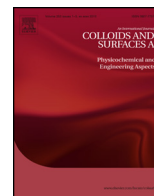




Contents lists available at ScienceDirect

Colloids and Surfaces A: Physicochemical and Engineering Aspects

journal homepage: www.elsevier.com/locate/colsurfa



A new method of extraction of amoxicillin using mixed reverse micelles

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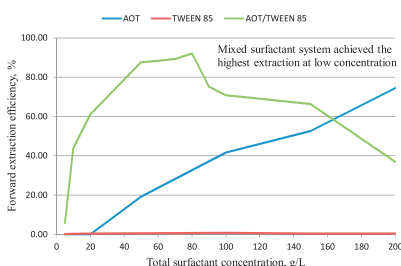
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HIGHLIGHTS

- Amoxicillin is extracted using novel AOT/TWEEN85 mixed reverse micelle system.
- Final extraction higher than 90% is obtained under optimised conditions.
- Mixed reverse micelle system reduces total amount of surfactants needed notably.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 23 December 2013

Received in revised form 27 March 2014

Accepted 30 March 2014

Available online xxx

Keywords:

Mixed reverse micellar system

AOT/TWEEN 85

Amoxicillin

ABSTRACT

A completely new method of extraction of amoxicillin using solubilisation by mixed reverse micelles was proposed and the optimal conditions for the process were found. Mixed AOT-TWEEN 85 reverse micelles were used for the first time as a new approach for extraction of amoxicillin. The effects of different process variables such as AOT-TWEEN 85 molar fractions, total surfactant concentration, pH of aqueous feed solution and potassium chloride concentration during forward extraction; stripping aqueous phase pH, potassium chloride (KCl) concentration and extraction time during backward extraction were investigated and the optimal conditions were found for all mentioned parameters. With the aid of response surface methodology, the optimum conditions for forward extraction are identified as (i) 5.5:1 molar ratio of AOT/TWEEN 85, (ii) total surfactant concentration 102.57 g/L, (iii) pH 1.90, and (iv) KCl concentration 8.54 g/L. The percentage of amoxicillin solubilised in isooctane was 95.54% under these optimal conditions. On the other hand, the optimum conditions for backward extraction are identified as (i) stripping aqueous phase pH 6.58, (ii) KCl concentration 11.02 g/L, and (iii) extraction time 15 min. Under these optimal conditions, the percentage of amoxicillin recovered was 90.79%. AOT/TWEEN 85 mixed surfactant system shows a significant advantage of saving the amount of surfactant for forward extraction. The addition of non-ionic surfactant helps to preserve natural function/activity of antibiotics as compared with a pure AOT surfactant used. The optimum conditions were also found for a backward recovery of amoxicillin.

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1. Introduction

Amoxicillin (a-amino-p-hydroxybenzylpenicillin) is one novel semi-synthetic β -lactam antibiotic and is widely used in medical therapy as a broad-spectrum bactericidal which is to be exposed to a variety of microorganisms β -lactamases produced

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by Gram-positive and many Gram-negative [1]. It is regularly combined with β -lactamase inhibitor Clavulanic Acid for oral antibacterial medicine and better protection against infections of intra-abdominal [2]. In industries, amoxicillin is presently produced through a chemical coupling process by using a β -lactam nucleus and appropriate acyl donors. Chemical coupling of amoxicillin involves the reaction of an amino β -lactam such as 6-aminopenicillanic acid (6-APA) usually having its carboxyl group protected with an activated side-chain derivative, where the protecting group is removed through hydrolysis [3].

There are a number of problems occurred during the purification of semi-synthetic antibiotics from a broth: separation of toxic solvents, waste produced, by-products and other impurities. As a result of separation stages the antibiotic yield and natural function/activity are reduced. Protection and controlled release of bioactive compounds can be done through encapsulation [4]. Reverse micellar extraction (RME) has some clear advantages as compared with other separation process in extracting antibiotics. These advantages are as follows: preservation of native function/activity, higher yield, low interfacial tension for better phase mixing, ease of scale up, and potential for continuous operation [5,6]. Electrostatic, steric, and hydrophobic interactions between antibiotic and reverse micelles are considered to be the driving forces for the diffusion of antibiotic into the reverse micellar core [7]. RME is usually optimised through adjusting various variables such as solution pH, surfactant concentration, salt concentration, and contact time [8,9]. However, most of the reports on RME deal with ionic surfactants and only a few reports have been published on the application of nonionic surfactants [10]. Extraction of large solutes (such as antibiotics) with nonionic surfactants was reported to be difficult due to a lack of strong electrostatic interaction between antibiotics and surfactant molecules.

Chatterjee et al. [11] found that the alteration of the interfaces between organic and aqueous solutions due to addition of a second surfactant can enhance the solubilisation capacity of mixed surfactant system. The improvement of solubilisation capacity of bio-molecule by reducing the charge density of AOT micellar surface in presence of non-ionic surfactant had been reported earlier [12]. However, studies regarding mixed reverse micellar systems had been restricted on their physico-chemical characterisations. Further, to the authors' best knowledge, none had been reported for RME of antibiotics using mixed reverse micellar system.

Below AOT/TWEEN 85 mixed anionic and non-ionic surfactant system was used as a new approach in RME and an alternative for conventional liquid–liquid extraction with a chemical solvent. TWEEN 85 is ethoxylated derivatives of sorbitan esters in which the substitution of the hydroxyl groups on the sorbitan ring with polyoxyethylene groups makes the surfactant hydrophilic heads bigger and able to occupy larger area on the interface. The focus of this research is extraction of the antibiotic amoxicillin using the reverse micelles mentioned above to enhance the extraction processes from aqueous solution of amoxicillin. The optimum conditions for extraction process to give a highest yield are determined.

2. Methodology

2.1. Chemicals

The bio-molecule used is amoxicillin trihydrate obtained from bio-WORLD, USA. The aqueous phase was prepared from fresh deionised water using Purite Select AN HP40 (Purite Ltd, England) with resistivity 15–16 M Ω cm. Reagent grade sodium di-2-ethylhexylsulfosuccinate (AOT) was used as anionic surfactant and non-ionic TWEEN 85 surfactant was used as the co-surfactant (Sigma Adrich Co). Various concentrations of KCl in aqueous

phase were used to compose the aqueous solution containing bio-molecule of amoxicillin. Isooctane was used as an organic phase for the reverse micelles formation. HCl or NaOH solutions were used to adjust pH of the aqueous phase during the experiment. All the chemicals were purchased from Sigma Adrich Co. (M). All reagents used in the experiment were of analytical grade.

2.2. Selection of surfactants for mixture and optimal surfactant molar ratio

AOT is capable of solubilising a huge quantity of water without any addition of co-surfactant [5]. However, denaturing of bio-molecule may occur due to the strong electrostatic interaction between the polar head of reverse micelles and bio-molecules. This results in a deactivation of bio-molecule and in a low yield of extraction. Most researchers are more focused on the extraction capability of anionic surfactants such as AOT. The potential of non-ionic surfactants or combination of ionic and non-ionic surfactants in reverse micelles for bio-molecules separation, especially antibiotic molecules is still to be investigated. Only a few studies have been reported on the application of non-ionic surfactant and these studies are limited to protein extraction [13].

There are several publications available where TWEEN85 reverse micelles were used for protein extraction and retention of enzyme activity [14]. TWEEN 85 was used in this research because it is able to solubilise a larger volume of water and protein than the classic anionic surfactants such as AOT [15]. However, single non-ionic surfactant systems were reported to be not effective in forward extraction of protein [16] because the electrostatic interactions between protein and surfactant are weak. Therefore, it should be used together with ionic surfactant to provide sufficient electrostatic interactions for forward extraction.

It was found earlier that TWEEN85 does not have detrimental effect on the structure, function, and stability of cytochrome c-subtilisin [17]. Pfammatter et al. [18] also had demonstrated the solubilisation and growth of whole cells in reverse micelles, composed of TWEEN 85 and Span 80. TWEEN 85 is biodegradable and has been successfully tested for use as an additive in fertilizer. TWEEN 85 also has a hydrophilic/lipophilic balance (HLB) of 11, which indicates that it is soluble in organic solvents [19]. It is the reason why TWEEN 85 was selected as a co-surfactant for formation of mixed reverse micelles.

In the course of the RME it is important to have a clear phase and avoid emulsion formation during the extraction process. The latter can be achieved by selecting a proper ratio of surfactant in the mixture. The optimum molar ratio of AOT/TWEEN 85 was determined beforehand. Various amount of TWEEN 85 was added into isooctane while keeping AOT concentration at 150 mM and forward extraction was conducted. Experimental results showed that only molar ratio of AOT/TWEEN 85 above 1.38:1.00 produced a clear transparent phase. Below this ratio (region to the right in Fig. 1, line not shown) precipitation of surfactants was observed during forward extraction. Furthermore, when the molar ratio is less than 1.00:1.00, a small precipitation was observed at the interface and emulsion was easy to occur. However, emulsion formation substantially reduced the amount of amoxicillin solubilised in the reverse micelle phase. The cloudiness observed also indicates that amoxicillin was denatured. The following ratio 5.50:1.00 was found to be the best ratio in the parameter range being investigated as shown in Fig. 1. All subsequent experiments were carried out with AOT/TWEEN 85 ratio of 5.50:1.00.

2.3. Critical micelle concentration (CMC)

Since reversed micelles formed in organic phase, the CMC refers to the concentration of surfactants in isooctane. The variation of

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