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The diffusion of dextran within poly(methacrylic acid) hydrogels

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ABSTRACT

We describe a fluorescence correlation spectroscopy investigation into the diffusion of fluorescein-tagged dextran (FDEX) in a poly(methacrylic acid) (PMAA) hydrogel. The temperature dependence of FDEX diffusion is shown to follow Zimm behaviour in pure water, and the decrease in the diffusion coefficient when in the PMAA hydrogel has been modelled. The addition of acid and alkali (HCl and NaOH respectively) not only control the swelling and collapse of the hydrogel but also reveal a strong pH dependence of the dextran diffusion coefficient, which shows a (non-monatonic) increase with pH. The addition of NaCl and $CaCl_2$ salts similarly showed evidence of network swelling, most notably at low salt concentration, but also that the diffusion coefficient within the gel at these low concentrations is larger that in the equivalent solution without the hydrogel, indicating that the combination of hydrogel and salt works to increase the diffusion coefficient above that in pure water.

KEYWORDS Diffusion, hydrogel, FCS

INTRODUCTION

The theory of polymer diffusion through a molten polymer network has already been well established by Doi and Edwards,[1] showing that the diffusion coefficient depends upon the distance between crosslinks known as mesh size. However a combination of this theory with the responsive behaviour of polymer hydrogel systems is of considerable practical importance because controlling the diffusion of polymers in a hydrogel network has applications in drug delivery systems[2,3] as well as in responsive adhesives,[4] biosensors,[5] and contact lens development.[6] The underlying phenomena of gelation and swelling have been extensively studied,[7, 8] with more recent developments utilising fluorescence[9,10] and light-scattering techniques[11] to investigate the swelling properties of hydrogels.

Diffusion through heterogeneous media is important in biological systems, ranging from examining the absorption of doxylamine in mice[12] to the controlled delivery of drugs from biocompatible responsive hydrogels such as hydroxypropyl methylcellulose,[13] or more complicated systems involving hydrogels impregnated with biodegradable microcarriers.[14] Theoretical work has also been published that provides some understanding of such network systems and highlights the parameters that can be modified to provide a hydrogel system that is specifically designed for a certain task.[15,16]

One of the drawbacks to studying the diffusion of molecules within such systems is that they either require large and expensive experimental setups (such as pulsed-field-gradient NMR[17,18]) or rely on measurements of molecules as they diffuse across a gel boundary rather than within the gel itself; details of such techniques can be found in the review by Pasch.[19]

EXPERIMENTAL

Gel Synthesis

A solution of 16.7% (by weight) methacrylic acid (MAA), 0.04% methylene-bis-acrylamide (MBA), 0.02% 2,2'-azobis (2-methylpropionamidine) dihydrochloride (AMPA), and the remainder HPLC grade water was prepared in a sealed container and flooded with nitrogen for 30 min. The solution was then placed in a vacuum oven at 65°C for 8h to ensure complete polymerisation of the MAA.

The resulting gel was then immersed in an excess of distilled water, such that the swelling of the gel was not limited by the environmental volume nor quantity of solvent available. When swelling had reached equilibrium (a constant mass of hydrated gel measured over 3 periods

separated by at least 4h), pieces of the gel were subsequently removed for analysis in the confocal microscope.

Dextran is a branched, neutral glucan widely used due to its biocompatibility and ease of conjugation with labels and functional groups.[20-22] In order to introduce fluorescein-tagged dextran molecules (FDEX) (M_w = 20 kDa) into the gel, a nanomolar concentration in either pure water, HCl acid, NaOH base, or salt solution (depending upon the experiment) was produced and a small volume of gel was allowed to rest in each solution for sufficient time that the probe penetrated the network and any new structural equilibrium had been reached. In order to exclude the possibility of free-dye diffusion competing with that of the dextran during the experiments, FDEX solutions were dialysed and measurements performed with this solution were compared to those using undialysed solutions. No change in the diffusion coefficients was found between dialysed and undialysed solutions.

Fluorescence Correlation Spectroscopy

FCS measurements were made using a ConfoCor2 FCS Module fitted to an LSM510 inverted confocal microscope (Zeiss) and temperature was controlled using a Linkam heating stage (Linkam Scientific Instruments Ltd, Surrey, UK) with TMS94 heat controller and LNP-1 nitrogen flow control.

Autocorrelation curves were fitted using the model described by Widengren and colleagues[23] using pro Fit v6.1.8 (Quantum Soft, Switzerland). A Monte Carlo algorithm was initially used to determine the starting parameters, and a Levenberg-Marquardt routine was used to find the final best fit parameters. The autocorrelation function is given by

$$G(\tau) = 1 + \frac{1}{N_V}\left[\frac{1}{1+\frac{\tau}{\tau_D}}\frac{1}{\sqrt{1+\frac{\tau}{\Gamma^2\tau_D}}}\right]\left[1+\left(\frac{P_t}{1-P_t}\right)\exp\left(-\frac{\tau}{\tau_t}\right)\right] \quad (1)$$

and depends upon the number of fluorescently labelled molecules N_V within the detection volume, the diffusion time τ_D, the confocal volume structure parameter Γ, and the fraction of excitations to the triplet state P_t that has a decay time τ_t. An example of fitted autocorrelation functions for typical data obtained in this work are shown in figure 1. The Widengren equation determines the diffusion time of a polymer species (that is, the average time taken to cross the detection volume), and therefore it is necessary to convert this into a diffusion coefficient *D* for use with the theory described in the following sections. For this purpose, the diffusion coefficient can be obtained from the diffusion time using the relationship defined by Varma and colleagues[24]

$$D = \frac{a^2}{4\tau_D} \quad (2)$$

where *a* is the average confocal width (300 nm for the experimental setup used in this work).

THEORY

Zimm Model

The Stokes-Einstein relationship is the standard model for characterising the diffusion of a particle through a solvent. The diffusing species is treated as a sphere of radius *R* moving through a solvent of viscosity η_S at absolute temperature *T*, with a diffusion coefficient given by

$$D_{SE} = \frac{k_B T}{6\pi R \eta_S} \quad (3)$$

where k_B is the Boltzmann constant.

Whilst equation 3 has been shown to hold true for the diffusion of spherical or nearly-spherical

particles, a polymer chain requires modifications to the theory. By approximating the polymer chain as a series of balls connected by springs, and by considering the drag effect of each monomer ball on the surrounding solvent, the Zimm model[25] gives

$$D_{\text{Zimm}} = \frac{k_{\text{B}}T}{\zeta_{\text{Zimm}}} = \frac{0.196k_{\text{B}}T}{\eta_{\text{S}}bN^{\nu}} \quad (4)$$

where ζ_{Zimm} is the polymer friction coefficient, b is the Kuhn monomer length and N is the number of monomers. The numerical prefactor is found for an ideal chain, and the polymer size is given by

$$R = bN^{\nu}$$

in which the exponent ν depends upon the solvent quality.

Swelling of Ionic Gels

The swelling of polymer networks comprising of charged constituents has been extensively studied. Flory[26] showed that, for dilute polymers, the swelling of an ionic gel can be expressed as

$$Q_{\text{m ion}}^{5/3} = Q_{\text{m non}}^{5/3} + \frac{V_0}{4\nu_{\text{e}}\nu_{\text{u}}^2}\frac{i^2}{S^*} \quad (5)$$

where $Q_{\text{m ion}}$ and $Q_{\text{m non}}$ are the equilibrium swelling ratios of the ionic and non-ionic gels respectively, V_0 is unswollen gel volume, ν_{e} the effective number of chains in the network, ν_{u} is the molar volume of a structural unit, i is the degree of ionisation per unit of polymer, and S^* is the ionic strength of the surrounding medium. Assuming that no structural changes occur within the gel upon swelling, it follows that an ionic gel will swell more than a non-ionic gel, and subsequently collapse back towards the non-ionic system with increasing ionic concentration.

RESULTS

Temperature dependence of dextran diffusion

For FDEX in pure water, the diffusion coefficient increases with temperature as expected from equation 4, after allowing for changes in the viscosity of water based upon a theory first proposed[27] in 1971 and subsequently expanded to account for the atypical increase in fluidity at higher temperatures due to a disruption in the hydrogen bond network with increased thermal energy.[28, 29]

When the FDEX solution is within a hydrogel the overall viscosity changes. Figure 2 shows that the network introduces an additional effect that overwhelms the normal thermal motion of diffusion (equation 4) and causes a decrease in the diffusion coefficient at higher temperatures. By consideration of the Zimm equation it follows that the viscosity of the system must contribute more than the effect of any change in temperature.

The change in gel viscosity can be characterised by considering the correlation length of the network, known also as the average mesh size ξ. De Gennes and colleagues proposed[30] that the diffusion of a molecule of diameter *d* through a network with this average mesh size follows an exponential relationship

$$D(T) = D_0 \exp\left[-\beta\left(\frac{d}{\xi(T)}\right)^{\delta}\right] \qquad (6)$$

where D_0 is the diffusion coefficient at a reference point, $\delta = 2.5$ for cross-linked networks and β is a constant of order unity.

The mesh size is a length scale of the network that describes the average length between crosslink sites, given by

$$\xi = Q^{1/3}\left(C_n n\right)^{1/2} l \qquad (7)$$

where Q is the equilibrium swelling ratio (determined experimentally through swelling measurements), C_n is a characteristic ratio of the polymer (14.6 for PMAA,[31] n is the number of crosslinks per chain, and l is the C-C bond length (0.154 nm). This expression for the mesh size can be substituted into equation 6 and the model applied to the data is presented in figure 2.

Whilst the model described above provides a good description of the data in figure 2, it is instructive to consider alternative explanations of our results. If we consider the viscosity of the system to be described by changes in the concentration of PMAA when the hydrogel undergoes swelling, we also can fit the data above and is presented here. Assuming that no polymer is lost from the hydrogel, any decrease of solvent mass (per unit volume) increases the polymer concentration, c. Substitution of the Huggins equation[25]

$$\frac{\eta - \eta_S}{\eta_S c} = [\eta] + k_H [\eta]^2 c + K \qquad (8)$$

into equation 4 produces a relationship that describes the data in figure 2. The change in polymer mass concentration can be inferred from the mass loss of the swollen network as given in figure 3.

Our use of the Huggins equation, which requires the radius of gyration of the diffusing molecule to be comparable to the mesh size as shown in figure 4 indicates that changes in hydrogel structure can be characterised by a change in the net viscosity. It is worth noting that increasing temperature also affects diffusion coefficient due to a change in the excluded volume of the dextran molecule within the gel. Separation of the chain size variation from the structural changes of the gel requires a thermal characterisation of FDEX molecules, which is not covered

in this work but has been extensively covered for other molecules such as polystyrene.[30] The change in polymer radius can be inferred from the measurements of dextran diffusion in pure water (figure 2).

It is found that this method also produces a good fit to the data in figure 2 although macroscopic swelling and how individual strands respond to changes in solvent concentration as shown in figure 3 must be considered. These are not affine networks described in this work; locally within the gel a great deal of molecular reorganisation can take place that is not mimicked on the macroscopic scale. This is a key consideration when attempting to produce hydrogels that control the release of absorbed molecules.

Diffusion of dextran in salt solutions

The effect of added salt on PMAA swelling is similar to the effect of pH in that *Q* can be made to change by over two orders of magnitude, although in this instance the most pronounced effect is at very dilute salt concentrations (figure 5).

As expected from inverse relation between swelling ratio and ion concentration given in equation 5, the diffusion coefficient drops rapidly over the dilute salt concentration range (up to 0.5 M L^{-1}) as the swelling of the hydrogel decreases towards the non-ionic system for increasing salt concentrations; what may be less obvious is that the gel-free system also follows this trend of a sharp decrease in *D* at low salt concentrations, although the overall decrease is less in magnitude when compared to the gel system. Reconsideration of equation 4 suggests that the dextran diffusion in the absence of gel may be affected by added salt due to an increase in viscosity or radius of hydration caused by a change in the solvent quality exponent

ν.

The ionic concentration dependence on viscosity has already been well investigated; Falkenhagen[33] derived an expression for symmetric electrolytes which was subsequently extended by Onsager and Fuoss to include asymmetric electrolytes.[34] Both derivations lead to the ionic concentration dependent viscosity relationship:

$$\eta(c) = \eta_0 + \frac{\kappa_D \zeta_0}{480\pi} \quad (9)$$

where η_0 is viscosity of pure solvent, ζ_0 is the friction coefficient of an ion in a solution of infinitesimal concentration, and κ_D is the inverse Debye screening length which scales as the square root of the ion concentration and linearly with ion valency. It should be noted however that the Debye screening length provides a poor model of the charge behaviour around a polymer chain especially in low salt concentrations: it has been demonstrated that the distribution of charges around a polymer chain is very different to that around free ions for which the Debye length model was originally derived.[35]

Another point of interest is that at the lowest salt concentrations, the diffusion coefficient of the dextran in the gel, D_{gel}, is greater than that in the absence of a gel, D_{water} (figure 7). This means that whilst there is extensive swelling of the gel (as predicted in equation 5 for low concentration), there is an additional effect causing the dextran molecules to diffuse faster than in pure water; it is expected that, for maximum swelling, the system will tend towards (but not exceed) pure water conditions – exceeding this would imply there is an additional component of the salt-gel-FDEX system that is causing the dextran to diffuse faster through the gel than in the equivalent situation without a gel. A possible explanation for this increase in dextran diffusion lies with the interaction between any additional charge and the dextran, either from

the salt solution itself or from any free charge released by the network. Indeed, PMAA has been found to ionise in the presence of salt,[36-38] which may provide some justification for the non-monotonic swelling behaviour of the gel, but does not suitably explain why the diffusion in the gel exceeds that in salt solution, nor the non-monotonic behaviour of dextran in the gel-free system.

The effect of electrolyte concentration on the radius of dextran molecules is not yet understood; it is not unreasonable to assume that the conformation of the dextran molecule will also affect the viscosity term described above, and therefore a theoretical model to fit the data presented in figures 6 and 7 would require a characterisation of the effect of ionic concentration on the labelled dextran molecule.

Finally, the presence of salt may affect or dissociate the fluorescein probe from the dextran molecule, but this is not considered to be a contributing factor to the observation that $D_{gel} > D_{water}$ as the diffusion through the gel is normalised to the corresponding diffusion in salt solution and consequently any effect on the dye due to the salt will be present in both the gel and gel-free diffusion measurements.

Variation of pH

Any change in hydrogel structure can again be determined by measuring Q for all pH values, which is shown in figure 8. Unlike the effect of temperature upon Q (figure 3) that shows very little swelling ($Q \approx 0$), the swelling ratio in alkaline pH can be several hundreds indicating a significant degree of swelling.

The introduction of acid or alkali has an effect not only upon the structure of the charged hydrogel but also on the dextran molecule itself. Figure 9 shows that the diffusion of dextran in

a gel-free environment is dependent upon the charge concentration. This result may be somewhat surprising considering that previous work[39] shows that the radius of hydration R_H for dextran in water and 0.5 mM NaOH solution follows the same relationship for different molecular weights of polymer. These authors also found that the intrinsic viscosity of dextran is comparable when in water and NaOH, which is in agreement with figure 9 in the basic regime. The apparent anomaly between pH 6 and 7 can easily be explained when the method used to prepare the pH solutions is examined. HPLC-grade water of pH 7 was initially used, into which different masses of HCl or NaOH were dissolved into the water to reach the required pH. Whilst the concentration of hydrogen ions was measured, the additional atoms from the original solutes form a solution of additional ions that will influence the entire system in a similar manner to that expressed in the previous section.

Even with this consideration in mind, it is now possible to examine the overall effect of charge upon the structure of the gel itself. As figure 9 shows the diffusion relationship between 'free' dextran and that confined in PMAA gel follow significantly different trends. More acidic environments result in a decrease in the diffusion coefficient, and given that the diffusion of 'free' dextran is maximised at these low pH values we can ascertain that the hydrogel itself has undergone a structural change, collapsing and thus impeding the motion of dextran, in agreement with the results shown in figure 8. As with the temperature effect, this pH-induced decrease in the diffusion coefficient can be interpreted as an increase in the hydrogel concentration as described by equation 8. Such a collapse has already been documented,[40] and indeed put into practical use.[2,4,41] Dextran diffusion in magnetite impregnated gels (ferrogels) has been shown to be controlled by the mesh size of the hydrogel,[42] but in those experiments

the swelling ratio changed by a factor of two compared to approximately 350 in these experiments.

CONCLUSIONS

It has been shown that FCS is a viable technique for measuring the diffusion of tagged molecules within a hydrogel. The expected Zimm diffusion of FDEX was observed in pure water over a range of temperatures, and that with suitable modification using the Huggins equation it is possible to model the change in viscosity of a hydrogel and related this to the change in diffusion of the probe molecule.

Furthermore we have shown that PMAA undergoes structural changes with the addition of charge into the surrounding solvent. Interestingly, the addition of salt into the hydrogel will induce swelling of the network as predicted by Flory,[26] but rather than bringing the in-gel diffusion closer to that in pure water we have shown that the diffusion exceeds that in pure water. Whether this is due to changes in the network itself or a consequence of salt-probe interactions is yet to be determined.

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FIGURE 1 Autocorrelation functions for one dataset of the diffusion of FDEX in pure water at different temperatures. The solid lines represent the fit of equation 1 to the data.

FIGURE 2 Temperature effect on diffusion of free dextran (open circles) and dextran in PMAA gel (crosses). The dotted line presents a fit using the Zimm model (equation 4) with temperature-dependent viscosity,[19-21] whereas the dashed line also utilises a Huggins relationship for viscosity (equation 6) and the solid line presents a fit of the mesh-size relation given by equation 7. The same data are shown in the lower figure but expanded for the gel data and two fitted models.

FIGURE 3 Swelling ratio (given as a percentage change in mass) and mesh size of swollen PMAA at different temperatures. Note that at the highest temperature the mass decreases only by 1% compared to the initial value at T = 283 K . Q values were determined experimentally whereas mesh size was determined from FCS measurements and modelled via equation 8. The data have been fitted to empirical functions $Q = A\left(\frac{1}{1+\exp\left(\frac{T-T_0}{K}\right)}\right)$ and $\xi = B\left(T+T_1\right)^{\sigma} + C$ to provide a guide to the eye, where A, T_0, K, B, T_1, σ, and C are empirical constants.

FIGURE 4 Comparison of the mesh size (determined using equation 8) and the radius of gyration (determined using equation 3 from the diffusion of dextran through pure water) plotted as a function of temperature. Note that these length scales are comparable over all temperature ranges supporting the use of the Huggins theory of viscosity (equation 8) in modelling diffusion through PMAA hydrogels.

FIGURE 5 Swelling ratio of PMAA for concentrations of NaCl and $CaCl_2$ over the concentration range used in the present study. Whilst the maximum swelling ratio is not as high as that for which pH was varied (figure 8) one can still see that very low concentrations of salt induce a dramatic structural change in the gel resulting in up to a factor of 60 increase in mass. The inset figure provides the same data on a log-linear plot but does not include the value for zero salt concentration.

FIGURE 6 Diffusion of FDEX in NaCl and $CaCl_2$ salt solutions, both with and without PMAA gel. The sharp increase in diffusion at low salt concentrations is evident in all cases, with the system without gel reaching a plateau at higher concentrations. The lower and unequal diffusion coefficient within the gels arises from different degrees of collapse due to the different valencies between the salts.

FIGURE 7 Normalised diffusion coefficients in NaCl and $CaCl_2$. D_N is the normalised diffusion coefficient, and is defined as $D_N = D_{gel} / D_{water}$. The dashed line at $D_N = 1$ represents a diffusion coefficient equal to that in water at the same salt concentration. Values of $D_N > 1$ indicate that the hydrogel is causing the diffusion of dextran to be greater than when it is not present.

FIGURE 8 Swelling ratio of swollen PMAA for the pH range. The two plots show the time given for the

hydrogel to test for equilibrium conditions. The effect of pH is the most pronounced, when compared to the other systems studied within this work, with a factor of 350 change in mass.

FIGURE 9 Diffusion of FDEX in different pH environments. It is worth noting that both the acid and alkali regions were produced by the addition of HCl and NaOH respectively and thus also include contributions from the additional ions (Cl^- and Na^+).

GRAPHICAL ABSTRACT

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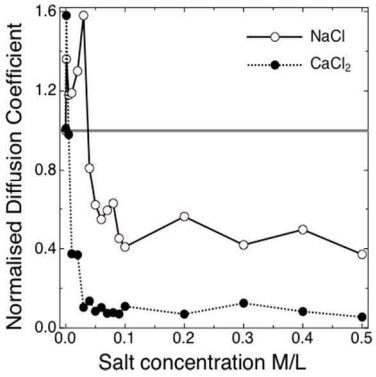
TITLE

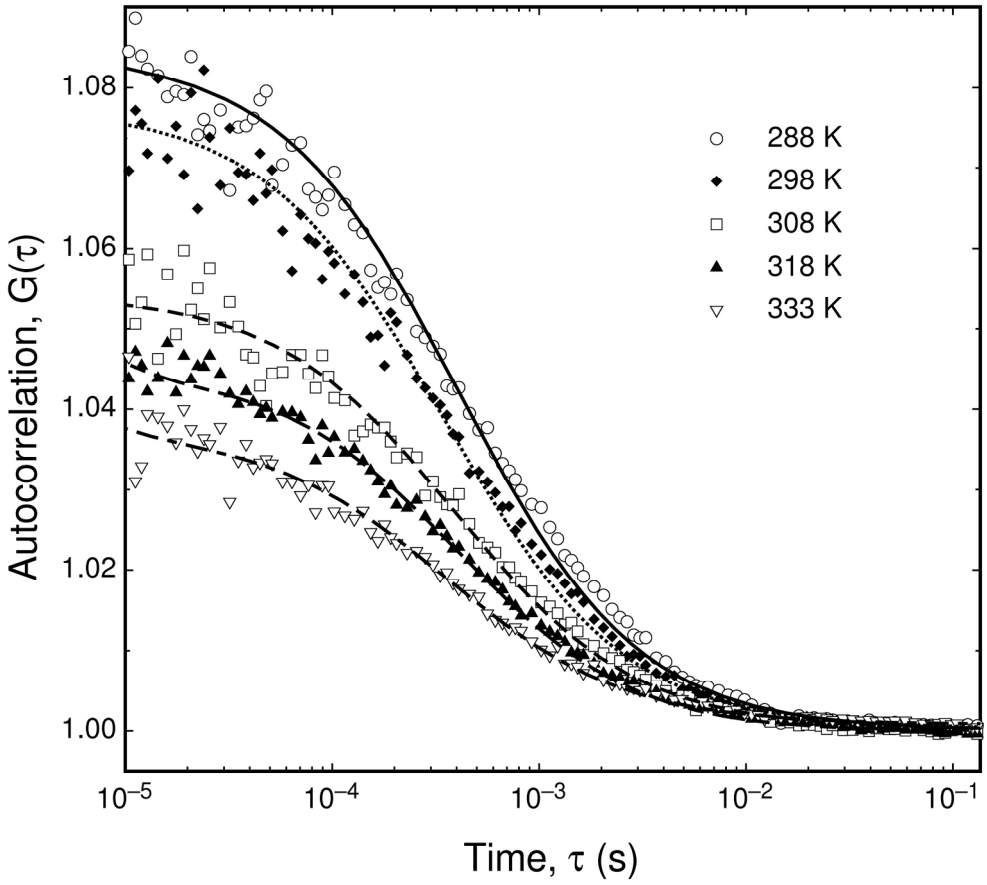
The diffusion of dextran within poly(methacrylic acid) hydrogels

TEXT ((up to 75 words, present tense, written for a non-specialist, see recent issue for examples))

Responsive hydrogels allow the diffusive properties of molecules within their network to be controlled. Here we show that poly(methacrylic acid) hydrogels respond to temperature, salt, and pH to alter the diffusion coefficent of fluorescently labelled dextran. The presence of ions in the surrounding environment cause significant swelling of the gel, with low ion concentrations providing the largest effect on both the mesh size of the gel and the diffusion of the dextran molecules.

GRAPHICAL ABSTRACT FIGURE ((50 mm wide by 50 mm high))





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200x181mm (300 x 300 DPI)

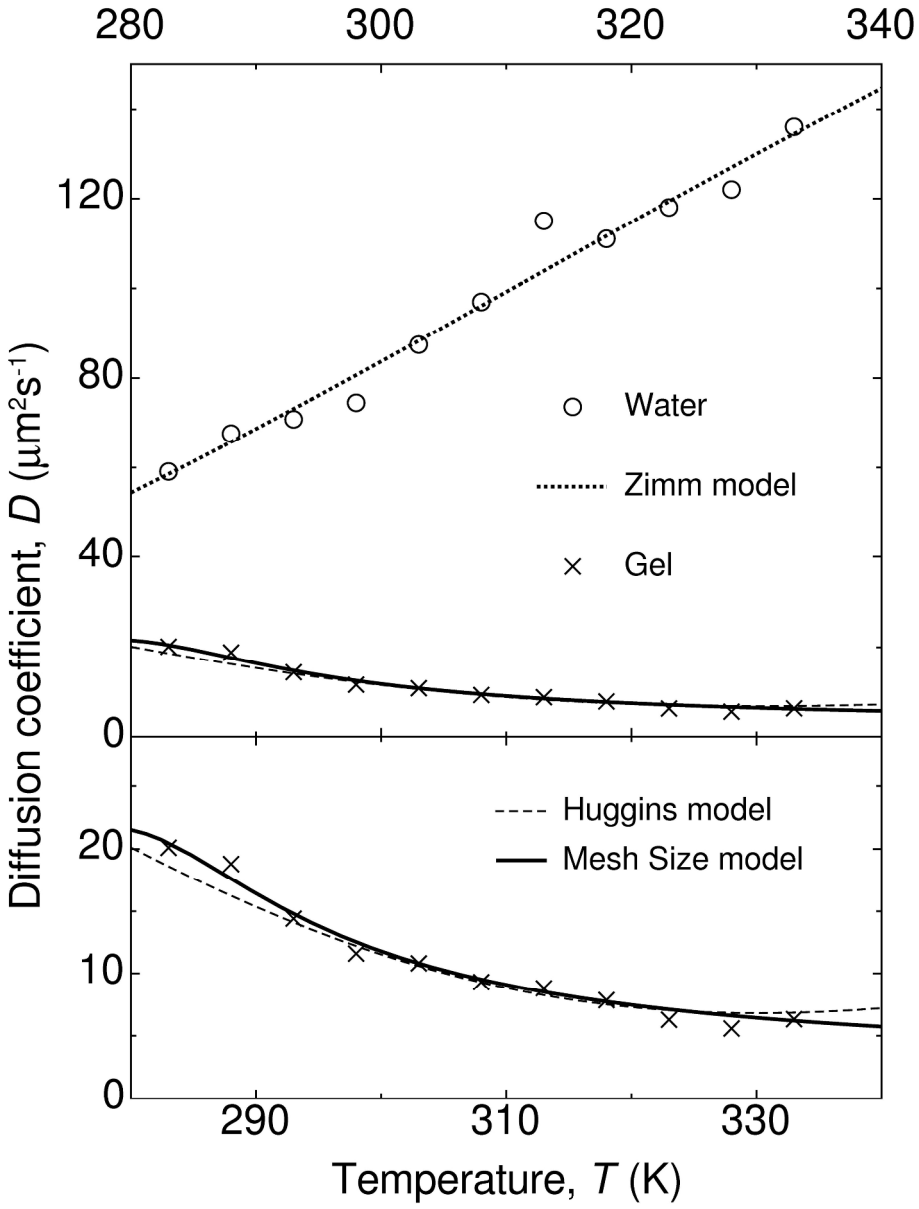

FIGURE 2 Temperature effect on diffusion of free dextran (open circles) and dextran in PMAA gel (crosses). The dotted line presents a fit using the Zimm model (equation 4) with temperature-dependent viscosity,19-21 whereas the dashed line also utilises a Huggins relationship for viscosity (equation 6) and the solid line presents a fit of the mesh-size relation given by equation 7. The same data are shown in the lower figure but expanded for the gel data and two fitted models.
242x319mm (300 x 300 DPI)

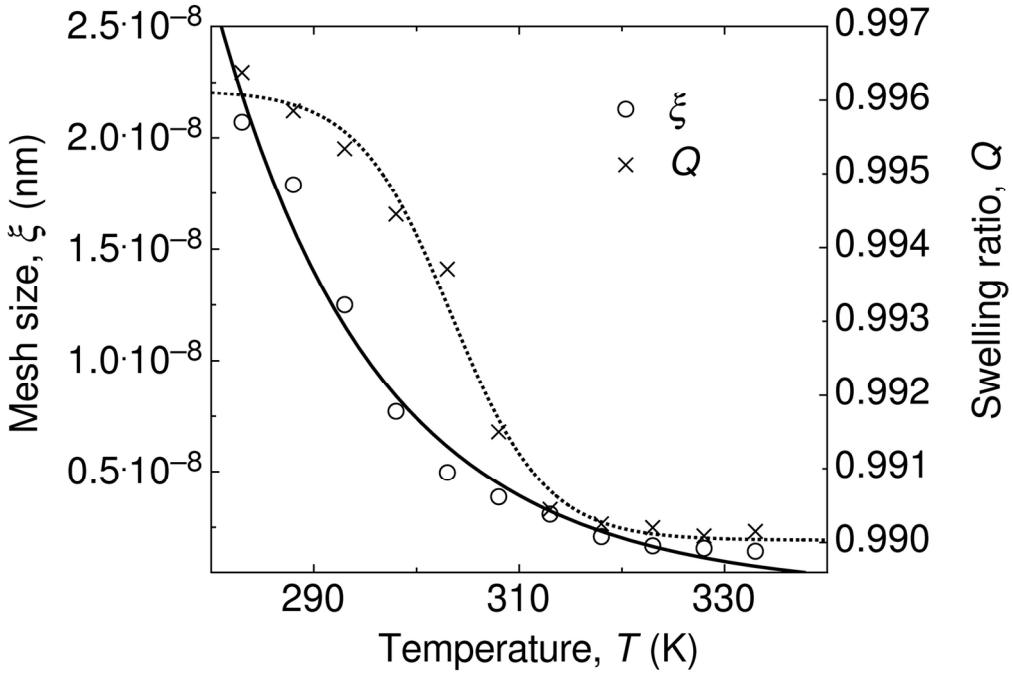

FIGURE 3 Swelling ratio (given as a percentage change in mass) and mesh size of swollen PMAA at different temperatures. Note that at the highest temperature the mass decreases only by 1% compared to the initial value at T = 283 K . Q values were determined experimentally whereas mesh size was determined from FCS measurements and modelled via equation 8. The data have been fitted to empirical functions and to provide a guide to the eye, where A, T0, K, B, T1, σ, and C are empirical constants.
149x100mm (300 x 300 DPI)

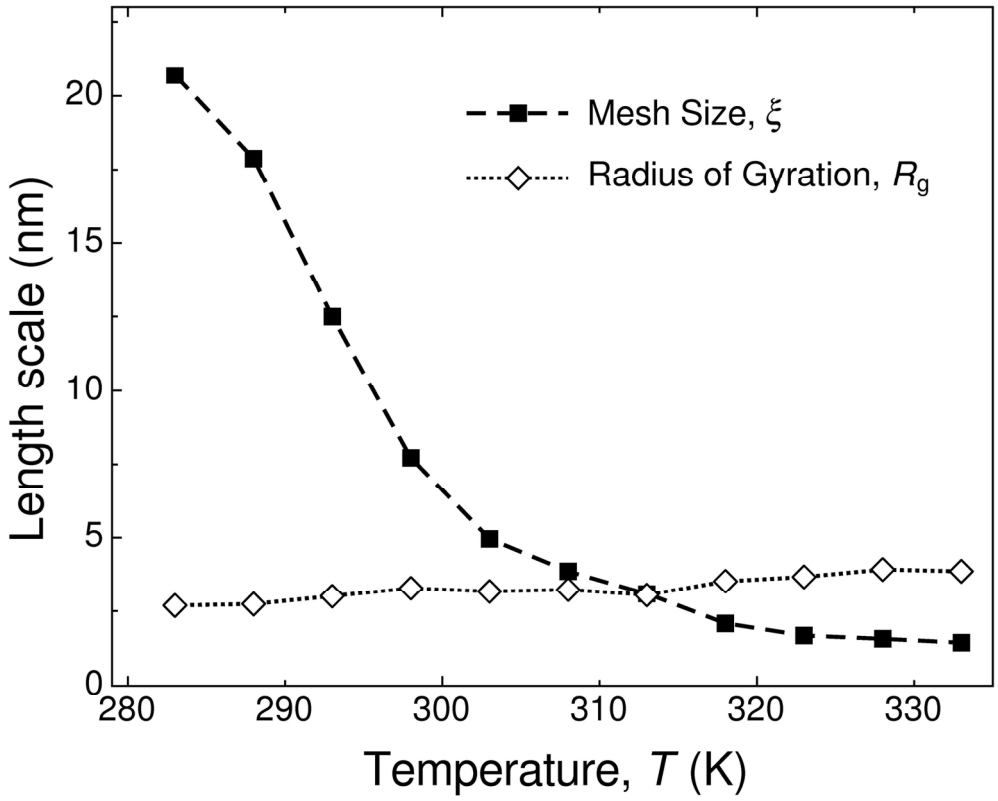

FIGURE 4 Comparison of the mesh size (determined using equation 8) and the radius of gyration (determined using equation 3 from the diffusion of dextran through pure water) plotted as a function of temperature. Note that these length scales are comparable over all temperature ranges supporting the use of the Huggins theory of viscosity (equation 8) in modelling diffusion through PMAA hydrogels.
152x125mm (300 x 300 DPI)

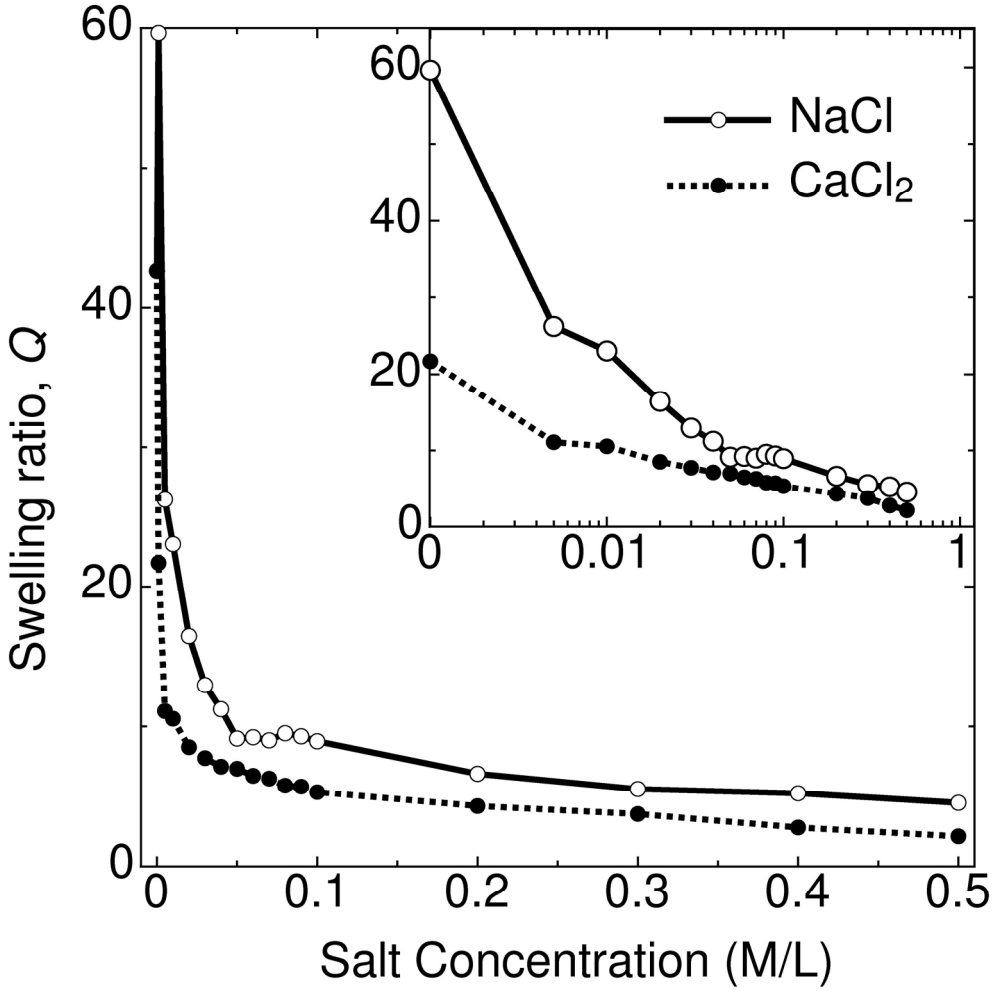

FIGURE 5 Swelling ratio of PMAA for concentrations of NaCl and CaCl2 over the concentration range used in the present study. Whilst the maximum swelling ratio is not as high as that for which pH was varied (figure 8) one can still see that very low concentrations of salt induce a dramatic structural change in the gel resulting in up to a factor of 60 increase in mass. The inset figure provides the same data on a log-linear plot but does not include the value for zero salt concentration.
177x177mm (300 x 300 DPI)

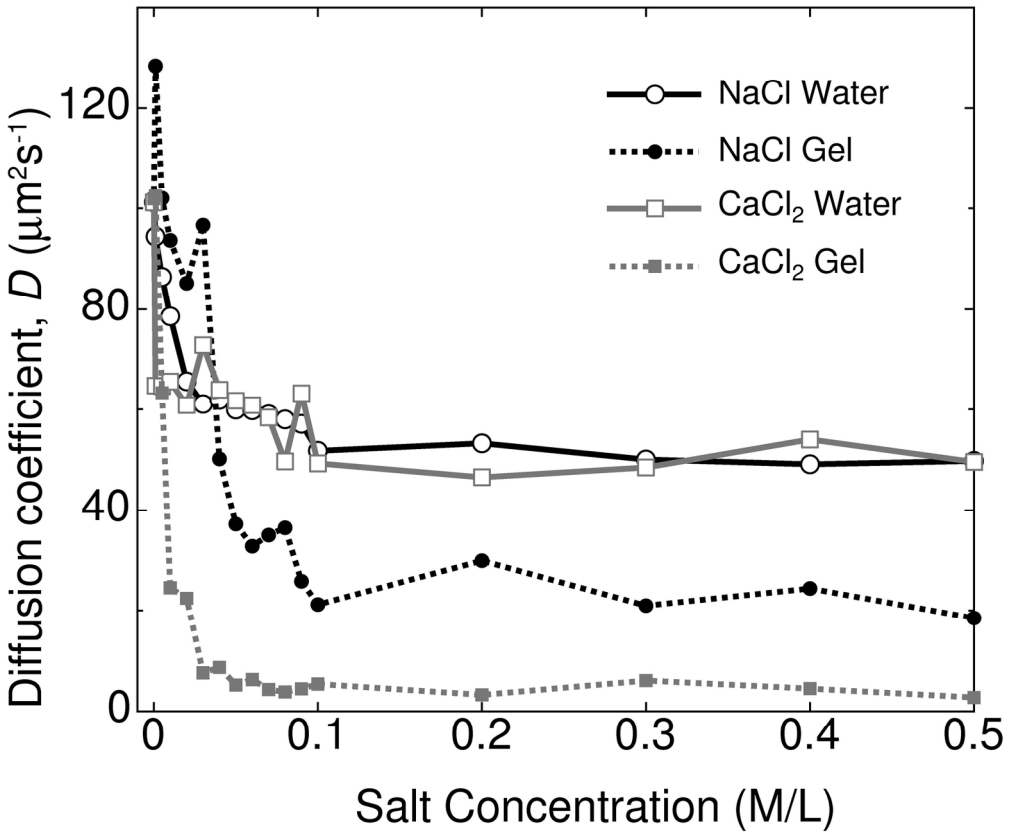

FIGURE 6 Diffusion of FDEX in NaCl and CaCl2 salt solutions, both with and without PMAA gel. The sharp increase in diffusion at low salt concentrations is evident in all cases, with the system without gel reaching a plateau at higher concentrations. The lower and unequal diffusion coefficient within the gels arises from different degrees of collapse due to the different valencies between the salts.
163x140mm (300 x 300 DPI)

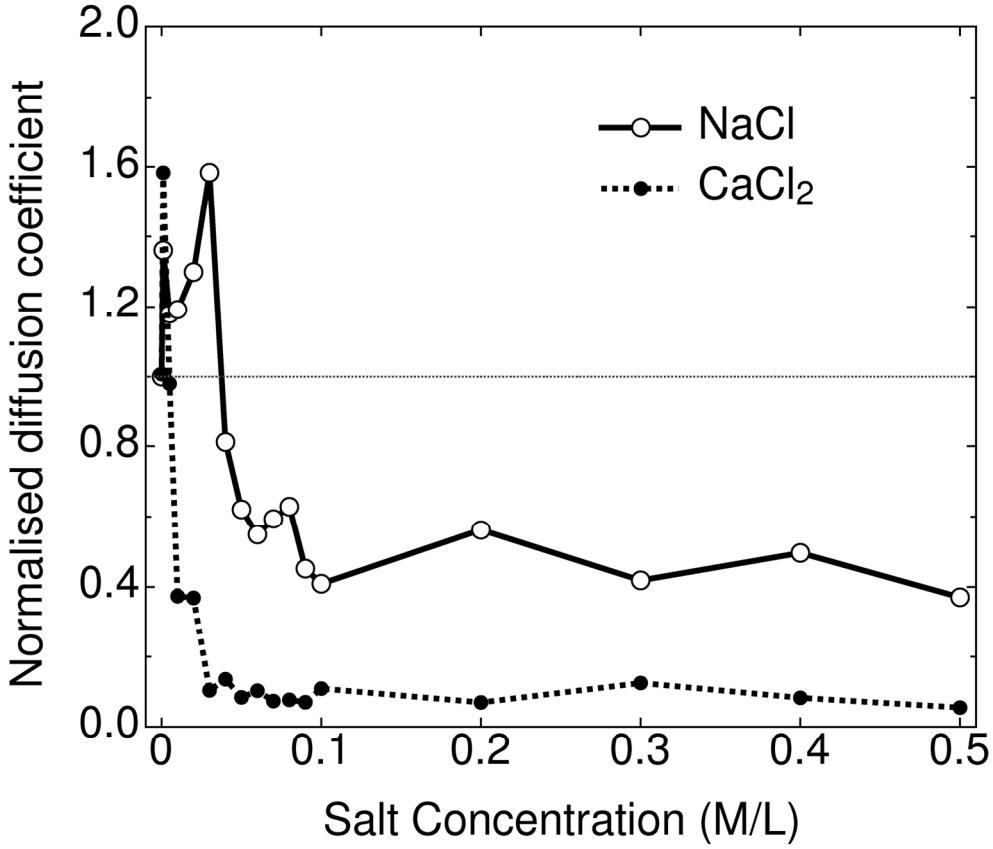

FIGURE 7 Normalised diffusion coefficients in NaCl and CaCl2 . DN is the normalised diffusion coefficient, and is defined as DN = Dgel / Dwater. The dashed line at DN= 1 represents a diffusion coefficient equal to that in water at the same salt concentration. Values of DN > 1 indicate that the hydrogel is causing the diffusion of dextran to be greater than when it is not present.
163x139mm (300 x 300 DPI)

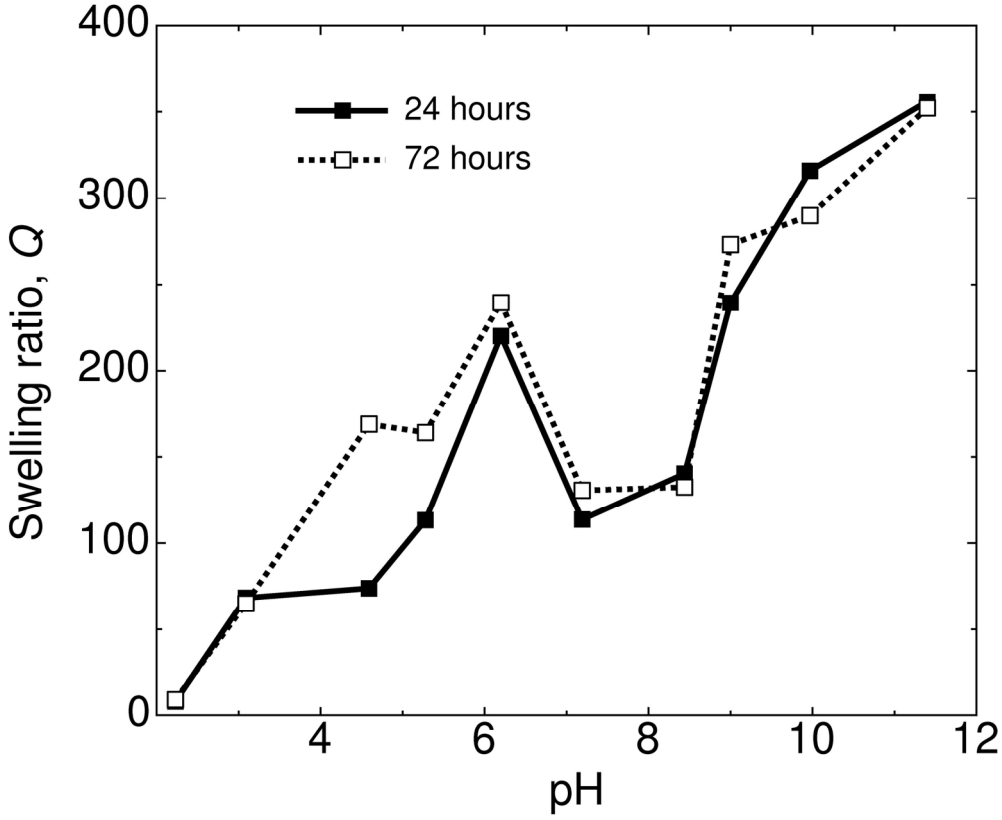

FIGURE 8 Swelling ratio of swollen PMAA for the pH range. The two plots show the time given for the hydrogel to test for equilibrium conditions. The effect of pH is the most pronounced, when compared to the other systems studied within this work, with a factor of 350 change in mass.
160x131mm (300 x 300 DPI)

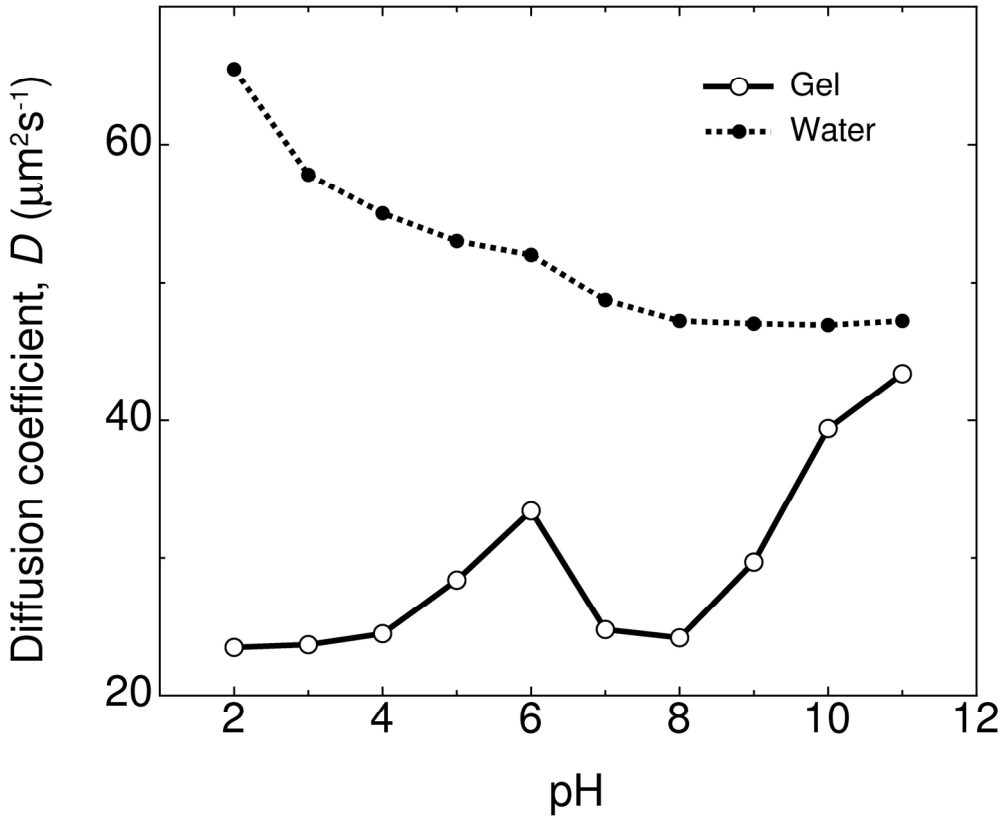

FIGURE 9 Diffusion of FDEX in different pH environments. It is worth noting that both the acid and alkali regions were produced by the addition of HCl and NaOH respectively and thus also include contributions from the additional ions (Cl- and Na+).
164x138mm (300 x 300 DPI)