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# Electrically enhanced solute permeation across poly(ethylene glycol)–crosslinked poly(methyl vinyl ether-co-maleic acid) hydrogels: Effect of hydrogel crosslink density and ionic conductivity

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ABSTRACT

Swelling kinetics, ionic conductivity and electrically assisted solute permeation (theophylline, methylene blue and fluorescein sodium) of poly(ethylene glycol) (PEG) crosslinked poly(methyl vinyl ether-co-maleic acid) (PMVE/MA) hydrogels are presented. The effects of PMVE/MA concentration and PEG molecular weight (MW) on swelling behaviour and network parameters were investigated in phosphate buffered saline (pH 7.4). The percentage swelling of hydrogels increased, and the crosslink density decreased, with a decrease in PMVE/MA content and with an increase in PEG MW. The ionic conductivity of the formulation was found to increase with an increase in PEG MW. The application of an electrical current led to a significant enhancement in the rate and extent of solute permeation across the swollen hydrogels. Furthermore, it was found that the extent of solute permeation enhancement following current application was dependent upon the crosslink density and ionic conductivity of the formulation. In general, a decrease in crosslink density and an increase in ionic conductivity led to a greater enhancement in solute permeation following current application. The electro-responsive nature of these hydrogels suggests that have a potential application in electrically controlled drug delivery systems.



## 1. Introduction

Following the successful development of a range of techniques to enable sustained controlled release, such as matrices with controllable swelling, diffusion or erosion profiles (Sershen and West, 2002), there has been a recent interest in the development of so called "intelligent" drug carriers (Murdan, 2003). An intelligent, responsive drug delivery system is one, which once implanted into the body, has the ability to release drug in a pulsatile or staggered fashion, typically in response to local changes in the environment, or following activation by an external stimulus (Sershen and West, 2002).

The use of an electric field as an external stimulus is a method that has been successfully employed to enhance the amount of released drug and the precise controls (Juntanon et al., 2008). Electro-responsive polymers can be used to prepare materials that swell, shrink, or bend in response to an electric field (Roy et al., 2010). Electro-sensitive hydrogels are normally composed of polyelectrolytes (polymers that contain a relatively high concentrations of ionisable groups along the backbone chain) and an insoluble, swellable polymer network containing fixed charge sites (Kaewpirom and Boonsang, 2006). Furthermore, electro-sensitive hydrogels have been widely investigated as matrices for sensing and responding to an electric stimulus, enabling drug release to occur in a pulsatile manner, or in a release rate determined as a function of the applied electric protocol (Im et al., 2010; Niamlang and Sirivat, 2009; Malay et al., 2009).

To date a wide variety of electrically responsive conducting polymer hydrogel composites have been investigated, including hydrogels based upon poly(acrylamide) (Niamlang and Sirivat, 2009; Aouada et al., 2006), Gum Arabica (Mallik and Sarkar, 2006), hydroxyethyl methacrylate (Mohomed et al., 2006), collagen (Marzec and Pietrucha, 2008) and chitosan (Kaewpirom and Boonsang, 2006) for biomedical and pharmaceutical applications. It has been shown that performance of an electrically responsive hydrogel is dependent upon a number of factors, including formulation conductivity (Im et al., 2010), degree of crosslinking and hydrogel swelling capability (Sheppard et al., 1997; Schwartz et al., 1997).

We have previously demonstrated that poly(ethylene glycol) (PEG) crosslinked poly(methyl vinyl ether-co-maleic acid) (PMVE/MA) hydrogels have a high swelling capability (Thakur et al., 2009), and that solute permeation across these hydrogels is dependent upon the crosslink density of the hydrogel as well as the hydrodynamic radius of the solute molecule (Thakur et al., 2010), suggesting use as a rate controlling membrane for drug

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**Table 1**
Formulation composition of PEG–crosslinked PMVE/MA hydrogels.

| Formulation code | % PMVE/MA | PEG MW | Ratio |
|---|---|---|---|
| F1 | 20 | 10,000 | 2:1 |
| F2 | 20 | 10,000 | 1:1 |
| F3 | 20 | 1000 | 2:1 |
| F4 | 20 | 1000 | 1:1 |
| F5 | 20 | 200 | 2:1 |
| F6 | 20 | 200 | 1:1 |
| F7 | 15 | 10,000 | 2:1 |
| F8 | 15 | 10,000 | 1:1 |
| F9 | 15 | 1000 | 2:1 |
| F10 | 15 | 1000 | 1:1 |
| F11 | 15 | 200 | 2:1 |
| F12 | 15 | 200 | 1:1 |
| F13 | 10 | 10,000 | 2:1 |
| F14 | 10 | 10,000 | 1:1 |
| F15 | 10 | 1000 | 2:1 |
| F16 | 10 | 1000 | 1:1 |
| F17 | 10 | 200 | 2:1 |
| F18 | 10 | 200 | 1:1 |

delivery applications. In the present study we have, for the first time, investigated the electrically assisted permeation of a range of drug molecules across PEG crosslinked PMVE/MA hydrogels, and evaluated the role of crosslink density and hydrogel composition on the electro-responsive nature of these hydrogels.

## 2. Methods

### 2.1. Materials

Gantrez® AN-139, a copolymer of methyl vinyl ether and maleic anhydride (PMVE/MAH, with a molecular weight, MW, of 1,080,000 Da) was a gift from ISP Corp. Ltd., Guildford, UK. PEGs of MWs 200, 1000 and 10,000 Da, theophylline anhydrous, minimum 99% (MW 180.17 Da), methylene blue (MW 373.90 Da), fluorescein sodium (MW 376.28 Da) were obtained from Sigma–Aldrich (Steinheim, Germany). Poly(ester) film, one-side siliconised, release liner (FL2000$^{TM}$ PET 75 μ 1S) was obtained from Rexam Release BV (Apeldoorn, The Netherlands). Glisseal®N vacuum grease was purchased from Borer Chemie (Zuchwil, Switzerland). Resealable poly(ethylene) bags (101 mm × 140 mm) were obtained from Agar Scientific (Essex, UK).

### 2.2. Preparation of hydrogels

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. This process causes hydrolysis of the anhydride moieties of PMVE/MAH to the free acid forms, yielding PMVE/MA (McCarron et al., 2004). Upon cooling, the required amount of PEG (200, 1000 or 10,000 Da) was added to PMVE/MA solution (at 10%, 15% and 20% (w/w)), in ratios of 2:1 and 1:1 (PMVE/MA:PEG), and the casting blend was adjusted to final weight with water (Table 1).

Films were prepared by slowly pouring the aqueous blend (30 g) into a mould consisting of a release liner (with siliconized side up) secured to a Perspex® base plate using a stainless steel clamp. Once assembled, the internal dimensions available for casting were 100 mm × 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 (Thakur et al., 2009).

### 2.3. Dynamic and equilibrium swelling studies

Crosslinked film sheets (1.0 cm × 1.0 cm) were weighed as $m_o$ (xerogels) and were then swollen in phosphate buffered saline (PBS) pH 7.4 (Sigma–Aldrich, Steinheim, Germany) for one week at room temperature. 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 under 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, respectively, by using Eqs. (1) and (2) (Wang and Wu, 2005).

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

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

To examine the controlling mechanism of the swelling process of PEG–crosslinked PMVE/MA hydrogels, the following second order kinetic model (Eq. (3)) was used to process the experimental data (Peniche et al., 1997):

$$\frac{t}{S} = A + Bt \quad (3)$$

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

### 2.4. Analysis of mechanism of water uptake

Dynamic swelling studies were undertaken to elucidate the mechanism of water diffusion into the polymer samples, as determined by the dynamic portion of the gravimetric curve. Eq. (4) was used to process the kinetic data of the swelling process, in order to gain insights into the mechanism of water transport through the hydrogels (Sunil and Surinderpal, 2006), as described previously (Thakur et al., 2010).

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

$M_t$ is the mass of water absorbed at time $t$, $M_\infty$ 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.

### 2.5. Network parameters

In the present study, the number average molecular weight between crosslinks, $\overline{M}$, was determined using equilibrium swelling theory, $\overline{M}$(Equi) The $\overline{M}$ can be determined by swelling studies according to the Flory and Rehner equation, Eq. (5) (Paul and John, 1943). The magnitude of $\overline{M}$ affects the mechanical, physical and thermal properties of crosslinked polymers. The volume fraction of a polymer, $\phi$, 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 (Eq. (6)).

$$\overline{M}(\text{Equi}) = \frac{-d_p V_s \phi^{1/3}}{[\ln(1-\phi) + \phi + \chi\phi^2]} \quad (5)$$

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

Here, $V_s$ is the molar volume of water (18 $cm^3$/mol), $\phi$ is volume fraction of polymer in the hydrogel, $\chi$ 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 $w$ weight of the film (Marcia et al., 2004).

The polymer–water interaction parameter ($\chi$) reflects the thermodynamic interaction in hydrogels, which in turn indicates the change of interaction energy when polymer and solvent mix together. The $\chi$ parameters of hydrogels can be obtained experimentally *via* Eq. (7) (Tuncer et al., 2006):

$$\chi = \frac{1}{2} + \frac{\phi}{3} \quad (7)$$

Eq. (7) neglects the $M_c$ dependence of the $\chi$ parameter, and therefore, Eq. (7) indicates that the $\chi$ values are always $\geq$0.50.

Knowledge of crosslink density is of great importance in characterization of hydrogels because of its effect on their mechanical and physical properties and their behaviour in practical applications (Paul and John, 1943). In the present study, crosslink density, $V_e$, was determined using Eq. (8). $V_e$ represents the number of elastically effective chains, totally induced in a perfect network, per unit volume. Where, $N_A$ is Avagadro's number ($6.023 \times 10^{23}$ $mol^{-1}$) (Sunil and Surinderpal, 2006).

$$V_e = \frac{d_p N_A}{M_c} \quad (8)$$

### 2.6. Conductivity measurements of PMVE/MA–PEG hydrogel films

Ionic conductivity of the PMVE/MA–PEG hydrogels (Table 1), after reaching equilibrium swollen state, in PBS pH 7.4, was determined by dielectric analysis (DEA) (DEA 2970, TA Instruments, Delaware, USA). The hydrogel membranes were swollen, in PBS at pH 7.4, to an equilibrium state and were then cut into a disc shape of 24 mm diameter using a cork bore. Measurements were carried out using DEA with the hydrogel disc placed onto a parallel plate ceramic sensor. The experiment was performed at 37 °C, with dry nitrogen gas adjusted to a flow rate of 50 ml $min^{-1}$ and ionic conductivity measured at a frequency of 1 kHz.

### 2.7. Permeation studies

To investigate the effect of PEG MW upon the passive and electrically assisted permeation of solute molecules across swollen hydrogel membranes, membranes composed of 15% PMVE/MA–7.5% PEG (PEG MW 200 or 10,000) were used for permeation studies. Formulations based on a 2:1 ratio of PMVE/MA:PEG, and a PMVE/MA concentration of 15% (w/w), were chosen for investigation due to their swelling and ionic conductivity properties, as well as their ease of preparation and handling in comparison to those formulations composed of 10% or 20% (w/w) PMVE/MA. Three model drug molecules, representing solutes of neutral (theophylline), positive (methylene blue), and negative (fluorescein sodium) charge at pH 7.4 were evaluated. Permeation studies were performed using side-by-side diffusion cells (PermeGear, Hellerton, PA, USA). Diffusion cells, consisting of donor and receptor half-cells, each of 3.4 ml volume were used with 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 phosphate buffered saline (PBS) at pH 7.4 to an equilibrium state and were then cut into a disc shape of 9 mm 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 $ml^{-1}$) in PBS pH 7.4, was added to the donor side of the diffusion cell and 3 ml of PBS pH 7.4 was added to the receptor side. For electrically assisted permeation, silver/silver chloride electrodes (silver–silver chloride segment 0.8 mm diameter × 8 mm length, total wire length 70 mm, In Vivo Metric, Healdsburg, CA, USA) were used as the cathode, and silver wire (1.0 mm diameter × 70 mm, Sigma–Aldrich, Steinheim, Germany, UK) used as the anode, with the drug electro-repulsion occurring by relevant electrode placement in either the receiver or donor compartment depending on the charged nature of the drug. A commercially available power supply (Phoresor II, Iomed, Lake City, FL, USA) was used to deliver a current of 0.5 mA/$cm^2$ for a 6 h period. At predetermined time intervals, the contents of the receptor cell were removed and replaced with an equal volume of PBS pH 7.4. The aliquot removed was analysed using UV-spectroscopy (Cary 50 Scan, Varian, Mulgrave, Victoria, Australia) at $\lambda_{max}$ = 271 nm (theophylline), $\lambda_{max}$ = 664 nm (methylene blue), and $\lambda_{max}$ = 497 nm (fluorescein sodium), respectively.

### 2.8. Statistical analysis

Dynamic equilibrium swelling data and ionic conductivity data was analysed using one-way analysis of variance, with Tukey's HSD post-hoc test used to compare the means of different treatment groups. Permeation study data was analysed using paired *t*-test. In all cases $P < 0.05$ was used to denote statistical significance.

## 3. Results

### 3.1. Dynamic swelling characteristics of PEG–crosslinked PMVE/MA hydrogels

The hydrogels containing 10%, 15% and 20% (w/w) of PMVE/MA crosslinked with PEG 10,000 showed the highest percentage swelling after 24 h, followed by hydrogels containing PEG 1000, and PEG 200, respectively ($P < 0.001$). The percentage swellings of hydrogels with polymer crosslinked ratios of 2:1 were higher at 24 h than those with ratios of 1:1 in hydrogels containing PEG 10,000 and PEG 1000 ($P < 0.001$). Representative dynamic swelling curves for PEG crosslinked PMVE/MA hydrogels, highlighting the effect of PEG MW is shown in Fig. 1.

Fig. 2 shows representative linear regression plots of the swelling curves derived from Eq. (3). As can be seen from Table 2, the theoretical equilibrium swelling of the hydrogels is comparable to their corresponding %EWC values. The initial swelling rates ranged from 5.20 to 9.43 $min^{-1}$, 1.54 to 2.94 $min^{-1}$ and 1.29 to 1.49 $min^{-1}$ for hydrogels containing PEG 10,000, PEG 1000 and PEG 200, respectively. The initial swelling rates were higher for the hydrogels containing PEG 10,000 followed by PEG 1000 and PEG 200 ($P < 0.001$). Interestingly, it was found that for these hydrogel systems that carrying out the swelling studies at an elevated temperature (37 °C) had no significant effect on the equilibrium water content. For example, the %EWC at room temperature for formulation F7 and F11 were found to be 645.22 ± 38.31, and 173.19 ± 8.03, respectively. Whilst the %EWC at 37 °C for formulation F7 and F11 were found to be 664.07 ± 32.59, and 178.41 ± 9.51, respectively.

### 3.2. Analysis of mechanism of water uptake

Table 3 shows that the diffusional exponents, $n$, for the hydrogels containing PEG 10,000 and PEG 1000 were >0.50, as calculated using Eq. (4), indicating either an Anomalous or Class II mechanism of water uptake. In contrast the diffusional exponents for hydrogels

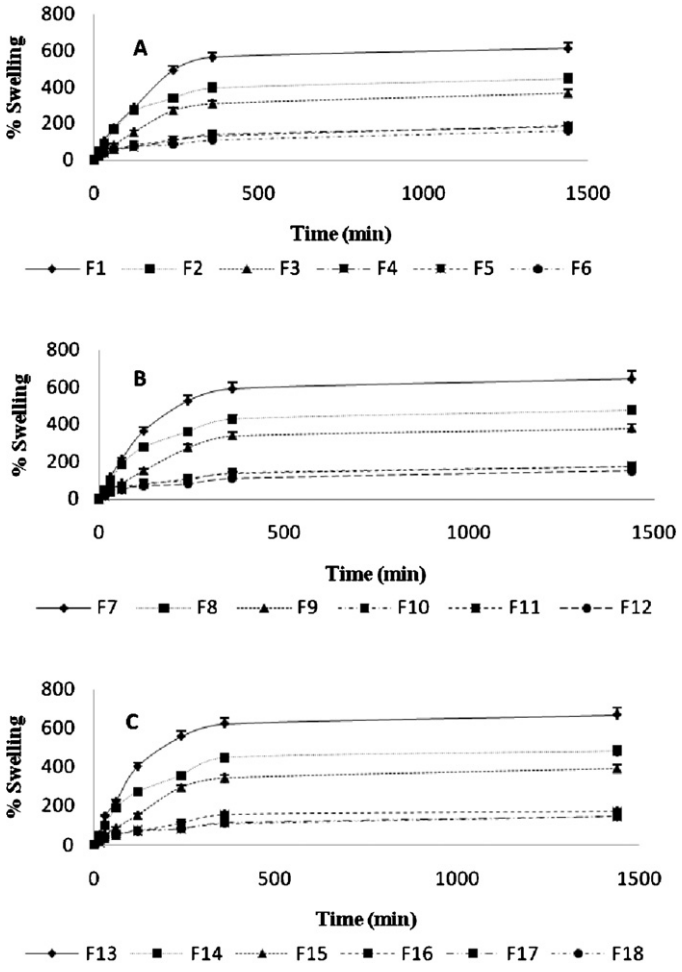


**Fig. 1.** Representative percentage swelling curves of 15% (w/w) PMVE/MA hydrogels crosslinked with PEG of different MW at a ratio of 2 PMVE/MA:1 PEG, (F7) crosslinked with PEG 10,000, (F9) crosslinked with PEG 1000, and (F11) crosslinked with PEG 200, respectively. Mean ± SD, $n = 3$.

**Table 2**
Dynamic swelling characteristics of PEG–crosslinked PMVE/MA hydrogels, $n = 3$.

| Formulation code | %EWC | $r_i$[a] | $k_s \times 10^{-5}$[b] | $S_{eq}$ %[c] |
|---|---|---|---|---|
| F1 | 613.29 ± 28.75 | 6.31 | 1.66 | 657.89 |
| F2 | 447.87 ± 22.89 | 5.20 | 2.29 | 476.19 |
| F3 | 368.26 ± 19.63 | 2.58 | 1.51 | 413.22 |
| F4 | 184.52 ± 9.44 | 1.54 | 3.45 | 200.00 |
| F5 | 186.45 ± 8.62 | 1.49 | 3.73 | 200.00 |
| F6 | 161.77 ± 7.88 | 1.38 | 4.64 | 172.41 |
| F7 | 645.22 ± 38.31 | 7.83 | 1.76 | 666.67 |
| F8 | 474.52 ± 25.31 | 5.48 | 2.19 | 500.00 |
| F9 | 378.49 ± 22.79 | 2.66 | 1.53 | 416.67 |
| F10 | 175.93 ± 9.36 | 1.78 | 5.20 | 185.19 |
| F11 | 173.19 ± 8.03 | 1.47 | 4.28 | 185.19 |
| F12 | 148.93 ± 8.34 | 1.34 | 5.30 | 158.73 |
| F13 | 668.66 ± 35.62 | 9.43 | 1.85 | 714.29 |
| F14 | 481.07 ± 24.04 | 5.55 | 2.01 | 526.31 |
| F15 | 392.25 ± 19.89 | 2.94 | 1.56 | 434.78 |
| F16 | 171.83 ± 8.17 | 1.73 | 5.23 | 181.82 |
| F17 | 144.35 ± 6.78 | 1.29 | 5.47 | 153.85 |
| F18 | 148.81 ± 7.45 | 1.44 | 5.90 | 156.25 |

[a] (g water/g gel)/min.
[b] (g gel/g water)/min.
[c] (g water/g gel).

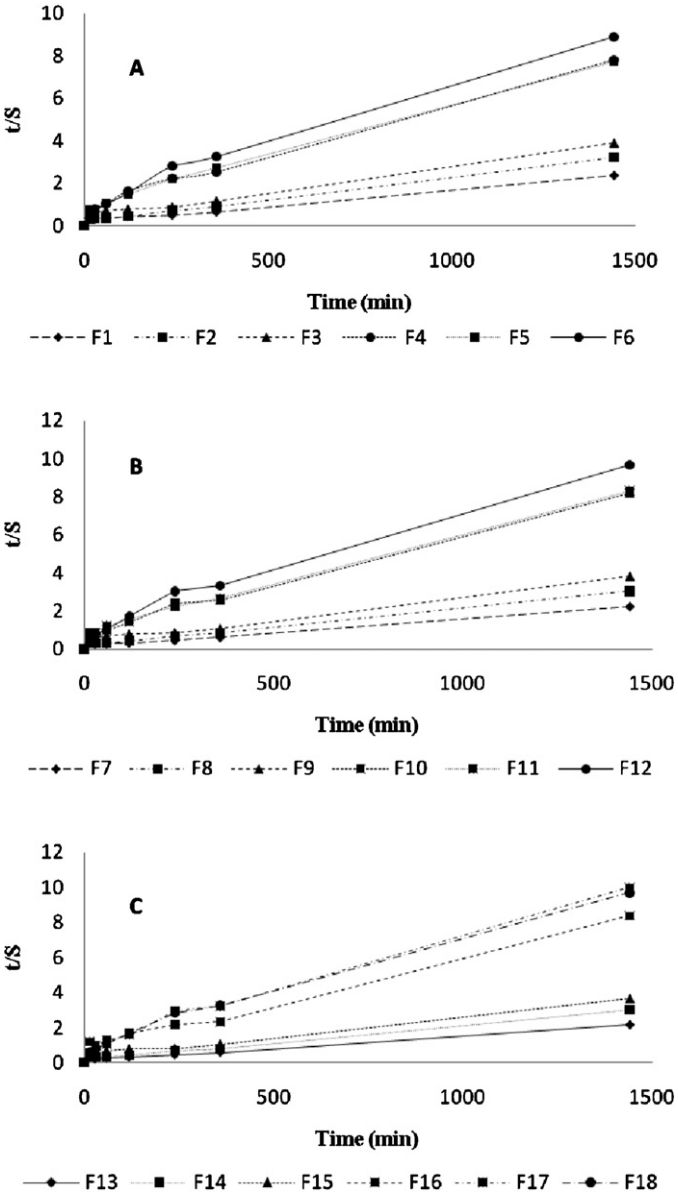


**Fig. 2.** Representative $t/S$ versus $t$ swelling rate curves of 15% (w/w) PMVE/MA hydrogels crosslinked with PEG of different MW at a ratio of 2 PMVE/MA:1 PEG, (F7) crosslinked with PEG 10,000, (F9) crosslinked with PEG 1000, and (F11) crosslinked with PEG 200, respectively. Mean value expressed.

containing PEG 200 were ≤0.50, indicating a Fickian mechanism of water uptake.

### 3.3. Network parameters

Table 4 displays different characteristic network parameters of the hydrogels. The volume fraction of polymer, $\phi$, determined using Eq. (6), showed values ranging from 0.12 to 0.16 for hydrogels crosslinked with PEG 10,000, and 0.18 to 0.34 and 0.32 to 0.38 for hydrogels crosslinked with PEG 1000 and PEG 200, respectively.

The number average molecular weight between crosslinks, $M_c$, determined by Eq. (5), is shown in Table 4. The values of $M_c$ were observed to range from 52,500 to 194,000 g mol$^{-1}$ for PMVE/MA hydrogels crosslinked with PEG 10,000 and 3750 to 67,300 g mol$^{-1}$ and 2120 to 4250 g mol$^{-1}$ for hydrogels crosslinked with PEG 1000 and PEG 200, respectively.

**Table 3**
Swelling rate and diffusion characteristics of PEG–crosslinked PMVE/MA hydrogel systems.

| Formulation code | $n$ | $k \times 10^{-3}$ | Mechanism |
|---|---|---|---|
| F1 | 1.00 | 6.30 | Class II |
| F2 | 0.73 | 11.77 | Anomalous |
| F3 | 0.79 | 5.45 | Anomalous |
| F4 | 0.45 | 13.86 | Fickian |
| F5 | 0.47 | 12.07 | Fickian |
| F6 | 0.42 | 14.59 | Fickian |
| F7 | 1.00 | 5.21 | Class II |
| F8 | 0.75 | 11.72 | Anomalous |
| F9 | 0.78 | 5.79 | Anomalous |
| F10 | 0.39 | 19.65 | Fickian |
| F11 | 0.51 | 9.60 | Fickian |
| F12 | 0.41 | 14.11 | Fickian |
| F13 | 1.00 | 5.85 | Class II |
| F14 | 0.73 | 12.57 | Anomalous |
| F15 | 0.73 | 7.87 | Anomalous |
| F16 | 0.44 | 14.98 | Fickian |
| F17 | 0.50 | 7.95 | Fickian |
| F18 | 0.39 | 16.60 | Fickian |

The crosslink density, $V_e$, determined using Eq. (8) was found to increase with a decrease in the chain length/MW of PEG (Table 4). For example, the crosslink density of hydrogels crosslinked with PEG 10,000 was between $3.5 \times 10^{19}$ and $13.0 \times 10^{19}$. For hydrogels crosslinked with PEG 1000 and PEG 200 crosslink densities were between $19.7 \times 10^{19}$ and $38.2 \times 10^{19}$, and $36.1 \times 10^{19}$ and $42.1 \times 10^{19}$, respectively. In addition, it can also be seen in Table 4, that there is a slight increase in the $\chi$ parameter with decrease in the chain length of PEG.

### 3.4. Conductivity measurements of PMVE/MA–PEG hydrogels

Fig. 3 shows the influence of PEG MW and PMVE/MA concentration on the ionic conductivity of the hydrogels (ratio 2:1) swollen to equilibrium in PBS. It was found that, both increasing the concentration of PMVE/MA ($P < 0.001$), as well as increasing the PEG MW ($P < 0.001$) in the hydrogel led to a significant increase in the ionic conductivity of the formulation. Fig. 4 shows the influence of PEG molecular and PMVE/MA concentration on the ionic conductivity of the hydrogels (ratio 1:1) swollen to equilibrium in PBS. The same relationship between PEG MW, and concentration of PMVE/MA found for hydrogels of a ratio 2:1 was once again observed, with increasing PEG molecular weight leading to a significant enhancement in the ionic conductivity of the hydrogel ($P < 0.001$). However, it is interesting to note that the ionic conductivity of the hydrogels

**Table 4**
Network parameters of PEG–crosslinked PMVE/MA hydrogel systems.

| Formulation code | $\Phi$ | $M_c$ (g mol$^{-1}$) | $\chi$ | $V_e \times 10^{19}$ |
|---|---|---|---|---|
| F1 | 0.13 | 146,000 | 0.54 | 4.67 |
| F2 | 0.16 | 52,500 | 0.56 | 13.00 |
| F3 | 0.19 | 28,300 | 0.57 | 24.10 |
| F4 | 0.32 | 3750 | 0.61 | 38.20 |
| F5 | 0.32 | 3870 | 0.60 | 37.90 |
| F6 | 0.35 | 2630 | 0.62 | 39.88 |
| F7 | 0.12 | 173,000 | 0.54 | 3.95 |
| F8 | 0.16 | 63,200 | 0.55 | 10.80 |
| F9 | 0.19 | 31,000 | 0.56 | 22.00 |
| F10 | 0.33 | 4100 | 0.61 | 37.60 |
| F11 | 0.34 | 4250 | 0.61 | 36.10 |
| F12 | 0.37 | 2120 | 0.62 | 42.10 |
| F13 | 0.12 | 194,000 | 0.54 | 3.52 |
| F14 | 0.15 | 67,300 | 0.56 | 9.60 |
| F15 | 0.18 | 34,600 | 0.56 | 19.70 |
| F16 | 0.34 | 4290 | 0.61 | 35.90 |
| F17 | 0.38 | 1960 | 0.63 | 39.80 |
| F18 | 0.37 | 2450 | 0.62 | 41.60 |

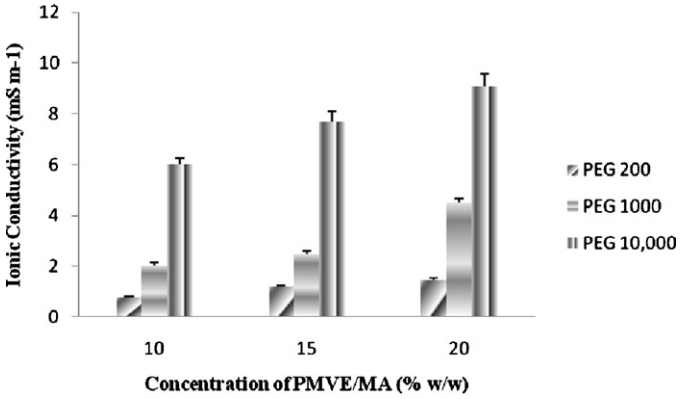


**Fig. 3.** The ionic conductivity (at 37 °C) of PMVE/MA:PEG hydrogels (ratio 2:1) swollen to equilibrium in a solution of PBS pH 7.4 (mean + SD, $n = 5$).

composed of a 1:1 ratio were significantly lower than that of the corresponding 2:1 ratio formulation ($P < 0.001$).

### 3.5. Permeation studies

Fig. 5A and C shows the percentage permeation of the three differents solutes from hydrogels composed of 15% PMVE/MA–7.5% PEG 10,000 under passive and electrically assisted conditions, respectively. The results indicate that the percentage permeation of solutes decreases with increasing MW of the solute ($P < 0.001$), whilst the nature of the charge on the solute has no effect upon the permeation of the solute through the hydrogel ($P = 0.622$). For example, under passive conditions the percentage permeation of theophylline, methylene blue and fluorescein sodium after 24 h was found to be 49.66%, 19.43%, and 18.96%, respectively. The application of an electrical current led to a significant enhancement in the permeation of all three molecules,when percentage permeation of theophylline ($P = 0.003$), methylene blue ($P < 0.001$) and fluorescein sodium ($P < 0.001$) after 24 h was found to be 63.22%, 38.86%, and 37.69%, respectively. Furthermore, a greater enhancement in permeation was noted for the charged molecules, methylene blue and fluorescein sodium (both 100% ionised at pH 7.4), in comparison to the neutral solute, theophylline (4% ionised at pH 7.4) ($P < 0.001$). For example, it can be seen in Table 5 that the enhancement ratio (ER) in permeation following the application of a current for 6 h, was found to be 2.14, for both methylene blue and fluorescein sodium permeation, whilst the ER for theophylline was only 0.47. Fig. 5B and D shows the percentage permeation of the three differents solutes from hydrogels composed of 15% PMVE/MA–7.5% PEG 200 under passive and electrically assisted

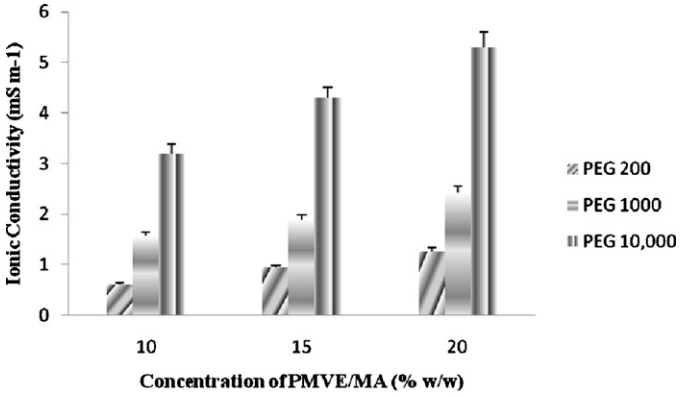


**Fig. 4.** The ionic conductivity (at 37 °C) of PMVE/MA:PEG hydrogels (ratio 1:1) swollen to equilibrium in a solution of PBS pH 7.4 (mean + SD, $n = 5$).

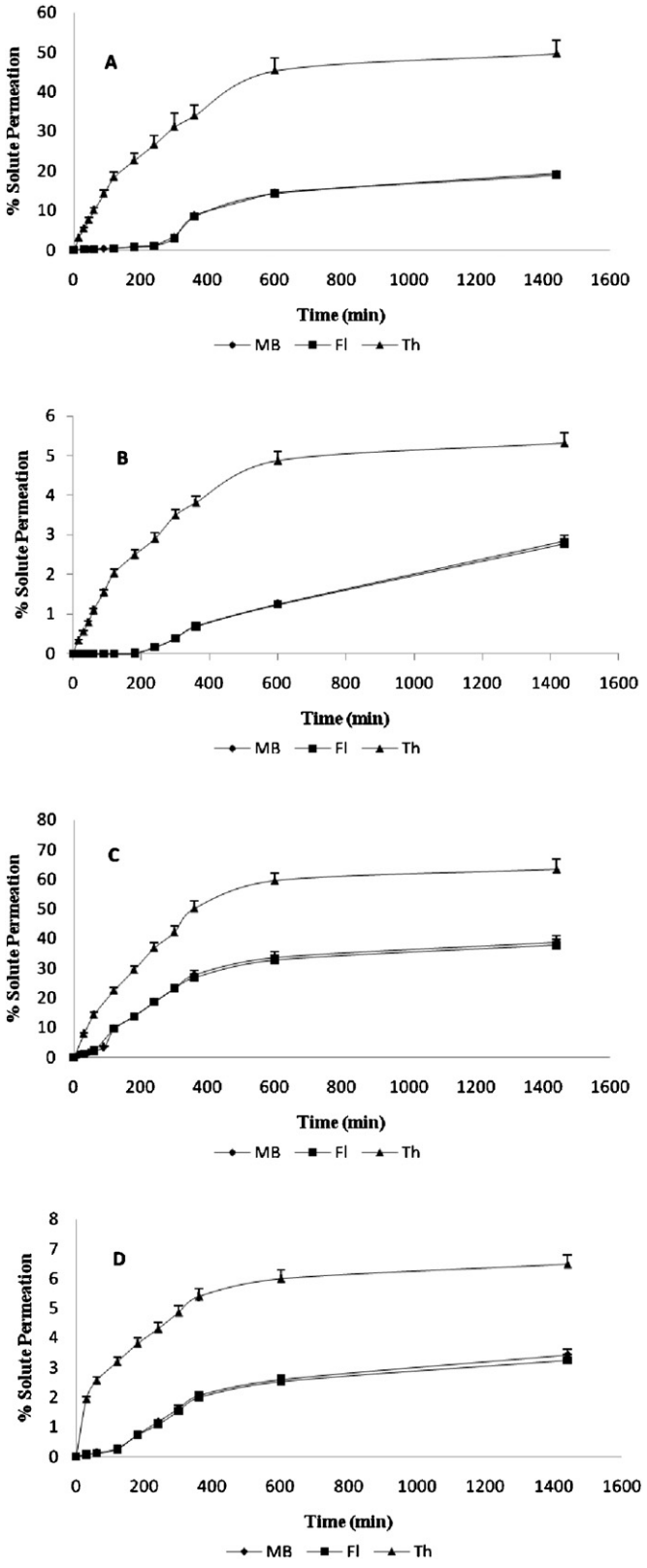


**Fig. 5.** % Solute permeated under passive (A and B) and electrically assisted (C and D) conditions across pre-swollen hydrogel membranes composed of F7 (A and C) and F11 (B and D), where MB = methylene blue, Fl = fluorescein sodium, and Th = theophylline. Mean + SD, $n = 5$.

**Table 5**
Enhancement ratio for amount of solute permeated across pre-swollen hydrogel membranes at 6 h, following the termination of an electrical current. Mean ± SD, $n = 5$.

| Formulation code | Enhancement ratio | | |
|---|---|---|---|
| | Methylene blue | Fluorescein sodium | Theophylline |
| F7 | 2.14 ± 0.02 | 2.14 ± 0.02 | 0.47 ± 0.01 |
| F11 | 1.96 ± 0.03 | 1.95 ± 0.03 | 0.42 ± 0.01 |

conditions, respectively. In comparison to the permeation of the solutes across hydrogels crosslinked with PEG 10,000 it can be seen that there was a highly significant reduction, an almost 10-fold reduction, in the permeation of all three molecules across the hydrogels crosslinked with PEG 200 ($P < 0.001$). For example, under passive conditions the percentage permeation of theophylline, methylene blue and fluorescein sodium after 24 h was only found to be 5.30%, 2.84%, and 2.77%, respectively. Similiarily to the permeation across hydrogels composed of PEG 10,000, the application of an electrical current led to a significant enhancement in the permeation of all three molecules,when percentage permeation of theophylline ($P = 0.002$), methylene blue ($P < 0.001$) and fluorescein sodium ($P < 0.001$) after 24 h was found to be 6.48%, 3.44%, and 3.25%, respectively. However, it was noted that the increase in solute permeation associated with electric current application across hydrogels composed of PEG 200 was not as great as that found for hydrogels crosslinked with PEG 10,000 ($P < 0.001$). For example the ER for theophylline, methylene blue, and fluorescein sodium across the hydrogels crosslinked with PEG 200 following current application was found to be only 0.42, 1.96, and 1.95, respectively.

## 4. Discussion

It is well known that swelling phenomena are directly related to the structure of the crosslinked polymer and/or the MW of the crosslinker. The higher percentage swelling of hydrogels containing PEG 10,000 could possibly be attributed to lower numbers of hydroxyl groups per unit mass reacting with PMVE/MA, compared to PEG 1000 and PEG 200 (Basel and Wolfgang, 2006; Michael et al., 1999). This is possible, since the number of moles of reactive hydroxyl groups on low MW PEGs is relatively higher. This means that greater numbers of ester links between PEG and PMVE/MA will form upon heating, resulting in a highly crosslinked system (Thakur et al., 2009). As a result, PEG 10,000 crosslinked hydrogels showed higher degree of equilibrium swelling, due to the reduced extent of crosslinking, followed by PMVE/MA–PEG 1000 and then PMVE/MA–PEG 200 hydrogels. Similarly, this could be the explanation for the greater percentage swelling observed for PMVE/MA–PEG hydrogels composed of a 2:1 ratio, in comparison to those of a 1:1 ratio.

The structure and properties of the polymeric network of hydrogels are important in the evaluation of potential as a drug delivery device. The most important parameters are polymer volume fraction, $\phi$, average molecular weight between two consective crosslinks, $M_c$, and the crosslink density, $V_e$, in swollen state.

The volume fraction of polymer, $\phi$, 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 (Lin and Metters, 2006). In this study, $\phi$ decreased with an increase in the chain length of PEG, which, in turn, indicates an increase in swollen polymer volume. The distance between two crosslinking points increases with increasing PEG chain length and the free volume also increases. Hence, the volume of fraction of polymer decreases.

In PEG–crosslinked PMVE/MA systems, the addition of high MW PEG resulted in higher $M_c$ values, which was due to lower crosslink densities, $V_e$, per unit volume of hydrogel in the swollen state (Table 4). By decreasing PEG MW, the number of free hydroxyl groups increases. Accordingly, this results in increased number of crosslinks with PMVE/MA (Thakur et al., 2009). Thus, the crosslink densities of hydrogels increased with a decrease in PEG MW. As such, decreasing PEG MW results in a more rigid network structure, due to the increased number of crosslinks per unit mass. Comparatively, such systems accommodate less solvent molecules. As a result, the PEG 200 showed higher crosslink densities and lower average molecular weight between crosslinks.

The polymer–water interaction parameter ($\chi$) increased with an increase in the crosslink density (Table 4). In polymer–water systems, the higher the value of $\chi$, the weaker is the interaction between polymer and water.

For the first time, the ionic conductivity of crosslinked PMVE/MA–PEG hydrogels has been shown to be a function of the concentration and ratio of PMVE/MA to crosslinking agent PEG, the molecular weight of PEG (Figs. 3 and 4). In agreement with previously published work on the conductivity of various polymer formulations, the ionic conductivity exhibited a qualitatively similar relationship to the percentage swelling data, as a function of PEG MW and PMVE/MA concentration and ratio. In addition to the effect of swelling capability on the conductivity of a hydrogel it has been shown that the presence, concentration and ratio of a crosslinking agent to the polymer fraction are all important parameters that should be considered in the formulation of a conducting hydrogel. (Aouada et al., 2006) investigated the electrical and mechanical properties of a range of crosslinked hydrogels based on poly(3,4-ethylene dioxythiophene)/poly(styrenesulfonate) (PEDOT/PSS) entangled in a polyacrylamide (PAAm) network. They found that conductivity of the PEDOT/PSS–PAAm hydrogel decreased with increasing apparent crosslinking density. Thakur et al., 2009 have demonstrated the significance of changing the MW of PEG on the properties of PMVE/MA hydrogels. They report that higher MW PEGs, having a greater chain length, produce hydrogel networks with lower crosslink density, and higher average MW between two consective crosslinks, thus increasing the porosity of the hydrogel. As such, the reason that hydrogels containing PEG 10,000 and ratio of 2:1 showed the greatest ionic conductivity could be that these hydrogels possessed a lower apparent crosslinking density, and as such could facilitate the passage of charge carriers more efficiently.

To investigate the role of hydrogel crosslink density and ionic conductivity on the permeation of solutes across the hydrogel following the application of an electrical current, permeation studies were carried out across hydrogels crosslinked with PEG 10,000 (F7, representing a hydrogel of low crosslink density and high conductivity) and PEG 200 (F11, representing a hydrogel of high crosslink density and low conductivity). Three model compounds were assessed for their permeation behaviour across the hydrogels, with theophylline representing a neutral molecule, methylene blue representing a positively charged molecule, and fluorescein sodium representing a negatively charged molecule. It was found that the MW of the solute had an effect on its permeation profile across both hydrogel membranes, with methylene blue (MW 380) and fluorescein sodium (MW 380) permeating to a lesser extent in comparison to theophylline (MW 180). This is in agreement with previously reported findings (Thakur et al., 2010). Interestingly, it was found that solute charge had no effect on the rate of permeation across both hydrogel systems. It is known that if the gel and the drug are ionised, interactions may occur that may hinder or assist in the diffusional process (Peppas and Wright, 1998). For example, if the solute and hydrogel possess similar charges then the hydrogel may repel the charge of drug, such that it may not hinder, but in some cases assists transport (Peppas and Wright, 1998). However, if the charges are opposite, interactions may occur that can hinder solute transport (Peppas and Wright, 1998). Given the fact that in this study, a positively charged solute (methylene blue) and a negatively charged solute (fluorescein sodium) permeated to the same extent across the hydrogel system suggests that permeation was not dominated by any potential solute–polymer interactions, but was controlled by solute size relative to the pore size of the hydrogel (Peppas and Wright, 1998; Thakur et al., 2009). Furthermore, the crosslink density of the hydrogel membrane was found to play a major role in determining the extent of solute permeation, with an approximate 10-fold reduction in the permeation of all three solutes noted across a hydrogel crosslinked with PEG 200, in comparison to a hydrogel crosslinked with PEG 10,000. This is attributed to the high %EWC, high MW between crosslinks and low crosslink density of the hydrogel crosslinked with PEG 10,000, resulting in a more porous network structure to readily enable solute diffusion (Thakur et al., 2010). Interestingly, it was found that the ionic conductivity of the hydrogel affected the ability of solutes to permeate through the membrane following the application of an electrical current. It can be seen from Table 5 that the enhancement ratio for solute permeation across the membranes was significantly greater when a current was applied across hydrogels crosslinked with PEG 10,000 in comparison to those crosslinked with PEG 200. This can be attributed to the ability of these hydrogels to allow the passage of charge carriers, with this study showing that an increase in the porous structure of a hydrogel (reflected by high %EWC and low crosslink density) is associated with an increase in the conductivity of the formulation (Figs. 3 and 4). The finding that the conductivity of the formulation can affect the electro-stimulated movement of solutes is in agreement with previously reported findings whereby it has been shown that the iontophoretic delivery of a drug may be hindered by the presence of high concentrations (>15%, v/v) of cosolvents (such as propylene glycol) in the formulation, a fact that has been attributed to a decrease in the conductivity of the drug solution (Jadoul et al., 1997). Similarly, regarding the iontophoretic delivery of sodium nonivamide acetate from a range of polymer formulations, it was found that the delivery decreased with the reduced conductivity of the formulation at high viscosity (Fang et al., 1998). Im et al. (2010) have also shown that the release profile of a drug loaded polyethylene oxide/pentaerythritol formulation following application of an electrical stimulus may be increased by enhancement of the formulation conductivity through the addition of multi-walled carbon nanotubes.

## 5. Conclusion

The present study illustrates the highly significant role that the crosslink density of a hydrogel plays in determining the swelling behaviour, network parameters, electrically responsive characteristics and solute permeation of hydrogels composed of PMVE/MA and PEG. When crosslinked with a higher MW PEG, PMVE/MA–PEG hydrogels produce networks with lower crosslink density, thus exhibiting higher swelling rates and greater ionic conductivity in comparison to PMVE/MA crosslinked with low MW PEGs. The more open network structure of low crosslink density hydrogels enables solute permeation to occur more readily, and the greater ionic conductivity of these formulations allows a greater solute permeation enhancement to occur when subjected to an external electric field.

From the results in this study, it is clear that the ability of solutes to permeate across the hydrogels described within can be easily adjusted through careful selection of hydrogel composition. Moreover, solute permeation may be readily enhanced through the application of an electric stimulus across these hydrogels. Conse-

quently, such hydrogels may have potential use as components of electrically controlled drug delivery systems. This could be in the form of an implantable hydrogel device where the rate and extent of drug release is controlled through an external electrical stimulus, or as an electroconductive hydrogel base for use in iontophoretic transdermal drug delivery systems.

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