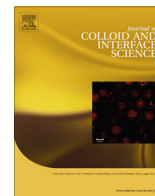




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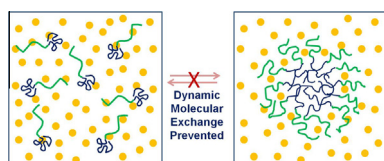


“Non-equilibrium” block copolymer micelles with glassy cores: A predictive approach based on theory of equilibrium micelles

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GRAPHICAL ABSTRACT



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ABSTRACT

Micelles generated in water from most amphiphilic block copolymers are widely recognized to be non-equilibrium structures. Typically, the micelles are prepared by a kinetic process, first allowing molecular scale dissolution of the block copolymer in a common solvent that likes both the blocks and then gradually replacing the common solvent by water to promote the hydrophobic blocks to aggregate and create the micelles. The non-equilibrium nature of the micelle originates from the fact that dynamic exchange between the block copolymer molecules in the micelle and the singly dispersed block copolymer molecules in water is suppressed, because of the glassy nature of the core forming polymer block and/or its very large hydrophobicity. Although most amphiphilic block copolymers generate such non-equilibrium micelles, no theoretical approach to *a priori* predict the micelle characteristics currently exists. In this work, we propose a predictive approach for non-equilibrium micelles with glassy cores by applying the equilibrium theory of micelles in two steps. In the first, we calculate the properties of micelles formed in the mixed solvent while true equilibrium prevails, until the micelle core becomes glassy. In the second step, we freeze the micelle aggregation number at this glassy state and calculate the corona dimension from the equilibrium theory of micelles. The condition when the micelle core becomes glassy is independently determined from a statistical thermodynamic treatment of diluent effect on polymer glass transition temperature. The predictions based on this “non-equilibrium” model compare reasonably well with experimental data for polystyrene–polyethylene oxide diblock copolymer, which is the most extensively studied system in the literature. In contrast, the application of the equilibrium model to describe such a system significantly overpredicts the micelle core and corona dimensions and the aggregation number. The non-equilibrium model suggests ways to obtain different micelle sizes for the same block copolymer, by the choices we can make of the common solvent and the mode of solvent substitution.

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1. Introduction

Classical surfactant molecules with short alkyl tails (typically 8–16 carbon atoms) as the hydrophobic part spontaneously dis-

solve in water and self-assemble into micelles when the surfactant concentration exceeds the critical micelle concentration. The formation of micelles involves the dynamic exchange of surfactant molecules between the bulk solvent and the micelles and between micelles and micelles, ensuring that the micelles formed are truly equilibrium structures. Because of the equilibrium nature of the process, quantitative *a priori* theoretical predictions of the self-

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assembly behavior has been possible using phenomenological and molecular thermodynamic approaches [1–6].

Paralleling the studies of classical surfactants, there has developed an extensive literature in the last forty years on the self-assembly of block copolymer molecules. In a diblock copolymer made up of repeating units A and B, the repeating units occur as blocks, covalently connected to one another. If one block (say, B) is hydrophilic while the other block (A) is hydrophobic, the amphiphilic molecule can be expected to self assemble into a micellar aggregate with a core of A blocks and a corona or shell of B blocks swollen in water [7,8]. However, in marked contrast to surfactants that spontaneously self-assemble in water, most amphiphilic block copolymers do not spontaneously self-assemble in water because of the large hydrophobicity and/or the glassy nature of the A block. Typically, micelles are formed in water using a widely practiced preparation protocol involving solvent exchange. In this protocol, the block copolymer is first dissolved in a solvent (referred to as the common solvent) that is good for both A and B blocks so that molecular scale dissolution of the block copolymer occurs. Subsequently, water is added to the system (water being the selective solvent for the hydrophilic block and non-selective solvent for the hydrophobic block) and the common solvent is gradually removed by evaporation or dialysis. During this process of solvent exchange, the increasing presence of the selective solvent (water) causes the hydrophobic blocks to separate out and begin to interact with one another to create a domain of their own resulting in micelle structures. Since the micelle characteristics are influenced by the method of preparation, namely the conditions of solvent exchange, these micelles have been called “non-equilibrium” micelles in the literature [9]. The term non-equilibrium emphasizes the fact that the dynamic exchange of the amphiphile between the bulk solvent and the micelle or among the population of micelles is drastically reduced if not eliminated. Although such non-equilibrium micelles are more the rule than the exception, theoretical models of block copolymer micelles have been limited to equilibrium self-assembly process [10–13] and have no predictive ability with regard to the non-equilibrium micelles.

The amphiphilic block copolymer micelles that have been extensively studied using the solvent exchange protocol are the diblock copolymer micelles formed from polystyrene–polyethylene oxide (PS–PEO), using tetrahydrofuran (THF) as the common solvent. Research groups of Mitchell Winnik and Gerard Riess have conducted pioneering studies to characterize the micelles generated from a wide range of block copolymer molecular weights and compositions [14–20]. High molecular weight polystyrene has a glass transition temperature of about 100 °C and therefore at room temperature the block will be in glassy state. Since most experimental data are available for this block copolymer, this paper will focus on how one can predict the properties of non-equilibrium micelles which have glassy cores prepared using tetrahydrofuran (THF) as the common solvent and a solvent exchange protocol. The model can be readily applied to other glassy polymers and common solvents that are used in current practice. The problem is of significant interest since many of the block copolymers that are actively being considered for drug delivery applications include hydrophobic polymer blocks that are glassy at room temperature, such as poly(ϵ -caprolactone) (PCL), polylactide (PLA), poly(D,L-lactide-co-glycolide) (PLGA), and polymethyl methacrylic acid (PMMA) [21–23].

It should be mentioned that a notable exception to such non-equilibrium micelles are the micelles formed from the symmetric triblock copolymer of polyethylene oxide–polypropylene oxide–polyethylene oxide (PEO–PPO–PEO), available commercially under the trade names of Pluronics, Polaxomer, etc. These triblock copolymers are in the molecular weight range of 1000–13,000,

with block composition ranging from 20 to 80 wt% ethylene oxide. Because of the weaker hydrophobicity of polypropylene oxide compared to the hydrophobic blocks of most other block copolymers investigated in the literature, the PEO–PPO–PEO block copolymers are relatively easily dispersed into water and are able to generate spontaneously self-assembled structures. Because of their equilibrium nature, the aggregation behavior of these block copolymers can be predicted using equilibrium theories. Indeed, predictive models have been developed in our earlier work to quantitatively estimate the properties of micelles formed, aggregate shape transitions as well as the solubilization of hydrocarbons by these micelles [24,25]. It is safe to assert that the PEO–PPO–PEO triblock copolymers are an exception and in general, most amphiphilic block copolymers cannot be dispersed into water because of the strong hydrophobicity associated with the hydrophobic block, even if the block length is small.

2. Approach to predictive modeling of non-equilibrium micelle

We develop an approach to predictive modeling by following the experimental procedure commonly used to generate the micelles. For example, let us start with diblock copolymers of polystyrene–polyethylene oxide (PS–PEO). The key stages in the self-assembly process are schematically shown in Fig. 1. The block copolymer is first dissolved in tetrahydrofuran (THF) which is a common solvent for both PS and PEO blocks. The dissolution occurs at the molecular scale and there is no driving force for self-assembly at this stage (Fig. 1A). Then water, which is a selective solvent for the PEO block and a non-selective (or poor) solvent for the PS block, is added to the system, progressively. The changing solvent composition induces the formation of block copolymer micelles in the solvent medium by bringing PS blocks closer together to aggregate (Fig. 1B). With sufficient water addition, a distinct micelle core emerges consisting of PS with THF solubilized in the core and water is excluded from the core (Fig. 1C). The corona region consists of PEO blocks and the solvent mixture of THF and water, the same as the surrounding bulk solvent. Since the good solvent THF is present in the core, it acts as a diluent to reduce the glass transition temperature of PS to experimental temperature or below so as to allow the dynamic exchange of the block copolymer molecules between the micelle and the bulk solvent. Under these conditions, the micelle is truly an equilibrium micelle formed in a mixed solvent of THF + water incorporating one of the solvent components (THF) as also the solubilize in the micelle core. With the addition of water and the slow removal of THF by evaporation or dialysis, the THF composition in the bulk solvent as well as in the micelle core decreases. At some critical volume fraction of THF in the micelle core, the liquid to glass transition of PS occurs at the experimental temperature. This critical volume fraction of diluent (THF, in this case) is a function of the experimental temperature, molecular weight of the PS block and the molecular volume of the diluent. At this condition the dynamic exchange of block copolymer molecules between the micelle and the surrounding solvent ceases to exist. The micelle core may be considered frozen in the sense that the number of block copolymer molecules in the micelle cannot change any further beyond this liquid to glass transition point. Further removal of THF simply shrinks the micelle core keeping the aggregation number unaffected. However the dimensions of the corona region continue to be modified because the changing core radius requires a corresponding change in the corona thickness in order to maintain the lowest free energy state for the system. On complete removal of THF, we have micelles in water (Fig. 1D) which are referred to as non-equilibrium micelles. Clearly, these micelles could not have been obtained by attempting to directly dissolve the block copolymer in water.

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