole/poly(acrylic acid) (PPY/PAA) hydrogels at various conditions. The higher *D* values of the drugs under these conditions are due to lower crosslinking ratios and smaller drug sizes. In addition, the *D* increases under applied electric field due to cathode-BA^- electrorepulsion, a larger mesh size, inducing easier drug mobility through the hydrogels. Nevertheless, the *D* of BA from the Alg hydrogel is higher than that of the BA-loaded PEDOT/Alg hydrogel without electric field because the free volume or pathway for drug diffusion is reduced by the presence of PEDOT particles. In addition, the *D* under applied electric field of the BA-loaded PEDOT is higher than that of BA-loaded Alg hydrogel. The *D* of the BA-loaded S-PEDOT/Alg hydrogel is the highest because it has the greatest electrical conductivity, resulting in easier electron transfer for the reduction reaction of BA-loaded PEDOT. On the other hand, Chansai *et al.* studied the *D* of sulfosalicylic acid (SSA) from the PPY/PAA hydrogel under electric field [37]. Sulfosalicylic acid (SSA) was loaded on the polypyrrole (PPY) structure by chemical oxidation reaction using ammonium persulfate as an initiator. The polypyrrole/poly(acrylic acid) blend film was prepared by dispersing SSA-loaded PPY powder in the acrylic solution and cast on mold to obtain the film. In Figure 12, the *D* of BA from the PEDOT/Alg hydrogel is higher than that of SSA diffusion from PPY/PAA hydrogel because of the larger mesh size of PEDOT/Alg hydrogel, greater electrical conductivity of PEDOT (electrical conductivity of SSA-doped PPY = 51.836 S/cm), and a smaller drug size.

Figure 12 Diffusion coefficient of drug from alginate, PEDOT/Alg, and PPY/PAA hydrogel at electrical potential of 1 V.

Thus, the diffusion of BA and SSA as anionic drug through the Alg, PEDOT/Alg, and the PPY/PAA hydrogel occur through the concentration gradient under no applied electric field, and by the electrophoresis of negatively charged drugs under applied electric field. The PEDOT/Alg hydrogel in this study is available for TDDS application because many available PEDOT size critically affect specific controlled release conditions, especially under applied electric field. In addition, the presence of PEDOT allows electrical triggering for drug release to exist in the matrix system.

Effect of drug characteristics

Figure 13 shows the amounts of the drugs released from the same alginate matrix (Alg_0.7) versus square root of time. At a given time, the amount of BA released is higher than those of FA and TA, respectively. The highest amount released belongs to BA due to its smallest size (5.58 Å). The lowest amount released belongs to TA because of its biggest size (36.84 Å). The intermediate amount released is FA; its size is 8.31 Å. The Ca-Alg hydrogel structure can create a negative charge on the

carboxylate group in the alginate structure, therefore it is expected that the electrostatic force affects the release behavior. BA and TA are negatively charged drugs; they generate a repulsive force with the negatively charged carboxylate group in the alginate structure. For the case of FA, the positively charged amine group (NH_2^+) in the FA structure can presumably bind with the negatively charged carboxylate group in the alginate structure via the attractive electrostatic force as proposed and shown in Figure 14. The released amounts of FA and TA are not significantly different, even though their sizes are different by a factor of four due to electrostatic effect of drug charge [17].

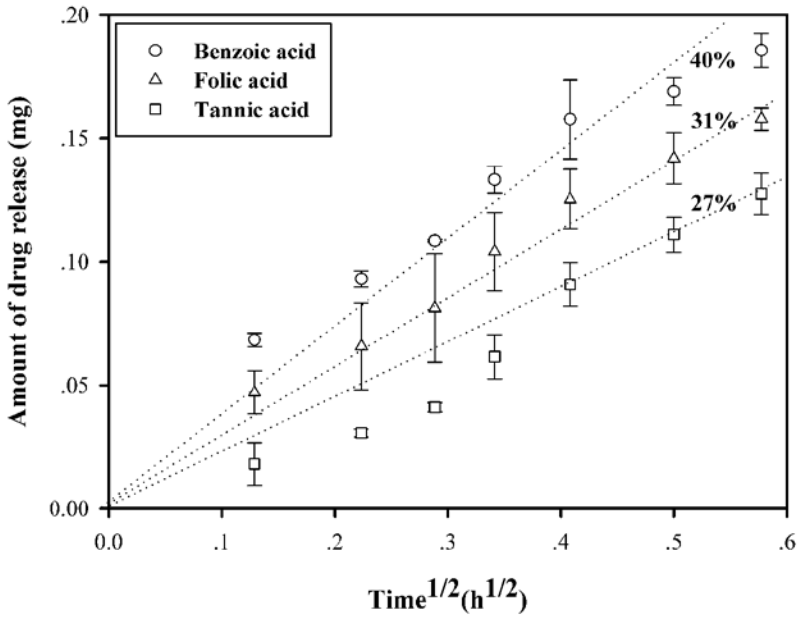

Figure 13 Amounts of drug released from Alg_0.7 hydrogels of various drug sizes versus time$^{1/2}$.

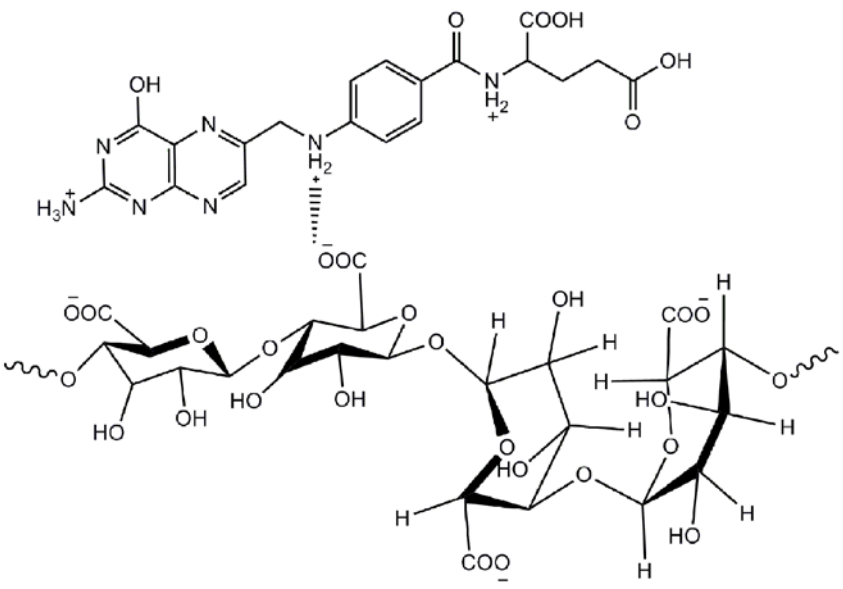

Figure 14 The interaction between folic acid and alginate.

In addition, the amount of drug release also depends on applied electrical potential. Figure 15 shows the diffusion coefficients of the drug loaded Ca-Alg hydrogels with a crosslinking ratio of 0.7 (Alg_0.7) versus electrical voltages under the negatively charged electrode (cathode in donor). The diffusion coefficients of BA and TA increase with increasing electrical voltage because both drugs are negatively charged; a higher electrical voltage induces a higher electrostatic force that drives the negatively charged drugs through the polymer matrix [35,36]. As expected, the diffusion coefficient of FA, a positively charged drug decreases with increasing electrical voltage because the drug diffusion is retarded by the electro-attractive force between positively charged drug and negative charged electrode [35,36].

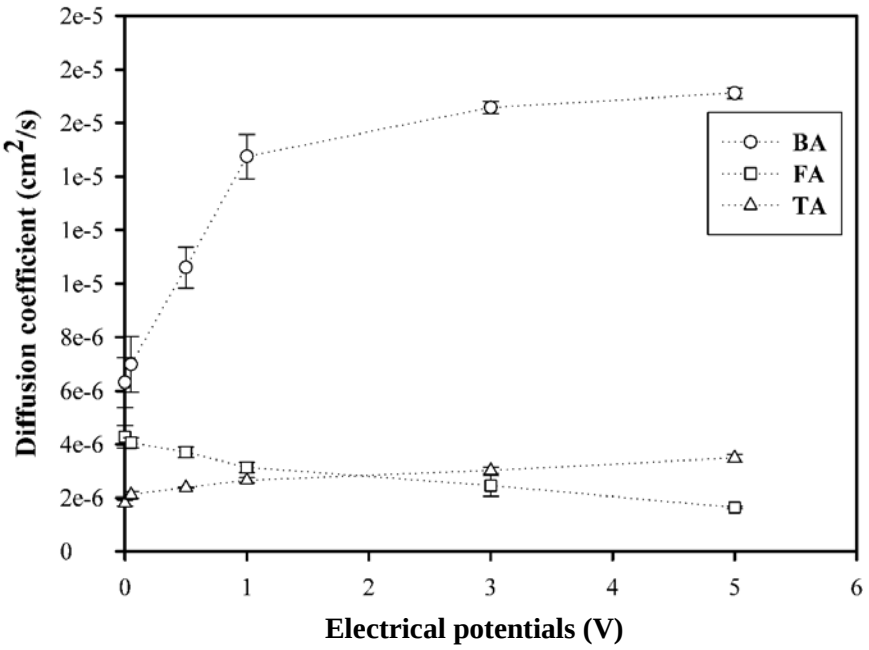

Figure 15 The diffusion coefficients of drugs (BA, FA, and TA from Ca-Alg hydrogels versus electric potentions of Alg_0.7 hydrogels.

CONCLUSIONS

Polyethylenedioxythiophene/alginate hydrogel acted as a carrier/matrix for the controlled release of benzoic acid. The release behavior and the diffusion coefficient were studied for the effect of crosslinking ratio, PEDOT particle size, electric field, and electrode polarity. The release mechanism of BA was the diffusion controlled mechanism or the Fickian diffusion because the diffusion scaling exponent is close to 0.5. The *D* of BA increased with decreasing crosslinking ratio due to the mesh size-hindering effect. When electric field was applied under cathode placed on the hydrogel, the *D* was greater than that of no electric field because the electric field induced cathode-BA^- electrorepulsion, electro-induced Alg expansion, and PEDOT electro-neutralization. The *D* of BA-loaded S-PEDOT was the greater under applied electric field at the PEDOT particle size was smallest resulting in the highest electrical conductivity. The *D* of BA depended on the electrode polarity, under cathode placed on the hydrogel, the *D* of BA was higher than that of no electric field and anode placed on the hydrogel because cathode-BA^- electrorepulsion was generated. Thus, the *D* of BA was critically dependent on the mesh size except when the drug size/mesh size was lower than 2.38×10^{-3}; the mesh size had no effect towards BA diffusion because the matrix provided a too large pathway relative to the drug size. Hence, the fabricated conductive polymer hydrogel blends is potentially applicable in TDDS under electrical stimulation. Moreover, the drug release in the TDDs application also depends on and can be controlled by many factors: the chemical composition of the drug; the drug molecular size; the drug size; the polymer matrix; and the drug-matrix interaction.

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