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Short Communication

Synergistic extraction of amoxicillin from aqueous solution by using binary mixtures of Aliquat 336, D2EHPA and TBP

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ABSTRACT

Amoxicillin extraction was conducted using the single organic extractant namely trialkylmethylammonium chloride (Aliquat 336), di-(2-ethylhexyl)-phosphoric acid (D2EHPA) and tributylphosphate (TBP) and followed by the synergistic extraction using the binary mixtures of the mentioned extractants. Maintaining an initial pH of amoxicillin aqueous solution at 10 yielded the highest extraction percentage for all extractants. Increasing extractant concentrations from 2 to 12 mM produced the positive effect on amoxicillin separation for all extractants except for TBP with the highest extraction percentage and distribution coefficient reported at 86.2 ± 1.10% and 6.25 ± 0.267, respectively when maintaining Aliquat 336 at 12 mM. Synergistic extraction was observed when the mixtures of D2EHPA and TBP as well as Aliquat 336 and TBP were employed with the maximum extraction percentage and distribution coefficient reported at 90.4 ± 0.39% and 9.44 ± 0.459, respectively when maintaining the molar ratio of Aliquat 336 to TBP at 10:2.

1. Introduction

Amoxicillin, a broad-spectrum β-lactam and penicillin-type antibiotic, is one of the most widely prescribed medications for treating bacterial infections in Thailand [1]. Contamination of amoxicillin in natural water resource as a result of wastewater discharge from pharmaceutical plants can trigger adverse effects towards human health and aquatic environment. Long term exposure of amoxicillin by bacteria in water resources can activate antibiotic resistant genes of bacteria that led to more treatment difficulty [2,3]. Moreover, the toxicity of amoxicillin towards bacteria and microalgae could result in biodiversity loss in natural aquatic ecosystem and may cause negative disturbance to the treatment efficiency of biological wastewater treatment plants [4–6]. Clearly, the removal of amoxicillin from pharmaceutical wastewater prior to the final disposal becomes necessary.

Solvent extraction, a separation method based on the difference in solubility of the solute between two immiscible solutions, has shown the potential for antibiotic separation from aqueous solution [7]. Recently, a commercial positive-charge basic extractant called Aliquat 336 was successfully employed to extract antibiotics in the β-lactam family [8,9]. For the case of amoxicillin, the previous work indicated that Aliquat 336 at 6 mM dissolved in 1-decanol was able to separate amoxicillin in the hollow fiber supported liquid membrane (HFSLM) system, resulting in the maximum removal efficiency at 85.2% when the initial pH of amoxicillin solution was maintained at 8.0 [10]. Strong electrostatic interaction between negative charges of amoxicillin and positive charges of Aliquat 336 promoted the extraction performance [10]. It is also important to point out that amoxicillin possesses three different acid dissociation constants, namely $pKa_1 = 2.68$ at the carboxyl group, $pKa_2 = 7.49$ at the amine group, and $pKa_3 = 9.63$ at the phenol group [11]. Thus, amoxicillin can exist in aqueous solution in four different forms (i.e., $Amox^+$, Amox, $Amox^-$ and $Amox^{2-}$) depending on the pH of solution as shown in Fig. 1. As pointed out earlier, Aliquat 336 was capable of extracting amoxicillin in the form of $Amox^-$ and $Amox^{-2}$ due to anionic attraction. Other types of commercial extractants besides Aliquat 336 that could be the candidates for extracting the remaining forms of amoxicillin (i.e., $Amox^+$ and Amox) include di-(2-ethylhexyl)-phosphoric acid (D2EHPA) and tributyl phosphate (TBP), whose molecular structures are illustrated in Fig. 2. D2EHPA was the negative-charged acidic carrier that is capable of extracting organic compounds containing protonated amine group ($-NH_3^+$) while TBP is the neutral phosphorous-bonded oxygen-composing extractant, which is efficient for organic acid extraction [12,13]. Moreover, past researches have demonstrated that the

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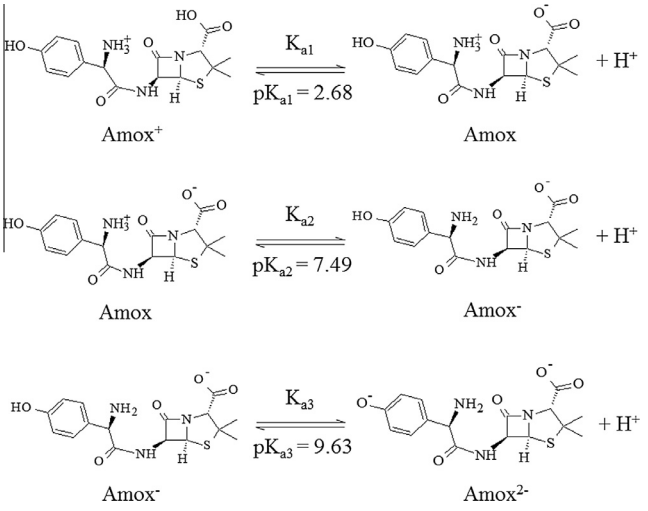

Fig. 1. Different forms of amoxicillin according to p*K*a values.

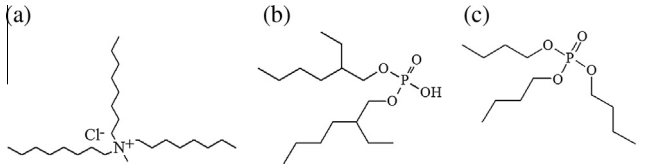

Fig. 2. Structures of commercial extractants used for amoxicillin extraction in this study (a) Aliquat 336 (b) D2EHPA and (c) TBP.

extraction efficiency of organic acids and metals from aqueous solution could be improved by using the mixture of several extractants to create synergistic effects [14–23]. Unfortunately, our literature review indicates that only limited information on amoxicillin extraction by Aliquat 336 are available but none could be found when using D2EHPA and TBP as well as the application of synergistic extraction by the mixture of mentioned solvents. Therefore, the experiment was set up to study the feasibility of amoxicillin extraction by Aliquat 336, D2EHPA and TBP and to obtain the optimal operating conditions, namely the initial pH of amoxicillin aqueous feed and the concentration of extractants. The experiment also explored the possibility of synergistic extraction of amoxicillin by the binary mixture of mentioned extractants.

2. Materials and methods

2.1. Chemicals

The following analytical-graded chemicals were used without pretreatment including Aliquat 336 (Sigma–Aldrich, St. Louise, USA), D2EHPA, 1-decanol (Merck, Darmstadt, Germany), TBP (Acros Organics, New Jersey, USA), acetic acid glacial (QReC chemical, New Zealand) and ammonia solution (Acros Organics, New Jersey, USA). Amoxicillin 500 mg capsules were provided by the Government Pharmaceutical Organization of Thailand. Deionized water (DI water) was obtained by passing tap water through water purification system (Barnstead™ Easypure™ II Ultrapure, Thermo Fisher Scientific, USA) with the resistivity maintained at least 17.8 MΩ cm.

2.2. Procedures

2.2.1. Effect of initial pH in amoxicillin feed

Synthetic feed containing amoxicillin was prepared by dissolving an amoxicillin capsule into DI water under continuous stirring for 1 h and adjusting the total volume to attain the final concentration of 500 mg/L (1.37 mM). After filtering the prepared solution through Whatman paper (average pore size 11 μm), the pH of aqueous solution was adjusted to the desired values ranged from 2 to 12 by adding acetic acid glacial or ammonia solution. Extracting solvents were prepared by mixing the extractants (Aliquat 336, D2EHPA or TBP) in 1-decanol to attain the extractant concentration of 6 mM. 1-Decanol was chosen as the diluent in this research due to its ability to prevent the third-phase formation, which lowered the extraction efficiency [24]. Extraction experiment was performed in triplicate by magnetic stirring the equal volumes (5 mL) of amoxicillin solution and organic extracting phases for 3 h under room temperature (30 ± 2 °C). Extraction systems were then kept idle and avoided from light exposure for the next 19 h to allow complete phase separation. Carefully withdraw the liquid in lower layer of approximately 4 mL and analyze photometrically by using Cary 60 UV–Vis spectrophotometer (Agilent Technologies, USA). Amoxicillin concentration in the organic phase was determined by mass balance calculation. The extraction percentage and distribution coefficient of amoxicillin were calculated using Eq. (1) and (2), respectively [24]:

$$\text{Extraction percentage} = \frac{[Amox]^*_{org}V^*_{org}}{[Amox]_{aq}V_{aq}} \times 100 = \left(1 - \frac{[Amox]^*_{aq}V^*_{aq}}{[Amox]_{aq}V_{aq}}\right) \times 100 \quad (1)$$

$$D_i = \frac{[Amox]^*_{org}}{[Amox]^*_{aq}} = \frac{[Amox]_{aq}V_{aq} - [Amox]^*_{aq}V^*_{aq}}{[Amox]^*_{aq}V^*_{org}}. \quad (2)$$

where D_i is the distribution coefficient of amoxicillin with extractant i; $[Amox]_{aq}$ is the initial amoxicillin concentration in aqueous phase (mg/L); $[Amox]^*_{aq}$ is the equilibrium amoxicillin concentration in aqueous phase after the completion of extraction process (mg/L); $[Amox]^*_{org}$ is the equilibrium amoxicillin concentration in organic phase after the completion of extraction process (mg/L); V^*_{org} is the equilibrium volume of organic phase (L); V_{aq} is the initial volume of aqueous phase (L); and V^*_{aq} is the equilibrium volume of aqueous phase (L). For extractant loading, it was determined according to Eq. (3) [22]:

$$z_i = \frac{[Amox]^*_{org}V^*_{org}}{[Ex_i]V_{org}} = \frac{[Amox]_{aq}V_{aq} - [Amox]^*_{aq}V^*_{aq}}{[Ex_i]V_{org}} \quad (3)$$

where z_i is loading of extractant i (mg/g); $[Ex_i]$ is the initial concentration of extractant i in organic phase (g/L); and V_{org} is the initial volume of organic phase (L).

2.2.2. Effect of extractant concentrations

The mixture of amoxicillin and extractant was prepared according to the method presented in the previous section. The initial amoxicillin concentration in aqueous phase was 500 mg/L (1.37 mM). The pH of the mixture was maintained at the optimal value obtained in Section 2.2.1 while extractant concentrations were varied from 2 to 12 mM. Amoxicillin extraction was conducted in triplicate for each extractant by continuous stirring under room temperature (30 ± 2 °C) for 3 h and then kept idle away from light exposure for the additional 19 h. Lower liquid layer of approximately 4 mL was obtained and analyzed for amoxicillin concentrations using Cary 60 UV–Vis spectrophotometer. Extraction percentage, distribution coefficient and extractant loading were calculated using Eq. (1), (2) and (3), respectively.

2.2.3. Synergistic extraction

The extraction procedure was similar to the previously described sections except that the mixture of two extractants