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Research paper

Drug diffusion mechanism through pH-sensitive hydrophobic/polyelectrolyte hydrogel membranes

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Abstract

Methylmethacrylate/dimethylaminoethyl methacrylate cross-linked with divinylbenzene is a pH-sensitive hydrogel. We have studied the diffusion mechanisms of drugs with different water solubilities through this hydrogel. A water-soluble model drug (aminopyrine) was used to study the diffusion coefficient changes in different pHs. The results showed a water-content dependent diffusion for this pH-sensitive polycationic hydrogel. However, decreasing the solubility of the drug and increasing the hydrophobic character of the polymer by changing the pH caused a greater affinity (or partition coefficient) between the hydrogel and the drug. Aminopyrine diffusion was shown to follow the free-volume theory, suggesting the 'pore' type mechanism for water soluble drugs, while the 'partition' or 'solution-diffusion' mechanism better described the slow diffusion of water insoluble solutes through this pH-sensitive hydrogel. Comparing the swelling interface number for aminopyrine release through this pH-sensitive hydrogel showed a non-Fickian mechanism in the hydrated form of the hydrogel (pH 1.2), while Fickian in the dehydrated form (pH 7.4).

Keywords: pH sensitive hydrogel; Free volume theory; Diffusion mechanism; Swelling interface number

1. Introduction

Stimuli-responsive polymers have recently been developed to regulate the degree of swelling of polymers in relation to external environmental conditions and pH-sensitive hydrogels are one of them [1].

Hydrogel drug delivery systems have attracted significant attention recently. In addition to their inertness and good biocompatibility, the ability of hydrogels to release entrapped drug in an aqueous medium and the ease of regulating such drug release by controlling water swelling and cross-linking density, make hydrogels particularly suitable as drug carriers in the controlled release of pharmaceuticals [2].

The permeability and release rate of drugs are influenced by the type of releasing agent and the water content in hydrogels [3]. Despite the high water content (10–95%) of the hydrogels, the systems may also be used for the release of drugs that are poorly soluble in water. Solute transport through a polymer membrane is either via the pore or partition mechanism. In the pore mechanism, the solute diffuses through the water filled pores and in the partition mechanism the solute transport is presumed to occur by a process involving the dissolution of the solute within the polymer followed by the diffusion through the membrane [4].

It has been reported that poly(methyl methacrylate/dimethylaminoethyl methacrylate) (MMA/DMA) and its heavier homologues cross-linked with 0.1% w/w divinylbenzene (DVB) are polycationic pH-sensitive hydrogels [5,6]. This hydrogel is quite hydrated in acidic pHs while glassy in alkaline and neutral pHs. The dehydrated hydrogel will swell in aqueous solutions to some equilibrium value [6]. Therefore, it seems that increasing the water content of this hydrogel increases the permeability of the solutes [3]. The objectives of this work were to examine: (i) the effect of pH and hydration of MMA/DMA (0.1% DVB) as a pH-sensitive hydrogel on drug diffusivity, (ii) the diffusion characteristics of drugs with different water solubilities and (iii) the drug release mechanism. The drugs were chosen according to their solubilities in different pHs, and included aminopyrine, caffeine and theobromine.

2. Materials and methods

2.1. Materials

Methyl methacrylate (MMA), *N,N*-dimethylaminoethyl

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methacrylate (DMA), 2,2-azobisisobutyronitrile (AIBN), tetrahydrofuran and divinylbenzene (DVB), were all obtained from Merck Co. (Germany). Aminopyrine, caffeine and theobromine from Sigma Chemical Co. (MO, USA) were used. Sodium dihydrogen orthophosphate, sodium chloride, sodium hydroxide and citric acid were analytical reagent grade products and were obtained from Merck.

2.2. Methods

2.2.1. Preparation of the hydrogel membranes

MMA/DMA hydrogel membranes cross-linked with 0.1% w/w DVB were prepared according to the method reported by Siegel et al. [5]. Briefly, all monomers were vacuum distilled prior to use in order to separate the polymerization inhibitors. After distillation each monomer was used immediately to prevent rapid further polymerization. Divinylbenzene was used as received. AIBN, the initiator of the polymerization reaction, was recrystallized from a 50:50 ethanol/water solution and refrigerated at 0–4°C. The mixture of MMA and DMA (70:30 mol%) was mixed with 0.1 wt% DVB (as cross-linking agent) and 0.5 wt% AIBN for 5 min by a magnetic stirrer under vacuum. The mixture was injected between two silanized glass plates kept apart by a 0.34-mm Teflon spacer. The glass plates were then transferred to a vacuum oven and polymerization reaction was conducted at 60°C for 18 h. Hydrogels obtained by this procedure were punctured into disks approximately 13 mm in diameter by a cork borer. The thickness of the films varied between 0.33 and 0.4 mm (Digimatic thickness gauge, Mituyo, Model 543-122B, Japan). The disks were swollen while stirred in methanol for 24 h, to extract any unreacted monomers, initiators and cross-linker. Methanol was changed many times during this period. The disks were then 'deswelled' by a solution of 50:50 methanol/water for 4 h. Finally, the gels were air-dried at room temperature for 24 h followed by a vacuum-drying cycle at 50°C for another 24 h.

2.2.2. Diffusion experiments

The hydrogel membranes were swollen in different pHs (1.2, 3, 5, 6 from citrate buffer and 7.4 from phosphate buffer solution) until their equilibrium state was reached. The swollen polymer was then placed between the two side-by-side diffusion cells (cell capacity was three ml and the surface area of the orifice was 0.81 cm^2). The donor cell was filled with 3 ml of a 1 mg/ml aminopyrine solution and the receptor cell with 3 ml of the same buffer solution used in the donor cell but without drug. The temperature of the cells was kept constant at 37°C using a water pump bath. At predetermined time intervals, 2.5-ml samples were taken and the absorbance was measured spectrophotometrically (Beckman DU-600). In order to have sink conditions, the volume of the receptor cell was held constant by adding 2.5 ml of fresh buffer solution after each sampling. Diffusion tests were also carried out in pH 1.2 using caffeine (at the same concentration) and theobromine (at 0.8 mg/ml concentration).

2.2.3. Partition coefficient and hydration measurements

Partition coefficients of caffeine and theobromine were measured in pH 1.2. A solution depletion method [7] was used to determine the K_d (partition coefficient) of the drug between the hydrogel and the soaking medium and the ratio of the solute concentration in the membrane to that in the bulk aqueous phase was measured. The initial solute concentrations were similar to those used in the diffusion tests. The hydrogel was soaked in the drug solution and the solute concentration in the solution was measured spectrophotometrically until a constant value was obtained. To estimate the volume of the swollen hydrogel (V_m), the equilibrium thickness of hydrogel (h) was measured at the end of the test with a Digimatic thickness gauge. The volume of each disk (V_m) was then calculated by Eq. (1) where r refers to the radius of the hydrogel

$$V_m = \pi r^2 h \tag{1}$$

then K_d was calculated according to Eq. (2)

$$K_d = V_S\ (C_0 - C_S)/V_m C_S \tag{2}$$

where V_S is the volume of the solution, V_m is the volume of the polymer film, C_0 is the initial solute concentration in the solution, and C_S is the solute concentration in the solution at the equilibrium.

The diffusion coefficients were calculated according to Fick's first law of diffusion [8]

$$dQ/dt = AD\ K_d(C_0 - C)/h \tag{3}$$

In which dQ/dt is the mass transfer rate, A is the film surface area, h is the hydrogel thickness, C_0 and C are the drug concentrations in the donor and receptor cells, respectively. Hydration of the polymer membrane was calculated by the following equation

$$\text{Hydration} = \frac{\text{water swollen polymer weight} - \text{dry polymer weight}}{\text{water swollen polymer weight}} \tag{4}$$

2.2.4. Calculation of diffusion coefficient and solute molecular radius

Stokes–Enstein equation [9] was used to determine D_0, the diffusion coefficient of drugs in infinite dilution:

$$D_0 = RT/6\pi\eta r N_A \tag{5}$$

Where R is the ideal gas constant, T is the absolute temperature (K), r is the molecular radius (cm), η is the medium viscosity (g/cm s), and N_A is Avogadro's number. The solute molecular radii were calculated from Eq. (6), assuming a spherical shape for them [8]

$$r^2 = (3V/4\pi N_A)^{3/2} \tag{6}$$

Where, r and N_A are defined previously and V is the molal

Table 1
Solubility (g/l) of the studied drugs in different pHs

pH	Aminopyrine	Caffeine	Theobromine
1.2	3.50×10^{5}	2.09×10^{1}	6.58×10^{-1}
3	5.62×10^{3}	1.67×10^{1}	5.03×10^{-1}
5	1.11×10^{2}	1.67×10^{1}	5.00×10^{-1}
6	6.11×10^{1}	1.67×10^{1}	5.00×10^{-1}
7.4	5.58×10^{1}	1.67×10^{1}	5.00×10^{-1}

volume of the solute, derived from the partial specific volume of the atomic contributions of LeBas [10].

2.2.5. Drug release studies through MMA/DMA (0.1% DVB) hydrogel

The hydrogels were equilibrated with a saturated solution of aminopyrine in a mixture of 8% drug/tetrahydrofuran, for 2 days. Then they were dried at ambient temperature for 5 days to evaporate the residual organic solvent. The surfaces of the dried transparent gels were washed with phosphate buffer, pH 7.4 (0.01 M) and allowed to dry again before being used. The release experiment was conducted in an adapted dissolution apparatus (Vankel V.K.6000, USA) at constant temperature of 37°C in citrate (0.01 M, pH 1.2) and phosphate (0.01 M, pH 7.4) buffer solutions. The release experiments were done in 200 ml of the buffer and the samples were placed in baskets rotating at 50 rev/min. Five milliliters were removed automatically at specific times over about 20 h and the concentration of aminopyrine released was monitored. Each sample aliquot was pumped back into the pot. The aminopyrine concentration was determined spectrophotometrically at 275 nm (pH 1.2) and 263 nm (pH 7.4).

To characterize the mechanism of solute transport through the hydrogel a dimensionless number called the 'swelling interface number', S_w [11] was used. A rough estimate to define this criteria is

$$S_w = \frac{v\delta(t)}{D} \tag{7}$$

Where v is the velocity of the penetrating swelling front, $\delta(t)$ is the time-dependent thickness of the swollen region through which solute diffusion occurs and D is the drug diffusion coefficient in the swollen region of the polymer. To calculate v, Eq. (8) was used [12]

$$v = \left(\frac{dgw}{dt}\right) \times \left(\frac{1}{\rho_w 2A}\right) \tag{8}$$

in which (dgw/dt) is the weight of water absorbed by the copolymer per unit time, ρ_w is the density of water at 37°C, A the area of one face of the disk, and the factor 2 accounts for the fact that diffusion is taking place through both faces.

The thickness of the swollen layer $\delta(t)$ in Eq. (7) changes with time and instead a maximum value of thickness, called δ_{max}, can be obtained from simple swelling measurements [13]. Assuming isotropic three-dimensional swelling, it can be written as

$$\left(\frac{\delta_{max}}{\delta}\right) = Q^{1/3} \tag{9}$$

Where δ is the initial thickness of the sample, and Q is the equilibrium degree of swelling of the polymer, expressed as the weight of penetrant per weight of dry polymer and according to swelling data as

$$Q = 1 + \left(\frac{\rho_p}{\rho_w}\right)q \tag{10}$$

in which ρ_p and ρ_w are the densities of dry polymer and penetrant, respectively, and q is the equilibrium weight of penetrant per weight of dry polymer [13].

3. Results

Table 1 shows the effect of pH changes on the solubility of the studied drugs. As all these drugs are weak bases they show their highest solubility at pH 1.2. The partition coefficients of aminopyrine between the membrane, i.e. MMA/DMA (0.1% DVB), and the medium with different pHs are shown in Table 2. Increasing the pH of the medium from 1.2 to 7.4 increases the K_d of aminopyrine (the water-soluble model drug) by as much as 9-fold.

The partition coefficient of aminopyrine at pH 6–7.4 is significantly different from that in the pH range 1.2–5 ($P < 0.05$). At higher pHs both the membrane and the drug are deprotonated and show greater lipophilicity which results in increased K_d values (Table 2).

Table 3 compares the results of the K_d values of aminopyrine, caffeine and theobromine at pH 1.2. The results

Table 2
Hydration and partition coefficient changes of aminopyrine through methyl methacrylate/dimethylaminoethyl methacrylate cross-linked with 0.1% divinylbenzene in different pHs

pH	Hydration (g water/g swollen polymer)	Partition coefficient (K_d) mean ± SD ($n = 3$)	Diffusion coefficient (D) (cm^2/s) mean ± SD ($n = 3$)
1.2	0.873	5.35 ± 0.30	$(3.30 \pm 0.79) \times 10^{-7}$
3	0.813	8.66 ± 0.15	$(3.00 \pm 0.17) \times 10^{-7}$
5	0.738	15.14 ± 0.11	$(1.40 \pm 0.13) \times 10^{-7}$
6	0.528	45.38 ± 0.68	$(0.00795 \pm 0.00183) \times 10^{-7}$
7.4	0.163	47.05 ± 0.33	$(0.00887 \pm 0.00054) \times 10^{-7}$

Table 3
Effect of drug solubility on their partition coefficient changes through methyl methacrylate/dimethylaminoethyl methacrylate cross-linked with 0.1% divinylbenzene in citrate buffer (pH 1.2)

Drug	Water solubility (g/ml)	Partition coefficient (K_d) mean ± SD ($n = 3$)	Diffusion coefficient (D) (cm^2/s) mean ± SD ($n = 3$)
Aminopyrine	1:18	5.35 ± 0.30	$(3.30 \pm 0.79) \times 10^{-7}$
Caffeine	1:60	10.99 ± 0.73	$(3.27 \pm 0.71) \times 10^{-7}$
Theobromine	1:2000	33.42 ± 1.09	$(1.25 \pm 0.19) \times 10^{-7}$

confirm that, decreasing the solubility of the drug increases the K_d by about 6-fold for theobromine, as compared to aminopyrine in pH 1.2 ($P < 0.05$). This suggests there may be a high affinity between theobromine and the hydrophobic regions of the hydrogel and perhaps the presence of strong interactions between theobromine and the macromolecular segments of the membrane. Caffeine, which has a lower water solubility (Table 3), also has a 2-fold greater K_d than aminopyrine ($P < 0.05$).

Table 2 shows the effect of pH changes on the diffusion coefficient (D) of aminopyrine through the hydrogel. The results show that, by increasing the pH, the diffusion coefficient of this water-soluble drug decreases significantly in pH 6 and 7.4 compared to acidic pHs ($P < 0.05$).

Table 3 also compares the diffusion coefficient of different drugs with different solubilities, through this hydrogel at pH 1.2. The results confirm that the higher the drug solubility (Table 1), the higher its D value. The water insoluble drug, theobromine (solubility in pH 1.2 = 0.0658 g/l) has a diffusion coefficient significantly different ($P < 0.05$) from the two other drugs.

The release profiles of aminopyrine from MMA/DMA in citrate buffer (pH 1.2) and phosphate buffer are shown in Fig. 1. As this figure shows, in citrate buffer aminopyrine was rapidly released during the first 2.5 h and is completely released after about 17 h but in phosphate buffer the fraction of the drug released is almost negligible (less than 10%) after the same time.

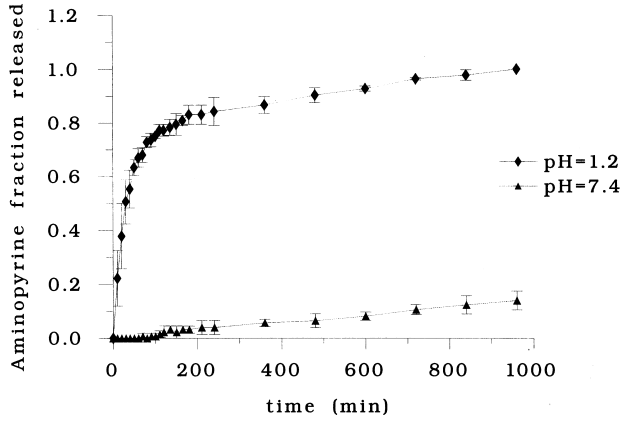

Fig. 1. Aminopyrine release profiles from methyl methacrylate/dimethylaminoethyl methacrylate cross-linked with 0.1% divinylbenzene at citrate (pH 1.2) and phosphate buffer solution (pH 7.4).

4. Discussion

The results show that the MMA/DMA hydrogel is pH-sensitive with a hydrated state in acidic pHs; in contrast, it is quite rigid and dehydrated near neutral pHs. This property facilitates drug diffusion through the hydrogel (Table 2). Increasing the pH causes a decrease in the ionization of both the cationic drug (aminopyrine) and the functional groups of the hydrogel, i.e. DMA. This gives a hydrophobic nature to the polymer at pH 7.4 which increases the K_d of aminopyrine between the hydrogel and the membrane.

Comparing the K_d of different drugs with different solubility at the pH when the hydrogel is quite rubbery (pH 1.2) showed a significant increase in the K_d for the drugs with lower water solubility, i.e. caffeine and theobromine (Tables 1 and 3). As a conclusion, it may be stated that the less water-soluble the drug, the more its affinity to this hydrogel. On the other hand, considering that both the hydrogel and the drug are cationic, increasing the pH decreases the degree of ionization of the polymer and so the K_d of the drug is increased.

According to Table 3, there are some differences in D values of different drugs, which may arise from the size, charge and hydration of the molecules. As the hydrogel is quite hydrated at the measuring pH (pH 1.2), the drugs can freely pass through the water fraction of the hydrated polymer.

Comparing the D values of aminopyrine at different pHs (Table 2) shows a reduction in permeability of the polymer to this drug upon increasing the pH or when the polymer is dehydrated ($P < 0.05$). This suggests a water content dependency for aminopyrine transport through the membrane because pH itself controls the degree of swelling of this hydrogel and hence the degree of permeability to the drug.

From the results discussed so far, it seems that when the polymer has a hydrophobic nature or when the drug has a low solubility, there is a high affinity between the drug and the hydrogel. In other words, the 'partition' or 'solution-diffusion' mechanism which occurs via dissolution and diffusion of the solute in segments of the polymer matrix can describe the passage of drugs in high pHs and the diffusion of the poorly water-soluble drugs. However, the water

content-dependent diffusion of aminopyrine, and its low partition coefficient at low pHs, i.e. when the polymer is swollen, suggests the 'pore' mechanism which occurs by the solute diffusion via bulk-like water regions present in the microchannels of pores [14].

To show the water-content or pH-dependent diffusion of aminopyrine through MMA/DMA, free-volume theory was used to confirm the pore type mechanism of this drug via the polymer [4]. According to this theory drug diffusivity depends on membrane hydration:

$$\mathrm{Ln}(D_m/D_0) \propto -Bq_2/V_f(1/H - 1) \quad (11)$$

In which D_m is the diffusion coefficient of the solute in a hydrated membrane, D_0 is the diffusion coefficient of the solute in water, Bq_2 is a constant proportional to the solute cross-sectional area (πr^2), V_f and H are the molar free-volume and water fraction of hydrated polymer, respectively [4].

Fig. 2 shows a linear relationship between $\mathrm{Ln}(D_m/D_0)$ vs. $(1/H - 1)$ in values of $(1/H - 1)$ less than unity for aminopyrine. This confirms that the transport of highly water-soluble drugs is greatly influenced by the degree of hydration and ionization of the hydrogel and that the drug diffusion is controlled by pH-sensitivity of this hydrogel. At low pHs the hydrogel is significantly hydrated and ionized which induces a great opening of pores and more rapid diffusion of highly water-soluble drugs.

Fig. 1 shows two different release profiles depending on pH. Siegel [15] explains the release of drugs from hydrogels in terms of an osmotic effect. A drug-loaded hydrogel imbibes water, and water uptake is augmented by the osmotic activity of the solute to be released. As the solute leaches out, this osmotic force is reduced and water is extruded from the hydrogel. Thus a maximum in water uptake is observed.

The dimensionless number S_w was used to analyze the release data. This parameter compares the relative mobilities of the penetrant and the solute in the presence of macromolecular relaxations in the polymer. If $S_w \ll 1$, the rate of drug diffusion through the swollen region is much faster than the rate at which the glassy/rubbery front advances, and a zero-order or case-II-release kinetic is expected. If $S_w > > 1$, the swelling front advances faster than the drug diffusion and so a Fickian release is observed. For values of $S_w \cong 1$, non-Fickian drug release behavior is anticipated [16].

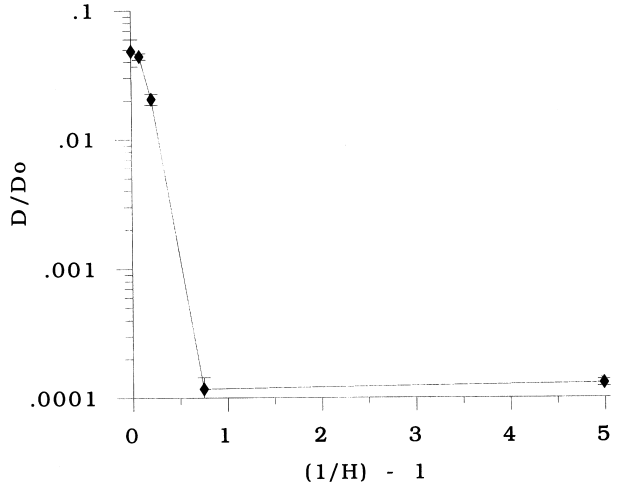

Fig. 2. Semilogarithmic plot of aminopyrine diffusivity in methyl methacrylate/dimethylaminoethyl methacrylate cross-linked with 0.1% divinylbenzene vs. the equilibrium hydration.

Table 4
Swelling interface number for aminopyrine release through MMA/DMA (0.1% DVB) hydrogel

pH	D (cm^2/s)	$Q^{1/3}$	v (cm/min)	δ_{max} (cm)	S_w
1.2	3.30×10^{-7}	1.816	5.87×10^{-4}	0.085	2.528
7.4	8.87×10^{-10}	1.044	1.05×10^{-5}	0.051	10.160

Table 4 summarizes the values of swelling interface number of aminopyrine release through MMA/DMA (0.1% DVB) hydrogel. As this table indicates, according to the S_w at pH 1.2, drug release is approaching to a non-Fickian mechanism ($S_w \cong 1$). Therefore, the swelling rate along with diffusion, control the drug release. However, at pH 7.4 its S_w value predicts a Fickian behavior. This means that a diffusion-controlled mechanism is expected to control drug release at this pH. Although the method for estimation of S_w is highly dependent on the diffusion coefficient of the solute and is not very conclusive, it can be used as a rough criterion for prediction of the mobility of drugs in polymers.

It can be concluded that MMA/DMA (0.1% DVB) is a stimuli-sensitive polymer. In response to an external stimuli, e.g. changes in pH, the structure of the hydrogel is modified and the rate of the drug delivery is modulated by changing its hydration properties. The effect of hydration in response to pH stimuli is much greater for highly water-soluble drugs than poorly soluble ones, because they diffuse predominantly by the pore mechanism.

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