9. Self Assembly of Block Copolymers and its applications in Drug Delivery

Review Article

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Abstract

Block copolymers are polymeric molecules that impart strong surface activity and adsorption to the surface. They have received great attention in the past decade due to their versatile properties. Their tendency to self assemble on nanometer length scales, makes them ideal for emerging nanotechnologies. This review encompasses various aspects involved in self assembly of block copolymer micelle. Thermodynamics, phase behaviour and modelling of block copolymer micelle are main contents of the article. Final section describes about the application of these copolymers in controlled drug release.

Keywords**:** Block copolymer, self assembly, controlled drug release.

1. Introduction

Most of the industrial formulations are in form of suspensions (solid – liquid) or emulsions (liquid – liquid). An energy barrier between particles is required for the stabilization of these dispersions against flocculation or coalescence such that it prevents their close approach where the van der Waals attraction is large. The stabilization can be achieved in two ways. The first is electrostatic stabilization. It is based on charge separation and formation of electrical double layers, a surface charge compensated by unequal distribution of counter and co-ions. When two particles approach to a distance of separation h that is smaller than twice the double layer thickness, repulsion occurs due the double layers. At low electrolyte concentrations, the double layers are extended and the repulsive energy at intermediate distances becomes larger than the van der Waals attraction, producing an energy barrier that prevents approach of the particles or droplets. But as industrial

formulations mostly contain high electrolytes and the ionic surfactants, producing surface charge, do not adsorb on the surface efficiently. This stabilization can be effectively achieved by polymeric surfactants due to their self assembling tendency when dissolved in selective solvent such that it is good solvent for one block and poor for the other. Such type of stabilization is called steric stabilization. They have a strong 'anchor' chain and a 'stabilizing' chain that extends from the surface giving a layer thickness of several nanometers.

The simplest type of a polymeric surfactant is a homopolymer (formed from same repeating units), but they show low surface activity at the oil/water interface. However, they have good adsorption capacity. A small variation in a typical polymer molecule opened door for wide range of applications. Attaching two different homoploymers in a certain fashion lead to synthesis of block copolymers. A block copolymer is a linear arrangement of blocks of varying composition (Figure 1):

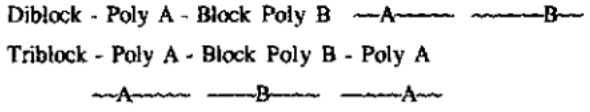

Figure 1[1]: Block Copolymers (A: Hydrophilic chain and B: Hydrophobic chain)

Since block copolymers are amphiphilic in nature, they aggregate in solution to form micelles. These molecules can be applied as emulsifiers and dispersants with the hydrophobic chain residing at the hydrophobic surface, leaving the hydrophilic chain dangling in aqueous solution (providing steric stabilization). They are widely used in dyestuffs, paper coatings, inks, agrochemicals, pharmaceuticals, personal care products, ceramics, and detergents.[1][2][3][12]

2. Synthesis and Properties

A triblock copolymer is synthesized by sequential addition of first the hydrophobic monomers and then hydrophilic part in presence of the alkaline catalyst. The cloud point, the temperature at which the copolymers phase separate from water, increases with increase in the hydrophilic content of the block copolymer. The rate of dissolution decreases as the hydrophilic content increases, due to increase in hydrogen bonding. Higher hydrophobic content leads to decrease in foaming ability. [4][7]

3. Micelle formation in Block Copolymer Aqueous Solutions

A micelle is an aggregate of surfactant molecule in a solution that is responsible for dispersion of two immiscible phases. Micellization or micelle formation is a

thermodynamically driven process. A typical block copolymer micelle consists of a core and a shell with core consisting of hydrophobic part and shell consisting of hydrophilic part. [4] (Figure 2)

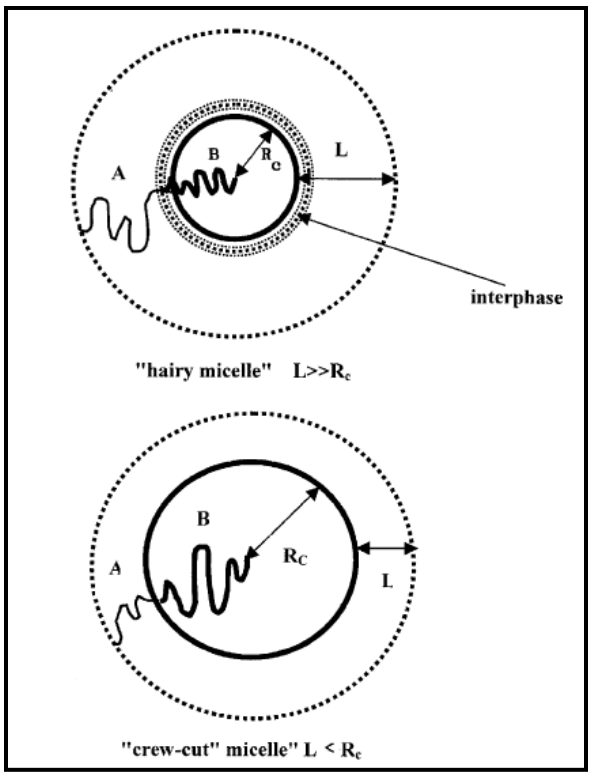

Figure 2 [7]: Schematic representation of AB diblock copolymer micelles in a selective solvent of the A block. Rc: core radius; L: shell (corona) thickness.

The critical micellization concentration (CMC), the amphiphile concentration at which micelles (thermodynamically stable polymolecular aggregates) start forming, is a parameter of great importance. The micellization of amphiphilic block copolymers is inherently more complex than that of conventional, low-molecular weight surfactants. The CMC of aqueous block copolymer solutions decreases with increasing temperature. Micellar growth increases with increase in the copolymer concentration at a particular temperature.

The CMC values of block copolymers (at a given solution temperature) decreased with increasing number of hydrophobic segments, indicating that polymers with a larger hydrophobic domain form micelles at lower concentrations. Higher temperatures resulted in lower CMC values. [4]

4. Thermodynamics

The block copolymers of the A-B or A-B-A type form micelles in selective solvents which are thermodynamically good solvents for one block and precipitants for the other. The standard free energy change for the transfer of 1 mol of amphiphile from solution to the micellar phase, ΔG (the free energy of micellization), in the absence of electrostatic interactions is given by:

$\Delta G = RT \ln(X_{CMC})$

where R is the gas law constant, T is the absolute temperature, and X_{CMC} is the critical micellization concentration in mole fraction units. This is the governing equation for micellization.

Obtaining ΔG, ΔH and ΔS values for certain block copolymers results that ΔH is a positive value, indicating that the transfer of unimers from solution to the micelle is

an enthalpically unfavorable endothermic process. The free energy, ΔG^0, is negative, since thermodynamically stable micelles are formed spontaneously. Thus, it becomes clear that a negative entropy contribution must be the driving force for micellization of the block copolymers. The traditional view of micelle formation is based on the "hydrophobic effect". The presence of hydrocarbon molecules in water causes a significant decrease in the entropy of the latter, suggesting an increase in the degree of structuring of the water molecules. When hydrocarbon residues aggregate in aqueous solution to form a micelle, the hydrogen bonding structure in the water is restored and the water entropy increases, overcoming the entropy loss due to the localization of the hydrophobic chains in the micelles. The entropy contribution usually dominates the micellization process in aqueous surfactant solutions, with the enthalpy playing a minor role. [4][7]

5. Phase Diagram

The phase behaviour of block copolymers dissolved in water was studied using small-angle neutron scattering and dynamic light scattering. At low temperature ($T \leq 15\ ^0$C) and low polymer concentrations, the unimers were fully dissolved gaussian chains with radius Rg = 1.7 nm. Close to ambient temperature, the hydrophobic part causes aggregation of the polymers into spherical micelles with core sizes of the order of 4-5 nm, somewhat temperature dependent. The core size increased with decreasing hydrophilic block size and with increasing temperature. The copolymer with the largest hydrophilic block aggregated in micelles with a core diameter which, within the whole temperature regime, was smaller than the length of a stretched hydrophobic chain. Micelles formed by copolymers of intermediate hydrophilic size had a core diameter which at high temperature approached the size of a fully stretched hydrophobic chain, thus causing an abrupt change from a spherical to a rod-like structure. The concentration of micelles increased roughly linearly with temperature until either saturation was reached (where all polymers were part of a micelle) or the volume density of micelles was so high that they "locked" into a crystalline structure of hard spheres. In the 60-70 ^{0}C temperature range, the micellar structure changed from spherical form to prolate ellipsoid, leading to a decreasing intermicelle interaction. At high copolymer concentration this caused melting of the cubic lattice and led

successively to the formation of a rod-like structure with hexagonal symmetry. Large aggregates of block copolymers ordered in lamellae structure were formed close to 95°C, leading to an opaque suspension. The phase diagram of PEO-PPO-PEO copolymer in water is presented in Figure 3, in which the concentration-temperature regions where the different aggregates (discussed in the previous paragraph) exist are also depicted. [4]

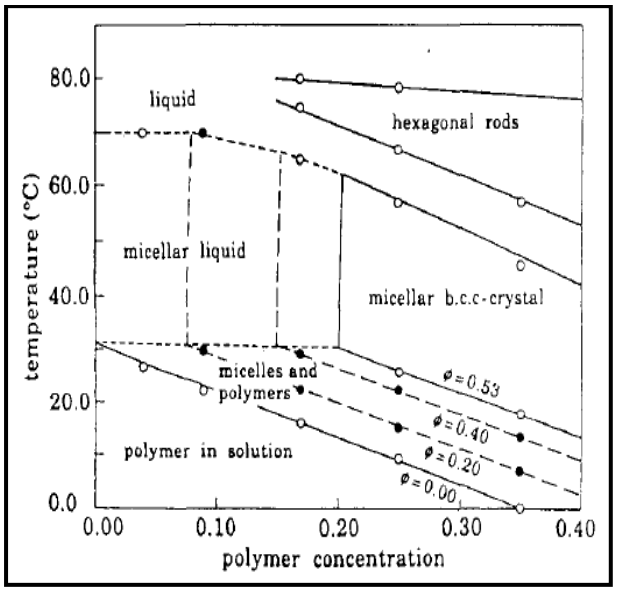

Figure 3[4]: Phase diagram of aqueous solution of bock copolymer, showing the fully dissolved polymers (unimers) at low temperatures and concentrations, the CMC-CMT line (¢=0), the $¢_o$=0.53 transition to b.c.c, micellar crystal, and the high temperature hexagonal phase (¢ is the hard-sphere micelle volume fraction). At T~ 60°C a liquid phase appears between the crystalline b.c.c, and hexagonal phases.

6. Modelling of self assembly

Block copolymer in the solution tend to self assemble and form microphases. In selective solvent, the bad solvency condition for one type of monomer and good one for the other type is important for self assembly along with repulsive interactions between monomers on different blocks. The structure and symmetry of micelles/ aggregates formed depends on relative strength of interactions as well as the composition and the architecture of block copolymer. Following is an overview of different theoretical treatments of the self assembly of block copolymers in selective solvent.

The concept of the scaling theories is to establish on the basis of simple model the correlations between the molecular characteristics of a given block copolymer, mainly diblock copolymers AB, and the characteristics, such as the core radius Rc ; the corona thickness L and the aggregation number Z of the resulting micelle in a selective solvent for one of the blocks. In this approach, monodispersed AB diblock copolymers are generally considered, where N_A and N_B are the number of A and B monomer units in the corresponding blocks.

Assuming uniformly stretched chains for the core radius Rc; with an aggregation number Z; the following relationships are predicted

$R_c \sim \gamma^{1/3} N_B^{2/3} a$

$Z \sim \gamma N_B$

where γ is the A/B interfacial tension and a the segment length.

In the second case, that of hairy micelles, the star polymer theory of Daoud and Cotton can be applied. These authors defined for star-like polymers in good solvents the segment density profile as a function of the distance of the core center. Their model predicts that the star polymer radius scales as

$R \sim N_A^{3/5} f^{1/5}$

where f is number of arms. As in a block copolymer micelle the number of arms corresponds to the aggregation number Z; it follows that $L \sim Z^{1/5} N_A^{3/5}$ with $Z \sim N_B^{4/5}$.

The application of the scaling concepts to the description of the polymer concentration profiles and free energy in micellar systems is largely restricted to long polymer chains in good solvents. In fact scaling models presented above are unable to include finite chain effects and polymer/solvent interactions. Furthermore, numerical values of the micellar characteristics are not directly accessible, as the scaling laws only predict the trends, e.g. how a given micellar parameter scales with a given copolymer parameter. The scaling models have thus to be complemented by more detailed mean-field calculations and molecular simulations.

The development of the self-consistent meanfield formalism provided the means to calculate the polymer concentration profiles in a relatively tractable form. Two approaches were considered, one by semi-analytical mean field models and other by numerical self-consistent mean field description. In the first approach, micellar characteristics were derived by minimizing the Gibbs energy of an isolated micelle using numerical values of the Flory–Huggins interaction parameters x; molecular weight and composition of the copolymer.

Complementary to these methods, computational simulations are used to study self assembly of block copolymers. The computer simulation proceeds with relatively very few approximations and without presumption of micelle geometry or chain conformation. It is possible also to vary intermolecular forces at will in a well-controlled manner. The main limitation of the simulation is the requirement for extensive computation and therefore simulations are mostly reported for 'short' block copolymers, e.g. with N_A or N_B from 2 to about 30. [2][4][7]

7. Application of self assembled Micelles in Drug Delivery

Many important therapeutic compounds exhibit poor aqueous solubility, rendering

delivery of those agents quite challenging. The development of effective delivery systems is crucial to the success of future drugs, which may include larger and more sophisticated synthetic compounds as well as complex natural molecules. The functional properties of micelles based on amphiphilic block copolymers render them ideal for encapsulation and delivery of hydrophobic drugs. During the micellization process, the hydrophobic blocks associate to form the core region, whereas the hydrophilic segments position between the core and the external aqueous medium. Hence, the hydrophobic core is stabilized by the hydrophilic shell, which serves as an interface between the bulk aqueous phase and the hydrophobic domain. This unique architecture enables polymeric micelles to serve as nanoscopic depots or stabilizers for poorly water-soluble compounds. These molecules are biologically stable. Nanocarriers with insufficient stabilities tend to break up and be removed rapidly from blood by kidneys. The molecular weight of polymeric micelles (10^6 g mol^{-1}) prevents renal elimination unless the micelle structure dissociates to unimers. Supramolecular structures with sufficient stability often end up accumulating in the liver and spleen due to a large size or protein adsorption, both triggering a rapid uptake by the reticuloendothelial system (RES). Delivery systems that are smaller than 200 nm have low uptake by RES and may circulate in blood for prolonged periods. Polymeric micelles usually range in size between 10 and 50 nm. Based on the results obtained for other colloidal delivery systems, the nanoscopic size is expected to facilitate the discharge of polymeric micelles at leaky sites of capillaries, e.g. tumours and sites of inflammation.

Sustained release of drugs for polymeric micelles can be achieved by chemical or physical means. The stability of the micellar structure is a prerequisite for control over the rate of drug release. For drugs physically encapsulated in stable structures of polymeric micelles, release is controlled by the rate of drug diffusion in the micellar core or break up of the micelles. The diffusion rate may be quite low if a favourable interaction exists between the solubilizate and the core-forming block in a rigid core. The physical state of the micelle core and encapsulated drug plays an important role. The localization of the solute in the core / shell structure, micellar size and molecular volume of the drug are among other factors influencing the rate of drug diffusion in the polymeric carrier. [5][6][8]

7.1 Micelle-forming for Drug Delivery

There are three different types of drug delivery systems:

7.1.1. Micelle-forming block copolymer–drug conjugates.

7.1.2. Micellar nano-containers.

7.1.3. Polyion complex micelles.

Micelles based on poly(ethylene oxide)-block- poly(L-aspartate), PEO-b-p(L-Asp), have been used extensively for drug delivery. Because of the carboxyl functionality, p(L-Asp) block, PEO-b-p(L-Asp) can be used for the chemical conjugation of drugs. This approach is appealing for the delivery of highly cytotoxic chemotherapeutic agents. In this case, polymer/drug conjugates are assembled into micelles, enabling drug molecules to be protected in the micelle core until the carrier vehicle accumulates at solid tumour sites. This strategy may minimize premature drug release and nonspecific action toward healthy cells, yet allowing for drug release in tumour tissues. [5] See Figure 4.

Micellar Nanocontainers

A more attractive approach is physical encapsulation of drugs within polymeric micelles since many polymers as well as drug molecules do not bear reactive functional groups, e.g. carboxyl, hydroxyl or amino groups, for chemical conjugation or the free functional site may be required for the pharmacological effectiveness of the drug.

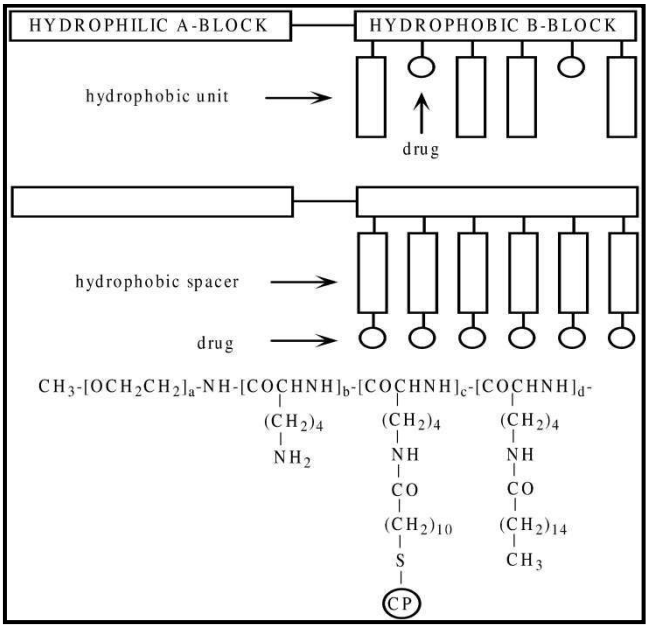

Figure 4[5]: First models of micelle-forming block copolymer–drug conjugate

In addition, conjugates of drugs may exhibit markedly dissimilar biological properties relative to parent drugs, leading to inherent difficulties in characterization and regulatory approval even for already approved drugs.

Physical encapsulation of drugs in the polymeric micelles is usually carried out through dialysis or O/W emulsion methods. In the dialysis method polymer and drug are both dissolved in an organic solvent. The solution is then dialyzed against distilled water to remove the free drug and organic solvent. In the O/W emulsion method, drug is dissolved in a volatile solvent, which is also immiscible

with water, such as chloroform, and added to an aqueous solution of polymeric micelles. The mixture is homogenized by sonication and chloroform is evaporated in an air open system. Free drug is removed by ultra-filtration. The choice of organic solvent and loading process seem to be important factors affecting micellar stability, size and extent of encapsulation. [5]

Polyion Complex Micelles

Depending on the type of amino acid, PEO-b- PLAA block copolymers may bear positive or negative charge at their side chains. Therefore, oppositely charged macromolecules such as DNA or peptides can form polyion complexes with the PLAA segment of the block copolymer, neutralize the charge and induce required amphiphilicity for micellization of the complex. The incorporation of DNA and peptides in polymeric micelles may lead to stabilization against digestive enzymes such as nuclease and facilitate their penetration in cells. [5]

8. Conclusion

The micellization of block copolymers is a unique example of self assembled nanoparticles. The phase behavior and aggregation properties of block copolymers in solution, as affected by the copolymer molecular composition and concentration, additives, and solution temperature, are important in understanding the mechanism of copolymer action underlying the various applications.

In drug delivery, polymeric micelles have huge potential. The thermodynamically stable micelle structure and its nanoscopic size are major advantages of block copolymers over other delivery agents. The effect of variations in chemical structure of polymeric micelle on drug delivery is currently the area of research.

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