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Research Paper

Investigation of solute permeation across hydrogels composed of poly(methyl vinyl ether-*co*-maleic acid) and poly(ethylene glycol)

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Abstract

Objectives Swelling kinetics and solute permeation (theophylline, vitamin B_{12} and fluorescein sodium) of hydrogels composed of poly(methyl vinyl ether-*co*-maleic acid) (PMVE/MA) and poly(ethylene glycol) (PEG) are presented.

Methods The effects of PMVE/MA and PEG 10 000 content on swelling behaviour (percentage swelling, the type of diffusion and swelling rate constant) were investigated in 0.1 M phosphate buffer. Network parameters, such as average molecular weight between crosslinks (M_c) and crosslink density, were evaluated.

Key findings The percentage swelling and M_c of hydrogels increased with decrease in PMVE/MA content, where the water diffusion mechanism into the hydrogels was Class-II type. In contrast, increase in PMVE/MA content caused an increase in the crosslink density. Permeation of theophylline, vitamin B_{12} and fluorescein sodium, with increasing hydrodynamic radii, was studied through the equilibrium swollen hydrogels composed of PMVE/MA and PEG. In general, the permeability and diffusion coefficients of all three solutes decreased with increase in the PMVE/MA content. In addition, permeability and diffusion coefficient values increased with decreases in the hydrodynamic radii of the solute molecules.

Conclusions The hydrogels have shown a change in swelling behaviour, crosslink density, M_c and solute permeation with change in PMVE/MA content, thus suggesting a potential application in controlled drug-delivery systems.

Keywords crosslink density; hydrogels; poly(ethylene glycol); poly(methyl vinyl ether-*co*-maleic acid); poly(methyl vinyl ether-co-maleic anhydride); solute diffusion

Introduction

Hydrogels are insoluble, crosslinked polymeric structures composed of hydrophilic homo- or hetero-co-polymers arranged in a three-dimensional network. Hydrogels can absorb and retain significant amounts of water without being dissolved.[1–4] Crosslinking in hydrogels can be due to covalent/non-covalent interactions, permanent physical entanglements or microcrystalline regions incorporating various chains. Crosslinks are responsible for retaining hydrogel structure.[4] Crosslinked polymeric materials have found many uses, such as controlled drug- delivery systems,[2] scaffolds for cell or tissue culturing,[5] contact lenses, surgical implants, anti-adherent catheters and suture coatings, wound dressings, absorbents, hybrid organs and biosensors.[6–8]

These applications are dependent on the swelling and diffusion behaviour of hydrogels, which is in turn controlled mainly by crosslinking density.[2] The degree of crosslinking in a hydrogel depends on structural properties, molecular weight, amount of polymer/crosslinking agent and the method of crosslinking.[9] Depending on the hydrogel type, they show dramatic changes in their swelling ratio due to changes in external pH, temperature, ionic strength, nature of the swelling agent and electromagnetic radiation.[10]

The crosslinks in hydrogels provide the characteristic network structures or pore size, which are the most important parameters in controlling the swelling of polymeric materials in solvents.[11,12] Knowledge of the swelling characteristics of a hydrogel is of utmost importance in biomedical and pharmaceutical applications, since the equilibrium degree of swelling influences solute diffusion, surface properties and surface mobility, and optical and mechanical properties. The diffusion of a solute, such as in a drug-delivery system, through the hydrogel is

significantly affected by both network structure and morphology. The effective diffusion coefficient of a solute through a hydrogel is dependent on a number of factors, such as the structure and pore size of the network, polymer composition, water content, polymer molecular weight, degree of ionisation and size of solute.[10]

Controlled-release drug-delivery systems are intended to provide the drug of interest in a predetermined concentration to fulfil specific therapeutic needs. Hydrogels have properties that make them ideal for controlled drug-delivery applications.[13] Understanding the network structure and transport behaviour of solutes through hydrogels is essential in modelling solute release from candidate hydrogel-based controlled drug-delivery systems.

We have recently investigated the ability of a Food and Drug Administration approved water-soluble polyhydric alcohol, poly(ethylene glycol) (PEG), to plasticise bioadhesive films cast from aqueous blends of a copolymer of methyl vinyl ether and maleic acid (PMVE/MA). These films were intended for use in a bioadhesive patch-based system containing aminolevulinic acid for photodynamic therapy.[14] We have also evaluated the crosslinking of PEG, of different molecular weights, with PMVE/MA, resulting in hydrogels of varying degrees of swelling in deionised water.[15] Hydrogels containing PEG with a molecular weight of 10 000 Da, crosslinked with PMVE/MA, showed the highest degree of swelling at equilibrium, followed by PEG 1000- and PEG 200-crosslinked hydrogels. We believe that hydrogels prepared from PEG 10 000 crosslinked with PMVE/MA may be useful as rate-controlling membranes for implantable controlled drug-delivery systems. In the present study we have, for the first time, investigated the swelling kinetics and network parameters of PMVE/ MA crosslinked with PEG 10 000 in buffered solution, which is intended to mimic in-vivo conditions. Importantly, we have also studied solute diffusion across the swollen hydrogel membranes. We have selected three model drugs with different hydrodynamic radii and molecular weights.

Materials and Methods

Materials

Gantrez AN-139, a PMVE/MAH (M_w = 1 080 000 Da), was a gift sample from ISP Corp. Ltd (Guildford, UK). Poly(ethylene glycol) (PEG) of molecular weight 10 000 Da (M_w = 11 000 and polydispersity index < 1.05) was obtained from Sigma-Aldrich (Steinheim, Germany). Poly(ester) film, one-side siliconised, release liner (FL2000 PET 75 μ 1S) was obtained from Rexam Release B.V. (Apeldoorn, The Netherlands). Glisseal N vacuum grease was purchased from Borer Chemie (Zuchwil, Switzerland). Resealable poly(ethylene) bags (101 × 140 mm) were obtained from Agar Scientific (Essex, UK). Theophylline, fluorescein and vitamin B_{12} were purchased from Sigma-Aldrich (Steinheim, Germany).

Preparation of crosslinked polymeric films

Aqueous polymeric blends were prepared using the required weight of PMVE/MAH, which was added to ice-cooled water (reagent grade 1) and stirred vigorously to ensure complete wetting and prevention of aggregation. The mixture was then heated and maintained between 95 and 100°C until a clear solution was obtained. As shown previously using nuclear magnetic resonance,[16] this process causes hydrolysis of the anhydride moieties of PMVE/MAH to the free acid forms, yielding PMVE/MA. On cooling, the required amount of PEG 10 000 was added to PMVE/MA gels (at 10, 15 and 20% w/w), in ratios of 2 : 1 (PMVE/MA : PEG), and the casting blend was adjusted to final weight with water (Table 1). The PMVE/ MA : PEG in 2 : 1 ratio was selected from our previous studies, since these proportions produced the highest percentage of swelling.[15]

Films were prepared by slowly pouring the aqueous blend (30 g) into a mould consisting of a release liner (with siliconised side up) secured to a Perspex base plate using a stainless steel clamp. Once assembled, the internal dimensions available for casting were 100 × 100 mm. The mould was placed on a levelled surface to allow the blend to spread evenly across the area of the mould. The cast blend was dried for 48 h at room temperature. After drying, the films were cured at 80 °C for 24 h to induce chemical crosslinking between PMVE/MA and PEG via an esterification reaction.[15]

Dynamic and equilibrium swelling studies

Swelling studies were carried out with a modification to the method described previously.[15] Briefly, crosslinked film sheets (1.0 × 1.0 cm) were weighed as m_o (xerogels) and were then swollen in 0.1 M phosphate buffer at pH 7.4 ± 0.05 for 48 h at room temperature, instead of the pure water used in our previous study. At regular intervals, the sheets were removed, blotted with filter paper to eliminate excess surface water and weighed as m_t (hydrogels). Hydrogel sheet samples at equilibrium were weighed as m_e, and were dried in a vacuum at 80°C for 24 h to obtain extracted xerogels, which were weighed as m_d. The percentage swelling (%S) and equilibrium water content (EWC) were calculated using equations (1) and (2).[1]

$$\%S = \left(\frac{m_t - m_o}{m_o}\right) \times 100 \quad (1)$$

$$\%EWC = \left(\frac{m_e - m_d}{m_d}\right) \times 100 \quad (2)$$

Table 1 Physical properties of model drug

Solute	Molecular weight (g/mol)	Hydrodynamic radius (Å)	Solubility in water at 25°C (mg/ml)
Theophylline	180	3.5	8
Fluorescein Na	376	5.0	600
Vitamin B_{12} (cyanocobalmin)	1355	8.7	12.5

To examine the controlling mechanism of the swelling process of hydrogels composed of PMVE/MA and PEG, the following second order kinetic model (equation 3) was used to process the experimental data:[17]

$$t/S = A + Bt \tag{3}$$

where $B = 1/S_{eq}$ is the reciprocal of the maximum or equilibrium swelling and $A = 1/(k_s S_{eq}^2)$ is the reciprocal of the initial swelling rate of the hydrogel (k_s is the swelling rate constant and t is time). To analyse the kinetic model, t/S versus t graphs were plotted and respective swelling rate parameters were determined.

Analysis of mechanism of water uptake and diffusion coefficient

Dynamic swelling studies were undertaken, as described previously,[15] to elucidate the mechanism of solvent diffusion into the polymer samples, as determined by the dynamic portion of the gravimetric curve. Equation (4) was used to process the kinetic data of the swelling process in order to gain insights into the mechanism of solvent transport through the hydrogels.[2]

$$\frac{M_t}{M_\infty} = kt^n \tag{4}$$

The portion of the water absorption curve with a fractional water uptake (M_t/M_∞) less than 0.60 was analysed using equation (4). M_t is the mass of water absorbed at time t, M_∞ is the water uptake at equilibrium, k is a gel characteristic constant, which depends on the structural characteristics of the polymer and its interaction with the solvent, and n is the swelling exponent, describing the mechanism of penetrant transport into the hydrogel. The constants n and k may be calculated from the slopes and intercepts of the plots of ln (M_t/M_∞) versus ln t obtained from the experimental data. Fickian diffusion and Case II transport are defined by n values of 0.5 and 1, respectively. Anomalous transport behaviour (non-Fickian diffusion) is intermediate between Fickian and Case II (relaxation controlled). This is reflected by n being between 0.5 and 1.[18]

Network parameters

Only average values for crosslinking density and molecular weight between crosslinks are represented using experimental and theoretical methods.[19,20] In the present study, the average molecular weight between cross-links, $\bar{M}_C$, was determined, as described previously[15] from the equilibrium swelling theory. The $\bar{M}_C$ can be determined by swelling studies according to the Flory and Rehner equation, equation (5).[21] The magnitude of $\bar{M}_C$ affects the mechanical, physical and thermal properties of the crosslinked hydrogels. The volume fraction of a polymer, φ, in the swollen state describes the amount of liquid that can be imbibed into a hydrogel and is described as a ratio of the polymer volume to the swollen gel volume (equation 6).

$$\bar{M}_C = \frac{-d_p V_s \varphi^{1/3}}{\left[\ln(1-\varphi) + \varphi + \chi\varphi^2\right]} \tag{5}$$

$$\varphi = \left[1 + \frac{d_p}{d_s}\left(\frac{m_a}{m_b}\right) - \frac{d_p}{d_s}\right]^{-1} \tag{6}$$

Here, Vs is the molar volume of water (18 cm^3/mol), φ is the volume fraction of polymer in the hydrogel and χ is the Flory-Huggins polymer–solvent interaction parameter. In the above equation, m_a and m_b are the mass of polymer before and after swelling and d_p and d_s are the densities of polymer and solvent, respectively. The density of the polymeric films was calculated using the following formula: $d_p = w/SX$, where X is the average thickness of the film, S is the cross-sectional area and w is the initial dry weight of the film.[22]

The polymer–water interaction parameter (χ) reflects the thermodynamic interaction in hydrogels, which in turn indicates the change of interaction energy when polymer and solvent mix together. The χ parameters of the hydrogels can be obtained experimentally via equation (7):[23]

$$\chi = \frac{1}{2} + \frac{\varphi}{3} \tag{7}$$

Equation (7) neglects the M_c dependence of the χ parameter, and therefore equation (7) indicates that the χ values are always ≥ 0.50.

Crosslink density, V_e, was determined using equation (8). V_e represents the number of elastically effective chains totally induced in a perfect network per unit volume. Here, NA is Avagadro's number (6.023×10^{23}/mole).[2,24]

$$V_e = d_p N_A / \bar{M}_C \tag{8}$$

Permeation studies

To investigate the diffusion behaviour of solute molecules in hydrogel membranes composed of PMVE/MA and PEG, permeation studies were performed. Three model drug molecules, of increasing hydrodynamic radius and molecular weight, were used and the permeability coefficient, P, and effective diffusion coefficient, D, of each solute in the hydrogels was determined (Table 1). Permeation studies were performed using side-by-side diffusion cells (PermeGear, PA, USA). Diffusion cells, consisting of donor and receptor half-cells of 3.4 ml volume were used. These had an effective diffusional area of 63.64 mm^2. A water jacket surrounded the cells and was maintained at 37°C and solutions were agitated at a speed of 600 rpm using small magnetic stirrers. The hydrogel membranes were swollen in 0.1 M phosphate buffer at pH 7.4, to an equilibrium state, and were then cut into a disc shape of 9 mm^2 diameter using a cork bore. Each membrane was then clamped between the two half cells and covered with Parafilm (Pechiney Plastic, WI, USA) to prevent evaporation. A 3.0 ml solution of known solute concentration (1 mg/ml) in 0.1 M phosphate buffer of pH 7.4, was added to the donor side of the diffusion cell and 3 ml of 0.1 M phosphate buffer was added to the receptor side. At predetermined time intervals the contents of the receptor cell were removed and replaced with an equal volume of 0.1 M phosphate buffer. The aliquot removed was analysed using UV spectroscopy (Cary 50 Scan, Varian, Mulgrave, Victoria, Australia) at λ_{max} = 271 nm (theophylline),

λ_{max} = 361 nm (vitamin B_{12}) and λ_{max} = 497 nm (fluorescein sodium). Membrane thicknesses were measured at the end of the study using a digital micrometer (Hilka, ProCraft, Surrey, UK). The solute permeability coefficient, P, was determined for each model drug using equation (9):

$$\ln\left(1-\frac{2C_t}{C_0}\right)=\frac{2A}{V}\int Pt \qquad (9)$$

Here, C_t is the solute concentration in the receptor cell at time t, C_0 is the initial solute concentration in the donor cell, V is the cell volume, A is the effective area of permeation and P is the membrane permeability coefficient. A plot of $-(V/2A) \times \ln(1 - 2C_t/C_0)$ versus t yields a slope from which the value of the permeability coefficient was calculated.[25]

The diffusion coefficient, D, was obtained from the permeability coefficient, P, and the solute partition coefficient, K_d, according to equation (10). L is the swollen membrane thickness.

$$D=\frac{PL}{K_d} \qquad (10)$$

K_d was determined from drug uptake experiments. Here, the crosslinked films were placed in 1 mg/ml solutions of the solutes until films were swollen to equilibrium. The concentration (C_s) of the surrounding solution at equilibrium was monitored at regular intervals using UV spectroscopy. The partition coefficient was then calculated according to equation 11.

$$K_d=\frac{C_m}{C_s}=\left(\frac{C_0}{C_s}-1\right)\frac{V_0}{V_m} \qquad (11)$$

Here C_m is the solute concentration in the membrane at equilibrium, C_s is the solute concentration in the solution at equilibrium, C_0 is the initial concentration in the surrounding solution, and V_o and V_m are the volumes of surrounding solution and the hydrogel membrane, respectively.

Scanning electron microscopy

Hydrogel samples were swollen to equilibrium in 0.1M phosphate buffer at room temperature, quickly frozen in liquid nitrogen thereafter and further freeze-dried in a VirTis freeze drier (Advantage XL-70, SP industries, NY, USA) under vacuum at –42°C for at least 48 h until all the solvent was sublimed. Freeze-dried hydrogels were then fractured carefully with forceps and their cross-sectional images were studied (JEOL 100 CXII, transmission electron microscope, Tokyo, Japan). Before scanning electron microscope (SEM) observations, specimens of the hydrogel were fixed onto aluminum stubs and coated at 2.5 kV, 18 mA with gold for 45 s (POLARON E5150, gold sputter coater, Quorum Technologies, East Sussex, UK).

Statistical analysis of data

One-way analysis of variance was used to assess the significance of the differences among different groups. Tukey's honestly significant difference posthoc-test was used to compare the means of different treatment groups. Results with $P < 0.05$ were considered to be statistically significant.

Results and discussion

In our previous study, hydrogels composed of PMVE/MA and PEG were characterised using ATR-FTIR in order to understand binding/crosslinking between PMVE/MA and PEG. ATR-FTIR spectra of hydrogels containing 10% PMVE/MA crosslinked with PEG 10 000 showed the presence of ester bonds between the polymers.[15]

In the present study, the swelling of hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA crosslinked with PEG 10 000 was determined over a 24 h period and the percentage swelling curves thus obtained are shown in Figure 1.

In the present study, we used 0.1 M phosphate buffer pH 7.4 as the swelling medium instead of pure water in order to mimic more closely in-vivo swelling conditions. It can be observed that the percentage swelling of crosslinked hydrogels increased over time before reaching the equilibrium state. Furthermore, the hydrogels with lower PMVE/MA contents showed greater initial swelling and reached equilibrium more quickly than those with higher PMVE/MA contents. For example, at 1.5 h, the percentage swelling of hydrogels prepared from aqueous blends containing 10% w/w PMVE/MA was 1269%, whereas it was 731 and 340% for hydrogels containing 15 and 20% w/w of PMVE/MA, respectively. Hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA showed a significant ($P = 0.005$ in each case) increase in percentage swelling up to 1.5 h, after which increases in percentage swelling were not significant. In contrast, hydrogels prepared from aqueous blends containing 15 and 20% w/w of PMVE/MA reached the equilibrium state at 4 and 6 h, respectively.

The percentage EWC values shown in Table 2 were calculated from swelling studies using equation (2). The percentage EWC values ranged from 1254 ± 65 to 1083 ± 163% for hydrogels prepared from aqueous blends containing 10–20% w/w of PMVE/MA, respectively. However, there was no significant difference in the percentage EWC values between

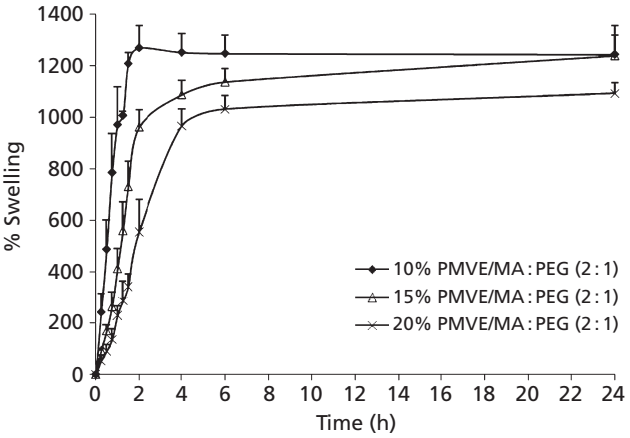

Figure 1 Percentage swelling of hydrogels in phosphate buffer. Hydrogels were composed of PMVE/MA and PEG 10 000 in 0.1 M phosphate buffer pH 7.4. Values are means ± SD, $n = 3$

Table 2 Swelling characteristics of hydrogels in phosphate buffer

Formulation (2 : 1)	Percentage EWC	r_i ((g water/g gel)/min)	ks 10^{-5} ((g gel/g water)/min)	S_{eq}% (g water/g gel)
10% PMVE/MA : PEG	1254 ± 65	84.43	5.40	1250
15% PMVE/MA : PEG	1234 ± 180	82.93	5.31	1250
20% PMVE/MA : PEG	1083 ± 163	73.53	5.96	1111

Hydrogels were composed of PMVE/MA and PEG 10 000 in 0.1 M phosphate buffer pH 7.4, $n = 3$. EWC, equilibrium water content.

the hydrogels studied. Figure 2 shows the linear regression plots derived from swelling curves using equation (3). The respective swelling parameters are shown in Table 2. As these data show, the theoretical equilibrium swellings of the hydrogels are comparable to their corresponding percentage EWC values. In addition, the initial swelling rates determined using equation (3) ranged from 84.43 to 73.53/min for hydrogels containing 10–20% w/w of PMVE/MA, respectively. The initial swelling rates (r_i) of hydrogels are comparable to their percentage swelling (Figure 1). For example, hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA showed r_i values of 84.43/min and the percentage swelling was 1220 ± 85% (after 2 h), whereas for hydrogels prepared from aqueous blends containing 20% w/w of PMVE/MA the r_i was 73.53/min and the percentage swelling was 556 ± 126% (after 2 h). Therefore, the swelling phenomenon of these hydrogels is directly related to the degree of crosslinking, which also depends on the polymer-to-crosslinker ratio. This means that the greater the ratio of polymer to crosslinker, the greater will be the number of ester links between PEG and PMVE/MA, and the more highly crosslinked the system.[15] As a result, hydrogels prepared from aqueous blends containing 10% w/w PMVE/ MA : PEG 10 000 (2 : 1) showed higher degrees of swelling and higher initial swelling rates because of the reduced extent of crosslinking, followed by hydrogels prepared from aqueous blends containing 15% w/w and then those prepared from aqueous blends containing 20% w/w PMVE/ MA. The decrease in swelling with increase in PMVE/MA concentration in the hydrogels was also observed in our previous studies.[15] This is probably due to increased extent of crosslinking between PMVE/MA and PEG chains in hydrogels, which leads to decrease in pore size and, therefore, decrease in water uptake capacity.

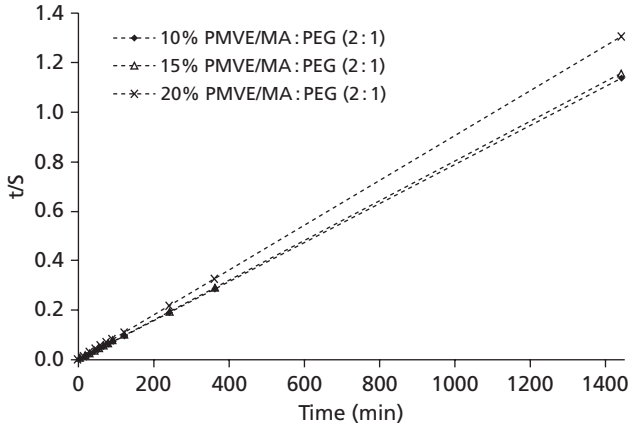

Figure 2 Swelling curves of hydrogels in phosphate buffer. Hydrogels were composed of PMVE/MA and PEG 10 000 in 0.1 M phosphate buffer pH 7.4. Curve is t/S versus t.

SEM images (Figure 3a–c) clearly show the appearance of a highly porous structure in the swollen hydrogel. The hydrogels prepared from aqueous blends containing 10 and 15% w/w PMVE/MA show more porous structures than hydrogels prepared from aqueous blends containing 20% w/w of PMVE/MA, which had less porous matrices.

It was seen in our previous studies that hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA crosslinked with PEG 10 000, when swollen in water, showed equilibrium swelling values of 461, 350 and 326%, respectively, in comparison to 1254, 1234 and 1083% when prepared in 0.1 M phosphate buffer at pH 7.4 in this study. This is because the swelling of anionic hydrogels is dependent on the changes in external environmental conditions, such as the pH, ionic strength, solvent composition and temperature. In the present study, the dramatic increase in swelling of hydrogels with the change in pH is likely to be due to increased ionisation, resulting in greater electrostatic repulsion between charged groups and, therefore, higher degrees of swelling.[26] This is likely to be the case should such materials be used as rate-controlling membranes for implantable drug-delivery systems and swollen *in vivo*.

Table 3 shows the diffusional exponent, n, gel characteristic constant, k, and the mechanism of diffusion of water molecules into the hydrogels. It is apparent that values of n were greater than 1.0, as calculated from equation (4), indicating a Class II type diffusion mechanism in the hydrogels. In such cases, the swelling depends on the ratio between the polymer relaxation rate (R_{relax}) and the solvent diffusion rate (R_{diff}) into the hydrogel.[20] The fundamental reason for Class II diffusion in polymer matrices is that the polymer relaxation rate is much slower than the solvent diffusion (i.e. $R_{diff} >> R_{relax}$).[18,27]

Despite the similar equilibrium water content (Table 2), the differences observed in the rates of diffusion of solute into these crosslinked systems could be attributed to the structure and network properties of the hydrogels. In this study therefore we have determined some of the network parameters of the hydrogels in the swollen state, such as polymer volume fraction, φ, average molecular weight between two consecutive crosslinks, $\bar{M}_C$, and the crosslink density, q.

The characteristic network parameters, as shown in Table 4, clearly indicate that as the content of PMVE/MA increases, the amount of water uptake at different time intervals decreases. The polymer volume fraction (φ), determined using equation (6), ranged from 0.067 to 0.078 for hydrogels containing 10–20% w/w of PMVE/MA. The φ in the swollen state describes the amount of liquid that can be imbibed into a

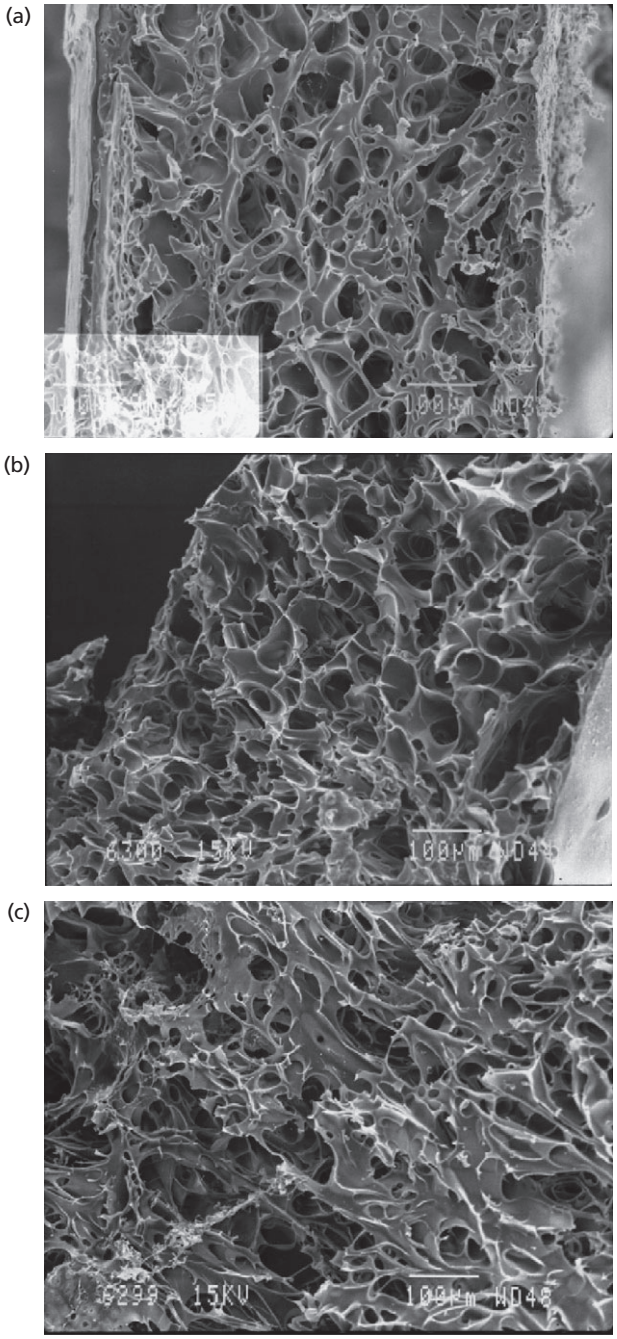

Figure 3 Scanning electron micrographs of the different hydrogels. Hydrogels were composed of PMVE/MA and PEG 10 000 in 2 : 1 ratio, with (a) 10%, (b) 15% and (c) 20% w/w of PMVE/MA.

Table 3 Swelling mechanisms of hydrogels in phosphate buffer

Formulation (2 : 1)	n	k (10^{-3})	Mechanism
10% PMVE/MA : PEG	1.0	12.44	Class II
15% PMVE/MA : PEG	1.0	2.80	Class II
20% PMVE/MA : PEG	1.0	2.85	Class II

Hydrogels were composed of PMVE/MA and PEG 10 000 in 0.1 M phosphate buffer pH 7.4.

Table 4 Network parameters of hydrogels in phosphate buffer

Formulation (2 : 1)	Φ	χ	$\bar{M}_C$ ((g/mol) × 10^5)	$V_e \times 10^{18}$
10% PMVE/MA : PEG	0.067	0.52	15.04	4.37
15% PMVE/MA : PEG	0.070	0.52	12.77	5.09
20% PMVE/MA : PEG	0.078	0.53	9.08	7.72

Hydrogels composed of PMVE/MA and PEG 10 000 in 0.1 M phosphate buffer pH 7.4.

hydrogel and is described as a ratio of the polymer volume to the swollen gel volume.[9] In this study, the change in the φ of the three hydrogels represented a similar trend, as seen in previous studies,[15] where the φ decreased with increase in the PMVE/MA content.

The number average molecular weights $\bar{M}_C$ between cross-links, determined by the equilibrium swelling method using equation (5), is also shown in Table 4. The values of $\bar{M}_C$ were observed to range from 15.04 to 9.08×10^5 g/mol for hydrogels prepared from aqueous blends containing 10–20% w/w PMVE/MA. The crosslink density, V_e, determined using equation (8), was increased with increase in the PMVE/MA content. For example, the V_e of hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA was 4.37×10^{18}, which was significantly ($P = 0.001$) lower than that of hydrogels prepared from aqueous blends containing 20% w/w of PMVE/MA (7.72×10^{18}). In addition, PMVE/MA content had no significant effect on the χ parameter of the crosslinked hydrogels. The network parameters clearly indicate that, with increase in PMVE/MA content, the number of crosslinks per unit volume also increases, causing a decrease in the molecular weight between two crosslinks ($\bar{M}_C$). This results in decreased free volume available, thus providing insufficient space for diffusion of water molecules into the crosslinked hydrogel network.[18]

In the present study, the three hydrogels were swollen to equilibrium to investigate the permeation of theophylline, fluorescein sodium and vitamin B_{12}. The three solutes selected were of increasing hydrodynamic radius, 3.5, 5.0 and 8.2 Å, respectively, as shown in Table 1.[25,28,29] Due to the ongoing dimensional changes of swelling hydrogels when initially immersed in aqueous fluid, in the present study it was necessary to swell the crosslinked hydrogels to equilibrium prior to performing the solute permeation studies. This approach is well accepted.[25,28,30]

Figure 4a–c shows the percentage permeation of the three different solutes from the hydrogels composed of PMVE/MA and PEG. The results indicate that the percentage permeation of solutes decreases with increasing hydrodynamic radius of the solute. For example, the percentage permeation of theophylline after 24 h was 66 ± 2%, 58 ± 3% and 47 ± 4% across hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA, respectively. The percentage permeation of fluorescein sodium after 24 h was 18 ± 1%, 21 ± 3% and 13 ± 1% across hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA, respectively. The percentage permeation of vitamin B_{12} after 24 h was 17 ± 4%, 13 ± 3% and 11 ± 2% across hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA, respectively.

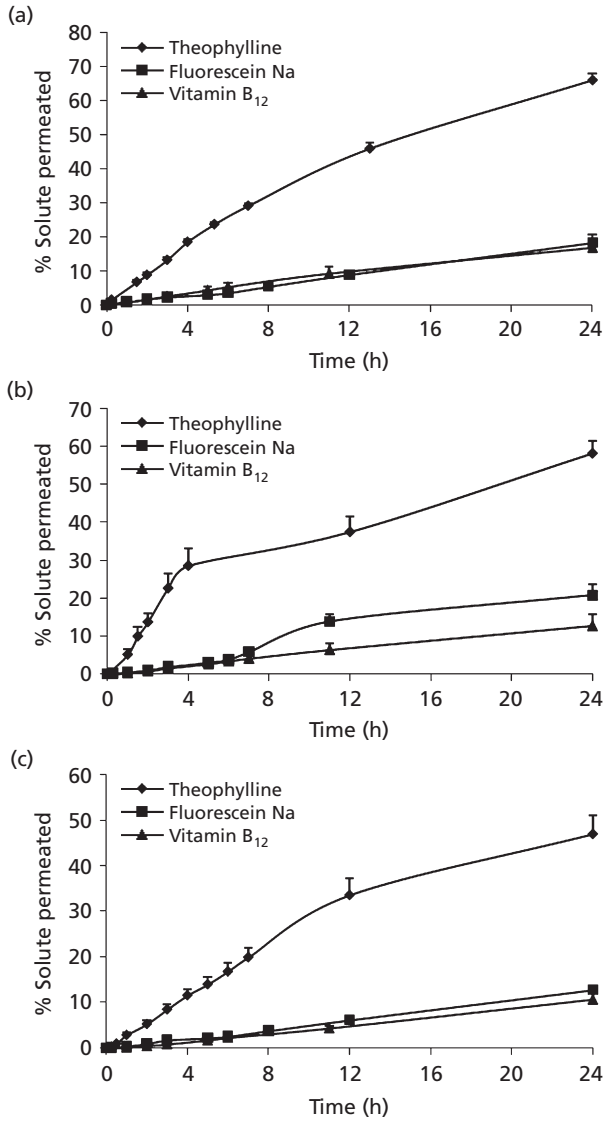

Figure 4 Percentage of solute permeated across pre-swollen hydrogel membranes. Membranes contained: (a) 10%, (b) 15% and (c) 20% w/w of PMVE/MA. Values are means ± SD, $n = 3$

Increasing the PMVE/MA content caused a decrease in the permeation of each solute, irrespective of the solute radius. This was due to higher V_e with increasing PMVE/MA content. Table 5 shows the values of P, D and K_d for the three solutes through the three different hydrogels determined using equations (9) to (11), respectively. The permeability coefficient, P, of theophylline was significantly higher than that of both fluorescein sodium and vitamin B_{12}. For example, the P values of theophylline, fluorescein sodium and vitamin B_{12} through the hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA were 12.87×10^{-4}, 1.23×10^{-4} and 1.33×10^{-4} cm/s, respectively. A similar trend in D values was observed for all three types of hydrogel. For example, for hydrogels prepared from aqueous blends containing 10% w/w PMVE/MA the values of D were theophylline 2.32×10^{-4} cm/s, fluorescein sodium 0.36×10^{-4} cm/s and vitamin B_{12} 0.43×10^{-4} cm/s.

The permeability of a given solute through a particular hydrogel membrane is dependent on solute size, crosslink density of hydrogelmembrane, pH of medium, temperature and the affinity of the solute to the hydrogel membrane.[31] The transport of the solute within a hydrogel will occur primarily within the water-filled space between the polymer chains. Any factor that affects the dimensions of these spaces will have a direct effect on the movement of the solute, therefore factors such as polymer chain mobility and the existence of charged groups on the polymer, which may bind the solute molecule, may further affect the diffusion of solute.[32] In heterogeneous hydrogels, showing a great deal of interpolymer interaction and limited polymer chain mobility, the openings between chains can be considered constant in size and location, such as in the polymer matrices used here.[33] In the present study, it can be seen that the transport of solutes through the equilibrium swollen hydrogel is affected by both the size of solute (hydrodynamic radius and molecular weight) and crosslink density of the hydrogels. The size of the solutes was an important parameter in determining the diffusion and thus the permeation of solutes through the equilibrium swollen hydrogel membranes. The permeation of solutes through the hydrogels was in accordance with the swelling behaviours of the hydrogels. As shown in Table 2, the degree of swelling became lower with increasing PMVE/MA content in the hydrogels, indicating a decrease in the available free volume for solute diffusion with increase in PMVE/MA content. This is explained by the fact that increasing the polymer content also increases the crosslink density of the hydrogels (Table 4).

Diffusion and permeability coefficients of all three solutes through the lightly crosslinked hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA were higher than those through highly crosslinked hydrogels prepared from aqueous blends containing 15 and 20% w/w of PMVE/MA. Furthermore, theophylline, a non-ionic solute, having the smallest molecular size of 3.5 Å, showed the highest permeation through all three hydrogels studied (Table 5). The transport of fluorescein sodium and vitamin B_{12} through the hydrogels was lower due to their greater size and molecular weights. The Stokes–Einstein equation, in an ideal aqueous medium, predicts that permeability declines as a linear function of molecular radius.[29] In addition, according to the free volume theory, the rate of solute diffusion is determined by the probability of a void space being formed of sufficient volume to allow the diffusion of a solute molecule.[32] However, in the present study, fluorescein sodium and vitamin B_{12} showed limited permeation and diffusion (Table 5), therefore these results are indicative of the fact that the permeation or diffusion of the solute is affected by the solute size and crosslink density of the hydrogels.

The partition coefficients (K_d) of solutes between the hydrogels and buffered solution are also shown in Table 5. The K_d values of solutes were lower for hydrogels prepared from aqueous blends containing 10% w/w of PMVE/MA followed by 15 and 20% w/w of PMVE/MA, respectively. For example, the K_d values for vitamin B_{12} were 0.24, 0.74 and 2.03 for hydrogels prepared from aqueous blends containing 10, 15 and 20% w/w of PMVE/MA. A low value of K_d indicates low solubility of solute molecule in the hydrogel membrane. A high value of K_d means that there is a possible interaction between

Table 5 Permeation parameters of solutes across pre-swelled hydrogels

Solutes	Hydrogel (2 : 1)	$P \times 10^{-4}$ cm/s	K_d	$D \times 10^{-4}$ cm^2/s
Theophylline	10% PMVE/MA : PEG	12.87 ± 1.78	0.43	2.32 ± 0.32
Theophylline	15% PMVE/MA : PEG	7.95 ± 1.90	0.49	1.97 ± 0.47
Theophylline	20% PMVE/MA : PEG	6.00 ± 1.11	0.90	0.59 ± 0.11
Fluorescein Na	10% PMVE/MA : PEG	1.23 ± 0.10	0.26	0.36 ± 0.03
Fluorescein Na	15% PMVE/MA : PEG	1.07 ± 0.16	0.27	0.48 ± 0.07
Fluorescein Na	20% PMVE/MA : PEG	0.77 ± 0.07	1.44	0.17 ± 0.01
Vitamin B_{12}	10% PMVE/MA : PEG	1.33 ± 0.37	0.24	0.43 ± 0.12
Vitamin B_{12}	15% PMVE/MA : PEG	0.88 ± 0.23	0.74	0.15 ± 0.04
Vitamin B_{12}	20% PMVE/MA : PEG	0.63 ± 0.08	2.03	0.09 ± 0.01

Hydrogels were composed of PMVE/MA and PEG 10 000. Values are means ± SD, $n = 3$.

the solute molecule and the polymer chains, thus the solute molecule is easily soluble in the hydrogel.[33] In the present study, it was observed that the K_d values of solutes were higher for hydrogels prepared from aqueous blends containing 20% w/w of PMVE/MA, which increased with increasing hydrodynamic radius of solute, indicating the presence of solute molecules within the hydrogel without diffusion.

Conclusions

The present study illustrated the swelling behaviour, network parameters and solute permeation of hydrogels composed of PMVE/MA and PEG in buffered solution. These hydrogels showed swelling and network parameters which changed with changes in content of PMVE/MA and PEG. The concentration of the polymer and crosslinker was directly related to the diffusion/permeation coefficients of the three different solutes studied. Hydrogels with lower PMVE/MA content showed lower crosslink density, $\underline{V}_e$, and higher molecular weight between two crosslinks, $\bar{M}_C$. The solute diffusion across swollen hydrogels was largely dependent on the solute size and the hydrogel crosslinking density. Theophylline, with the lowest hydrodynamic radius, 3.5 Å, showed the greatest permeation across the three hydrogels studied compared to both fluorescein sodium and vitamin B_{12}, with higher hydrodynamic radii of 5.0 and 8.7 Å, respectively. This means that the degree of crosslinking plays a very important role in the rate and extent of delivery of a given solute from these hydrogels.

It is obvious that permeation or transport of solutes with different hydrodynamic radii can easily be modulated by controlling the crosslink density of the hydrogels studied here. Consequently, such hydrogels may have potential as components of controlled drug-delivery systems. We are currently evaluating these hydrogels for use as rate-controlling membranes in implantable sustained-release devices delivering therapeutic proteins and peptides of high molecular weight and hydrodynamic radius.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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