Disentangling Polymer Network and Hydration Water Dynamics in Polyhydroxyethyl Methacrylate Physical and Chemical Hydrogels

Daria Noferini,^{§,∇}[®] Antonio Faraone,[‡][®] Marta Rossi,[§] Eugene Mamontov,[⊥][®] Emiliano Fratini,^{*,§}[®] and Piero Baglioni

[§]Department of Chemistry "Ugo Schiff" and CSGI, University of Florence, Via della Lastruccia 3, 50019 Sesto Fiorentino, Florence, Italy

[‡]NIST Center for Neutron Research, National Institute of Standards and Technology, Gaithersburg, Maryland 20899-6100, United States

¹Neutron Scattering Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37831, United States

Supporting Information

ABSTRACT: The cross-linker nature and water content may impact the microscopic dynamics of hydrogels components and thus their properties in applications such as drug delivery and water confinement. To investigate these aspects, we used quasi-elastic neutron scattering with contrast variation to distinctly study the polymer and water dynamics in polyhydroxyethyl methacrylate (pHEMA) chemical (cg) and physical (pg) hydrogels with various water contents. For the polymer network, a distribution of relaxation processes was observed, mainly related to the side chains. Water dynamics was found to occur as a H-bond governed process with a jump-diffusion mechanism. The interaction with the polymer matrix considerably slows the water dynamics with respect to bulk water and other confined systems and leads to a fraction of water molecules appearing as immobile. With a higher hydration level, the mobility of both the water and the polymer network increases. For the same water content, pg presents slower relaxation processes and a smaller explored space than their cgequivalents as a result of side chains involvement in the formation of the three-dimensional network typical of hydrogels. In the less hydrated gels, water mobility is sensibly reduced in



the cg compared with pg, whereas at higher hydration the mobilities are similar but with shorter residence times in cg.

INTRODUCTION

Hydrogels are mainly cross-linked polymeric three-dimensional (3D) networks where a continuous water phase is "confined". They can be classified as physical or chemical depending on the nature of the cross-linker. In the first case, the polymeric chains are held together by physical interactions such as hydrophobic forces, hydrogen bonds, electrostatic interactions, and entanglements, whereas if the chains are connected by real chemical bonds the hydrogel is a continuous polymeric network falling in the second class by definition. 2-Hydroxyethyl methacrylate (HEMA) based chemical hydrogels are one of the very first examples of synthetic hydrogels. They were developed in the 1960s by O. Wichterle and D. Lim.^{2,3} Since their synthesis, they have been extensively employed in many biomedical fields (orthopedics, surgery, burned skin treatments, artificial tissues, contact lenses, etc.),^{3–9} due to their excellent biocompatibility, permeability, and tunable mechanical properties. At equilibrium, they reach a water content (EWC) of about 40% w/w. The attention to these systems, even in the presence of comonomers, has been particularly focused onto soft contact lenses and drug delivery applications, mainly for transdermal and ophthalmic delivery.^{10–14} Very recently, various hydrogels and, in particular, polyhydroxyethyl methacrylate (pHEMA) semi-interpenetrated with linear polyvinylpyrrolidone (PVP) have also been used in exotic applications such as cultural heritage conservation of water sensitive artifacts,¹⁵⁻¹⁸ due to the possibility to load water-based nanofluids (i.e., micellar systems and microemulsions) and tune the transport properties of the continuous aqueous phase by simply changing the HEMA/ PVP ratio.^{19,20} Intimate knowledge of the transport properties in these materials is of fundamental importance when the final application needs to be optimized,¹⁴ and a better understanding of the dynamics at the molecular scale has often been proven beneficial.²¹⁻²⁵

To this aim, quasi-elastic neutron scattering (QENS) represents a very powerful technique to study the dynamics of hydrogenated systems thanks to the peculiarities of neutrons as a probe such as the high incoherent cross section for hydrogen and the time window associated with the exchanged energy.²⁶ QENS was successfully exploited for the investigation of the dynamic behavior of hydrogel components at the molecular level and in the nano-/picosecond time scale in similar systems.^{27–30} Very interestingly, in the case of a

Received: May 3, 2019 **Revised:** June 21, 2019 Published: July 8, 2019

thermoresponsive hydrogel (i.e., poly(vinyl alcohol)/poly-(methacrylate-*co*-*N*-isopropylacrylamide) network), a distinctive change in the values of the diffusion coefficient of bound water was observed at the transition temperature as a consequence of the structural collapse induced by temperature,³¹ as well as at a lower temperature, around 250 K, in connection with a dynamical transition of the polymer.³²

In this paper, we present a systematic study on pHEMA hydrogels, both chemical and physical, with different weight fractions of water (hereafter indicated as w/w). The proposed systems, even if rather simple, allow us to investigate the effect of the water content and the nature of the cross-linker on the final transport properties of the hydrogel. QENS and thermal analysis were used to depict the confining effect of the polymer network on the water molecules in fully hydrogenated systems, while gels loaded with deuterated water were used to study the dynamics of the 3D polymeric network.

MATERIALS AND METHODS

Preparation of the Hydrogels. Water was purified by using a MilliRO-6 Milli-Q gradient system (Milli-pore, resistance >18 M Ω cm). Deuterium oxide (D₂O, 99.90% D) was purchased from Eurisotop, France, and all the other reagents were purchased from Sigma-Aldrich, Milan, Italy, and used as received.

Physical gels (pg) with 10% to 41% w/w hydration levels were prepared by adding the corresponding amount of H₂O (or D₂O) to poly(2-hydroxyethyl methacrylate) with an average molecular weight of 20000 Da (CAS: 529265). The so-obtained dispersions were centrifuged at 500 r.p.m. until a homogeneous transparent gel was obtained.

Chemical gels (cg) with an equilibrium water content of 40% w/w were prepared through radical copolymerization of HEMA monomer, 2-hydroxyethyl methacrylate (CAS: 128635, assay $\geq 97\%$), and EGDMA cross-linker, ethylene glycol dimethacrylate (CAS: 335681, assay \geq 98%), which was added as 2% w/w with respect to the monomer. The obtained product, water (or D_2O), and the radical initiator ammonium persulfate (APS), (purity >98%) added as 2.5 mg per each gram of HEMA, were mixed under a flux of N₂ for about 10 min to remove O_2 . To promote the homolysis of APS, 80 μ L of TEMED, N, N, N', N'-tetramethylethylene-diamine (purity \geq 99%), were added as a catalyst. The polymerization was thermally initiated at 40 °C in a 0.25-0.5 mm thin flat demountable and gastight container, to obtain gels already shaped for the neutron scattering experiment. The matrix was polymerized for at least 4 h. So-obtained gels were washed five times with water (or D₂O) to remove unreacted reagents (and totally exchange the labile H with D). Finally, 10%, 20%, and 30% w/w hydration levels were reached by dehydrating the 40% w/w gel in a controlled humidity chamber with a relative humidity of about 50% (i.e., MgNO₃ saturated solution).

The pHEMA/H₂O samples are hereafter indicated as pg for physical gels and cg for chemical gels, followed by the hydration percentage (e.g., pg20 for physical gel with 20% w/w hydration level). Samples hydrated with heavy water, pHEMA/ D₂O systems, are marked by adding the suffix _D (e.g., $pg20_D$ for a physical gel hydrated at 20% w/w with D₂O).

Thermal Analysis Experiments. Differential scanning calorimetry (DSC) measurements were carried out with a Q2000 calorimeter (TA Instruments) at a constant nitrogen flow rate of 50 mL/min on about 10–20 mg of hydrogel. Samples were loaded in a closed aluminum pan, and an empty

pan was used as a reference. The thermograms were recorded with the following cycle: equilibrate at 278 K, ramp 0.50 K/ min to 193 K, ramp 0.50 K/min to 350 K.

Thermogravimetric analysis (TGA) measurements were performed by SDT Q600 (TA Instruments) in a N₂ atmosphere with a purge flow rate of 100 mL/min. The balance sensitivity is 0.1 μ g with respect to the weight change in the sample. The samples (10–15 mg) were placed in open aluminum pans and dehydrated by heating 10 K/min from room temperature up to 523 K.

Quasi-Elastic Neutron Scattering Experiments. QENS spectra were acquired for *cg20*, *cg30*, *pg20*, and *pg30*, and for *cg20_D*, *cg30_D*, *pg20_D*, and *pg30_D* with the high-resolution near-backscattering crystal-analyzer spectrometer BASIS at the Spallation Neutron Source (SNS) of the Oak Ridge National Laboratory (ORNL) in Tennessee, USA. The energy of the neutrons scattered by a sample, Bragg-selected by Si(111) crystal analyzers at 88° scattering angle, is 2.082 meV, giving an accessible scattering vector Q range of about 0.25–2 $\text{\AA}^{-1.33}$ The maximum accessible neutron energy transfer window was ± 0.1 meV.

The samples were arranged as to take an annular shape with a thickness of ~0.25 mm, to obtain a transmission of about 90%. Data were collected at 10 K (or 20 K), 270 K, 280 K, 290 K, and 300 K. The temperature was controlled within ± 0.5 K by a closed cycle refrigerator. Because of the available beamtime constraint, cg20 and cg20 D were measured only at 270 and 300 K. The low-temperature measurements (10 or 20 K) were used to determine the instrumental resolution function. This approach is well justified as the recorded signal is dominated by incoherent scattering from hydrogen atoms, and nonvibrational dynamics measurable at BASIS are frozen out at such low temperatures. An average full width at half-maximum (FWHM) of $(4.0 \pm 0.5) \mu eV$ was derived, in agreement with the specifications of the BASIS³³ spectrometer for the used experimental setup. Raw data were reduced to a dynamic structure factor S(Q, E) using software available at SNS. For each sample, 16 spectra in a Q range from 0.35 Å⁻¹ to 1.85 Å⁻¹ (step = 0.1 Å^{-1}) were obtained and analyzed.

The difference in the hydrogen and deuterium incoherent cross sections³⁴ allows us to isolate the dynamics of the polymer network in the hydrogel by replacing the hydration water with D₂O. The incoherent contribution of the heavy water is negligible, being about 1.2% (20% w/w hydrated samples) and 1.8% (30% w/w hydrated samples) with respect to the total signal. Furthermore, the signal from the hydration water, $S_w(Q, E)$, was obtained by subtracting the spectra of the pHEMA/D₂O hydrogel out of the correspondent pHEMA/ H₂O spectra, using standard routines provided at SNS as part of the raw data reduction package. The so-obtained data are labeled with the suffix w (e.g., $pg20_w$ for the signal obtained by subtracting the spectra obtained for pg20 D from those obtained for pg20). The fitting procedures were carried out with routines and χ^2 minimization algorithms of the software DAVE,³⁵ Matlab, and IgorPro.

POLYMER NETWORK

QENS Data Analysis. To derive a model for the description of the S(Q, E), considerations on the composition and structure of the polymer were taken into account. Figure 1 shows the HEMA monomer chemical formula. For the pHEMA/D₂O systems, only nine H atoms have to be considered after the H–D exchange: three from the methyl



Figure 1. Structure of the main repetition unit present in both physical and chemical pHEMA hydrogels. (A) Stick/space-filling mixed model with standard color-codes for elements (C = gray, O = red and H = white). (B) Structural formula. The different colors for H indicate the different parts in which the monomer unit has been ideally divided: orange for the methyl group, red for the backbone, green for the side chain and light blue for the hydroxyl group.

moiety (in orange), two from the ethylene groups present in the backbone (in red), and four from the ethylene group constituting the side chain (in green) attached to the backbone; the hydrogen on the hydroxyl group (in light blue) is totally exchanged with deuterium and washed away during sample preparation. Moreover, in the case of the chemical gels, the cross-linker contribution has been neglected since it accounts only for 2% w/w with respect to the HEMA monomer constituting a small contribution to the backbone dynamics.

We define $S_B(Q, E)$ as the dynamic structure factor of the backbone hydrogen atoms. The dynamic structure factors of the methyl group and the side chain, with respect to the backbone, are indicated as $S_M(Q, E)$ and $S_{SC}(Q, E)$, respectively. The methyl group and the side chain move together with the backbone; hence, to describe the dynamics of their H atoms, $S_M(Q, E)$ and $S_{SC}(Q, E)$ have to be convoluted with $S_B(Q, E)$. Within these approximations, the following expression can be used to analyze the data:

$$S(Q, E) = A'(Q) \left\{ S_{B}(Q, E) \otimes \left[\frac{2}{9} \delta(E) + \frac{1}{3} S_{M}(Q, E) + \frac{4}{9} S_{SC}(Q, E) \right] \right\} \otimes \operatorname{Res}(Q, E) + \operatorname{bkg}(Q, E)$$
(1)

where A'(Q) is a normalization constant, \otimes indicates the convolution product, $\operatorname{Res}(Q, E)$ is the experimental resolution function, and $\operatorname{bkg}(Q, E)$ is a linear background which takes into account dynamical processes too fast to fall within the instrumental window and instrumental noise.

A segmental backbone dynamics characterized by a relaxation distribution and a Q dependence from Q^2 and Q^4 was identified in previous studies, for example, on poly(vinyl methyl ether) solutions.²⁸ The presence of a delta function in all our fits, in agreement with many studies on the polymer network dynamics in various hydrogels,^{27,29,31,36–38} points toward the assumption that the long-range backbone dynamics

is too slow to be resolved with our experimental setup. However, some localized dynamics might be still appreciable in the probed length and time window. For this reason, assuming localized motions, the backbone dynamics can be modeled as

$$S_{\rm B}(Q, E) = {\rm EISF}_{\rm B}(Q)\delta(E) + (1 - {\rm EISF}_{\rm B}(Q))Y_{\rm B}(Q, E)$$
⁽²⁾

 $\text{EISF}_{B}(Q)$ and $Y_{B}(Q, E)$ provide information on the explored volume of the dynamics and its time scale, respectively. Assuming that the backbone explores uniformly a region of space with dimension R_{B} , its elastic incoherent structure factor $\text{EISF}_{B}(Q)$ can be modeled as

$$EISF_{B}(Q) = \exp\left(-\frac{1}{3}Q^{2}R_{B}^{2}\right)$$
(3)

where $R_{\rm B}$ is assumed to be small on the order of 1 Å. The functional form of $Y_{\rm B}(Q, E)$ will be discussed in the following.

Under the assumption that the methyl carbon atom is rigidly attached to the backbone (i.e., no dynamics), the motion of the hydrogen atoms of the methyl can be modeled simply as a 3fold rotation:

$$S_{\rm M}(Q, E) = {\rm EISF}_{\rm M}(Q)\delta(E) + [1 - {\rm EISF}_{\rm M}(Q)]L_{\rm M}(E)$$
(4)

with the elastic incoherent structure factor proper of the methyl group rotation, $\text{EISF}_{M}(Q)$, taking the form:

$$EISF_{M}(Q) = \frac{1}{3} [1 + 2j_{0}(\sqrt{3} QR_{M})]$$
(5)

where j_0 is the first-order spherical Bessel function and R_M is the radius of the methyl group (i.e., about 1 Å).^{34,39} At the measurement temperatures we used, the half-width at halfmaximum (HWHM) of the Lorentzian function L_M is expected to be around 1 meV,^{34,39} which is much broader than our experimental energy window, suggesting no contributions to the observed QENS signal. Even considering a distribution of jumping rates for the methyl rotation in polymers,⁴⁰ the contribution to the observed signal in the current dynamical window at the measured temperatures is expected to be marginal.

The motions of the side chain with respect to the backbone can be considered as localized, with no long-range diffusion. An acceptable approximation is therefore

$$S_{\rm SC}(Q, E) = {\rm EISF}_{\rm SC}(Q)\delta(E) + [1 - {\rm EISF}_{\rm SC}(Q)]Y_{\rm SC}$$

$$(Q, E)$$
(6)

The elastic incoherent structure factor $\text{EISF}_{\text{SC}}(Q)$ can also be modeled as

$$\text{EISF}_{\text{SC}}(Q) = \exp\left(-\frac{1}{3}Q^2 R_{\text{SC}}^2\right)$$
(7)

where R_{SC} is expected to be about 5 Å, from a rough estimation of the bond distances. Therefore, its contribution is mostly limited at low Q. The quality of the data does not warrant the use of a more detailed approach.

The functional form of $Y_B(Q, E)$ and $Y_{SC}(Q, E)$ needs to be determined. For a simple, i.e., exponential, relaxational process it would be a Lorentzian; for more complex processes and, as often is the case with polymers, when there is a distribution of relaxation times, the Fourier transform of a stretched exponential is a suitable model.

With the above-mentioned considerations, the expression for the observed S(Q, E) is

$$S(Q, E) = A'(Q) \left\{ \left[\frac{2}{9} \text{EISF}_{B}(Q) + \frac{1}{3} \text{EISF}_{B}(Q) \text{EISF}_{M}(Q) + \frac{4}{9} \text{EISF}_{B}(Q) \text{EISF}_{SC}(Q) \right] \delta(E) + [1 - \text{EISF}_{B}(Q)] \right\}$$

$$\left[\frac{2}{9} + \frac{1}{3} \text{EISF}_{M}(Q) + \frac{4}{9} \text{EISF}_{SC}(Q) \right] Y_{B}(Q, E)$$

$$+ \frac{1}{3} [1 - \text{EISF}_{M}(Q)] [\text{EISF}_{B}(Q) L_{M}(Q, E)$$

$$+ [1 - \text{EISF}_{B}(Q)] Y_{B}(Q, E) \otimes L_{M}(Q, E)]$$

$$+ \frac{4}{9} [1 - \text{EISF}_{SC}(Q)] [\text{EISF}_{B}(Q) Y_{SC}(Q, E)$$

$$+ [1 - \text{EISF}_{B}(Q)] Y_{B}(Q, E) \otimes Y_{SC}(Q, E)] \right\}$$

$$\otimes \text{Res}(Q, E) + \text{bkg}(Q, E) \qquad (8)$$

The dynamics of the methyl group is much faster than the backbone motion, and therefore we can approximate $Y_{\rm B}(Q, E)$ $\otimes L_{\rm M}(Q, E) \approx L_{\rm M}(Q, E)$. Under the above introduced assumption that the methyl group dynamics is much faster than the investigated time scale, the above equation can be simplified:

$$S(Q, E) = A'(Q) \left\{ \left[\frac{2}{9} \text{EISF}_{B}(Q) + \frac{1}{3} \text{EISF}_{B}(Q) \text{EISF}_{M}(Q) + \frac{4}{9} \text{EISF}_{B}(Q) \text{EISF}_{SC}(Q) \right] \delta(E) + [1 - \text{EISF}_{B}(Q)] \right\}$$
$$\left[\frac{2}{9} + \frac{1}{3} \text{EISF}_{M}(Q) + \frac{4}{9} \text{EISF}_{SC}(Q) \right] Y_{B}(Q, E)$$
$$+ \frac{4}{9} [1 - \text{EISF}_{SC}(Q)] [\text{EISF}_{B}(Q) Y_{SC}(Q, E)$$
$$+ [1 - \text{EISF}_{B}(Q)] Y_{B}(Q, E) \otimes Y_{SC}(Q, E)] \right\}$$
$$\otimes \text{Res}(Q, E) + \text{bkg}'(Q, E) \qquad (9)$$

The backbone and side chain dynamics are expected to have similar time scales so that the experimental separation of $Y_B(Q, E)$, $Y_{SC}(Q, E)$, and $Y_B(Q, E) \otimes Y_{SC}(Q, E)$ is beyond current experimental capabilities, especially because each of these functions is already likely representing a distribution of relaxation times, and the instrumental resolution function further smears the signal. Therefore, the data have been analyzed in terms of the simplified scattering law:

$$S(Q, E) = [A_{\text{EL}}(Q)\delta(E) + A_{\text{QE}}(Q)Y_{\text{polymer}}(Q, E)]$$

$$\otimes \text{Res}(Q, E) + \text{bkg}(Q, E)$$
(10)

The analysis of $Y_{polymer}(Q, E)$ yields insights into the time scale of the polymer motions, whereas the a posteriori analysis of the EISF(Q):

$$\text{EISF}(Q) = \frac{A_{\text{EL}}(Q)}{A_{\text{EL}}(Q) + A_{\text{QE}}(Q)}$$
(11)

will provide information on the dynamics of the different hydrogen groups in the polymer.

Results and Discussion. As anticipated, the functional form of Y_{polymer} was determined during the fitting procedure as the Fourier transform (FT) of a stretched exponential (or Kohlrausch–Williams–Watts, KWW, function):

$$FT_KWW = FT\left[exp\left(-\frac{t}{\tau'}\right)^{\beta}\right]$$
(12)

where τ' is the relaxation time and β is the stretching exponent, which can take values between 0 and 1. In polymer dynamics, the exponent is usually on the order of 0.5.²⁸ This functional form can be the result of a distribution of relaxation processes in the system. It is well established that polymer networks in general can be characterized by heterogeneous environments at the molecular scale, which give rise to nonexponential relaxation functions.⁴¹ In this respect, β indicates the extent of the heterogeneity. For all the samples, β was found to be almost Q independent. Figure 2a shows the Q dependence of β



Figure 2. (a) Example of the stretching exponent as a function of Q. The dashed blue line represents the average value. In (b), the stretching exponent averaged in the whole Q range for the different samples and temperatures is reported.

in $pg30_D$ at 280 K, taken as an example. To reduce the number of free parameters in the fitting routines, final fits were thus carried out fixing β on the calculated average for each sample and temperatures. The averaged stretching exponents $\langle \beta \rangle_{Q'}$ Figure 2b, are in the range from 0.45 to 0.56 and do not vary significantly among different temperatures and samples. In Figure 3, we report the dynamic structure factors of the hydrogels loaded with D₂O at 300 K and $Q = 0.95 \text{ A}^{-1}$ and their fits. The good agreement between fits and experimental data supports the approximation of the use of $\langle \beta \rangle_{Q'}$.

The average relaxation time, $\frac{42}{\tau}$, can be derived as

$$\overline{\tau'} = \frac{\tau'}{\beta} \Gamma\!\left(\frac{1}{\beta}\right) \tag{13}$$

where Γ is the Gamma function. The obtained values (comprised between 0.073 and 0.312 ns) do not show a significant trend with Q, validating the assumption that the dynamics of the side chain is localized. In the following, their Q-averaged values $\langle \tau^7 \rangle_Q$ are discussed. Increasing the temperature, $\langle \tau^7 \rangle_Q$ generally decreases, showing that the relaxation dynamics is activated by thermal fluctuations. Moreover, pg samples present slower relaxation processes than their cg equivalents, of about 40% (pg20) or 10% (pg30)



Figure 3. Dynamic structure factor for the pHEMA/D₂O samples at 300 K and Q = 0.95 Å⁻¹ and relative fit. The different components of the fit, i.e., elastic (delta function convoluted for the experimental resolution), quasi-elastic (FT_KWW convoluted with instrumental resolution), and background, are shown for completeness. Throughout the paper, error bars represent one standard deviation.

on average, depending on *T*. This reduced mobility of the side chain for the physical hydrogels of pHEMA is a clear evidence of the hydroxyl group involvement in the network formation. Figure 4 shows the Arrhenius plots of the relaxation times.



Figure 4. Arrhenius plots for pHEMA (a) *cg* and (b) *pg*. Dashed lines show the fits for the low hydrated samples. With only two temperatures, the Arrhenius behavior for *cg20_D* is assumed and expected in analogy with *pg20_D*.

Although the probed temperature range is quite limited, it seems that hydrogels with 20% w/w of water content follow an Arrhenius law much better than 30% w/w samples. Such a difference with hydration could be due to the plasticizer role of the solvent, which allows a higher mobility and thus several local minima in the energy landscape.43,44 In the scheme proposed by Angell,⁴⁵ this would correspond to a more fragile behavior. As a matter of fact, considering the composition of the samples, we expect to have about one water molecule per -OH group (side chain) in the 10% w/w sample, two in the case of the 20% w/w, four in the 30% w/w hydrogels, and six when the water content is 40% w/w. Going from two water molecules per hydroxyl group to four changes the response to the temperature from Arrhenius to super-Arrhenius and the hydrogel from strong to fragile-like. For pg20 D, an activation energy of -0.10(2) eV (or -10(2) kJ/mol) was found. Assuming an Arrhenius behavior for cg20 D, a similar, slightly higher, value is obtained (-0.14 eV).

The analysis of the EISF(Q), Figure 5, can provide insights into the geometry of the motion of the different hydrogen



Figure 5. Elastic incoherent structure factor EISF(Q). Lines are fit according to eq 14 (dashed lines) and eq 15 (dotted lines), with the color code referring to the different temperatures, as in the legend.

groups in the polymer. It can be noted that the profile is fairly similar for all the samples and temperatures, suggesting that the same dynamical processes are observed. The decay is slightly more pronounced at increasing the temperature and hydration, evidencing an increased mobility. In deriving an expression for the EISF, it is assumed that the methyl group dynamics is fast, so that it contributes to the background only, therefore being counted out of the total spectral area. Support for this idea comes from the analysis of the normalized total integrated intensities, calculated as the ratio between the sum of the integrated intensity of the delta function and the FT_KWW function $(A_{EL} + A_{QE} = A_{tot})$ and the integrated intensity of the measurements below 50 K (Ares). Its Qdependence shows that the mean squared displacements obtained by considering simply a Debye-Waller factor, in the range from 0.16 $Å^2$ to 0.4 $Å^2$, are much higher than those expected for pure atomic vibrations⁴⁶ (about 0.01 Å²), suggesting that the background indeed comprises also other kinds of fast motions. The EISF fits were carried out in accordance with two different hypotheses: (i) the backbone dynamics is too slow and constrained to be appreciated, $S_{\rm B}(Q,$ $E \approx \delta(E), R_{\rm B} \approx 0$; (ii) the backbone explores a region of space of radius $R_{\rm B}$. The dashed lines in Figure 5 are fits using an expression derived from eq 9 under the first scenario:

$$EISF(Q) = \frac{A + B(1 - A)EISF_{M}(Q) + (1 - A)(1 - B)EISF_{SC}(Q)}{A + B(1 - A)EISF_{M}(Q) + (1 - A)(1 - B)}$$
(14)

where $\text{EISF}_{M}(Q)$ and $\text{EISF}_{SC}(Q)$ are the contributions of methyl groups and side chains to the total EISF(Q), as defined in eq 5 and eq 7, respectively.

Conversely, the fits represented by the dotted lines are in accordance with the second scenario and thus to the equation:

$$\operatorname{EISF}(Q) = [A \operatorname{EISF}_{B}(Q) + B(1 - A)\operatorname{EISF}_{B}(Q)\operatorname{EISF}_{M}(Q) + (1 - A)(1 - B)\operatorname{EISF}_{B}(Q)\operatorname{EISF}_{SC}(Q)] / [A + B(1 - A)\operatorname{EISF}_{B}(Q)\operatorname{EISF}_{M}(Q) + (1 - A)(1 - B)]$$
(15)

For both eq 14 and eq 15 and according to stoichiometry of the polymer (see Figure 1), A and B are supposed to take the values of 2/9 and 3/7, respectively. However, in the fitting according to eq 14 A, B, R_{SC} were all free fitting parameters, whereas in the fitting according to eq 15 B(1 - A) was fixed to 1/3, the fraction of hydrogen atoms in the methyl groups, to maintain the number of fitting parameters as three, i.e., A, R_{B} , and R_{SC} , manageable considering the experimental uncertainties.

Both models give similar results and well approximate the data. In this context, we note that a small contribution from the methyl rotation to the observed signal would be compatible with the EISF data in the accessible Q range. Fit parameters are reported in Figure S1 in the Supporting Information, SI. $R_{\rm B}$ values range from 0.36(2) Å to 0.72(2) Å, increasing with both water content and temperature. For the *cg20* D sample, $R_{\rm B} \approx$ 0.4 Å, for $pg20_D R_B \approx 0.5$ Å, and for both $cg30_D$ and $pg30_D R_B \approx 0.6$ Å. These values are consistent with a strongly constrained dynamic. The radius of the region explored by the side chains, R_{SC} , takes physically reasonable values in the range of 4.4-5.8 Å (4.5-6.5 Å for eq 15), with uncertainties on the order of 2-10%. The values moderately increase with increasing temperature and are higher in cg with respect to *pg*. Similar to the results obtained for the relaxation time, the involvement of the side chain in the network formation might be the reason for the reduced mobility in the physical gels compared with the cross-linked equivalents. The obtained weights of the different parts of the polymer are slightly different from the expected values. In the fits using eq 14, A is smaller than 2/9 and B(1 - A) is larger than 1/3, which is indicative of some mobility of the backbone. On the other hand, the fact that A takes values larger than 2/9 for eq 15 indicates that some of the side chain hydrogens explore a region smaller than 1 Å. In summary, the data indicate that the hydrogens in the system explore the surrounding space with a distribution of accessible volumes. The model underlying eq 15 simplifies this picture considering only two possible sizes. However, the limited number of data points do not warrant the analysis in terms of a distribution of $R_{\rm B}$ and $R_{\rm SC}$. Moreover, the analysis employed provides us with the relevant information on the size of the space explored by the backbone and side chain, at least as an average.

HYDRATION WATER

The analysis of the dynamic structure factor of the hydration water $S_w(Q, E)$, obtained as described in the Materials and Methods, was carried out for Q < 1.4 Å⁻¹, i.e., in the region where the contribution from the center of mass dynamics is the major component of the scattering, thus allowing the rotational motions to be ignored.⁴⁷ Referring to the Sears expansion,⁴⁸ the translational dynamics of water dominates the spectra up to ~ 1 Å⁻¹. However, simulation results⁴⁹ indicate that, because of translational-rotational coupling,⁵⁰ the translational intermediate scattering function (ISF) approximates the ISF of the hydrogen atoms. Furthermore, within this Q range and in the probed time scale, the short-time vibrational motion of the water molecules can be considered as equal to $1.^{42,49}$. It is therefore justified to consider the scattering function as approximated by its translational part only.

During a first, model-free analysis, we tried to assess the best functional form for the fit of the $S_w(Q, E)$. Very good agreement with the data was reached already using a simple

combination of a delta function, $\delta_w(E)$, a Lorentzian function, $L_w(Q, E)$, and a linear background, $bkg_w(Q, E)$:

$$S_{w}(Q, E) = C(Q) \{\delta_{w}(E) \text{EISF}_{w}(Q) + L_{w}(Q, E)$$

$$(1 - \text{EISF}_{w}(Q))\} \otimes \text{Res}_{w}(Q, E)$$

$$+ \text{bkg}_{w}(Q, E)$$
(16)

where $\operatorname{Res}_{w}(Q, E)$ is the experimental resolution function, C(Q) is a normalization constant, and $\operatorname{EISF}_{w}(Q)$ is the elastic incoherent structure factor of the water. Such a model has been previously used, for example, for water confined in Vycor.⁵¹

This approach is also justified by DSC measurements (see Figures S2 and S3 in the Supporting Information, SI), which clearly evidence two fractions of water in pHEMA hydrogels with up to 40% w/w of water content according to their diverse response to freezing/melting cycles: one fraction is bound (i.e., interacting with the polar groups of the polymer), and thus it does not freeze and melt, and one is free (i.e., in a bulk-like state). In particular, DSC detects the amount of water that is still freezable in the sample, and, if combined with TGA determining the total amount of water in the hydrogel, the free water index, FWI, can be calculated as⁵²

$$FWI = \frac{\Delta H_{exp}}{W\Delta H_{th}}$$
(17)

where ΔH_{exp} is the enthalpy associated with the water melting determined by the peak integral in the DSC heating scan, *W* is the water weight fraction in the sample, and ΔH_{th} is the theoretical value of the melting enthalpy for pure water (333.55 J/g).²³ Results, summarized in Table 1, show a consistent fraction of water, BWI (i.e., bound water index), still not frozen at -80 °C in all samples.

From the DSC thermograms reported in Figures S2 and S3 in the Supporting Information, it is possible to observe that the freezing temperature of the water is higher for the most hydrated samples, in accordance with previous results by Lee et al.²² For *cg20*, transition peaks were observed neither in the

Table 1. Free Water and Bound Water Index Derived from Thermal Analysis for pg and cg Hydrogels with Water Content up to about 40% w/w^a

	hydration, % (±0.1)	FWI (±0.01)	BWI (±0.01)	free water, % (±0.1)	bound water, % (±0.1)
pg11	11.5	0	1	0	11.5
pg18	18.4	0.03	0.97	0.6	17.8
pg20	20.4	0.06	0.94	1.2	19.2
pg25	24.9	0.37	0.63	9.2	15.7
pg27	26.6	0.41	0.59	10.9	15.7
pg28	28.0	0.42	0.58	11.8	16.2
pg41	41.3	0.48	0.52	19.8	21.5
cg6	5.7	0	1	0	5.7
cg11	11.1	0	1	0	11.1
cg19	18.8	0.01	0.99	0.2	18.6
cg25	24.9	0.07	0.93	1.79	23.1
cg27	27.4	0.05	0.95	1.4	26.0
cg33	33	0.34	0.66	11.2	21.8
cg40	40.2	0.40	0.60	16.2	24.0
cg43	42.8	0.40	0.60	17.1	25.7

"Bound and water content % are reported as well to show the distribution of the total water content in the two states.



Figure 6. (a, b) Bound and free water in pg and cg pHEMA hydrogels. Dashed lines are only a guide for the eye.

cooling nor in the heating thermograms, in agreement with previous works on pHEMA hydrogels²² and commercial contact lenses.²¹ In the case of *pg20*, a small amount of free water (<0.05) is still detectable.

Figure 6 shows the fractions of bound and free water with respect to the total water content for both pg and cg, to better emphasize how the water is distributed in the two different states. Bound water fraction increases with the water content and gets to a plateau after 20% w/w (see Figure 6a) as a consequence of the limited binding capacity of the hydroxyl group that can strongly coordinate about two water molecules. The plateau value results are lower in the pg case, thus confirming that the hydroxyl groups are not completely available but also involved in the hydrogel network formation. When the two water molecules threshold is reached, additional water behaves like bulk water maintaining its ability to freeze; see Figure 6b.

Such findings are consistent with the presence of diverse fractions of water with different mobilities, either more similar to the bulk water or more associated with the polymer matrix, thus justifying the use of a delta plus a Lorentzian function in the fitting of the QENS data relative to the total hydration water signal. The addition of a second Lorentzian, following the approach of several studies on analogous systems, ^{27,31,36–38,53,54} could not be justified in our experimental window, as the broader component was mainly a background, as similarly reported for PVA hydrogels.²⁷ The use of a FT KWW function was also considered, according to the study of Zanotti et al.⁵¹ for water confined in Vycor glass. The agreement with the data slightly improved, but being yet comparable to the single Lorentzian model, the use of a higher degree of complexity was beyond the aims of the present paper. Indeed, the FT KWW can easily superimpose with the elastic fraction and/or with the background, making it more difficult to distinguish among different populations with different dynamical behavior and to determine possible trends as a function of T, hydration, and type of gel.

A preliminary fit was also used to investigate a possible effect of the confinement imposed by the gel on the probed dynamics. For a mesh size of ca. 7 Å, or below, characteristic of these gels,¹⁹ a signature of confined diffusion would be a *Q*independent value of the HWHM of the Lorentzian function, $\Gamma/2(Q)$, up to ca. 1 Å^{-1,55,56} Conversely, we observed an increasing $\Gamma/2(Q)$, following roughly a Q^2 dependence up to 0.6–0.8 Å⁻¹ and then plateauing at higher *Q*-values. We thus concluded that the elastic part of the spectra does not originate from a confinement effect, as for example in refs 51 and 57, but it is rather primarily related to the existence of a hydrogen atoms population whose dynamics is too slow to be appreciated within the experimental resolution. This population is related to the bound water fraction evidenced by DSC. The slight Q-dependence observed in EISF_w(Q) is likely reminiscent of the water molecule rotation.³⁴ In order to reduce the number of free parameters during the fit, we thus fixed EISF_w(Q) to its averaged value in Q for each sample and temperature, <EISF_w>_Q. Figure 7 shows the fits of the S_w(Q, E)



Figure 7. Dynamic structure factor of hydration water in pHEMA gels and relative fit according to eq 16. The different components of the fit, i.e., elastic (delta function convoluted for the experimental resolution), quasi-elastic (Lorentzian function convoluted with instrumental resolution), and background, are shown for completeness.

for the different hydrogels at 300 K and $Q = 0.95 \text{ Å}^{-1}$ taken as examples. It can be noted that the good agreement with the experimental data is maintained when introducing such an approximation.

The relative weight of the elastic part $\langle EISF_w \rangle_Q$ can be therefore regarded as the fraction of water that strongly interacts with the polymer network, motionless in our time scale, and $(1 - \langle EISF_w \rangle_Q)$ as the fraction of water that is free to diffuse. The observation of several populations with distinct dynamic behavior is quite common in liquids under confinement, as evidenced by neutron scattering studies on other hydrogels^{27,31,37,53} and studies conducted with ¹H NMR and DSC on pHEMA hydrogels.^{23,58} Figure 8 shows $\langle EISF_w \rangle_Q$ as a



Figure 8. <EISF_w>_Q as a function of *T* for the different investigated pHEMA hydrogels.

function of temperature. In all the samples, part of the immobile water fraction converts into mobile water as the temperature increases. Moreover, the relative amount of immobile water is higher in the less hydrated gels, in agreement to results obtained with other techniques as reported in literature^{22,58} and to the DSC analysis of the present study (see Figure 6).

The results of Figure 8 indicate that in the 20% w/w chemical gel, the vast majority of the water molecules are tightly bound to the polymer chains at the investigated temperatures. At the same hydration, the physical gel is less effective in binding the water in agreement with DSC results. At higher water contents, i.e., 33% w/w, the *cg* and *pg* present almost the same distribution of immobile/mobile water.

The Q-dependence of $\Gamma/2$ are shown in Figure 9. A clear slowing down of the dynamics with respect to bulk water at the same temperature, induced by the confinement, can be identified, for example, by comparison with the work of Teixeira et al. on translational diffusion of bulk water.^{59,60} Indeed, it was proposed that dynamics of the interfacial water, confined within nanocavities or on the surface of biological materials, resembles the dynamic behavior of bulk water at temperatures lower by 20 K.⁶¹

The typical shape of the jump-diffusion can be observed: a Q^2 profile at low Q-values and a leveling off toward a plateau at high Q's. In this respect, it should be also noted that the

spectrum at the lowest Q-value in the $pg20_w$ is extremely noisy, and the derived fit parameters are not reliable. In $cg20_w$, a large part of the water is immobile at the time scale of the experiment. As a consequence, the visibility of the quasielastic broadening with respect to the elastic line is very reduced. Furthermore, QENS widths are found to be extremely narrow, at the edge or below the resolution limit of the instrument. At 270 K, almost exclusively elastic scattering is observed. Although with a prominent contribution from the elastic line, for the same sample at 300 K the mobile water fraction is increased and the dynamics is faster, and it is possible to recognize the jump-diffusion behavior.

Some general differences among the investigated systems can be noted. The less hydrated hydrogels show a narrower Lorentzian component, i.e., slower dynamics, for both cg and pg. In the 30% w/w hydrated samples, the widths are overall slightly larger for $cg30_w$. However, while at low temperatures the differences among the samples are quite constant in the entire Q range, at high temperatures the values are almost identical at low Q and become larger for increasing Q, as highlighted in Figure 10. Considering a jump-diffusion



Figure 10. Difference of quasi-elastic widths between chemical and physical gels at 30% w/w of hydration. $\Delta\Gamma/2 = \Gamma/2_{cg30 w} - \Gamma/2_{pg30 w}$.

mechanism, this suggests shorter residence times, τ , for the chemical gel and different *T*-dependence of the residence time and jump length, *l*, within the two systems. As opposed to the higher hydrated samples, the widths of $pg20_w$ are much larger than those of $cg20_w$, both at low and high temperatures.

In Figure 9, the lines are fits according to the wellestablished jump-diffusion models of Singwi and Sjölander⁶² (SSM), Hall and Ross⁶³ (HRM), and Chudley and Elliot⁶⁴ (CEM), which are all parametrized in terms of τ and *l*.



Figure 9. Q-dependence of $\Gamma/2$. Lines refer to jump-diffusion models (see text): CEM (sold line), SSM (dashed line), HRM (dotted line); color code for temperature follows that of symbols.

However, whereas the CEM refers to a jump process with a well-defined jump length, the SSM and HRM take a jump length uncertainty into consideration, following exponential and Gaussian distributions, respectively. More details on the models are given in the Supporting Information. For both cg30 w and pg30 w, the use of a distribution of jump lengths seems to be needed, as SSM and HRM better approximate the experimental data compared with the CEM. Conversely, the CEM seems to be the most consistent to approximate the experimental points for the 20% w/w hydrated systems. In the following, we will therefore refer to values from the HRM and SSM for the 30% w/w samples and CEM for the 20% w/w samples. For completeness, the fit parameters obtained for the different models and samples are reported in Tables S1 and S2 of the Supporting Information. A distribution of jump lengths is usually employed to describe the diffusion of bulk water.

In this respect, it is perhaps not surprising to observe an analogous behavior in the higher hydrated materials. The better agreement with a model based on a well-defined jump length for the less hydrated materials conversely points toward a higher degree of order when the number of water molecules per hydroxyl group is about 2, likely due to the strong interactions with the polymer. Such observations are in agreement with the different fragility behavior for the different hydrations, as previously discussed in the case of the polymer mobility. The values of the (averaged) jump length *l* are overall similar, around 3-4 Å (see Supporting Information for exact values and uncertainties), with a slight increase at higher temperature. In the $cg30_w$ the T-dependence is less pronounced than in the physical gels, possibly because a real mesh, created by the cross-linker, is present only in the former systems, whereas the structure of the physical gel likely evolves more drastically with the temperature changes.

Figure 11 shows the values for the residence time, τ , (a) and the diffusion coefficient, D, (b), calculated as $D = \frac{l^2}{6\tau}^2$. The lines represent fits according to an Arrhenius law: $\tau = \tau_0 \exp\left(\frac{-E_\tau}{k_B T}\right)$ in (a), and $D = D_0 \exp\left(\frac{-E_D}{k_B T}\right)$ in (b), where E_{τ} and $E_{\rm D}$ are activation energies for residence time and diffusion coefficient, respectively, $k_{\rm B}$ is the Boltzmann constant, and τ_0 and D_0 are the high temperature limits for residence time and diffusion coefficient. In general, diffusion coefficients become larger as the temperature increases, whereas residence times become smaller, as expected and in agreement with previous studies on bulk^{59,60} and confined water.^{27,38,51,65,66} We note here that diffusion in bulk water is not an Arrhenius process,⁵³ but in the limited temperature range investigated here, the Arrhenius fit provides for water hydrating pHEMA gels a reasonable approximation useful for comparison with other systems. As already pointed out, at 30% w/w of hydration the chemical gels show shorter residence times than the physical gels. The difference between the τ values obtained using the SSM or HRM model provides an estimate of the experimental uncertainty. However, E_{τ} is the same, within error bars, for both models, indicating the robustness of this insight. The temperature dependence is steeper (larger absolute values of E_{τ}) in cg30 w than in $pg30_w$ and τ_0 is much smaller (see Table S3 in Supporting Information); i.e., the attempt frequency for the jump, τ_0^{-1} , is higher for the chemical gels. Within the same type of gel, a higher water concentration corresponds to shorter residence times, closer to those of bulk water. The values of E_D , ranging



Figure 11. Residence times (a) and diffusion coefficients (b). Lines are fits according to Arrhenius law (solid lines for $pg20_w$, dashed lines for $pg30_w$, dotted lines for $cg30_w$; color code according to the different models used to derived $\tau[D]$ for the different samples, as in the legend).

from 0.11(1) eV [11(1) kJ/mol] to 0.18(1) eV [17(1) kJ/mol], are similar to those obtained in other confined media such as Vycor glass (0.12 eV [12 kJ/mol])⁶⁶ or PVA hydrogels (0.16(2) eV [15(2) kJ/mol]),²⁷ and anyway comparable to those of bulk water (~0.2–0.26 eV [19–25 kJ/mol]),^{59,67} showing that water diffusion in pHEMA hydrogels remains an H-bonding governed mechanism. Nevertheless, considering for example the values at 300 K, where the signal is clearer (because of a higher quasi-elastic to elastic ratio), the diffusion coefficients are smaller and residence times are larger than the values for water in confinement in both hard and soft media, such as Vycor and PVA hydrogels,^{66,27} underlining a severely reduced water mobility and strong interactions with the pHEMA matrix.

CONCLUSIONS

Hydrogels with optimal release and confining properties, such as HEMA based systems, are highly relevant for medical and cultural heritage applications. The intimate comprehension of transport phenomena in these systems constitutes a basis in the fine-tuning of their delivery properties from a molecular point of view. Quasi-elastic neutron scattering with contrast variation was used to selectively investigate the dynamics of the polymer network and the transport properties of the water confined into the hydrogel matrix, and how such dynamics are affected by temperature, cross-linker nature, and water content.

A distribution of relaxation processes was observed for the polymer network, mainly associated with the side chain dynamics. The dynamics is faster with increasing temperature and hydration, the latter underlining the plasticizer role of the

solvent, which also leads to a more fragile behavior. In physical gels, the relaxation is slower with a smaller portion of the space explored than in the chemical equivalents, likely because of the involvement of the side chains in the network formation. In order to better discriminate the motions of the different part of the polymer chain, further investigation could be extended to selectively deuterated polymer segments, also combining different dynamical ranges.

Regarding the hydration water, a very strong confining effect imposed by the gel matrix was observed. The presence of a fraction of water strongly associated with the polymer matrix and immobile in the experimental time scale (up to few nanoseconds), and a mobile fraction, was detected. The ratio of the two fractions depends on T, hydration, and cross-linker nature. The dynamics of the mobile fraction well agrees with an H-bond governed process with activation energies on the order of 0.11-0.18 eV and jump-diffusion mechanism. The jumps lengths are on the order of 3-4 Å, and well-defined for the less hydrated gels. For the 30% w/w hydrated gels a distribution of jump lengths needs to be considered, consistently with the plasticizer effect observed in the polymer network dynamics. The diffusion coefficients increase and residence times decrease with increasing temperature and hydration. At 20% w/w hydration, the water mobility is considerably higher in the physical gels, whereas at 30% w/w the water mobilities are more similar between the physical and chemical gels, although with slightly shorter residence times in the second case.

Our approach represents a useful starting point for the investigation of more sophisticated hydrogel systems.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpcc.9b04212.

Polymer network EISF fitting parameters, jump-diffusion models, DSC thermograms for chemical and physical gels, tables with residence times, jump lengths, diffusion coefficients and activation energies (PDF)

AUTHOR INFORMATION

Corresponding Author

*Phone: +39 055 457 3037. E-mail: emiliano.fratini@unifi.it. Web: www.csgi.unifi.it.

ORCID 🔍

Daria Noferini: 0000-0002-7680-8415

Antonio Faraone: 0000-0002-3783-5816

Eugene Mamontov: 0000-0002-5684-2675

Emiliano Fratini: 0000-0001-7104-6530

Piero Baglioni: 0000-0003-1312-8700

Present Address

^V(D.N.) Forschungszentrum Jülich GmbH, JCNS at Heinz Maier-Leibnitz Zentrum, Lichtenberstraße 1, 85747, Garching, Germany.

Notes

The full description of the procedures used in this paper requires the identification of certain commercial products and their suppliers. The inclusion of such information should in no way be construed as indicating that such products or suppliers are endorsed by NIST or are recommended by NIST or that they are necessarily the best materials, instruments, software or suppliers for the purposes described.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

D.N., M.R., E.F., and P.B. thank MIUR and CSGI for partial financial support. A.F. acknowledges support from the Center for High Resolution Neutron Scattering, a partnership between the National Institute of Standards and Technology and the National Science Foundation under Agreement No. DMR-1508249. The neutron scattering experiments at Oak Ridge National Laboratory's (ORNL) Spallation Neutron Source were supported by the Scientific User Facilities Division, Office of Basic Energy Sciences.

REFERENCES

(1) Donnelly, R. F.; Laverty, G.; Singh, T. R. R. Hydrogels: Design, Synthesis and Application in Drug Delivery and Regenerative Medicine; CRC Press/Taylor & Francis Group, 2017.

(2) Wichterle, O.; Lím, D. Hydrophilic Gels for Biological Use. Nature 1960, 185 (4706), 117-118.

(3) Kopeček, J. Hydrogels From Soft Contact Lenses And Implants To Self-Assembled Nanomaterials. J. Polym. Sci., Part A: Polym. Chem. 2009, 47 (22), 5929–5946.

(4) Montheard, J.-P.; Chatzopoulos, M.; Chappard, D. 2-Hydroxyethyl Methacrylate (HEMA): Chemical Properties and Applications in Biomedical Fields. *J. Macromol. Sci., Polym. Rev.* **1992**, 32 (1), 1–34.

(5) Dvorankova, B.; Holikova, Z.; Vacik, J.; Konigova, R.; Kapounkova, Z.; Michalek, J.; Pradn, M.; Smetana, K. Reconstruction of Epidermis by Grafting of Keratinocytes Cultured on Polymer Support - Clinical Study. *Int. J. Dermatol.* **2003**, *42* (3), 219–223.

(6) Bhatia, S.; Bergethon, P. R.; Blease, S.; Kemper, T.; Rosiello, A.; Zimbardi, G. P.; Franzblau, C.; Spatz, E. L. A Synthetic Dural Prosthesis Constructed from Hydroxyethylmethacrylate Hydrogels. *J. Neurosurg.* **1995**, *83* (5), 897–902.

(7) Bavaresco, V. P.; de Carvalho Zavaglia, C. A.; de Carvalho Reis, M.; Malmonge, S. M. Devices for Use as an Artificial Articular Surface in Joint Prostheses or in the Repair of Osteochondral Defects. *Artif. Organs* **2000**, *24* (3), 202–205.

(8) Ronel, S. H.; D'Andrea, M. J.; Hashiguchi, H.; Klomp, G. F.; Dobelle, W. H. Macroporous Hydrogel Membranes for a Hybrid Artificial Pancreas. I. Synthesis and Chamber Fabrication. *J. Biomed. Mater. Res.* **1983**, *17* (5), 855–864.

(9) Studenovská, H.; Slouf, M.; Rypácek, F. Poly(HEMA) Hydrogels with Controlled Pore Architecture for Tissue Regeneration Applications. J. Mater. Sci.: Mater. Med. 2008, 19 (2), 615–621.

(10) Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. Hydrogels in Pharmaceutical Formulations. *Eur. J. Pharm. Biopharm.* **2000**, 50 (1), 27–46.

(11) Ferreira, L.; Vidal, M. M.; Gil, M. H. Evaluation of Poly(2-Hydroxyethyl Methacrylate) Gels as Drug Delivery Systems at

Different pH Values. Int. J. Pharm. 2000, 194 (2), 169–180. (12) He, H.; Cao, X.; Lee, L. J. Design of a Novel Hydrogel-Based

Intelligent System for Controlled Drug Release. J. Controlled Release 2004, 95 (3), 391-402.

(13) Lu, S.; Anseth, K. S. Photopolymerization of Multilaminated Poly(HEMA) Hydrogels for Controlled Release. *J. Controlled Release* **1999**, 57 (3), 291–300.

(14) Gulsen, D.; Chauhan, A. Dispersion of Microemulsion Drops in HEMA Hydrogel: A Potential Ophthalmic Drug Delivery Vehicle. *Int. J. Pharm.* **2005**, *292* (1–2), 95–117.

(15) Baglioni, P.; Carretti, E.; Chelazzi, D. Nanomaterials in Art Conservation. *Nat. Nanotechnol.* **2015**, *10* (4), 287–290.

(16) Bonelli, N.; Montis, C.; Mirabile, A.; Berti, D.; Baglioni, P. Restoration of Paper Artworks with Microemulsions Confined in

Hydrogels for Safe and Efficient Removal of Adhesive Tapes. Proc. Natl. Acad. Sci. U. S. A. 2018, 115 (23), 5932-5937.

(17) Chelazzi, D.; Giorgi, R.; Baglioni, P. Microemulsions, Micelles, and Functional Gels: How Colloids and Soft Matter Preserve Works of Art. *Angew. Chem., Int. Ed.* **2018**, 57 (25), 7296–7303.

(18) Baglioni, P.; Berti, D.; Bonini, M.; Carretti, E.; Dei, L.; Fratini, E.; Giorgi, R. Micelle, Microemulsions, and Gels for the Conservation of Cultural Heritage. *Adv. Colloid Interface Sci.* **2014**, *205*, 361–371.

(19) Domingues, J. A. L.; Bonelli, N.; Giorgi, R.; Fratini, E.; Gorel, F.; Baglioni, P. Innovative Hydrogels Based on Semi-Interpenetrating p(HEMA)/PVP Networks for the Cleaning of Water-Sensitive Cultural Heritage Artifacts. *Langmuir* **2013**, *29* (8), 2746–2755.

(20) Baglioni, M.; Domingues, J. A. L.; Carretti, E.; Fratini, E.; Chelazzi, D.; Giorgi, R.; Baglioni, P. Complex Fluids Confined into Semi-Interpenetrated Chemical Hydrogels for the Cleaning of Classic Art: A Rheological and SAXS Study. *ACS Appl. Mater. Interfaces* **2018**, *10* (22), 19162–19172.

(21) Tranoudis, I.; Efron, N. Water Properties of Soft Contact Lens Materials. *Cont. Lens Anterior Eye* **2004**, 27 (4), 193–208.

(22) Lee, H. B.; Jhon, M. S.; Andrade, J. D Nature of Water in Synthetic Hydrogels. I. Dilatometry, Specific Conductivity, and Differential Scanning Calorimetry of Polyhydroxyethyl Methacrylate. J. Colloid Interface Sci. **1975**, *51* (2), 225–231.

(23) Roorda, W.; Bouwstra, J.; de Vries, M. A.; Junginger, H. Thermal Analysis of Water in p(HEMA) Hydrogels. *Biomaterials* **1988**, *9* (6), 494–499.

(24) Peschier, L.J.C.; Bouwstra, J.A.; de Bleyser, J.; Junginger, H.E.; Leyte, J.C. Water Mobility and Structure in Poly[2-Hydroxyethylmethacrylate] Hydrogels by Means of the Pulsed Field Gradient NMR Technique. *Biomaterials* **1993**, *14* (12), 945–952.

(25) Manetti, C.; Casciani, L.; Pescosolido, N. Diffusive Contribution to Permeation of Hydrogel Contact Lenses: Theoretical Model and Experimental Evaluation by Nuclear Magnetic Resonance Techniques. *Polymer* **2002**, *43* (1), 87–92.

(26) Sears, V. F. Neutron Scattering Lengths and Cross Sections. *Neutron News* **1992**, *3* (3), 26–37.

(27) Paradossi, G.; Cavalieri, F.; Chiessi, E.; Telling, M. T. F. Supercooled Water in PVA Matrixes: I. An Incoherent Quasi-Elastic Neutron Scattering (QENS) Study. *J. Phys. Chem. B* **2003**, *107* (33), 8363–8371.

(28) Capponi, S.; Arbe, A.; Cerveny, S.; Busselez, R.; Frick, B.; Embs, J. P.; Colmenero, J. Quasielastic Neutron Scattering Study of Hydrogen Motions in an Aqueous Poly(Vinyl Methyl Ether) Solution. J. Chem. Phys. **2011**, 134 (20), 204906.

(29) Rubio Retama, J.; Frick, B.; Seydel, T.; Stamm, M.; Fernandez Barbero, A.; López Cabarcos, E. Polymer Chain Dynamics of Core– Shell Thermosensitive Microgels. *Macromolecules* **2008**, *41* (13), 4739–4745.

(30) Rubio-Retama, J.; Frick, B.; Seydel, T.; López-Ruiz, B.; Fernandez-Barbero, A.; López-Cabarcos, E. Molecular Motions in Low Cross-Linked Poly(N-Isopropylacrylamide) Microgels. *Colloids Surf., A* **2008**, 319 (1–3), 149–153.

(31) Ghugare, S. V.; Chiessi, E.; Telling, M. T. F.; Deriu, A.; Gerelli, Y.; Wuttke, J.; Paradossi, G. Structure and Dynamics of a Thermoresponsive Microgel around Its Volume Phase Transition Temperature. J. Phys. Chem. B 2010, 114 (32), 10285–10293.

(32) Zanatta, M.; Tavagnacco, L.; Buratti, E.; Bertoldo, M.; Natali, F.; Chiessi, E.; Orecchini, A.; Zaccarelli, E. Evidence of a Low-Temperature Dynamical Transition in Concentrated Microgels. *Sci. Adv.* **2018**, *4* (9), eaat5895.

(33) Mamontov, E.; Herwig, K. W. A Time-of-Flight Backscattering Spectrometer at the Spallation Neutron Source, BASIS. *Rev. Sci. Instrum.* **2011**, 82 (8), 085109.

(34) Bée, M. Quasielastic Neutron Scattering: Principles and Applications in Solid State Chemistry, Biology and Materials Science; Adam Hilger: Bristol and Philadelphia, 1988.

(35) Azuah, R.; Kneller, L.; Qiu, Y.; Tregenna-Piggott, P. L. W.; Brown, C. M.; Dimeo, R. M.; Copley, J. R. D. DAVE: A Comprehensive Software Suite for the Reduction, Visualization, and Analysis of Low Energy Neutron Spectroscopic Data. J. Res. Natl. Inst. Stand. Technol. 2009, 114 (6), 341-358.

(36) Paradossi, G.; Cavalieri, F.; Chiessi, E.; Mondelli, C.; Telling, M. T. F. Structural Fluctuations in Cross-Linked Matrices with Narrow Pore Size Distribution. *Chem. Phys.* **2004**, *302* (1–3), 143–148.

(37) Paradossi, G.; Cavalieri, F.; Chiessi, E. Proton Fluctuations and Water Diffusion in Dextran Chemical Hydrogels Studied by Incoherent Elastic and Quasielastic Neutron Scattering. *Carbohydr. Res.* **2005**, *340* (5), 921–927.

(38) Paradossi, G.; Di Bari, M. T.; Telling, M. T. F.; Turtu', A.; Cavalieri, F. Incoherent Quasi-Elastic Neutron Scattering Study of Chemical Hydrogels Based on Poly(Vinyl Alcohol). *Phys. B* **2001**, 301 (1–2), 150–156.

(39) Roh, J. H.; Curtis, J. E.; Azzam, S.; Novikov, V. N.; Peral, I.; Chowdhuri, Z.; Gregory, R. B.; Sokolov, A. P. Influence of Hydration on the Dynamics of Lysozyme. *Biophys. J.* **2006**, *91* (7), 2573–2588.

(40) Chahid, A.; Alegria, A.; Colmenero, J. Methyl Group Dynamics in Poly(Vinyl Methyl Ether). A Rotation Rate Distribution Model. *Macromolecules* **1994**, *27* (12), 3282–3288.

(41) Colmenero, J.; Arbe, A.; Alegría, A.; Monkenbusch, M.; Richter, D. On the Origin of the Non-Exponential Behaviour of the α -Relaxation in Glass-Forming Polymers: Incoherent Neutron Scattering and Dielectric Relaxation Results. *J. Phys.: Condens. Matter* **1999**, *11* (10A), A363–A370.

(42) Zhang, Y.; Lagi, M.; Ridi, F.; Fratini, E.; Baglioni, P.; Mamontov, E.; Chen, S. H. Observation of Dynamic Crossover and Dynamic Heterogeneity in Hydration Water Confined in Aged Cement Paste. J. Phys.: Condens. Matter 2008, 20 (50), 502101.

(43) Bizzarri, A.; Cannistraro, S. Molecular Dynamics of Water at the Protein-Solvent Interface. J. Phys. Chem. B 2002, 106, 6617–6633.

(44) Katava, M.; Stirnemann, G.; Zanatta, M.; Capaccioli, S.; Pachetti, M.; Ngai, K. L.; Sterpone, F.; Paciaroni, A. Critical Structural Fluctuations of Proteins upon Thermal Unfolding Challenge the Lindemann Criterion. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114* (35), 9361–9366.

(45) Ito, K.; Moynihan, C. T.; Angell, C. A. Thermodynamic Determination of Fragility in Liquids and a Fragile-to-Strong Liquid Transition in Water. *Nature* **1999**, *398* (6727), 492–495.

(46) Thiessen, W. E.; Narten, A. H. Neutron Diffraction Study of Light and Heavy Water Mixtures at 25 °C. J. Chem. Phys. 1982, 77 (5), 2656.

(47) Gallo, P.; Sciortino, F.; Tartaglia, P.; Chen, S. Slow Dynamics of Water Molecules in Supercooled States. *Phys. Rev. Lett.* **1996**, *76* (15), 2730–2733.

(48) Sears, V. F. Cold Neutron Scattering by Molecular Liquids: III. Methane. *Can. J. Phys.* **1967**, *45* (2), 237–254.

(49) Chen, S.-H.; Gallo, P.; Sciortino, F.; Tartaglia, P. Molecular-Dynamics Study of Incoherent Quasielastic Neutron-Scattering Spectra of Supercooled Water. *Phys. Rev. E: Stat. Phys., Plasmas, Fluids, Relat. Interdiscip. Top.* **1997**, 56 (4), 4231–4243.

(50) Faraone, A.; Liu, L.; Chen, S.-H. Model for the Translation-Rotation Coupling of Molecular Motion in Water. *J. Chem. Phys.* **2003**, *119* (12), 6302–6313.

(51) Zanotti, J.-M.; Bellissent-Funel, M.-C.; Chen, S.-H. Relaxational Dynamics of Supercooled Water in Porous Glass. *Phys. Rev. E: Stat. Phys., Plasmas, Fluids, Relat. Interdiscip. Top.* **1999**, *59* (3), 3084–3093.

(52) Carretti, E.; Grassi, S.; Cossalter, M.; Natali, I.; Caminati, G.; Weiss, R. G.; Baglioni, P.; Dei, L. Poly(Vinyl Alcohol)–Borate Hydro/Cosolvent Gels: Viscoelastic Properties, Solubilizing Power, and Application to Art Conservation. *Langmuir* **2009**, 25 (15), 8656– 8662.

(53) Cavalieri, F.; Chiessi, E.; Finelli, I.; Natali, F.; Paradossi, G.; Telling, M. T. F. Water, Solute, and Segmental Dynamics in Polysaccharide Hydrogels. *Macromol. Biosci.* **2006**, *6* (8), 579–589.

(54) Cavalieri, F.; Chiessi, E.; Villa, R.; Viganò, L.; Zaffaroni, N.; Telling, M. T. F.; Paradossi, G. Novel PVA-Based Hydrogel

Microparticles for Doxorubicin Delivery. *Biomacromolecules* 2008, 9 (7), 1967–1973.

(55) Volino, F.; Dianoux, A. J. Neutron Incoherent Scattering Law for Diffusion in a Potential of Spherical Symmetry: General Formalism and Application to Diffusion inside a Sphere. *Mol. Phys.* **1980**, 41 (2), 271–279.

(56) Volino, F.; Perrin, J.-C.; Lyonnard, S. Gaussian Model for Localized Translational Motion: Application to Incoherent Neutron Scattering. J. Phys. Chem. B **2006**, 110 (23), 11217–11223.

(57) Faraone, A.; Fratini, E.; Garai, S.; Müller, A.; Tyagi, M.; Jenkins, T.; Mamontov, E.; Paul, R. L.; Copley, J. R. D.; Baglioni, P. Incoherent Quasielastic Neutron Scattering Study of the Relaxation Dynamics in Molybdenum-Oxide Keplerate-Type Nanocages. *J. Phys. Chem. C* **2014**, *118* (24), 13300–13312.

(58) Ghi, P. Y.; Hill, D. J. T.; Whittaker, A. K. (1)H NMR Study of the States of Water in Equilibrium Poly(HEMA-Co-THFMA) Hydrogels. *Biomacromolecules* **2002**, *3* (5), 991–997.

(59) Teixeira, J.; Bellissent-Funel, M.-C.; Chen, S.-H.; Dianoux, A. Experimental Determination of the Nature of Diffusive Motions of Water Molecules at Low Temperatures. *Phys. Rev. A: At., Mol., Opt. Phys.* **1985**, *31* (3), 1913–1917.

(60) Teixeira, J; Bellissent-Funel, M -C Dynamics of Water Studied by Neutron Scattering. J. Phys.: Condens. Matter 1990, 2, SA105– SA108.

(61) Chen, S.-H.; Gallo, P.; Bellissent-Funel, M.-C. Slow Dynamics of Interfacial Water. *Can. J. Phys.* **1995**, 73 (11–12), 703–709.

(62) Singwi, K. S.; Sjölander, A. Diffusive Motions in Water and Cold Neutron Scattering. *Phys. Rev.* **1960**, *119* (3), 863–871.

(63) Hall, P. L.; Ross, D. K. Incoherent Neutron Scattering Functions for Random Jump Diffusion in Bounded and Infinite Media. *Mol. Phys.* **1981**, *42* (3), 673–682.

(64) Chudley, C. T.; Elliott, R. J. Neutron Scattering from a Liquid on a Jump Diffusion Model. *Proc. Phys. Soc., London* **1961**, 77 (2), 353-361.

(65) Chiessi, E.; Cavalieri, F.; Paradossi, G. Supercooled Water in PVA Matrixes. II. A Molecular Dynamics Simulation Study and Comparison with QENS Results. *J. Phys. Chem. B* **2005**, *109* (16), 8091–8096.

(66) Bellissent-Funel, M.; Chen, S.; Zanotti, J.-M. Single-Particle Dynamics of Water Molecules in Confined Space. *Phys. Rev. E: Stat. Phys., Plasmas, Fluids, Relat. Interdiscip. Top.* **1995**, *51* (5), 4558–4569.

(67) Mills, R. Self-Diffision in Normal and Heavy Water in the Range 1-45°. J. Phys. Chem. 1973, 77 (5), 685-688.