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Micelles from PEO–PPO–PEO block copolymers as nanocontainers for solubilization of a poorly water soluble drug hydrochlorothiazide

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ABSTRACT

The effect of molecular characteristics of EO–PO triblock copolymers viz. Pluronic® P103 ($EO_{17}PO_{60}PEO_{17}$), P123 ($EO_{19}PO_{69}EO_{19}$), and F127 ($EO_{100}PO_{65}EO_{100}$) on micellar behavior and solubilization of a diuretic drug, hydrochlorothiazide (HCT) was investigated. The critical micellization temperatures (CMTs) and size for empty as well as drug loaded micelles are reported. The CMTs and micelle size depended on the hydrophobicity and molecular weight of the copolymer; a decrease in CMT and increase in size was observed on solubilization. The solubilization of the drug hydrochlorothiazide (HCT) in the block copolymer nanoaggregates at different temperatures (28, 37, 45 °C), pH (3.7, 5.0, 6.7) and in the presence of added salt (NaCl) was monitored by using UV–vis spectroscopy and solubility data were used to calculate the solubilization characteristics; micelle–water partition coefficient (P) and thermodynamic parameters of solubilization viz. Gibbs free energy (ΔG_s°), enthalpy (ΔH_s°) and entropy (ΔS_s°). The solubility of the drug in copolymer increases with the trend: P103 > P123 > F127. The solubilized drug decreased the cloud point (CP) of copolymers. Results show that the drug solubility increases in the presence of salt but significantly enhances with the increase in the temperature and at a lower pH in which drug remains in the non-ionized form.

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1. Introduction

Block copolymers are composed of at least two generally incompatible polymer segments that differ in physicochemical properties e.g., charge and/or polarity and self-assemble in selective solvent (good for one block but poor solvent for the other) to form micelles like conventional surfactants [1–10]. Amphiphilic block copolymers (copolymeric surfactants) have hydrophobic and hydrophilic moieties and they do aggregate to form nano size micelles in aqueous media.

Micellization of polymeric surfactants has been examined in detail and the most extensively studied copolymers are ethylene oxide–propylene oxide based symmetrical triblock copolymers. Poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO) amphiphilic copolymers are often known by their trade name Pluronic® (BASF) and have numerous industrial applications as detergents, dispersants, stabilizers, solubilizers, emulsifiers etc. In aqueous solutions, Pluronics® behave as nonionic surfactants and form micelles of core–shell architecture above a certain temperature called the critical micellization temperature, CMT, which depends on the concentration/molecular characteristics of the copolymer. These micelles have hydrophobic core formed by PPO chains and hydrophilic shell formed by PEO chains; the micellization is an entropy-driven process as a consequence of hydrophobic interactions and alteration in water structure in the vicinity of the polymer chains. The self-assembled structures can be spheroidal/ellipsoidal/cylindrical/worm-like or vesicles depending upon the EO/PO ratio, total molecular weight and concentration of block copolymer. These structures are strongly affected by temperature and the presence of additives like electrolytes/nonelectrolytes, hydrotropes or conventional surfactants [2]. The micelle formation and phase behavior of Pluronic® has been investigated by several workers and is extensively reviewed [1,2,9,10].

Pluronics® are being examined as drug delivery vehicles due to their surfactant abilities, low toxicity and minimal immune response [11–15]. The core formed by PO chains is water incompatible and is separated from the aqueous compartment by hydrated chains of EO corona and serves as a reservoir for the hydrophobic compounds. Another important feature of the polymeric micelles which makes them efficient drug delivery carrier is the size of the micelles. The average hydrodynamic diameter of spherical Pluronic® micelle is ca. 2 to about 30 nm and aggregation number ca. 10 to hundred [11–19] which increase on micellar fractions

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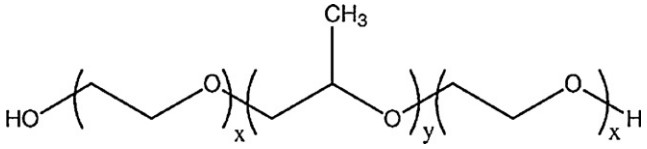
Table 1
Physicochemical characteristics of Pluronic® block copolymers.

Pluronic®	MW[a]	Structure	HLB[b]	CP (1%), °C[b]	CMC[c] ($g\,l^{-1}$) at 30 °C
P103	4950	$EO_{17}PO_{60}EO_{17}$	9	86	3.0×10^{-2}
P123	5750	$EO_{19}PO_{69}EO_{19}$	8	90	2.5×10^{-2}
F127	12,600	$EO_{100}PO_{65}EO_{100}$	22	>100	3.5×10^{-2}

[a] The average molecular weights provided by the manufacturer (BASF, Wyandotte, MI).
[b] HLB values of the copolymers; the cloud points were determined by the manufacturer.
[c] CMC values were determined using pyrene probe Ref. [27].

usually for systems close to cloud point. This nanoscale size variation strongly affects the blood circulation time and bioavailability of the drugs within the body. Following the systemic administration, particles ranging from 70 to 200 nm have the most prolonged circulation time; particles larger than 200 nm are frequently sequestered by the spleen due to mechanical filtration followed by eventual removal by the cells of the phagocyte system. On the other hand, particles smaller than 5–10 nm are rapidly removed through extravasations and renal clearance. As compared to the conventional surfactants, block copolymers have much less CMCs making their micelles thermodynamically more stable. In case of water soluble EO–PO block copolymers with adequate hydrophobicity, the CMC is remarkably reduced at elevated temperatures. Increased thermodynamic stability of micelles makes them less prone to disassembly at low concentration than low molecular weight surfactants [16–19]. For the above mentioned reasons, Pluronic® or modified Pluronic® micelles are considered ideal drug delivery vehicles as they have preferred blood circulating properties, adequate stability in the blood and high drug loading capacity for poorly water soluble drugs [12–14,18]. Other potential advantages of micellar drug delivery include passive tumor targeting, alteration of drug residence time in the body and protection of drugs from metabolism and degradation in the bloodstream [11,16–18]. While amphoteric and ionic surfactants have been used for formulation purposes, the non-ionics generally offer the most advantages. Non-ionic surfactants are typically less toxic, less hemolytic, less irritating to the skin and tend to maintain near physiological pH values when in solution [12,13]. Several drug formulations based on polymeric micelles are now in phase I–III clinical trials, and soon a number of them will be expected to be released in the market [14–18].

Incorporation of drug into core of polymeric micelles may be carried out by chemical conjugation or physical entrapment [16,18]. Depending on steric properties and interrelations of drug and polymer, a drug can be solubilized with polymer of suitable molecular geometry and composition. Hydrochlorothiazide (HCT) (6-chloro-3,4-dihydro-2H-1,2,4-benzo-tiodiazine-7-sulfonamide1,1dioxide), is a diuretic and anti-hypertensive drug used for the treatment of diabetes [20–22]. It has a half-life of about 5.6–4.8 h and is eliminated through kidney. Although HCT has high intestinal permeability, the bioavailability is limited by its low water solubility. The reactivity and biological activity of HCT in relation to other compounds of the thiazide family have been extensively studied by Latosińska [21]. There exists very few reports on pharmaceutical application of HCT in the presence of Pluronics® [23,24]. Desai et al. [23] studied Povidone and Pluronic® mediated degradation of HCT and found improved stability of the drug, whereas the potential utility of copolymers comprising Pluronic® covalently conjugated with poly(acrylic acid) (PAA) as excipients for sustained-release tablets of HCT and other drugs was explored by Barreiro-Iglesias et al. [24]. However, there has not been any systematic study on solubilization of HCT in Pluronic® micelles with varying structure and molecular characteristics, at different temperatures, pH and added salt concentrations.



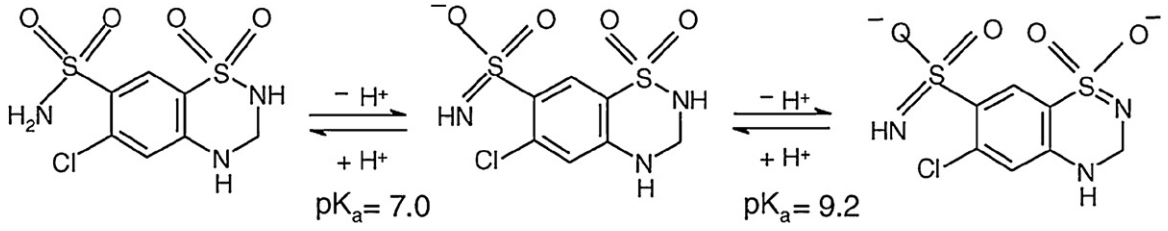
Scheme 1. Structural formula of the Pluronic® block copolymers.

The objective of the present study is to investigate micellar structure of Pluronic® (P103, P123 and F127) block copolymer nanoaggregates under different conditions and their application for solubilization of a model drug, hydrochlorothiazide (HCT). The effect of temperature, pH and salt (NaCl) concentration on the solubility of the drug in the micelles of three Pluronic® is examined. Dynamic light scattering was used to characterize the dimension of micellar aggregates which changed dramatically due to interaction with hydrophobic drug. The drug solubility and the micelle–water partition coefficient (P) were measured using ultraviolet spectroscopy. Thermodynamic parameters of solubilization viz. changes in Gibbs free energy (ΔG_s°), enthalpy (ΔH_s°) and entropy (ΔS_s°) are also discussed.

2. Materials and methods

2.1. Materials

Pluronics® P103, P123 and F127 (Scheme 1) were received as gifts from BASF Corp. Parsippany, NJ, USA and used without further purification. Their molecular characteristics are described in Table 1. Hydrochlorothiazide (6-chloro-3,4-dihydro-2H-1,2,4-benzo-tiodiazine-7-sulfonamide1,1dioxide) (Scheme 2) was from Sigma–Aldrich, Co. (St. Louis, MO) and used as received.



Scheme 2. Structural formula of hydrochlorothiazide (HCT) at different pK_a [25]. MW = 297.74 g/mol, the aqueous solubility at 37 °C = 3.3×10^{-3} mol l^{-1} [3.6×10^{-3} mol l^{-1} [26]].

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