Electronic Supplementary Information

Poly(ethylene glycol)-*graft*-poly(vinyl acetate) single-chain nanoparticles for the encapsulation of small molecules

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DLS and SLS background and analysis models

In DLS experiments the time correlation functions $G_2(\tau)$ of the scattered light were measured at different angles and the normalized intensity autocorrelation function ($g_2(q,\tau)$) are obtained directly from the software during the measurement. $g_2(q,\tau)$ is connected to the normalized electric field autocorrelation function $g_1(q,\tau)$, by the Siegert relation (Eq. S1)

$$g_2(q,\tau) = 1 + \beta^2 |g_1(q,\tau)|^2 \quad \text{(S1)}$$

with $\beta^2 \leq 1$ a coherence factor that depends on the experimental conditions.

For a suspension of polydisperse Brownian spheres, $g_1(q,\tau)$ decays exponentially[25]

$$g_1(q,\tau) = \int_0^\infty P(q,D) exp(-q^2 D\tau) dD \quad \text{(S2)}$$

where D is the diffusion coefficient and $P(q,D)$ is the intensity-weighted probability distribution function of the diffusion coefficient.

Particle sizing is performed by extracting D from $g_2(q,\tau)$ fitting and applying the Stokes-Einstein equation

$$D = \frac{k_B T}{6\pi\eta R_h} \quad \text{(S3)}$$

where k_B is the Boltzmann constant, T is the absolute temperature, η is the viscosity of the solvent, and R_h is the hydrodynamic radius of the spheres.

In the SLS experiment the measurements were performed over an angular range between 35° and 135°, performing 10 acquisitions for 1 s at each angle. The scattering vector Q is calculated according to Eq. S4

$$Q = \left(\frac{4\pi\, n_d}{\lambda}\right)\sin\frac{\vartheta}{2} \tag{S4}$$

where n_d is the refractive index of the solvent, λ is the laser wavelength and ϑ is the scattering angle.

The measured average intensity (*I'*) is the total counts divided by the duration (units of counts/seconds). *I'* is corrected for dark count rate, dead time τ_d (for BI-9000AT, τ_d is 25 ns) and reflection. The value obtained represents the intensity scattered by all the particles in the scattering volume as observed by the detector optics. To compare the intensity scattered at various angles, the intensity per unit volume (*I*) is calculated according to Eq. S5.

$$I = I'\sin\vartheta \tag{S5}$$

Cumulant analysis

In the classic cumulant method analysis, we have that ln[g1(q,τ)] is written as a Taylor series in the correlation time

$$ln[(g_1(q,\tau)] = ln\beta^2 + 2[-\Gamma_1\tau + \frac{\Gamma_2\tau^2}{2!} + \ldots + \frac{(-1)\Gamma_n\tau^n}{n!}] \tag{S6}$$

and by stopping to the second order we have

$$\Gamma_1 = \bar{D}q^2 \tag{S7}$$

and

$$\Gamma_2 = \frac{\bar{D}^2 - \bar{D}^2}{\bar{D}^2}\Gamma_1^2 \tag{S8}$$

where

$$\bar{D}^n = \int_0^\infty D^n P(D) dD \tag{S9}$$

is the *n*th order of the intensity-weighted probability distribution function of *D* (*P(D)*).

The polydispersity index (PDI) is defined as

$$\sigma^2 = \frac{\Gamma_2}{\Gamma_1^2} \tag{S10}$$

CONTIN analysis

In the CONTIN analysis method is more precise than the cumulant method when dealing with multimodal polydisperse systems. Detailed information about the CONTIN algorithm is given in (A. Scotti et al., *J. of Chem. Phys.*, **2015**, 142, 234905).

AP1 and AP2 multiangle-DLS

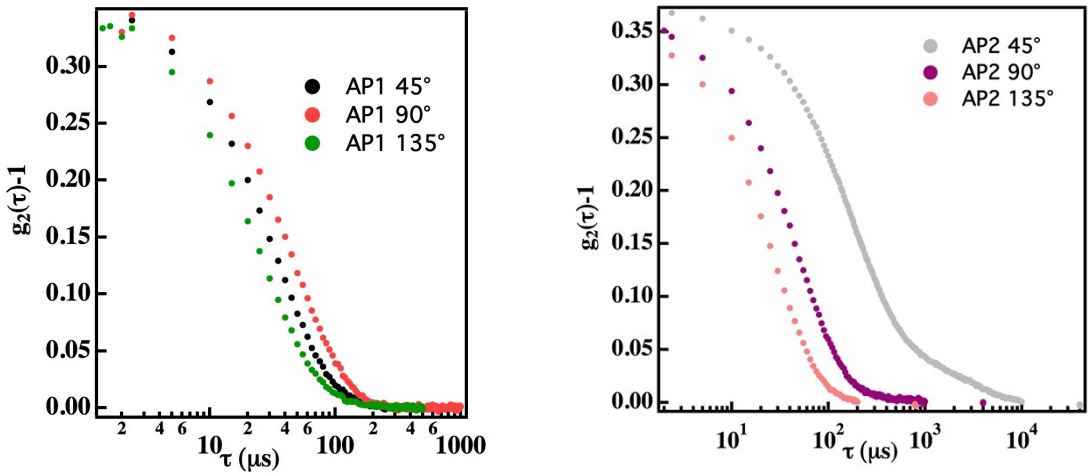

Figure S1. DLS autocorrelation curves of AP1 (left) and AP2 (right) at 45°, 90°, and 135°.

Diameter distribution by Volume of samples AP2, AP5 and AP10

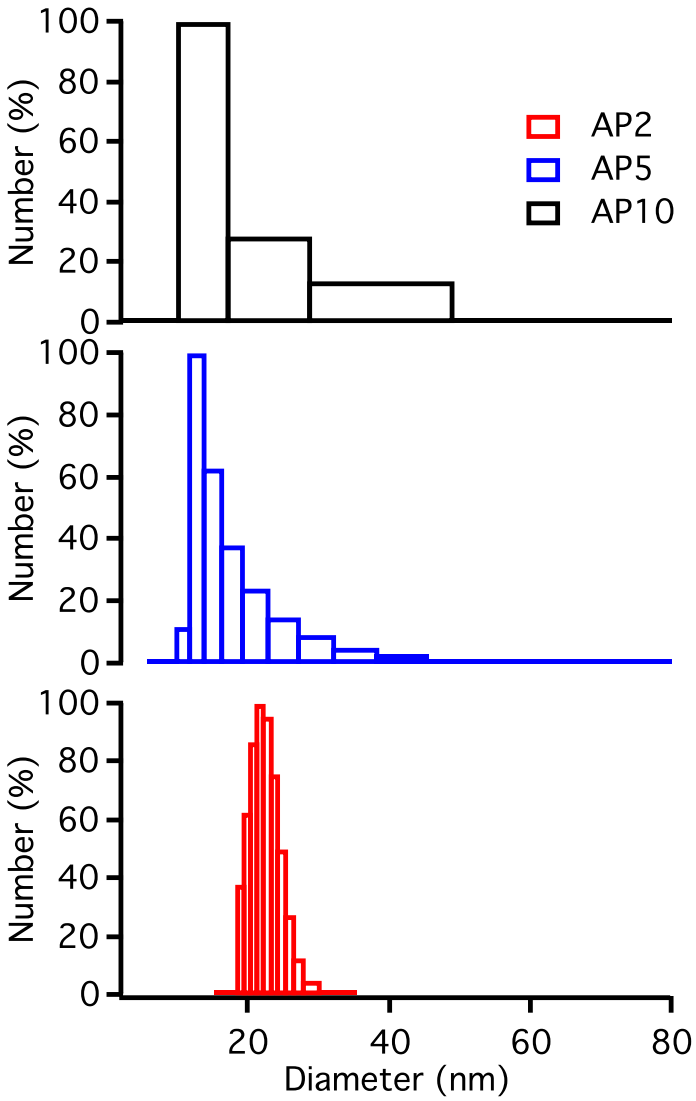

Figure S2. Hydrodynamic diameter distribution by number for samples AP2, AP5 and AP10. One major distribution is present for all samples. Aggregates are detected in sample AP10 only and with a very low relative weight (≤ 1%).

^{1}H-NMR spectrum of PEG-g-PVAc

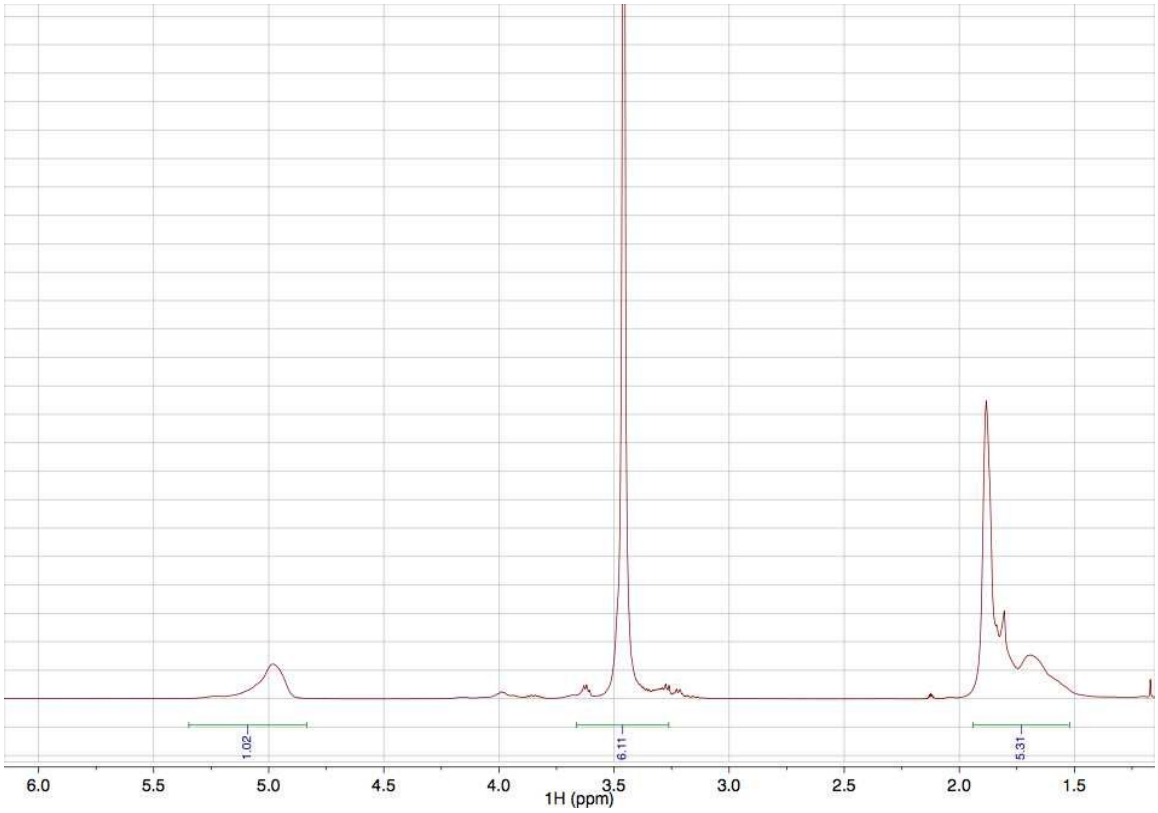

Figure S3. ^{1}H-NMR spectrum of PEG-g-PVAc in toluene-d_8.

^{13}C-NMR spectrum of PEG-g-PVAc

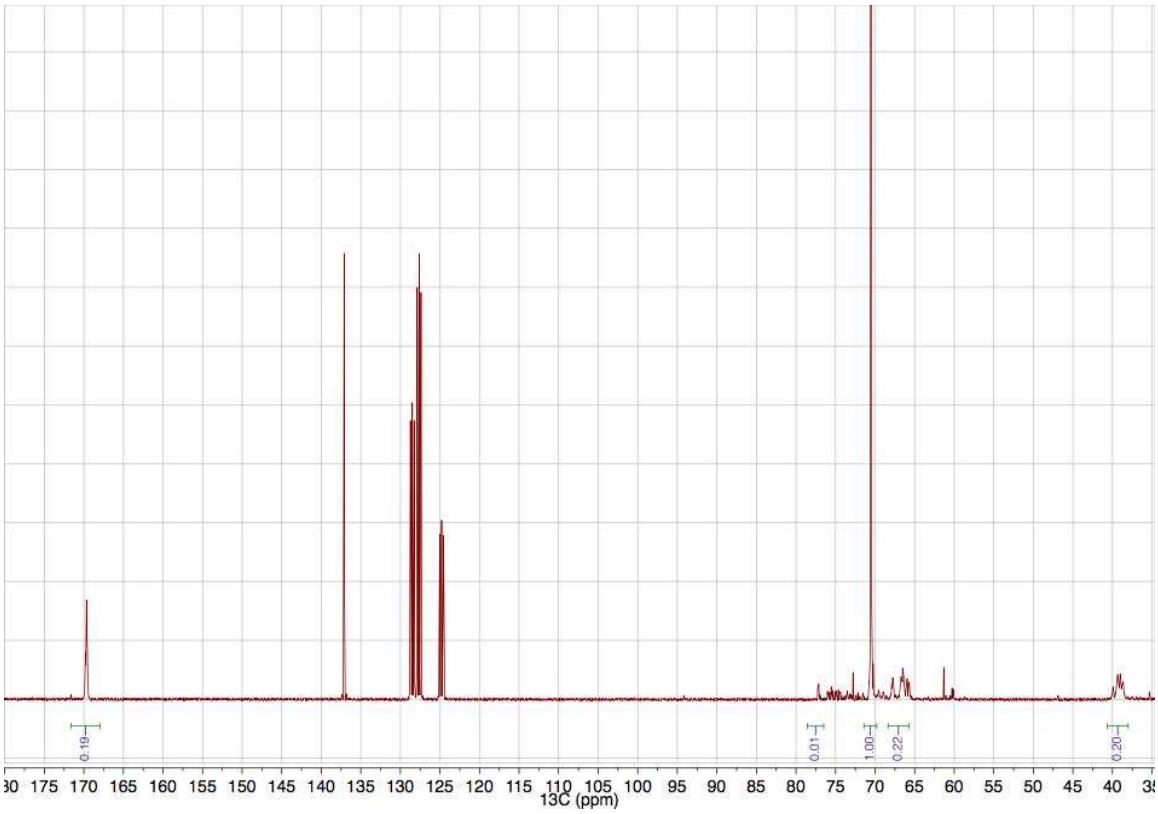

Figure S4. ^{13}C-NMR spectrum of PEG-g-PVAc in toluene-d_8.

^{1}H-^{13}C HSQC NMR spectrum of PEG-g-PVAc

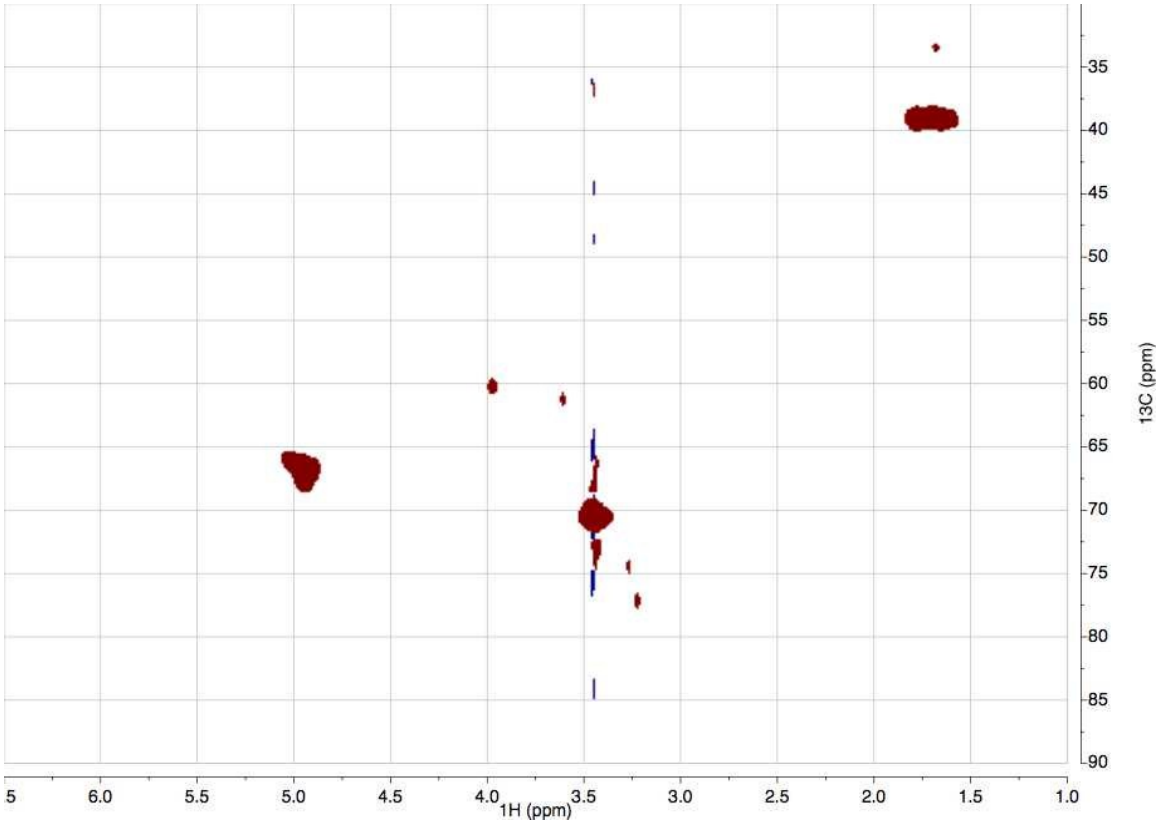

Figure S5. HSQC spectrum of PEG-g-PVAc in toluene-d_8.

Size Exclusion Chromatography (SEC)

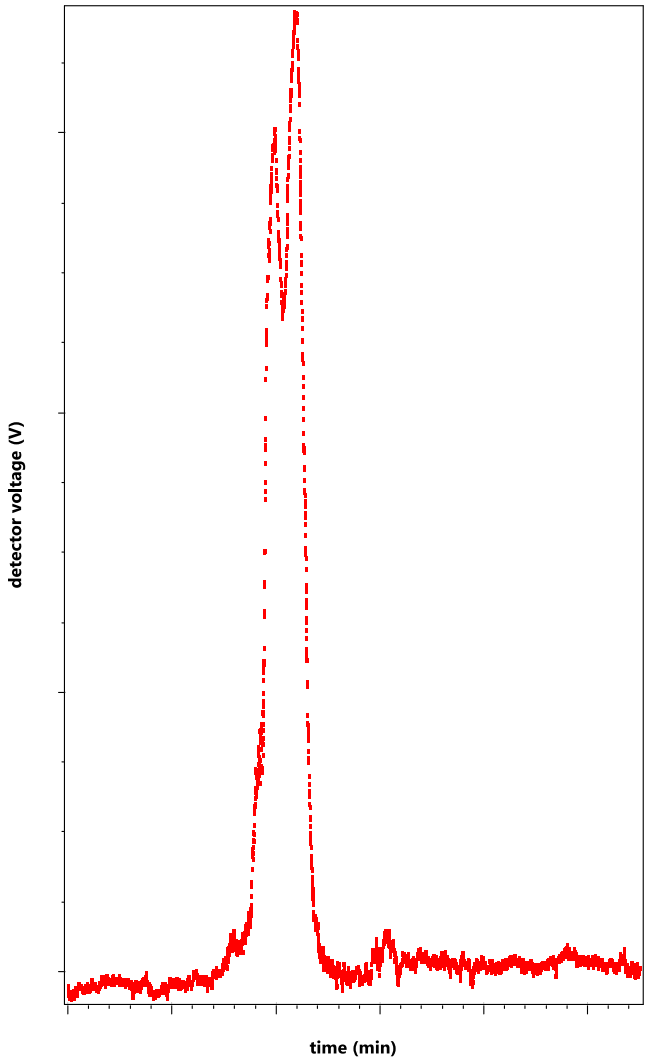

Figure S6. SEC-trace of PEG-g-PVAc in THF.

SAXS form factors models

In a SAXS experiment, the intensity contains information about the shape, size and interactions between scattering objects.

$$I(Q) \propto n_p P(Q) S(Q) + bkg \tag{S11}$$

where n_p is the number density of the scattering objects, *P(Q)* and *S(Q)* are respectively the form and the structure factor of the scattering particles, and *bkg* represents the incoherent background.

The structure factor *S(Q)* equals 1 for diluted samples, while the form factor *P(Q)* is sensitive to the shape of the scattering objects.

In all our scattering experiments, the scattering length density of the particles was set equal to 1.1 10^{-5} Å^{-2}, while that of water was 5.9 10^{-6} Å^{-2}.

Polydisperse Spheres

In the polydisperse spheres model, the probability distribution function for radii of the spheres (Gaussian distribution) is

$$f(R) = \frac{1}{\sigma\sqrt{2\pi}} exp[-\frac{1}{2\sigma^2}(R - R_{avg})^2] \tag{S12}$$

where R_{avg} is the averaged radius and p is the polydispersity, defined as follows:

$$p = \frac{\sigma}{R_{avg}} \tag{S13}$$

where σ is the variance of the distribution.

In a scattering experiment the returned form factor is normalized by the average particle volume

$$\langle V \rangle = \frac{4\pi}{3}\langle R^3 \rangle (1 + 3p^2) \tag{S14}$$

The radius of gyration, R_g, is obtained by:

$$R_g = R_{avg}\sqrt{3/5}\frac{(1 + 28p^2 + 210p^4 + 420p^6 + 105p^8)}{(1 + 15p^2 + 45p^4 + 15p^6)} \quad \text{(S15)}$$

Uniform Ellipsoids

The form factor for uniform ellipoids of revolution is

$$P(Q) \propto \Delta\rho^2 \frac{A}{V_{ell}} \quad \text{(S16)}$$

where A is a scale factor, $\Delta\rho$ is the difference between the scattering length density of the ellipsoid and the solvent, and

$$V_{ell} = \frac{4\pi}{3} R_a R_b^2 \quad \text{(S17)}$$

where R_a is the cross-sectional radius and R_b the major radius. The ellipsoid is rotated along R_a.

SAXS and USAXS of sample AP1

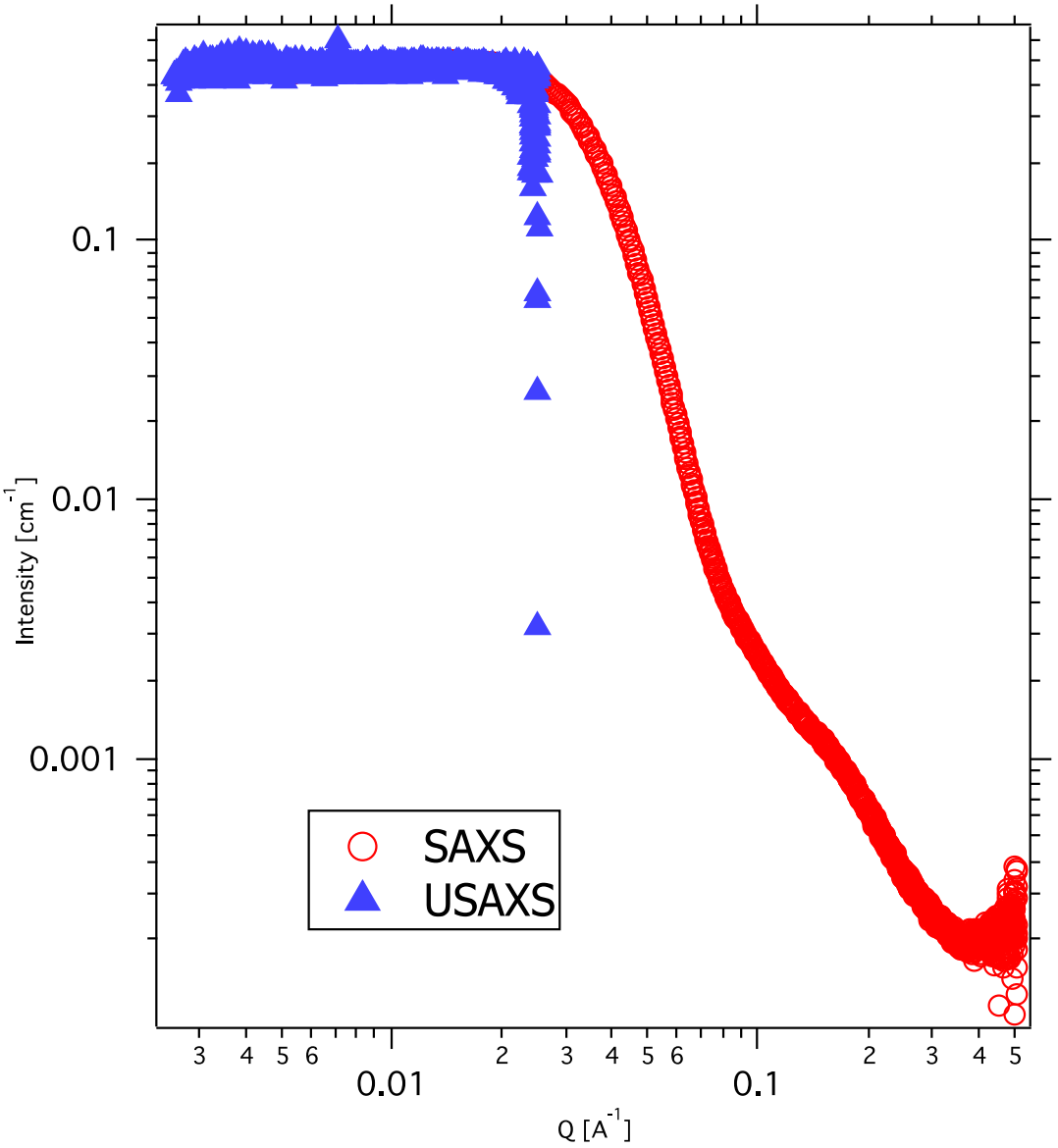

Figure S7. SAXS (red circles) and USAXS (blue triangles) curves for sample AP1

Cloud points for terpinyl acetate- and limonene-loaded PEG-g-PVAc unimeric micelles

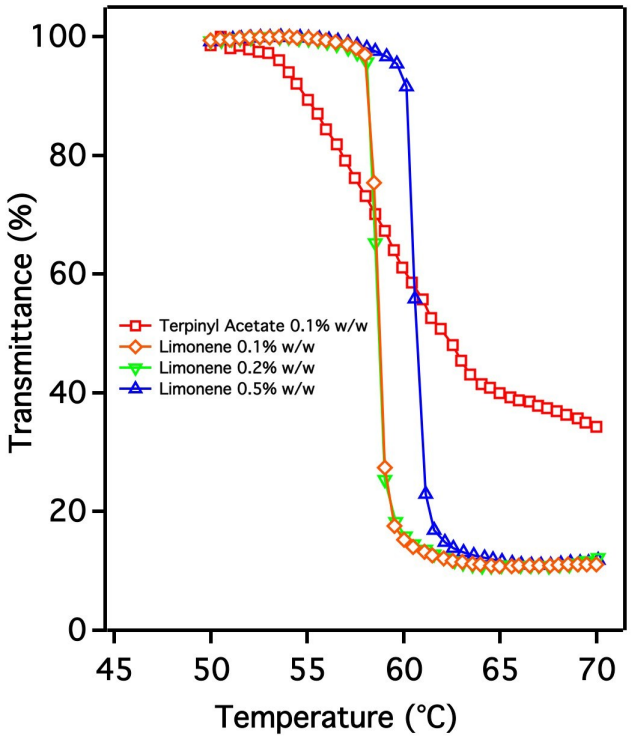

Figure S8. Temperature-turbidity spectra for flavor-loaded PEG-g-PVAc unimer micelles. The profile of the terpinyl acetate-loaded sample is due to partial creaming at 25°C.