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NMR and Texture Analyses in Relation to Swelling Kinetics of 2-Hydroxyethyl Methacrylate/*N*-Vinylpyrrolidinone Hydrogels

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Summary: This study investigates the relationship between swelling kinetics and the relative stress relaxation (SR) values from texture analysis, as well as the relaxation times from proton NMR analysis of photopolymerized 2-hydroxyethyl methacrylate (HEMA)/N-vinyl pyrrolidinone (NVP) hydrogels with varying HEMA and NVP contents. Swelling tests in Milli-Q water at 37 °C showed that hydrogels of higher NVP content displayed non-Fickian diffusion kinetics. Texture analysis indicated the existence of a trend between SR values and diffusion kinetics with the hydrogels that displayed non-Fickian diffusion having significantly lower SR values. Proton NMR analysis showed that the hydrogel with higher NVP content (non-Fickian diffusion kinetics) displayed substantially longer relaxation times, which indicated slower exchange of water molecules between different sites within the meshes of the polymer matrix, attributable probably to hydrogen bonding and hydrophilic attraction between polymer and the water molecules. A relationship appeared to exist for the hydrogels understudy with hydrogels exhibiting non-Fickian diffusion kinetics displaying lower SR values and longer relaxation times.

Keywords: correlation; HEMA-*co*-NVP hydrogels; proton NMR analysis; swelling kinetics; texture analysis

Introduction

Poly(2-hydroxyethyl methacrylate) (PHEMA) besides being a proven versatile homopolymeric biomaterial,[1] its monomer, HEMA could be combined with hydrophilic co-monomers such as NVP to produce copolymers with enhanced structural properties. Polymers of HEMA and NVP have been investigated in recent years as potential hydrogel materials for biomedical applications such as sustained drug delivery systems and contact lenses.[2–7] The attractive bioapplications of HEMA-*co*-NVP hydrogels is attributed to their remarkable water absorption ability and durability in harsh environments.[4,6] The water absorption ability of a polymer is dependent on the nature and the composition of the monomers in the polymer[6] as well as the inclusion of additives such as crosslinking agents.[3,4]

The diffused water in hydrogel is evidenced to vary in molecular form. Khare and Peppas[8] suggest the existence of water molecules in the polymer in three states, bound water (associated with the polymer chains by means of hydrogen bonding), interfacial water (hydrophobic interactions between the functional groups on the polymer chain) and bulk water (water not attached to the polymer matrix).

Researchers have commonly resorted to Nuclear Magnetic Resonance (NMR) experiments to investigate the water sorption, the diffusion coefficient and the state of water in the hydrogels.[9,10] The spin-lattice relaxation time (T_1) and transverse relaxation (T_2) obtained from NMR

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experiments have been shown to indicate the relative mobility of water in the polymer network. The stress relaxation in polymers which could be termed as the viscoelasticity of the polymer is another interesting feature for investigation. Hong et al.[11] from their studies on the hydrated copolymers of HEMA and NVP reported the dependence of viscoelasticity on the monomer compositions.

In the present study, HEMA and NVP in a range of varied compositions were photopolymerized in the presence of a photoinitiator, Irgacure 819 in the absence of any crosslinking agent. The hydrogels formed were evaluated for their equilibrium swelling ability at 310 K. Texture analysis experiments were conducted on the hydrogels to investigate their relative stress relaxation phenomena after an applied stress, and proton NMR experiments were performed to measure the relaxation times, T_1 and T_2 in the fully hydrated hydrogel samples. The objective of this study was to evaluate the correlationship between swelling kinetics, proton NMR, and relative stress relaxation values of these hydrogels.

Experimental Part

Materials

HEMA and NVP were purchased from Sigma-Aldrich. NVP was purified by vacuum distillation and HEMA, was purified by passing through a pre-packed column supplied by Sigma-Aldrich to remove the stabilizer, hydroquinone. A sample of Irgacure 819 was from Ciba Specialty Chemicals.

Methods

Hydrogel Preparation

Hydrogels were formed from NVP:HEMA (%w/w) formulated in the following ratios: 00:100 (Gel A), 20:80 (Gel B), 50:50 (Gel C), 80:20 (Gel D) and 100:00 (Gel E) in the presence of 0.1 %w/w Irgacure 819. These hydrogels were prepared using the same procedure as previously described.[12] Essentially, the reacting solutions were each placed in a non-pigmented polypropylene mould and subjected to UV exposure with a 90 W medium pressure mercury lamp model 93110E_2 mounted in a vertical configuration. All experiments were performed at room temperature at a distance of 30 cm from the radiation source with a peak irradiance of 0.80 mW/cm^2 as measured by a 1L390A curing radiometer from International Light. The polymeric gels formed were continually washed with fresh de-ionised water until the concentration of the leached unreacted monomers in the wash solution was <1 ppm, estimated using the spectrophotometric technique. The samples were then dried in a vacuum oven.

Swelling Test

Procedures and techniques were similar to those outlined in a previous publication.[12] The equilibrium water content (EWC) values were calculated according to Equation (1).

$$\mathrm{EWC}\,(\%) = \frac{W_t - W_o}{W_t} \times 100 \qquad (1)$$

W_o = mass of dry polymer and W_t = swollen polymer mass.

Texture Analysis

A TA.XT2 texture analyser from Stable Micro Systems was used to evaluate the stiffness and the viscoelasticity of the swollen hydrogel networks. A 1/2″ ebonite cylinder was used as the probe. The hydrated samples were in a cylindrical shape. The probe was set to approach the sample at 1.0 mm s^{-1} with a trigger force of 0.01 N. Once the probe was in contact with the sample, the test duration was 30 seconds with increase in compression distance from 0–1.0 mm at a rate of 0.1000 ± 0.0001 mm s^{-1} in the first 10 seconds and maintained compression distance of 1.0 mm in the later 20 seconds. The samples were subjected to a load for a brief period and allowed to relax back to their original physical state. A stress-strain graph was obtained for each sample in order to compute the Young's modulus (E). The values of E can be calculated according to Equation 2, where stress is the measured compression force F (N) divided by the contact surface area (m^2) of sample and the strain is the ratio of the deformed length and the undeformed length of the sample.

$$Young's\ Modulus\,(MPa) = \frac{Stress}{Strain} \qquad (2)$$

The relative stress relaxation (SR) values were calculated according to Equation 3 where F_1 is the measured compression force at $t = 10$ seconds and F_2 is the measured relaxation force exerted by the sample post the stress period.

$$Relative\ SR = \frac{F1 - F2}{F1} \qquad (3)$$

Proton NMR Relaxation (T_1 and T_2 Measurements)

Proton NMR T_1 and T_2 measurements were conducted on Varian unity-plus 300 MHz NMR spectrometer equipped with micro-imaging accessory at ambient temperature. A micro-imaging probe was employed for these measurements. The swollen hydrogel samples were inserted into the micro-imaging probe with 30 mm insert. T_1 measurements were performed using inversion recovery technique while T_2 measurements were performed employing spin-echo technique with CPMG pulse sequence.

Results and Discussion

Swelling Evaluation-Effect of the Monomeric Composition on Swelling

Poly(NVP) (Gel E) disintegrated upon a short exposure to Milli-Q water attributable to insufficient crosslinkage in the polymer network, and was thus not used for further test. Graphical representations of the swelling behaviour observed in the NVP-HEMA hydrogels, Gels A -D in Milli-Q water are illustrated in Figure 1.

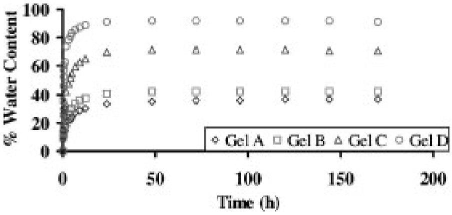

Figure 1.
Plot of % water content in Gels A-D at 37 °C in Milli-Q water as a function of time in hours.

The swelling data are expressed as percentage water content at respective time intervals in hours. Data in Figure 1 show an increase in water uptake from Gel A (100 HEMA) to Gel B, (20 NVP-80 HEMA), then Gel C (50 NVP-50 HEMA) and then Gel D (80 NVP-20 HEMA) yielded equilibrium water content (EWC) values of 36.6%, 41.9%, 70.9% and 91.6% respectively. The kinetics of diffusion can generally be described by Fickian and non-Fickian diffusion mechanisms in swellable polymers. Alfrey et al.[13] proposed that Fickian diffusion or Case I diffusion occurs when the rate of diffusion is significantly slower than the rate of relaxation of the polymer chains, whereas Case II diffusion occurs when the rate of penetrant diffusion is greater than the rate of relaxation of the polymer chains. Case III diffusion (anomalous diffusion) occurs in the transition region between Case I and Case II diffusions when the rates of penetrant diffusion and polymer relaxation are comparable. The swelling action in polymers is generally time dependent. Diffusion kinetics can be determined according to a power law expression as shown in Equation 4.

$$M_t/M_{infinity} = Kt^n \qquad (4)$$

The relationship, $M_t/M_{infinity} = Kt^n$ describes the time dependent swelling of a polymer, where M_t is the mass of water incorporated at time, t, and $M_{infinity}$ is the mass of water incorporated at infinite time, K is a constant specific to the polymer/solvent system and the parameter n defines the diffusion mechanism in operation in the polymer matrix. The diffusion mechanisms in polymers can be observed by plotting the fractional swelling data as a function of the square root of time. A LOG plot derived from this information gives quantitative information on the diffusion kinetics. A n value of 0.5 is indicative of Fickian diffusion while a value of n higher than 0.5 represents non-Fickian diffusion behaviour. This could be further described as anomalous (Case III) when the value of n lies between 0.5 and 1.0, and Case II when $n = 1$. Peppas and Brannon-Peppas[14] reported an extension of this equation and proposed that for a cylindrical geometry, $n \sim 0.45$ for Fickian diffusion, and ~ 0.89 for Case II diffusion.

Using the swelling test data of these hydrogel samples, LOG of $M_t/M_{infinity}$ versus LOG of time were plotted for Gels A - D as shown in Figure 2.

The n values of these hydrogels calculated using Equation 2 are summarised in Table 1. n values of 0.39 ± 0.05 for Gel A, 0.47 ± 0.02 for Gel B and 0.53 ± 0.01 for Gel C indicated that the diffusion of water into these hydrogels in the early stages adhered to the Fickian model of diffusion into a cylinder, thus suggesting that the hydrogels with higher HEMA content or equal %w/w of HEMA and NVP, the rate of water diffusion was significantly slower than the rate of relaxation of the polymer chains.

As depicted in Figure 1, Gel D (80 NVP-20 HEMA) showed an exponential increase in water uptake in the first hour followed by a gradual decrease in the swelling around 48 hours yielding an EWC value of 91.6%. The diffusion kinetics in this hydrogel system was a characteristic of a high order non-Fickian diffusion in the initial stages followed by Case II diffusion in the later stages. The non-Fickian diffusion behaviour was confirmed by a LOG plot (Figure 2) which yielded an average n value of 0.62 ± 0.01. The high water content of the hydrogels containing higher NVP content is due to hydrophilicity/polarity nature of NVP.

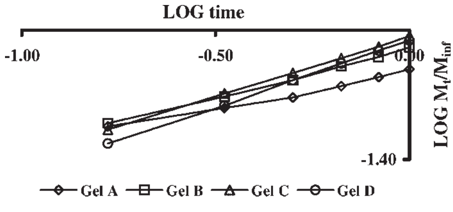

Figure 2.
Plot of the LOG of fractional swelling as a function of the LOG of time, in the initial stages of the swelling in Gels A, B, C and D at 37 °C in Milli-Q water.

Table 1.
Characteristic exponential n values for Gels A–D diffusion in Milli-Q water.

Hydrogels	n values
Gel A	0.39 ± 0.05
Gel B	0.47 ± 0.02
Gel C	0.53 ± 0.01
Gel D	0.62 ± 0.01

Korsmeyer and Peppas[5] have reported non-Fickian swelling kinetics in copolymers of HEMA and NVP whilst Bhardwaj et al.[15] reported Fickian diffusion kinetics in copolymers of HEMA and NVP. These researchers have made use of copolymers of varying ratios of HEMA and NVP. Franson and Peppas[16] have suggested the dependence of diffusion kinetics on the copolymer composition of HEMA and NVP. Thus the present results obtained for diffusion kinetics of the hydrogels under study ranging from Fickian to non-Fickian with increasing NVP content is in agreement with these researchers.

Proton NMR Relaxation (T_1 and T_2) Measurements

The T_1 and T_2 relaxation measurements were performed on fully hydrated hydrogel samples. These hydrogel samples were chosen due to their significant difference in HEMA and NVP contents, with Gels A and D having much higher HEMA or NVP content respectively and Gel C had similar content of HEMA and NVP by weight.

Relaxation times of Gel A (neat PHEMA), Gel C (50 NVP-50 HEMA) and Gel D (80 NVP-20 HEMA) show that Gel A displayed significantly shorter relaxation times ($T_1 = 0.45830$ s, $T_2 = 0.00321$ s) as compared to Gel C ($T_1 = 0.66080$ s, $T_2 = 0.03678$ s) and Gel D ($T_1 = 1.86500$ s, $T_2 = 1.01300$ s). These data give clear indication that the copolymers of HEMA and NVP displayed longer relaxation times with longer T_1 and T_2 values with increasing NVP content in the copolymer. In addition, these experimental data also suggested that the T_2 values were more sensitive to the variation in the polymer composition and their relative water content than the T_1 values. Hence, T_2 values will be used for comparative purposes in the discussion. Relaxation times reflect the dynamics of water molecules in the polymer matrix. A short relaxation time indicates high exchange of water molecules in the polymer matrix, thus indicating that the water present is interfacial water, which is repelled by the relative hydrophobicity of the polymer and is effectively mobile.[17] Hence, in this study, relatively short T_2 value obtained in the PHEMA sample could be attributable to an increase in exchange of water molecules within the meshes of the sample due to minimum hydrogen bonding or hydrophilic attraction between the polymer and the water molecules.

The HEMA-*co*-NVP copolymers exhibited relatively longer T_2 times compared to PHEMA with increase in T_2 value observed with increase in NVP content in the hydrogel. This is indicative of the fact that these copolymers have increased in hydrophilicity in comparison to the neat PHEMA, attributable to the comparatively higher hydrophilic nature of NVP. This study suggests that the proportion of bound water, which is associated with hydrogen bondings between the polymer chains and water molecules is significantly higher in HEMA-*co*-NVP hydrogels in comparison to the PHEMA hydrogel. The increase in bound water would result in lower exchange of water molecules within the meshes of the polymer matrix. This finding is in agreement with Quinn and co-workers[18] who utilized the NMR technique to study relaxation times of hydrated PHEMA and poly(NVP/methyl methacrylate) of different water contents at various temperatures, as well as the study by Barbucci and co-workers[17] who measured the relaxation times of hyaluron-based native hydrogels and the sulfated hydrogels (more hydrophobic). They reported that the hydrogels with enhanced hydrophilic characteristics displayed longer T_2 values.

The T_1 and T_2 relaxation data also correlate to the diffusion kinetics of the hydrogels under-study. Shorter relaxation times are indicative of Fickian diffusion kinetics while longer relaxation times are indicative of non-Fickian diffusion kinetics. Barbieri *et a* [19], Ghi and co-workers[9] in their study on the diffusion kinetics of HEMA based hydrogels have reported similar results. They also suggest a direct relevance of relaxation times to the swelling kinetics in polymers.

Texture Analysis

Stress relaxation (SR) evaluation was conducted on the hydrated Gels A–D hydrogel samples. The stress relaxation phenomenon is related to the viscoelasticity of the polymer. The Young's modulus (E) values of the samples were computed from the linear portion of the stress-strain curves. The relative E and SR and values were calculated using Equations 2 and 3 respectively. The SR and E values are summarised in Table 2.

Texture analysis experiments revealed that the hydrogels under-study were viscoelastic. However, the hydrogels displayed varying degrees of viscoelasticity. The SR values of the hydrogels decreased with increasing NVP content of the hydrogels. PHEMA showed a SR value of 0.1302. In comparison, hydrogel D which contained higher NVP content displayed a significantly lower SR value of 0.0347. The viscoelasticity of a polymer can be described in terms of local frictional forces encountered by a short segment of a moving chain, together with additional entanglement coupling to other chains. The SR data suggested that the stress relaxation process in high HEMA content

Table 2.
Relative SR and *E* values of the hydrogel samples.

Hydrogel samples	Relative SR values	E (MPa)
Gel A	0.1302 ± 0.0291	0.3572 ± 0.0218
Gel B	0.1231 ± 0.0182	0.0837 ± 0.0030
Gel C	0.1020 ± 0.0070	0.0468 ± 0.0071
Gel D	0.0347 ± 0.0109	0.0135 ± 0.0003

hydrogels (Gels A, B) was relatively slower in comparison to high NVP content hydrogels (Gel D). The longer stress relaxation time in high HEMA content hydrogels could be attributed to the compact nature of the networks. The compactness of the networks gives rise to increased local frictional force restricting the conformational rearrangement and separation of the chains.

Hong et al.,[11] Chirila and Hong[20] reported stress relaxation behaviour in HEMA and NVP based hydrogels. They observed a decrease in the SR value with increasing NVP content in the hydrogels. The SR data from the present study is in agreement these researchers. The present study suggests that high HEMA content hydrogel networks (Gels A, B) are more elastic whilst the hydrogels (Gel D) with high NVP content hydrogel networks have characteristics similar to that of a viscous fluid.

PHEMA displayed the highest Young's modulus value of 0.3572 MPa followed by hydrogels B (0.0837 MPa), C (0.0468 MPa) and D (0.0135 MPa) indicating increasing stiffness with increasing HEMA content of the copolymer. Furthermore, it is indicative from this study that there exists a trend between Fickian and non-Fickian diffusion to the SR values. Hydrogels, which displayed non-Fickian diffusion kinetics, were observed to behave more like viscous fluid whilst the opposite was observed for hydrogels displaying Fickian diffusion kinetics.

Conclusions

Experimental swelling data revealed that the diffusion kinetics in HEMA-*co*-NVP hydrogels range from Fickian for hydrogels with higher HEMA content to high order non-Fickian (anomalous) diffusion behaviour for hydrogels with higher NVP content in the earlier stages of the experiment. The proton NMR relaxation times, T_1 and T_2 were found to correlate with the diffusion kinetics in polymers. Longer relaxation times were observed in hydrogels that displayed non-Fickian diffusion behaviour while hydrogels, which adhered to Fickian diffusion kinetics displayed shorter relaxation times. Longer relaxations times resulted from a larger proportion of bound water was due to enhanced hydrophilic nature of the hydrogels that contained NVP. Hydrophobic interactions between the polymer, PHEMA and water molecules resulted in interfacial water, which was increasingly mobile (increase in exchange of water molecules between different sites within the meshes of the hydrogel) leading to shorter relaxation times. The texture analysis indicated that hydrogels understudy were viscoelastic with longer stress relaxation time in high HEMA content hydrogels. The Young's modulus values indicated that hydrogels with high HEMA content were more rigid.

The present study suggests a possible trend between the SR data, proton NMR relaxation times and the diffusion kinetics with the hydrogels exhibiting non-Fickian diffusion kinetics displaying lower SR values and longer relaxation times.

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