Influence of hydrophobic additives on micellar growth and intermolecular interactions in Pluronics® block copolymers

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सत्यम् ज्ञानम् अनन्तम्

Abstract:

This study presents a comprehensive evaluation of 5 %w/v Pluronics® block copolymers, specifically P84 and P104, with varying poly(ethylene oxide)-poly(propylene oxide) (PEO-PPO) content. The evaluation includes the effects of hydrophobic additives such as 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole, utilizing physicochemical techniques. These techniques include examining solution behaviour through cloud point (CP) measurements and relative viscosity (ηrel), along with spectral analysis using Fourier-transform infrared (FT-IR) spectroscopy and dynamic light scattering (DLS). CP measurements show a consistent decrease as the concentration of additives increases, indicating enhanced hydrophobic interactions within the Pluronics® assemblies. This trend correlates with a significant rise in viscosity, which increases at higher temperatures, suggesting improved intermolecular interactions and structural changes within the system. The impact of the additives on the PEO and PPO regions of the Pluronics® was assessed using FT-IR spectroscopy to identify variations in bond stretching. The combined findings demonstrate a strong relationship between the reduction in cloud point and the increase in viscosity, highlighting how additive-induced structuring affects the temperature and flow characteristics of the system. DLS results indicate a steady increase in hydrodynamic diameter (Dh) with rising concentrations of additives and temperatures, which suggests additive-induced micellar growth. Overall, this study provides valuable insights into drug delivery systems, controlled release formulations, and various Food and Drug Administration (FDA) applications.

Introduction:

Non-ionic amphiphiles are water-soluble tri-block copolymers (BCPs) that comprise two distinct moieties, i.e. hydrophilic (PEO≡poly-ethylene oxide or (EO)x) side blocks and hydrophobic (PPO≡poly-propylene oxide or (PO)Y) core block, which are often marketed as Pluronics® by BASF. Where units of ethylene oxide and propylene oxide per block are indicated by the variables x and y, respectively, which are available in a range of x and y values. The study examining several types of triblock copolymers in aqueous medium has led to the conclusion that these block copolymers can produce a variety of micellar structures (Causse, Lagerge, de Menorval, & Faure, 2006; Desai, Jain, Sharma, & Bahadur, 2001; Ganguly, Kuperkar, Parekh, Aswal, & Bahadur, 2012; Kadam, Savle, Nakarani, Parikh, & Mishra, 2024; Liu, Nace, & Chu, 1997; Tejas Patel, Bahadur, & Mata, 2010). In an aqueous solution, these BCPs exhibit self-assembly characteristics due to variations in the solubility of the constituent blocks. The lowest concentration of BCPs in aqueous medium at which micelles begin to form is known as the critical micelle concentration (CMC). The copolymers primarily exhibit in the solution as unimers below CMC. Micelles with hydrophilic-PEO shell and hydrophobic-PPO core are formed when the concentration rises above CMC, and hydrophobic-PPO blocks aggregate to reduce their exposure to water. The minimum temperature required for micelle formation at a specific copolymer concentration is called the critical micelle temperature (CMT). Below CMT, the formation of micelles is thermodynamically not favourable (Naharros-Molinero, Caballo-González, de la Mata, & García-Gallego, 2022; Divya Patel, Gawali, Kuperkar, Hassan, & Bahadur, 2023; Vyas, Pillai, & Bahadur, 2020). A further increase in temperature causes phase separation due to a significant decline in the solubility of PEO chains the process called cloud point (CP) (Vyas et al., 2020). The copolymers with longer hydrophilic-PEO chains exhibit phase separation at extremely high temperatures as opposed to those with shorter ones. In addition, the self-associative behaviour of block copolymers is influenced by molecular weight, PEO/PPO ratio and hydrophilic-lipophilic balance (HLB), which can be further altered with the addition of additives (Parekh, Ganguly, Aswal, & Bahadur, 2012; Vyas et al., 2020) such as organic solvents (Amstrong, Chowdhry, Mitchell, Beezer, & Leharne, 1996; Ganguly et al., 2012; Kwon, Park, Hwang, & Char, 2001; Parekh, Ganguly, et al., 2012; Parmar, Singh, Bahadur, Marangoni, & Bahadur, 2011), surfactants (Desai et al., 2001; Ganguly, Aswal, Hassan, Gopalakrishnan, & Kulshreshtha, 2006; Jansson, Schillen, Olofsson, Cardoso da Silva, & Loh, 2004; Vijay Patel et al., 2018), electrolytes (Bahadur, Li, Almgren, & Brown, 1992; Denkova, Mendes, & Coppens, 2008; Jørgensen, Hvidt, Brown, & Schillen, 1997; Kadam et al., 2009; Parekh, Singh, Marangoni, & Bahadur, 2012; Su, Liu, Wang, & Chen, 2002), non-electrolytes (Amstrong et al., 1996; Desai et al., 2001; Joshi, Varade, & Parikh, 2006; Kadam et al., 2010; Watlaufer, Malik, Stoller, & Coffin, 1964), hydrotropes (Bharatiya, Ghosh, Aswal, & Bahadur, 2010; da Silva & Loh, 1998; Parekh, Singh, et al., 2012; Shaheen, Kaur, & Mahajan, 2008; Varade, Sharma, Aswal, Goyal, & Bahadur, 2004) etc. Based on several studies, hydrophobic additives often depress the CMT and promote micellar growth, whereas hydrophilic substances exhibit the reverse trend. Since these substances are highly attractive as hydrophobic drug nanocarriers. The FDA (Food and Drug Administration) has already approved these substances (Parekh, Ganguly, et al., 2012; Dhruvi Patel, Ray, Kuperkar, Aswal, & Bahadur, 2020; Pillai et al., 2018). Therefore, to understand how Pluronics® behaves in solutions with hydrophilic and hydrophobic additives as well as how they react with external stimuli are of great significance given their fundamental and practical interest.

Amphiphilic block copolymers (BCPs) have extensive industrial applications due to their distinct physicochemical characteristics, such as Pharmaceutical and biomedical: which include drug delivery, tissue engineering, and gene therapy. Cosmetics and personal care: includes formulation stabilizers, controlled release agents. Industrial and manufacturing applications: water treatment, food industries, surfactants and emulsifiers. Biotechnology and research: cell culture, 3D bio printing and Material science: synthesis of mesoporous materials have all been investigated recently (Causse, Lagerge, de Ménorval, Faure, & Fournel, 2005; Di Spirito, Grizzuti, & Pasquino, 2024; Kabanov, Lemieux, Vinogradov, & Alakhov, 2002; Liang et al., 2007; Liu et al., 1997; Nagarajan, 1999; V Patel et al., 2013).

Patel et al. (Dhruvi Patel et al., 2020) investigated the effect of pharmaceutically active antioxidants, in particular parabens including methyl paraben, ethyl paraben, propyl paraben, butyl paraben and benzyl paraben on micellar transitions in thermo responsive Pluronic® P84 and Tetronic® T1304 block copolymers in aqueous solution employing variety of techniques such as CP, ɳrel, Simulation, UV-vis, FT-IR, DLS, SANS to understand how temperature transformed spherical micelles into more intricate structure like polymersomes. Patel et al. (A. Patel et al., 2021) study examined the hydrophobic amphiphilic diol Surfynol®104 how impact on the micellar structure and self-assembly of the non-ionic surfactant Triton X-100 in aqueous solution. CP, ɳrel, DLS, and SANS techniques determined that Surfynol®104 triggers decreases CP and increases viscosity causes a transition from ellipsoidal to rod-like micelles. By increasing the temperature or adding NaCl, this transformation can also be induced. The results demonstrate the ability to adjust micellar morphology through hydrophobic interactions by altering the concentration of Surfynol®104, temperature, or salt content. Jain et al. (Jain, Aswal, Goyal, & Bahadur, 2000) using several techniques, including CP, ɳrel and SANS study, explored that two moderately hydrophilic PEO-PPO-PEO linear triblock copolymers, P84 and P104, formed spherical micelles in 5 wt% solutions with hydrated PEO shells and PPO core. Moreover, they also examined lower concentrations and temperatures, with the addition of KCl promote micellar growth. Patidar et al. (Patidar & Bahadur, 2018) investigated the impact of several additives on CP and micellar behaviour of Pluronic® P104 and Tetronic® T1304. This study aims to investigate the impact of chemicals and biomolecules, salts, sugars, amino acids, alcohols, urea, polymers and ionic liquids on CP and self-assembly behaviour. Using 5 %w/v copolymer solutions, CP was measured visually, and the size of the micelles was measured by the DLS technique. The findings demonstrated that the effect of additives depends on hydrophobicity, solubility and molecular interactions. The CP was increased with the addition of short-chain alcohols and chaotropic ions, while it was decreased by long-chain alcohols and kosmotropic salts. The study focuses on the relationship between changes in micellar size and variations in CP demonstrated the potential to modify polymer for industrial and pharmaceutical uses. Parmar et al. (Parmar et al., 2011) study explored the solubilization and interaction of Pluronic® P104 in the presence of four phenolic antioxidants, PHBA, syringic acid, sinapic acid and quercetin, using various techniques such as ɳrel, UV-vis spectroscopy, DLS, and 2D NOESY (2D NMR), where the study investigated the effect of salt concentration, temperature and pH on micellar transition. According to the findings, which were in accordance with their hydrophobicity, solubility rises with temperature and salt in the following order: PHBA> syringic acid > sinapic acid > quercetin. Their localization was determined by NOESY with PHBA in the palisade layer, syringic and sinapic acids close to PPO chains and quercetin in the micellar core.

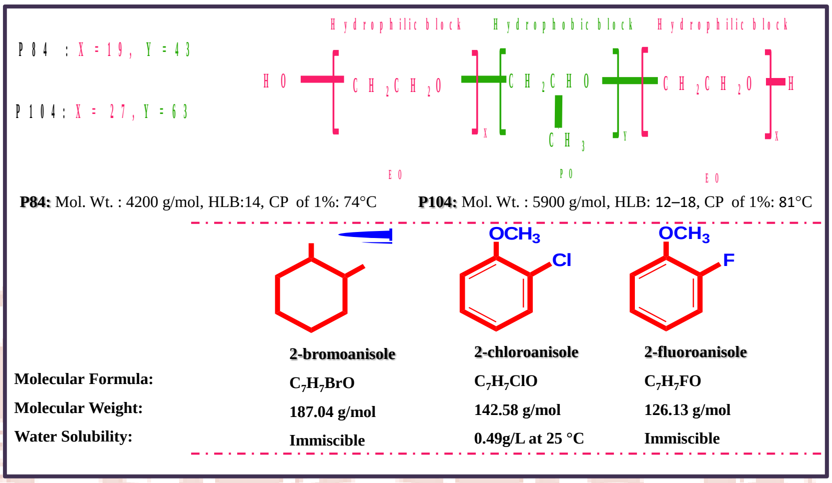
According to the literature, several hydrophobic species, including 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole can dissolve in micellar systems. All these hydrophobic additives are building blocks for Active Pharmaceutical Ingredients, novel drug prospects and intermediates in designing substances for potential applications in therapeutic, drug targeting agent as well as industrial applications in dyes and agrochemicals.

The purpose of this study to investigate interaction of selective hydrophobic additives with 5 %w/v solution of moderately hydrophilic copolymers P84 and P104. Hydrophobic additives 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole were studied as novel additives. This study aimed to deeply investigate the impact of all three additives on the physicochemical properties of a block copolymer system. The main goal was to explore how additives incorporation affects polymer-water interactions and micellar arrangement in aqueous environments. CP measurements were conducted to assess alterations in phase transition temperature and Pluronics® dehydration characteristics. Viscosity (ɳrel) investigations were performed to investigate alterations in flow properties and structural enhancement of the micellar system. FT-IR spectroscopy was utilized to observe changes in hydrogen bonding interactions, namely in the O–H stretching and bending areas. Dynamic light scattering (DLS) experiments were conducted to assess variations in hydrodynamic diameter and micellar expansion. The study proposes to explore a direct correlation among molecular interactions and overall characteristics through the combining of different methodologies. The findings of this research could possibly applicable in drug delivery systems, controlled release formulations and various Food and Drug Administration (FDA) applications.

Experimental

Materials

The Pluronics® block copolymers P84 and P104 were received as a gift from BASF Corp. (Parsippany, NJ), USA and were used without any further purification. 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole used in this study were of analytical AR-grade reagent. The block copolymer solutions with various additives concentrations for CP, viscosity, and DLS measurements were prepared in deionized water from the Millipore Milli-Q system where the percentage (%wt) copolymer solution was prepared through weighing the necessary amount of copolymer and water and storing them in a refrigerator overnight in tightly closed stoppered glass vials (Kadam et al., 2010; Parekh, Singh, et al., 2012; Vijay Patel et al., 2018; Varade et al., 2004).



Scheme 1: General structure of EO-PO-EO based copolymer and chemical structures of different additives used in the present study. The average molecular weight (Mol. Wt) and Hydrophilic lipophilic balance (HLB) value provided by BASF and Cloud point (CP) value taken from reference (Causse et al., 2006; Causse et al., 2005; Chakrabarti et al., 2021; Kadam et al., 2010; D. Patel et al., 2021; Dhruvi Patel et al., 2020; Patidar, Pillai, Bahadur, & Bahadur, 2017; Tripathi, Singhvi, Roy, Kuperkar, & Bahadur, 2023).

Methods

Phase behaviour

Cloud-point (CP) were determined at fixed concentration of block copolymers in the absence and presence of different additives by visual observation of the temperature at which the copolymer solution becomes cloudy during gradual heating of the solution in 20 ml thin glass tubes immersed in a temperature-controlled water bath. The temperature at which the first appearance of turbidity was observed was taken as the CP. The process of taking the CP was repeated thrice and the variation was reproducible up to ± 0.5 °C.

Viscosity

The absolute viscosities of copolymer solutions were measured as a function of additives concentrations and as a function of temperature by using a calibrated viscometer. The viscometer was placed vertically in the temperature-controlled (kinematic viscosity) bath to measure the flow time of the solution at different temperatures for temperature studies and at 30 °C for concentration studies. The solution's flow time was recorded by a calibrated stopwatch. The results were repeatable up to ±5 s.

Spectral analysis

Possible shifts and molecular associations within the chemical environment of the Pluronics®-additives assemblies have been investigated using Fourier transform infrared (FT-IR) spectroscopy. The PerkinElmer Spectrum BXw FT-IR spectrometers, fitted with a precise transmission adaptor, were utilized to get the spectra. The samples were prepared using the standard Potassium Bromide (KBr) pellet method. 100 mg of dry, spectroscopic-grade KBr was accurately triturated in an agate mortar. Additionally, 2-3 mg of the sample was added and thoroughly mixed to produce a homogenous mixture. The resultant powder was tested with hydraulic pressure of up to 150 psi within a stainless-steel container that produced a transparent pellet suitable for transmission examination. Thereafter, the pellet was fixed in the sample holder and introduced into the instrument chamber. Spectra were acquired by 16 co-added scans at a resolution of 4 cm^{-1} across the 400-4000 cm^{-1} range. Data was recorded in percentage (%) transmittance mode. To ensure accuracy and reduce moisture interference, each measurement was performed under controlled laboratory conditions.

Dynamic light scattering

The size distribution and mean hydrodynamic diameter (Dh) of the Pluronics® micelles were analyzed via dynamic light scattering (DLS) at a fixed scattering angle of 90° utilizing a Zetasizer Nano-Zs (Malvern Instruments, UK). The instrument was equipped with a He-Ne laser emitting light at a fixed wavelength of around 633 nm. To minimize the interference of dust particles, the Pluronics® was solubilized in Milli-Q water. All solutions were subjected to filtration using a 0.45 µm nylon filter for preparation. Each measurement was conducted a minimum of three times to verify repeatability, and the resultant average value was recorded.

Results and Discussions

Phase behaviour

An indication of Pluronic® block copolymers phase separation in the presence of various additives is explained by cloud point (CP). CP is a unique characteristic property of Pluronic® block copolymers, and it is identified based on the size/ratio of PEO and PPO blocks, a phenomenon in which their aqueous solutions become cloudy before undergoing phase separation (2ϕ) upon heating to a specific temperature (CP) (Kadam et al., 2010; Kadam et al., 2024; Patidar et al., 2017), where the palisade layer of the Pluronic® micelle becomes less soluble as the temperature rises, exhibiting a correlation with the CP transition.

Figure 1 demonstrates the clouding behaviour of P84 and P104 in the presence of 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole.

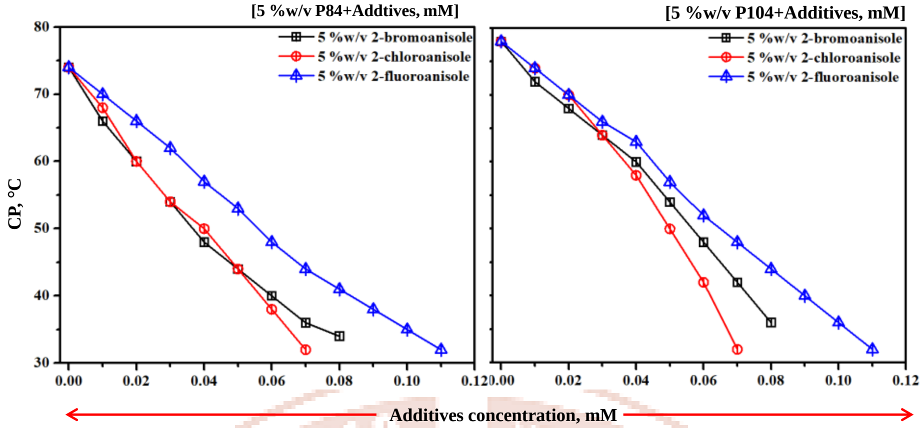


Figure 1: Effect of various additives on cloud point (CP) of 5 %w/v P84 and P104 copolymers in aqueous solutions.

In these findings, we examine the CP of selected moderately hydrophilic 5 %w/v P84 and 5 %w/v P104 block copolymer solutions. Below their CMT (critical micelle temperature), these copolymers remain molecularly dissolved in aqueous solutions as unimers (colourless transparent solution). As shown in figure 1 at fixed concentration (5 %w/v) of P84 and P104 having 40% PEO in its constitution with moderate hydrophilicity, exhibit phase separation (2ϕ) at 74°C and 78°C, respectively. It was also discovered that the CP value increased in the order: P104>P84 due to the larger molecular weight of their central PPO blocks. In this case, a gradual rise in temperature likely results in the formation of spherical micelles with significant size variation, which may transition into worm like micelles as the system nears the cloud point (CP). The solution becomes bluish transparent, known as Blue Point (BP), which is only a few degrees below the actual CP. It then seems to be an unstable turbid system with apparent phase separation (2ϕ). Their characteristic solution behaviour for moderately hydrophilic Pluronics® has been studied previously (Chakrabarti et al., 2021; D. Patel et al., 2021; Wang & Feng, 2010).

Furthermore, we examined the effect of various additives, including 2-bromoanisole, 2-chloroanisole and 2-fluoroanisole on the CPs of 5 %w/v P84 and 5 %w/v P104 block copolymer solutions **figure 1**. For both copolymers, the CP was decreased almost linearly as a function of all additive concentrations. In the case of P84, the cloud point (CP) diminishes gradually from approximately 74 °C to nearly 32–34 °C, based upon the nature and concentration of additives. 2-bromoanisole consistently reduces the CP in a progressive and nearly linear trend within the examined range, signifying a gradual breakdown of Pluronics®–water hydrogen bonding and an increasing incorporation with the hydrophobic regions. 2-

chloroanisole exhibits the most significant drop at varying concentrations (approximately 0.01–0.07 mM), suggesting significant disruptions to hydration and increased hydrophobic interactions across the micellar core. 2-fluoroanisole exhibits an almost gradual drop, indicating formation of micelles. While in P104, the initial CP (~78 °C) significantly diminishes with the addition of hydrophobic additives, validating the dehydration of the polymer chains caused by the additives. 2-chloroanisole and 2-fluoroanisole induces a notably larger decrease in CP, suggesting a more pronounced interaction with hydrophobic regions and a sharper occurrence of phase separation. Conversely, 2-bromoanisole exhibit a more steady decrease, indicating a considerable disruption of the hydration layer **figure 1**.

Overall, 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole remove the sheath of water molecules that surround PEO and PPO blocks in the micelles, which brings them closer together and makes the micelle bigger close to the cloud point, resulting in turbidity and macroscopic phase separation (2ϕ). There are same trend of CP reported in the literature (Chakrabarti et al., 2021; Desai et al., 2001; Kadam et al., 2010; Mehul Khimani, Rao, Bahadur, & Bahadur, 2014; M Khimani et al., 2015; Parekh, Ganguly, et al., 2012)

Solution flow behaviour

The relative viscosity (ηrel) technique is an incredibly reliable method for studying the morphological transition of self-assembled block copolymers in solution. In order to gain a better understanding of the micellar transition characteristics caused by the addition of various hydrophobic substances and temperature variations, a study of relative viscosity was conducted. The relative viscosity (ηrel) of Pluronics® P84 and P104 copolymer solutions was measured as a function of various concentrations of hydrophobic additives such as 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole and as a function of temperature **figure 2**. These measurements offer in elucidating the impact of micellar growth, additive-induced micellar core expansion, and thermal dehydration on the flow behaviour of the system.

Figure 2 illustrates the impact of hydrophobic additives on 5 %w/v P84, the figure shows that the ηrel does not initially alter when hydrophobic additives 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole are added until it reaches the concentration 0.05 mM, but further increase in concentration of all the additives, the addition of 2-bromoanisole, 2-fluoroanisole are significantly affect the ηrel of 5 %w/v P84 solution. Where an increase in viscosity suggests growth of micelles or intermicellar interaction and/or structural transition, similar to the literature (Kadam et al., 2010; M Khimani et al., 2015; Patidar et al., 2017). Likewise, the addition of 2-chloroanisole slightly alters the solution viscosity at room temperature. While in the case of 5 %w/v P104, the concentration of 2-bromoanisole, 2-

chloroanisole and 2-fluoroanisole increased above 0.04 mM, which notably raised the ηrel of the solution. However, no change in ηrel was detected before the concentration of 0.04 mM of 2-bromoanisole, 2-chloroanisole and 2-fluoroanisole.

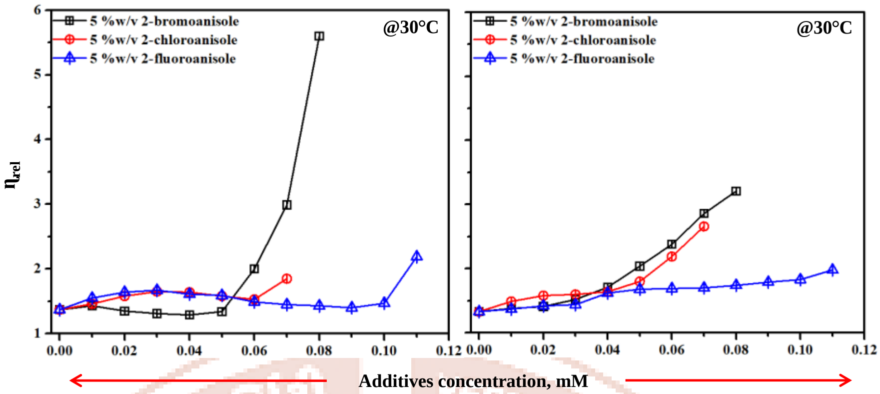


Figure 2: Relative viscosity of 5 %w/v solution of Pluronics® P84 and P104 in the presence of various additives at 30°C.

Figure 3 demonstrates that the ηrel of 5 %w/v P84 and P104 solutions was plotted against various temperatures with the addition of different additive concentrations. At fixed 5 %w/v concentrations, both block copolymers display distinct behaviour when various hydrophobic additives 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole are added.

For P84 and P104 with moderately hydrophilic properties, the addition of all hydrophobic additives concentrations and a gradual increase in temperature increases the ηrel, which suggests micellar growth because EO-PO blocks become more dehydrated with an increase in temperature. At lower temperatures (~ 30–40 °C), the relative viscosity approximates identical for all the additives, signifying a large number of well-dispersed spherical micelles with slight intermicellar interaction. With rising temperature, viscosity exhibits a gradual increase, resulting in a pronounced increase near the cloud point, indicative of the increased dehydration of PEO chains and the enhancement of hydrophobic interactions.

In the case of 5 %w/v P84, all additives facilitate a quicker and more significant increase in viscosity at higher concentrations, indicating additive-induced micellar expansion and probable transitions from spherical to rod-like or worm-like structures before macroscopic phase separation occurs. In other cases, the sudden increase in viscosity at high temperatures signifies the growth of elongated micelles, resulting in micellar transition. P104 demonstrates a very slight or delayed increase in viscosity for most additives, while certain additives exhibit strong temperature-additive interactions resulting in abrupt increases at the transition domain shown in **figure 3**. The temperature at which viscosity increases aligns significantly with the previously discovered cloud point depression, validating that additives enhancing CP decrease also facilitate structural transformation. Thus, more and more monomers are involved in micelle formation, which ultimately results in micellar growth. As the temperature continues to increase and different concentrations of hydrophobic additives are used, the copolymer solutions exhibit a variety of morphologies (Vyas, Pillai, Bahadur, & Bahadur, 2018).

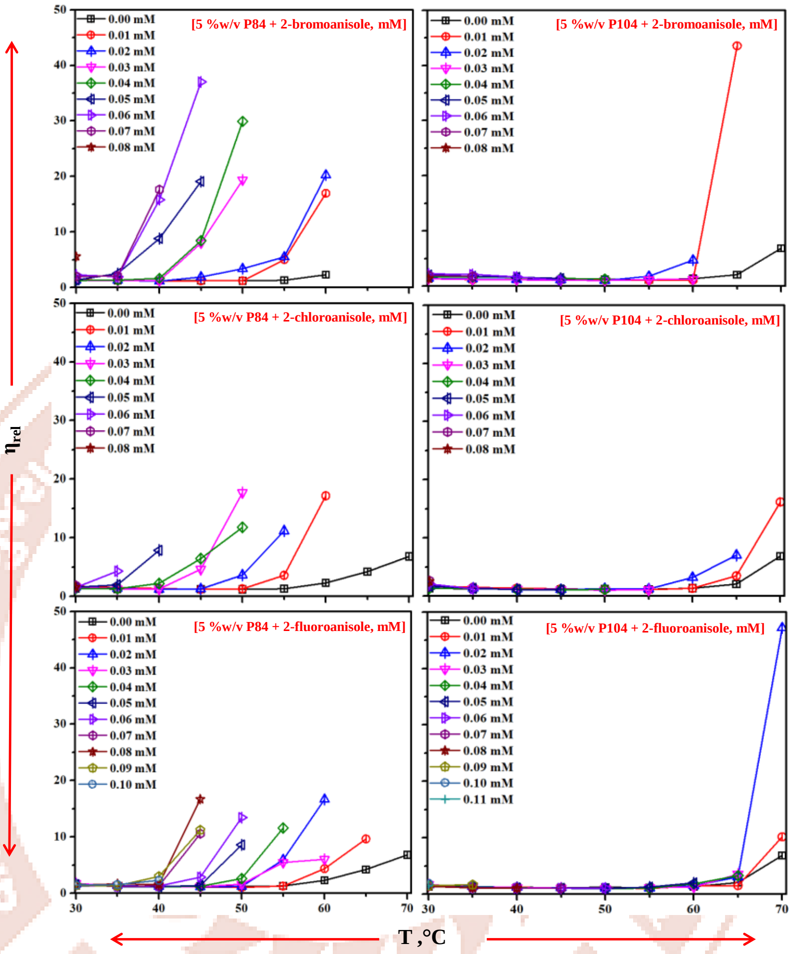


Figure 3: The relative viscosity of 5 %w/v solution of P84 and P104 in the presence of various hydrophobic additives as a function of temperature.

Spectral analysis

Figure 4 exhibits the Fourier transform infrared (FT-IR) spectra that demonstrate the structural interactions among 5 %w/v BCPs and hydrophobic additives, including 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole at 30 °C. The 5 %w/v P84 (without the hydrophobic additives) display distinct vibrational modes, including O-H stretching ~ 3468.26 cm^{-1} linked to hydrogen bonding from the hydrophilic PEO blocks, C-H stretching ~ 2872.76 - 2970.51 cm^{-1} from the alkyl chains in PPO and PEO segments, a band at ~ 1642.81 cm^{-1} corresponding to hydrophilic PEO segments, CH_2/CH_3 bending at ~ 1373.49-1455.85 cm^{-1} and C-O-C stretching ~ 1105.11cm^{-1} involving ether linkages in the Pluronic® backbone, consistent with the literature (Tushar Patel, Bhattacharya, Patel, & Parekh; Tripathi et al., 2025).

With the addition of 2-bromoanisole, the O–H band is observed at ~ 3469.08 cm^{-1}, the ether band at ~ 1106.11 cm^{-1}, and the bending peak moves to ~ 1639.90 cm^{-1}, suggesting the H–O–H bending vibration associated with PEO domains, confirming a weak interaction with a minor interaction towards the PPO block. 2-chloroanisole exhibits a noticeable O–H shift to ~ 3507.24 cm^{-1}, an ether incorporation at ~ 1106.72 cm^{-1}, and a bending mode at ~ 1641.16 cm^{-1}, suggesting considerable hydrogen bonding predominantly with the PEO block. In the case of 2-fluoroanisole, the O–H band alteration into ~ 3495.31 cm^{-1}, the ether band to ~ 1109.21 cm^{-1}, and the bending line significantly reduces to ~ 1616.51 cm^{-1}, indicating a more pronounced alteration of the PEO ether environment.

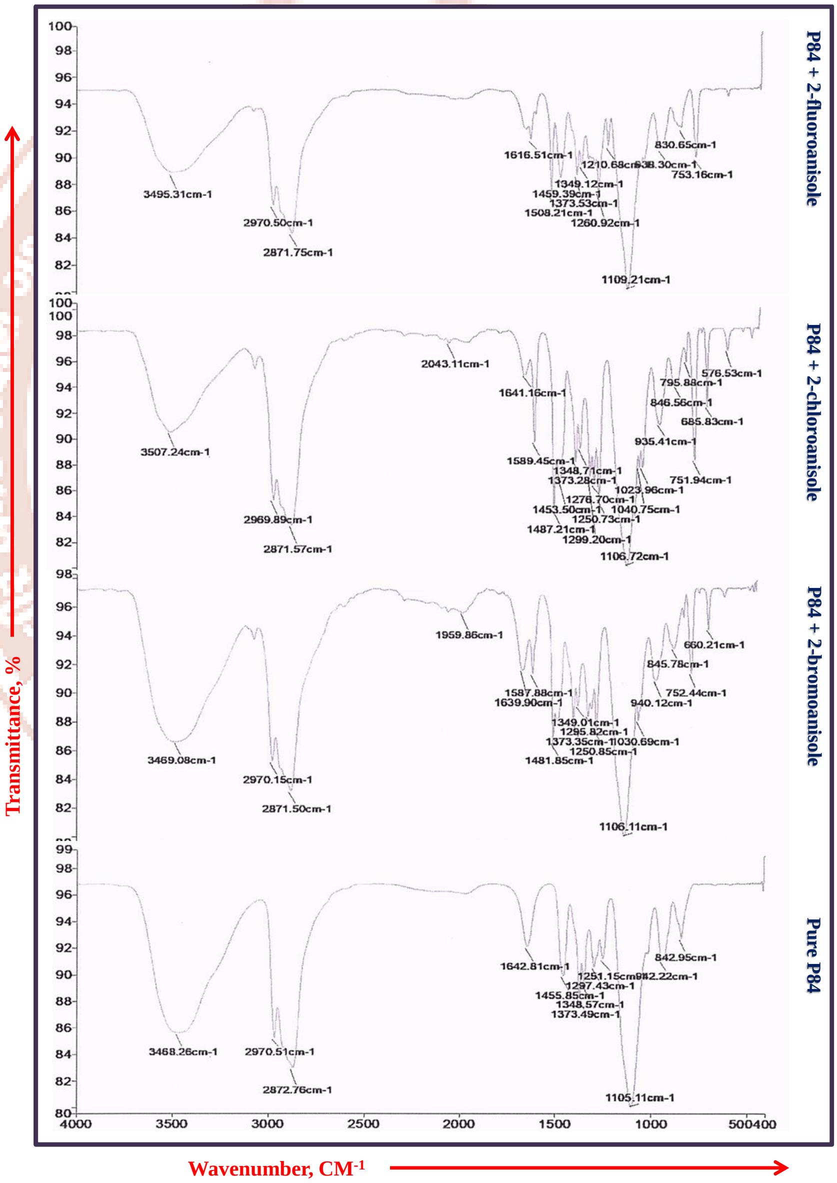


Figure 4: The FT-IR spectra of the optimized structure illustrate the favourable interactions among the examined system.

Hydrodynamic size profile

The size and several hydrodynamic and thermodynamic characteristics of the particles (micelles) are analyzed by dynamic light scattering (DLS), often referred to as photon correlation spectroscopy (PCS), which assesses the Brownian motion exhibited by their hydrated dispersion states. DLS observations are often expressed as distributions of hydrodynamic diameter (Dh) in terms of number, intensity, and volume. This study elucidates the concept in terms of intensity. The intensity distribution demonstrates that heavier particles scatter light more effectively than smaller particles, indicating the existence of larger particles. The size of individual molecules (unimers) typically ranges from approximately 1 to 4 nm, while micelles measure around 10 nm.

This study evaluated the apparent hydrodynamic diameters (Dh) of 5 %w/v solutions of P84 and P104 in the absence and presence of varying amounts of hydrophobic additives at 30°C. The Dh values were also assessed in relation to temperature. The outcomes are illustrated in a figure 5. In the absence of hydrophobic additives, the value of Dh for 5% w/v P84 and P104 is around 12.0 nm and 14.6 nm, respectively, aligning with existing findings **(Chakrabarti et al., 2021; Dhruvi Patel et al., 2020; Patidar et al., 2017; Singla et al., 2022).**

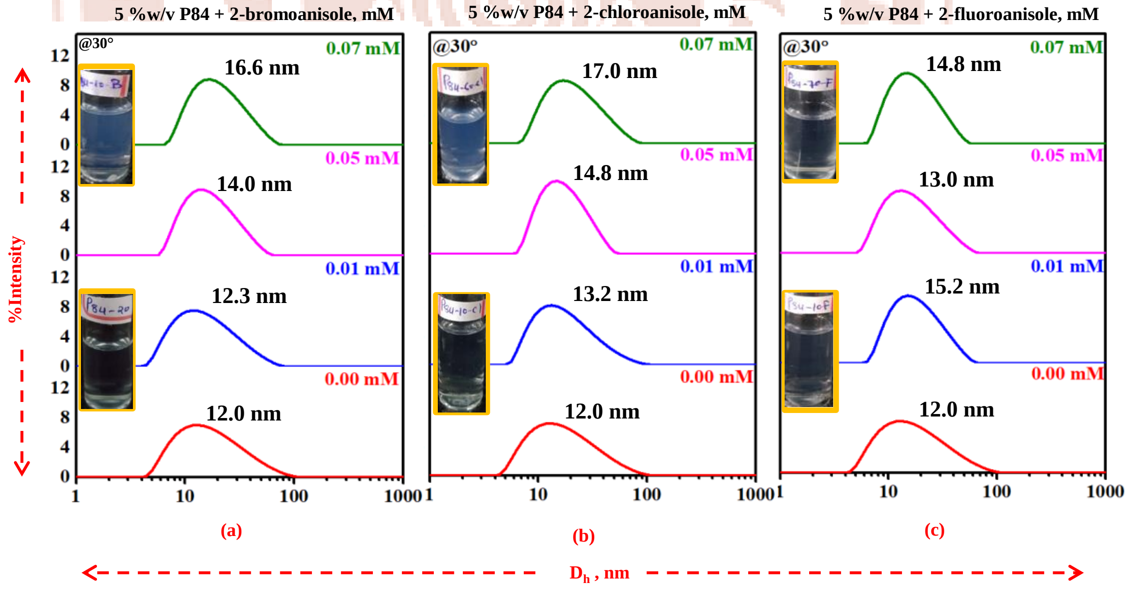


Figure 5(I): Distribution profile of hydrodynamic diameter (D$_h$) in a 5 %w/v P84 copolymeric solution containing 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole as a function of concentration.

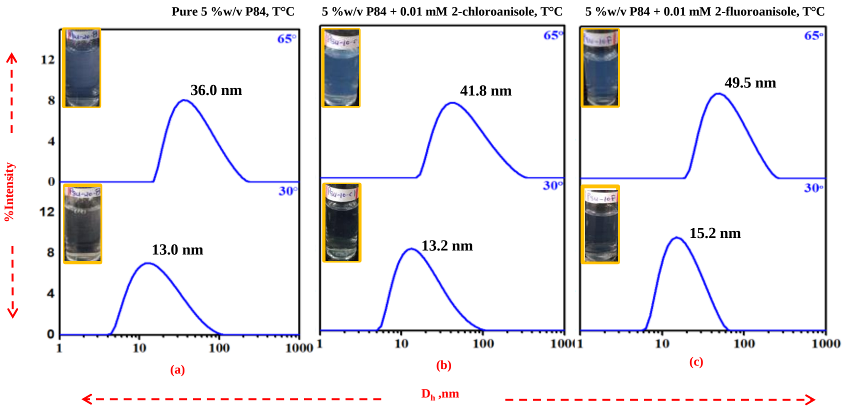


Figure 5(II): DLS profile of hydrodynamic diameter (D_h) in a 5 %w/v P84 in presence of 0.01 mM 2-chloroanisole, and 2-fluoroanisole as a function of temperature.

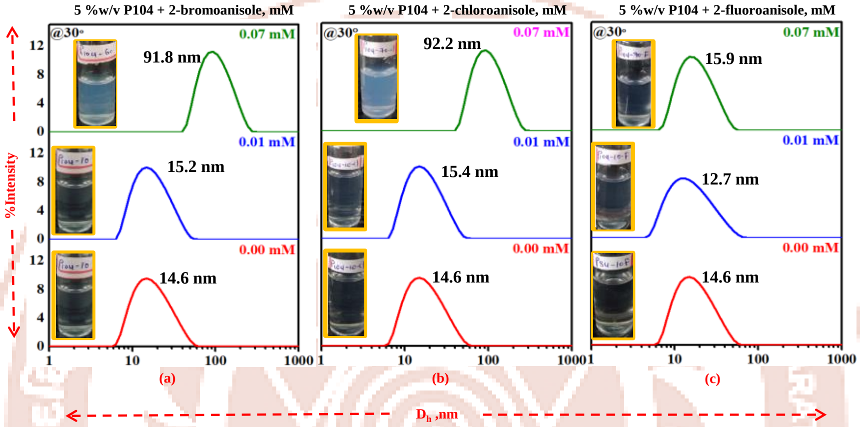


Figure 5(III): Size distribution curve of 5 %w/v P104 with the addition of 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole as a function of concentration.

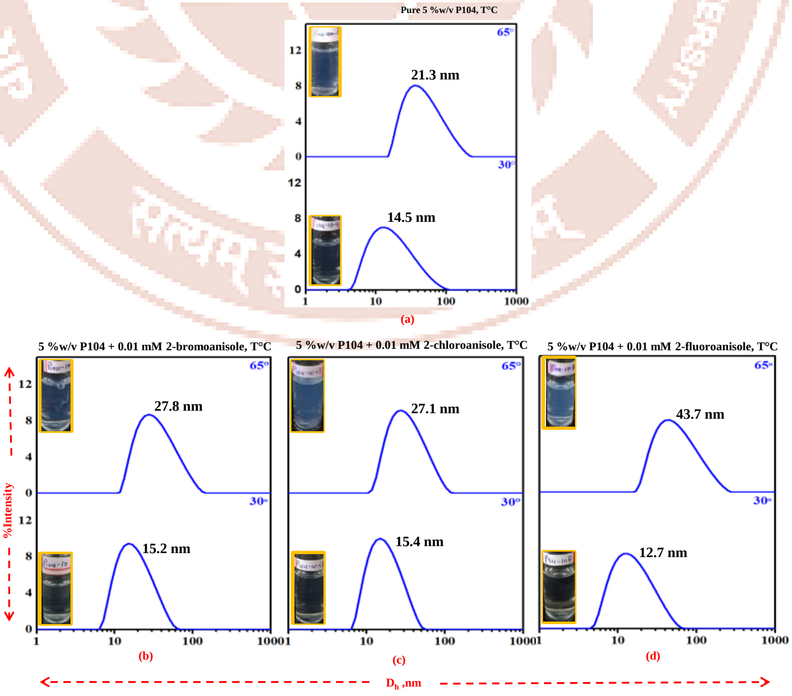


Figure 5(IV): DLS stack of hydrodynamic diameter (D_h) in a 5 %w/v P104 in existence of 0.01 mM 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole as a function of temperature.

Figure 5(I) illustrates that at 30℃, for 5 %w/v P84, the addition of various compounds, specifically 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole, results in an increase in the hydrodynamic diameter (Dh). The corresponding Dh measurements for these compounds are approximately 12.0 - 16.6 nm, 12.0 - 17.0 nm, and 12.0 - 14.8 nm, respectively, at different concentrations of additives respectively. Furthermore, the hydrodynamic diameter (Dh) of P104 varies from 14.6 to 91.8 nm, 14.6 to 92.2 nm, and 14.6 to 15.9 nm, respectively, as a function of various concentrations of additives, suggesting substantial micellar expansion, as depicted in the **figure 5(I) and 5(III).**

The Dh of micelles at 65℃ temperature for 5% w/v Pluronics® was examined both in the absence and presence of additives, as illustrated in the **figure 5(II) and 5(IV).** In a 5% w/v solution of P84 and P104 containing a 0.01 mM concentration of 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole, observations were made at 65 °C. At this temperature, the Dh shifted to a peak of greater intensity, indicating micellar expansion. This phenomenon suggests that the Dh values increase with temperature due to the dehydration of the EO/PO blocks, as well as the synergistic effects of the additives and temperature. Consequently, additional unimers aggregate to form micelles, resulting in elevated Dh values. These findings align with the ηrel results (Kadam et al., 2024; A. Patel et al., 2021; A. Patel et al., 2023; D. Patel et al., 2023; Tripathi et al., 2023).

Conclusion

This study demonstrates that the incorporation of hydrophobic additives 2-bromoanisole, 2-chloroanisole, and 2-fluoroanisole markedly affects the physicochemical characteristics and self-assembly of Pluronics® block copolymers P84 and P104 in aqueous solutions. An increase in additives concentration and temperature leads to a progressive decline in cloud point (CP), indicating reduced phase stability attributed to enhanced Pluronic®–additives interactions and dehydration of the polymer chains. This behaviour is characterized by a significant rise in viscosity, indicating the growth of stronger, interconnected micellar structures. FT-IR spectroscopy provides clear evidence of pronounced intermolecular interaction, substantial hydrogen bonding, and segmental interaction between Pluronic® blocks and additives. The results from the dynamic light scattering experiment confirm micellar formation, as seen by the increase in hydrodynamic diameter (Dh) with elevated amounts of additives and temperature. These findings offer critical insights for Pluronic®-based formulations in drug delivery systems, solubilization of hydrophobic compounds, and controlled release systems, among others.

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