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ScienceDirect
International Journal of Pharmaceutics 357 (2008) 305–313
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

Release kinetics of procaine hydrochloride (PrHy) from pH-responsive nanogels: Theory and experiments

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Received 30 July 2007; received in revised form 10 January 2008; accepted 29 January 2008
Available online 8 February 2008

Abstract

pH-responsive nanogels consisting of methacrylic acid–ethyl acrylate (MAA–EA) cross-linked with di-allyl phthalate (DAP) were synthesized via emulsion polymerization. Drug release studies were conducted under different pHs, drug loading and concentration gradient difference. The drug loading capacity depended on the cross-link density and MAA–EA molar content, where a lower cross-link density and higher MAA–EA molar content resulted in higher loading capacity. A drug selective electrode was used to directly measure the concentration of procaine hydrochloride (PrHy) released from MAA–EA nanogels. More than 50 data points were acquired, where the mathematical fitting to the Berens and Hopfenberg model allowed the parameters describing the contributions of chain relaxation and diffusion process to be determined. The release rate increased with pH and concentration gradient difference due to a reduction in diffusion barrier and higher concentration gradient driving force, respectively, but it decreased with drug loading as the nanogel could not relax from the compact structure as evident from the contribution of Fickian diffusion, ϕ_F, and chain relaxation, ϕ_R. A balance between chain relaxation and Fickian diffusion process controlled the release of drugs from these pH-responsive nanogels. Exponential relationships could be established between diffusion coefficient, characteristic relaxation time and various physical parameters, where the drug release kinetics could be predicted in a quantitative manner.

Keywords: pH-responsive nanogels; MAA; In vitro release; Drug selective electrode; Berens and Hopfenberg model

1. Introduction

New controlled release systems such as nanogels that are responsive to pH (Pillay and Fassihi, 1999; Kim and Peppas, 2003; Kurkuri and Aminabhavi, 2004) or ionic strength (Sutani et al., 2002) are interesting and could be considered for possible applications as specific drug carriers. They are useful in pulsed drug delivery, where their structures or intra-molecular interactions will change in response to external stimuli. Various types of controlled drug delivery formulations have been considered, depending on the end-use requirements, the most popular being nanoparticles followed by microparticles and hydrogels (Kumar et al., 2002). Various pH-responsive nanogels consisting of methacrylic acid–ethyl acrylate (MAA–EA) cross-linked with di-allyl phthalate (DAP) (Tan et al., 2004, 2005) have been synthesized via the emulsion polymerization technique, where the polymers exist as insoluble lattices at low pH. By increasing the pH, ionization of acid groups is enhanced, which increases the solubility and enhances the electrostatic repulsion between polymeric chains, yielding interesting changes in particle interaction potential. An advantage of using pH-responsive nanogels is that the release profile of drugs can be controlled by manipulating the pH or ionic strength.

Recently, we have reported the benefits of using a drug selective electrode (DSE) for measuring the drug release from pH-responsive microgels (Tan and Tam, 2007). Previous studies on drug release using nanoparticles have focused on using techniques such as UV-spectroscopy (Govender et al., 1999; Soppimath et al., 2001; Yang et al., 2004) or high-performance liquid chromatography (HPLC) (Torres-Lugo and Peppas, 1999; Foss et al., 2004) to monitor the concentration of drugs. All these techniques required the use of a dialysis membrane or centrifugal machine to isolate the nanoparticles from drugs prior to measurements. Such techniques are often fraught with problems, such as the probable absorption of drugs on the dialysis membrane (yielding a lower measured drug concentration), and the intro-

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doi:10.1016/j.ijpharm.2008.01.058

duction of an additional diffusion barrier. The high-centrifugal force will drive out the drug molecules from the nanoparticles, giving rise to a higher drug concentration. The advantage of the drug selective electrode is that intermediate steps such as dialysis or centrifugation can be eliminated, and automation of the whole process is feasible. This method yielded reproducible drug release profiles, and hence is more efficient. As will be shown later, large number of data points can be obtained, and this enhances the accuracy and viability in the mathematical modeling of release profiles using a non-linear release kinetic model.

Mathematical modeling plays an important role in elucidating the drug release mechanism, thus facilitating the development of new delivery systems by a systematic rather than trial and error method (Arifin et al., 2006). Base on the physical or chemical characteristics of the polymer, drug release mechanism from a polymer matrix can be categorized according to three processes (systems) (Leong and Langer, 1987), namely: diffusion, swelling or erosion controlled. In a swelling controlled system (our nanogel), the drug release is not only controlled by diffusion of drugs from polymeric matrix, but also by disentanglement of polymeric chains within the matrix resulting in the dissolution (chain relaxation) of the nanogel. The "anomalous transport" of drug released is often present in swelling controlled systems since both diffusion and chain relaxation occur together (Arifin et al., 2006). Higuchi and the power law models (Higuchi, 1963; Ritger and Peppas, 1987) are the two most widely used models for predicting drug release kinetics, where only the diffusion contribution was considered. This constraint was introduced because of the limited number of data points obtained in a typical drug release study using the traditional mode of data acquisition. A more comprehensive model that describes both diffusion and relaxation contributions to drug release kinetics has been proposed by Berens and Hopfenberg (Enscore et al., 1977; Berens and Hopfenberg, 1978). Since this is a non-linear model, larger number of data points would be required to generate a statistically meaningful model fitting, and hence this model was not often used. In most drug release kinetic studies, the release of drugs from dialysis membrane and nanoparticles were measured. Hence, the relaxation contribution of drug release from nanoparticle often cannot be observed. With the use of DSE, dialysis membrane was not necessary, thus the relaxation contribution of drug release from the nanoparticles can now be quantified. Although Torres-Lugo and Peppas (1999) and Soppimath et al. (2001) did use the Berens and Hopfenberg model to fit their results, they did not present the relaxation contribution of drug release kinetics. To the best of our knowledge, this is the first detailed analysis of drug release kinetics, where chain relaxation and diffusion processes governing the drug release behavior is differentiated.

The overall goals of this research are to: (i) prepare and characterize the release kinetics of PrHy loaded MAA–EA nanogels; (ii) understand the release mechanism using the Berens and Hopfenberg model from release kinetic data obtained with the DSE and (iii) predict the drug release profiles at different pHs, concentration gradient and initial drug loading content.

2. Materials and methods

2.1. Materials and reagents

Procaine hydrochloride (PrHy, from Sigma), a local anesthetic used in dental surgery, was used. Carboxylated poly(vinyl chloride) (PVC) and poly(ethylene-co-vinyl acetate-co-carbon monoxide) (PE-co-PVA-co-CO) were purchased from Sigma. Sodium tetraphenylborate (NaTPB) was obtained from Fulka. All the solutions were prepared using distilled de-ionized water obtained from Millipore Alpha-Q water purification system which has a resistivity of 18.2 μS/cm.

2.2. Methods

2.2.1. Nanogel synthesis

The polymeric nanogels were prepared by conventional semi-continuous emulsion polymerization of MAA and EA cross-linked with DAP. The detailed synthesis procedures were described previously (Tan and Tam, 2007). Nanogels at low pH (1.8–2.5) were dialyzed in distilled de-ionized water using regenerated cellulose tubular membrane over a 1-month period, where the water was replaced every 2–3 days. This cleaning process removed all the impurities and unreacted chemicals. The chemical structure and properties of the cross-linked MAA–EA nanogel can be found in our previous publication (Tan and Tam, 2007).

These nanogels were designated as HASE *x*–*y*–*z*, where *x* and *y* correspond to the molar fractions of MAA and EA, respectively and *z* denotes the weight percentage of cross-linker. For example, HASE 50–50–4 refers to a nanogel with MAA–EA molar ratio of 50:50 and cross-linked density of 4 wt%. The nanogels were neutralized with standard 1 M sodium hydroxide, and the degree of neutralization (α) corresponding to the molar ratio of added base to acid groups was determined.

2.2.2. Preparation of drug selective membrane

The preparation of the polymeric membrane was carried out as described previously (Tan and Tam, 2007). Specifically, carboxylated PVC weighing 0.5 g was dissolved in 30 ml of tetrahydrofuran (THF) and gradually added to 0.955 g of PrHy dissolved in distilled de-ionized water and THF mixture of ratio 1:9. The carboxylated PVC–PrHy complex was precipitated in distilled de-ionized water, and filtered using a 20–25-μm filter paper and repeatedly washed with distilled de-ionized water and dried at room temperature. The second step involved the formation of drug selective membrane by dissolving an optimum amount (weight percent) of carboxylated PVC–PrHy complex, polymeric plasticizer (PE-co-PVA-co-CO), and ion-exchanger, sodium tetraphenylborate, totaling 0.3 g in THF. The optimum ratio of the complex to plasticizer to ion-exchanger was 38:60:2 (Tan and Tam, 2007). When the dissolution was completed, the mixture was poured into a petridish of diameter 55 mm and the solvent was evaporated at room temperature for 2–3 days. The preformed membrane was cut into disks of 12 mm diameter, which was then attached onto the Teflon tubing.

2.2.3. Electrode system

The electrochemical system is comprised of the following electrode arrangement: Ag/AgBr/internal solution/membrane/test solution/Ag/AgCl reference electrode. The inside of the Teflon tubing was filled with 1 mM PrHy in 10 mM NaBr solution and the membrane was conditioned for half an hour prior to use. In all experiments, the temperature was kept to within ±0.1 °C by a circulating thermostated water bath flowing through a 100 ml jacketed glass vessel and the test solution was stirred continuously during measurement.

2.2.4. Particle size characterization

Dynamic light scattering (DLS) experiments were performed using the Brookhaven BIS 200 system to determine the particle size. The light source is a power adjustable vertically polarized 350 mW argon ion laser with a wavelength of 488 nm. The frequency of scattered light fluctuates around the incident light due to the Brownian motion of polymer molecules. The DLS measures the intensity fluctuations with time and correlates these fluctuations to the properties of the scattering objects. The time correlation function of the scattering intensity, $G_2(t)$, was analyzed using the inverse Laplace transformation technique (Regularized Positive Exponential Sum in our case) to produce the distribution function of decay times. With this, the apparent hydrodynamic radius R_h, can be determined from the decay rate using the Stoke–Einstein equation:

$$R_h = \frac{kTq^2}{6\pi\eta\,\Gamma} \quad (1)$$

where k is the Boltzmann constant, T is the absolute temperature, η is the solvent viscosity, Γ is the decay rate and q is the scattering vector ($q = (4\pi n/\lambda)\sin(\theta/2)$, where θ is the scattering angle, n is the refractive index of the solution and λ is the wavelength of the incident laser light in vacuum).

2.2.5. Drug loading

To 0.1 wt% nanogel, various amounts of PrHy solution was added, and by varying the amounts of PrHy, a variety of nanogels to PrHy weight ratios were prepared. After the addition of PrHy, the drug–polymer solutions were left to equilibrate for 24 h at 25 °C. The temperature was controlled by a PolyScience water bath and the temperature fluctuation was kept to within ±0.1 °C.

2.2.6. Determination of drug content in nanogel

Free or unbounded PrHy was collected by passing the drug–polymer solutions through the ultrafiltration cell (Funasaki and Hada, 1980; Warr et al., 1983; Huang and Somasundaran, 1993; Makayssi et al., 1993) with cut-off size filters of 20 nm (Whatman, Anodisc 25). No loss of drug was found when pure PrHy solution was passed through the filter, and the concentration before and after filtration was identical. The concentration of free PrHy in the filtrate was measured using the HP 8453 UV-spectrophotometer with a path length of 1 cm equipped with an HP 89090A temperature control system. Appropriate dilutions were performed to ensure that the absorbance was within the linear range of Beer's law. The uptake of PrHy by nanogels (g of drug/g of polymer) was calculated using the following equation:

$$\text{Uptake} = \left(\frac{A_c - A_s}{A_c}\right) V_{sys} m_{nanogel}^{-1} C_{stock} \quad (2)$$

where A_c and A_s are the absorbance of the control (contained only drug solution) and sample (contained drug–polymer solution) solution, respectively, V_{sys} is the volume of the system, $m_{nanogel}$ is the mass of nanogels in the system and C_{stock} is the concentration at which the drug stock solution was prepared.

2.2.7. Measurements of electrode potential

Electromotive force (EMF) measurements were recorded by the Radiometer ABU93 tri-burette titration system with a built-in micro-voltmeter. During the EMF measurements, the concentration of test solution was varied by adding a known volume of PrHy solution into the initial sample of 30 cm^3 of 10 mM NaCl solution using the Eppendorf micropipette. The response of the drug electrode was tested in the concentration range of 1×10^{-6} to 1×10^{-1} M at 37 °C. The electrode potential was recorded as a function of PrHy concentration (log[PrHy]), and the calibration plot in Fig. 1 was used to determine the concentration of PrHy.

2.2.8. In vitro drug release studies

Nanogels loaded with PrHy were added to a double-wall jacketed vessel containing 100 ml of 10 mM NaCl solution of varying pHs and the drug release studies were performed. For varying volume studies, the volume of 10 mM NaCl was varied from 20 to 200 ml. A constant temperature of 37 °C was maintained throughout the experiments. The in vitro drug release kinetics of MAA–EA nanogels were determined using the DSE. EMF measurements were recorded by the Radiometer ABU93 tri-burette titration system at a regular interval of 5 min. The effects of varying parameters such as pH, drug loading and volume of 10 mM NaCl medium solution on the in vitro drug release were investigated.

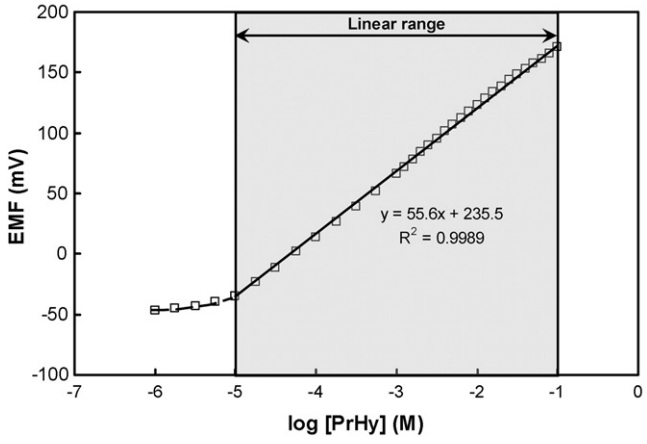

Fig. 1. Calibration curve for procaine hydrochloride electrode obtained in 10 mM NaCl at 37 °C.

Table 1
Results of drug loading capability and hydrodynamic radius of nanogel particles

Name of nanogel	Loading (g of drug/g of polymer)	Particle size, R_h (nm)
HASE 20–80–1	1.95	29.9
HASE 20–80–2	1.88	35.5
HASE 20–80–4	1.80	36.0
HASE 30–70–4	2.00	53.2
HASE 40–60–4	2.27	57.1
HASE 50–50–4	2.44	81.1

3. Results and discussion

3.1. Drug loading capacity

Different drug concentrations were loaded to the nanogel and the amounts of PrHy loaded are summarized in Table 1. The drug loading capacities of nanogels containing 20 mol% MAA and varying cross-link densities (HASE 20–80–1, HASE 20–80–2 and HASE 20–80–4) were compared at a drug loading concentration of 0.018 M. The loading capacity of nanogels exhibited a decreasing trend with increasing cross-link density, where the drug loading decreased from 1.95 to 1.80 g drug/g polymer. Higher cross-link density produced a more compact nanogel and a lower free volume within the polymer matrix, which lowered the drug loading capacity. The drug loading capacities of 4 wt% DAP nanogels with varying MAA–EA molar ratio (HASE 20–80–4, HASE 30–70–4, HASE 40–60–4 and HASE 50–50–4) increased with increasing MAA–EA molar ratio due to the larger free volume, where the drug loading increased from 1.80 to 2.44 g drug/g polymer.

3.2. Particle size of nanogel at varying drug loading

The pH-responsive nanogels loaded with different concentrations of PrHy were characterized in dilute solution (0.1 wt%) using the Brookhaven DLS system in 10 mM NaCl. The R_h at varying drug loading were normalized against the hydrodynamic radius of nanogel in the absence of drug $R_{h(c=0)}$. Figs. 2a and b shows the dependence of particle size on the drug concentration for nanogels of different cross-link densities and MAA–EA content, respectively. The particle sizes decreased with increasing drug concentration. As more drugs were incorporated into the nanogel, the charged shielding effect on ionized groups within the nanogel was enhanced, resulting in the reduction of charge repulsion between ionized MAA groups. The overall effect of drug loading produced a less polar environment within the nanogel due to the hydrophobicity of PrHy, which produced a more compact nanogel structure (Bromberg, 1998; Lopez et al., 2005). Fig. 2a shows that HASE 20–80–1 possessed the lowest $R_h/R_{h(c=0)}$, as the particle size at $R_{h(c=0)}$ of 81 nm for HASE 20–80–1 was the largest due to the lowest cross-link density. The polymer network of HASE 20–80–1 was also the most flexible, resulting in the largest de-swelling in the presence of drug (open squares). Fig. 2b shows that HASE 20–80–4 possessed the lowest MAA content, and the impact of hydrophobic force from the drug and EA segments brought

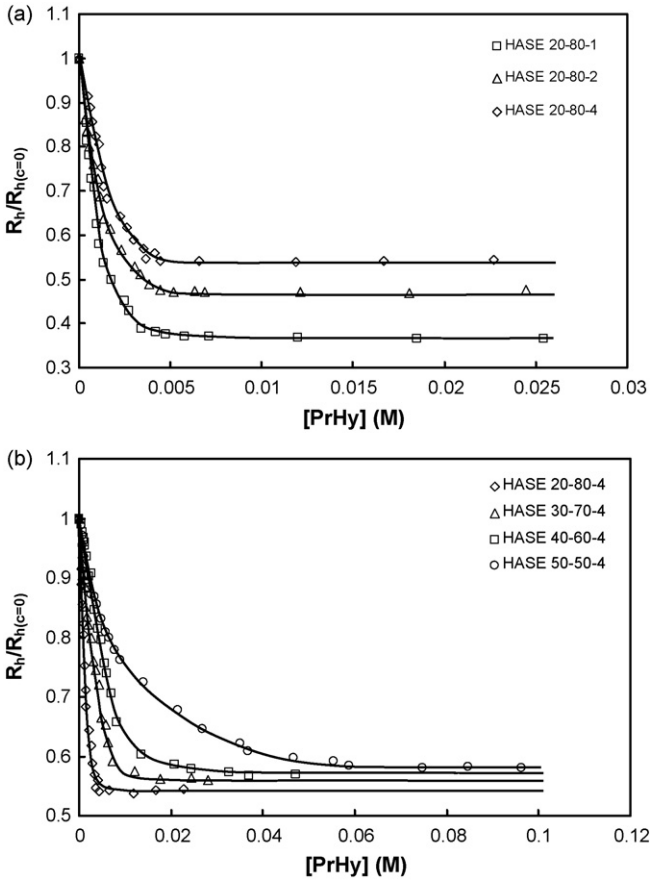

Fig. 2. Dependence of the ratio of hydrodynamic radius with drugs concentrations for: (a) nanogels with 20 mol% MAA with varying cross-linked densities in 10 mM NaCl solution and (b) nanogels with 4 wt% DAP with varying MAA–EA molar ratio in 10 mM NaCl solution.

about the largest reduction in the particle size. Since the particle size decreased with increasing PrHy content, the driving force for the loading and release was due to the concentration gradient between the interior and exterior of the nanogel matrix.

3.3. In vitro drug release study

3.3.1. Effect of pH

In vitro release studies were performed at varying pH, namely at pH of 5, 6, 7.4 and 8. The drug release was conducted on 0.1 wt% HASE 50–50–4 loaded with 2.44 g of drug/g of polymer in 10 mM NaCl solution. The drug release from nanoparticles appeared to possess two components comprising of a burst release in the first 15 min that was related to the release of drugs from the nanogel surface and a slow exponential release of drugs embedded within the nanogel matrix. This delayed exponential release may be attributed to the diffusion of drug within the core of the nanogel to the bulk solution. The ratio of M_t/M_∞ is the ratio of moles of drug released at time, t, against moles of drug that has been partitioned to the nanogels. As shown in Fig. 3, the fraction of PrHy released at pH 8 was ~0.9 compared to ~0.3 at pH 5. The degree of neutralization α, was 0.9 at pH 8 and 0.0 at pH 5 and the difference in the amounts of PrHy released was

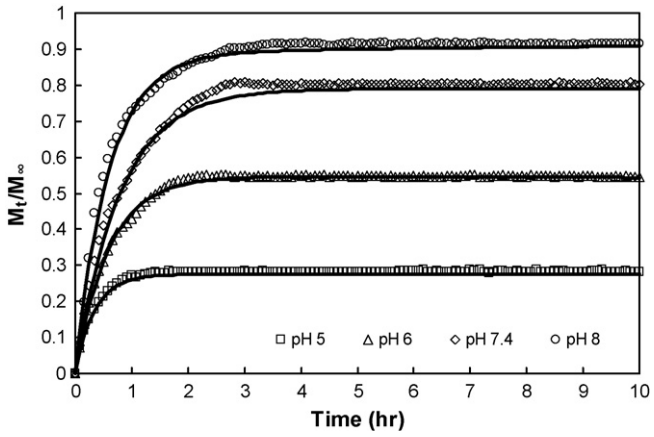

Fig. 3. Experimental in vitro release profile of procaine hydrochloride from 0.1 wt% HASE 50–50–4 at varying pH: (a) pH 5 (□), (b) pH 6 (△), (c) pH 7.4 (◊) and (d) pH 8 (◯) and theoretical fit of the mathematical model taking into account drug diffusion and chain relaxation (solid lines).

due to the different degree of neutralization of COOH groups. At low pH, the nanogel possessed a compact structure and a lower porosity, which resulted in a lower release of drug due to the larger diffusion barrier. However, at high pH, the nanogel was swollen and possessed a higher porosity, which enhanced the release of PrHy due to the reduction in the diffusion resistance. Similar to our previous studies, the particle size decreased at pH lower than 6.5 and increased at pH greater than 6.5 (Tan and Tam, 2007). The diffusion rate of PrHy from nanogels will change with pH since the free volume of the nanogels depended on the pH. A swollen nanogel possessed a higher porosity that will impact the diffusion rate of PrHy. The effect of pH on the diffusion coefficient will be discussed later.

3.3.2. Effect of initial drug loading

The initial PrHy loading had a significant effect on the in vitro release from 0.1 wt% HASE 50–50–4 in 10 mM NaCl solution (pH 7.4) as shown in Fig. 4. When a larger amount

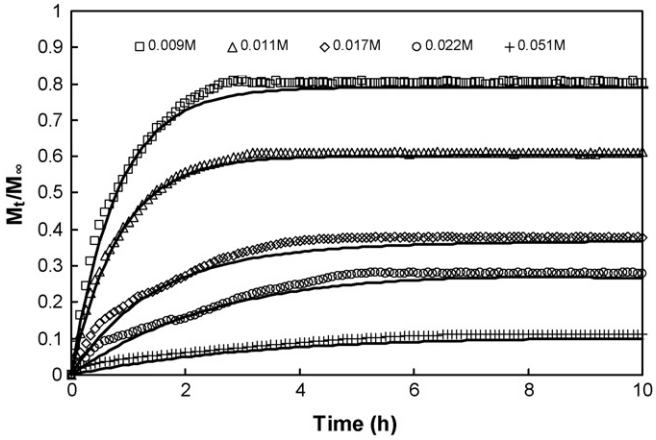

Fig. 4. Experimental in vitro release profile of procaine hydrochloride from 0.1 wt% HASE 50–50–4 at varying initial drug loading: (a) 0.009 M (□), (b) 0.011 M (△), (c) 0.017 M (◊), (d) 0.022 M (◯) and (e) 0.051 M (+) and theoretical fit of the mathematical model taking into account drug diffusion and chain relaxation (solid lines).

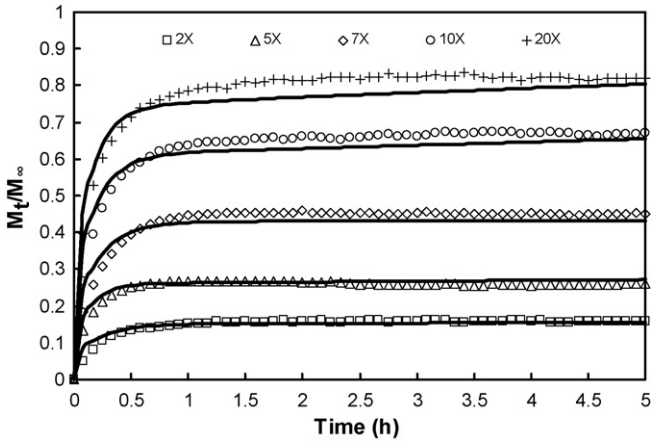

Fig. 5. Experimental in vitro release profile of procaine hydrochloride from 0.1 wt% HASE 20–80–1 at varying volume of release medium: (a) 2× (□), (b) 5× (△), (c) 7× (◊), (d) 10× (◯) and (e) 20× (+) and theoretical fit of the mathematical model taking into account drug diffusion and chain relaxation (solid lines).

of drug was loaded, the fractional amount of drug release decreased. For example, at a drug content of 0.009 M, the amount released was ∼0.8, and it decreased to ∼0.11 for drug content of 0.051 M. When more drugs were loaded to the nanogel, the particles became more compact induced by hydrophobic forces. Since PrHy was mildly hydrophobic, the drug molecules self-aggregated within the nanogel matrix, resulting in a reduction in the release rate. Such phenomenon was also reported by Benita et al. (1990), Liu et al. (2001) and Toti and Aminabhavi (2004) for polyacrylate/nifedipine, sulfopropyl dextran/doxorubicin and poly(acrylamide-g-guar gum)/diltiazem, respectively.

3.3.3. Effect of varying volume of release medium

The concentration of drug in the bulk solution is dictated by the volume of release medium, and this has an impact on the amount of drugs released from the nanogels. The volume of release medium was varied from 20 to 200 ml representing 2 to 20 times the volume of 0.1 wt% HASE 20–80–1 nanogels (10 ml) loaded with PrHy and the release profiles are shown in Fig. 5. More PrHy was released at higher volume of release medium (corresponding to increasing concentration gradient). The amount of PrHy release increased from ∼0.15 to ∼0.8 when the volume was increased from 2 to 20 times. When the nanogel loaded with drugs was released to the pH 7.4 solution, the nanogel swelled and this promoted the release of drugs driven by concentration gradient between the internal and external nanogel environment. As PrHy was loaded to the nanogel via diffusion, the increase in concentration gradient enhanced the release of drugs from the nanogel due to a larger concentration driving force. Therefore, there exists a concentration gradient between interior and exterior of the nanogel matrix, which drives the release of PrHy.

3.4. Mathematical modeling

The diffusion behavior of the drug from the interior of nanogel to the bulk solution can be mathematically described

by the following equation (Frisch, 1969):

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left[D\frac{\partial C}{\partial x} - vC\right] \tag{3}$$

where C is the concentration of solute, x is the diffusional path, D is the diffusion coefficient, v is the velocity of the solvent front and t is the time. This equation contains both the Fickian behavior, described by $D(\partial C/\partial t)$ and the non-Fickian behavior given by vC.

To obtain a better approximation, an exact solution of Eq. (3) was proposed by Berens and Hopfenberg (Enscore et al., 1977; Berens and Hopfenberg, 1978) having the form shown in Eq. (4):

$$\frac{M_t}{M_\infty} = 1 - \phi_F\left[\frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(\frac{-4\pi^2 n^2 Dt}{d^2}\right)\right] - \phi_R\exp(-kt) \tag{4}$$

where D is the diffusion coefficient for the Fickian portion of the transport, k is the first-order relaxation constant, ϕ_F and ϕ_R are the fractions of sorption contributed by Fickian diffusion and chain relaxation respectively, d is the diameter of sphere and t is the time. The above model describes the overall release behavior in terms of Fickian and non-Fickian contributions. This analysis can lead to the determination of diffusion coefficient D, and characteristic relaxation time τ, which is a reciprocal of k.

In this section, the importance of diffusion (ϕ_F) and chain relaxation (ϕ_R) was examined by fitting the release kinetic data to Eq. (4). Both Torres-Lugo and Peppas (1999) and Soppimath et al. (2001) could not fit the Berens and Hopfenberg equation (Eq. (4)) to all the experimental data to determine the values of ϕ_F and ϕ_R since the assumption at long times, solvent transport are dominated by non-Fickian term. There were insufficient experimental data points to fit the non-linear equation described by Eq. (4), thus the first term of Eq. (4) was ignored. However, in the present study, the complete Berens and Hopfenberg model equation was fitted to more than 50 data points (compared to less than 10–15 data points in previous reported studies) to obtain both ϕ_F and ϕ_R as well as D and τ. When using Eq. (4) to fit the kinetic data of between 10 and 15 data points, the R^2 values for the fittings were all below 0.7, and when more than 50 data points were used, all fittings possessed R^2 values exceeding 0.9.

The model fitting to the experimental data shown in Figs. 3–5 using the Berens and Hopfenberg model (Eq. (4)) was used to determine the parameters D, k, ϕ_F and ϕ_R in the model equation. The solid lines in Figs. 3–5 are the Berens and Hopfenberg model fitting using the non-linear least squares fitting routine of MATLAB. Excellent agreement between the experimental and predicted kinetic profiles was obtained in all cases. From the model fittings, ϕ_F and ϕ_R were found to vary with pH, [PrHy] and concentration gradient as shown in Figs. 6a–c, respectively. The parameter ϕ_F was found to dominate the release process at high pH and concentration gradient and low [PrHy] as these factors either contributed to a swollen or more porous nanogel particle, which facilitated the diffusion process since the chains do not relax before the drug was released. However, at low pH and concentration gradient and high [PrHy], ϕ_R dominated. Under

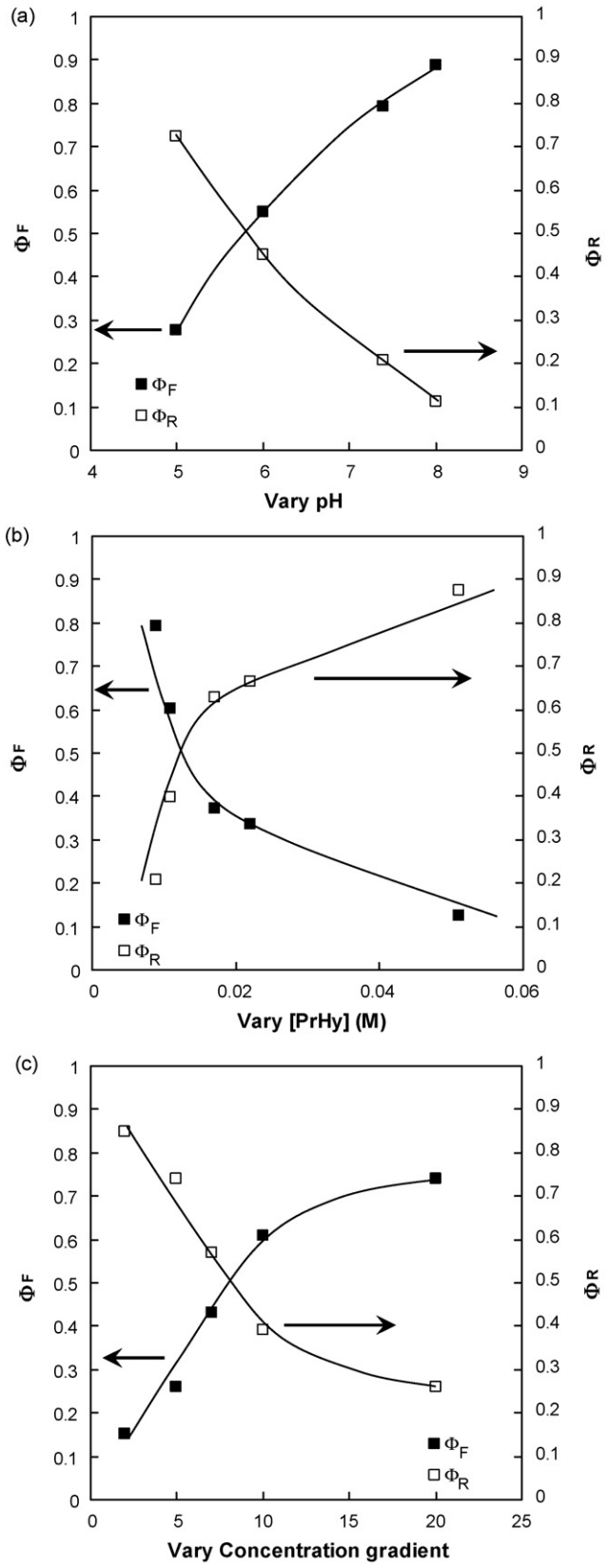

Fig. 6. Dependence of ϕ_F and ϕ_R against (a) vary pH, (b) vary [PrHy] and (c) vary concentration gradient obtained by the Berens and Hopfenberg model.

such circumstances, the nanogel assumed a compact structure, where the polymeric chains must relax before the diffusion of drugs could take place. Therefore, in the drug release process, we demonstrated that the release of drugs from pH-responsive nanogels was governed by a combination of chain relaxation and diffusion processes, and this will change depending on the characteristics of the gel network (note: such evidence may not be obvious if the release kinetic data were obtained using the conventional dialysis method as the dialysis membrane may have obliterated the chain relaxation process).

From the fittings to the Berens and Hopfenberg model, the dependence of diffusion coefficient and characteristic relaxation time on pH, concentration gradient and [PrHy] were determined and shown in Figs. 7 and 8, respectively. From Fig. 7a, the diffusion coefficient decreased with increasing pH up to pH of 7 before it increased. At low pH of 5 and 6, the high-diffusion coefficient was due to the collapse of nanogel resulting in expulsion of drug molecules (Torres-Lugo and Peppas, 1999). The nanogel particle swelled at pH greater than 7, which promoted the release of drugs that corresponded to a higher diffusion coefficient. The characteristic relaxation time decreased with increasing pH as shown in Fig. 8a. With increasing pH, the polymeric chains were in a more relaxed state, therefore a low characteristic relaxation time was observed. An empirical relationship between diffusion coefficient or characteristic relaxation time and pH of the release medium is given below:

$$D = (0.81\,\mathrm{pH}^2 - 11.32\,\mathrm{pH} + 41.8) \times 10^{-15} \quad (5a)$$

$$\tau = 1.34 \times 10^8 \exp(-2.19\,\mathrm{pH}) \times 10^5 \quad (5b)$$

Based on these relationships, it is possible to determine the diffusion coefficient and characteristic relaxation time at any arbitrary pH.

As shown in Figs. 7b and 8b, the diffusion coefficient increased while the characteristic relaxation time decreased in proportion to the concentration gradient. With a larger concentration differences, the driving force for diffusion was greater and this enhanced the release of drugs leading to a larger diffusion coefficient. An empirical relationship between diffusion coefficient or characteristic relaxation time and concentration gradient difference, dx/dt is shown as below:

$$D = 0.82 \exp\left(0.09 \frac{\mathrm{d}x}{\mathrm{d}t}\right) \times 10^{-15} \quad (6a)$$

$$\tau = 245.99 \exp\left(-0.19 \frac{\mathrm{d}x}{\mathrm{d}t}\right) \times 10^4 \quad (6b)$$

Based on these relationships, the diffusion coefficient and characteristic relaxation time at any arbitrary concentration gradient can be predicted.

From Figs. 7c and 8c, the diffusion coefficient decreased while the characteristic relaxation time increased with increasing [PrHy]. Due to a more compact structure at higher drug loading, the nanogel particle cannot readily relax, and this increased the relaxation time and decreased the diffusion coefficient. The compact structure of the nanogel retarded the release of drugs, which significantly lowered the diffusion coefficient. An empirical relationship between diffusion coefficient or characteristic relaxation time and [PrHy] is shown below:

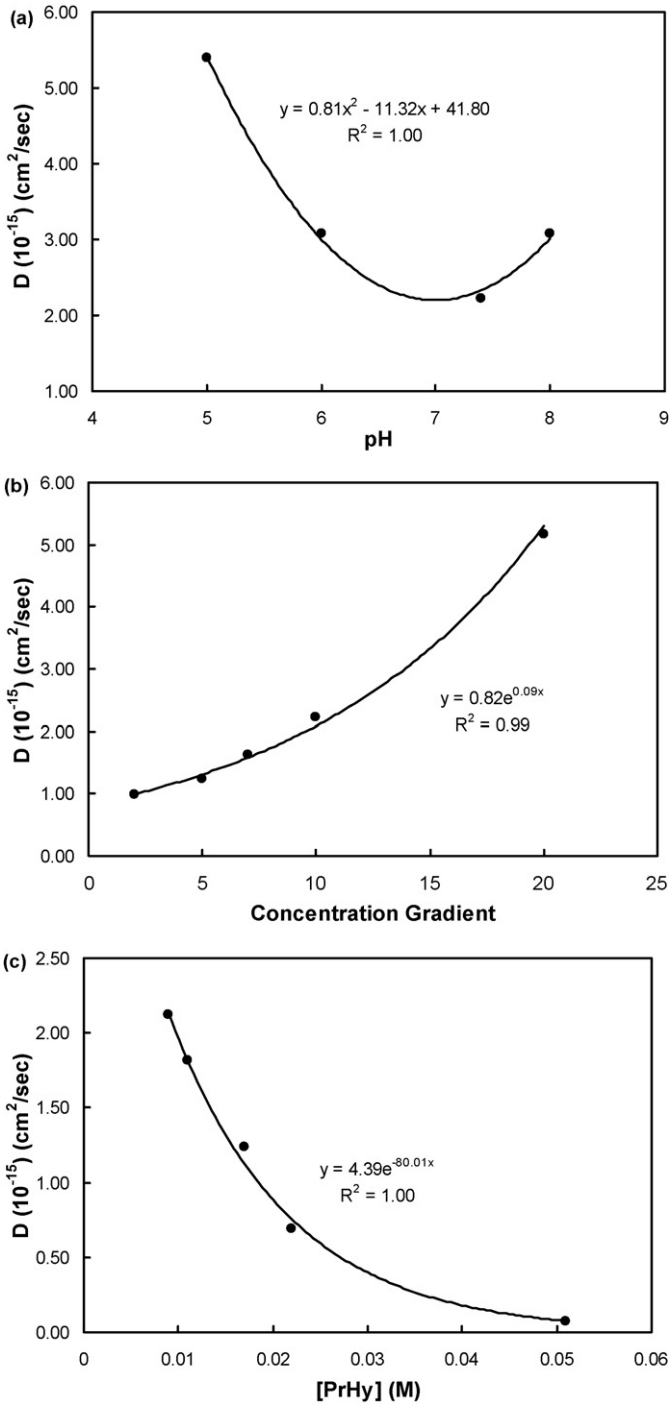

Fig. 7. Dependence of (a) diffusion coefficient, D_o (solid curve: quadratic fit) of PrHy from nanogel particles on the pH of the release medium, (b) diffusion coefficient, D_o (solid curve: exponential fit) of PrHy from nanogel particles on the concentration gradient difference and (c) diffusion coefficient, D_o (solid curve: exponential fit) of PrHy from nanogel particles on the [PrHy].

$$D = 4.39 \exp(-80.01[\mathrm{PrHy}]) \times 10^{-15} \quad (7a)$$

$$\tau = 1.00 \exp(15.8[\mathrm{PrHy}]) \times 10^6 \quad (7b)$$

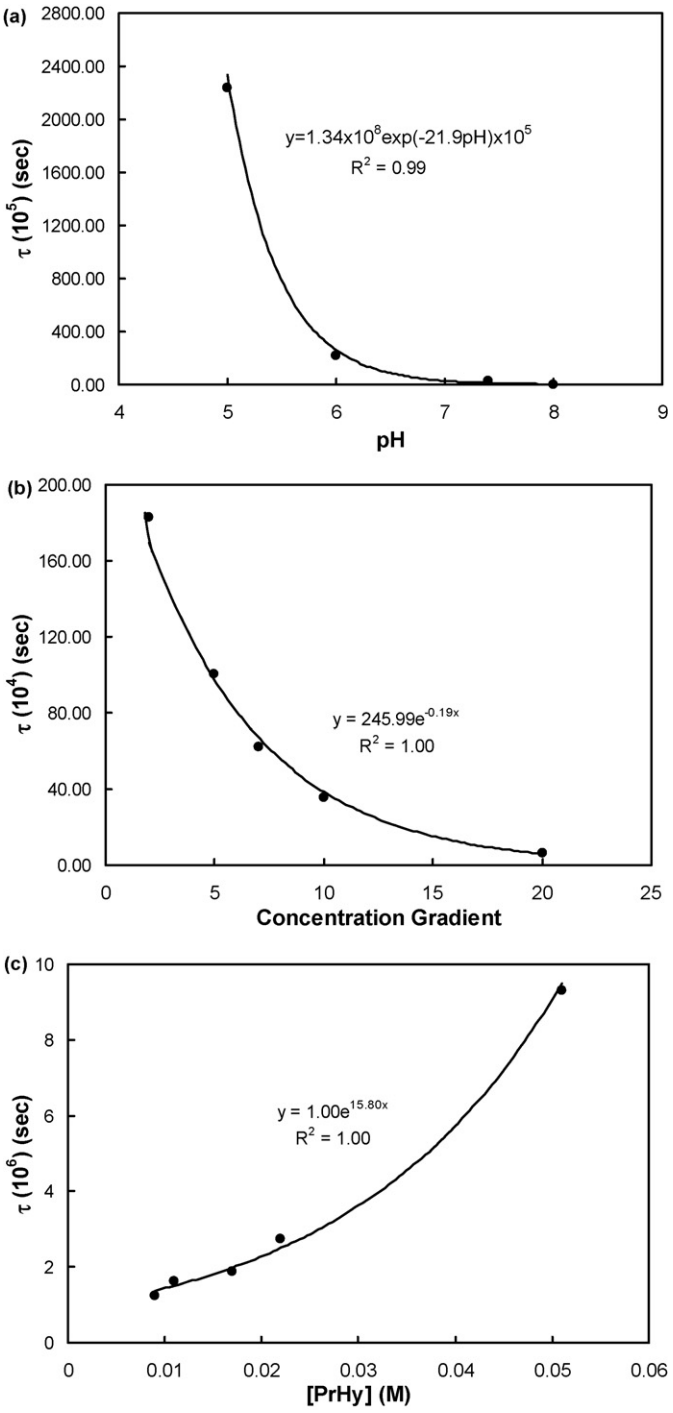

Fig. 8. Dependence of (a) characteristic relaxation time, τ (solid curve: exponential fit) of polymeric chains on the pH of the release medium, (b) characteristic relaxation time, τ (solid curve: exponential fit) of polymeric chains on the concentration gradient difference and (c) characteristic relaxation time, τ (solid curve: exponential fit) of polymeric chains on the [PrHy].

4. Conclusions

The drug loading capacity of MAA–EA nanogel was investigated as a function of cross-link density and MAA–EA molar content. The nanogel with a lower cross-link density and higher MAA–EA molar content possessed a higher drug loading content due to a larger free volume within the nanogel. Drug release was performed using the DSE as a function of concentration gradient, pH and drug loading ratio. The amount of drugs release increased with increasing concentration gradient difference and pH. A higher concentration gradient would increase the driving force for the diffusion of loaded drugs, while an increase in pH led to an expansion of the size of nanogel, thus reducing the diffusion barrier and increasing the fractional release of drugs. We have successfully fitted the Berens and Hopfenberg model to the kinetic data, and distinguished the role of chain relaxation ϕ_R, and diffusion process ϕ_F, for drug release from a pH-responsive nanogel.

Acknowledgements

The authors wish to thank Prof. Wyn-Jones for his valuable advice on the preparation of the drug selective electrode. The financial support given by Ministry of Education (MOE) and the Agency for Science, Technology and Research (A*STAR). JPK Tan acknowledges Nanyang Technological University (NTU) and MOE for the graduate scholarship.

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