Effect of the composition of pluronic copolymers on the interaction with hydrophilic modified ibuprofen

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HIGHLIGHTS

- Interaction of modified ibuprofen with different composition copolymers is compared.
- Shorter PEO chains promote the formation of loosely coiled complex.
- About 7 IP800 molecules can disrupt F127 micelles but about 13 for P123 micelles.
- Shorter PPO chains promote the interaction.

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ABSTRACT

Interactions between hydrophilic modified ibuprofen (Ibuprofen-PEG800, IP800) and copolymers (poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide), PEO–PPO–PEO) were systematically investigated by nuclear magnetic resonance (NMR), dynamic light scatter (DLS), and freeze-fractured transmission electron microscopy (FF-TEM). EO18PO35EO18 (P123) and EO85PO30EO85 (F68) were chosen to explore the effect of chain lengths of copolymers on the interaction by comparison with EO100PO65EO100 (F127) previously studied by us. For P123 with shorter PEO chains compared to F127, the general microstructural transition of P123/IP800 complex was quite similar to F127 irrespective of the initial conformation state of the copolymer. In P123 micelle dominated solutions, it was found that about 13 IP800 molecules were required to disarrange P123 micelles, while about 7 sufficed to disrupt F127 micelles. For F68 with shorter PPO chains compared to F127, there were no loosely coiled aggregates formed in F68 unimer dominated solutions. In the intermediate state of F68 aggregation, an increase of IP800 concentration or temperature induced the formation of the loose F68 micelle/IP800 complex, and eventually disintegrated the complex to form small complex as several IP800 molecules adsorbing on F68 unimers while the complexes with a skeleton of IP800 micelles and copolymer chains threading through were formed in F127 and P123 systems.

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1. Introduction

The mixtures of the surfactants and copolymers attract an extensive attention due to great performances in drug delivery, cosmetic, functional nanomaterial preparation and so on. The interaction between surfactants and copolymers is of great importance that determines the properties of the mixtures [1–4]. It is revealed that extensive reorganization of the copolymer aggregations and surrounding water occurs during the interaction in aqueous solutions, and dehydration of the copolymer induced by the surfactant plays an important step in the interaction [5–7]. A widely acceptable binding model transition of the surfactant/copolymer is described as follows [8,9]: in the pre-micelle region of small surfactant, monomers of surfactant associate with unimeric copolymer leading to the formation of surfactant–micelle aggregation complexes; and when the micelles of surfactant are formed, they interact...
with the copolymer generating the copolymer–micelle aggregates; finally the interaction between surfactant and copolymer leads to the disruption of the copolymer–micelle aggregates and accompanying rehydration of the PPO blocks of copolymer. These transitions are strongly dependent on temperature, the concentration of surfactant and copolymer, and the molecular weight and PPO/PEO ratio of copolymer [5–7, 10–12].

Many efforts were done to discriminate the effect of copolymer composition contributing to the formation of different aggregates. De Lisi et al. [6,13,14] proposed that the hydrophobic character of the copolymer played a more important role than the molecular weight with the same PEO/PPO ratio. Cardoso da Silva et al. [5] studied the interaction between ionic surfactant and copolymers with different PEO chain lengths but the same PPO chain lengths using differential scanning calorimetry and isothermal titration calorimetry. They found that the interaction between anion surfactant and F127 micelles was stronger than that for P123 and L121 possessing shorter PEO chains, while there was no difference in strength of the binding of surfactant to the copolymer unimers due to the same PPO chains. Whereas, the report by Li et al. [10] revealed that shorter PEO chain length of P103 was in favor of the interaction between gemini surfactant and copolymer unimers compared to F108. As we can see the effect of the copolymer chains on the interaction is obscure and specificity, which needs more elaborate studies.

In this contribution, we concern about the effect of individual chain lengths of copolymers on the interaction between copolymer and a new drug, hydrophilic modified ibuprofen (IP800). The hydrophilic modified ibuprofen performing as a nonionic surfactant (Scheme 1) has been systematically investigated in our previous work [15]. In order to get more stable and controllable drug delivery formula [16–18], the investigation about the interaction mechanism between copolymers and IP800 is of great interest.

In our last paper, it was found that the binding model of IP800 to copolymer F127 strongly relied on the concentration of IP800 and the initial aggregation state of F127. In this study, P123 and F68 are chosen to explore the chain length effect by comparison with F127 [19]. P123 possesses the same PPO chains as F127 while shorter PEO chain length. F68 possesses a slightly shorter PEO chains and significant shorter PPO chains compared to F127. The copolymers are all available in pharmaceutical grade. The copolymer concentration was fixed to 1 mg/mL for P123 system and to 250 mg/mL for F68 system to make sure that the critical micelle temperatures (cmt) of the copolymers was covered in the temperature range investigated.

2. Experiments

2.1. Materials

Pluronic copolymers P123 and F68 were Sigma–Aldrich Corp. Products, and used without further purification, the compositions of copolymers are listed in Table 1. 2-dimethyl-2-silapentare-5-sulfonate sodium (DSS, >97%) was also purchased from Sigma–Aldrich. D₂O (≥99.9 at% ²H) was obtained from Qingdao Tenglong Microwave Corp. Ltd. Hydrophilic modified ibuprofen (IP800) was synthesized according to Ref. [15], the molecular formula is as following.

2.2. Methods

The NMR chemical shifts were determined using Bruker Avance 600 spectrometer with a ¹H frequency of 600.13 MHz. DSS was directly added into the solutions as an internal reference [1,8,15] to eliminate the temperature-induced shifts. The error of the chemical shift obtained was ±0.001 ppm.

The relaxation time distributions and hydrodynamic radius values were determined using an ALV 5022 laser light scattering (LLS) instrument [20]. Solutions of P123 systems were filtered through a Millipore filter with a 0.8 μm pore size. F68/IP800 aqueous solutions were measured without filtering due to higher viscosity, which might involve an unwell-defined slow mode around 50 ms probably aroused from the dust. This mode is ignored to well illustrate the mode at faster relaxation time. All solutions were thermostatted for 10 min or more at desired temperature before measurement [9].

The freeze-fractured apparatus (Balzers BAF 400D) was used to prepare the sample replicas which were examined by transmission electron microscope (TEM, Tecnai 12 Philip, Holland).

All details about the methods can be found in our previous study [19].

3. Results and discussion

3.1. Effect of hydrophilic chain length on the interaction mechanism

P123 possesses the same length of PPO chains and shorter length of PEO chains compared to F127. Fig. 1 shows the chemical shift of PO–CH₃ protons as a function of temperature. As shown in Fig. 1b, the chemical shift changes insignificantly first, and then decreases suddenly with increasing temperature, finally decreases slowly with further increasing temperature. The sudden decrease indicates the micellization of copolymer. The cmt values of the copolymers can be determined according to the first inflection (dashed lines), and the second inflection represents the completion of copolymer micellization. The cmts are plotted as a function of IP800 concentration in the inset. As noticed, decreasing cmt curve of P123 is steeper than that of F127 system, which implies that the promotion of IP800 to the micellization of P123 is more significant. At higher IP800 concentration (>47.73 mM), the chemical

Table 1

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<th>Compositions of the pluronic copolymers.</th>
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shift starts from higher values compared to that at lower IP800 concentration, and exhibits a monotonous decrease by heating. The higher chemical shift might be attributed to the stretching of P123 unimer induced by the adsorption of IP800 micelles and subsequently enhanced hydration of PPO chains [8]. The level of the chemical shift curves increases more significantly with further increasing IP800 concentration compared to F127, which is well illustrated as followed.

The effect of IP800 concentration on the chemical shift of PO—CH₃ protons for P123/IP800 system is presented in Fig. 2b. At low temperature (5 °C) where P123 mainly exists in unimer determined from Fig. 1b, the chemical shift remains constant at low IP800 concentration, and increases abruptly to a maximum value after which a sudden decrease is followed with further increasing IP800 concentration. The increasing chemical shift reflects enhancing hydration of PPO chains due to the stretching of PPO chains induced by the adsorption of IP800 micelles [8]. The trends of the chemical shift curves are the same as that in F127 unimer dominated solutions, and the concentrations of IP800 at the inflections are also close despite of the different concentrations of copolymers. These observations suggest that the aggregation of IP800 determines the hydration of PPO chains of copolymer unimers, which is in line with Ref. [5] where no difference in strength of surfactant binding to the unimers of P123 and F127 is observed. The sudden decrease is a reflection of the dehydration of PPO chains, which might be induced by descending chemical potential of free water due to more amount of water binding to IP800 micelles at higher IP800 concentration [21]. This effect has been thoroughly elaborated in our previous paper, which is not the subject of this article [19]. As the state of P123 is in the intermediate stage of aggregation (20 °C), the chemical shift decreases slightly first, and then suddenly decreases to a minimum after which a significant increase is followed, finally the chemical shift tends to be constant as IP800 concentration reaches 146.91 mM. The sudden decrease reflects the dehydration of PPO chains and subsequent the aggregation of P123 unimers. By comparison, the chemical shift curves of PO—CH₃ protons are quite similar to that in F127 system except for the lower minimum values which implies PPO segments of P123 undergo more hydrophobic environment. The molar ratio of IP800 to P123 at the minimum is about 118, which is higher than 30.5 in IP800/F127 systems. This result reflects more amount of IP800 molecules adsorbing on one P123 chain even with the same PPO chain length as that of F127, resulting in the lower chemical shift. However, the constant chemical shift at higher IP800 concentration is close to that for F127 system, which presumably indicates the same microstructure of the aggregations. In other words, the structure of complexes for both systems ends up with IP800 micelles as skeleton and copolymers threading through. In P123 micelle dominated solutions (40 °C), the chemical shift curve of PO—CH₃ protons is similar to that in the intermediate stage of P123 aggregation, except that the change of chemical shift begins from lower values due to the completion of P123 micellization. The continuous decrease demonstrates straightforwardly that the gradual insertion of IP800 into interface of corona-core of P123 micelles excludes the bound water out of P123 micellar core. This process accompanies with the rearrangement of P123 aggregates, which can be verified by DLS measurements.

The chemical shift of proton H1 of IP800 molecules as a function of IP800 concentration in the absence and presence of P123 is shown in Fig. 3a. The chemical shift of H1 exhibits insignificant changes first and then a sudden decrease with rising IP800 concentration, finally a slight increase is observed with further increasing IP800 concentration. The sudden decrease arises from the dehydration of IP800 molecules forming IP800 micelles, and the inflection is defined as the cmc of IP800. Compared to pure IP800 aqueous solutions, the chemical shift at low IP800 concentrations shifts towards higher values and the cmc value is a slight higher in the presence of P123 unimer. These results seem to be different from F127 system where no changes are observed, which imply that the interaction between IP800 and P123 unimers occurs from the lowest IP800 concentration and is stronger than F127. This result is probably attributed to that longer PEO chain length of F127 might impede the approach of IP800 molecules to a hydrophobic site on the copolymer [10]. Whereas, the interaction is still relatively weak due to high hydrophilicity of PPO chains, so

Fig. 2. Effect of IP800 concentration on the chemical shifts of PO—CH$_3$ protons of the copolymers in 20 mg/mL F127 (a), 1 mg/mL P123 (b), and 250 mg/mL F68 (c) aqueous solutions at various temperatures. Data of F127 were taken from Ref. [19].

chemical shift of PO—CH$_3$ protons remains constant (Fig. 2b). As the initially dominated state of P123 is in intermediate stage of aggregation or micelles (Fig. 3b and c), the trends of the chemical shift change of H1 are similar to that in unimer dominated solutions (Fig. 3a), except that the difference between P123/IP800 system and IP800 system is enhanced. This is caused by the stronger hydrophobic interaction between IP800 hydrophobic group and PPO chains due to increased hydrophobicity of PPO chains by heating.

Fig. 3 displays the relaxation time distribution change with IP800 concentration in P123/IP800 system. In P123 unimer dominated solutions (Fig. 4a), the relaxation time distributions begin from three modes at low IP800 concentrations: the fast mode corresponds to P123 unimers, the medium mode is ascribed to P123/IP800 complex, and the slowest mode is attributed to large clusters of unimers induced by more hydrophobic impurities of P123 [7]. The complex mode is dominant even at the lowest IP800 concentration, which implies that P123 unimers are more ready to form loosely coiled aggregates (44.4 nm) compared to F127 based on the unchanged chemical shift of PO—CH$_3$ protons (Fig. 2b) [7,22]. The relative intensity of complex mode increases with increasing IP800 concentration accompanying with the disappearance of unimer mode and cluster mode, which manifests the promotion of IP800 to the formation of loosely coiled aggregates. At higher IP800 concentration (>98.72 mM), a well-defined slow mode appears, and the relative intensity of the mode increases

Fig. 3. Dependence of the chemical shifts of H1 protons on IP800 concentration with (solid) and without (hollow) copolymers at three temperatures (a) 5 °C, (b) 20 °C, (c) 40 °C. Data of pure IP800 solutions were taken from Ref. [19].
with further addition of IP800. As described in NMR results, P123 unimers tend to wrap around IP800 micelles, which lead to enhanced hydration of PPO chains of P123 due to the excluded effect of IP800 micelles. Increasing IP800 micelle content leads to increasing interaction probability between P123 unimers and IP800 micelles, which might give the chance to P123 unimer interacting with several IP800 micelles at one time. Hence, it is reasonable to deduce that the slow mode is ascribed to the cluster formed by IP800 micelles which are packaged together by P123 chains, and the amount of this cluster increases with IP800 concentration. This binding model is the same as that in the similar system of copolymer and nonionic surfactant [8]. In the intermediate stage of P123 aggregation (Fig. 4b), bimodal modes are observed at low IP800 concentration which suddenly turn into a faster monomodal mode attributed to P123 micelle/IP800 complex, indicating the promotion of IP800 to the formation of compact P123 micelles. The monomodal mode shifts gradually towards faster times with further IP800 concentration, and becomes broadening accompanying with the appearance of IP800 micellar cluster mode. The shift and the broadening of the complex mode indicate the change of P123 micelle/IP800 complex into smaller and more polydisperse particles [23]. In addition, the amplitude of IP800 micellar cluster mode becomes weaker compared to that in P123 unimer dominated solutions, which indicates that PPO segments restricted in IP800 micellar core due to the stronger hydrophobic interaction render the formation of IP800 micellar cluster less favorable. This phenomenon becomes more significant in P123 micelle dominated solutions (Fig. 4c), which can be well demonstrated by temperature effect on the relaxation time distribution in supplementary material (Fig. s1). As indicated in Fig. 4c, only a monomodal mode attributed to P123 micelle/IP800 complex is observed at lower IP800 concentration. Increasing IP800 concentration induces the shift and broadening of the complex mode, which directly demonstrates the rearrangement of P123/IP800 complex.

The $R_{\text{app,h}}$ values of the complex modes are plotted in Fig. 5. In P123 unimer dominated solutions (Fig. 5a), the $R_{\text{app,h}}$ of the complex mode decreases dramatically with increasing IP800 concentration and then tends to be constant. The dramatic decrease is a reflection of the disassociation of the loose complex into smaller complex. It is reasonable to deduce the microstructure of the smaller complex as P123 unimer wrapping around IP800 micelle according to the increased chemical shift of O–CH$_3$ protons (Fig. 2b), which resembles that in F127 unimer dominated system. The lower level of the complex $R_{\text{app,h}}$, curve compared to F127 system is probably attributed to smaller size of P123 molecules introducing less volume effect to IP800 micelles. The volume effect decreases at higher IP800 concentration leading to close $R_{\text{app,h}}$ values to IP800 micelles, since PPO chains can in part penetrate into IP800 micelles as discussed above. In the intermediate stage of P123 aggregation (20 °C, Fig. 5b), the $R_{\text{app,h}}$ of the complex is about 27 nm at low IP800 concentration (0.60 mM). Increasing IP800 concentration leads $R_{\text{app,h}}$ to change into about 11.0 nm, and then to a continuous decrease, finally to a constant value (4.3 nm). As can be observed in chemical shift curve of PO–CH$_3$ protons, there is almost no change at lower IP800 concentration (0.60 mM), indicating well hydrated PPO chains. These phenomena indicate that loosely coiled P123 aggregates are formed

![Fig. 4. IP800-induced change of relaxation time distributions for a 1 mg/mL P123 solution at different temperatures (a) 5 °C, (b) 20 °C, (c) 40 °C.](image-url)
Fig. 5. Corresponding hydrodynamic radius (R_{app,h}) of the complex mode as a function of IP800 concentration for the solutions of 1 mg/mL P123 and of 20 mg/mL F127, and as well as R_{app,h} values of IP800 micelles (a) 5 °C, (b) 20 °C, (c) 40 °C. The error bars represent ± standard deviation from repeated measurements. Data of F127 and IP800 were taken from Ref. [19].

Fig. 6. Freeze fracture replicas of the solutions of 1 mg/mL P123 (a–c) and of 250 mg/mL F68 (d–f) at 20 °C with various IP800 concentrations (a, d) 1.00 mM, (b, e) 11.25 mM, (c, f) 9.50 mM. All the scar bars are 200 nm except the inset of 50 nm. The circles and arrows indicate different aggregates.
at low IP800 concentration even at 20 °C, confirmed by FF-TEM images below. The change of \( R_{app,h} \) from 27 nm to 11 nm implies that increasing IP800 concentration facilitates the formation of compact P123 micelles, which exhibits the same effect as temperature as shown in supplementary materials (Figs. s1 and s2). The continuous decrease of \( R_{app,h} \) arises from the disintegration of compact P123 micelle/IP800 complex induced by further addition of IP800. The constant \( R_{app,h} \) is close to that in F127 system overlapping with IP800 micelles. This result straightly confirms the same structure of the copolymer/IP800 complex in line with NMR result. The structural transition of the aggregates is directly monitored using FF-TEM method (Fig. 6). Big complexes corresponding to loosely coiled P123 aggregates/IP800 complex are observed at low IP800 concentration (radius: about 42 nm, circle, Fig. 6a), and then turn into many spherical and well-defined aggregates ascribed to compact P123 micelle/IP800 complex with increasing IP800 concentration (about 25 nm, circle, Fig. 6b), finally some larger aggregates of about 43 nm attributed to IP800 micellar cluster as well as smaller spherical aggregates of about 7 nm assigned to IP800 micelles are found at higher IP800 concentration (circle, Fig. 6c). The size values of the aggregates seem to be larger than those determined by DLS measurements. The difference might originate from that the frozen samples gilded with platinum make the replica much larger, but the morphology and relative size obtained by FF-TEM are in agreement with the result of DLS. In P123 micelle dominated solutions, the decrease of \( R_{app,h} \) begins from IP800 concentration of 2.27 mM, which is lower than that in F127 system of 11.28 mM. It means that about 13 IP800 molecules per copolymer molecule are required to disintegrate P123 micelle/IP800 complex while about 7 suffice to disrupt F127 micelle/IP800 complex [5].

### 3.2. Effect of hydrophobic chain length on the interaction mechanism

F68 possesses almost the same length of PEO chains and shorter length of PPO chains compared to F127. The chemical shift curves of PO—CH3 protons are presented in Figs. 1c and 2c, respectively. The cmt value of F68 per se obtained from the first inflection in Fig. 1c is about 30 °C, which is in line with Ref. [24]. In contrast to F127, the slope of the cmt plots is the smallest (the inset, Fig. 1), which indicates that the promotion of IP800 to the micellization of F68 is feeble due to shorter PPO chains. Moreover, the second inflections of the chemical shift curves are not observed, which mean uncompleted micellization of F68 [25]. This conclusion is supported by DLS results where a fast mode ascribed to F68 unimer is observed within all the conditions investigated (Fig. 7). Therefore, only two predominant states of F68 are involved in this section, i.e. unimers, intermediate stage of aggregation [26].

As F68 exists mainly in unimer (5 °C, Fig. 2c), the chemical shift changes of PO—CH3 protons exhibit similar manners to F127, which imply similar interaction mechanism between copolymer and IP800. The IP800 concentration at the sudden increase of the chemical shift coincides precisely with that in F127 system, which also verifies that the conformation of PPO chains is determined by the aggregation of IP800. However, the IP800 concentration at the maximum shifts to lower value (97.92 mM) compared to that in F127 system (146.91 mM), indicating easier dehydration of PPO segments. It is presumably ascribed to a decrease of chemical potential of free water as more amount of water binding to F68 unimers at such a high F68 content cooperating with increasing IP800 concentration, which is in favor of the dehydration of PPO
In the intermediate stage of F68 aggregation (20 °C), the trend of the chemical shift curve of PO–CH₃ protons is quite different from F127, which is related to shorter PPO chains since PPO chains are responsible for the micellization of copolymer and the hydrophobic interaction between copolymer and IP800 [12,27]. As noticed in Fig. 2c, the chemical shift starts to decrease as IP800 concentration above 45.81 mM and then maintains a continuous decline without a minimum. The phenomena manifest that significant dehydration of PPO segments happens until 45.81 mM and the aggregation of F68 is not completed. The result at higher temperature (40 °C) is also presented for comparison with F127, though it is not F68 micelle dominated solution. The level of chemical shift curves of PO–CH₃ protons becomes lower compared to lower temperatures as a result of increased dehydration of PPO blocks by heating. And consequently, stronger hydrophobic interaction between IP800 molecules and F68 unimers is involved leading to the steeper decrease at lower IP800 concentrations (<11.28 mM).

On the aspect of the aggregation of IP800, the dependence of chemical shift of H1 protons on IP800 concentration is shown in Fig. 3. As shown in Fig. 3a, a slight upward shift of the chemical shift is observed, indicating the interaction between IP800 and F68 unimer. This phenomenon is similar to P123 system but different from F127. In contrast to P123, the interaction originates from the increased interaction probability between F68 and IP800 molecules at higher concentration of F68. As indicated in Fig. 3b, the chemical shift level of proton H1 increases greatly in the presence of F68, and the chemical shift decreases abruptly without a minimum point with increasing IP800 content after a slight decrease. The significantly increased levels arise from the increased hydrophobic interaction between IP800 and PPO chains due to their enhanced hydrophobicity, which definitely delays the association between IP800 molecules confirmed by the higher cmc values. The continuous decrease of chemical shift implies that no free IP800 micelles are formed. What is more, rising temperature renders the changes described above more significant as indicated in Fig. 3c, stemming from stronger hydrophobic interaction between IP800 and PPO chains.

Fig. 7 shows the relaxation time distributions in IP800/F68 aqueous solutions. In F68 unimer dominated solutions, bimodal distributions are mainly observed, which show undistinguished change at low IP800 concentrations. The fast mode is ascribed to F68 unimers which is illustrated as Fig. 8a, and the slow mode is attributed to the clusters of F68 unimers induced by hydrophobic impurities in F68. As IP800 concentration reaches 11.58 mM, a new mode at around 2 ms close to IP800 micellar clusters appears, and its amplitude increases with increasing concentration. There is no mode corresponding to the loosely coiled aggregates as described in P123 system. It is therefore deduced that a small amount of IP800 molecules influence insignificantly conformation of F68 coils (Fig. 8b), and further increasing IP800 concentration induces the association of IP800 micellar clusters as described in P123 system ($R_{app,h} \sim 200$ nm, Fig. 8c and d). At 20 °C (Fig. 7b), the amplitude of the slow mode attributed to F68/IP800 complex enhances gradually with IP800 concentration below 45.84 mM, and then recedes with further increase of IP800 concentration. The $R_{app,h}$ values of the complex modes are about 60–90 nm, which are in well agreement with the FF-TEM images where some spherical aggregates are observed (radius: 50–100 nm, circles, Fig. 6d and e). In combination with unchanged chemical shift of PO–CH₃ protons, the F68/IP800 complexes consist of loosely coiled F68 aggregates as skeleton and IP800 monomers (Fig. 8e and f). The diminishing amplitude of the complex mode indicates that the F68 aggregate/IP800 complex can be easily broken up by further addition of IP800 (>45.84 mM, Fig. 8g). Moreover, there is no distinguished mode close to IP800 micelles, which presumably suggests that no IP800 micelle/F68 complexes or free IP800 micelles are formed in line with NMR measurement (Fig. 3). It is therefore inferred that the complex formed after the disassociation of F68 aggregate/IP800 complex is close to F68 unimer and might comprise several IP800 molecules adsorbing on F68 unimer by hydrophobic interaction (Fig. 8g). The amount of IP800 molecules per F68 unimer increases with IP800 concentration, which is confirmed by the continuous decrease of the chemical shift of both PO–CH₃ and H1 protons. Fig. 7c shows that a fast mode close to F68 unimers predominates within all the concentration range, which might imply that the F68 unimer complexes are more readily formed at higher temperature.
To well demonstrate the unexpected temperature effect, the examples of temperature dependent relaxation time distribution for F68/IP800 solution are depicted in Fig. 9. As indicated in Fig. 9a, increasing temperature induces the appearance of the slow mode ascribed to F68 aggregate. The F68 aggregate mode shifts towards faster time with increasing temperature. In the previous literatures [28,29], this behavior is explained as originating from the dehydration of PEO corona enhanced by temperature. In this contribution, the dehydration of PPO segments occurs with an increase of temperature according to the chemical shift curves of PO–CH₃ protons of F68 (Fig. 1), which might also contribute to the decrease of the slow mode. As a few of IP800 micelles are added (Fig. 9b), the IP800 micelle clusters are formed at low temperature as described above. Hence, the complex mode shifts significantly towards faster time, which might be caused by the dehydration of PEO chains and of PPO chains and by the conformation change of the complex from IP800 micelle cluster to F68 aggregates/IP800 complex. The relative intensity of F68/IP800 complex mode enhances by heating first, and then decreases with further increasing temperature. It seems that increasing temperature induces the formation of F68 aggregate/IP800 complex first, and then restrains its formation to form the F68 unimer complex. At IP800 concentration of 98.72 mM (Fig. 9c), the amplitude of F68/IP800 complex mode decreases progressively with rising temperature. Based on the deduction above, it is reasonable to infer that F68/IP800 complexes are more easily disassociated into the F68 unimer complexes due to stronger hydrophobic interaction induced by heating or increasing IP800 concentration (Fig. 8e–g). It is interpreted that the dehydration of PPO chains upon heating is easier to happen for copolymer chains containing higher fraction of PEO [21], which reduces the energy barrier that the interaction between IP800 molecules and F68 unimers needs to overcome.

4. Conclusion

The interaction mechanism between IP800 and copolymers strongly depends on the composition of copolymers. For P123 with shorter PEO chains compared to F127, the loosely coiled aggregates are more easily formed in P123 unimer dominated solutions. As the form of P123 begins from the intermediate stage of aggregation, the addition of IP800 promotes P123 unimers to form more compact complex which ends up with the complex possessing the same structure as that in F127 as IP800 micelle/copolymer complex. In P123 micelle dominated solutions, it is found that about 7 IP800 molecules are required to disintegrate F127 micelles, while about 13 suffice to disrupt P123 micelles. For F68 with shorter PPO chains compared to F127, the formation of loose F68 aggregates induced by the addition of IP800 is not observed in F68 unimer dominated solutions. In the intermediate stage of F68 aggregation, loose F68 micelles begin to form with increasing IP800 concentration or temperature first, and then are disintegrated to form small complex as several IP800 molecules adsorbing on F68 unimers with further increase of concentration and temperature.

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Appendix A. Supplementary data

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References