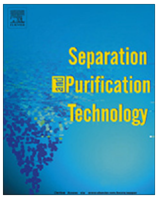
Separation and Purification Technology 122 (2014) 315–322

Contents lists available at ScienceDirect

Separation and Purification Technology

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



Recovery of paracetamol from pharmaceutical wastes

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ARTICLE INFO

Article history:
Received 21 March 2013
Received in revised form 11 September 2013
Accepted 14 November 2013
Available online 23 November 2013

Keywords:
Pharmaceutical wastes
Active compounds
Paracetamol
Aqueous biphasic systems
Ionic liquid
Extraction efficiency

ABSTRACT

The concern about the impact of active pharmaceutical compounds on the environment has been growing for decades. This work looks at pharmaceutical wastes as a source of valuable active compounds proposing the use of novel aqueous biphasic systems (ABS) composed of quaternary ammonium compounds and different salts to the extraction of active substances from pharmaceutical wastes. The phase diagrams of ABS of six quaternary ammonium halides ($[N_{2,2,2,2}]$Br, $[N_{2,2,2,2}]$Cl, $[N_{3,3,3,3}]$Br, $[N_{3,3,3,3}]$Cl, $[N_{4,4,4,4}]$Br and $[N_{4,4,4,4}]$Cl) and three different salts (potassium citrate buffer, potassium carbonate and potassium phosphate buffer) were established at 298 (±1) K. These systems allow the investigation of the influence of the ammonium structure, the salting-out agent, and the pH of the aqueous medium. They were then applied to the extraction of paracetamol that displays an extensive partition towards the ammonium-rich phase. All the studied systems, employing both the model compound and real matrix reveal a great aptitude to recover paracetamol from pharmaceutical wastes, presenting extraction efficiencies ranging from around 80% up to 100%.

1. Introduction

The pharmaceutical industry in Europe has been growing and with it, the consumption of drugs and medicines. This increasing consumption is nowadays responsible for a big society problem due to the high level of waste produced, and its crescent environmental impact [1–4]. This demand can only be solved by a better control and processing of the pharmaceutical wastes. In Portugal, the pharmaceutical waste management company VALORMED collected, in 2011, 853.8 tons of pharmaceutical wastes (packaging and pharmaceutical drugs), of which 0.638 tons were composite packaging (blister) [5]. The pharmaceutical waste is sent to sorting centers, where it is directed to recycling centers or energy recovery [5]. This amount of pharmaceutical waste results from drugs past of expiration date that no longer can be used for human therapy or drugs that are not used due to the mismatch between the package content and the treatment needs [4,6]. The expiration date of drugs is assessed by the application of the knowledge acquired through stability studies [7]. By definition, during this period, the physical, chemical, microbiological, galenic, therapeutic and toxicological properties remain as unchanged within acceptable and well-defined limits [7]. However, even past the expiration date, drugs still retain their active substances, notwithstanding in quantity/quality that do not assure the therapeutic effect [5]. In fact, the intensive use and disposal of those substances results in their occurrence in natural environments such as water channels and soils [2]. Antibiotics, cancer and endocrine system drugs, anthelmintics and antidepressants are some examples of the pharmaceutical groups with more environmental persistence [8].

In this context, green and sustainable pharmacy appears as an emerging and essential topic [3,4]. The concepts brought by the fields of sustainability and green chemistry highlight the relevance of considering each stage comprising the life cycle of a compound to identify opportunities to manage and reduce risk potential [9]. Accordingly, the last chapter of drugs life represents an excellent opportunity to drug recovery, adding value to those active pharmaceutical substances. So, it is of great interest the development of novel strategies that combine the extraction and purification of drugs from pharmaceutical wastes. The high environmental and economic potential lies on the possibility to prevent the entrance of these compounds in the environment and to resell the recovered compounds for further purification and use.

Aqueous biphasic systems (ABS) are a well-known liquid–liquid extraction technique, formed by two aqueous phases of different compounds that are immiscible above given concentrations. These are highly versatile extraction systems, since a great variety of compounds can be used in their preparation [10–20]. IL-based ABS have been the subject of vast attention and widely used for the extraction of several biomolecules [21] such as alkaloids [22], antibiotics [23], amino acids [24] and enzymes [25,26], showing high effectiveness, yields and selectivities. They allow the concentration of biomolecules present in very low amounts in complex matrices in one aqueous phase [22,27] as also has been shown for the extraction of antibiotics from fermented broth [28].

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http://dx.doi.org/10.1016/j.seppur.2013.11.018

In this work, ammonium-based ILs, reported as being cost-effective ILs [29,30] of low toxicity, and as promising biocompatible solvents to stabilize biomolecules [31], are investigated to extract active substances from pharmaceutical wastes. The paracetamol (Fig. 1) is here used as a model drug to evaluate the extraction capabilities of the IL-based ABS. Six short-chain quaternary ammonium compounds and three salts are used to prepare the ABS, aiming at investigating the influence of the alkyl chain of the cation and the anion effect. A systematic analysis of the aptitude of ammonium compounds to form ABS is performed by changing the salt, the ammonium type and the medium pH. These systems are further applied in the extraction of paracetamol from both model and real pharmaceutical matrices. The model matrix is adopted to develop an optimization study aiming at evaluating the operating conditions of the ABS (ammonium structure, salt agent, tie-line length – TLL – and pH of the aqueous medium), in order to achieve the highest extraction efficiencies (EE_{PC}, %). Subsequently, representative conditions are employed with the objective to demonstrate the possibility to apply these extraction systems to pharmaceutical matrices.

2. Materials and methods

2.1. Materials

The paracetamol, also known as N-(4-hydroxyphenyl)acetamide or acetaminophen, had a quoted purity $\geqslant$99 wt% and was acquired at the Sigma–Aldrich (Fig. 1). The quaternary ammonium compounds were tetraethylammonium bromide $[N_{2,2,2,2}]Br$ (98 wt%); tetraethylammonium chloride $[N_{2,2,2,2}]Cl$ (98 wt%), tetrapropylammonium bromide, $[N_{3,3,3,3}]Br$ (98 wt%), tetrapropylammonium chloride $[N_{3,3,3,3}]Cl$ (98 wt%), tetrabutylammonium bromide $[N_{4,4,4,4}]Br$ (>98 wt%), tetrabutylammonium chloride $[N_{4,4,4,4}]Cl$ (97 wt%). All quaternary ammonium compounds were purchased from Sigma–Aldrich. The chemical structures of all compounds used in this work are depicted in Fig. 2. The purity of each ammonium was further checked by ^{1}H and ^{13}C NMR and found to be in accordance with the stated purity level provided by the suppliers. Potassium phosphate monobasic KH_2PO_4 (99.5 wt%), potassium carbonate K_2CO_3 (99 wt%) and potassium citrate tribasic monohydrate $C_6H_5K_3O_7{\cdot}H_2O$ ($\geqslant$99 wt%) were acquired from Sigma–Aldrich, potassium phosphate dibasic K_2HPO_4 (>98 wt%) was supplied by JMVP and the citric acid monohydrate $C_6H_8O_7{\cdot}H_2O$ (100 wt%) was purchased at Fisher Scientific. The water used was double distilled, passed by a reverse osmosis system and further treated with a Milli-Q plus 185 water purification apparatus.

The drug *Ben-u-ron® 500* was produced in Portugal by Neo-Farmacêutica.

2.2. Phase diagrams and tie-lines

The binodal data were determined through the cloud point titration method at 298 (±1) K and atmospheric pressure, as previously described in literature [17–20]. The ABS were measured by using ammonium aqueous solutions ($[N_{2,2,2,2}]Br$, $[N_{2,2,2,2}]Cl$, $[N_{3,3,3,3}]Br$, $[N_{3,3,3,3}]Cl$, $[N_{4,4,4,4}]Br$ and $[N_{4,4,4,4}]Cl$) at concentrations ranging from ≈40 wt% to ≈80 wt% and aqueous solutions of three different salt species. The potassium phosphate buffer solution (pH 7) was prepared by adding $K_2HPO_4 + KH_2PO_4$ (*at circa* 40 wt%) [19], the potassium citrate buffer solutions (pH 5–8) were composed of $C_6H_5K_3O_7 + C_6H_8O_7$ (*at circa* 50 wt%) [32] and the potassium carbonate aqueous solution was prepared *at circa* 50 wt% (pH ≈ 13).

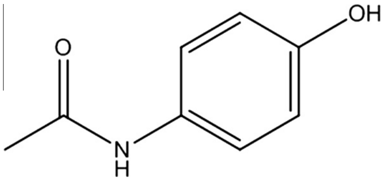

Fig. 1. Chemical structure of paracetamol.

Each tie-line (TL) was measured through a well-established gravimetric method firstly proposed by Merchuk and co-workers [33] and validated by us for this purpose [17–20]. A mixture at the biphasic region was prepared, vigorously stirred and allowed to reach the equilibrium by the phases separation for at least 18 h and at 298 (±1) K, using small ampoules (10 cm^3) specially designed for this purpose. After the separation of the co-existing phases, they were carefully and individually weighed. The tie-lines (TLs) were determined by the application of the lever-arm rule and the experimental solubility curves were correlated using the Merchuk Equation (Eq. (1)) [33],

$$[ammonium] = A\ exp[(B[salt]^{0.5}) - (C[salt]^{3})] \qquad (1)$$

where [ammonium] and [salt] represent, respectively, the ammonium and salt mass fraction percentages, and *A*, *B* and *C* are the constants obtained by the regression of the experimental binodal data. The compositions adopted at the biphasic region in order to determine the TLs were the same as those further applied in the paracetamol extraction studies (within ±10^{-4} g).

The tie-line length (TLL) was determined using the Eq. (2),

$$TLL = \sqrt{([salt]_T - [salt]_B)^2 + ([ammonium]_T - [ammonium]_B)^2} \qquad (2)$$

and denotes the distance between the bottom (*B*) and the top (*T*) phase compositions.

2.3. Optimization study of the paracetamol partition

The systems for the optimization study of the paracetamol extraction were gravimetrically prepared in glass vials by adding the appropriate amounts of ammonium, of an aqueous solution of the salt component and 0.5 g of an aqueous solution containing the paracetamol (≈0.001 g mL^{-1}), for a total mass of the extraction systems prepared of 5 g. The influence of different parameters was analyzed, namely the ammonium structure, the salt component, the TLL and finally, the pH. The extraction points used were chosen in accordance with the conditions investigated and presented in Table 1.

Subsequently, the mixtures were vigorously stirred and the systems were placed at 298 (±1) K, for at least 18 h, to assure the complete equilibrium of the phases and the total paracetamol partition. The degree of agitation used in the ABS preparation was controlled and maintained at 2400 rpm, avoiding any limitations related with mass transfer problems and guarantying that equilibrium was reached while minimizing the time of each essay. At this point, the systems were clear and a well-defined interface between the coexisting phases was observed. Finally, the phases were carefully separated and collected for the measurement of their weight, volume and pH. At the conditions used in this work, the system resulted in the ammonium-rich phase as the top layer while the salt-rich is representing the bottom phase. In this work, the extraction efficiencies of paracetamol (EE_{PC}, %) were calculated for each system studied following the Eq. (3),

$$EE_{PC} = \frac{[PC]_T \times V_T}{[PC]_i \times V_i} \times 100 \qquad (3)$$

where V_i and $[PC]_i$ are the initial volume and the initial paracetamol concentration added to prepare the extraction systems, while V_T and $[PC]_T$ represent the volume and paracetamol concentration of the top phase, respectively.