Chapter 5: Micellar behaviour of PPO-PEO-PPO block copolymers and mixtures with PEO-PPO-PEO copolymers
Introduction

Poly(ethylene oxide)--poly(propylene oxide)--poly(ethylene oxide) (PEO–PPO–PEO), triblock copolymers (commercially known as Pluronics), due to high biocompatibility show great potential to be used as vehicles in drug delivery systems. Past three decades have shown a plethora of research devoted to their surface activity, micelle formation, thermo rheological phase behaviour, their surfactant based applications such as, wetting, emulsifying, foaming, dispersing, solubilizing, as templates for fabricating meso- and nano-structured materials, in solubilization of hydrophobic drugs and their release as potential carriers for delivery systems. They are available in different mol wt and EO/PO ratio (i.e. variable HLB) and show strong temperature dependent aqueous solution behavior which gets remarkably affected in the presence of salts, non electrolytes, hydrotropes, and low mol wt. surfactants provide easy manipulation to optimize their performance. All these studies have been summarized in excellent reviews from different active groups [1-4].

Though much has been extensive literature on Pluronics®, PPO–PEO–PPO, triblock copolymers (reverse Pluronics®) have not been examined in detail. These are used in personal care products, in paints and coatings and may be of interest for in pharmaceutics and biomedical use [5].

Zhou and Chu [6] and Mortensen et al [7, 8] showed the formation of supramolecular structures in Pluronic® 17R4 [PPO14-PEO24-PPO14] in aqueous solutions. From scattering studies it was shown that 17R4 exists as single coil at room temperature even at fairly high concentrations and formed micelles at elevated temperatures. High CMC and low aggregation number were observed for reverse pluronic®. This was explained due to entropy loss associated with the looping geometry of the central PPO block in micelle formation responsible for marked decrease in micellization ability of 17R4 in water.

While normal pluronic form starlike micelles, reverse pluronic® micelles are anticipated flowerlike as shown schematically below.
Pluronic® 25R4 has been investigated by NMR-PGSE, $^2$H NMR quadrupolar splitting and SAXS measurements and phase diagram constructed by D’Errico and coworkers[9]. From scattering studies on isotropic solutions of 25R4 in water, the presence of Gaussian coil unimers and at higher temperature and composition, the L$_1$ phase is structured as a network of interconnected micelles were seen. The ability of reverse Pluronics® to form micelles in water is greatly reduced when compared with that of normal ones, thus demonstrating the profound influence of the triblock chain architecture.

Huff et al. [10] observed that 17R4 shows both a transition to aggregated micellar species at lower temperatures and a separation into copolymer-rich and copolymer-poor liquid phases at higher temperatures; the cloud point and critical micellization temperature were found little different in H$_2$O and D$_2$O.

Dai et al. [11] used ITC to study interaction between SDS and PPO-PEO-PEO and observed binding on SDS monomers to PPO and then to PEO. The SDS-polymer aggregates formed as complex through entropy driven process. Ortona et al. [12] also examined the interaction of 25R4 with SDS. Kadam [13] reported cloud points of reverse Pluronics® in the presence of ionic surfactants.

**Fig. 1.** Flowerlike (PPO-PEO-PPO) and Starlike (PEO-PPO-PEO) micelles
Li et al examined[14] micellization and gelation of mixed systems of Pluronic® F127 and 25R4 by calorimetric and rheology studies. 25R4-F108 mixed system were also used by this group[15].

Huang et al. [16] synthesized highly ordered mesoporous carbonaceous frame works with diverse symmetries have been successfully synthesized by using phenol /cresols as a carbon precursor using (PEO–PPO– PEO) and reverse PPO–PEO–PPO mixtures. Earlier studies on normal Pluronics® have shown that they form micelles at temperature above about 15-20 °C when PPO block becomes hydrophobic and thus the copolymer behave amphiphilic. But micelles were seen over a wide range of temperature between the CMT and CP. In case of reverse Pluronics®, however a different behavior is seen.

This chapter concerns with the micelle formation of reverse Pluronic® (PPO-PEO-PPO) block copolymers in water. The micellization temperatures determined from NMR and UV-VIS spectroscopy for copolymers under different conditions are discussed. Micellization of mixtures of PEO-PPO-PEO and PPO-PEO-PPO is also discussed.

**Experimental**

Two reverse Pluronics R® (17R4 and 25R5) and two normal Pluronics® (L64, P84 and F88) used in this study were from BASF with following molecular characteristics(Table 1).

Table 1: Molecular characteristics of the copolymers used.

<table>
<thead>
<tr>
<th>Copolymer</th>
<th>Avg. M.W.</th>
<th>% PEO</th>
<th>CP,°C</th>
<th>CP,°C (literature)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pluronic® L64</td>
<td>2900</td>
<td>40</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>Pluronic® P84</td>
<td>4200</td>
<td>40</td>
<td>76</td>
<td>74</td>
</tr>
<tr>
<td>Pluronic® F88</td>
<td>11400</td>
<td>80</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Pluronic R® 17R4</td>
<td>2650</td>
<td>40</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Pluronic R® 25R4</td>
<td>3600</td>
<td>40</td>
<td>24</td>
<td>24</td>
</tr>
</tbody>
</table>
**Cloud point**

The cloud points were measured at a fixed concentration of the copolymer (5%). This was done by gently heating the solutions in thin 20 ml glass tubes immersed in a water bath, which was continuously well stirred with a magnetic bar. The heating rate of the samples was adjusted to 1 °C/min. The first appearance of turbidity was taken as the cloud point. The CP values were reproducible to within 0.5 °C.

**Ultraviolet spectroscopy (UV)**

Shimadzu (UV-2450) UV-visible double beam spectrophotometer was used. To prepare standard KI/I₂ solution 0.5 g of iodine and 1 g of potassium iodide was dissolved in 50 ml distilled water. For CMT determination, different concentrations of copolymers solution were prepared. To each of the copolymer solutions, 25μl KI/I₂ standard preparation was added before measurement and the absorbance at 366 nm for varying copolymer concentrations was measured. The absorption intensity was plotted against the temperature for CMT determination, at 366 nm using thermoelectrically controlled cell. The temperature was scanned at a heating rate of 1 °C/min. The CMT values correspond to the temperature at which the sharp increase in absorbance is observed.

**Dynamic light scattering (DLS)**

Dynamic light scattering (DLS) was used to determine micelle size and polydispersity. DLS measurements were carried out 90° scattering angle on solutions using Malvern Zeta sizer. The average diffusion coefficients and hence the hydrodynamic diameter was obtained by the method of cumulants.

**¹H NMR**

NMR spectra were recorded on a BrukerAvance600 spectrometer at a Larmor frequency of 600.13 MHz for the proton; the spectrometer was equipped with a microprocessor-controlled gradient unit. The sample temperature was kept constant to within 0.1 °C by use of a Bruker BCU-05 temperature control unit. The samples were allowed to equilibrate at the desired temperature for at least 15 min prior to measurement. DSS was directly added into the sample solutions as an internal reference to eliminate temperature-induced shifts.
Results and Discussion

Increase in temperature causes less aqueous solubility. The dehydration of the PEO moiety, hydrogen bonding between the ethereal oxygen atoms of the PEO molecule to water molecules, and polar-nonpolar conformational changes in the PEO molecule all provide effective mechanisms for understanding the phase separations and structural transitions in block copolymer systems. The polymer solutions transform into a two-phase system above the CP. The measured CP values of copolymer at 5% are reported in Table 1 and agree with the literature values. While CP of F88 was above 100°C, L64 showed a lower CP value due to its more hydrophobic character. The reverse Pluronic® 17R4 (with similar mol characteristics as L64) has much lower CP. This is because of two end blocks of PPO in the later. 25R4 has still lower CP than 17R4 due to its more hydrophobic character.

The copolymers form micelles when PPO gets sufficiently hydrophobic. As demonstrated before, starlike micelles are anticipated for normal Pluronics®, flowerlike micelles are formed by reverse Pluronic®. As a consequence of this the aggregation number of reverse Pluronic® micelles is less.

The CMTs of three copolymers L64, P84, F88 were determined by UV-Vis where clear break points at CMC were visible. However, for reverse Pluronic® UV-Vis did not provide CMTs and these were measured from NMR. Both these methods in case of normal Pluronics® showed similar micelles. The CMTs for 5% L64, P84, F88, 17R4 and 25R4 are 26°C, 23°C, 35°C, 39°C, and 25°C, respectively.

The CMTs obtained from each technique were in close agreement. In UV-Vis, iodine was used as a hydrophobic probe at several different temperatures of copolymers and solubilized I₂ prefers to partition in the hydrophobic microenvironment of micelles, causing the conversion of I₃⁻ to I₂ from the excess KI in the solution, in order to maintain the saturated aqueous concentration of I₂. The break point was taken as the CMT(Fig.2).
**Fig. 2. UV-Vis Spectrophotometric determination of CMT of Pluronic.**

In Fig. 3 is shown as a representative set of $^1$H NMR spectra of 5% Pluronic® 17R4 in D$_2$O solution in water measured at various temperatures, and the local expanded regions of the HDO, EO -CH$_2$, PO -CH$_2$, and PO-CH$_3$ signals are shown. The triplet at 1.18 ppm is attributed to the protons of the PO–CH$_3$ groups, the broad peaks from about 3.65 to 3.45 ppm belong to the PO -CH$_2$ protons, the sharp singlet at 3.7 ppm belongs to the EO -CH$_2$ protons, and the signal at 4.8 ppm is the residual signal of HDO. Distinct signals for all protons can be clearly observed at low temperatures. The PO –CH$_2$ signals show a hyperfine structure, and the PO -CH$_3$ signal exhibits a triplet.
Fig. 3. Stack plots of the PEO –CH$_2$– (A), PPO –CH$_2$– (B), and PPO –CH$_3$ (C) proton signal of 5% PPO-PEO-PPO in D$_2$O recorded at various temperatures.
Fig. 4. Temperature-dependent chemical shift (in ppm) and half-height width (in Hz) of the PPO-CH$_3$ signal of 5% 17R4 in D$_2$O solution.

The chemical shift of methyl protons of PO and their half-width are plotted as a function of temperature which clearly indicates a break point at CMT (Fig. 4). A close observation reveals that the gap between CP and CMT values for PEO-PPO-PEO copolymer is much larger than in PPO-PEO-PPO polymers. While very hydrophilic F88 with CP >100 forms micelles at 35°C, micelles in P84 can be seen even at 20°C. However, in case of reverse Pluronics® the very interesting feature is of a narrow gap between CP and CMT which is perhaps the main reason why these copolymers have not been studied in more detail.

In dynamic light scattering measurements, the Brownian motion of the "wet" dispersed particles or "wet" macro-molecules is monitored to provide the size of solvated colloidal particles or solvated polymer chains. The dynamic light scattering studies of 17R4 show single peak of unimer at ~4 nm with much larger interacting clusters shown at 25°C and become large vesicular structure with approximately 854.6 nm at 37.5°C shown in Fig. 5a. But the ability of 17R4 to form micelles in water is largely reduced, which can be attributed to most likely looping geometry of the middle PEO block. 25R4 with lower temperature ~4 nm unimer disperse in solution and higher temperature form clusters shown in Fig. 5b.
Fig. 5. Dynamic light scattering of (a) 17R4 (b) 25R4 as a function of temperature and (c) Different weight fraction of 17R4 and P84 at 30°C

The phase behavior of 17R4 in water and its tendency toward self-assembly dramatically differ from P84. Thus, the construction sequence of blocks has significant influence on their solution properties. In strong contrast to P84, the 17R4 unimer region extends over a broad concentration range and a large temperature range. But 17R4 forms micelles only at high concentrations within a narrow, wedged-shape temperature range, the width of which expands moderately with increasing concentration. Fig. 5c display scattered light intensity versus hydrodynamic diameter of different weight fraction of reverse 17R4 and P84 at 30°C. An increase in weight fraction of P84 led to shift micelle peak. Thus, the results given in figure 5c confirm that for the 17R4+P84+water system, a micelle exists at lower weight fraction of 17R4, at high copolymer concentrations large amount of clusters 17R4 cannot be neglected and are in equilibrium with micelles.
References:


