Communications to the Editor

pH-Dependent Micellization of Poly(2-vinylpyridine)-*block*-poly(ethylene oxide)

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Our interest in polymeric micelles has led us to synthesize and study the poly(2-vinylpyridine)-*block*-poly(ethylene oxide) diblock copolymer (PVP-*b*-PEO). So far as we know, very little literature exists on this copolymer.[1] We report here the spontaneous micelle formation by PVP-*b*-PEO in aqueous solutions when increasing the pH from acidic to neutral or basic conditions. The micellization process is completely reversible if the pH is cycled above and below the critical pH (ca. pH 5). This polymer will also comicellize with homopolymer poly(2-vinylpyridine) (PVP). The properties of the PVP-*b*-PEO or PVP/PVP-*b*-PEO micelles seem to defy the condition of closed association which has been demonstrated in many block copolymer micelle systems.[2,3] We will argue that this is because of the kinetics of PVP aggregation with simultaneous stabilization by PVP-*b*-PEO.

pH-dependent structural changes such as micellization have generated a great deal of interest in the area of drug delivery.[4,5] A hydrophobic substance which is suspected to have therapeutic activity will have limited circulation *in vivo* due to its poor solubility. Materials such as liposomes, microspheres, and micelles exhibit hydrophobic protection and enhanced solubility for such materials in aqueous media.[6] If the carrier is able to disassemble when arriving at the target because of the local pH, the release of the drug is facilitated.[7] Polymeric micelles with glassy cores have the property that they have extremely low critical micelle concentrations (cmc), such that at extreme dilution the micelles do not disassociate into unimers. PEO, which is known to be nontoxic,[6,8] comprises the shell region. Therefore these micelles are reasonably expected to remain intact and circulate for long periods within the vascular system.

Two PVP-*b*-PEO samples were used, both synthesized by stepwise anionic polymerization.[2,9] The polymerization carried out in our laboratory was performed in THF at −78 °C using rigorously purified monomers, solvents, and high-vacuum techniques.[10] A cumylpotassium/18-crown-6 complex[11] was used to initiate 2-vinylpyridine. This was followed by the addition of ethylene oxide and termination by methanol. The initial PVP block had a narrow molecular weight distribution as expected. However, in our hands the PVP$^-$ anion did not fully initiate EO to produce the PEO block. As a result, a significant fraction (∼30% by weight) of PVP homopolymer exists in the PVP-*b*-PEO sample. The effect of this homopolymer played an important role in the observations reported herein. This sample is denoted PVP-*b*-PEO_{280}. A second sample was prepared by Polymer Sources, Inc. (Dorval, Quebec), denoted PVP-*b*-PEO_{350}, using (diphenylmethyl)potassium as initiator. This latter polymer contained no more than 3 wt % of PVP, according to our GPC analysis. For both polymers, a sample of the PVP block was removed before the addition of the EO, both for molecular weight analysis and for the comicellization studies discussed later. For both polymers, the PVP block length was ca. 133 units (see Table 1).

Table 1. Polymer Characteristics

sample	M_n(PVP)[a]	M_n(PEO)[a]	wt % PVP[b]
PVP-*b*-PEO_{280}	14 000 (1.18)	12 300 (1.28)	53
PVP-*b*-PEO_{350}	14 100 (1.05)	15 400 (1.04)	47

[a] Block M_n values are based on GPC elution curves using polystyrene standards (value in parentheses is M_w/M_n). For PVP, the values are obtained from the PVP aliquot removed from the anionic polymerization before the addition of EO. [b] Based on proton NMR.

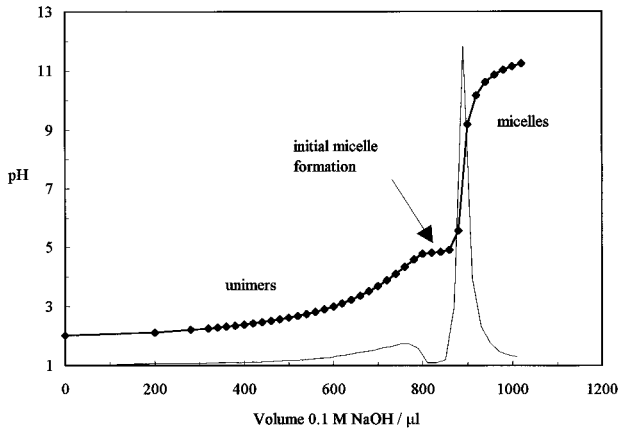

Figure 1. Acid/base titration curve for PVP-*b*-PEO_{280} (1.8 mg/mL) in 0.02 M HCl titrated with 0.1 M NaOH. Stable micelles are present at pH > 5.0. The first derivative of the pH is also plotted.

PEO is soluble in aqueous solutions independent of pH but PVP is soluble in water only when protonated. Both PVP-*b*-PEO block copolymers are, as expected, soluble at low pH (we typically dissolve the polymer in 0.1 M HCl). When the pH is increased by the dropwise addition of 0.1 M NaOH, micelles with well-defined hydrodynamic diameters form spontaneously at ca. pH 5. Further basification produces stable micelle structures. A typical titration curve for these materials is presented in Figure 1 (this curve is for PVP-*b*-PEO_{280}, which contains ca. 30 wt % PVP; PVP-*b*-PEO_{350} behaves similarly). Reacidification of the micelle solution produces a mirror image of this titration curve, which demonstrates that protonation/deprotonation and micelle formation is a completely reversible process. Visual inspection of the unimer/micelle solution during

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titration is informative. When adding dilute NaOH to a stirred solution of PVP-*b*-PEO within the pH range of 4−5, blue scattering swirls are produced in the solution where the local concentration of NaOH is higher. As the solution is homogenized, the blue scattering disappears. This further confirms that the micelles form by a dynamic and reversible process. When the pH reaches 4.8, the blue scattering spreads over the entire volume and remains constant. This property is qualitatively the same as a phenolphthalein indicator in normal acid/base titrations.

Since neutral PVP-*b*-PEO is dissolved in standardized HCl, the total acid content is known. The neutralization point shows that all the acid is titratable; i.e., no detectable pyridinium units remain within the micelle at pH 7. The point at which scattering begins in the solution corresponds exactly with the inflection point on the titration curve at pH 4.8. Calculations based on volumetric and gravimetric variables for this system indicate that ca. 15% of the pyridine units are protonated at the point of micelle formation. The pK_a for pyridine in water is 5.3 and that for 2-ethylpyridine is 5.9.[12] The polymer backbone has the effect of concentrating pyridine units such that the effective pK_a may be lower than for these model compounds as a result of charge repulsion along the chain. It has been shown that this effective pK_a varies with the fraction of protonation of PVP.[13] Therefore, the inflection point in the titration curve is not a true measure of the pK_a for the PVP block.

The size of the final micelles as measured by quasi-elastic light scattering (QELS) does not vary significantly with the basification rate for either polymer. NaOH (0.1 M) may be added to 5.0 mL of the acidified solution of unimers at rates that vary from 0.1 to 8.0 mL/min to a final pH (anywhere in the range 9−11) to produce micelles with little variation in hydrodynamic diameter (d_h) or polydispersity (PD = $\mu_2/\langle\Gamma\rangle^2$).[14] There is, however, a marked dependence of the d_h on initial concentration of PVP-*b*-PEO$_{280}$ (Figure 2a). For PVP-*b*-PEO$_{350}$ variable mass ratios of the corresponding homopolymer could be added to the initial 0.1 M HCl solution and for a constant weight ratio of PVP/PVP-*b*-PEO$_{350}$, the observed d_h also depends on the total polymer concentration (Figure 2b). Once formed at pH above 5, the measured d_h did not change with dilution down to ca. 10^{-5} mg/mL (within ±2 nm) and the scattering intensity was linear in micelle concentration.[15] Hence we conclude that the cmc is below 10^{-5} mg/mL for these diblock polymers. For the data shown in Figure 2, the PD for all cases was ≤0.1. However, for total concentrations higher than the data points shown, the solution becomes milky, indicating the formation of aggregates, and ultimately precipitate formed in most cases. This behavior is unusual compared to most polymer micelles. It is usually observed that the micelles are comprised of a constant average number of unimers (aggregation number) that depends on the molecular weights of the two blocks but not the initial polymer concentration.[3]

We believe these observations are the result of the nucleation of deprotonated PVP at pH ≈ 5, followed by stabilization by the PVP-*b*-PEO. As mentioned above, the micelle size is not dependent on the rate of addition of base. An exception to this statement is the special case in which the PVP-*b*-PEO$_{280}$ solution is allowed to remain at a pH close to 5 for long periods of time (several minutes to hours or days). At this pH, the

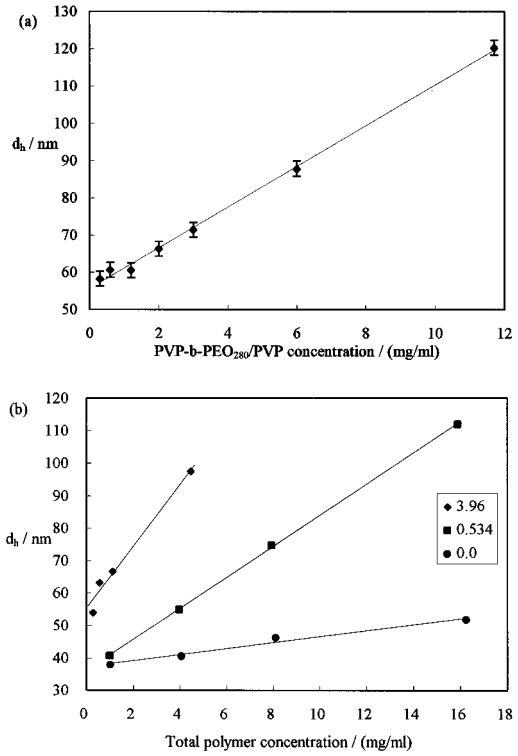

Figure 2. Hydrodynamic diameter dependence on initial polymer concentration. The polydispersity is in the range 0.04−0.08 and does not increase with micelle size. (a) PVP-*b*-PEO$_{280}$ which contains ca. 30 wt % of PVP. (b) PVP-*b*-PEO$_{350}$ with added PVP (PVP/PVP-*b*-PEO$_{350}$ mole ratio indicated on figure).

micelles grow in size (e.g., from ca. 100 to 170 nm in 90 min, data not shown) although the PD of the micelles remains low. We interpret this as the result of imperfect segregation of the partially protonated PVP into the core, thereby reducing the ability of the PEO to provide steric stabilization, which in turn leads to continued growth of the micelle size. Analogous phenomena have been observed in producing micelles by the use of a selective solvent that is not sufficiently poor for the core block.[16] At slightly higher pH (5.13) the micelle size does not change (d_h ≈ 68 nm). We speculate that the core of the PVP-*b*-PEO micelle at pH 5 may be slightly protonated (we estimate 5 mol %) and contain water. Our interpretation of the effect of the total polymer concentration of d_h (Figure 2) is as follows: for a given ratio of the PVP to PVP-*b*-PEO copolymer, the higher the total polymer concentration, the more rapidly PVP blocks aggregate and thereby form a nucleation center for the adsorption of stabilizing PVP-*b*-PEO. If the PVP core grows too rapidly for stabilization by PVP-*b*-PEO (which is governed by the kinetics of aggregation), the particles are not stabilized, leading to aggregation. This argument implies the coexistence of a population of smaller (and presumably well-defined) micelles, but these cannot be detected by QELS. Similar conclusions have been reached in related work on comicellization of different diblock polymers containing PVP.[17] Work is continuing to elucidate the mechanism of the comicellization.

The PVP-*b*-PEO$_{350}$ polymer without added PVP shows a relatively weak dependence of d_h on the total polymer concentration (Figure 2b). We suspect this is the result of the presence of a small fraction of PVP, which is difficult to detect by GPC (as mentioned earlier, we put an upper limit of 3 wt % for PVP in this polymer). It

seems likely that the apparent violation of closed association by these polymers is really an example of one mechanism for "anomalous micellization", in which a residual homopolymer causes aggregation.[3] The unique features of the present system are (1) control of micellization by pH and (2) formation of well-behaved micelles of variable d_h by titration of different ratios and different total polymer concentrations of PVP/PVP-*b*-PEO.

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(15) This concentration is the approximate limit of detection for our system with these micelles. For the very highest concentations, the apparent d_h is slightly larger (ca. 10 nm) because of multiple scattering. These light scattering results and pyrene uptake will be reported in detail elsewhere.

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