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^{1}H NMR T_2 relaxation in contact lens hydrogels as a probe of water mobility

P. McConville, J.M. Pope*

Centre for Medical and Health Physics, School of Physical Sciences, Queensland University of Technology, Gardens Point Campus, 2 George Street, G.P.O. Box 2434, Brisbane 4001, Australia

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Abstract

NMR proton T_2 relaxation time measurements have been performed as a function of temperature for a set of nine commercially available contact lens hydrogels of varying composition and equilibrium water content (EWC). The study was undertaken to quantify the behaviour of the water in each material in terms of its average mobility and binding. The resulting complex T_2 behaviour was analysed using a model that incorporates chemical exchange between water protons and exchangeable polymer protons. Using this analysis it is shown that the water in these hydrogels is perturbed only slightly with respect to bulk water by the polymer. Analysis of the fit parameters suggests that the average water mobility correlates approximately with overall water content, approaching that of bulk water as the EWC is increased. No significant dependence of this mobility on polymer composition was found for the range of materials studied.

Keywords: Water mobility; Contact lens; Hydrogel

1. Introduction

Over the last half century, much interest has been shown in the chemical and physical properties of hydrogels. They are commonly used for the manufacture of soft, or disposable contact lenses, but are also used in other biomedical applications [1] such as artificial implants, and as matrix materials for controlled drug release. Many of the properties of hydrogels are governed by the interaction between the polymer and the water that it absorbs or binds. A range of techniques have been used in an attempt to better understand these hydration properties, including differential scanning calorimetry [2,3], differential thermal analysis [3], sorption/desorption experiments [4,5] and nuclear magnetic resonance (NMR) [6,7]. However, in spite of extensive research, the state of water in hydrogels remains poorly understood.

A significant disadvantage of hydrogels, particularly as contact lens materials, is their tendency to dehydrate when on the eye. It has been shown clinically, (although there are some conflicting results), that this on-eye dehydration tends to be more severe for higher equilibrium water content (EWC) materials [8–10]. Consequently a better understanding of the state of binding and mobility of water in hydrogels is important for optimisation of material properties in this and other applications.

Proton NMR has the potential to characterise water binding and mobility in a quantifiable manner, and has been commonly used in studies of the water–polymer interaction [11,12]. In particular, it has been suggested that the proton NMR spin–lattice and spin–spin relaxation times, T_1 and T_2, may be very sensitive to water binding and mobility in contact lens hydrogels [6]. Recently, Barbieri and co-workers [7] performed measurements of T_2 as a function of temperature in contact lens hydrogels, but the study was limited to three materials of similar composition and the measurements were carried out over a limited temperature range (5–50°C). These authors invoked an equation involving proton exchange between water and hydroxyl groups on the polymer to interpret the data. However, they were forced to make several somewhat arbitrary assumptions in their analysis (as will be detailed in the discussion), leaving some uncertainty as to the validity of their interpretation of the results. Their study was also limited to materials that contained exchangeable (hydroxyl) polymer protons.

The current study was undertaken to examine the temperature dependence of T_2 for a wider range of commercial contact lens hydrogels of varying composition and EWC, including materials that do not contain exchangeable polymer protons. It was anticipated that this would lead to a

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* Corresponding author. Tel.: +61-7-3864-2325; fax: +61-7-3864-1804.
E-mail address: j.pope@qut.edu.au (J.M. Pope).

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Table 1
Composition of hydrogels used in the study

Hydrogel name	Composition	Measured EWC at 80°C (%wt./wt.)
IGEL 58	NVP/MMA	37.8
IGEL 67	NVP/MMA	49.7
IGEL 77	NVP/MMA	63.7
Benz 38	HEMA	34.7
Benz 45	HEMA/NVP	37.2
Benz 55	HEMA/NVP	42.9
Benz G-3X	HEMA/GMA	43.9
Benz G-5X	HEMA/GMA	56.1
Benz G-7X	HEMA/GMA	74.5

more complete understanding of the molecular binding and mobility of water in hydrogel contact lenses, and provide some insights into how this might relate to dehydration on the eye.

2. Experimental

2.1. Sample protocol

A set of commercially available contact lens hydrogels in the Benz and IGEL ranges were supplied by Benz Research and Development Corporation, Sarasota, FL, USA, and Capricornia Contact Lens, Brisbane, Australia, respectively. The materials used, together with their composition and EWCs are shown in Table 1.

All hydrogel samples were stored in sealed vials and equilibrated in phosphate buffered saline (PBS) in an oven at 80°C[1]. PBS is a standard diluent used to hydrate commercial contact lenses and has constituents that mimic the pH and osmolality of the tears. Before measurement, each sample was removed from its vial, blotted thoroughly and quickly with lint free tissue, wrapped in clear polyethylene film and placed in a standard NMR tube. The film prevented excessive dehydration during the measurements. A teflon vortex plug was used to restrict the air around the sample, and the tube sealed. It was then placed on a balance (accurate to ±0.05 mg) and weighed.

The NMR tube containing the sample was then placed in the magnet and equilibrated for at least 15 min at the required temperature. Following the NMR measurements, the sample was removed, re-weighed and the water loss (if any) calculated. In all cases this water loss was less than 5%. The hydrogel was then dried at least overnight (for the larger samples the period was several days) at 80°C in a drying oven, re-weighed and the water content determined.

2.2. NMR measurements

Experiments were carried out using a Bruker MSL200 NMR spectrometer operating at 200 MHz for protons, with variable temperature control (accurate to ±0.1°C). At each temperature the RF coil was tuned, the static magnetic field shimmed and pulse lengths measured. Following this, an FID was acquired, the spectrum examined and water peak linewidth measured.

T_2 measurements were performed using a standard Carr–Purcell/Meiboom–Gill (CPMG) pulse sequence for temperatures from 80°C down to −30°C, in 10°C intervals. Initial experiments showed that the 180° pulse spacing did not affect the measured T_2 for the hydrogels used. This spacing was then fixed at 2.4 ms, (the minimum spacing allowed by our hardware), for all T_2 measurements. For each sample, a repeat T_2 measurement was made 15 min after the original measurement to check for reproducibility, and to ensure that the temperature was equilibrated. The number of points on each T_2 decay varied from eight up to several thousand, such that a baseline was achieved by the end of the measured decay. The data set was then baseline corrected and fitted using a Levenberg–Marquardt non-linear least squares fitting routine to a single exponential decay with two free parameters (T_2 and I_0, the signal at zero time).

At temperatures above about 50°C the polyethylene film in which the sample was wrapped was shown to contribute a short T_2 component to the start of the measured decay. In such cases, the initial data on the decay was discarded point by point until the fitted T_2 approached an asymptotic value (and the decay was well fitted by a single component exponential).

3. Results

3.1. Phosphate buffered saline

To establish a 'baseline' for the behaviour of T_2 for water in the hydrogels, T_2 was initially measured as a function of temperature for PBS, the medium in which the hydrogels were hydrated. These data are shown in Fig. 1, plotted in Arrhenius form as T_2 (on a logarithmic scale) against reciprocal temperature ($1/T$). We can extract information about the molecular motion(s) responsible for modulating the dipolar interaction (and hence causing T_2 relaxation) by using a simple Bloembergen Purcell and Pound (BPP) [13] description for T_2. The BPP equation describes the dependence of T_2 on the correlation time (τ_c) for the motion of water in the sample:

$$\frac{1}{T_2} = \frac{C}{2}\left[3\tau_c + \frac{5\tau_c}{1+\omega_0^2\tau_c^2} + \frac{2\tau_c}{1+4\omega_0^2\tau_c^2}\right] \tag{1}$$

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[1] Since increasing temperature will tend to decrease the EWC of a hydrogel, the samples (in PBS) were pre-equilibrated in an oven at the highest temperature of the range to be studied, and transferred quickly to the NMR probe, which had also been pre-equilibrated at this temperature. The measurements of the temperature dependence of T_2 were then made as a function of decreasing temperature, in order to keep the water content constant over the entire temperature range.

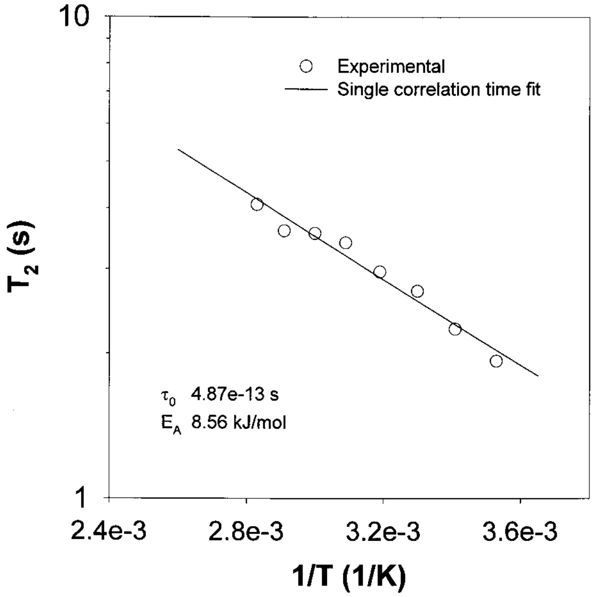

Fig. 1. Arrhenius plot of T_2 against $1/T$ for PBS.

where ω_0 is the Larmor frequency and the constant C is a measure of the strength of the magnetic dipolar interactions that couple the water protons. For water, C can be calculated to be $5.33 \times 10^9\ \mathrm{s}^{-20}$ [14]. This value was used in all subsequent calculations. We further assume that τ_c is thermally activated and described by an Arrhenius activation law of the form:

$$\tau_c = \tau_0\, e^{E_A/kT} \tag{2}$$

where τ_0 is the 'Arrhenius coefficient' (correlation time at infinite temperature) and E_A is the activation energy.

The data were fitted using these equations and this fitted line is also shown in Fig. 1. From the fit, we can extract the activation energy and the 'Arrhenius coefficient' for T_2 relaxation in PBS. Using this description, the activation energy for T_2 relaxation in PBS was calculated to be 8.56 kJ/mol and the 'Arrhenius coefficient' was found to be 4.87×10^{-13} s.

3.2. Hydrogel T_2 measurements

Results for the hydrogel samples are shown in Fig. 2, again plotted in the form of an Arrhenius plot of T_2 against $1/T$. The graphs are divided for greater clarity, but are shown on the same scale in each case. The data shows a monotonic decrease in T_2 with $1/T$ for the IGEL materials, and a more complex behaviour for the Benz materials, with local minima and maxima observed in the temperature range studied. The type of behaviour seen for the Benz materials is consistent with water–polymer proton chemical exchange [7]. In contrast the IGEL materials do not exhibit exchange characteristics, as they do not contain any exchangeable polymer protons. The IGEL materials used in this study are co-polymers of methyl methacrylate (MMA) and N-vinyl pyrrolidone (NVP), neither of which contain exchangeable protons. However, the Benz materials all contain hydroxyethyl mathacrylate (HEMA) which has an exchangeable hydroxyl proton on the side-chain of each monomer. The Benz G materials also contain glycerol methacrylate (GMA) which itself contains two exchangeable hydroxyl protons per monomer.

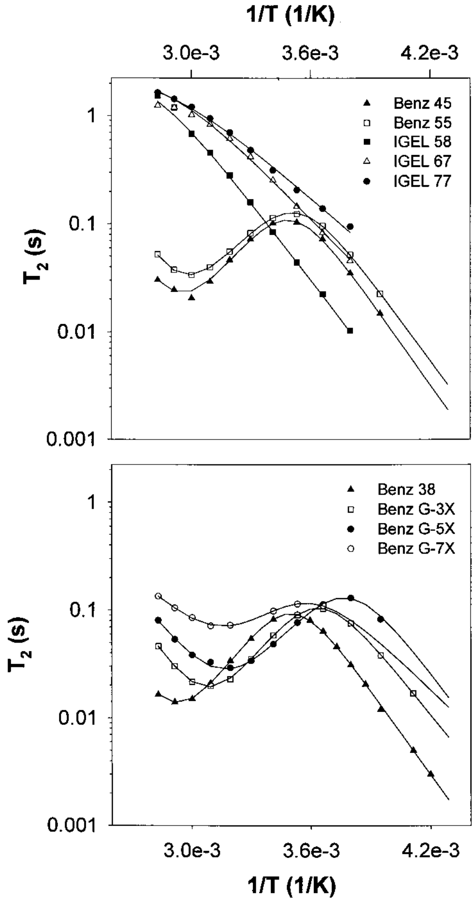

Fig. 2. Arrhenius plot of T_2 against $1/T$ for nine hydrogels. The graph is divided for clarity, with each plot on the same scale. The solid lines are fits to the proton exchange model for T_2 relaxation.

3.3. The T_2 exchange model

The theory of relaxation in systems undergoing exchange was first described by Swift and Connick [15]. The theory developed by these authors incorporated multiple proton species with exchange of magnetisation between them. This theory was applied to water proton relaxation in gel systems by Ablett et al. [16], and Walker et al. [17], who invoked a model with multiple water species, each in a different average state of 'binding' to the gel polymer. Following the work of these authors and that of Barbieri et al. on hydrogels, [7] we have adapted and refined the model to describe T_2 relaxation both in the presence and absence of chemical exchange of protons between water and the polymer (depending on the polymer composition).

Our model assumes a two component system, the components being the gel water protons (labelled 'b') and exchangeable polymer protons with relatively short T_2 (labelled 'c') which form two pools, coupled by chemical exchange. [Note that the label 'a' was reserved in our model for a separate phase of bulk water on the surface of the samples. However, careful blotting of the samples was found to remove this component]. For the hydrogels in this study the c protons were assumed to be exclusively hydroxyl protons. The non-exchangeable polymer protons were not included in the model since they were not 'visible' in our experiments due to their extremely short T_2 (≤ 100 μs). The hydroxyl (or 'c') protons exist on polymer side-chains and are therefore expected to have a restricted mobility and hence a short T_2, compared with the water protons. However, they are 'NMR visible' since they can chemically exchange with neighbouring water protons and will therefore contribute to the measured T_2. If the proportion of c protons is termed p_c, and expressed as a fraction, the basic equation for T_2 in the presence of proton exchange can be written [15]:

$$\frac{1}{T_{2(\mathrm{measured})}} = \frac{1-p_c}{T_{2b}} + \frac{p_c}{T_{2c}+\tau_{ex}} \tag{3}$$

The model used by Ablett et al. [16] and Walker et al. [17] for polysaccharide based gels was similar in form to the model we have used. However, they did not provide clear evidence as to the origin of the shortest T_2 component. While Ablett et al. [16] indicated that circumstantial evidence favoured the assignment of this species to hydroxyl protons, in the later paper by Walker et al. [17] this component was assigned to 'tightly bound' water. The model used by Barbieri and co-workers differs from ours (and that of Ablett et al. [16] and Walker et al.[17]) in that it assumes that all the water in the gel is identical to 'bulk' water. Their model did not allow for a contribution from water that was modified with respect to the behaviour of 'bulk' water by interaction with the polymer, as will be discussed below.

Eq. (3)[2] was used to fit the data shown in Fig. 2, using a Levenberg–Marquardt non-linear least squares routine in Jandel Scientific Sigmaplot. For the IGEL materials, since there are no exchangeable polymer (c species) protons, the measured T_2 is simply equal to the intrinsic T_2 value for the hydrogel water (T_{2b}). T_{2b} and T_{2c} were both initially assumed to be described by a single correlation time according to the BPP model (Eq. (1)), and the correlation times were in turn assumed to obey Arrhenius laws (Eq. (2)).

3.4. The fitting process — basic approach and considerations

Since Eq. (3) incorporates a large number of potentially free parameters, it was very important to attempt to constrain the parameters as much as was realistically possible in a systematic way. Our approach in the modelling of the T_2 hydrogel data was therefore to start with the IGEL materials, which could be described by a simpler equation. Initial fits to the IGEL materials were always performed with all parameters free, but constrained to physical values.

However, once trends in these parameters could be established, they were constrained further. In certain cases (as will be described in detail below), parameters were fixed in the final fitting process. However, this was not done unless:

1. It was shown for the IGEL materials that these parameters converged to values in a relatively small range, when they were not constrained in the fitting process.
2. It was verified through thorough testing of the model that reliable fits were obtained for *all* materials (IGEL and Benz) with these parameters fixed to their respective average values (see below).

Without these constraints, for the more complex Benz materials, it was found that reliable and consistent fits could not be obtained.

3.5. Results of the fitting process

It was found in fitting both the IGEL and Benz data that satisfactory fits could only be obtained by invoking at least *two* correlation times for the water protons (see Eq. (4)). With a single correlation time, the method consistently gave poor fits, which deviated systematically from the experimental data and could not account for the curvature seen for the IGEL materials in the plots of Fig. 2. It was also shown later, in fitting the T_2 data for the *Benz* materials, that elimination of the second water proton correlation time led to fits that consistently undershot the maximum seen in the plots for these materials (see Fig. 2).

One obvious explanation for the need for more than one correlation time is that there exist water protons in different environments that are in fast exchange over the temperature range studied and which can be adequately described by two correlation times each of which characterises the motion of a water molecule in a different environment. These might be ascribed for example, to 'bound' and 'free' water, or 'interfacial' and 'bulk' water and characterised by long and short correlation times, respectively. However, an alternative explanation is that the water protons exhibit anisotropic reorientation that can be described in terms of two distinct motions, each characterised by a single correlation time. In the remainder of this paper, the subscripts 'f' (fast) and 's' (slow) refer to these two types of motion corresponding to short and long correlation times. No clear distinction can be made between the two cases described above, the first in

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[2] An underlying assumption of this equation is that the chemical shift difference between the water protons and the hydroxyl protons can be neglected. Measurements of T_2 as a function of the CPMG 180° pulse spacing, suggested this was the case, since T_2 was shown to be independent of this spacing for the Benz materials. If a significant chemical shift difference exists between the water protons and hydroxyl protons, T_2 should vary with 180° pulse spacing [18].

Table 2
T_2 fit parameters for the IGEL materials

Gel name	τ_{bf0}(s)	E_{bf}(kJ/mol)	τ_{bs0}(s)	E_{bs}(kJ/mol)
IGEL 58	4.87×10^{-13}	8.56	3.5×10^{-16}	46.6
IGEL 67	4.87×10^{-13}	8.56	4.47×10^{-15}	37.6
IGEL 77	4.87×10^{-13}	8.56	3.15×10^{-14}	32.0

which there are assumed to be two distinct water proton pools ('bound' = slow; 'free' = fast) in fast exchange on the NMR time scale and the second invoking a single population of water molecules undergoing anisotropic molecular motion. However, the latter appears less plausible in view of the heterogeneous nature of hydrogels on the molecular level. Eq. (4) describes the contribution of each intrinsic T_2 (T_{2bf} and T_{2bs}) to the overall water T_{2b}:

$$\frac{1}{T_{2b}} = \frac{w_{bf}}{T_{2bf}} + \frac{w_{bs}}{T_{2bs}} \qquad (4)$$

Once again, both T_{2bf} and T_{2bs} were assumed to be described by Eqs. (1) and (2).

It was found in all cases that the fitted T_{2bf} (the T_2 corresponding to the faster motion in the water) tended towards the T_2 measured for PBS (see Fig. 1). There was also no obvious trend as a function of EWC or polymer composition in the parameters that described T_{2bf}. It was further found that T_{2bf} could indeed be adequately represented in the fitting process by the behaviour measured for T_2 in PBS (see Fig. 1). The T_{2bf} parameters were therefore fixed in all cases to these experimental values.

It was also found initially for the IGEL materials, that the weighting factors w_{bs} and w_{bf} were in all cases within 1% of 98% and 2%, respectively. Later fits to the Benz materials followed a similar behaviour, with w_{bf} lying within the range 1–5% for all materials, regardless of EWC. Further, there was no clear trend in the weighting factors, as a function of EWC or polymer composition. These weighting factors were therefore fixed to the average value observed in the initial fits, ($w_{bf} = 2\%$; $w_{bs} = 98\%$). It was also found that fixing the weighting parameters led to consistently reliable fits for the Benz materials, but did not generally have a significant effect on the values of the remaining fitted parameters.

Finally, the proportions of the c species hydroxyl protons were fixed for the Benz materials to values based on the formulae for these materials that can be found in the patent literature [19–22] and set to zero for the IGEL samples. This effectively left six free parameters in the model for the Benz materials and only two for the IGEL samples. Initial estimates of their values were obtained based on a linear analysis of the behaviour in the limit of high and low temperature, and previous results obtained by Walker [23]. This procedure was found to give consistent and reliable fits that converged to realistic values in all cases.

In the above manner, each of the T_2 data sets obtained from samples in which chemical exchange contributed to spin–spin relaxation was fitted to the model. As shown in Fig. 2, the fitted (solid) lines generally agree well with the data. In all cases, residuals were less than 5% (and usually <1%) as well as random about zero. The fit parameters, are listed in Table 2 for the IGEL materials and in Table 3 for the Benz materials.

4. Discussion

4.1. Origin of the double correlation time behaviour for the water protons

It might be expected that, if anisotropic motion were responsible for the double correlation time behaviour of the water molecules in these hydrogels, then this would pertain also to the c species protons, which exist on the polymer side-chains. It might then be expected that such protons would exhibit two distinct motions — a relatively fast rotational motion about the side-chain axis, and a second slower motion of the side-chain axis itself [23]. While anisotropic reorientation might also be expected for water molecules in a layer adjacent to the polymer, it was anticipated that the overall hydrogel water proton relaxation behaviour would show less evidence of anisotropy because of the averaging effects of exchange with 'bulk' water molecules. However, the fit parameters point to the opposite being the case. That is, in order to fit the data well over the entire temperature range, while the T_2 relaxation behaviour of the c species could be described using a single motional correlation time, the b species could only be adequately described in terms of a double correlation time model.

A possible explanation for this result that does not discount anisotropic motion for both b and c species, is that the motion of the hydroxyl protons is so dominated

Table 3
Fit parameters for Benz materials

Gel name	τ_{bs0}(s)	E_{bs}(kJ/mol)	τ_{c0}(s)	E_c(kJ/mol)	τ_{ex0}(s)	E_{ex}(kJ/mol)	p_c
Benz 38	2.56×10^{-17}	50.0	5.65×10^{-16}	55.4	5.60×10^{-11}	47.0	0.1150
Benz G-3X	1.10×10^{-16}	44.5	5.60×10^{-16}	52.5	3.53×10^{-11}	46.0	0.0860
Benz G-5X	7.50×10^{-18}	48.0	7.20×10^{-15}	44.0	3.65×10^{-10}	39.0	0.0680
Benz G-7X	7.35×10^{-15}	35.0	3.95×10^{-13}	32.5	2.45×10^{-9}	35.0	0.0365
Benz 45	1.65×10^{-17}	50.5	4.60×10^{-16}	58.0	7.70×10^{-11}	43.5	0.0300
Benz 55	2.82×10^{-17}	48.5	2.87×10^{-17}	62.0	1.19×10^{-9}	39.0	0.0381

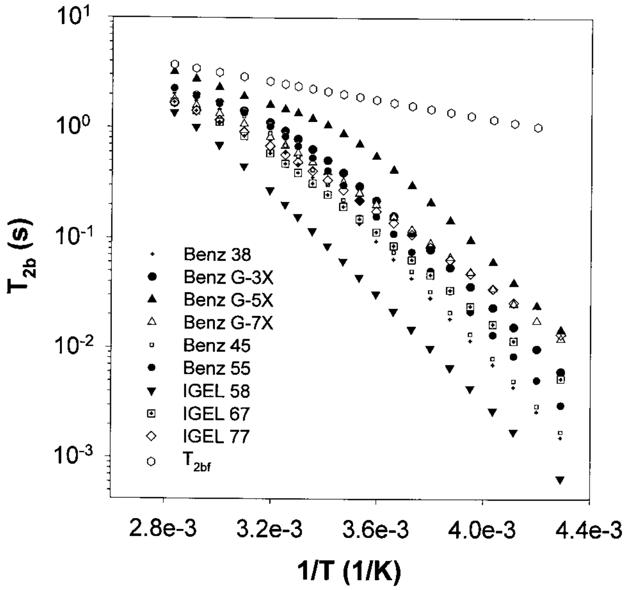

Fig. 3. Plot of T_{2b} against $1/T$ for the hydrogels studied.

by the slower motion of the side-chain itself that the weighting factor for the faster rotational motion (w_{cf}) is very small. Since T_2 relaxation is dominated by slower motions, the fast motion term in Eq. (4) has negligible contribution. The opposite would apply for the b species water protons. Here the weighting factor for the slower motion (w_{bs}) is very small, but because T_2 in general is dominated by slower motions, this motion still significantly contributes to the overall relaxation of the water protons. In this case the faster anisotropic motion term also contributes due to its very large weighting factor (98%).

However, the results can equally well be interpreted in terms of exchange of water molecules between ‘bound’ and ‘free’ environments. In fact this appears to be the more obvious explanation, and is consistent with the interpretation of Barbieri and co-workers [7] who performed similar studies on three of the Benz range of contact lens hydrogels. If the behaviour can be well represented by two distinct water species, the model tells us that they are effectively in rapid exchange with each other over the complete temperature range studied. It is not surprising that the rate of exchange between two such water species would be greater than that between water protons and hydroxyl protons. However, at sufficiently low temperature, even this exchange rate would decrease, until the two water species appear in the decay as separate components. This behaviour was not observed, and there was no appreciable drop in signal, suggesting that low enough temperatures for this to occur were not reached in this study.

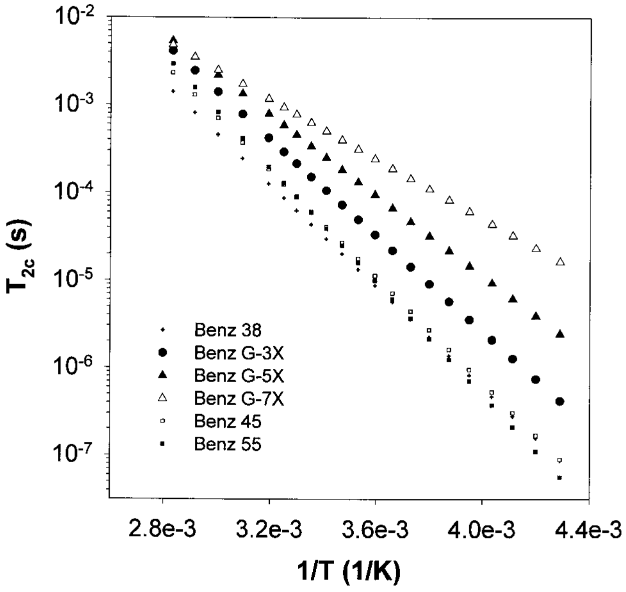

Fig. 4. Plot of T_{2c} against $1/T$ for the Benz hydrogels.

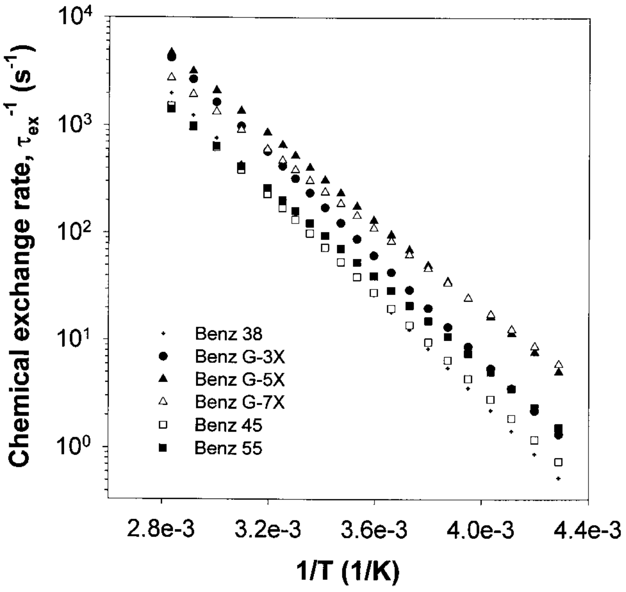

Fig. 5. Plot of τ_{ex} against $1/T$ for the Benz hydrogels.

4.2. Behaviour of the fitted parameters

From the model, the temperature dependence of the parameters describing the intrinsic relaxation of the hydrogel water protons (T_{2b}), that of the hydroxyl protons (T_{2c}) and the chemical exchange between them (τ_{ex}) was examined. Fig. 3 is an Arrhenius plot of T_{2b} for all the hydrogels studied, and Figs. 4 and 5 are Arrhenius plots of T_{2c} and $1/\tau_{ex}$ for the Benz hydrogels. Fig. 3 includes, for comparison, a plot of T_{2bf} also, remembering that this is the T_2 behaviour measured for bulk PBS (fixed in the fitting procedure for all materials).

From Fig. 3 we can firstly appreciate the significant modification that the T_{2bs} term imparts to the total T_{2b}, relative to T_{2bf}, despite the very high weighting factor (fixed at 98% for all the gels studied) of the T_{2bf} term. This is particularly

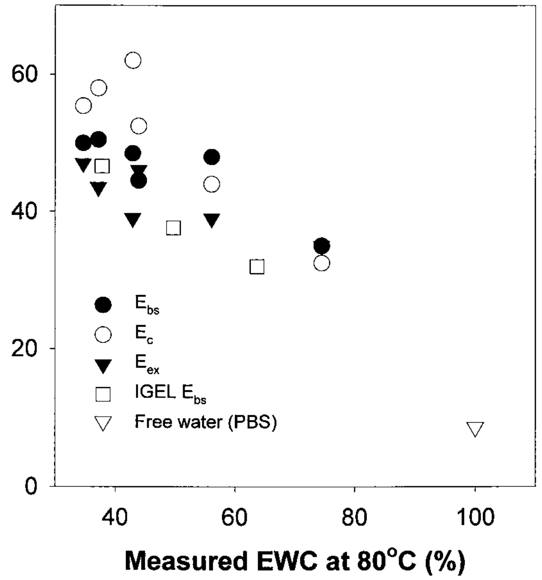

Fig. 6. Activation energies derived from the T_2 relaxation model, plotted as a function of measured EWC for the hydrogels studied. The result for PBS is also shown.

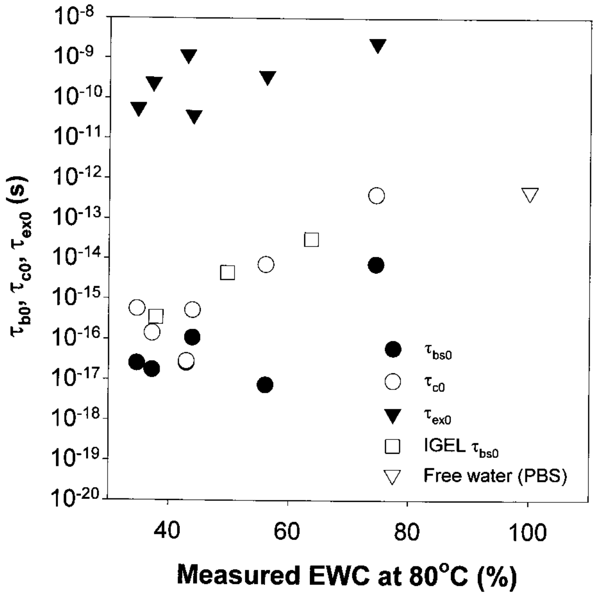

Fig. 7. Arrhenius law coefficients derived from the T_2 relaxation model, plotted (on a log scale) as a function of measured EWC for the hydrogels studied. The result for PBS is also shown.

evident at the lower temperatures (right hand side of the $1/T$-axis). It can also be seen that, within a given series and except for the anomalous behaviour of Benz G-5X, T_{2b} generally deviates increasingly from T_{2bf} (and is increasingly shorter relative to T_{2bf}) as EWC decreases. That is, the T_{2bs} term contributes increasingly as EWC decreases.

The anomalous behaviour of the Benz G-5X could be explained by partial freezing of water at the lowest temperature (−20°C) in this sample (see Fig. 2), giving an anomalously low T_2 value and making the fitted parameters for T_{2bs}, (which can be approximated to the measured T_2 at low temperatures), unreliable. The behaviour of the remaining hydrogels suggests that the slower motion contributing to T_{2b} is more highly constrained (slower) for the lower water content hydrogels. This implies more tightly ‘bound’ water (in the bound/free water model) or possibly slower motion of the polymer side-chains (in the anisotropic motion description). It could be speculated that the T_{2bs} weighting factor (w_{bs}) actually increases with decreasing water content (increasing the proportion of ‘bound’ water), and that T_{2bs} might in fact be relatively constant for each gel. However, as described above, the fitting showed that the weighting factors were relatively constant for these materials, regardless of water content. Significantly better fits could not be obtained by freeing up the weighting factors in the fitting process.

As shown in Fig. 4, T_{2c} also generally increases with EWC for the Benz hydrogels. This suggests that the average rate of molecular motion for the hydroxyl protons is also reduced as the EWC decreases, presumably because these protons (and the associated polymer side-chains) are increasingly constrained as the ratio of water molecules to polymer units decreases, since water acts as a plasticiser in these materials. However, there is also some suggestion that the differences in T_{2c} could stem from differences in the relative mobility of HEMA hydroxyl protons vs that of the GMA hydroxyl protons. The polymers that contain exchangeable polymer protons from HEMA only (ie. contain no GMA) show a very similar behaviour for T_{2c} (see Fig. 4). Increasing the proportion of GMA in the HEMA/GMA copolymers (Benz G materials) seems to increase the hydroxyl mobility (seen by the increase in T_{2c}). For example, the Benz G-3X (EWC = 43.9%) hydrogel shows a significant increase in T_{2c} from the non-GMA-containing hydrogel Benz 55 (EWC = 42.9%), although they have very similar EWC. However, the EWCs at 80°C of all the non-GMA-containing polymers (Benz 38/45/55) were similar (34.7–42.9%) and substantially less than those of the GMA-containing polymers. This may indicate that this effect on T_{2c} could in fact be simply due to the increased EWC (and hence polymer mobility) of the GMA-containing materials.

The behaviour of the exchange correlation time (τ_{ex}) is shown in Fig. 5. This behaviour is once again consistent with the picture of increasingly constrained water motion as EWC decreases. In this case, the exchange rate ($1/\tau_{ex}$) is generally slower (τ_{ex} higher) for the lower EWC gels. This is thought to be due to the decreased rotational and translational mobility [7] of the water molecules. Reduced translational mobility will decrease the probability of a water molecule diffusing to a hydroxyl proton with which it can chemically exchange.

In order to demonstrate the EWC dependence of the fitted parameters more explicitly, the individual activation energies and Arrhenius coefficients were plotted against measured EWC. (Figs. 6 and 7, respectively). (The Arrhenius

Table 4
A comparison of the findings of this study for the chemical exchange rate (τ_{ex}^{-1}), vs those of Barbieri (k_m)

Gel name	EWC (%)	Current study		Barbieri	
		τ_{ex}^{-1}(s^{-1})	E_{ex}(kJ/mol)	k_m(s^{-1})	E_{ex}(kJ/mol)
Benz 38	38	126	47	2041	27.6
Benz G-3X	49	284	46	1300	25.1
Benz G-5X	58	476	39	578	20.5

coefficients are plotted on a logarithmic scale). For the more constrained b species protons, these parameters (E_{bs}, τ_{bs0}) approach the values measured for PBS (also shown on the plots) as EWC increases towards 100% (effectively the EWC of free water in PBS). The activation energies, E_{bs} and E_c decrease with EWC in the range 45–65 kJ/mol down to about 30 kJ/mol at the highest EWC, approximately linearly. In the case of the IGEL values for E_{bs} there is strong evidence for a trend towards the value for PBS, and there is some indication that E_{bs} for the remaining materials may also approach this value. These activation energies should reflect approximate energies for breaking and reforming hydrogen bonds, which is the energy barrier that must be overcome for molecular motion to occur in the hydrogel. Hydrogen bonds in these types of systems (e.g. alcohols, hydrates and biological molecules) are classed as moderate in strength and are quoted by Jeffrey to lie in the approximate range of 16.7–62.8 kJ/mol [24], consistent with the values obtained in this study.

The Arrhenius coefficients for the slower motions show an increase with increasing EWC, but also approach the value measured for PBS, allowing for one anomaly in the τ_{bs0} values arising from Benz G-5X, (see explanation above). These trends suggest that as EWC increases the average motion of the water molecules is less constrained, or faster. This is consistent with the fact that there will in general be more water molecules per unit mass of polymer for higher EWC materials. Thus as EWC increases the measured (overall) water behaviour is weighted increasingly towards free water and the measured parameters reflect this.

Also plotted in Figs. 6 and 7 are the exchange parameters that were calculated for those materials that exhibited proton exchange behaviour. Barbieri and co-workers also measured T_2 as a function of temperature for a set of three of the Benz hydrogels, Benz 38, Benz 45G (virtually identical in composition to Benz G-3X) and Benz 55G (virtually identical in composition to Benz G-5X). They adopted a similar model to the one we have used, but assumed that T_2 for the hydrogel water (T_{2b}) was simply equal to the value measured for distilled water. However, they did not fit the data over the entire temperature range using this model. Rather, they calculated chemical exchange rates τ_{ex}^{-1} (which they termed k_m) and T_{2c} (T_{2m} in their notation) by assuming that at the T_2 minimum, T_{2c} is equal to k_m^{-1}, and at higher temperatures, T_{2c} increases in the same relative proportion as is observed for distilled water over the same temperature range. They then plotted the exchange rates over a limited temperature range (approximately 3–30°C) and calculated the apparent exchange activation energies in this range. A comparison of their exchange parameters with those obtained from our own modelling is shown in Table 4. As can be seen, the E_{ex} values measured by Barbieri were almost half those measured for the same or similar hydrogels in this study. In addition, their values for the chemical exchange rate ($\tau_{ex}^{-1} = k_m$) at 28°C were significantly greater than those calculated in this work at the same temperature (see Table 4), but still generally less than those reported in the literature for solutions (e.g. glucose, methanol, BSA [18,25,26]) or very high WC (>90%) gels (e.g. polysaccharide gels [27,28]). The values reported for these systems lie in the range 1400–5000 s^{-1}. However, it is expected that the chemical exchange rate in systems with significantly lower WC (such as the contact lens hydrogels of this study) will be substantially reduced.

Barbieri et al. also found that k_m increased with decreasing EWC, again in contrast to the findings of the current study. They suggested that this might be due to an increased ratio of hydroxyl sites to water molecules in the lower EWC hydrogels. However, our results suggest that the average mobility of the water molecules (which decreases with decreasing EWC) is the more dominant factor in this chemical exchange process, rather than the relative numbers of hydroxyl and water protons.

We believe these discrepancies are primarily due to the limitations of the model that Barbieri et al. used. They assumed that all the gel water behaves exactly as bulk water and made no allowance in their model for the presence of a slower component of molecular motion, in contrast to the findings of this study. Neglecting the presence of this slower motion component in the water, would lead to artificially short τ_{ex} values, as Barbieri et al. acknowledge. While they did consider the possibility of a bound water component, they argued that such a contribution would have a negligible effect on the overall T_2 relaxation compared with that of the chemical exchange of water and hydroxyl protons. However, the results of the current study suggest that this component cannot be neglected, even in spite of its small weighting factor. Particularly at lower temperatures, the slow component of water motion significantly modifies the water relaxation relative to that of bulk water. Some differences might also be attributable to the different fitting method for τ_{ex} that Barbieri et al. used. They assumed $T_{2c} = \tau_{ex}$ at the T_2 minimum, then calculated τ_{ex} at other temperatures by assuming that the change in T_{2c} with temperature relative to T_2 at the minimum, was the same as that which they had measured previously for free water (over the same temperature range). However, the results of this study show that in this temperature range, T_{2c} for these materials varies by almost an order of magnitude. In contrast, the T_2 value for PBS varies by a factor of less than 2. A third possibility that could explain some slight differences is the temperature at which the materials were hydrated. For this study the hydration temperature was 80°C, while Barbieri hydrated the gels at room temperature, resulting in slightly higher EWCs. While the lower EWCs would tend to increase τ_{ex}, the relatively small ($<10\%$) differences in EWC arising from this effect would make this unlikely to be the dominant cause of the discrepancies.

Despite these differences, the dependence of E_{ex} on EWC was similar to that which Barbieri and co-workers reported. As shown in Figs. 6 and 7, E_{ex} decreases with increasing EWC while τ_{ex0} increases with EWC. This behaviour resembles that of the b and c species parameters and reflects the fact that as EWC increases, the chemical exchange of water protons is made easier due to the increase in average water mobility. However, the exchange parameters appear to have a significantly weaker dependency on EWC than those governing the intrinsic relaxation times T_{2b} and T_{2c} so that the chemical exchange rate is only slightly dependent on water content.

5. Conclusions

The results of this study have shown that the ^{1}H NMR T_2 relaxation of a range of contact lens hydrogels can be well characterised over a wide temperature range by a relatively simple model that incorporates chemical exchange of protons between water and polymer, combined with two component relaxation for the hydrogel water. The reliability of our model is seen in the consistent trends shown for a wide variety of polymers which span a relatively large EWC range. While our model has a potentially large number of free parameters, we believe our systematic approach to modelling the data has led to a new understanding of the parameters that dominate the observed T_2 relaxation behaviour for these materials and ultimately the hydrogel properties that most strongly influence the water mobility and binding.

The motional correlation times resulting from our analysis can then be related to the average mobilities of (i) the water molecules and (ii) the polymer chains. The model suggests that the water in these hydrogels is only slightly perturbed relative to bulk water and can be described by either:

1. the presence of 'bound' (or interfacial) and 'free' (or bulk) water in fast exchange, where the 'free' water has similar properties to water in PBS, and accounts for 98% of the total water, while the 'bound' water shows significantly restricted motion; or
2. a single water species that is slightly modified in its behaviour relative to the behaviour of free water in PBS. This water exhibits slightly anisotropic motion that is well described by two correlation times, one of which is similar to that for free water in PBS.

We have shown that this model can equally well describe both the behaviour of materials which contain exchangeable polymer protons and those that do not (the Benz and IGEL materials, respectively). By modelling the behaviour of both of these types of materials, we have presented strong evidence that the c species originates from exchangeable polymer protons.

Overall, the results suggest that the average mobility of the water in the hydrogels studied is largely dependent on the water content of the gel and increases with increasing water content towards that of free water in PBS. No significant dependence of this mobility on polymer composition could be found in this study that could not be related to EWC. These results are consistent with the majority of clinical findings concerning on-eye dehydration, which suggest that the higher EWC materials generally dehydrate to a greater extent on the eye [8–10]. However, the possibility remains that similar studies may be used in the future to identify materials that exhibit anomalous behaviour and do not agree well with the general trends shown in Figs. 6 and 7. Such studies may have the potential to identify new materials with improved potential to maintain their EWC on the eye.

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