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Interactions between a triblock copolymer and hydroxyethyl cellulose in aqueous solution and their use in the solubilization of Amiodarone

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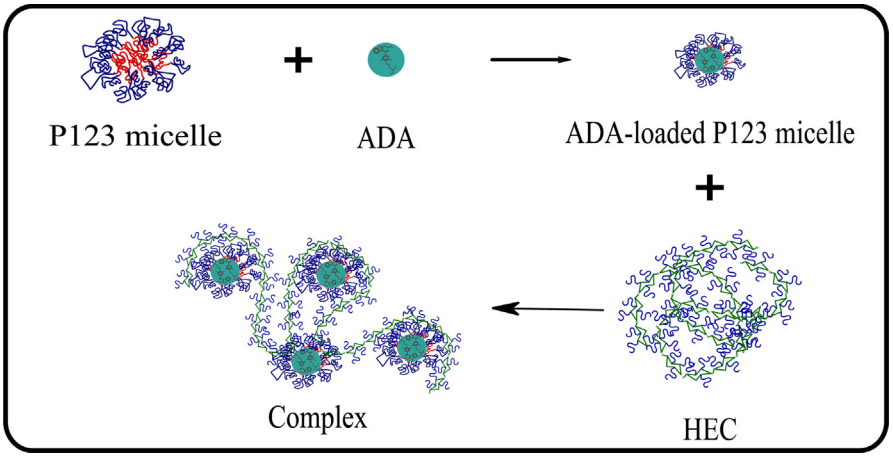
HIGHLIGHTS

- Adding HEC to P123 solution promotes the appearance of CAC_1, C_s and CAC_e.
- P123-drug interaction is strong and reduces the micellar size.
- DSC shows that drug-loaded P123 micelles interact more with HEC than the empty ones.
- HEC associates ADA-loaded P123 micelles, providing the drug with a double encapsulation shell.

GRAPHICAL ABSTRACT



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ABSTRACT

A physicochemical characterization of the mixtures of triblock copolymer PEO_{20}-PPO_{70}-PEO_{20}, (P123) and hydroxyethyl cellulose (HEC) in aqueous solutions, with and without the hydrophobic drug amiodarone (ADA), was performed by pendant drop tensiometry, differential scanning calorimetry (DSC) and dynamic light scattering (DLS). The results allowed us to propose a detailed diagram for the formation of the different aggregates in water. The equilibrium surface tension values showed that adding HEC to P123 solutions promotes the aggregation of the P123 monomers on the HEC polymer until saturation. By adding ADA into the P123 micelles, the same equilibrium surface tension values were obtained as the ones found in the pure solution of P123. This suggests that the drug is mostly encapsulated. The DSC experiments showed that the critical micelle temperature and the enthalpy of aggregation of P123 were not modified by the presence of HEC. But the incorporation of ADA to the micelles showed a reduction of 40% in the enthalpy of aggregation, indicating a strong interaction between P123 and ADA. In contrast to the empty micelles, when HEC is added to the loaded micelles, the enthalpy of aggregation increases and the interaction of HEC-P123 becomes evident. The DLS results support that the hydrodynamic diameter of the ADA-loaded micelles is 17% smaller than the diameter of the empty P123 micelles. In the presence of HEC, the empty or loaded micelles form a larger complex. This suggests that HEC surrounds the micelles and provides the drug with a second protecting shell. This system could be a good candidate for the hydrophobic drug delivery.

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1. Introduction

Mixtures of polymers and surfactants play an important role in several industrial applications, for instance in personal care and pharmaceutical products, detergents and foams [1–3]. Polymer-surfactant interactions have fundamental importance for understanding the behavior of their mixtures, in which the surfactant bounds to polymer up to the saturation point forming different nanostructures that can be change by their composition [4–7]. These structures change the original behavior of individual constituents, such as the rheological properties, appearance, and improve the stability of dispersions [8–10]. The possible formation of different nanostructures makes them prospective vehicles for the drug and gene delivery [11–15]. In this respect, a detailed knowledge on their formation, structure and properties is desirable. We have been working with different systems designed to nanoencapsulate hydrophobic drugs that include cyclodextrins and polymer- surfactant complexes [16–18]. We continue testing this kind of complexes in the same research line.

Hydroxyethyl cellulose (HEC) is a non-ionic amphiphilic cellulose derivative polymer, which shows a lower critical solution temperature [9]. HEC is characterized by a mixture of hydrophobic and hydrophilic structural units distributed along the polymer backbone. This arrangement leads to a complex structure with an irregular distribution of hydrophobic microdomains, and interactions between polymer chains [19]. This polymer has been widely studied in combination with ionic surfactants such as sodium dodecyl sulfate [8,20,21], sodium dodecanoate [22,23] and cetyltrimethylammonium bromide [24], as well as non-ionic surfactants such as polyehthoxylates [25,26], tritons [27] and poloxamers [10,28]. In these mixtures, it has been suggested that the alkyl chains of the surfactant molecules interact with the hydrophobic domains of the polymer, increasing the intermolecular association through a “bridging-type” mechanism [25], with weak non-ionic polymer-surfactant interactions [29], forming mixed clusters that may include substituents from more than one polymer chain [9,19].

The triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), PEO-PPO-PEO, are examples of nonionic surfactants that form polymeric spherical micelles in water solution. They are also called pluronics or poloxamers. The polymeric micelles formed have a PPO hydrophobic core protected from the surrounding water by a water swollen PEO layer [30–34]. Their aggregation processes, at a specific concentration, start at a critical micellar temperature (CMT) and it is mainly entropy driven [35–38]. The ΔH for this process can be measured by differential scanning calorimetry (DSC). In this kind of experiments, when the temperature is raised, the hydrophobicity of the PPO and PEO groups increases, which is most likely due to the change of the segments conformation [34,38]. The main feature of these kinds of systems includes their capacity to solubilize hydrophobic compounds and their release in a controlled form. These characteristics have made poloxamer micelles very promising vehicles for drug delivery [13,39–41]. However, when the polymeric micelles are exposed to physiological media, they tend to disaggregate. Taking this phenomenon into consideration, the triblock polymers have been mixed with other polymers to delay this effect [10,42].

A technique that has been used in the study of the surfactant-polymer mixtures is the surface tension, which is a useful tool that allows to study the air/solution interface and with which the patterns of behavior of the mixture have been established [43,44]. In this work, tensiometry, DSC and dynamic light scattering (DLS) were used to study the effect of adding HEC to the triblock copolymer PEO_{20}-PPO_{70}-PEO_{20} (P123) in aqueous solutions. We selected these compounds because they are biodegradable, biocompatible and they have a low toxicity. The results indicate that HEC and P123 form aggregates that are concentration-dependent. These mixtures were tested to nanoencapsulate amiodarone (ADA), a hydrophobic [45] and antiarrhythmic drug found to be active against a neglected tropical disease [46].

2. Materials and methods

2.1. Materials

The triblock copolymer of average composition PEO_{20}-PPO_{70}-PEO_{20} (P123) was purchased from Aldrich and used without further purification. The molar mass reported by the supplier is 5750 g mol^{-1}. The hydroxyethyl cellulose (HEC) (Natrosol 250 GR) was supplied by Hercules, Aqualon Division and its molar mass was determined in this work by using the intrinsic viscosity method, resulting in a value of 335000 g mol^{-1}. The amiodarone hydrochloride (pharmaceutical grade) was obtained from Parafarm and was used without further purification. The molar mass reported by the supplier is 681.77 g mol^{-1}. The aqueous solutions of these polymers were prepared using analytical grade water from a Millipore filtration system (Simplicity) and they were stirred at room temperature for 24 h before each experiment was carried out.

2.2. Amiodarone solubility studies and determination of entrapment efficiency (EE%)

Aqueous solutions of P123 (1, 2.5, 3, 5 and 10 wt.%), and one of HEC (1 wt.%) were used to evaluate the drug solubility. After a weighted amount of amiodarone (about 10 mg) was placed into different vials, aliquots (5 mL) of the aforementioned solutions were added. The systems were kept under stirring at room temperature for 48 h, in triplicate. The saturated solutions samples were filtered with a 0.20 μm pore size PVDF membrane and placed into a quartz cuvette which was thermostatized for 15 min before data acquisition. Control experiments were carried out by only using water. The concentration of the dissolved drug was determined with a UV–vis spectroscopy at 240 nm (UV spectrophotometer, Cary-Bio50 Varian/Agilent, Australia), after an adequate dilution.

The percentage entrapment efficiency (EE%) was determined according to Ref. [47] for the following systems: (P123x + W) with x = 1 and x = 3 wt.%; and (P123x + W) + HECy with x = 1, y = 0.5 wt.%; and x = 3, y = 0.62 wt.%. Briefly, solutions of P123 with ADA were prepared as mentioned above, followed by the addition of solid HEC. After 24 h stirring, complete dissolution was obtained for the mixtures, which were then centrifuged at 14 000g using Amicon Ultra 0.5 mL Centrifugal Filters with 10 K molecular weight cut off (Millipore Co.) to remove the non-encapsulated drug. ADA concentration was determined from the filtered solution as above. The EE% was calculated as follows:

$$EE\% = \frac{C_{total} - C_{free}}{C_{total}} \times 100$$

Abbreviations: DSC, differential scanning calorimetry; DLS, dynamic light scattering; CAC, critical aggregation concentration; CAC_1, initial interaction concentration; C_s, saturation concentration; CAC_e, extended critical aggregation concentration; ΔH_{agg}, enthalpy of aggregation; T_m, melting temperature; CMT, critical micelle temperature; d_h, hydrodynamic diameter; P123, PEO_{20}-PPO_{70}-PEO_{20}; HEC, hydroxyethyl cellulose; ADA, amiodarone; W, water.

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