CHAPTER IV

Polythiophene/Carrageenan Hydrogel as Drug Release Matrix under Electric Field

Sanita Pairatwachapun, Anuvat Sirivat*

*Conductive and Electroactive Polymer Research Unit

The Petroleum and Petrochemical College, Chulalongkorn University

Abstract

Development of the conductive polymer-hydrogel blend between polythiophene (PTh) doped with a drug and a carrageenan hydrogel for the transdermal drug delivery was investigated, in which the characteristic releases depend on the electric field applied. The carrageenan and their blend films were prepared by the solution casting using acetylsalicylic acid as the model drug and doping agent for PTh and $MgCl_2$, $CaCl_2$, and $BaCl_2$ as the crosslinking agents. The average molecular weight between crosslinks, the crosslinking density, and the mesh size of the carrageenan hydrogels were determined using the equilibrium swelling theory. The release mechanism and diffusion coefficients of blend PTh/Carrageenan hydrogels and the non-blended ones were determined by using a modified Franz-Diffusion cell in an MES buffer solution, pH 5.5, at 37 °C, for a period of 48 h in order to investigate the effects of the crosslinking ratio, the type of crosslinking agent, and the electric field strength. The diffusion coefficient decreases with increasing crosslinking ratio and decreasing crosslinking ion size with and without the conductive polymer. The diffusion coefficients are greater at the applied electric field of 2.0 V by an order of magnitude relative to those without electric field. Moreover, the diffusion coefficients with the conductive polymer are higher than without the conductive polymer.

Keywords: Carrageenan hydrogel; Polythiophene; Acetylsalicylic acid; Diffusion coefficient; Electrically controlled release

1. Introduction

Hydrogel technologies have stimulated development in many biomedical applications such as controlled drug delivery due to their non-toxicity, biocompatibility, and similarity to biological tissues (Langer *et al.*, 2003 and Peppas *et al.*, 2004). Hydrogels are water-swollen polymeric materials possessing three-dimensional network structures. The network provides physical integrity and it is insoluble due to the presence of chemical or physical crosslinks (Peppas *et al.*, 2004 and Kim *et al.*, 2003).

Polysaccharides are one choice to be used as a hydrogel because they are quite similar to living tissues, useful for a wide variety of biomedical applications. Moreover, they are usually non-toxic, biocompatible, and show a number of peculiar physico-chemical properties. Carrageenan, a polysaccharide, has the ability to form thermo reversible hydrogels and is extensively used as a gelling agent in food and pharmaceutical industries. Because of its gelling, viscosity building properties, and proven safety, it has been utilized in sustained-release materials (Gupta *et al.*, 2001). Carrageenan comprises a family of linear water-soluble sulfated polysaccharides extracted from red seaweeds. The well-known carrageenan is kappa-carrageenan (κ-carrageenan) that can form a hydrogel easily. It is mostly alternating polymer of D-galactose-4-sulfate and 3,6-anhydro-D-galactose (Nijenhuis, 1997 and Zhai et al., 1998). The gelation of κ-carrageenan involves a coli to helix conformational transition followed by helix aggregation. The process is thermo reversible and can be induced by cooling or promoted by multivalent cations. The thermo-sensitive nature of κ-carrageenan hydrogels makes this biopolymer an interesting choice in drug delivery applications. In addition, the structure of κ-carrageenan includes a variety of chemical functional groups, providing the possibility for future derivatization and bioconjugation (Daniel-da-Silva *et al.*, 2011).

However, the limitations of controlled release by hydrogel are the slow response which limits their ability to deliver the stimuli efficiently throughout the gel (Lira *et al.*, 2005). The use of an electric field as an external stimulus is a method that has been successfully employed to enhance the amount of drug release and the

precise controls (Chien *et al.*, 1990). Because the electronic conductivity of a hydrogel is generally low, the current from an electric stimulus is not readily transmitted throughout the structure.

Recently, a conductive polymer combined with a hydrogel has attracted attentions as an electroactive hydrogel which is capable of chemical or physical transformations in response to electrical potential. Therefore, the conductive polymers and hydrogel blends have been extensively investigated for controlled drug release (Tao *et al.*, 2005).

Polythiophene (PTh) is an important class of conjugated polymers due to its high thermal stability, processibility, solubility, and excellent electrical conductivity when in a doped state (Stevenson *et al.*, 2010). PTh results from the polymerization of thiophenes which can become conducting when electrons are added or removed from the conjugated π-orbitals via doping (Lee *et al.*, 2008). PTh is synthesized by the electrochemical and chemical polymerization methods. But the chemical oxidative polymerization is more applicable than electrochemical method because of controllable sizes and a higher yield (Gnanakan *et al.*, 2009).

In this work, PTh/carrageenan blend films will be prepared. The release mechanism will be investigated in terms of crosslinking agent type and ratio and electric field strength. Furthermore, the electrically stimulated controlled release behavior of the acetylsalicylic acid as model drug from the blend film will be investigated and reported here.

2. Materials and methods

2.1 Materials

2.1.1 Synthesis of polythiophene (PTh)

In the polymerization process of polythiophene, these chemicals were used: thiophene (Sigma Aldrich) as a monomer, iron (III) chloride (Ajax Chemicals) as an oxidant, acetylsalicylic acid (Sigma Aldrich) as a dopant. Methanol (AR grade,

RCI Labscan), chloroform (AR grade, RCI Labscan), hydrogen peroxide, H_2O_2, (AR grade, RCI Labscan), and distilled water were used as solvents.

2.1.2 Preparation of polythiophene/carrageenan blend films (PTh/carrageenan blend films)

κ-carrageenan (Thai Food and Chemicals co., ltd.) was used as the polymer matrix. Acetylsalicylic acid (Sigma Aldrich) was used as the model drug. Barium chloride, calcium chloride, and magnesium chloride (Ajax chemicals) were used as the crosslinking agents. 2-(N-morpholino) ethanesulfonic acid, MES, (Sigma Aldrich) was used as the buffer solution.

2.2 Method

2.2.1 Preparation of acetylsalicylic acid-loaded carrageenan hydrogels (ASA-loaded carrageenan Hydrogels)

Carrageenan powder was dissolved in distilled water under stirring at 60 °C to prepare a carrageenan solution at concentration of 1.3 %w/v. Then, 2.5 %wt (based on the weight of carrageenan) of acetylsalicylic acid was added into the carrageenan solution under a constant stirring. The salt solution ($CaCl_2$, $MgCl_2$, and $BaCl_2$) as a crosslinker was added into the solution at various crosslinking ratios (moles of crosslinker to moles of ester sulfated group monomer units) and then cast onto a mold (8 cm diameter) at room temperature.

2.2.2 Synthesis of PTh

PTh was synthesized via the Fe^{3+}-catalyzed oxidative polymerization according to the method of Sugimoto *et al.* (1986). Thiophene (1 mol) was dispersed into chloroform (50 ml) at constant stirring for 45 min. $FeCl_3$ (5 mol) in 30 ml chloroform was added to the monomeric solution. The polymerization was allowed to proceed for 24 h with stirring at room temperature. The collected sample was washed with methanol in order to remove the excess $FeCl_3$ and then, the sample was dried at 80 °C for 24 h.

2.2.3 Preparation of acetylsalicylic acid-doped polythiophene (ASA-doped PTh)

The acetylsalicylic acid-doped polythiophene was prepared by the acid-assisted redox doping reaction according to the method of Sanden *et al.* (1997). 1 g of PTh was stirred with 100 ml of ASA solution and 50 ml H_2O_2 for 24 h ASA-doped PTh particles were filtered and vacuum dried for 24 h.

2.2.4 Preparation of polythiophene/carrageenann blend films (PTh/carrageenan blend films)

The ASA-doped PTh (0.1 g) was dispersed into the carrageenan solution, and the mixture was stirred for 30 min. The mixture was cast on the mold (8 cm diameter) and dried at room temperature.

2.3 Characterizations

The morphology of the carrageenan hydrogels were examined using a scanning electron microscope (SEM, Hitachi, S4800). After the hydrogel was immersed in distilled water at 37 °C for 3 days, it was rapidly frozen in liquid nitrogen at -40 °C for 24 h, and lyophilized at -50 °C for 24 h in a freeze-dryer (LABCONCO, Freezone 2.5). The sample was scanned at a 120x magnification.

The carrageenan hydrogel swelling was studied to determine the degree of swelling of in a MES buffer solution at 37 °C for 2 days, using the following Eq.1 (Peppas *et al.*, 1998);

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

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

In order to correlate the release behavior of the loaded drug to the physical characteristics of the carrageenan hydrogels, experiments were carried out to

determine the molecular weight between crosslinks, $\bar{M}_c$, the mesh size, ξ, and the crosslinking density, ρ_x. A sample of the carrageenan hydrogel was cut, then immediately placed in distilled water at 37 °C. For 5 days it was allowed to swell to equilibrium, and then weighed in air and heptane. Finally, the sample was dried at 25 °C in a vacuum oven for 5 days. Once again, it was weighed in air and heptane. These weights were used to calculate the $\bar{M}_c$, ξ, and ρ_x (Peppas *et al.*, 1998).

The Flory-Rehner equation modified using Bray and Merrill equation as in Eq. 2 was used to determine the $\bar{M}_c$ (Peppas *et al.*, 1998).

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

where $\bar{M}_n$ is the number-average molecular weight of the polymer before crosslinking (400,000 g/mol), $\bar{v}$ is the specific volume of carrageenan (0.49 ml/g) (Wang *et al.*, 2009), V_1 is the molar volume of water (18.1 cm^3/mol) (Wells *et al.*, 2011), $\upsilon_{2,r}$ is the polymer volume fractions of the relaxed polymer gel, $\upsilon_{2,s}$ is the polymer volume fractions of the swollen polymer gel, x is the Flory interaction parameter of carrageenan = 0.44 (Wang *et al.*, 2009), and the dissociation constant is pKa = 4.7.

The hydrogel mesh size, ξ, was calculated using Eq. 3 (Peppas and Wright, 1996)

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

where C_n is the Flory characteristic ratio for carrageenan (33) (Marcelo *et al.*, 2004), l is the carbon-carbon bond length of the monomer unit (5.5 Å), $\bar{M}_r$ is monomer molecular weight (385 g/mol), and $\bar{M}_c$ is the molecular weight between crosslinks.

The crosslinking density of the hydrogel, ρ_x, was calculated by using Eq. 4 (Peppas *et al.*, 1996).

$$\rho_x = \frac{1}{\bar{v}\bar{M}_c} \quad (4)$$

2.4 Drug release experiments

2.4.1 Preparation of MES Buffer

An MES buffer solution was chosen to simulate the human skin pH condition of 5.5. To prepare 200 ml of MES buffer solution, 0.1 M of MES pH 5.5 was poured into the receptor chamber of a modified Franz-diffusion cell.

2.4.2 Spectrophotometric Analysis of Model Drug

A UV-Visible spectrophotometer (UV-TECAN infinite M200) was used to determine the maximum spectra of the model drug. The characteristic peak at 230 nm was observed. The absorbance value at the peak wavelength of the 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 ASA in the ASA-loaded carrageenan hydrogels and PTh/carrageenan blend films were measured by the UV-Visible spectrophotometer at a wavelength of 230 nm. The ASA solution was prepared by dissolving the sample (circular disc with 2.5 cm in diameter) in 5 ml of dimethylsulfoxide (DMSO) and then 0.1 ml of the solution was added into 0.4 ml of DMSO.

2.4.4 Transdermal transport studies

The diffusions of drug were carried out by the modified Franz-Diffusion cells at the MES buffer (pH 5.5), a constant temperature, 37 °C in a circulating water bath. The ASA diffused through a nylon net (mesh size = 2.25 mm^2) which was placed on top the MES buffer solution. The nylon net was allowed

to come into contact with the MES buffer in the receptor chamber; the buffer was magnetically stirred throughout the experiment period (48 h) at a thermostatically maintained temperature. For the study of the effect of crosslinking ratio, ASA-loaded Ba-carrageenan (Ba-CAR) hydrogels of various crosslinking ratios (0.4, 0.6, 1.0, 1.4, and 2.0) were placed on top of a similar nylon net above the receptor compartment. For the study of the effect of type of crosslinking agent, Ba-CAR, Mg-CAR, Ca-CAR hydrogels at crosslinking ratio of 1 were placed on top of a similar nylon net above the receptor compartment. Then, for the study of the effect of electric field strength on the release of the ASA from the carrageenan hydrogel, a cathode electrode (aluminum) was connected to a power supply (KETHLEY 1100V Source Meter). The total duration of the constant applied electric field strength to the experiment setup was 48 h. The drugs diffused through a polymer matrix and the membrane into the solution. A sample of 0.1 ml was withdrawn at various time intervals and simultaneously replaced with an equal volume of the fresh buffer solution. The drug amount in the withdrawn solution sample was determined by the UV-visible spectrophotometer.

3. Results and discussion

3.1 Characterization

3.1.1 Swelling behavior of drug-loaded carrageenan hydrogel

The carrageenan hydrogels were prepared by varying the crosslinking ratio to study the effect on the swelling behavior, the molecular weight between crosslinks, the mesh size, and the drug diffusion characteristics.

Fig. 1 shows the degree of swelling of Ba-CAR hydrogels at various crosslinking ratios (0.4, 0.6, 1.0, 1.4, and 2.0) with and without electric field after immersion in MES buffer solution at 37 °C for 5 days. The results show the degree of swelling decreases with increasing crosslinking ratios because the lesser crosslinked hydrogel has a longer carrageenan strand between crosslinks producing a looser network for easier diffusion. It can be swollen appreciably and the pore sizes

are larger, as determined by using the Eq.1 and shown in the SEM images of the carrageenan hydrogels after swelling (Fig. 2). Moreover, when an electric field is applied, the degree of swelling is larger than that without electric field resulting in the larger mesh size (Fig. 3).

Table 1 shows the molecular weights between crosslinks and the mesh size of carrageenan hydrogels at various crosslinking ratios with and without electric field. An increase in the crosslinking agent decreases the molecular weight between crosslinks leading to the smaller mesh size (Serra *et al.*, 2006). The mesh sizes of the hydrogels vary between 265 and 1,229 Å under no current and between 455 and 1,771 Å under applied current. Thus, the comparison of mesh size values between the system with electric field and without electric field indicates that the electric field has an effect on the carrageenan structure through the generated electro repulsive force between the negatively charged electrode and the negatively charged sulfate group in the structure (Fig. 3).

Fig. 2 shows the morphologies of carrageenan hydrogels of various crosslinking ratios after swelling without an electric field. Fig. 2(a)-(c) show the porous structures and the pore sizes which are larger at lower crosslinking ratios. Fig. 3(a)-(c) show that smaller pore sizes are visibly present without an electric field relative to those of the carrageenan under electric field.

3.2 Release kinetics of model drug

3.2.1 Determination of actual drug content

The actual amount of ASA present in the carrageenan film is reported as the percentage of the initial content of ASA loaded into the carrageenan. The actual amount of ASA present in the sample is about 95.16 % ± 4.57%

3.2.2 Release kinetic of model drug from ASA-loaded carrageenan hydrogel and ASA-loaded PTh/carrageenan blend film

The experimental data were analyzed by two diffusion models. The drug release is described by the Korsmeyer-Peppas model (Korsmeyer *et al.*, 1983), which describes the drug release from a polymeric system according to Eq. 5. The

amount of drug released can be generally fitted to the Korsmeyer-Peppas model, a power law in time:

$$\frac{M_t}{M_\infty} = kt^n \quad (5)$$

where M_t/M_∞ is fraction of drug released at time *t*, *k* is the kinetic constant (with units of T^{-n}) and n is the diffusional exponent for drug release that is used to characterize different release mechanisms. In particular, the Higuchi's equation (Higuchi, 1961) describes the fraction of drug release from a matrix which is proportional to the square root of time.

$$\frac{M_t}{M_\infty} = k_H t^{1/2} \quad (6)$$

where M_t and M_∞ are the masses of drug released when the time equals t and infinite time, respectively, and k_H is the Higuchi constant (with the unit of T^{-n}). The Higuchi Eq. 6 corresponds to a particular case of Eq. 5 when n is exactly equal to one half.

When the Higuchi model of drug release (i.e., Fickian diffusion) is obeyed, then a plot of M_t/M_∞ versus $t^{1/2}$ will be a straight line with a slope of k_H.

The diffusion coefficients were calculated from the slopes of the plot of the amounts of acetylsalicylic acid released from carrageenan hydrogels at time t versus the square root of time according to Higuchi's equation (Higuchi, 1961 and Reichling *et al.*, 2006).

$$M_t = 2C_0A\left(\frac{Dt}{\pi}\right)^{1/2} \quad (7)$$

where M_t is the amount of drug released (g), A is the diffusion area (cm^2), C_0 is the initial drug concentration in the hydrogel (g/cm^3), and D is the diffusion coefficient of the drug (cm^2/s).

3.2.3 Effect of crosslinking ratio

The amounts of acetylsalicylic acid (ASA) released from ASA-loaded Ba-CAR hydrogels at time t versus t and $t^{1/2}$ at various crosslinking ratios (0.4, 0.6, 1.0, 1.4, and 2.0) in an absence of electric field during 48 h are shown in Fig. 4(a) and (b), respectively. The amounts of drug released gradually increase with time until reaching equilibrium, while the plots of the amount of drug released as a function of square root of time show a linear relationship. The amount of drug released decreases with increasing crosslinking ratio due to the larger pore size of the carrageenan hydrogel at the lesser crosslinking ratio (Serra *et al.*, 2006) because the crosslinking agent results in denser and more rigid hydrogel leading to a reduction in the degree of swelling (Hezaveh *et al.*, 2012). When an electric field is applied, the amount of ASA released increases at a given crosslinking ratio. The primary force is the high electrostatic force pushing the negatively charged drug through the polymer matrix (Murden, 2003 and Kantarial *et al.*, 1999). The second driving force comes from the expansion of the mesh size of hydrogel (Niamlang *et al.*, 2009), as shown in Table 2.

From a plot of $\ln(M_t/M_\infty)$ versus ln(t), the scaling exponent n was determined from Eq. 5 as show in Table 2. The n value of crosslinked carrageenan hydrogel without electric field vary between 0.33 and 0.60 is near the Fickian exponent value of n = 0.5. Thus, the drug release mechanism from carrageenan hydrogel is diffusion controlled by the Fickian diffusion mechanism and the change in their structure may have an effect on the mechanism of release.

The diffusion coefficient of each system is calculated from the slope of the plot M_t/ M_∞ versus $t^{1/2}$ using the Higuchi's equation. The diffusion coefficient of drug increases with decreasing crosslinking ratio due to the larger pore size at the lower crosslinking ratio resulting in a bigger pathway for the drug to diffuse. When an electric field is applied, the diffusion coefficient of drug increases due to the electrostatic force driving the charged drug; the negatively charged drug is driven towards to the oppositely charged electrode.

3.2.4 Effect of type of crosslinking agent

Fig. 5 shows the amounts of ASA released from ASA-loaded carrageenan hydrogels versus time$^{1/2}$ at various crosslinking ratios, E = 0 V, pH 5.5, and at 37 °C. The results show the amount of drug released decreases with decreasing the crosslinking agent ion size ($Ba^{+} > Ca^{2+} > Mg^{2+}$), resulting in compacting the carrageenan molecules (Al-Musa *et al.*, 1999).

3.2.5 Effect of electric field strength

Fig. 6 shows amounts of ASA released from the Ba-CAR hydrogel or the Ba-CAR_1.4 hydrogel versus $t^{1/2}$ at various electric field strengths from the negatively charged electrode (cathode in the donor part). The amount of drug released increases with increasing electric field strength due to the electrostatic interaction between the negatively charged drug and the negatively charged electrode. In addition, the diffusion coefficient of drug released increases with increasing electric field strength because the higher electric field strength induces a higher electrostatic force that drives the negatively charged drug through the polymer matrix (Juntanon *et al.*, 2008).

3.2.6 Effect of electrode polarity

Fig. 7 shows amounts of ASA released from the Ba-CAR hydrogel or the Ba-CAR_1.4 hydrogel versus $t^{1/2}$ under the negatively charged electrode (cathode in the donor part), the positively charged electrode (anode in the donor part), and without an applied electric field. The amount of drug released and the diffusion coefficient under cathode are higher than those under no electric field and under anode, respectively. This is a direct result of the electro repulsion between the negatively charged drug and the negatively charged electrode driving the charged drug through the polymer matrix into the buffer solution (Green, 1996). Passive delivery (without electric field) results in a lower permeation. With the same electric field and under the anode, the amount of drug released and the diffusion coefficient

are lowest among the three cases because of the electro attractive force. The electro attractive force is generated between the negatively charged drug and the positively charged electrode (Juntanon *et al.*, 2008).

3.2.7 Effect of conductive polymer

The amounts of drug released from PTh/carrageenan blend films are higher than that from carrageenan hydrogel due to the electro repulsive force is generated between the negatively charged drug and the negatively charged electrode. Fig. 8 shows the diffusion coefficients of ASA from carrageenan hydrogels and ASA-doped PTh/carrageenan blend films versus mesh size and crosslinking ratio, E = 2 V, pH 5.5, 37 °C. The diffusion coefficients of drug released increase with decreasing crosslinking ratio due to the larger pore size or the lower crosslinking ratio. As PTh is added into the hydrogel, the diffusion coefficients increase because the electro repulsive force between the negative charged drug and the cathode electrode can occur easily that can drive the drug into matrix (Murdan, 2003 and Kantaria *et al.*, 1999).

Fig. 9 shows the log-log plot of diffusion coefficients of acetylsalicylic acid from carrageenan hydrogel and drugs from alginate hydrogel versus the drug size/mesh size of hydrogels at electric field strength 0, 1, and 2 V at 37 °C. The data are tabulated in Table 3. The diffusion coefficients of drug released in all of these generally decrease with increasing drug size/mesh size or crosslinking ratio due to the reduction of the mesh size of hydrogel (Ferreira *et al.*, 2001).

From the data, the scaling exponent, m, can be determined from the following equation;

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

where D is the diffusion coefficient of a drug, D_0 is the diffusion coefficient for a very small drug size, a is the drug size, ξ is the mesh size of hydrogels, and m is the scaling exponent (Juntanon *et al.*, 2008).

The scaling exponent m values for the acetylsalicylic acid to diffuse through the carrageenan hydrogels under the electric field strengths of 0 and 2 V and the acetylsalicylic acid to diffuse through the PTh/carrageenan film under electric

field strength of 2 V are 0.96, 0.97, and 5.20, respectively. Corresponding D_o values are 1.05×10^{-6}, 1.64×10^{-6}, and 6.32×10^{-6} cm^2/s, respectively.

In comparing the data (Fig. 9) between the carrageenan hydrogel of the current work and the Ca-Alg hydrogel, the diffusion coefficients of anionic drugs (BA and TA) in the Ca-Alg hydrogel under applied electric field are larger than that no electric field due to electro repulsive between the negatively charged drug and the negatively charged electrode. On the other hand, the diffusion coefficients of cationic drug (FA) are smaller than without electric field due to the electro attractive fore between the positively charged drug and the negatively charged electrode. However, the diffusion coefficients of drug from alginate hydrogels are lower than those the carrageenan hydrogels. In case of the alginate hydrogel, the hydrogen bond provides the intermolecular interaction between the hydroxyl group of the alginate hydrogel and the carboxyl group of the anionic drugs, which is stronger than the van der Waals bond between the carboxyl group of acetylsalicylic acid and the sulfate group of the carrageenan hydrogel (Paradee *et al.*, 2012).

Moreover, the diffusion coefficients of drug are the highest in case of adding PTh as the drug carrier because of the reduction reaction ASA-doped PTh under an electric field, expansion of chain of conductive polymer, and electroporation. Thus, the electro repulsive force between the negative charged drug and the cathode electrode occur more easily with the conductive polymer (Niamlang *et al.*, 2009).

4. Conclusion

The ASA-loaded carrageenan hydrogels and the ASA-doped PTh/carrageenan blend films were prepared by varying the crosslinking ratio to study release mechanism characteristics and the diffusion coefficient of the drug with and without electric field. The swelling ability and the mesh size of each carrageenan hydrogel were characterized. The degree of swelling and the mesh size decrease with increasing crosslinking ratio. The diffusion coefficients were determined with respect to the effects of crosslinking ratio, type of crosslinking agent, and electric field strength. For the effect of crosslinking ratio, the diffusion coefficients of the drug from the carrageenan hydrogels and PTh/carrageenan blend film increase with

decreasing crosslinking ratio due to the larger mesh size. For the effect of crosslinking agent type, the diffusion coefficients of the drug from the carrageenan hydrogel and PTh/carrageenan blend films decrease with decreasing the crosslinking agent ion size ($Ba^{+} > Ca^{2+} > Mg^{2+}$) at the same crosslinking ratio. Under applied electric field, the diffusion coefficient of the drug from the carrageenan hydrogel is higher than that without electric field due to the electrostatic interaction between the negatively charged drug and the negatively charged electrode (under cathode) and the enhanced hydrogel mesh size. Moreover, the diffusion coefficients of the drug from the PTh/carrageenan blend films are greater than the diffusion coefficients of the drug from the carrageenan hydrogel, the presence of a conductive polymer can enhance the drug delivery rate considerably.

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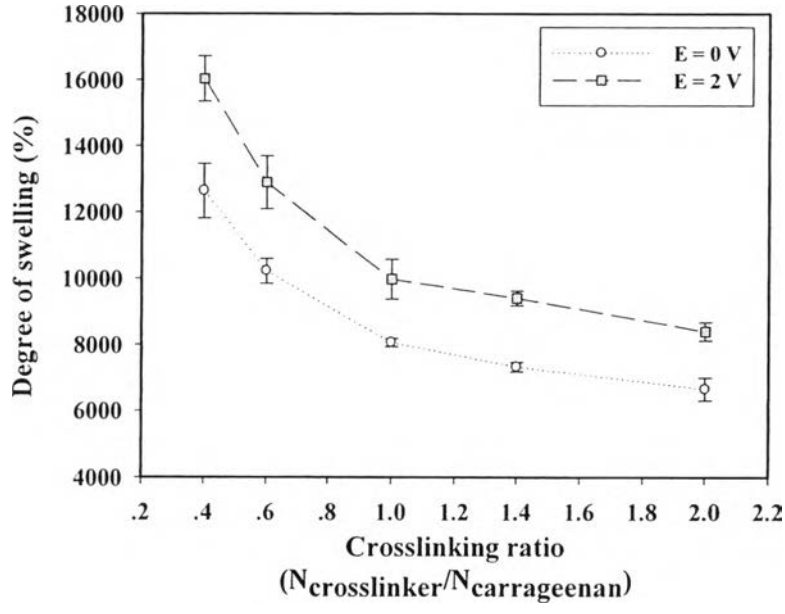


Figure 1 Degree of swelling (%) of carrageenan hydrogels at various crosslinking ratios of E = 0 and 2 V, at 37 °C after 5 days.

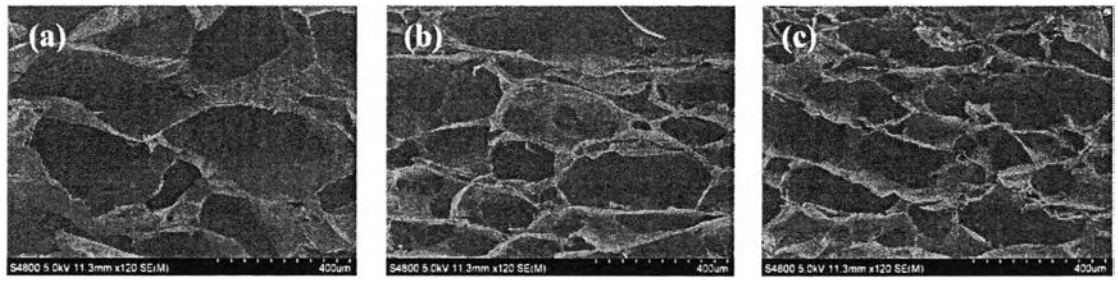


Figure 2 The morphology of Ba-CAR hydrogel after swelling: (a) Ba-CAR_0.4; (b) CAR_1.0; and (c) CAR_2.0 at 120x magnification.

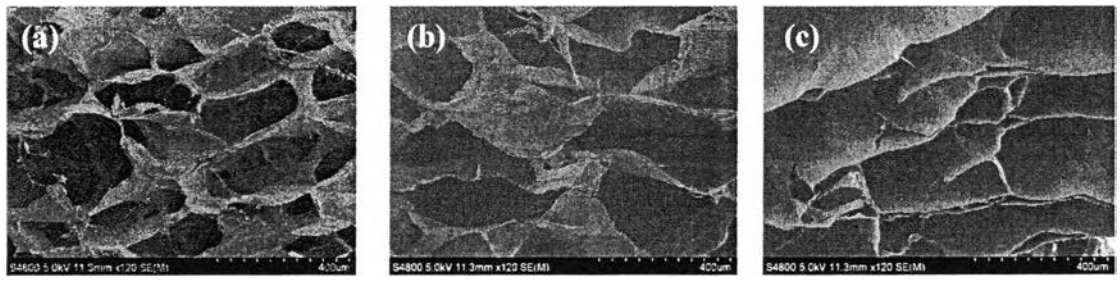
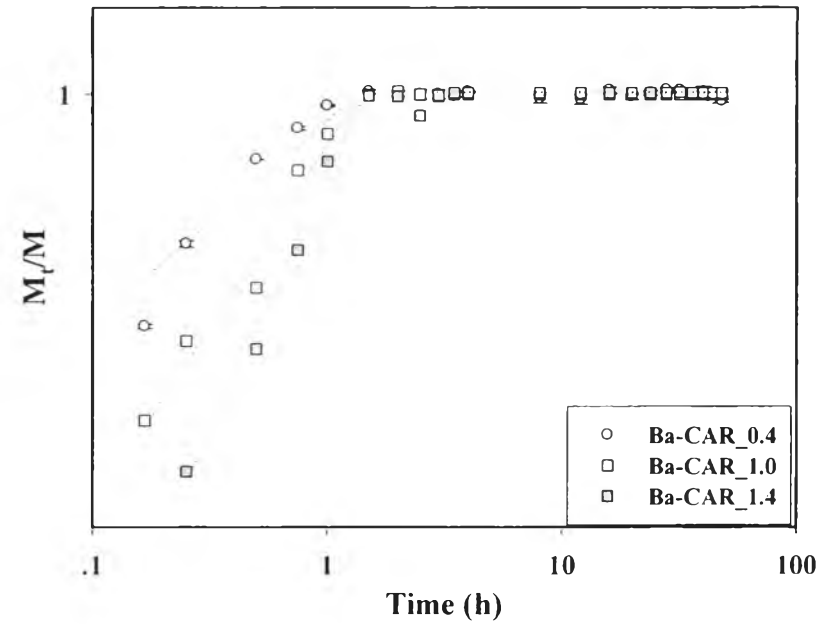
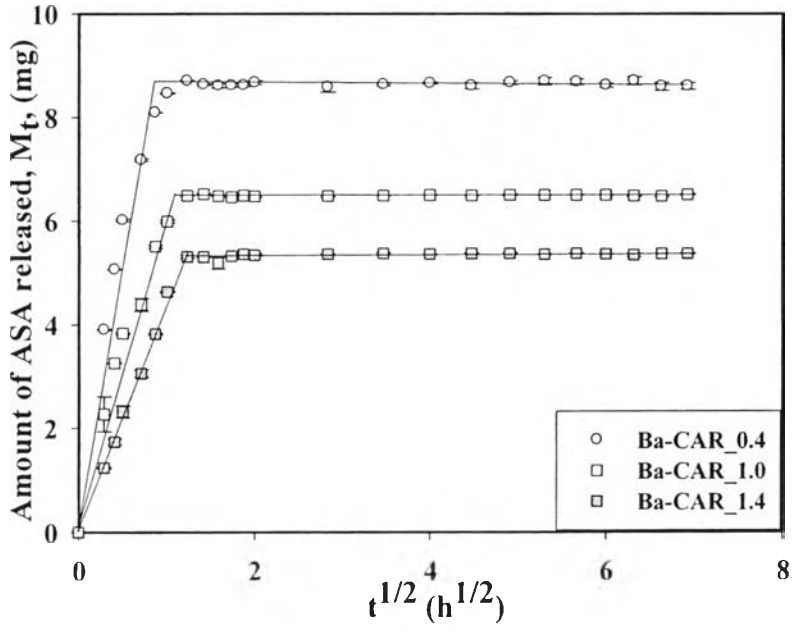


Figure 3 The morphology of Ba-CAR (CAR_1.4) after swelling under electric field strengths of: (a) 0 V; (b) 2.0 V; and (c) 5.0 V at 120x magnification.



(a)



(b)

Figure 4 Amounts of ASA released from Ba-CAR hydrogels of various crosslinking ratios versus: (a) time; and (b) time$^{1/2}$.

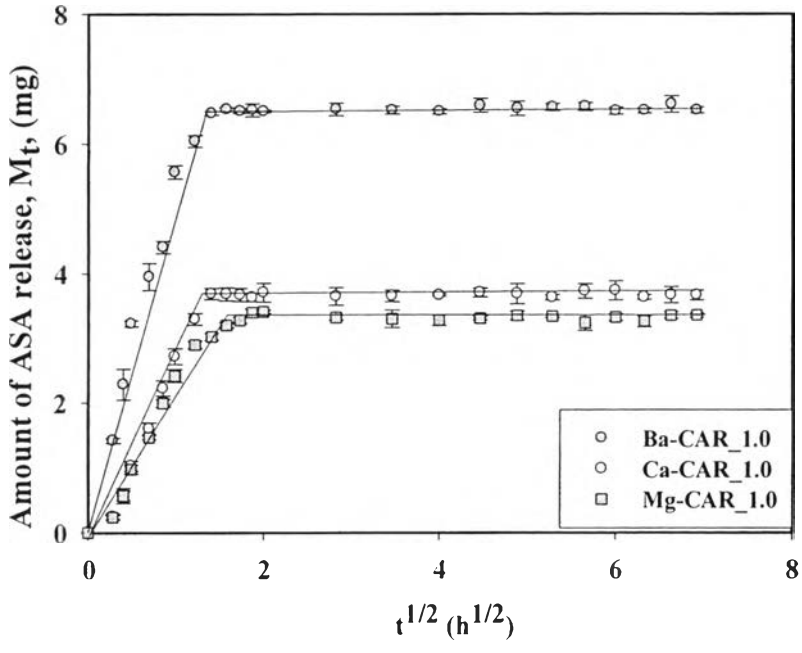


Figure 5 Amounts of ASA released from ASA-loaded carrageenan hydrogels versus time$^{1/2}$ at various crosslinking ratios of 3 crosslinking agent, E = 0 V, pH 5.5, and at 37 °C.

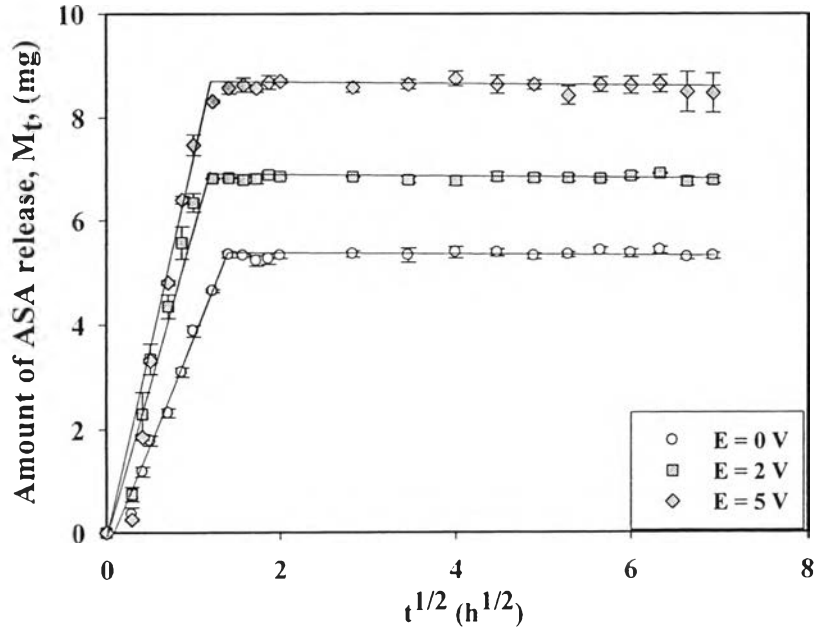


Figure 6 Amounts of ASA released from ASA-loaded Ba-CAR hydrogels versus time$^{1/2}$ at crosslinking ratio = 1.4 and at various electric field strengths, pH 5.5, and at 37 °C.

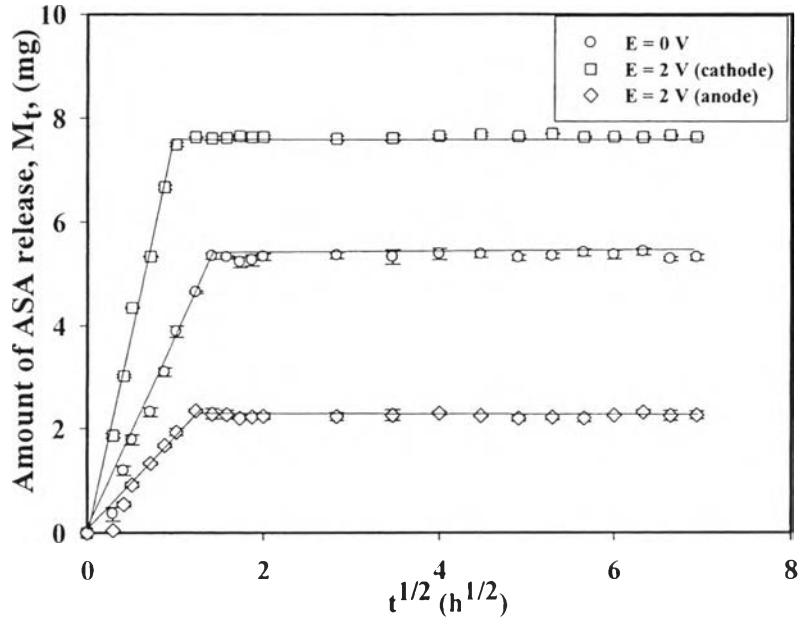


Figure 7 Amounts of ASA released from Ba-CAR hydrogels versus time$^{1/2}$ with the hydrogel samples attached to the anode or cathode, Ba-CAR_1.4 hydrogels.

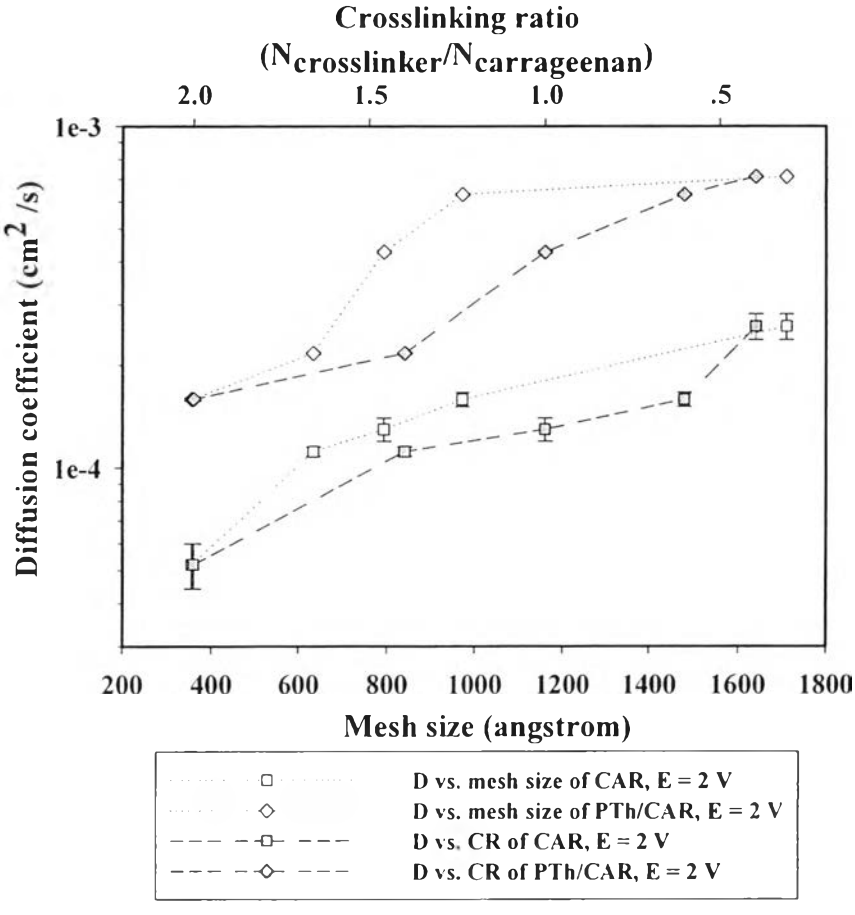


Figure 8 Diffusion coefficients of ASA from carrageenan hydrogels and PTh/ carrageenan blend films versus mesh size and crosslinking ratio, E = 2 V, pH 5.5, 37 °C.

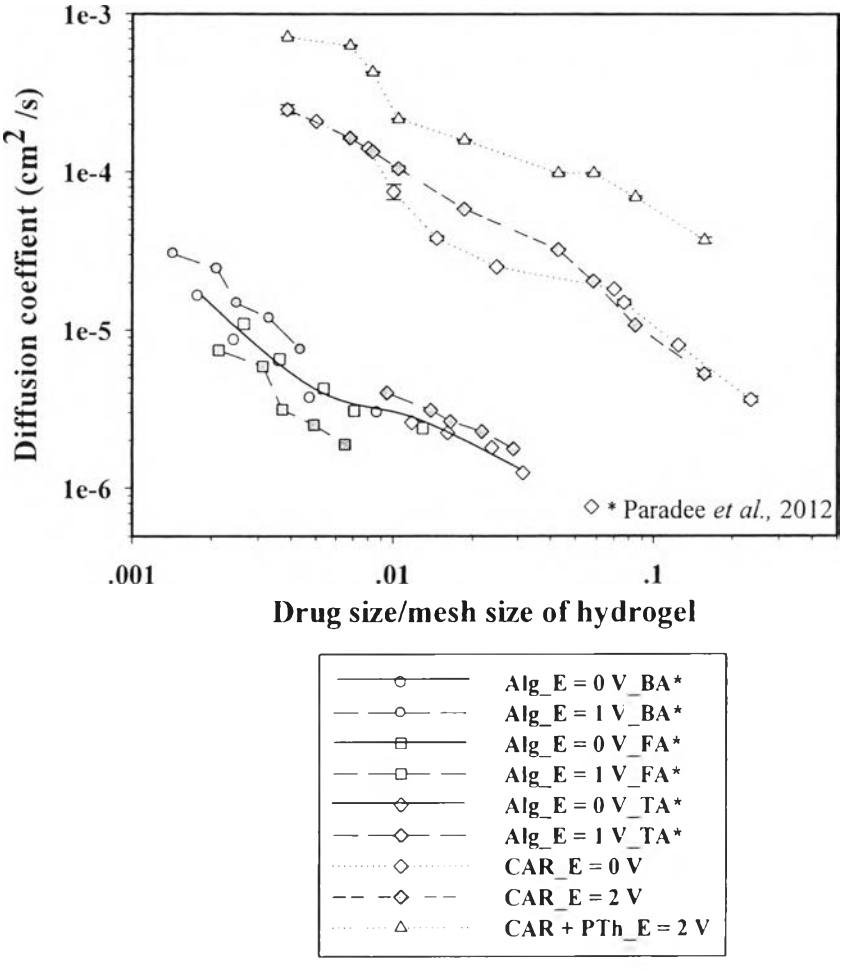


Figure 9 Diffusion coefficients of drug-loaded alginate and carrageenan hydrogels in relation to drug size/mesh size at the electric field strength between 0 and 2 V, at pH 5.5, and 37°C.

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

Sample	Crosslinking ratio	Number-average molecular weight between crosslinks, $\bar{M}_c$ (g/mol)		Mesh size, ξ (Å)		Crosslinking density, ρ_x (mol/cm^3 × 10^4)	
		E = 0 V	E = 2 V	E = 0 V	E = 2 V	E = 0 V	E = 2 V
Ba-CAR_0.4	0.4	(1.99 ± 0.65) x 10^4	(3.64 ± 0.21) x 10^4	1229 ± 289	1710 ± 112	1.03 ± 0.01	0.96 ± 0.15
Ba-CAR_0.6	0.6	(1.52 ± 0.68) x 10^4	(2.41 ± 0.16) x 10^4	713 ± 162	972 ± 164	1.34 ± 0.20	1.21 ± 0.13
Ba-CAR_1.0	1.0	(0.93 ± 0.10) x 10^4	(1.86 ± 0.09) x 10^4	656 ± 49	794 ± 104	2.19 ± 0.05	2.05 ± 0.05
Ba-CAR_1.4	1.4	(0.84 ± 0.02) x 10^4	(1.72 ± 0.15) x 10^4	451 ± 121	634 ± 79	2.43 ± 0.12	2.31 ± 0.21
Ba-CAR_2.0	2.0	(0.33 ± 0.05) x 10^4	(0.96 ± 0.07) x 10^4	265 ± 10	356 ± 34	6.18 ± 0.09	6.04 ± 0.11
Ca-CAR_1.0	1.0	(7.89 ± 0.12) x 10^3	(8.96 ± 0.04) x 10^3	99 ± 7	154 ± 16	9.42 ± 0.03	9.15 ± 0.31
Mg-CAR_1.0	1.0	(6.39 ± 0.09) x 10^3	(7.59 ± 0.11) x 10^3	90 ± 4	113 ± 21	15.01 ± 0.31	14.81 ± 0.08
Ca-CAR_2.0	2.0	(3.32 ± 0.13) x 10^3	(4.73 ± 0.15) x 10^3	57 ± 11	78 ± 17	23.15 ± 0.21	21.03 ± 1.21
Mg-CAR_3.0	3.0	(1.33 ± 0.04) x 10^3	(2.12 ± 0.05) x 10^3	25 ± 4	42 ± 11	44.21 ± 8.76	29.26 ± 5.12

Table 2(a) Release kinetic parameters and linear regression values obtained from fitting drug release experimental data to the Ritger-Peppas model without electric field

Sample	Diffusional exponent (n)	Kinetic constant (K)(h^{-n})	r^2
Ba-CAR_0.4	0.33	1.21	0.98
Ba-CAR_0.6	0.34	1.15	0.99
Ba-CAR_1.0	0.36	0.99	0.98
Ba-CAR_1.4	0.52	0.83	0.99
Ba-CAR_2.0	0.57	0.80	0.99
Ca-CAR_1.0	0.60	0.84	0.96
Mg-CAR_1.0	0.56	0.87	0.97
Ca-CAR_2.0	0.59	0.72	0.95
Mg-CAR_3.0	0.54	0.76	0.94

Table 2(b) Release kinetic parameters and linear regression values obtained from fitting drug release experimental data to the Ritger-Peppas model with electric field of 2 V

Sample	Diffusional exponent (n)	Kinetic constant (K)(h^{-n})	r^2
Ba-CAR_0.4+E	0.46	1.06	0.92
Ba-CAR_0.6+E	0.47	0.96	0.94
Ba-CAR_1.0+E	0.48	0.92	0.95
Ba-CAR_1.4+E	0.44	0.85	0.98
Ba-CAR_2.0+E	0.54	0.81	0.97
Ca-CAR_1.0+E	0.60	0.83	0.94
Mg-CAR_1.0+E	0.60	0.65	0.95
Ca-CAR_2.0+E	0.56	0.49	0.96
Mg-CAR_3.0+E	0.74	0.35	0.95
Ba-CAR_0.6+PTh+E	0.23	1.31	0.92
Ba-CAR_1.0+PTh+E	0.43	1.23	0.94
Ba-CAR_1.4+PTh+E	0.45	1.03	0.98
Ba-CAR_2.0+PTh+E	0.49	0.94	0.99
Ca-CAR_1.0+PTh+E	0.39	1.47	0.98
Mg-CAR_1.0+PTh+E	0.40	1.06	0.98
Ca-CAR_2.0+PTh+E	0.40	0.79	0.98
Mg-CAR_3.0+PTh+E	0.39	0.67	0.96

Table 3 The diffusion coefficient of the drug on carrageenan and Ca-Alg hydrogels at temperature of 37 °C and pH 5.5

Sample	Drug	M_w	Drug size (Å)	Mesh size (Å)	D (cm^2/s)	E(V)	Remarks
Ba-CAR	Acetylsalicylic acid	180	6.6	1,229	2.04×10^{-4}	-	Crosslink ratio = 0.4
				656	7.83×10^{-5}	-	Crosslink ratio = 1.0
				256	2.48×10^{-5}	-	Crosslink ratio = 2.0
Ca-CAR				99	1.82×10^{-5}	-	Crosslink ratio = 1.0
				27	1.50×10^{-5}	-	Crosslink ratio = 2.0
Mg-CAR				90	8.09×10^{-6}	-	Crosslink ratio = 1.0
				25	3.66×10^{-6}	-	Crosslink ratio = 3.0
Ba-CAR	Acetylsalicylic acid	180	6.6	1,710	2.60×10^{-4}	2	Crosslink ratio = 0.4
				794	1.29×10^{-4}	2	Crosslink ratio = 1.0
				356	5.20×10^{-5}	2	Crosslink ratio = 2.0
Ca-CAR				154	3.24×10^{-5}	2	Crosslink ratio = 1.0
				78	2.50×10^{-5}	2	Crosslink ratio = 2.0
Mg-CAR				113	1.08×10^{-5}	2	Crosslink ratio = 1.0
				42	5.32×10^{-6}	2	Crosslink ratio = 3.0
Ba-CAR + PTh	Acetylsalicylic acid	180	6.6	1,710	7.12×10^{-4}	2	Crosslink ratio = 0.4
				794	4.28×10^{-4}	2	Crosslink ratio = 1.0
				356	1.59×10^{-4}	2	Crosslink ratio = 2.0
Ca-CAR + PTh				154	9.80×10^{-5}	2	Crosslink ratio = 1.0
				78	3.70×10^{5}	2	Crosslink ratio = 2.0
Mg-CAR + PTh				113	6.92×10^{-5}	2	Crosslink ratio = 1.0
				42	2.14×10^{-5}	2	Crosslink ratio = 3.0

Sample	Drug	M_w	Drug size (Å)	Mesh size (Å)	D (cm^2/s)	E(V)	Remarks
Ca-Alg	Benzoic acid[a]	122	5.58	3,313	1.64×10^{-5}	-	Ca-Alg_crosslink ratio = 0.3
				2,289	8.63×10^{-6}	-	Ca-Alg_crosslink ratio = 0.5
				1,545	6.31×10^{-6}	-	Ca-Alg_crosslink ratio = 0.7
				1,174	3.72×10^{-6}	-	Ca-Alg_crosslink ratio = 1.0
				641	3.01×10^{-6}	-	Ca-Alg_crosslink ratio = 1.3
				3,887	3.04×10^{-5}	I	Ca-Alg_crosslink ratio = 0.3
				2,657	2.44×10^{-5}	I	Ca-Alg_crosslink ratio = 0.5
				2,236	1.48×10^{-5}	I	Ca-Alg_crosslink ratio = 0.7
				1,689	1.19×10^{-5}	I	Ca-Alg_crosslink ratio = 1.0
				1,277	7.53×10^{-5}	I	Ca-Alg_crosslink ratio = 1.3
	Tannic acid[a]		8.31	3,313	2.61×10^{-6}	-	Ca-Alg_crosslink ratio = 0.3
				2,289	2.25×10^{-6}	-	Ca-Alg_crosslink ratio = 0.5
				1,545	1.81×10^{-6}	-	Ca-Alg_crosslink ratio = 0.7
				1,174	1.25×10^{-6}	-	Ca-Alg_crosslink ratio = 1.0
				641	7.64×10^{-7}	-	Ca-Alg_crosslink ratio = 1.3
				3,887	4.02×10^{-6}	I	Ca-Alg_crosslink ratio = 0.3
				2,657	3.13×10^{-6}	I	Ca-Alg_crosslink ratio = 0.5
				2,236	2.65×10^{-6}	I	Ca-Alg_crosslink ratio = 0.7
				1,689	2.29×10^{-6}	I	Ca-Alg_crosslink ratio = 1.0
				1,277	1.78×10^{-6}	I	Ca-Alg_crosslink ratio = 1.3

Sample	Drug	M_w	Drug size (Å)	Mesh size (Å)	D (cm^2/s)	E(V)	Remarks
Ca_Alg	Folic acid[a]	122	36.84	3,313	1.10×10^{-5}	-	Ca-Alg_crosslink ratio = 0.3
				2,289	6.57×10^{-6}	-	Ca-Alg_crosslink ratio = 0.5
				1,545	4.28×10^{-6}	-	Ca-Alg_crosslink ratio = 0.7
				1,174	3.08×10^{-6}	-	Ca-Alg_crosslink ratio = 1.0
				641	2.40×10^{-6}	-	Ca-Alg_crosslink ratio = 1.3
				3,887	7.45×10^{-6}	1	Ca-Alg_crosslink ratio = 0.3
				2,657	5.87×10^{-6}	1	Ca-Alg_crosslink ratio = 0.5
				2,236	3.14×10^{-6}	1	Ca-Alg_crosslink ratio = 0.7
				1,689	2.51×10^{-6}	1	Ca-Alg_crosslink ratio = 1.0
				1,277	1.89×10^{-6}	1	Ca-Alg_crosslink ratio = 1.3

[a] Paradee *et al.*, 2012