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Surface Tension of Aqueous Amoxicillin + Peg Systems

Lays B. Vieira, Michael W. Casimiro, Ronaldo G. Santos*

Chemical Engineering Department, Centro Universitário FEI, São Bernardo do Campo, SP 09850-901, Brazil

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ABSTRACT

This work presents a study on the interfacial activity of amoxicillin in aqueous systems containing polyethylene glycol (PEG). The results showed that aqueous systems containing different amounts of PEG and amoxicillin reach promptly the chemical equilibrium, displaying a small variation in surface tension over the time. However, the PEG concentration increasing causes a surface tension reduction, which indicates increasing the surface-active component amount on the interface. It was not identified the occurrence of critical micelle concentration for the amoxicillin within the concentration range of this study. Data must be useful for design and operation of processes involving the amoxicillin extraction in two phase aqueous systems containing polyethylene glycol.

Many organic compounds administrated as drugs exhibit amphiphilic behavior in aqueous solution because of the presence of dissimilar functional chemical groups on the same structure. At properly high concentrations, these compounds can form aggregates, adsorb on interfaces and reduce the interfacial tension [1,2]. Particularly, amphiphilic properties of Penicillins have received extensive attention since the effective application of these compounds as antibiotics [3]. Penicillins are antibiotics, which the core chemical structure is composed of bicyclic β-lactam rings.

Amoxicillin is a β-lactam antibiotic that has been widely applied in the treatment of bacterial infections. The large amoxicillin consumption is a worldwide concern because of the discharge of these antibiotics into the environment, including watercourses [4]. The removal of antibiotic from the environment has been investigated in recent works [5]. The occurrence of interfacial phenomena must affect noticeably the performance of the current technology for production and purification of amoxicillin, as well as the effectiveness of removal methods.

The typical industrial production of β-lactam antibiotics is usually carried out by means of chemical processes involving the use of chlorinated solvents, which are toxic, difficult to handle and generate non-recyclable and environmentally harmful residue [6,7]. The up-to-date standards for the antibiotic extraction and purification have headed for the pharmaceutical companies to focus on cleaner technologies with concern to environmental issues. This headline points out to the organic solvent rejection from the process. The target molecule differential partition between two liquid phases has been proposed as a biomolecule purification process [8]. In this way, biomolecules can be recovered by means of their solubility in two immiscible aqueous phases, instead of extraction by organic solvents. Aqueous two-phase systems (ATPS) constitutes an environment-friendly alternative for recovery of biological materials [9].

Polyethylene glycols (PEGs) are widely known to form an aqueous two-phase system with neutral polymers and inorganic salts, such as potassium phosphate, sodium phosphate, potassium carbonate and sodium sulphate [10–12]. The adding of inorganic salts into a polymer aqueous system at critical concentrations leads commonly to the formation of two distinct aqueous phases. In addition, the phase separation occurs readily because of the higher phase density difference [13]. In large-scale purification techniques, PEG and sodium chloride (or sodium sulphate) may be used, however, sodium phosphate have been preferred because of high biomolecule partition coefficient in relation to other systems [14].

Fig. 1(a) displays the schematic illustration of the production of aqueous two-phase systems containing PEG and inorganic salt. The phase compositions leading to the phase separation must be determined from thermodynamic equilibrium data, which can be described by the phase diagram. Fig. 1(b) displays a typical phase diagram of aqueous two-phase systems containing salt and PEG [15].

The phase diagram outlines the salt and polymer concentration limit to guarantee the phase separation, given by the bimodal curve (B-C-T line), where C represents the critical point. The amount of biomolecule in each phase depends on compound partition coefficient between the polymer and salt phases. In Fig. 1(b), the T-B line is a tie-line that determines the equilibrium compositions of the heavy (bottom) and light (top) phases, which are represented respectively by B point and C point.

The application of immiscible aqueous two-phase systems (ATPS) to

* Corresponding author at: Chemical Engineering Department, Centro Universitário FEI, Avenida Humberto de Alencar Castelo Branco 3972, São Bernardo do Campo, SP 09850-901, Brazil.
E-mail address: rgsantos@fei.edu.br (R.G. Santos).

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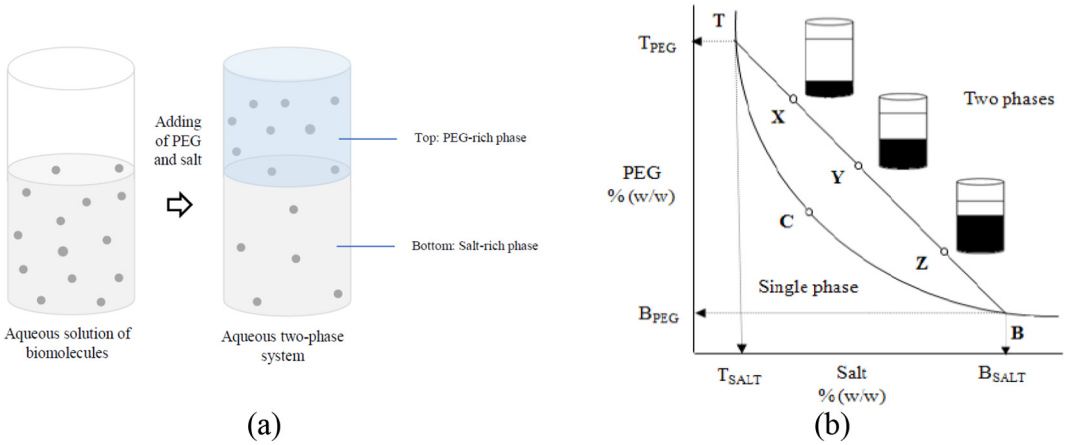

Fig. 1. Illustration of aqueous two-phase system. (a) Phase separation driven by PEG and salt addition. (b) Phase diagram displaying tie-line and bimodal curve. Fig. 1(b) was obtained from [15].

recovery bioproducts is feasible. However, biocompounds can self-aggregate and display interfacial adsorption phenomena originated from their amphiphilic character. Then, it is critical to determine the interfacial properties of these compounds to evaluate their aggregation state and surface accumulation. In aqueous systems, the critical micelle concentration can be understood in terms of aggregate formation of surface-active substances oriented in such way that allows the non-polar groups to avoid the contact with the aqueous medium [16]. The amphiphilic concentration in which the micelle formation beginning is called the critical micelle concentration (C.M.C.). The micelle formation occurs after the interface saturation [17].

In this work, the surface tension of systems containing amoxicillin and PEG was evaluated. The study investigated Polyethylene Glycol (PEG) with different molar weight (400, 600, 1000 and 4000 $g{\cdot}mol^{-1}$) purchased from Merck, and Amoxicillin (potency ≥ 900 µg per mg), purchased from Sigma. All the experiments used demineralized water. Water was purified by means of a Quimis reverse osmosis, model Q842, resulting in electric conductivity lower than 0.5 µS.

Surface tensions were assessed through pendant drop method, using an optical tensiometer, Attension Theta model (Biolin Scientific, Sweden). A 1 ml Hamilton precision syringe coupled to a gauge 22 needle was used to generate the droplet. The equipment captures successive images of the droplet through a CCD camera. The evaluation system applies the axisymmetric drop shape analysis (ADSA) method along with the Laplace equation. Surface tension analysis was supported by OneAttension software. Tensiometry has been a useful method to describe the interfacial behavior of amphiphiles [18]. The data analysis was carried out by means of the Axisymmetric Drop Shape Analysis (ADSA). The method applies the Young-Laplace equation on successive droplet imaging acquired by a high-resolution CCD camera.

Results were reported as equilibrium surface tension, which was obtained from the time-dependent surface tension curve at a time long enough to reach a constant value. The equilibrium state was always achieved before 300 s. The tensiometry measurements were performed in three replicates at least. The ST measurement uncertainty was calculated as the average deviation of the equilibrium surface tension values obtained at each replicate. The experimental error was described by the mean value of the measurement, labeled $< X >$, and its standard deviation, labeled σ_x. The mean value $< X >$ was calculated by the Eq. (1) for a set of N measurements of the property X [19]. In Eqs. (1) and (2), X_i represents each individual measurement of X. In this study, X refers to equilibrium surface tension.

$$< X > = \frac{1}{N} \cdot \sum_{i=1}^{N} X_i \tag{1}$$

$$\sigma_x = \sqrt{\frac{1}{N-1} \cdot \sum_{i=1}^{N} (x_i - < x >)^2} \tag{2}$$

Stock solution concentrations were 10%, 20%, 30% and 40% of polyethylene glycol on a mass basis. The corresponding molal concentrations for PEG aqueous solutions were 0.28–1.67 $mol.L^{-1}$ for PEG 400, 0.19–1.11 $mol.L^{-1}$ for PEG 600, 0.11–0.67 $mol.L^{-1}$ for PEG 1000, and 0.03–0.17 $mol.L^{-1}$ for PEG 4000. The PEG concentration interval was select from the phase diagram built for PEG-Phosphate-amoxicillin systems obtained from literature [12] and from the author's current studies. Amoxicillin was added into the PEG stock solutions at concentrations of 0, 0.2, 0.4, 0.6, 0.8 and 0.9 $g.L^{-1}$. This concentration range was chosen to guarantee the whole amoxicillin solubility. The amoxicillin concentration was obtained from a specified tie-line of an aqueous two-phase diagram containing PEG and sodium phosphate, used in our experimental studies on biomolecules partition. Amoxicillin fresh solutions were prepared daily to avoid degradation. Fig. 2 shows the color changes resulting from amoxicillin degradation after three weeks aging.

Results of equilibrium surface tension of amoxicillin aqueous solutions are shown in Table 1. The amoxicillin adding increases the solvent surface tension. The surface tension variation of amoxicillin aqueous solutions is attributed to the solute solubility. When amoxicillin is solubilized in water, the interactions between solvent molecules is changed because the hydration phenomena. As a consequence of the solvent assembly around the solute, the chemical bonds can become higher and the surface tension slightly increases. The surface tension raising is a well-known phenomenon; however, it depends on the solute

Fig. 2. Aqueous solutions of amoxicillin + PEG: fresh (left) and after 3 weeks aged (right).