“An Updated Review on Pluronics® and Tetronics® Block Copolymers: Fundamentals and Industrial Perspectives”

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Abstract:

This article highlights the micellization behaviour of linear (Pluronics®) and star-shaped (Tetronics®) block copolymers with the focus on key differences between both architectures. Pluronics®, also known as poloxamers or synperonics, are triblock copolymers made up of poly-ethylene oxide (PEO)-poly-propylene oxide (PPO) form self-assembly aggregates and demonstrate thermo-reversible gelation, while Tetronics® or poloxamines are a branched structure with four poly-ethylene oxide (PEO)-poly-propylene oxide (PPO) blocks attached to a central ethylenediamine core. Due to their branched structure, they display unique aggregation tendencies. Moreover, their aggregation ability is influenced by several factors, including concentration, temperature, composition of block copolymers, hydrophilic-lipophilic balance, and molecular weight. These amphiphilic block copolymers (ABCs) have fascinating interest due to their numerous industrial applications, including pharmaceutical, nanotechnology, biological science, material science, etc. We also discuss several experimental techniques such as cloud point (CP), viscosity (ηrel), dynamic light scattering (DLS), and small-angle neutron scattering (SANS) to characterize their critical micelle concentration (CMC), critical micelle temperature (CMT), micellar shape/size, and morphological transitions in various copolymer systems. This review also highlights the theoretical and practical advancements in this area of research. As well as this review offers a comprehensive analysis of the aggregation behaviour of poloxamers and poloxamines in solution, addressing fundamental concepts, influencing factors, and practical applications.

Highlights

- The micellization behaviour of Pluronics® and Tetronics® block copolymers, with the focus on key differences between both architectures.
- These amphiphilic block copolymers (ABCs) have fascinating interest due to their numerous industrial applications.
- This review highlights the theoretical and practical advancements.

Introduction:

1. Block copolymers

An amphiphilic block copolymer (ABCs) is a type of polymer composed of two or more distinct blocks of different chemical compositions that are chemically bonded together in a linear and branched manner. These copolymers are characterized by having at least one block with hydrophilic (water-attracting) properties and one block with hydrophobic (water-repelling) properties. The combination of these two kinds of blocks within a single molecule, these block copolymers, exhibits unique characteristics and behaviour [1, 2].

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Multiple blocks of variable types, sizes, and shapes, as well as a wide range of polar and non-polar substances, are covalently joined together by chemical bonding to form block copolymers (BCPs). These ABCs form self-assemblies in aqueous solutions as well as at (air/ water, oil/ water, and solid/ water) interfaces. A variety of commercially available non-ionic surfactants, including Tween®, Brij®, Pluronic®, Tetronic®, Triton®, Solutol®, Soluplus®, Cremophor® EL, HS15, and others, are produced by connecting a polyoxyethylene (PEO) block (of varying molecular weight) to a variety of hydrophobic (PPO) moieties [3]. These copolymers are classified according to their (i) number of blocks they contain and (ii) arrangement of these blocks. Linear block copolymer, which consists of two distinct blocks covalently bonded together, is referred to as "di block AB" [4] while those with three blocks are called “tri block” and can be classified as either "ABA," "BAB," "ABC," "ACB," or "BAC" type depending on their arrangements [4, 5]. Copolymers with a number of blocks are possible,

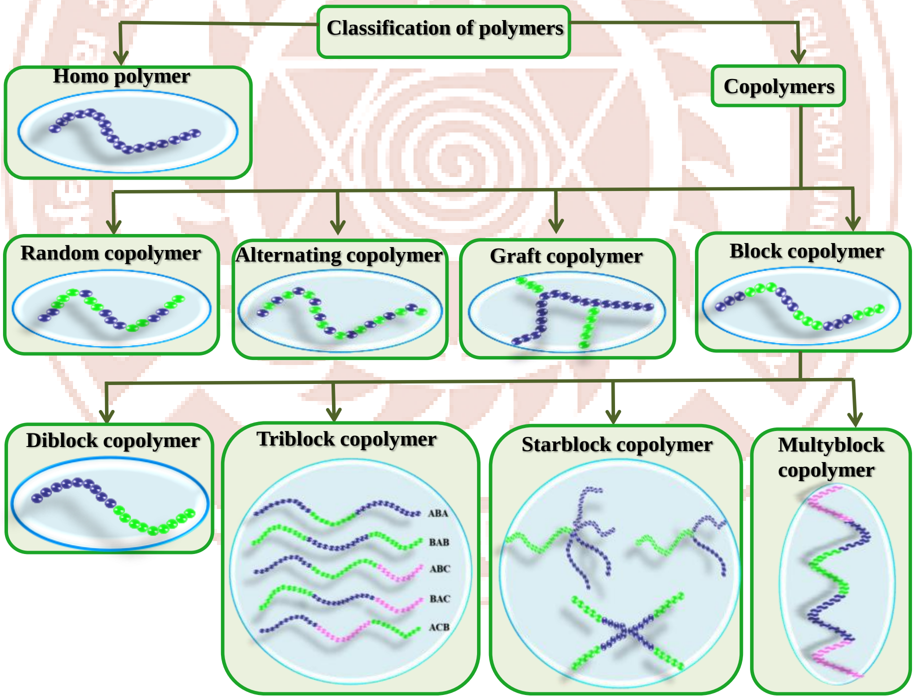


Figure 1: Schematic representation of polymers classification on the basis of arrangement of monomers.

multi-block or non-linear blocks are referred to as star-block copolymers, where two AB-type blocks cross each other and exhibit in 3D arrangement [6-9]. A schematic representation of the several kinds of block copolymers can be observed in **Figure 1**. These BCPs are available in a broad range of hydrophilic-lipophilic balance (HLB), which enhances their performance and solution behaviour by using a variety of hydrophobic elements and PEO molecular weights. These BCPs are to serve as adaptable precursors in detergency, catalysis, pharmaceuticals, etc. [10].

When a BCP is dissolved in water in minimal amounts (at the mm or ppm level), it dramatically lowers the surface tension of water due to the adsorption of such surface-active molecules at air-water or even oil-water interfaces. Another interesting behaviour due to its adsorption capabilities, BCPs exhibit the self-assembly of molecules into nanoscale entities called micelles in aqueous solution. These BCPs form a core (hydrophobic encapsulation region)-shell (hydrophilic corona Surroundings) micellar architecture above the critical micelle concentration CMC)/temperature CMT). A wide range of nanoscale micellar shapes exists at concentrations near CMC. These include ellipsoidal, spherical, rod-like, or worm-like structures. A variety of liquid crystalline phases also appear at high concentration. All depend on the total molecular weight of BCP, the EO/PO block ratio, concentration, temperature, pH, and additive presence. Most of the BCP solutions have characteristics of viscous or viscoelastic solutions that create large micellar structures, which might be highly beneficial for targeted applications **Figure 2** [1, 11].

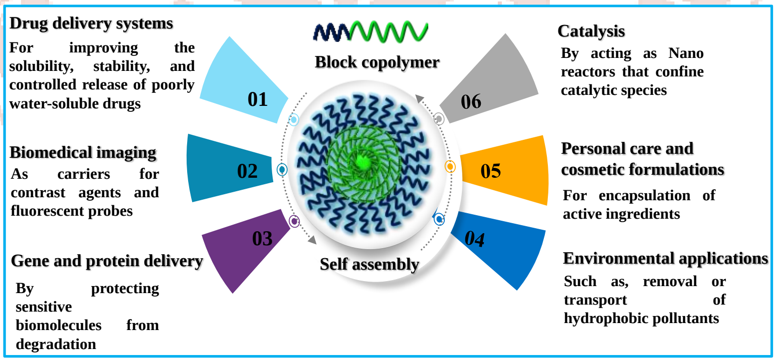


Figure 2: An illustration of amphiphilic BCPs self-assembly for various applications.

1.1 General aspects of linear (Pluronics®) Block copolymer Micelles

Linear block copolymer first introduced in 1950 by BASF corporation (Parsippany, USA) known by the trade name "Pluronics®" are synthetic amphiphilic block copolymer which consist of two hydrophilic polyethylene oxide (PEO) blocks flank a central hydrophobic polypropylene oxide (PPO) block, which are non-ionic triblock copolymers also commonly referred to as synperonics, proxanols, Lutrol® or by the generic name poloxamers [12-17].

Examples of commercially available Pluronics® are shown in Table 1. The concentration and temperature at which copolymers self-assemble into micelles in aqueous solution are called critical micelle concentration (CMC) and critical micelle temperature (CMT) (Figure 3C). Thus, temperature is a crucial factor for change in size, shape and morphology of Pluronics® micelles. A significant rise in temperature causes phase separation. The reason for this phase separation is that the PEO blocks become less soluble at higher temperatures, which causes them to aggregate and eventually separate. To stabilize the micelles in aqueous solution, the hydrophilic PEO blocks made a corona, while the hydrophobic PPO blocks made a core. The PEO/PPO ratio and molecular weight of the copolymer affect the CMC and CMT [14, 18-26]. Whereas, these copolymers have PEO content varied from 10-80% and are available in a broad range of molecular weights usually between 2000-20,000 g/mol. The solubility, CMC and aggregation behaviour of EO-PO blocks are influenced by their precise length and composition [2, 18]. There are four structural arrangements of these copolymers possible depending upon their EO-PO configuration: (i) linear PEO-PPO-PEO, which is commercialised by the name Pluronic®, (ii) linear PPO-PEO-PPO - Pluronic®-R shown in Figure 3a, (iii) non-linear star-shaped Tetronic®, (iv) Tetronic®-R are shown in Figure 3b. These copolymers are commonly represented by the formula (EO)X-(PO)Y-(EO)X or (PO)Y-(EO)X- (PO)Y, where X and Y represent the number of PEO-PPO repeating units, respectively [27]. Due to their non-toxicity, the Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA) agencies have approved these copolymers, especially Pluronic® block copolymers, for a variety of industrial and pharmaceutical applications [28-30].

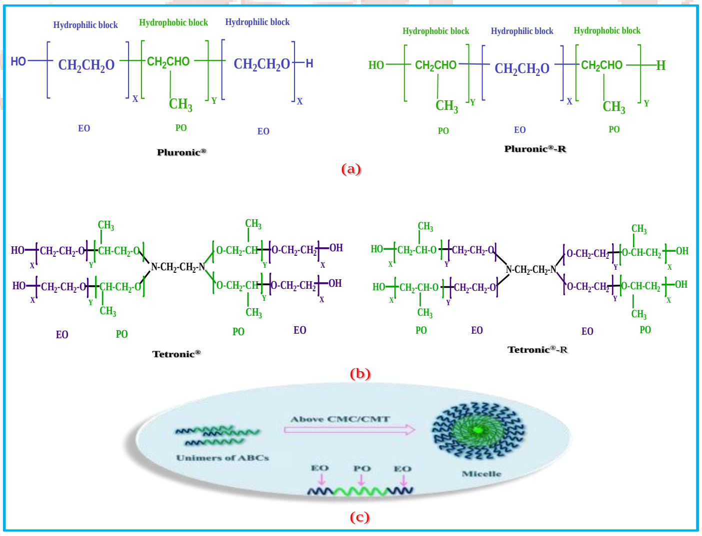
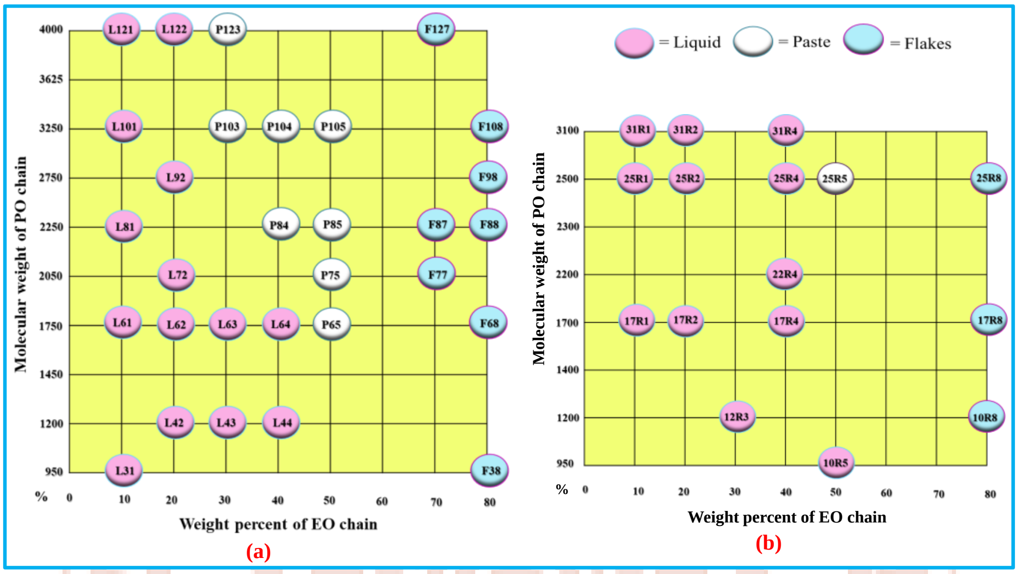


Figure 3: Represents the general structure of Pluronics® and Tetronics® block copolymers (a) & (b) respectively, and the formation of micelle above CMC/CMT (c).

Pluronics®	Average no. of EO units	Average no. of PO units	Molar mass (g mol−1)	CP (1 wt%) (°C)	CMC mM 37 °C	CMT (1 wt%) (°C)	HLB	Ref
L35	22	17	1900	73	5.3	-	19	[31, 32]
F38	86	16	4700	>100	-	>70	31	[33]
L42	22	17	-	37	-	-	8	
L43	12	23	1850	42	2.2	-	12	[32]
L44	20	24	2200	65	3.6		16	[32, 34]
L61	4	31	2000	-	0.11	-	-	[2, 34]
L62	12	34	2500	32	0.4	-	7	[35]
L63	22	17	-	34	-	-	11	[32]
L64	26	30	2900	58	0.48	31.5	15	[32]
P65	40	30	3400	82	-	36	17	[32]
F68	160	30	8750	>100	0.48	50	29	[2, 36]
L72	22	17	-	25	-	-	7	[2]
P75	22	17	-	82	-	-	17	[2]
F77	106	35	6600	>100	-	-	25	[32]
L81	6	22	2750	-	0.023	-	-	[2, 32]
P84	38	43	4200	74	0.071	28.5	14	[2, 37]
P85	52	41	4600	85	0.065	29.5	16	[32, 38]
F87	122	41	7700	>100	0.091	30	24	[32]
F88	208	46	11,400	>100	0.25	38	28	[32, 39]
L92	16	47	3650	-	0.088	-	-	[2, 34]
P94	42	47	4600	-	0.3	23	-	[32]
F98	236	46	13,000	>100	0.077	-	28	[2, 34]
L101	8	61	3800	-	0.0021	-	-	[2, 34]
P103	34	62	4950	86	0.07	20	9	[34]
P104	54	63	5900	81	0.1	22	13	[32, 40]
P105	74	58	6500	91	0.2	22	15	[40]
F108	264	52	14,600	>100	0.022	29.5	27	[32, 41]
L121	10	70	4400	8	0.001	-	-	[34]
L122	22	70	5000	19	0.01	18	4	[2, 34]
P123	40	72	5750	90	0.03	16	8	[2]
F127	198	69	12,600	>100	0.7	24	22	[2, 34]

Table 1: Using a fluorescent probe (pyrene) approach, the CMC of Pluronic® block copolymers was measured at 37 °C and pH 7.4.

The nomenclature of Pluronics® involves alphanumeric two or three-digit codes, including the letters F (flaks-solid), P (paste) and L (liquid), which provide information regarding hydrophilic-lipophilic balance (HLB) and relative molecular weight (MW) [42, 43]. The first one or two digits represent the molecular weight (MW) of PPO, where the corresponding value must be multiplied by 300, and the last digit multiplied by 10 represents wt. % of PEO content. (e.g. P103, where P indicates Pluronics® in paste state involving 10×300=3000 g/mol MW of PPO content and 3×10=30 wt. % PEO content **Figure 4** [17, 30, 44].



(a) (b)

Figure 4: Illustrate molecular characteristics of (a) Pluronics® (b) Pluronics® -R; Colour code indicates the copolymers physical state in ambient conditions.

These triblock PEO-PPO-PEO copolymers, abbreviated as: For example, P103, consist of 17-EO units in each end (Total EO units-34) and 60-PO units in its middle $(EO)_{17}$-$(PO)_{60}$-$(EO)_{17}$. These compositions can be calculated as, $(EO)_X$-$(PO)_Y$-$(EO)_X$

Take 3-digit value of the Pluronics® e.g. P103 (MW=4950 g/mol, provided by BASF)

Ethylene oxide EO (C_2H_4O) MW=44 g/mol, X= Number of EO units?

Propylene oxide PO (C_3H_6O) MW=58 g/mol, Y= Number of PO units?

Step-1

First one or two digit × by 300, (10×300 = 3000 MW of PPO core) [2, 42, 44]

Last digit × by 10, (3×10 = 30% approximate wt. % of PEO corona) [2, 42, 44]

Step-2

M_total = Total MW of that particular polymer (provided by BASF) [2, 42, 44]

f_PEO = Weight fraction of PEO = PEO wt. %/100, (30%/100) [2, 42, 44]

f_PPO = Weight fraction of PPO = 1 – f_PEO, (1 - 0.3) [2, 42, 44]

Now,

MW of PEO = f_PEO × M_total (0.3 × 4950 = 1485),

Then,

X = MW of PEO / 44 (1485/44 = 33.75 ≈ **34)**

MW of PPO = f_PPO × M_total (0.7 × 4950 = 3465), **Y =** MW of PPO / 58 (3465/58 = 59.74 **≈ 60)**

Therefore, P103 contains 34 units of PEO and 60 units of PPO blocks, where their structure is represented as $(EO)_{17}$-$(PO)_{60}$-$(EO)_{17}$.

1.2 General aspects of star-shaped (Tetronics®) Block copolymer Micelles

Over the past few decades, X-shaped amphiphilic block copolymers (ABCs), poloxamines, have attracted interest due to their unique chemical structure. These copolymers are commercially accessible with the trade name Tetronics®, consist of four chains of poly-ethylene oxide (PEO), poly-propylene oxide (PPO) blocks bonded to the ethylenediamine central group [29, 45]. To synthesize the regular Tetronics®, the acceptor ethylenediamine molecule reacts sequentially with precursors of propylene oxide (PO) and ethylene oxide (EO) to form a tetra-block PEO-terminated molecular structure (Figure 3a). while reverse sequential Tetronics® can be formed when the acceptor molecule is first reacted with EO and subsequently with PO, resulting in tetra-functional block copolymers that have PPO terminal ends (Figure 3b) [2, 30, 46-48]. These types of block copolymers exhibit unique and varied structures, making them multi-stimuli responsive due to the two tertiary amine central groups, which confer pH sensitivity and thermodynamic stability [24, 49-51]. As compared to Pluronics®, star-shaped Tetronics® remain more soluble in water because the huge solubility difference between the hydrophobic and hydrophilic parts can form polymeric micelles in an aqueous environment [28, 49, 52]. The lowest concentration of copolymers needed for micelle formation in aqueous solution is known as the critical micelle concentration (CMC), while the minimum temperature at which micelle formation occurs is well known as the critical micelle temperature (CMT). For Tetronics®, CMC and CMT depend on the ratio of EO/PO blocks, molecular weight, environmental conditions, hydrophilic-lipophilic balance (HLB), and degree of protonation of amine groups [9, 45, 46]. The unique core-shell structure of these polymeric micelles is characterized by the hydrophilic PEO blocks forming the water-soluble outer palisade layer, while PPO blocks convolute to form the inner core. Therefore, these copolymers exhibit attractive attention for promoting the solubilization of several additives that would otherwise be poorly soluble in water [45, 46, 53].

Tetronics® block copolymers exhibit in broad range of molecular weights and EO/PO ratios. Thus, these copolymers are classified in three categories, based on their HLB values. (i) Highly hydrophilic, (ii) moderately hydrophobic, and (iii) highly hydrophobic Figure 5 [30, 45, 54].

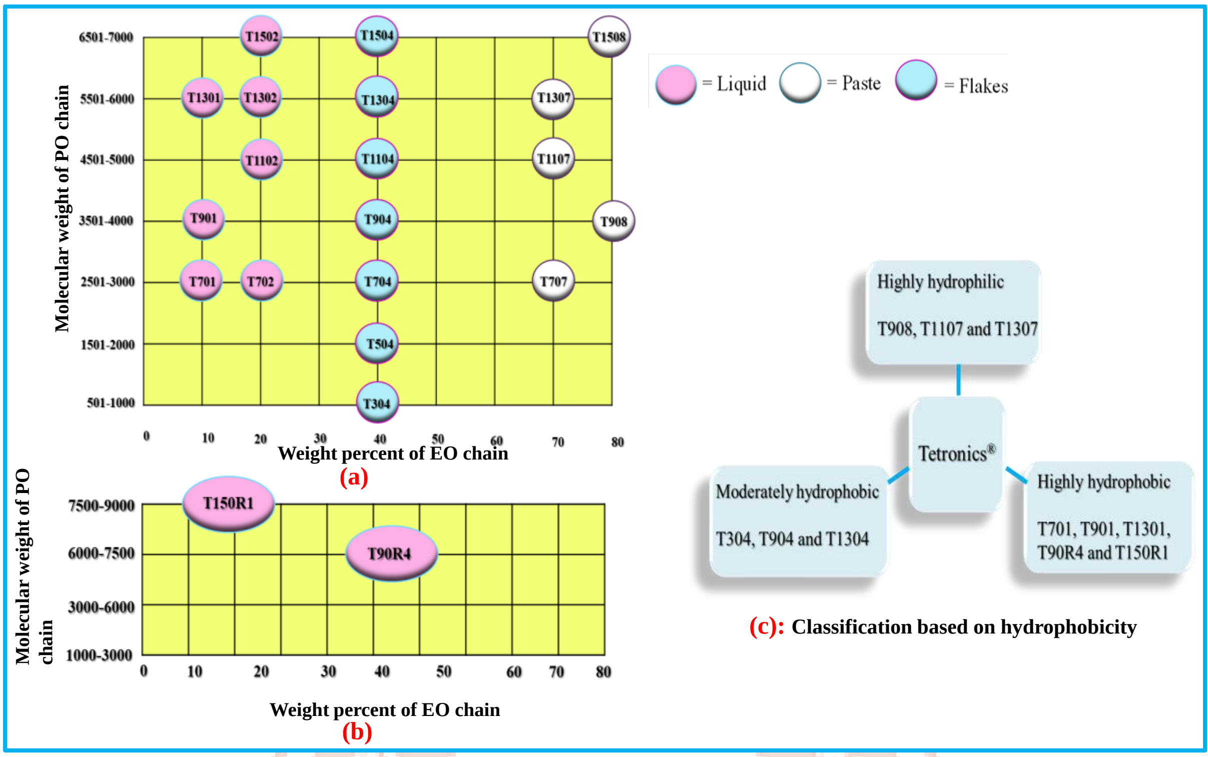


Figure 5. Illustrates molecular characteristics of (a) Tetronics® (b) Tetronics® -R; Colour code indicates the copolymers physical state in ambient conditions. (c) Demonstrates the classification of Tetronics® block copolymers based on hydrophobicity.

Poloxamers and poloxamines based polymeric micelles

Several key parameters determine the formation of micelles by block copolymers, including copolymer architecture, CMC, CMT, cloud point, HLB, pH, ionic strength, and EO/PO ratios. Polymeric micelles are macromolecular assemblies formed when amphiphilic copolymers self-aggregate. These assemblies often consist of two or three synthetic copolymer blocks, such as poloxamers and poloxamines [30, 55]. The resulting micelles have a two-phase architecture, with an outer shell made up of hydrophilic-EO blocks and an inner core constituted by hydrophobic-PO blocks. These micelles are nano-sized structures, typically ranging from 10 to 100 nm, which self-assemble in a micellar structure above critical micelle concentration (CMC) [55-58]. The formed micelles are thermodynamically stable if the concentration of amphiphilic copolymers is above the CMC. But, when the concentration falls below the CMC, these copolymers exist as unimers/monomers in aqueous solutions. Several techniques, including surface tension, calorimetry, conductivity, fluorescence spectroscopy, scattering techniques, UV-vis spectroscopy, and voltammetry, can be used to calculate CMC values [30, 59-61]. Beyond CMC, these copolymers have another significant factor that can influence their micellization, which is known as critical micelle temperature (CMT). It has been demonstrated that CMT is related to a lower molecular weight and a higher content of PEO blocks. Likewise, a high content of hydrophobic blocks PPO results in lower CMC and CMT values. According to the literature, a variety of techniques are used to determine CMT [50, 62-

65]. The CMT of copolymers is highly influenced by their EO/PO ratios and the presence of additives. Patidar *et al*. investigated, improved the solubilizing power in the presence of glucose and a sharp decrease in the CMT of T1307 [66]. Kadam et al., using spectroscopic and calorimetric techniques, examined the CMT of T904 and observed a significant decrease with the addition of salt [67]. Likewise, Vyas *et al*. compared the copolymer solution behaviour of three Tetronics® T304, T904, and T908, which differ broadly in hydrophobicities, and found that the micellization and solubilization abilities were enhanced in the presence of salt [28]. Here, the presence of additives increases the hydrophobicity of copolymers and promotes micellization in the system. High-sensitivity differential calorimetry (HSDSC) was used to examine temperature-dependent micellization [7, 28, 52, 63, 65, 68, 69]. Thus, for tuning the size, shape, and structure of polymeric micelles, the temperature is frequently employed as a control parameter [70]. When the temperature further increases, these non-ionic copolymers cause diminishes aqueous solubility, and the solution turns turbid/opaque above cloud point (CP). The CP or phase separation temperature of the copolymer is increased with the percentage of hydrophilic-EO blocks. At CP, the solvation and desolvation states of the micellar solution are in equilibrium, and this can be changed by the addition of additives that move the equilibrium and affect the polymer-water interaction. This phenomenon is reversible, and after cooling the solution below CP, it becomes clear. The CP values of copolymers with highly hydrophobicity (low HLB) are below room temperature (<20 °C), whereas those with highly hydrophilic (high HLB) may have no cloud point at all or CP beyond 100 °C in aqueous solution.

For the micelles formation, hydrophilic-lipophilic balance (HLB) is another important factor. Block copolymers have varying lengths of hydrophilic-PEO and hydrophobic-PPO blocks. The number of repeating units “N” determines the length of EO/PO blocks. The copolymers with longer EO chains and shorter PO chains are hydrophilic, whereas those with shorter EO chains and longer PO chains are identified as hydrophobic. The ratios of the length/repeating units of EO/PO blocks defined the HLB. In particular, the HLB of copolymers is represented through the following empirical equation, which is inversely proportional to the portion of the PO block repeating units [2, 9, 71].

$$Hydrophilic - Lipophilic\ Balance\ = -36.00\frac{N_{PO}}{N_{PO} +\ N_{EO}} + 33.20$$

The size and strength of the hydrophilic and hydrophobic (lipophilic) components of the BCP molecule are precisely balanced in HLB. The scale has a range of 0 to 18. The HLB range of surfactants or BCPs used in W/O emulsions is 3.5 to 6.0, whereas O/W emulsions typically utilize BCPs with HLB values between 8 and 18 shown in **Figure 6**.

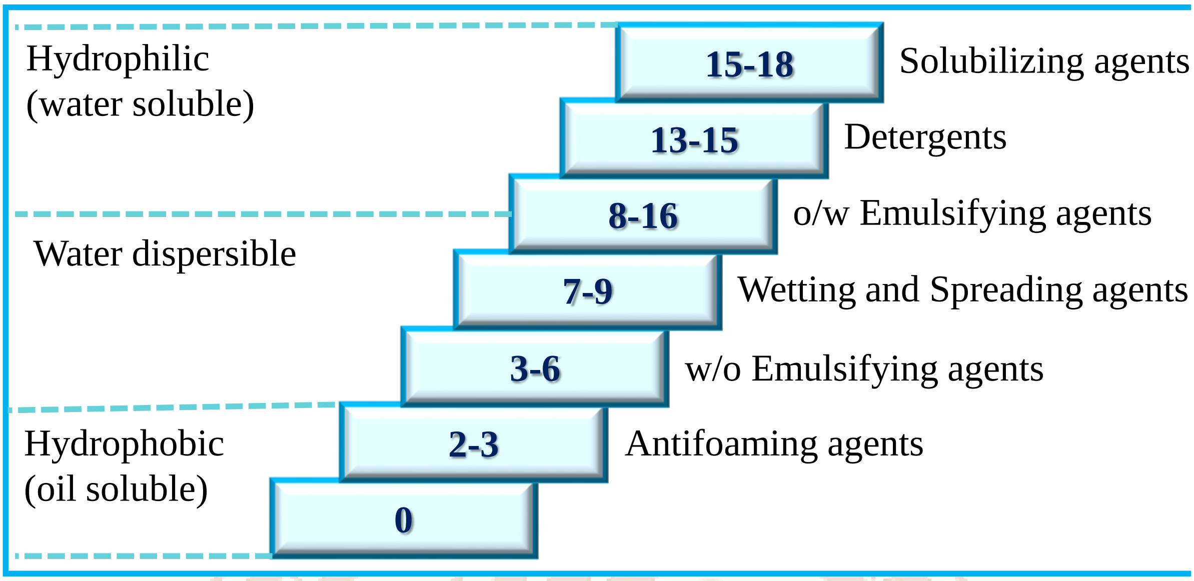


Figure 6: Demonstrates the function of the HLB scale of the role of BCPs for varied applications.

Moreover, for Pluronics® micelles at a certain concentration, the association and dissociation of hydrophobic-PO and hydrophilic-EO blocks is temperature sensitive. These copolymers only form micelles when they become highly lipophilic, reach their CMT [17, 30, 72]. While Tetronics® block copolymers aggregation behaviour is highly pH dependent because it contains amine groups with two pKa values, the first value between 3.8-4.0 and the second value around 8.0. Tetronics® micellization requires deprotonation, which is verified by a propensity to disaggregate when pH is decreased. The core of the Tetronics® micelles differs from Pluronics® micelles because in the Tetronics® micelles, the diamine groups link to the hydrophobic-PPO blocks, which provide unique properties and structures [30, 49, 73, 74].

Over the previous few years, the phase behaviour of several non-ionic copolymers in water and with different additives has been extensively investigated. Jain et al. [22] examined that NaCl significantly increases micellization of P65 by reducing its CP and CMC and promoting micelle formation at higher temperatures. Kadam et al. [75] investigated that SDS and DTAC raise the CP of Pluronic® P84 because of micellar charge repulsion, whereas salts tend to decrease the CP, indicating salting-out effect in accordance with Hofmeister series (Na3PO4 > Na2SO4 > NaCl). Mata et al. [76] studied that halide anions have an effect on both CMT and CP in the following order: F- > Cl- > Br- > I-, and DSC data indicated that as the concentration of salt increases, the CP and CMT decrease. Furthermore, aggregation behaviour and micellar characteristics of L64 are strongly influenced by temperature, salt concentration and polymer concentration. Patidar et al. [77] study discovered that several additives affected the cloud point (CP) of Pluronic® P104 and Tetronic® T1304 copolymers. Whereas NaI and Ethanol increased the CP because of the “salting-in” effect, whereas salts NaCl, NaBr and Urea decreased the CP, displaying the salting-out effect. Due to hydrophilicity, sugar and amino acids reduced the CP. Pillai et al. [78] examined the impact of several cationic surfactants, including Gemini surfactant (GS) and conventional surfactant, on cloud point behaviour of Tetronic® T1304 star block copolymer in aqueous solution. Patel et al. [79] the study explored that the higher concentration of C14 diol in Tetronic® T1304 initially decreases the CP and increases viscosity (ƞrel). According to SANS analysis proved the addition of C14 diol causes growth of micelles and increases CP, ultimately forming vesicles. While Tetronic® T1307 interacts less with C14 diol and causes a minor change in CP and viscosity. Patel et al. [80] investigated the CP of Tetronics® solutions is considerably lowered by the addition of cresols, especially for T1304, which has greater hydrophilicity compared to T904 and T304. Stronger hydrophobic interactions between the cresol and copolymeric micelles cause this decrease in CP. The study also explores the significant variation in the impact of cresol derivatives. Due to stronger intermolecular interaction, o-cresol (OC) reduced the CP most rapidly. While p-cresol (PC) and 4-n-butylphenol (BP) showed a lesser effect. Chakrabarti et al. [11] examined the addition of polycyclic aromatic hydrocarbons (PAHs) to the PEO-PPO-PEO-based block copolymers Pluronic® - P104 and Tetronic® - T1304, which considerably improve their solubility and change their phase behaviour, especially by decreasing the cloud point. This study also examined the solubility of naphthalene, where T1304 is more efficient at solubilized hydrophobic substances as compared to P104. Patel et al. [81] study explores that normal block copolymers (BCPs) such as L31, L35, L64, and L65 clearly transitioned from unimers to ellipsoidal, spherical, rod-like micelles with an increase in temperature, while reverse BCPs such as 31R1, 17R4, 25R4, and 10R5 mostly remained unimers or formed weak clusters without distinct micelle formation. For normal block copolymers, the cloud point reduces with a rise in concentration of BCPs, while reverse BCPs showed diminished CP values than their normal counterparts. The CP also decreased in mixed systems by adding reverse BCPs to normal BCPs, suggesting homogeneous mixing and synergistic interactions.

Several kinds of polymeric micelles can be formed, based on the architecture of the amphiphilic block copolymers used and the solution parameters such as solvent type block copolymer concentration, temperature, ionic strength, pH, solvent/co-solvent ratio and others. In this manner, several micelle-like structures with various morphologies can be formed. The shape and morphology of the self-assembled aggregates of amphiphilic molecules can be predicted using the Critical Packing Parameter (CPP), which is a widely recognized concept in polymer science. The following equation can be used to determine the critical packing parameter (CPP) [9, 55, 62, 74, 82]:

$$Critical\ Packing\ Parameter\ (CCP) = \frac{v}{a_0 lc}$$

Where,

v = it indicates space occupied by hydrophobic-PO part in core of the micelles

a_0 = it indicates surface area occupied by hydrophilic-EO part at the water-surface.

l_c = it indicates the maximum length of the hydrophobic chain that can be extended inside the micelle core

The polymeric micelles with varying morphologies, which are crucial for a variety of advanced nanotechnology applications [83]. In addition to the previously mentioned parameters, the length of the PEO and PPO block will influence the micelle shape of poloxamers and poloxamines. When using a polymer with a hydrophilic block longer than the hydrophobic block, the simplest method is often to achieve spherical micelles [83, 84]. The formation of lamellar structures usually occurs at high concentrations, exhibiting longer hydrophobic blocks and elevated temperatures [85]. Moreover, rods or polymeric vesicles (polymersomes) can be produced with longer hydrophobic blocks [84]. The general structures of copolymeric micelles are shown in **Figure 7**.

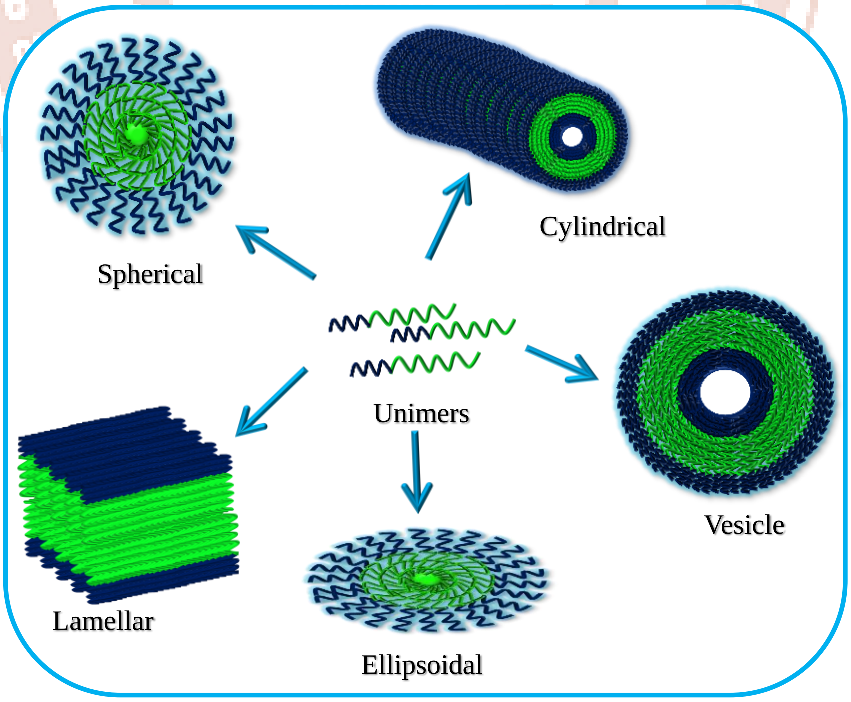


Figure 7: Possible structural shapes of copolymeric micelles.

Characterization techniques for polymeric micelles

The PEO-PPO-PEO type copolymers have been widely investigated using a variety of techniques over the last few years. As previously mentioned, polymeric micelles can serve as a reservoir for therapeutic compounds, exhibiting specific time-release characteristics for both drugs and nucleic acids. It is essential to consider the structural and chemical characterization of polymeric micelles since these features have a direct impact on the efficacy of these nanocarriers. Characterization of polymeric micelles is essential in this context in order to validate their physicochemical properties and, consequently, evaluate their encapsulation efficiency (EE) and drug loading capacity (DL). Additionally, it is important to understand the zeta potential, polydispersion index, and micelle size. These parameters can be evaluated using a range of techniques, which are broadly classified into two categories, as outlined below [32, 83]. I. Chemical characterization II. Structural and morphologic analysis

I. Chemical characterization

Physicochemical characterization can be performed by differential scanning calorimetry (DSC). This offers information about heat flow and thermochemical changes related to micellar systems. Phase transitions in DSC are usually represented by abrupt endothermic or exothermic peaks, which reflect variations in the differential power applied to the sample. The cloud point (CP) [36], the critical micellization temperature (CMT) [69] and the enthalpy of micellization [69] are all frequently found using this method. Furthermore, sol–gel transitions (gelation) in micellar systems can be detected by DSC [32, 86]. X-ray diffraction, which can be carried out as powder X-ray diffraction (PXRD) or single-crystal X-ray crystallography (XRD), is an additional technique for physicochemical characterisation. These methods reveal details about the arrangement of atoms in crystalline structures [83]. One of the most effective analytical techniques is nuclear magnetic resonance (NMR) spectroscopy, which allows for the study of atoms and molecules in both solid and liquid phases. Numerous studies have used this technique to examine the micellar structures of EO–PO block copolymers. NMR can detect the start of micellization when it is monitored in D_2O. In particular, at the critical micellization temperature (CMT), the resonance signals corresponding to the PO units, which are easily visible for molecularly dissolved unimers, decrease because of the decreased mobility of PO segments within the hydrophobic micellar core. It is a non-destructive method that offers comprehensive details about the dynamic behaviour, molecular interactions, and chemical structure of organic systems [32, 83, 87-89]. Many vibrational spectroscopies are used for micellar characterisation, including Fourier-transform infrared (FT-IR) and Raman spectroscopies. Infrared radiation is employed in FT-IR, while monochromatic light is used in Raman spectroscopy. Both methods provide a distinctive molecular fingerprint of the material, which makes it possible to extract quantitative structure information and identify functional groups [83, 90, 91]. One of the most popular chromatographic techniques for drug quantification is high-performance liquid chromatography (HPLC). It can also be used for nucleic acid analysis with the relevant columns, providing high sensitivity, selectivity, and versatility [83, 92]. Furthermore, agarose gel retardation studies are frequently used to assess how well micelleplexes or similar systems encapsulate and preserve nucleic acids [93].

II. Structural and morphologic analysis

A well-known, non-invasive method for figuring out the hydrodynamic size and size distribution of proteins, lipids, polymers, emulsions, and nanoparticles scattered in a fluid medium is dynamic light scattering (DLS) [32, 83, 94, 95]. Additionally, DLS offers the polydispersity index (PDI), which can reveal the presence of aggregation and represents the homogeneity of particle populations. Using equipment like a Nano ZS with a zeta potential unit, electrophoretic light scattering (ELS) is used in parallel to detect the surface charge of nanoparticles, which is commonly expressed as zeta potential [83, 96]. Powerful analytical techniques that produce two- and three-dimensional images of samples include advanced microscopic techniques like scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These techniques allow for the comprehensive assessment of dispersion properties, morphology, aggregation state, and particle size and size distribution [83, 96, 97]. A very sensitive method for examining the nanostructure of polymeric micelles in solution is small-angle neutron scattering (SANS). Since SANS employs neutrons that interact with atomic nuclei rather than electrons or X-rays. SANS offers comprehensive data on factors like polydispersity, aggregation number, internal structure, micelle size, and shape [32].

Application of Pluronics® and Tetronics® Micelles

Application of Pluronics® Micelles

Pluronics® block copolymers are extensively used in a variety of industrial applications (Figure 7) due to their amphiphilic nature and functional adaptability. Among other things, they can be employed to make oily or hydrophobic substances more soluble. Because of this, these EO–PO block copolymers are frequently utilized in oil recovery, cosmetics, lubricants, and pharmaceutical formulations. Pluronics® block copolymers have also been used for a variety of drug delivery applications. They are also used in cell culture medium for their cell cushioning properties in bioprocess applications. However, Pluronics® has been used in materials science to produce mesoporous materials. Among these, a few Pluronics® uses are explained in depth [32].

In the biomedical and pharmaceutical industries, Pluronic® micelles are frequently employed as nanocarriers to improve the solubility, stability and bioavailability of drugs that are poorly soluble in water [98-101]. Additionally, they are used in injectable depots, gene delivery platforms, and controlled drug release systems. Moreover, some formulations have progressed into clinical trials for cancer therapy due to their ability to overcome multidrug resistance [98, 102, 103]. In personal care and cosmetics, Pluronic® micelles behave as emulsifiers and solubilizers for essential oils, fragrances and hydrophobic active substances, enhancing skin penetration and stability in cosmetics [95, 104, 105]. In material science and nanotechnology, Pluronics® block copolymers play an important role due to their tunable size and shape [106]. In detergent and cleaning formulations, they are effective surfactants for eliminating hydrophobic or oily impurities due to their amphiphilic nature [107, 108]. Pluronic® micelles are used in the food industries to enhance dispersibility in aqueous formulations and protect flavours, antioxidants, and nutraceuticals against degradation [109, 110]. In environmental applications, Pluronic® micelles are being investigated for soil and wastewater treatment because they improve the solubilization of hydrophobic organic contaminants [111, 112].

Application of Tetronics® Micelles

Tetronics® block copolymer has a core diamine unit that is sensitive to pH and can be protonated in an acidic solution. Thus, low temperature and pH may prevent micelle formation. Studies on Tetronics® have demonstrated their potential in a variety of applications Figure 8. These have a wide range of applications, notably in the petroleum industry, where they are employed as de-emulsifiers or antifoaming agents in relatively higher concentrations [28, 45]. In the biomedical and pharmaceutical industries, as ingredients in transdermal formulations [113], as an essential ingredient in cleaning solutions for contact lenses [45, 114, 115], as tissue scaffoldings [116-118] and in nanoparticle engineering [119]. Kaur et al. [120] demonstrated the use of T304 for the synthesis of gold nanoparticles. By using ligand to metal charge transfer (LMCT) intermediate states to correlate the medium's pH, they produced industrial-scale Au NPs with the expected morphologies. In order to understand the microenvironments of Tetronics® micelles of T1304 and T1307, Samanta et al. [121] conducted extensive photophysical studies and demonstrated their suitability for adjusting electron transfer processes between aromatic amines and coumarin dyes.

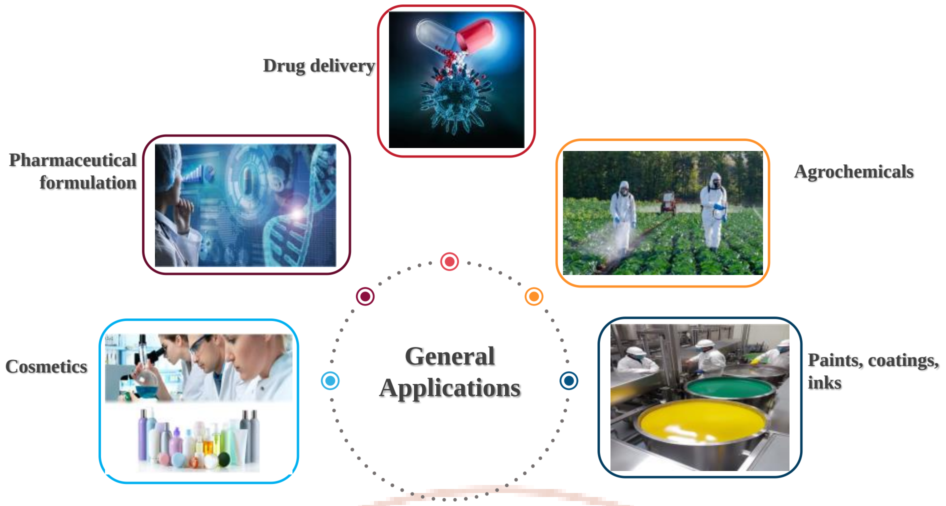


Figure 8 : General applications of Pluronics® and Tetronics® block copolymers

Conclusion

This review focuses on fundamental ideas, factors influencing self-assembly, and the diverse range of useful applications of PEO-PPO-PEO type block copolymers of Pluronics® and Tetronics® in aqueous solution, highlighting their unique aggregation behaviour. From the reported literature, it has been observed that improvements in characterization techniques and chemical modifications have greatly enhanced our comprehension of their structural dynamics and increased their applicability in pharmaceutical, biomedical and industrial applications. Even though these copolymers are currently incredibly versatile as stabilizers, emulsifiers, drug carriers, and templates for nanostructures, further research into responsive alterations and scalable production is required. In addition to addressing current issues like stability and controlled release, ongoing multidisciplinary research will open up new opportunities for effective therapeutics, environmentally friendly formulations, and sophisticated material design, which will ensure that Pluronics® and Tetronics® block copolymers stay at the forefront of applied polymer science.

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