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Pluronic–cationic surfactant mixed micelles: Solubilization and release of the drug hydrochlorothiazide

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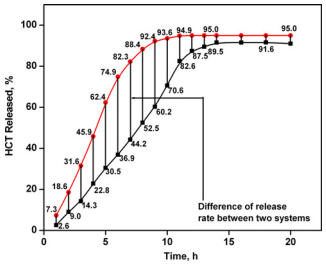
HIGHLIGHTS

- Aqueous mixed systems of Pluronics® with cationic surfactants were studied.
- Pluronic®–surfactant systems were found to be more efficient for HCT loading.
- Drug release rates can be tune by the addition of varying amounts of cationic surfactant.
- Different kinetic models are used to explain the *in vitro* drug release profile.

GRAPHICAL ABSTRACT



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ABSTRACT

Moderately hydrophobic poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO) block copolymers [Pluronics® with 20 > % PEO < 80] form micelles in water with a hydrodynamic diameter of about 20 nm. The aqueous mixed systems of Pluronics® P103, P104 and P105 [Pluronics® with molecular weight of PPO = 3250, and % of PEO 30, 40 and 50 respectively] with cationic surfactants of the type alkyltrimethylammonium bromide (C_nTAB, n = 10, 12, 14 and 16) were studied in water and salt solution. It is apparent that the presence of trace amounts of cationic surfactant induces a charge on nonionic Pluronics® micelles and leads to a decrease in their size. The efficiency of surfactants to decrease micellar size depends on the alkyl chain length of the surfactants. A representative system, P103-C_{14}TAB was chosen to investigate and the feasibility of using Pluronic®–surfactants systems compared with pure Pluronic® micelle as an *in vitro* release vehicle for hydrochlorothiazide (HCT); a hydrophobic diuretic drug with poor aqueous solubility. Pluronic®–surfactant systems were found to be more efficient for HCT loading; their loading capacity can be tuned by changing the surfactant concentration and pH. Drug release profiles were established for P103 and P103-C_{14}TAB mixed systems. The rate of controlled release of HCT from micelles was explained by employing different kinetic models to examine the *in vitro* release profile.

1. Introduction

Surfactants are often added to polymer solutions to modify rheological properties and to enhance the stability of dispersions [1]. Aqueous mixtures of water soluble polymer and surfactant are used in laundry detergents, cosmetics, paint, coating, petroleum and pharmaceutical industries [2,3] and therefore, the interaction between nonionic polymers and ionic surfactants in aqueous solution has been extensively studied [4–11]. Often mixed systems of surfactants and polymers in aqueous solution form a complex by the binding of the surfactant molecules/micelles onto the polymer chain. The nature and strength of this interaction depends on the charge and hydrophobicity of both the polymer and surfactant [12].

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Polymers can also behave as surfactants (amphiphilic character). One kind of interesting amphiphilic polymers are triblock-copolymers of polypropylene oxide (PPO) and polyethylene oxide (PEO) known as Pluronics®. They are commercially available in a range of molecular weights and PEO/PPO ratios and thus with variably hydrophilicity/hydrophobicity. The amphiphilic nature of these block copolymers has led to interesting adsorption features at the air/water interface and in self-aggregation in aqueous solutions [13]. In water, Pluronics® can form a wide variety of aggregates such as micelles, vesicles and liquid crystalline phases above a certain concentration or temperature. Due to this characteristic, Pluronics® find widespread applications in emulsification, solubilization, controlled additive release and product formulation ranging from agriculture to pharmaceuticals fields [14,15]. They have also been used as templating agents in the preparation of mesoporous metal oxide and thin films [16,17], as well as for separation of DNA and proteins, etc. [18,19].

Aqueous mixtures of Pluronic® and surfactants can be employed to design and create a new functional aggregate, which can be used in many industries [20–22]. Interaction of Pluronic® and conventional surfactants is of general interest and solution properties of such mixtures depend on the concentration and structure of both components of the mixture. Thus, properties of such solutions can be tuned according to their applications [23–26]. Interaction of anionic surfactants with Pluronics® have been the most studied though there are also few reports on interaction with cationic surfactants [9,27–33]. Bahadur and co-workers [32–34] examined Pluronic®–ionic surfactant mixed systems and observed stronger interaction of copolymer with anionic surfactant than with cationics. Sing et al. [28] showed Pluronics®–cetyltrimethylammonium bromide (CTAB) supramolecular assemblies, in which the hydrophobic chains of CTAB occupy the hydrophobic core of the Pluronics® micelle while the positively charged head groups reside at the micellar core–shell interface. The influence of the ionic surfactants on the self aggregation of Pluronic® F127 has been studied by Hecht et al. [35–37] using differential scanning calorimetry, static light and small-angle neutron scattering, and temperature jump measurements. The properties of aggregates formed in systems consisting of Pluronic® and ionic surfactant are dominated by the surfactant concentration. Charged complexes and small mixed micelles are formed in the presence of very low and moderate concentrations of surfactant, respectively. Therefore, to apply a Pluronics®–surfactant system efficiently it is important to choose a particular concentration range [38].

The core–shell (core of PPO and shell of PEO) micelles of Pluronic® can be used to solubilize poorly water soluble drugs and can function as effective drug carriers [39,40]. The hydrophobic core of a micelle serves as a microenvironment that can enhance the loading efficiency of hydrophobic drugs and the outer hydrophilic shell serves as a stabilizing interface between the hydrophobic core and the aqueous medium [41,42]. This will also protect against undesirable phenomenon such as inter micellar aggregation, inactivation of drugs under a biological environment and possible side effects of drugs on healthy cells and tissues. From previous studies [43,44] it has been observed that the solubilization capacity of Pluronics® increases with their hydrophobicity. It is now of interest to examine how the presence of ionic surfactants affect the solubilization capacity of Pluronic® micelles.

In order to quantify the solubilization capacity of Pluronic® and Pluronic®–surfactant mixtures we measured the solubility of hydrochlorothiazide (HCT) in such systems. HCT belongs to a class of medicines known as thiazide diuretics. It is a type of diuretic that works by increasing the amount of salt and water that the kidneys remove from the blood, which causes a decrease in blood volume. It acts by reducing the re-absorption of salts from the renal tubules, thereby increasing the excretion of sodium and chloride ions, and consequently of water. Hydrochlorothiazide treats oedema (fluid retention) associated with patients with congestive heart failure, cirrhosis of the liver or kidney disorders. It is also employed for the treatment of high blood pressure. HCT is used alone or with angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists. [45]

In this paper we report results on the aqueous solution behaviour of Pluronics® P103, P104 and P105 in the presence of cationic surfactants (C_nTAB, n = 10, 12, 14 and 16) with and without salt as studied by cloud point (CP) and dynamic light scattering (DLS) measurements. P103 micelles have been successfully employed as novel polymer therapeutics for drug delivery; we attempted to solubilize a sparingly water soluble drug, HCT into aqueous solution of Pluronic® as well as Pluronic®–surfactant mixtures. The release study was done in phosphate buffer saline (PBS) solution at 37 °C as a function of surfactant concentration. Our aim was to examine the interaction between cationic surfactant and Pluronics® of varying hydrophobicity and to study the potential of this system for drug solubilization and release.

2. Experimental

2.1. Materials

The Pluronics® P103, P104 and P105 were received from BASF Corp. Parsippany, NJ, USA as a gift sample. C_nTAB (n = 10, 12, 14 and 16) of >99% purity were from Sigma-Aldrich. Sodium chloride (NaCl) of analytical reagent grade was purchased locally. The drug hydrochlorothiazide was a gift sample from a local pharmaceutical company and was used as received.

2.2. Methods

Cloud points were determined at fixed P103 concentration (5%, w/v) in the absence and presence of varying amounts of ionic surfactants (with and without NaCl) by gently heating the solution in thin 20 ml glass tubes immersed in a beaker containing water; well stirred with a magnetic bar while being heated. The heating rate was controlled to 1 °C/min. The first appearance of turbidity was taken as the cloud point.

The dynamic light scattering (DLS) experiments were carried out at a fixed scattering angle of 90° on solutions using a Zeta sizer Nano-ZS 4800 (Malvern Instruments, UK) equipped with a He–Ne laser operating at a wavelength of 633 nm. The average diffusion coefficients and hence the hydrodynamic size was obtained by the method of cumulants. Each measurement was repeated at least four times.

A Shimadzu (model UV-2450) UV–vis double beam spectrophotometer was used to determine the solubility of the HCT. The amount solubilized was determined by measuring absorbance at 271 nm. Calibration with dilute solutions of HCT ranging from 0 to 0.2 mM dissolved in methanol gave a satisfactory Beer-Lambert plot with R^2 = 0.9991. For drug solubility measurements, excess amounts of the HCT were added to 5 mL each of either Pluronics® or Pluronics®–surfactant solutions which were then shaken in a thermostatted water bath at constant temperature (37 ± 0.5 °C) for at least 48 h. Then the solutions were filtered (Millipore, 0.45 μm) to remove unsolubilized drug; the filtered solutions were diluted properly with methanol. All data reported are the average taken of at least three independent samples.

A Himedia dialysis membrane bag (cut-off molecular weight: 12000–14000 kD) previously soaked in water clamped at the one end, was used for drug release. It was placed in a 500 ml beaker and 5 ml of P103 solution containing HCT was subjected to