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► **To cite this version:**

Hernan Garate, King-Wo Li, Denis Bouyer, Patrick Guenoun. Optical tracking of relaxation dynamics in semi-dilute hydroxypropylcellulose solutions as a precise phase transition probe. *Soft Matter*, 2017, 10.1016/S0375-9601(99)00347-3 . cea-01588251v1

HAL Id: cea-01588251

<https://cea.hal.science/cea-01588251v1>

Submitted on 15 Sep 2017 (v1), last revised 19 Sep 2017 (v2)

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Optical tracking of relaxation dynamics in semi-dilute hydroxypropylcellulose solutions as a precise phase transition probe

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Abstract

Phase separation of thermo-responsive polymers in solution is a complex process, whose understanding is essential to screen and design materials with diverse technological applications. Here we report on a method based on dynamic light scattering (DLS) experiments to investigate the phase separation of thermo-responsive polymer solutions and precisely define the transition temperature (T_{PS}). Our results are applied on hydroxypropylcellulose (HPC) solutions as an important biosourced green water-soluble polymer. As determined by DLS, the amplitudes of the fast and slow modes of relaxation dynamics evolve as temperature gets closer to the phase transition point eventually leading to phase separation. The evolution of the modes with temperature is markedly different for concentrations below the overlap concentration (c^*) (dilute regime), above c^* (semi-dilute regime) and above the entanglement concentration (c_e). In the three cases though, the fast and slow mode amplitudes undergo a sharp transition in a narrow temperature range, defining accurately the phase separation locus. The results agree with turbidimetric analysis for the phase transition determination but with a better precision. Our results also show that the one-phase dynamics and phase separation dynamics in the two-phase region are only in continuity for $c > c_e$, revealing mechanistic details about the HPC phase separation process. Above T_{PS} we identify a temperature range where the intensity autocorrelation function has a single-exponential shape. In the latter regime, we monitor the

30 growth kinetics of polymer domains and provide clues to rationalize the stabilizing effects of
31 the interfaces leading to the arrested-like phase separation behavior observed for HPC.

32

33 **Introduction**

34 Phase separation of thermo-responsive water-soluble polymers is an intense research field in
35 polymer science driven by promising technologies in a diverse range of fields, among
36 biomedicine¹ and environmentally friendly materials.²⁻⁴ Critical aspects to designing and
37 screening such systems rely on a better understanding of the phase transition and the
38 determination of well-characterized phase diagrams and phase transition solution temperatures
39 since the latter temperatures are the main experimental data needed to further investigate the
40 fundamentals of phase separation mechanisms and kinetics. Different approaches based on
41 optical measurements (transmittance, scattering intensity at different angles and refractometry)
42 and differential scanning calorimetry are currently utilized to approach and locate the phase
43 boundary (T_{PS}) of thermo-responsive water-soluble polymers in a broad range of
44 concentrations. However, the typical criteria to define such transition are rather arbitrary
45 without a clear physical significance that justifies a particular choice, which represents one of
46 the major sources of diversity (as much as 20 % of T_{PS}) of phase diagrams for several thermo-
47 responsive polymers widely used in applications, such as poly(*N*-isopropylacrylamide)
48 (PNIPAm)⁵, hydroxypropylcellulose (HPC)^{6,7}, methylcellulose⁸⁻¹⁰, hydroxypropylmethyl
49 cellulose^{8,9}, among others. Taking into account that phase separation mechanisms of thermo-
50 responsive polymers strongly depend on the temperature quench depth¹⁰ the arbitrariness in
51 defining T_{PS} represents a clear limitation to investigating phase separation mechanisms and
52 kinetics in a temperature range close to T_{PS} .

53 In this article we are interested in exploring another approach to define the phase separation
54 transition of a thermo-responsive water-soluble polymer in a broad range of concentrations

55 based on Dynamic Light Scattering (DLS). DLS is a well suited technique to investigate
56 polymer dynamics over a large concentration range and a large temporal window of relaxation
57 times.¹¹ In the dilute regime, at which polymer concentration is below the overlap concentration
58 (c^*), the intensity autocorrelation function ($g_2(t)$) reports a single relaxation mode which
59 describes Brownian motion of single coils for monodisperse systems¹² whatever the solvent
60 quality is.¹³ At concentrations above c^* the system resides in the semi-dilute regime, at which
61 polymer chains overlap and possibly entangle. Li *et al.* demonstrated that for poly(styrene) in
62 a thermodynamically good solvent (benzene) at $c/c^* = 30$, $g_2(t)$ is still described by a single
63 diffusive relaxation mode,¹⁴ while a second non-diffusive relaxation mode is evidenced (slow
64 mode) at higher t when the solvent quality gets poorer.^{13,14} The interpretation of the latter slow
65 mode has been controversial and the subject of extensive research in the last decades for
66 deciphering its origin with respect to blobs relaxations below or above the entanglement
67 concentration (c_e). Pioneering works by Brown *et al.*^{15,16} and more recently Yuan *et al.*¹³
68 attributed the slow mode relaxation to permanent aggregates in the single-phase region, while
69 more recent experiments^{11,17} described the slow relaxation dynamics of aqueous PNIPAm
70 solutions as originating from transient clusters having a non-diffusive nature. **In addition, a**
71 **second slow dynamic was identified for shape persistent polymers (Fytas, Somma).** Several
72 studies in this area focused on the effect of polymer concentration, polymer architecture, and
73 temperature on the slow mode¹⁷⁻²⁰ in order to **explain the origin of this slow relaxation dynamic.**
74 **Here our goal is different: we address the question of whether it is possible to extract relevant**
75 **quantitative information about the phase transition of a polymer solution in the semi-dilute**
76 **regime by following the fast and slow mode evolution as temperature gets closer to phase**
77 **separation.** For this study we selected HPC aqueous solutions as a thermo-responsive
78 biosourced polymer which was recently designed as an excellent candidate for making porous
79 membranes excluding the use of organic solvents.³ It displays lower critical solution

80 temperature behavior in water at $\sim 40^\circ\text{C}$ (up to 40 %),^{21,22} a very convenient feature for many
81 applications, and was first characterized in 1988 to phase separate by spinodal decomposition
82 at $c = 10\%$.²³

83 In this article we show that the approach of HPC phase transition significantly impacts the fast
84 and slow mode behaviors. By following the latter modes up to the phase boundary, we
85 demonstrate that it is possible to define the phase transition temperature with a remarkable
86 accuracy. This methodology provides a more precise and physically meaningful approach to
87 determine the phase transition temperature than the commonly used turbidimetry method.

88 We also show that the evolution of relaxation modes for HPC is strongly concentration
89 dependent and provides clues to describe the phase separation mechanisms by varying the
90 concentration. For instance, a remarkable continuity of modes from the single-phase region to
91 the two-phase region observed for entangled solutions reveals that the non-diffusive transient
92 clusters formed in the single-phase region are precursors of the phase separating objects.

93 Finally, we show that DLS can be used to resolve the growth kinetics of HPC domains for
94 concentrations as high as 5 % and small thermal quenches, at which the single exponential
95 nature of $g_2(t)$ is preserved.

96

97 **Experimental**

98 **Sample preparation**

99 A commercial HPC (Sigma-Aldrich) was employed for this study since the very same polymer
100 proved to be a valuable choice for further applications for membranes.³ The weight average
101 molecular weight (M_w), evaluated by size exclusion chromatography (Shimadzu LC-20AD)
102 using a Shodex OHpak SB-803/SB-804 column and poly(ethylene glycol) molecular weight
103 standards, is 72 kg/mol and PDI \sim 3. HPC aqueous solutions in the concentration range 0.5 to 30
104 % (wt.%) were prepared by fully dispersing HPC powder in preheated Milli-Q water at 60°C

105 with stirring for 2 h. The samples were then cooled and stored at 4°C overnight to complete
106 hydration of the polymer. The aqueous solutions were transparent at room temperature.
107 Samples with $c \leq 10\%$ were filtered using 0.45 μm Millipore filters directly into dust-free
108 PMMA light scattering cuvettes. Solutions with concentration higher than 20% were prepared
109 from filtered 10% solution and concentrated under reduced pressure (220 mbar) at 60°C due to
110 the impossibility to filter such concentrated samples. The overlap concentration c^* was
111 determined from the definitions $c^* = 3M/(4\pi N_A R_g^3)$, $M/(2^{3/2} N_A R_g^3)$, and $[\eta]^{-1}$, where M ,
112 R_g , N_A and $[\eta]$ are the molar mass, the radius of gyration of polymer chains, the Avogadro
113 constant and the intrinsic viscosity, respectively. In this work we use the c^* value obtained from
114 $[\eta]^{-1}$, since the other two definitions are less precise due to the uncertainty in R_g as PDI is
115 high. The entanglement concentration c_e , representing the concentration above which the
116 polymer chains form an entangled network, was estimated as $c_e \approx 10c^*$, as reported by Colby²⁴
117 for neutral polymers in good solvent conditions. The radius of gyration of polymer chains was
118 determined as $R_g = 1.56R_h$, assuming good solvent conditions far enough from T_{PS} , where R_h
119 is the hydrodynamic radius calculated from diffusion coefficient D obtained by DLS
120 experiments of diluted samples employing the Stokes-Einstein equation, $R_h = (k_B T / 6\pi\eta_0) / D$,
121 where k_B , T and η_0 are the Boltzmann constant, the absolute temperature, and the solvent
122 viscosity, respectively. Since the polymer is polydisperse, D means actually an average D over
123 the size distribution of chains. Intrinsic viscosity was measured by the rolling ball principle
124 using a microviscometer Lovis 2000M (Anton Paar) at a fixed angle of 85°. HPC solutions were
125 prepared by dilution in the concentration range of 0.01-2% and measured at 30°C.

126

127 **Dynamic light scattering**

128 Back-scattering intensity autocorrelation function ($g_2(t)$) was obtained using a Zetasizer Nano
129 ZS (Malvern Instruments Ltd., Worcestershire, UK) (temperature control range 0-90°C, \pm

130 0.1°C) equipped with a 4 mW He-Ne laser of $\lambda_0 = 633$ nm. The angle between the laser beam
 131 and the detector (avalanche photodiode) was $\theta = 173^\circ$ and the scattering vector (q) ($q =$
 132 $(4\pi n/\lambda_0) \sin(\theta/2)$) was 0.02633 nm^{-1} . The laser power was automatically attenuated to
 133 collect an optimal scattered intensity. The measurement penetration depth into the sample was
 134 set to 2 mm. A 30 s acquisition time was generally enough to obtain a stable intensity
 135 autocorrelation function. Increasing the acquisition time up to 100 times the slower dynamical
 136 mode relaxation time did not provide any additional change in the signal of the intensity
 137 autocorrelation function. HPC solutions were heated at different T in the range between 29.4
 138 and 48°C in which T_{PS} is found. The heating rate (3 °C/min) allowed a fast thermal
 139 equilibration at each final temperature (equilibration time was measured using a thermocouple
 140 within solution). Measurements in the two-phase region ($T > T_{PS}$) were performed either close
 141 to T_{PS} ($T - T_{PS} \leq 4 \text{ }^\circ\text{C}$) or well above T_{PS} ($T - T_{PS} \geq 10 \text{ }^\circ\text{C}$). The final temperature was
 142 reached after 1 min heating in the two-phase region at T close to T_{PS} and up to 4 min heating in
 143 the two-phase region at T well above to T_{PS} . Intensity autocorrelation functions were measured
 144 at different temperatures as a function of time at 5 min time intervals until no significant
 145 differences were observed in consecutive measurements (between 10-30 min). Repeated
 146 measurements were performed at each temperature at 1 h interval to ensure data are in steady
 147 state. Before each measurement at a certain temperature, an equilibration step at 29.4°C for 30
 148 min was performed.

149 $g_2(t)$ can be related to the normalized electric field correlation function $g_1(t)$ by the Siegert
 150 relation as¹²

$$151 \quad g_2(t) = \beta |g_1(t)|^2 \quad (1)$$

152 where $0 < \beta < 1$ is a constant related to the coherence of the detection optics. For a polydisperse
 153 system,²⁵ $g_1(t)$ is related to the distribution of the characteristic relaxation time distribution
 154 ($G(\tau)$) as

155 $|g_1(t)| = \int_0^\infty G(\tau)e^{-t/\tau}d\tau$ (2)

156 In this study ($G(\tau)$) was calculated using the Laplace inversion of $g_1(t)$ (normalized to 1 at
157 $t = 0$) on the basis of eqs 1 and 2 by the Maximum Entropy Method.^{12,26} $G(\tau)$ usually displays
158 two major relaxation modes (fast and slow). Fast mode correlation time (τ_{fm}) and slow mode
159 correlation time (τ_{sm}) were extracted from the mean peak position of fast and slow relaxation
160 modes, respectively. The contribution of each mode (amplitude) was obtained from the relative
161 peak area of each distribution mode. Additionally, correlation times and amplitudes were also
162 obtained by a similar analysis than that reported by Yamamoto *et al.*¹⁸ by fitting to a sum of
163 single-exponential functions. The obtained results (data not shown) were in good agreement
164 with those obtained from Maximum Entropy Method.

165

166 **Turbidimetric measurements**

167 Phase separation temperatures were determined by optical transmittance method using a quartz
168 cell filled with HPC solutions inserted in a thermostat (0.01°C precision). For determining T_{PS} ,
169 a 5 mm thick cell was used, shined by a laser beam ($\lambda = 632.8$ nm). Two photodiodes were
170 placed before and after the sample to measure the transmission of the light through the sample.
171 Thermal steps of 0.2°C followed by 30 min equilibration time were performed to monitor the
172 transmittance versus time. As the temperature approached T_{PS} the transmittance decreased with
173 time asymptotically, and therefore the transmittance at infinite time τ_∞ (T_∞) at each thermal
174 step was extrapolated by fitting to $y = A_1 \exp(-t/t_1) + T_\infty$. From transmittance vs temperature
175 curves, T_{PS} was determined by two different criteria: i) As the abscissa of the intercept between
176 the horizontal asymptote at low temperatures and the tangent to the transmission decrease (T_-);
177 ii) As the middle point on the slope of variation between τ_∞ and τ_0 ($T_{1/2}$).

178

179 **Confocal laser scanning microscopy**

180 HPC phase separation was monitored using an Olympus Fluoview FV1000 inverted confocal
181 microscope. HPC solution ($\sim 10 \mu\text{L}$) was sandwiched between two glass slides separated and
182 sealed by a polydimethylsiloxane ring ($200 \mu\text{m}$ thick). Rhodamine 6G Chloride was used as the
183 hydrophilic fluorophore. Micrographs were collected with a 40X objective. A thermal stage
184 (Linkam PE 94) was used to control the temperature. The solutions were equilibrated at 30°C
185 for 30 min followed by heating to the final quench temperature at a rate of $5^\circ\text{C}/\text{min}$. The working
186 distance of the objective was focused in a plane inside the solution, away ($\sim 40 \mu\text{m}$) from the
187 cover glass, in order to avoid interface effects.

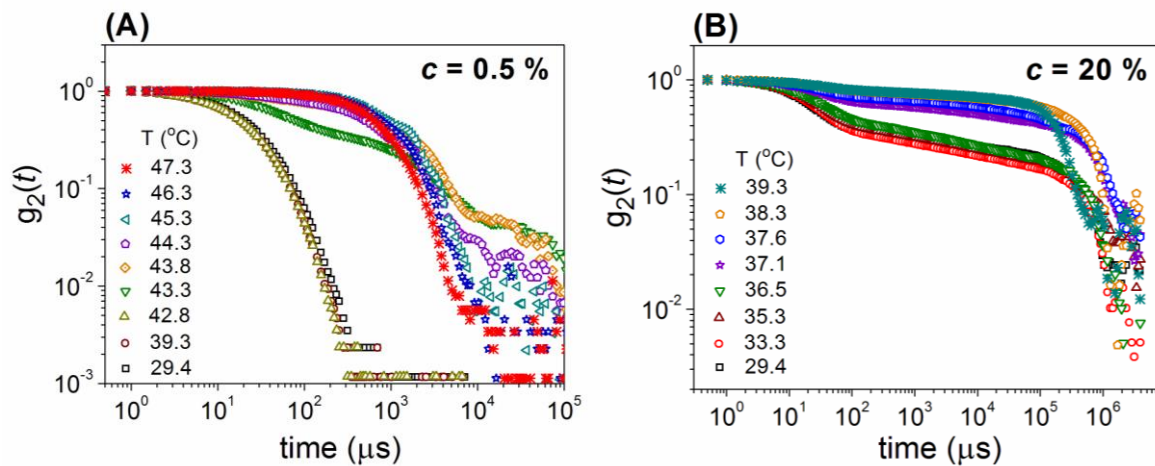
188

189 **Results and discussion**

190 The overlap concentration (c^*) was estimated to be 1.2 % as defined in the experimental section.
191 In the dilute regime the product $q \cdot R_g$, where q is the scattering vector and R_g the radius of
192 gyration of the polymer, was estimated to be 0.592 ($q = 0.02633 \text{ nm}^{-1}$, $R_g = 22 \text{ nm}$)
193 satisfying $q \cdot R_g < 1$. Under these experimental conditions the correlation function yields
194 information about the whole macromolecular motion and not about internal motions of single
195 coils.²⁷ At $c = 0.5 \%$ the system is in the dilute regime and T_{PS} was determined to be $\sim 44^\circ\text{C}$
196 from turbidimetric measurements. The entanglement concentration c_e for aqueous HPC at 30°C
197 should be close to 10 % based on c^* value. Figure 1 shows the intensity-intensity time
198 correlation function $g_2(t)$ variation in the T range between 29.4 and 47.3°C for HPC aqueous
199 solutions in the dilute regime ($c = 0.5 \%$) (Figure 1a) and semi-dilute regime above c_e ($c =$
200 20%) (Figure 1b) collected after 30 min equilibration. By increasing T in a narrow temperature
201 range (42.8 - 43.8°C at 0.5% and 36.5 - 37.6°C at 20%) the $g_2(t)$ signal presents an abrupt
202 change, corresponding to the phase separation transition. Decay time distribution functions
203 ($G(\tau)$) were obtained from the Laplace inversion by the Maximum Entropy Method. The

204 temperature evolution of $G(\tau)$ at different concentrations is presented in Figure 2 where the
 205 relaxation time distribution is plotted as a function of $\tau T/\eta_0$ at different polymer concentrations
 206 and temperatures, where η_0 is the solvent viscosity at each T. This renormalization of time was
 207 adopted to suppress trivial thermal dependence not related to phase separation, enabling direct
 208 comparison of peak position at different T.^{14,15,28}

209



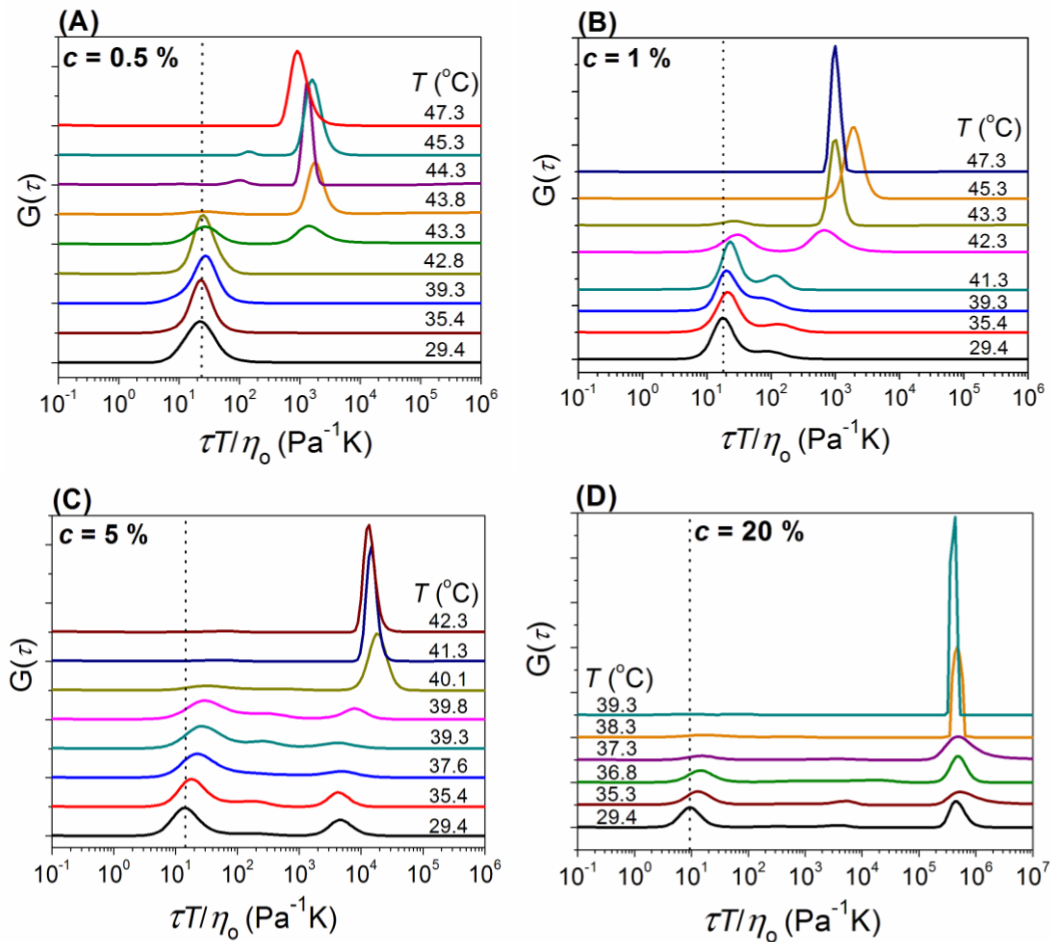
210

211 **Figure 1.** Temperature dependence of intensity autocorrelation function $g_2(\tau)$ for
 212 concentrations (a) 0.5 % and (b) 20 % at a scattering angle of 173°.

213

214 At $c = 0.5 \%$ $G(\tau)$ reports a single relaxation mode (at $\tau T/\eta_0 \sim 27 \text{ Pa}^{-1}\text{K}$) below 42.8°C, which
 215 turns into a single relaxation mode with higher $\tau T/\eta_0$ ($\sim 10^3 \text{ Pa}^{-1}\text{K}$) from 43.8°C, as the polymer
 216 phase separates (Figure 2a). It is worth noting that at $c < c^*$ in the single-phase region ($T \leq$
 217 42.8 °C) the distribution observed for the single relaxation mode is rather broad as a result of
 218 the polydisperse nature of the biosourced commercial HPC. By increasing c to 1 % (roughly at
 219 c^*), turbidimetric analysis estimates a T_{PS} of 42.7°C. Figure 2b shows that relaxation time
 220 distribution at $c = 1 \%$ displays a principal mode ($\tau T/\eta_0 \sim 20 \text{ Pa}^{-1}\text{K}$) together with a slow
 221 mode of small amplitude at higher $\tau T/\eta_0$ ($\sim 100 \text{ Pa}^{-1}\text{K}$). Fast and slow modes are almost

222 constant in reduced τ by increasing T in the range (29.4-41.3) $^{\circ}\text{C}$. However, in the narrow T
 223 range 41.3-43.3 $^{\circ}\text{C}$ around T_{PS} the proportion of the fast and slow mode inverts showing a
 224 marked shift in amplitudes downwards and upwards, respectively. Additionally, the slow mode
 225 increases in $\tau T/\eta_0$ by a noticeable amount at the transition.
 226



227
 228 **Figure 2.** Relaxation time distribution $G(\tau)$ at different temperatures for concentrations (a)
 229 0.5 %, (b) 1 %, (c) 5 % and (d) 20 %.
 230
 231 At $c \geq 5\%$ the complexity of $G(\tau)$ increases. Two major modes (fast and slow) are observed
 232 in combination with a small contribution of a third mode at $\tau T/\eta_0$ between fast and slow modes.

233 However, due to the negligible contribution of this third mode, we shall ignore this intermediate
234 relaxation mode in the following analysis. A first qualitative analysis of relaxation mode
235 evolution with T in the semi-dilute regime indicates that at $c = 5\%$ ($T_{PS} \sim 40^\circ\text{C}$ by turbidimetry)
236 the fast and slow mode contributions are equivalent and constant with increasing T until a
237 narrow temperature range ($39.3\text{-}40.1^\circ\text{C}$) at which the fast mode decreases to almost zero and
238 the slow mode amplitude increases sharply, as presented in Figure 2c. Moreover, reduced
239 relaxation time of fast mode undergoes a slight shift to higher $\tau T/\eta_0$ in the range $29.4\text{-}39.8^\circ\text{C}$,
240 while that for the slow mode is roughly constant in the same T range. However, the slow mode
241 undergoes a marked shift to higher $\tau T/\eta_0$ in the T range ($39.3\text{-}40.1^\circ\text{C}$) close to T_{PS} .

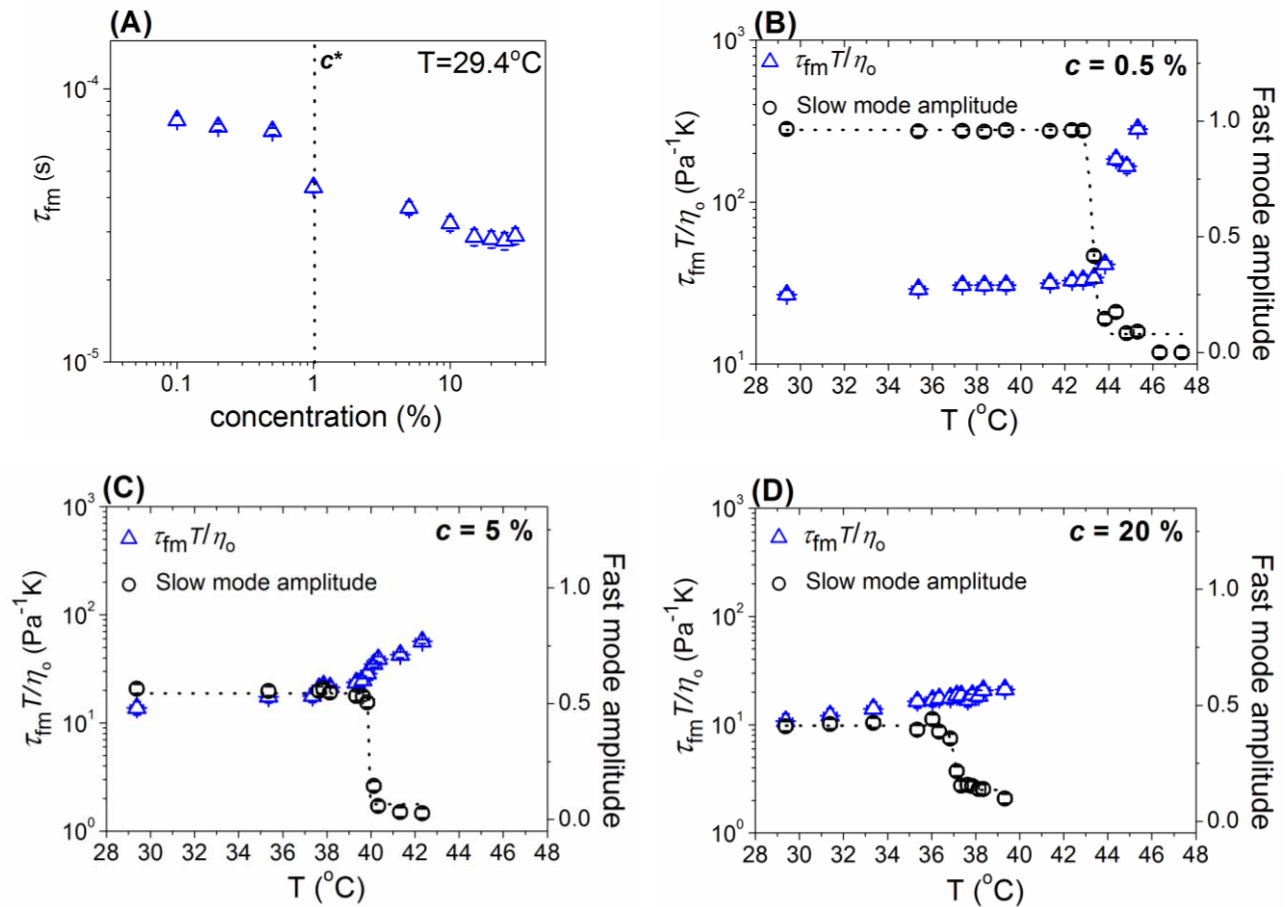
242 At $c = 20\%$ (Figure 2d) the behavior of the fast mode is similar to that observed at $c = 5\%$,
243 showing a marked shift to higher $\tau T/\eta_0$ with increasing T. However, the slow mode now
244 displays a remarkable continuity in $\tau T/\eta_0$ in the entire T range analyzed in this study.
245 Interestingly, at all concentrations it is observed that above the temperature range at which the
246 fast mode vanishes i.e. in the two-phase region, $G(\tau)$ turns out to be a single narrow mode
247 related to phase separation under the form of polymer aggregates. Small variations in
248 normalized τ at this T range are likely due to the aggregate size dependence on the thermal
249 quench, an effect consistent with previous phase separation studies on HPC²³ and PNIPAm.²⁹

250

251 **Fast mode**

252 When the polymer concentration is below c^* the single relaxation mode is attributed to
253 Brownian motion of single coils,¹² whereas for concentrations above the overlap concentration
254 ($c > c^*$) this mode reflects cooperative diffusion of chain segments between each blob.³⁰
255 Figure 3a shows the polymer concentration dependence of fast mode relaxation time at $T=29.4$
256 $^\circ\text{C}$. An approximate plateau region is found at concentrations below 0.5% whereas τ_{fm}
257 decreases more markedly with polymer concentration above 0.5% . This observation suggests

258 that the solution below 0.5 % is in the dilute regime ($c < c^*$) while at $c > 1$ % the system enters
 259 the semi-dilute regime, in agreement with c^* estimation (~ 1.2 %). The decrease in τ_{fm} as the
 260 polymer concentration increases above 1 % indicates that the average segment correlation
 261 length decreases as concentration increases, following a similar trend as that reported for
 262 PNIPAm.³¹



263
 264 **Figure 3.** (a) Fast mode relaxation time vs. concentration in the single phase region at 29.4°C
 265 and normalized fast mode relaxation time ($\tau_{\text{fm}}T/\eta_0$) vs. T for concentrations (b) 0.5 %, (c) 5
 266 % and (d) 20 %.

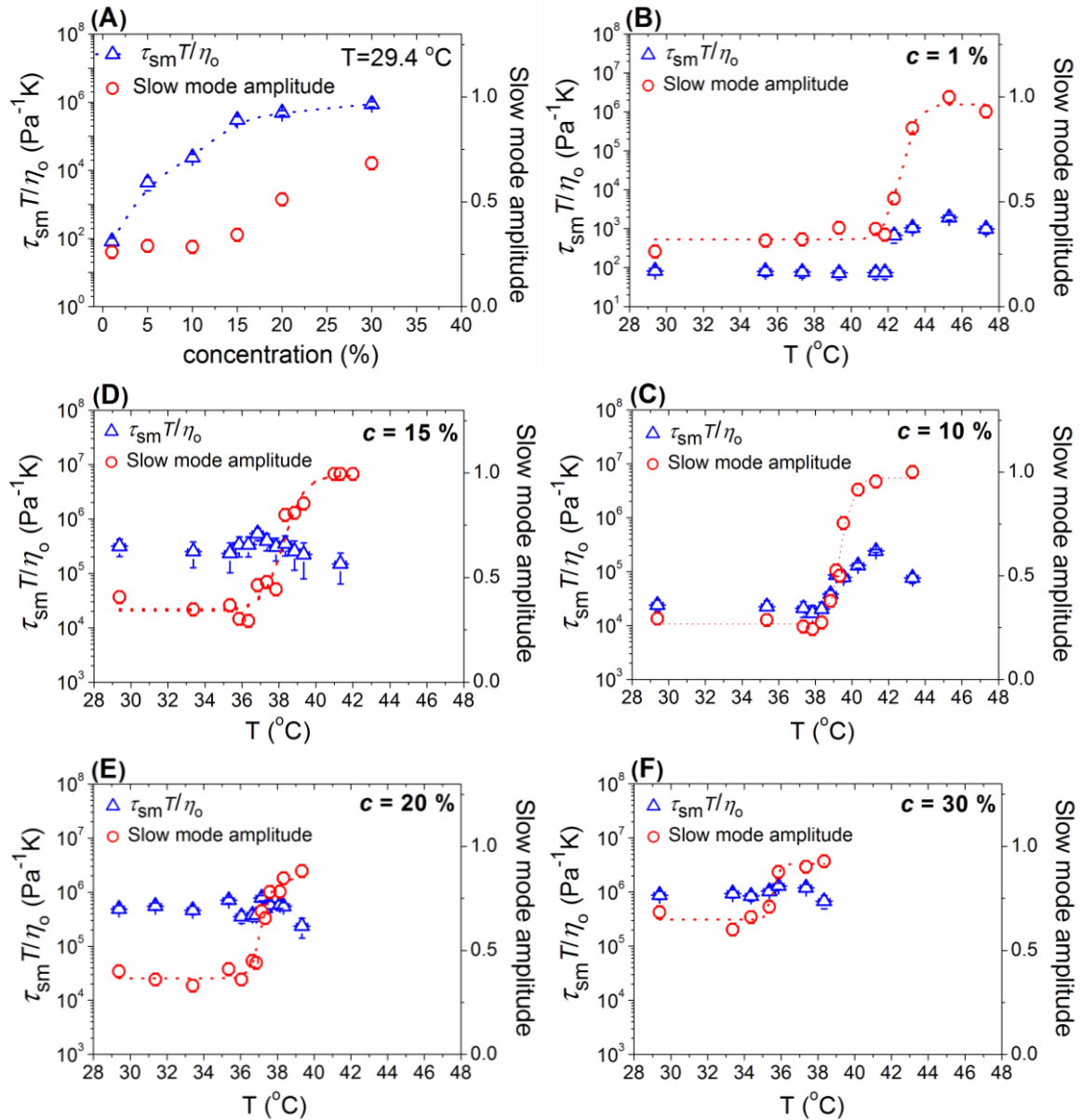
267
 268 Figures 3b-d display the temperature dependence of the reduced fast mode relaxation time
 269 ($\tau_{\text{fm}}T/\eta_0$) at three different concentrations (0.5, 5 and 20 %). As discussed before, when the
 270 polymer phase separates by increasing T the slow mode becomes the major distribution and the

271 fast mode contribution decreases to almost zero. However, in a temperature range above the
272 transition but close enough to it, the decay time distribution functions obtained by the Maximum
273 Entropy Method still evidence a small contribution of fast mode that is reported in Figure 3. At
274 $c = 0.5 \%$, $\tau_{\text{fm}}T/\eta_0$ undergoes a slight increase with T up to $\sim 43^\circ\text{C}$ above which it displays an
275 abrupt shift to higher values as the fast mode disappears. Reduced relaxation time at $c = 5 \%$
276 shows a slight increase with T below 39°C , which becomes more notorious above 39°C , likely
277 due to PS into a polymer rich and a polymer lean phase. However, the latter increment of
278 $\tau_{\text{fm}}T/\eta_0$ in the two-phase region at $c = 5 \%$ is notably less marked than that at $c = 0.5 \%$. On
279 the contrary, at $c = 20 \%$ the reduced relaxation time $\tau_{\text{fm}}T/\eta_0$ steadily increases with T, but
280 no sharp transition is observed within the analyzed temperature range. The slight increment of
281 $\tau_{\text{fm}}T/\eta_0$ observed below PS in the entire concentration range is likely due to the gradual
282 decrease in solvent quality as the temperature increases from 30°C (relatively good solvent
283 condition) to the vicinity of theta condition ($\sim 40^\circ\text{C}$)³² where the interactions between segments
284 and segment-solvent gradually change. Brown *et al.* showed a similar slight increase of fast
285 relaxation time for polystyrene semi-dilute solutions from good solvent (toluene) to theta
286 solvent (2-butanone) conditions, while the fast mode amplitude remained constant.²⁷ A similar
287 trend was observed by Li *et al.*¹⁴ by cooling polystyrene solution in cyclohexane. The authors
288 explained these results by considering that when the solvent quality decreases, polymer chains
289 contract, resulting in an increase of c^* and therefore a slight shift in fast mode relaxation time
290 to higher values, as shown in Figure 3a. Interestingly, over the entire concentration range
291 studied here the fast mode amplitude remains constant up to a temperature at which it decreases
292 sharply, which is likely due to phase separation transition. Also, our results show that the
293 temperature variation of the reduced fast mode relaxation time has no clear dependence with
294 the concentration ranges delimited by c^* or c_e .

295

296 **Slow mode**

297 Figure 4a shows the concentration dependence of the reduced slow mode relaxation time
298 ($\tau_{sm}T/\eta_0$) at 29.4°C in the single phase region and the corresponding amplitude. As the
299 concentration increases, $\tau_{sm}T/\eta_0$ is larger and the slow mode amplitude increases. These
300 observations indicate that the slow dynamic process is closely related to chain
301 clustering/entanglement effects.¹⁷ DLS experiments in the forward-scattering configuration
302 ($\theta = 13^\circ$, $q^2 = 8.925 \times 10^{-6} \text{ nm}^{-2}$) at $c = 20\%$ provided values of $\tau_{sm} = 29.3 \text{ s}$ and fast
303 mode amplitude/slow mode amplitude = 0.59, while the corresponding values for back-
304 scattering ($\theta = 173^\circ$; $q^2 = 6.9327 \times 10^{-4} \text{ nm}^{-2}$) were 1.2 s and 1.05, respectively. The plot
305 $1/\tau_{sm}$ vs. q^2 deviates from a straight line passing through the origin, evidencing the non-
306 diffusive nature of the slow mode as previously observed for different polymer solutions.¹³ The
307 plots of the slow mode amplitude vs T shown in Figure 4b-f reveal that at some temperature
308 the amplitude undergoes a sharp transition to higher values in the entire concentration range
309 between 1 and 30 %. Moreover, the temperature of this transition decreases with polymer
310 concentration and coincides with the fast mode amplitude transition. Therefore, we can now
311 rationalize the fast and slow amplitude shifts with increasing temperature as coinciding with
312 the HPC phase separation transition, where polymer chains collapse into polymer aggregates.



313

314 **Figure 4.** (a) Reduced slow mode relaxation time ($\tau_{sm}T/\eta_0$) and slow mode amplitude vs.
 315 concentration in the single-phase region at 29.4°C. Reduced slow mode relaxation time and
 316 amplitude dependence on T for concentrations (b) 1%, (c) 10 %, (d) 15 %, (e) 20 % and (f) 30
 317 %. Dotted lines correspond to sigmoidal fittings for amplitude vs T plots.

318

319 Note that at $c \leq 10$ % there is a narrow T range at which $\tau_{sm}T/\eta_0$ shifts to larger correlation
 320 times, as presented in Figure 4b-d. This temperature range coincides with the temperature at
 321 which the slow mode amplitude increases sharply and is the evidence of HPC demixing process.

322 This behavior is consistent with results by Yamamoto *et al.*¹⁸ for semi-dilute aqueous PNIPAM
323 solutions showing a sharp transition in slow mode relaxation time at $T \sim T_{PS}$. However, it is
324 worth highlighting that the slow mode behavior with increasing temperature observed for HPC
325 is in marked contrast to that reported by Yuan *et al.* for aqueous PNIPAm in semi-dilute regime,
326 where the slow mode reduced τ was observed to become faster by increasing T below T_{PS} .¹³
327 This suggests that the slow mode reduced τ variations with temperature could be dependent on
328 the nature of the thermo-responsive polymer. Remarkably, this behavior is no longer observed
329 for HPC solutions above $c = 15\%$ as the reduced τ_{sm} shows a clear continuity before and after
330 phase separation, as presented in Figures 4e,f. In this regard, we suggest that the different T
331 dependence of $\tau_{sm}T/\eta_0$ at $c \leq 10\%$ and at $c \geq 15\%$ is related with the transition between
332 the overlap and entanglement regimes (c_e is roughly 10%). In the non-entangled range ($c^* <$
333 $c \leq c_e$), at which polymer chains overlap to some extent without entanglement formation, the
334 shift of $\tau_{sm}T/\eta_0$ to higher values by increasing T at $\sim T_{PS}$ reflects chain and clustering
335 association at the phase separation condition. By contrast, in the entangled range ($c > c_e$) the
336 fact that $\tau_{sm}T/\eta_0$ is constant below and above T_{PS} would imply that no additional or further
337 chain/cluster association occurs during phase separation in this concentration range. This
338 presumably reflects that the transient clusters present in the single-phase region are precursors
339 of polymer aggregates formed in the two-phase region. This picture of phase separation of HPC
340 aqueous solutions at $c > c_e$ raises the question of the nature of the molecular organization
341 occurring at the phase separation transition. While the observation that the fast mode amplitude
342 decreases abruptly at T_{PS} reflects the formation of HPC-HPC contacts/interaction, the almost
343 identical relaxation dynamics found between the slow mode below T_{PS} and the single mode
344 above T_{PS} suggest that preformed aggregates in the two-phase region may retain considerable
345 amount of hydrogen bonded water molecules, as recently described by Patra.³³

346

347 **Phase diagram**

348 From the analysis of fast and slow correlation times and amplitudes it was evidenced that PS
349 temperatures at different concentrations cannot be obtained by following the evolution of the
350 reduced relaxation times only, in particular at $c > c_e$. Although this approach could be useful in
351 the dilute regime,⁹ the lack of sharpness in temperature dependence when the concentration is
352 above 5 % precludes a precise definition of the phase separation transitions.

353 By contrast, the observed transitions in the fast and slow mode amplitudes could be employed
354 to precisely map phase separation diagram of HPC in a broad concentration range and this
355 approach compares favorably to T_{PS} determination obtained by other methods. For comparison,
356 Figure 5a shows that the phase separation temperatures determined by the fast and slow mode
357 amplitude evolution with T are identical. The advantage of this approach is that this DLS
358 analysis conducts to sharp transitions that can be used to accurately define T_{PS} as the
359 temperature at which the fast and slow mode amplitude diverges (experimental error $\pm 0.3^\circ\text{C}$).
360 On the other hand, the typical method employed to map phase separation diagrams of HPC,
361 based on following the drop in transmittance as the polymer phase separates with increasing
362 temperature, provides a transmittance signal that decreases slowly with T (Figure 5a). The latter
363 approach prevents a well-defined T_{PS} determination because the transition lacks sufficient
364 sharpness, reducing the accuracy of the method.⁶ In fact, this drawback is one of the main
365 factors contributing to diversity of phase separation diagrams since different criteria can be
366 selected to determine T_{PS} , as outlined in a recent work of Halperin *et al.*⁵ In this regard, a
367 significant discrepancy (see Figure 3 in Marsano *et al.*⁷) was found by comparing previously
368 reported phase diagrams of aqueous HPC based on turbidity measurements from HPC with
369 similar molecular weight and structure for which no discrepancy is expected.^{6,34} Figure 5b
370 displays the phase separation diagrams for aqueous HPC solutions in the concentration range
371 $c = (0.5 - 30)\%$ obtained by DLS from sigmoidal fittings of fast and slow mode amplitude

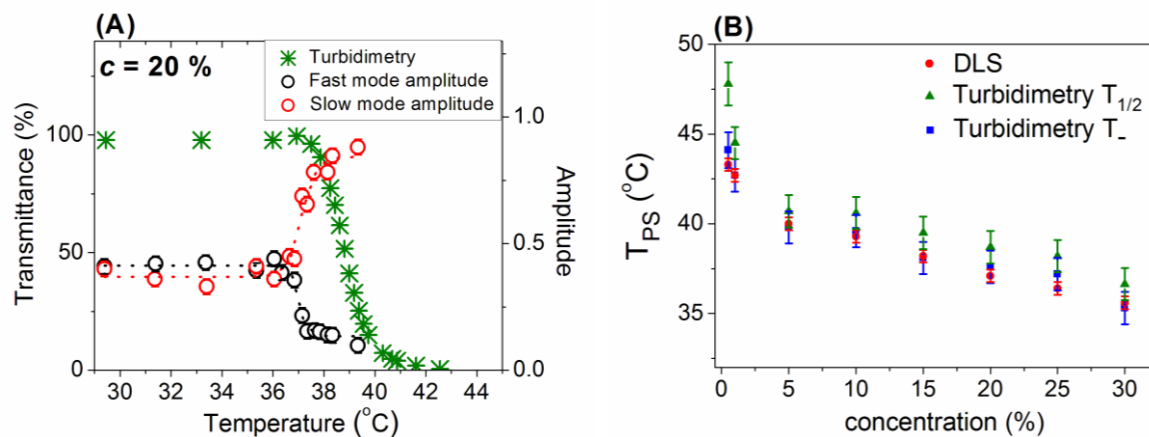
372 transitions (red) and turbidimetry analysis taken as the midpoint of the transition ($T_{1/2}$) (green)
373 and by the tangent method (T_{-}) (blue). We found that T_{PS} obtained by DLS are in very good
374 agreement with optical transmittance results T_{-} but with much smaller error bars for the DLS
375 determination. By contrast, the $T_{1/2}$ method appears to exceed T_{PS} obtained by DLS at
376 equivalent polymer concentration by an average of 2.0°C (experimental error $\pm 0.3^{\circ}\text{C}$), which
377 becomes even larger at the lowest concentration ($T_{1/2} - T_{PS} = 4.5^{\circ}\text{C}$). However, the general
378 trend of the diagrams is very similar with a pronounced decrease of T_{PS} at $0.5\% < c < 1\%$
379 and a gradual decrease at $1\% < c < 30\%$, in agreement with some previous theoretical and
380 experimental HPC phase diagrams reported by Lárez-V *et al.*³⁵ This approach thanks to DLS
381 fully clarifies why the so far rather empirical choice of T_{-} as the PS temperature is probably
382 justified but much less precise.

383 Additional experiments performed on aqueous poly(vinyl)alcohol solutions (10 wt.%) with a
384 degree of hydrolysis of 72 % also showed good agreement between the T_{PS} obtained by DLS
385 (36°C , data not shown) and the onset of phase separation previously reported by turbidimetric
386 analysis,² suggesting that the method to track the T_{PS} presented here is probably relevant for
387 many thermo-responsive water-soluble polymer solutions in the semi-dilute regime.

388

389

390



391
 392 **Figure 5.** (a) Transmittance, fast and slow mode amplitude temperature dependence for $c =$
 393 20 %. Dotted curves correspond to sigmoidal fittings. (b) Phase diagram of aqueous HPC
 394 obtained by DLS and turbidimetry (T_- , $T_{1/2}$) in the range $c = (0.5 - 30)\%$.

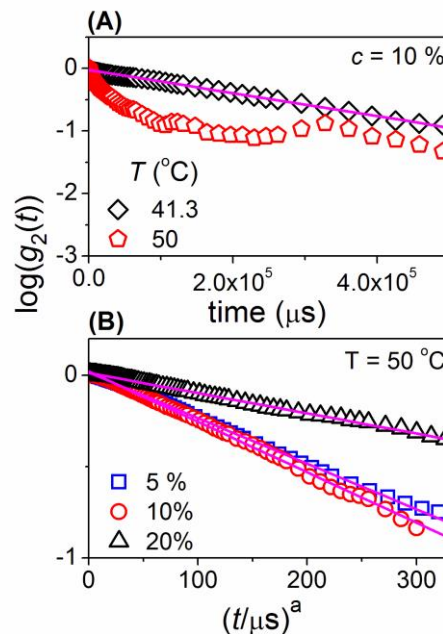
395
 396 **Insights into the two-phase region**

397 A correct interpretation of $g_2(t)$ in the two-phase region may give access to monitoring the
 398 phase separation kinetics and measuring characteristic size of polymer aggregates which may
 399 form and grow with time. However, DLS theory can only be applied to interpret $g_2(t)$ signal
 400 provided multiple-scattering effects are absent. As HPC aqueous solution enters into the two-
 401 phase region, the system gets turbid (near T_{PS}) and by further heating the sample well above
 402 T_{PS} ($T - T_{PS} \geq 10$ °C), it turns into a cloudy phase separated system. Despite this apparent
 403 multiple-scattering character above T_{PS} , the correct interpretation of $g_2(t)$ actually depends on
 404 the T quench depth. To illustrate this effect, $g_2(t)$ was collected at different temperatures using
 405 a heating rate of 3 °C/min to allow for a fast quenching experiment (less than 1 or 4 min
 406 heating in the two-phase region for the lower and higher T quench, respectively). Figure 6a
 407 shows that $g_2(t)$ signal is mostly a single exponential in the two-phase region near T_{PS} ($T -$
 408 $T_{PS} \leq 4$ °C). By contrast, for a higher T quench ($T - T_{PS} \geq 10$ °C), $g_2(t)$ deviates from the
 409 single exponential behavior, as represented in Figure 6a at the same concentration. This is likely

410 due to the formation of denser polymer aggregates that act as efficient scatterers bringing
 411 multiple-scattering effects. Indeed, in the multiple-scattering regime, in the back-scattering
 412 geometry, $g_2(t)$ can be fitted to Eq. 3 according to diffusing-wave spectroscopy theory (DWS)
 413 assuming spherical scatterers.³⁶

$$414 \quad g_2(t) = e^{-2\gamma\left(\frac{t}{t_0}\right)^a} \quad (a = 0.5) \quad (3)$$

415 with $\gamma = \frac{\langle z_0 \rangle}{l^*} + \frac{2}{3}$, where $2/3$ is an empirical fitting parameter, l^* is the transport mean free path
 416 and $\langle z_0 \rangle$ is the average penetration depth into the sample (2 mm in the experiments), t_0 is the
 417 characteristic relaxation time and the exponent a is 0.5 in DWS theory. The $g_2(t)$ signal was
 418 measured as a function of time at 50°C for concentrations 5, 10 and 20 % and fitted to Eq 3. At
 419 30 min, the best-fitted values of a are 0.65, 0.51 and 0.49 (± 0.03) at 5, 10 and 20 %,
 420 respectively. Figure 6b displays the logarithm of the normalized autocorrelation function at $c =$
 421 5 %, 10 % and 20 % plotted as a function of $\left(t/t_0\right)^a$ using the best values of a .



422
 423 **Figure 6.** $\text{Log}(g_2(t))$ collected in the back-scattering geometry (173°) after 30 min
 424 equilibration. Data is plotted as function of time (a) at 41.3°C (diamonds) and 50°C (pentagons)

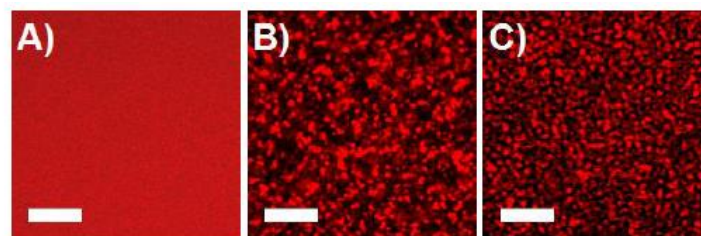
425 ($c = 10\%$) and as a function of $\left(t/t_0\right)^a$ (b) at 50°C at concentrations 5% (squares), 10%
426 (circles) and 20% (triangles).

427

428 The data are described satisfactorily by Eq. 3 ($a = 0.5$) at $c = 10\%$ and 20% , while a slight
429 deviation to a higher a value is encountered for $c = 5\%$.

430 These results give evidence of the existence of two regimes within the 2-phase region: (1)
431 Single-scattering regime, in the T range close to T_{PS} ($T - T_{\text{PS}} \leq 4^\circ\text{C}$), where the single-
432 exponential nature of $g_2(t)$ is preserved for at least 6 h; (2) Multiple-scattering regime, in the
433 T range well above T_{PS} ($T - T_{\text{PS}} \geq 10^\circ\text{C}$), presumably by the formation of denser polymer
434 aggregates. Confocal microscopy images taken at $c = 5\%$ in both regimes reveal that deeper
435 T ($T - T_{\text{PS}} \geq 10^\circ\text{C}$) quenches lead to denser structures, as presented in Figure 7, supporting
436 the picture of multiple-scattering regime produced by denser particles.

437



438

439 **Figure 7.** Confocal scanning microscopy images for $c = 5\%$ taken at (a) 30°C (clear solution),
440 (b) 43°C and (c) 50°C after 30 min equilibration. The red features are attributed to water-rich
441 domains, whereas the darker regions correspond to polymer-rich phases. Scale bar is $20\ \mu\text{m}$.

442

443 We now address the question of whether the characteristic size of polymer aggregates can be
444 estimated in the single-scattering (DLS) and multiple-scattering (DWS) regimes. For
445 comparison, the average distance (the domain length, d_{Confocal}) was determined by Fourier
446 transform analysis of confocal microscopy images collected as time elapses at identical quench

447 temperatures. The diffusion coefficient (D) was obtained from the correlation time of the single
 448 mode ($\tau = 1/Dq^2$) above T_{PS} (single-scattering regime) at different concentrations between
 449 0.5 and 10 %. From D values, we estimate the characteristic diameter (d_{DLS}) of aggregates
 450 using the Stokes-Einstein relation, assuming spherical shapes of polymer domains and
 451 negligible interactions between them. The estimated aggregate sizes in the single-scattering
 452 regime after 30 min equilibration are in good agreement with $d_{Confocal}$ for dilute enough
 453 solutions ($c \leq 5$ %), as presented in Table 1. However, the large differences observed for
 454 concentrated solutions ($c = 10$ %) manifest that the diffusion coefficient of the aggregates
 455 cannot be interpreted as originating from non-interacting objects and that the diffusion
 456 coefficient deviates from the dilute limit (Stokes-Einstein value).

457

458 **Table 1.** Characteristic HPC domain size in the two-phase region obtained in the concentration
 459 range (0.5-10 %).

460

c (%)	Single-scattering regime ($T-T_{PS} = 4^\circ\text{C}$)		Multiple-scattering regime ($T-T_{PS} = 10^\circ\text{C}$)	
	d_{DLS} (μm)	$d_{Confocal}$ (μm)	d_{DWS} (μm)	$d_{Confocal}$ (μm)
0.5	1.5 ± 0.5	3 ± 1	(*)	2 ± 1
1	2 ± 1	4 ± 1	(*)	3 ± 1
5	12 ± 2	10 ± 2	74 ± 8 ($\gamma=1.33$) 3 ± 1 ($\gamma=0.3$)	4 ± 1
10	64 ± 5	9 ± 2	740 ± 80 ($\gamma=1.33$) 3 ± 1 ($\gamma=0.1$)	3 ± 1

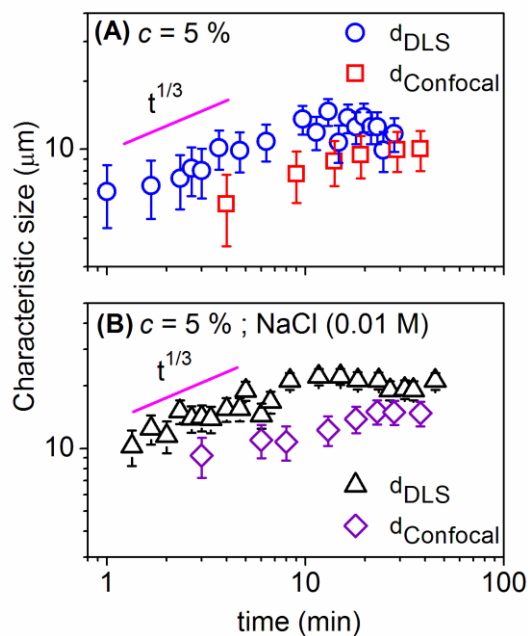
461 *Experimental data of $g_2(t)$ does not fit to Eq. 3

462

463 Regarding the multiple-scattering regime, fits of $g_2(t)$ to Eq. 3 assuming a γ value of 1.33
 464 (non-interacting particles) conducts to significant overestimations of the characteristic domain
 465 size with respect to confocal microscopy analysis, which evidence that the interactions between
 466 polymer aggregates cannot be neglected in the concentration range considered here. It is worth
 467 noting that Sanyal *et al.*³⁷ showed that γ decreases with the repulsive interactions between

468 particles and found γ values as low as 0.1 for strongly interacting systems. By fitting $g_2(t)$ to
 469 Eq. 3, assuming that $d_{DWS} = d_{Confocal}$ as obtained in the multiple-scattering regime, one gets
 470 a γ value of the order of 0.3 at $c = 5\%$ and 0.1 at $c = 10\%$. Although this is consistent with
 471 expectations, a precise determination of γ for HPC at different compositions is clearly out of
 472 the scope of this report.

473 Figure 8a shows the evolution of d_{DLS} with time at $c = 5\%$ (single-scattering regime, 43°C).
 474 In the earlier stage of the experiment ($t \leq 10$ min), d_{DLS} satisfies a scaling law $d_{DLS}(t) \sim \sqrt[3]{t}$,
 475 suggesting that HPC domain growth may follow a classical coarsening behavior.^{23,38} Note that
 476 for $t > 10$ min, d_{DLS} reaches a plateau indicating that further coarsening of polymer domains
 477 is impeded. Such arrested phase separation behavior is consistent with the absence of
 478 macroscopic phase separation in the entire concentration range considered in this study (even
 479 after 5 days at 43°C). DLS results compare favorably well with the growth kinetics captured by
 480 confocal microscopy (Figure 8).



481
 482 **Figure 8.** Evolution of characteristic dimension d_{DLS} and $d_{Confocal}$ as a function of time during
 483 phase separation of HPC solutions at $c = 5\%$ in (a) pure water and (b) NaCl 0.01 M.

484

485 The arrested-like phase separation behavior observed for other LCST nonionic water-soluble
486 polymers has been regarded as originating from gelation (methylcellulose,^{8,10}
487 hydroxypropylmethylcellulose⁸) or from the effect of electrostatic charges at the interface of
488 polymer aggregates inducing colloidal stability (PNIPAm²⁹). However, our results show that
489 HPC phase separation is fundamentally different from those systems since phase separation
490 does not induce gelation, and the arrested-like behavior after the growing stage persists by
491 increasing the ionic strength (Figure 8b), which rules out a pure electrostatic effect as for the
492 case of PNIPAm. In addition, confocal microscopy analysis revealed that the arrested phase
493 separation behavior is also observed for higher T quenches (50°C, data not shown) where the
494 multiple-scattering regime is relevant. A potential explanation to the observed HPC arrested-
495 like phase separation mechanism could be the formation of polymer aggregates concentrated
496 enough (glassy) to prevent colloidal coalescence. However, validation of this hypothesis would
497 require direct measuring of the aggregate composition, and is left for a future work.

498

499 **Conclusions**

500 The thermo-responsive phase separation of commercial hydroxypropylcellulose was
501 investigated in a broad concentration range covering the dilute and semi-dilute regime by
502 dynamic light scattering. Our results show that the fast and slow mode amplitudes undergo a
503 sharp transition by increasing the temperature near the phase separation temperature.
504 Accordingly, we propose that by following those transitions, it is possible to define the phase
505 separation boundary with a remarkable accuracy. Solutions with concentrations in the range
506 ($c^* < c \leq c_e \approx 10c^*$) undergo phase separation with a marked shift of $\tau_{sm}T/\eta_0$ to higher
507 values, reflecting clustering association at the phase separation condition. On the contrary,
508 solutions in the range $c > c_e$ phase separate with a remarkable continuity of normalized

509 relaxation times between the slow mode (below T_{PS}) and the single mode characteristic of the
510 two-phase region. This behavior suggests that transient clusters formed in the single phase
511 entangled region may act as precursors of polymer aggregates in the two-phase region, at
512 temperatures close to T_{PS} .

513 The resulting phase separation diagram was compared to studies conducted by turbidimetric
514 analysis using different criteria to define the phase boundary, showing that DLS transition
515 temperatures reflect the onset of phase separation.

516 Within the two-phase region two temperature dependent regimes were identified. A single-
517 scattering regime in the temperature range close to T_{PS} ($T - T_{PS} \leq 4^\circ\text{C}$), characterized by
518 slightly turbid samples. In this regime, monitoring growth kinetics of HPC solutions at $c \leq 5\%$
519 it is possible by means of tracking the relaxation time of $g_2(t)$. Characteristic domain size
520 growth at $c = 5\%$ follows the power law $d_{DLS}(t) \sim \sqrt[3]{t}$ in the earlier stage of phase separation
521 ($t \leq 10$ min), suggesting a diffusive or coalescence/aggregation coarsening behavior. After
522 the initial growing stage, the characteristic domain size levels off, suggesting an arrested-like
523 phase separation mechanism, which inhibits macroscopic phase separation regardless of the
524 ionic strength and quench temperature. A multiple-scattering regime was found at higher
525 temperature quenches ($T - T_{PS} \geq 10^\circ\text{C}$) at which the samples adopt a turbid and milky
526 appearance. In this regime the system cannot be regarded as originating from non-interacting
527 particles and therefore domain sizing and kinetic studies require a correct determination of γ
528 values for a DWS model to be applied in the back-scattering geometry.

529 We suggest that the method described here to map the phase separation diagram and kinetically
530 resolve domain growth in the two-phase region is general and applies to other polymers
531 displaying lower (or upper) critical solution temperature, provided the single scattering regime
532 is correctly determined.

533

534 **Acknowledgements**

535 This work was supported by the French National Research Agency, GASPOM Project, Grant
536 N° ANR34GASPOMZ. H.G. acknowledges postdoctoral fellowship from CEA-Enhanced
537 Eurotalents co-funded by FP7 Marie Skłodowska-Curie COFUND Programme, Grant
538 agreement N° 600382. The authors also thank Dr. Jan Ilavsky at Argonne National Laboratory
539 for his help in using Clementine software and Prof. Catherine Amiel at Institut de Chimie et
540 des Materiaux Paris-Est, CNRS for viscosimetry experiments.

541

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