Article

# Removal of Non-Steroidal Anti-Inflammatory Drugs from Aqueous Environments with Reusable Ionic-Liquid-based Systems

Hugo Ferrão Dias Almeida, Isabel M. Marrucho, and Mara G. Freire

*ACS Sustainable Chem. Eng.*, **Just Accepted Manuscript** • Publication Date (Web): 11 Jan 2017

# Removal of Non-Steroidal Anti-Inflammatory Drugs from Aqueous Environments with Reusable Ionic-Liquid-based Systems

*Hugo F. D. Almeida[†‡], Isabel M. Marrucho[‡§], and Mara G. Freire[†]**

† CICECO – Aveiro Institute of Materials, Chemistry Department, University of Aveiro, Campus Universitário de Santiago, 3810-193 Aveiro, Portugal.

‡ Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, 2780-157 Oeiras, Portugal.

§ Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Avenida Rovisco Pais, 1049-001 Lisboa, Portugal.

***Corresponding author email address**: maragfreire@ua.pt

**KEYWORDS:** Active Pharmaceutical Ingredients, Removal, Wastewater Treatment Plants, Aqueous Biphasic Systems, Ionic Liquids, Extraction Efficiency, Recovery

**ABSTRACT:** In the current era of human life, we have been facing an increased consumption of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Nevertheless, NSAIDs are not entirely metabolized by humans, and are thus excreted into domestical effluents, whereas expired medications are recurrently straightly disposed into wastewaters. Several studies already demonstrated that an extensive diversity of pharmaceuticals is present in aqueous effluents and are therefore a matter of serious concern to wildlife and public health. In this perspective, this work is focused on the use of a liquid-liquid extraction approach for the removal of NSAIDs from aqueous media. In particular, aqueous biphasic systems (ABS) composed of ionic liquids (ILs) and aluminium-based salts were used for the removal of diclofenac, ibuprofen, naproxen and ketoprofen. With these systems, extraction efficiencies of NSAIDs up to 100% into the IL-rich phase were obtained in a single-step. Further, the recovery of NSAIDs from the IL medium and the recyclability of the IL-rich phase were ascertained aiming at developing a more sustainable and cost-effective strategy. Based on the remarkable increase of NSAIDs solubility in the IL-rich phase (from a 300- to a 4100-fold when compared with pure water), water was used as an effective anti-solvent, where recovery percentages of NSAIDs from the IL-rich phase up to 91% were obtained. After the "cleaning" of the IL-rich phase by the induced precipitation of NSAIDs, the phase-forming components were recovered and reused in four consecutive cycles, with no detected losses on both the extraction efficiency and recovery of NSAIDs.

## INTRODUCTION

In the past years, the detection of emerging pollutants in diverse environmental matrices has been the focus of large concerns and debate. The classification of pharmaceuticals and personal care products (PPCPs) as relevant pollutants was firstly recommended by Daughton and Ternes,[1] being currently classified as emerging contaminants according to the United Nations Environmental Program (UNEP).[2] Advances on analytical techniques have allowed their identification in an increasing number of environmental matrices.[3-6] Active pharmaceutical ingredients (APIs) belong to the PPCPs class, and have particularly raised severe concerns in more recent years after their non-negligible levels identification in aqueous environments.[7-14] APIs, known as mutagenic, carcinogenic, and endocrine disruptors, have been found in concentrations up to $\mu g.L^{-1}$ in worldwide effluents of sewage treatment plants (STPs), wastewater treatment plants (WWTPs), freshwaters (rivers and lakes) and estuarine/marine waters.[7, 10, 13, 15-18] A global occurrence and perspective of pharmaceuticals in the environment has been summarized by aus de Beek et al.[18] APIs found in the environment include prescription drugs, drugs used in hospital by humans and veterinary drugs.[10, 19-21] Variable quantities of the taken doses are metabolized by organisms whereas the rest is excreted (in either metabolized or unchanged forms).[9, 10, 22-28] According to Heberer[29] and Daughton and Ternes,[1] the consumed PPCPs are mainly excreted through urine or feaces as a mixture of their original and metabolized forms. For instance, Vieno and Sillanpää[30] investigated the metabolic path of diclofenac in humans, showing that between 65% and 75% and between 20% and 30% of the orally administered dose is excreted through urine and feaces, respectively, as the parent drug or in the form of metabolites. Furthermore, according to Dias-Ferreira et al.[31] each household

keeps an average of 1097 g of pharmaceutical products, with 20% in current use, 72% not in use, and 8% as expired products ready to be discarded. As a result, most of the unnecessary or expired medications are recurrently straightly disposed into wastewaters.[10, 20, 21] Even at low concentrations, the continuous contact with APIs leads to deleterious effects in living organisms.[10] These compounds have important side effects, where different organs, tissues, cells or biomolecules, may be affected.[10]

Based on extensive criteria, the Global Water Research Coalition (GWRC) selected ten priority APIs.[32] This list comprises antibiotics, anti-epileptics, anti-inflammatory drugs, β-blockers and lipid regulators.[10, 20, 21] Although WWTPs use advanced processes for water purification, such as membrane filtration, ozonation, chlorination, flocculation/sedimentation and adsorption, none of these processes was specifically designed to remove APIs,[9, 10, 12-14, 28] and some of these emerging pollutants were already identified in drinking water.[29,33, 34]

Within APIs, the non-steroidal anti-inflammatory drugs (NSAIDs) diclofenac, ibuprofen and naproxen are included in the list of the top 10 persistent pollutants.[19] These compounds display a high-octanol partition coefficient ($K_{ow}$), and thus a high ability to passively diffuse across biological membranes, low p$K_a$ values and high persistence in aquatic environments.[35] Some classic methods have already been tested for the removal of NSAIDs; in particular, the addition of several salts to promote the coagulation of ibuprofen, naproxen, diclofenac, carbamazepine and diazepam was investigated, whereas the best results were obtained for diclofenac with 50% of removal efficiency.[36] Ozonation[37] and chloride oxidation[38] have also been studied for NSAIDs degradation, where ozone was found to be the most effective oxidizer. Kahn et al.[39] compared several techniques, such as

lime clarification, dissolved air flotation, dual media filtration, combined reverse-osmosis/nanofiltration, adsorption by activated carbon, ozonation, and UV disinfection units for the removal or degradation of NSAIDs. The authors[39] concluded that reverse osmosis is an effective process for removing a wide range of pharmaceuticals, yet it is highly energy-intensive. Therefore, the development of a cost-efficient removal technique for NSAIDs from aqueous media is an urgent requirement of modern society.

Aqueous biphasic systems (ABS) are liquid-liquid extraction systems formed by two aqueous-rich phases, which result from the dissolution in water of two water-soluble phase-forming components above certain concentrations. Generally, two non-volatile compounds, such as two polymers, a salt and a polymer or two salts, allow the creation of ABS.[40, 41] In addition to the two phase-forming components, ABS are mainly composed of water and are thus considered as more environmentally friendly liquid-liquid extraction approaches. The partition/extraction of given compounds occurs between the two phases in equilibrium, in which the chemical nature and physical properties of both the phase-forming components and solute are crucial. Nevertheless, more conventional polymer-based ABS display a limited polarity difference between the two phases, resulting in restricted extraction performance and selectivity. To overcome this constraint, the polymers functionalization and addition of ligands have been investigated in the past few years.[42, 43]

In 2003, Rogers and co-workers[44] demonstrated the formation of ABS by adding an inorganic salt to an aqueous solution of a given ionic liquid (IL). After this pioneering work, it was latter demonstrated that these systems can be created with a large number of salts, amino acids, carbohydrates and polymers, offering a new plethora of extraction/separation systems.[45] Even though many ILs display some exceptional

properties, namely a negligible vapor pressure, non-flammability, high thermal and chemical stabilities, and a large liquid temperature range,[46-49] the most important feature conveys on their tailoring ability (by a suitable choice of their ions), which is transferrable to IL-based ABS.[50] In fact, IL-based ABS already proved a superior performance on extraction efficiencies and selectivity for a wide range compounds, comprising proteins, alkaloids, phenolic compounds, dyes, among others.[45] In particular, IL-based ABS have also been investigated for the extraction of pharmaceuticals,[51-56] mainly to evaluate their performance as purification and concentration techniques,[51-54] as well as to recover value-added compounds from pharmaceutical wastes.[55, 56]

From a different perspective to the previously published works regarding the use of IL-based ABS for the concentration and purification of pharmaceuticals,[51-56] herein, we propose an integrated and highly efficient ABS-based strategy to remove and recover NSAIDs (diclofenac, ibuprofen, naproxen, and ketoprofen), as current persistent pollutants, from aqueous environments. Since STPs and WWTPs currently use $Al_2(SO_4)_3$ for the purification of drinking water, as a flocculating agent, this salt was chosen to create the IL-based ABS under study. Three different stages (mechanical, biological and disinfection treatments) are combined in a simplified version of a WTTP,[57] whereas the ABS strategy designed here for the NSAIDs removal is envisioned to be introduced in the final stage. Finally, and aiming at developing a more sustainable technique for the removal of persistent pollutants from aqueous environments, the recovery of the investigated NSAIDs from the IL-rich phase and the IL recycling were also established, allowing us to propose an integrated and highly efficient process which comprises the removal and recovery of NSAIDs and the phase-forming components recovery and reuse.

## EXPERIMENTAL SECTION

**Materials.** The non-steroidal anti-inflammatory drugs investigated were diclofenac sodium salt (2-[(2,6-Dichlorophenyl)amino]benzene acetic acid sodium salt, CAS# 15307-79-6), ibuprofen ((±)-2-(4-Isobutylphenyl)propanoic acid, CAS# 15687-27-1), naproxen ((S)-(+)-2-(6-Methoxy-2-naphthyl)propionic acid, CAS# 22204-53-1) and ketoprofen ((RS)-2-(3-Benzoylphenyl)propionic acid, CAS# 22071-15-4), with a purity level ≥ 99% for diclofenac, and ≥ 98% for ibuprofen, naproxen and ketoprofen. All NSAIDs were acquired from Sigma-Aldrich, and used as received. The chemical structures of the NSAIDs investigated are depicted in Figure 1.

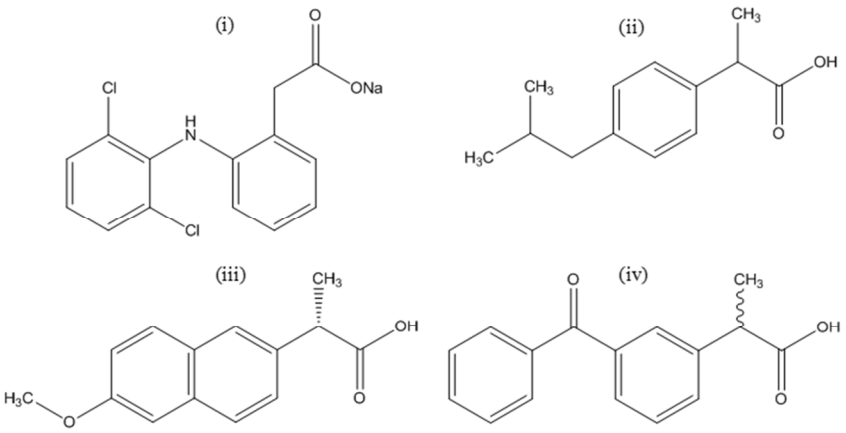



**Figure 1.** Chemical structures of the NSAIDs investigated: diclofenac sodium salt (i), ibuprofen (ii), naproxen (iii), and ketoprofen (iv).

The ILs used were 1-ethyl-3-methylimidazolium trifluoromethanesulfonate (triflate) ($[C_2C_1im][CF_3SO_3]$, purity 99 wt%, CAS# 145022-44-2); 1-butyl-3-methylimidazolium trifluoromethanesulfonate (triflate) ($[C_4C_1im][CF_3SO_3]$, purity 99 wt%, CAS# 174899-66-2); 1-butyl-3-methylimidazolium tosylate ($[C_4C_1im][Tos]$, purity 99 wt%, CAS# 410522-

18-8); tri(isobutyl)methylphosphonium tosylate ([$P_{i(444)1}$][Tos], purity 98 wt%, CAS# 374683-35-9); tributylmethylphosphonium methylsulfate ([$P_{4441}$][$CH_3SO_4$], purity 96-98 wt%, CAS# 69056-62-8); tetrabutylphosphonium bromide ([$P_{4444}$]Br, purity 95 wt%, CAS# 3115-68-2); and tetrabutylphosphonium chloride ([$P_{4444}$]Cl, purity 97 wt%, CAS# 2304-30-5). All imidazolium-based ILs were purchased from Iolitec, while the phosphonium-based fluids were gently supplied by Cytec Industries Inc. In order to reduce the volatile impurities and water content in the IL samples, these were placed under constant stirring, at vacuum and 50 ºC, for a minimum of 24h. Only [$P_{4444}$]Br and [$P_{4444}$]Cl, which are samples commercially provided with higher amounts of water, were purified at a higher temperature (100 ºC), under vacuum, and for a minimum of 72h. The purity of each IL was further checked by $^{1}H$ and $^{13}C$ NMR spectra. The chemical structures of the ILs investigated are shown in Figure 2.

The inorganic salt $Al_2(SO_4)_3$ (CAS# 17927-65-0) was acquired from José Manuel Gomes dos Santos, Lda. (purity ≥ 98.0 wt%). The water applied was doubled distilled, passed across a reverse osmosis system and further treated with Milli-Q plus 185 water purification equipment. Buffers solutions with pH of 4.00 and 7.00, acquired from Panreac, were used for the pH meter equipment calibration.

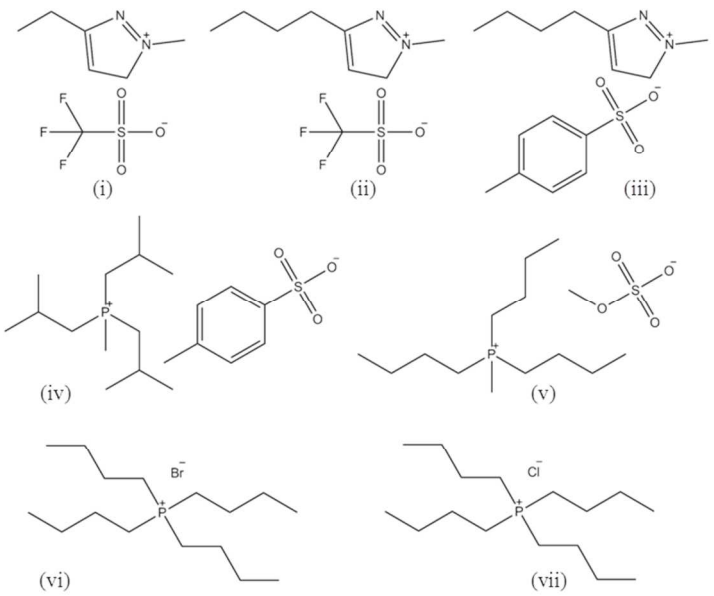



**Figure 2.** Chemical structures of the ILs used to form ABS: $[C_2C_1im][CF_3SO_3]$ (i), $[C_4C_1im][CF_3SO_3]$ (ii), $[C_4C_1im][Tos]$ (iii), $[P_{i(444)1}][Tos]$ (iv), $[P_{4441}][CH_3SO_4]$ (v), $[P_{4444}]Br$ (vi), and $[P_{4444}]Cl$ (vii).

**Phase diagrams and tie-lines.** The ABS ternary phase diagrams used in the current work were taken from the literature.[58] However, additional tie-lines (TLs), which describe the compositions of the phases in equilibrium for given mixture compositions, were determined in this work. Each TL was determined according to the lever-arm rule originally proposed by Merchuk et al.[59] Additional details on the TLs determination and respective length (tie-line length, TLL) are provided in the Supporting Information.

**Removal of NSAIDs using IL-based ABS.** IL-based ABS investigated for the removal of NSAIDs from aqueous media require the use of ternary mixtures (ionic liquid + salt + aqueous solutions containing the target NSAID) within the biphasic region of each system. The concentration of NSAIDs in the aqueous solutions was of 0.060 $g.L^{-1}$, 0.049 $g.L^{-1}$ and 0.046 $g.L^{-1}$ for diclofenac sodium salt, naproxen and ketoprofen, respectively. These

concentrations are significantly higher than those found in STPs and WWTPs, thus guaranteeing that there is no saturation of each NSAID in the coexisting phases when envisaging the use of the proposed technology in real water samples. The ternary mixtures were prepared gravimetrically within ± $10^{-4}$ g, using a Mettler Toledo Excellence XS205 DualRange analytical balance, according to given weight fraction composition percentages (shown thereinafter as wt%). All mixtures were stirred and left in equilibrium for 24 h at (25 ± 1) ºC, to allow the complete separation of both liquid phases and consequent NSAIDs partitioning. The two phases were then separated, and both IL- and salt-rich phases were weighted and each NSAID quantified through UV-spectroscopy, using a Shimadzu UV-1700, Pharma-Spec UV-Vis Spectrophotometer, at a wavelength of 276, 221, 230 and 258 nm for diclofenac sodium salt, ibuprofen, naproxen and ketoprofen, respectively, using calibrations curves formerly determined. To avoid interferences of the IL and salt in the quantification of each NSAID, ternary mixtures with the same weight fraction compositions were prepared using pure water. However, in the extractions of ibuprofen and ketoprofen using the $[C_4C_1im][CF_3SO_3]$- and $[C_4C_1im][Tos]$-based ABS, a large interference of the ILs on the UV-spectroscopy quantification method was observed. Since the extraction efficiencies could not be accurately determined for these two particular systems, they are not presented.

The percentage extraction efficiencies (%*EE*) of each system for NSAIDs are defined according to:

$$\%EE = \frac{[\mathrm{NSAID}]_{\mathrm{IL}} \times w_{\mathrm{IL}}}{([\mathrm{NSAID}]_{\mathrm{IL}} \times w_{\mathrm{IL}}) + ([\mathrm{NSAID}]_{\mathrm{salt}} \times w_{\mathrm{salt}})} \times 100 \qquad (1)$$

where $w_{IL}$ and $w_{salt}$ are the total weight of the IL-rich phase and salt-rich phase, respectively, and $[NSAID]_{IL}$ and $[NSAID]_{salt}$ are the concentration of each NSAID in the IL-rich phase and salt-rich phase, respectively.

At least three individual systems were prepared for each ABS and each NSAID, allowing to determine the average %*EE* value and respective standard deviation. The possible loss of each NSAID (e.g. by precipitation and/or saturation of the phases) was evaluated by comparing the amount of each NSAID added and that quantified in each phase, showing that no losses of NSAIDs occurred in the systems investigated.

**pH determination.** The pH values (± 0.02) of the ABS coexisting phases were measured at (25 ± 1) ºC, using a Mettler Toledo S47 SevenMulti™ dual meter pH/conductivity. The calibration of the pH meter was beforehand performed with two buffers solutions with pH values of 4.00 and 7.00.

**Solubility of NSAIDs in the IL-rich phase.** To infer on the possible saturation of the systems investigated with NSAIDs, the solubility of each pharmaceutical in the IL-rich phase of the system composed of 58.5 wt% of $[P_{4441}][CH_3SO_4]$ + 2.2 wt% of $Al_2(SO_4)_3$ + 39.5 wt% of $H_2O$ was determined at (25 ± 1) ºC. At least three individual systems were prepared for each NSAID, allowing to determine the average solubility value and standard deviation. To a total weight of 1 g of the IL-rich phase, small amounts of each NSAID were added, (from 0.002 up to 0.005) g, and stirred under controlled temperature (25 ± 1) ºC using an Eppendorf Thermomixer® comfort equipment. The samples were left to equilibrate and NSAIDs were continuously added until the detection of a cloud point (visual identification of the first solid in solution). After the identification of the cloud

point, the samples were left under stirring for at least 24 h at (25 ± 1) ºC to guarantee that no further NSAID is dissolved and no saturation of the IL-rich phase was achieved.

**Recovery of NSAIDs and IL Recycling.** To ascertain on the recycling ability of the studied ABS, the recovery of the NSAIDs from the IL-rich phase was first addressed followed by the IL reuse in a new cycle of NSAIDs removal. After the extraction step and NSAIDs enrichment in the IL-rich phase, water was added to this phase as an anti-solvent, in different amounts, and the mixture was vigorously stirred. Since NSAIDs have a low water solubility,[60] and considering the recently demonstrated ILs hydrotropic effect,[61] the precipitation of NSAIDs is easily achieved by the simple addition of water. All these steps were carried out at (25 ± 1) ºC. The precipitated NSAIDs were recovered by filtration under vacuum, using a Sartorius Stedim Biotech Cellulose Nitrate filter, with a pore size of 0.45 $\mu$m. The acquired precipitate was further washed with 10 mL of deionized water, and dried at 70 ºC until constant weight.

The percentage of recovered NSAIDs (%Recovery) was determined according to:

$$\%\text{Recovery} = \frac{(w_{\text{NSAID}})_{\text{recovered}}}{(w_{\text{NSAID}})_{\text{IL-rich phase}}} \times 100 \qquad (2)$$

where $(w_{NSAID})_{recovered}$ and $(w_{NSAID})_{IL\text{-}rich\ phase}$ is the total weight of each NSAID after the filtration and drying step and the total NSAID weight at the IL-phase, respectively.

In order to explore the viability of the ABS reuse, it is necessary to know the composition of the IL-rich phase, so that the necessary weight of $Al_2(SO_4)_3$ and aqueous solutions containing NSAIDs for the formation of a new ABS can be directly added. This information was obtained from the phase's compositions and TLs data given in detail in the

Supporting Information (Table S1 to S4). After the recovery step of NSAIDs, the IL aqueous solution was placed in a rotary evaporator at 70 ºC for the removal of excess water. The water content of the IL-rich phase was further determined by Karl-Fischer titration, using a Metrohm 831 Karl Fischer coulometer, with the Hydranal - Coulomat AG from Riedel-de Haën reagent. Then, the concentrated IL aqueous solution was recovered and different amounts of $Al_2(SO_4)_3$ and aqueous solutions of each NSAID were added to proceed with a new extraction step. The removal of NSAIDs and recycling of the IL-rich was repeated for 4 consecutive cycles.

## RESULTS AND DISCUSSION

**Removal of NSAIDs using IL-based ABS.** The compositions of each ABS used in the removal of NSAIDs from aqueous media ranged between (29.97 and 42.03) wt% for the IL, whereas a fixed composition (15 wt%) was selected for $Al_2(SO_4)_3$. These compositions were chosen in order to carry out the extraction studies at a fixed TLL (≈70), *i.e.* to maintain the difference between the compositions of the two phases, allowing therefore a better evaluation of the IL chemical structure influence. Furthermore, the use of a long TLL usually leads to an increase in the extraction efficiency[55] and to a lower cross-contamination by the constituent enriched in the opposite phase.[58] As described before, the liquid–liquid ternary phase diagrams used in this work were taken from the literature.[58] However, as stated in the experimental section, additional TLs (composition of each phase for a given mixture) were determined in this work for the mixtures compositions used in the extraction/removal studies of NSAIDs. The detailed initial mixture compositions and respective TLs used in the extraction studies of each NSAID are presented in Tables S1 to S4, in the Supporting Information. The values of the extraction efficiencies and pH of the

IL-rich phase, as well as the respective standard deviations, are also provided in the Supporting Information (Tables S1 to S4).

The pH values of the IL-rich phases of the ABS prepared ranged between 1.48 and 3.17 - a consequence of the $Al_2(SO_4)_3$ acidic nature in aqueous media. Therefore, in the studied ABS, the NSAIDs investigated are preferentially in a non-charged form (pKa values > 3.88),[62] meaning that electrostatic interactions do not play a major role in the investigated ABS extraction performance. The only exception occurs for diclofenac that is a sodium salt. However, no major differences in the diclofenac partition behavior are observed, as discussed below, confirming the negligible effect of electrostatic interactions. The respective dissociation curves and pKa values of each NSAID are shown in the Supporting Information (Figures S1 to S4).

Figure 3 depicts the extraction efficiencies (%*EE*) of the investigated ABS for NSAIDs (*cf.* Figures S5 to S8 in the Supporting Information for more details). In general, all studied ABS display a remarkable one-step performance to extract NSAIDs to the IL-rich phase from aqueous media, with %*EE* varying from 91% to 100%. NSAIDs are highly hydrophobic molecules (log$K_{ow}$ values ranging between 3.12[63] and 4.51[64] – Supporting Information, Table S5) and thus preferentially partition to the less hydrophilic and of lower ionic strength IL-rich phase. Also, the preferential partition of NSAIDs to the IL-phase is also a consequence of the strong salting-out effect of the salt used.[65]

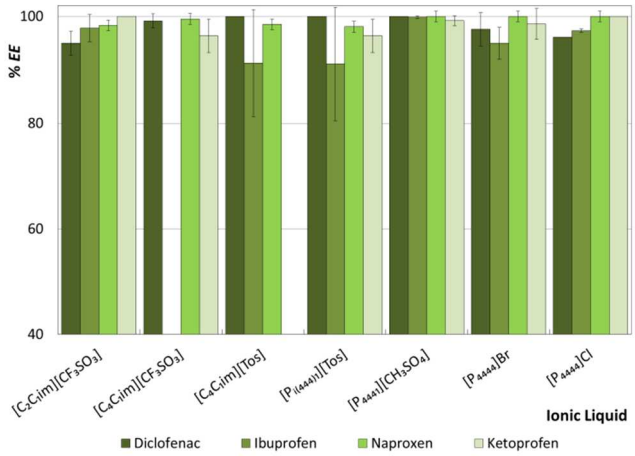



**Figure 3.** Extraction efficiencies (%*EE*) of ABS composed of IL + $Al_2(SO_4)_3$ + $H_2O$ (at 25 ºC) for non-steroidal anti-inflammatory drugs.

In general, the differences on the %*EE* are dependent on both the IL employed and NSAID used. An increase in the cation alkyl side chain length (from $[C_2C_1im][CF_3SO_3]$ to $[C_4C_1im][CF_3SO_3]$), leads to an increase in the %*EE* for diclofenac and naproxen, and to an opposite behavior for ketoprofen. Regarding the IL anion effect, the $[C_4C_1im][CF_3SO_3]$-based ABS leads to higher %*EE* for diclofenac than $[C_4C_1im][Tos]$-based ones, while the opposite trend is observed for naproxen. On the other hand, small differences are observed in the %*EE* of all NSAIDs with the $[P_{4444}]Br$- and $[P_{4444}]Cl$-based systems, with the exception of ketoprofen where the last ABS seems to be more promising.

Although imidazolium-based ILs are amongst the most investigated ILs for ABS creation and further use in extraction/purification processes,[45] it is here shown that phosphonium-based ILs display a higher ability to extract NSAIDs from aqueous media. It was already demonstrated that phosphonium-based ILs are more efficient to form ABS,[58, 66, 67] *i.e.*, require lower amounts of IL and salt to undergo phase separation, in agreement

with their higher hydrophobic nature. This phenomenon is independent of the salt used and aqueous media pH.[58, 66, 67] This higher hydrophobic nature of phosphonium-based salts mainly derives from the butyl chains at the quaternary cation, which seem to be favorable for the extraction of highly hydrophobic compounds, such as NSAIDs. Moreover, lower losses of IL for the salt-rich phase (cross-contamination) are observed when phosphonium-based ILs are used. For instance, for the mixtures under study, the amount of all phosphonium-based ILs in the $Al_2(SO_4)_3$-rich phase is *ca.* or below 1 wt% – Supporting Information with detailed TL data, Tables S1 to S4. Phosphonium-based ILs also are less toxic, thermally more stable, commercially produced in larger scales, and less expensive than imidazolium-based fluids,[68, 69] which can be seen as further advantages in large-scale operations.

The NSAIDs diclofenac, ibuprofen and naproxen are included in the top 10 persistent pollutants.[19] As mentioned before, several methods have already been tested for APIs removal, such as the addition of salts[36] and reverse osmosis,[39] and APIs degradation, such as ozonation[37] and chloride oxidation.[38] However, the low extraction efficiencies provided by these techniques as well as their high energy requirements clearly indicate that the development of a cost-efficient removal technique for NAIDs from aqueous media is a crucial requirement. In this work, and amongst all the ABS investigated, the $[P_{4441}][CH_3SO_4]$-based one led to %*EE* of 100% of all NSAIDs to the IL-rich phase at 25 ºC, achieved in a single-step, thus representing a promising alternative strategy for the treatment of aqueous environments. Taking into account these results and the advantages associated to phosphonium-based ILs discussed above, this IL was chosen for the next steps of NSAIDs recovery and IL regeneration and reuse.

**Recovery of NSAIDs and IL Recycling.** The solubility of all NSAIDs in the $[P_{4441}][CH_3SO_4]$-rich phase of the respective ABS was determined at 25 ºC for better understanding the high extraction ability of IL-based ABS and to design more sustainable NSAIDs removal techniques. Table 1 presents the solubility (saturation point) of each NSAID in the $[P_{4441}][CH_3SO_4]$-rich phase and in pure water for comparison purposes.

NSAIDs are highly hydrophobic compounds, and thus present a low solubility in pure water.[60] However, from the data shown in Table 1, it is clearly shown that the solubility of NSAIDs in the $[P_{4441}][CH_3SO_4]$-rich phase is significantly higher. The solubility of NSAIDs in the IL-rich phase increases from a 300- to a 4100-fold (≈4100-fold for diclofenac, ≈1100-fold for ibuprofen, ≈1400-fold for naproxen and ≈300-fold for ketoprofen) when compared with pure water. This increase in solubility closely follows the log$K_{ow}$ values of the investigated NSAIDs, meaning that the higher the hydrophobic nature of the drug (log$K_{ow}$ values shown in Table S5 in the Supporting Information), the higher is the increase in the solubility observed in the IL-rich phase. This remarkable increase in the solubility of NSAIDs in aqueous media is a consequence of the ILs hydrotropic ability recently proposed.[61] Cláudio et al.[61] reported a maximum in the solubility of antioxidants in aqueous solutions of imidazolium-based ILs of 40-fold. In this work, a significantly higher increase in the solubility of NSAIDs was observed further suggesting that phosphonium-based ILs are a skilled class of hydrotropes, and that ILs can act as excellent hydrotropes of highly hydrophobic substances.

**Table 1.** Solubility of NSAIDs in water[60] and in the $[P_{4441}][CH_3SO_4]$-rich phase at 25 ºC.

| | **Solubility of NSAIDs / mg.L$^{-1}$** |
|---|---|

| | Water[60] | $[P_{4441}][CH_3SO_4]$-rich phase |
|---|---|---|
| **Diclofenac** | 2.37 | 9720 ± 142 |
| **Ibuprofen** | 21.0 | 23024 ± 257 |
| **Naproxen** | 15.9 | 22594 ± 210 |
| **Ketoprofen** | 51.0 | 16780 ± 130 |

The boosted solvation ability of ILs for drugs (*e.g*. analgesic, non-steroidal anti-inflammatory drugs and antibiotics) has been studied by other authors,[70-72] where a significant dependence on both the IL and drug hydrophobicity-hydrophilicity character was observed. Nevertheless, in all of these studies, pure and non-water miscible ILs were investigated. Although out of the scope of this work, the remarkable ability shown here of phosphonium-based ILs to perform as hydrotopes leading to an exceptional increase on the solubility of highly hydrophobic drugs in aqueous media should be stressed. Aqueous solutions of water-soluble ILs can thus be seen as promising alternatives to increase the bioavailability of relevant pharmaceuticals.

The significantly high solubility values of NSAIDs in the IL-rich phase support the possibility of using the same system to recover large amounts of NSAIDs from aqueous media or to be used in continuous processes before reaching the system saturation. For instance, and amongst the studied NSAIDs, diclofenac presents the lowest solubility in the $[P_{4441}][CH_3SO_4]$-rich phase (9720 $mg.L^{-1}$). According to Pal et al.,[15] diclofenac is found in WWTP/STP effluents at a concentration *ca*. 0.0033 $mg.L^{-1}$. Thus, working at the composition studied in this work for the $[P_{4441}][CH_3SO_4]$-based ABS, ideally, it would be possible to treat 3319 L of water with 1 g of $[P_{4441}][CH_3SO_4]$, *i.e.*, up to the saturation of diclofenac in the IL-rich phase.

After the IL-rich phase saturation with each NSAID, the drugs recovery was carried out followed by the reuse of the IL, aiming at developing cost-efficient and more sustainable removal technologies. As clearly demonstrated in this work as well as in the literature,[45] the application of ILs as constituents of ABS leads to exceptional extraction performances compared to other traditional routes. Nevertheless, the ILs recovery and/or recycling lagged behind and still remain a challenging assignment. Due to the negligible volatility of ILs, the recovery of the compounds extracted and the ILs reutilization are still major obstacles towards the development of more sustainable IL-based techniques. Taking into account the ILs hydrotropic nature and the low solubility of NSAIDs in pure water, the recovery of NSAIDs was herein addressed by induced precipitation from the IL-rich phase through the addition of water (the greenest solvent overall) as an anti-solvent. Several volume ratios of the IL-rich-phase:water were investigated. Table 2 presents de percentage recovery of each NSAID (%Recovery) from the IL-rich phase by the addition of different amounts of water.

**Table 2.** Recovery of NSAIDs from the IL-rich phase (%Recovery) and respective standard deviation ($\sigma$) by adding different volumes of water as anti-solvent.

| | **Volume ratio of the IL-rich-phase:water** | | |
|---|---|---|---|
| | 1:1 | 1:3 | 1:5 |
| | **%(Recovery ± σ)** | | |
| **Diclofenac** | 53 ± 3 | 68 ± 6 | 69 ± 3 |
| **Ibuprofen** | 76 ± 2 | 80 ± 3 | 83 ± 3 |
| **Naproxen** | 79 ± 4 | 86 ± 5 | 91 ± 2 |
| **Ketoprofen** | 40 ± 3 | 46 ± 4 | 48 ± 3 |

As expected, an increase in the volume of water added (as anti-solvent) leads to an increase of the NSAIDs precipitation, although non-significant differences are seen between the 1:3 and 1:5 volume ratios. The NSAIDs recovery from the IL-rich phase by induced precipitation ranges between (40 and 91)%, obtained in a single-step. The NSAIDs recovery efficiency follows the order: naproxen > ibuprofen > diclofenac > ketoprofen. With the exception of the diclofenac sodium salt, the recovery of NSAIDs closely follows their hydrophobic nature, *i.e.,* the higher the log$K_{ow}$ value the higher the recovery of each NSAID by the addition of water (*cf.* Table S5 in the Supporting Information). It seems thus that the induced precipitation of a NSAID in a salt form is more difficult to achieve by the addition of water as anti-solvent – an expected trend since salts display a higher solubility in water than their non-charged forms.

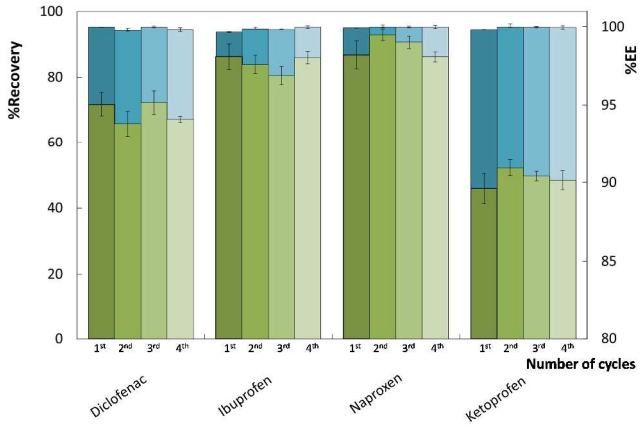



**Figure 4.** Recovery of non-steroidal anti-inflammatory drugs (%Recovery) from the IL-rich phase (green bars) and extraction efficiencies of non-steroidal anti-inflammatory drugs (%*EE*) (blue bars), in four consecutive cycles.

Based on the possibility of saturating the IL-rich phase and its further "cleaning", the IL-rich phase was recovered and reused in the formation of new ABS to explore their

viability as continuous removal platforms for NSAIDs. At least in four sequential cycles, a decrease on the ABS ability to extract NSAIDs from aqueous media was not observed nor a decrease on the NSAIDs recovery by induced precipitation from the IL-rich phase – Figure 4 (detailed data in Table S6 in the Supporting Information). The %*EE* of the ABS is maintained at 100%, in a single-step, along the four cycles. Thus, the $[P_{4441}][CH_3SO_4]$-based system does not lose its ability to completely remove NSAIDs from aqueous media after recovery and reuse. In the 4 cycles, more than 94 wt% of the IL was recovered and reused. This remarkable recovery of the IL is a main result of the strong salting-out ability of the salt used, $Al_2(SO_4)_3$, as previously discussed, with the additional advantage of being currently used in the treatment of drinking water.[73] Furthermore, the NSAIDs recovery efficiencies in the four cycles are similar to those previously presented (Table 2). Table S6 in the Supporting Information presents the detailed results in the four sequential cycles.

In summary, the use of ABS composed of $[P_{4441}][CH_3SO_4]$ + $Al_2(SO_4)_3$ allows the complete removal of NSAIDs from aqueous media in a single-step, the further cleaning of the IL-rich phase and NSAIDs recovery by the addition of water as anti-solvent, and further IL reuse in the creation of new ABS. Figure 5 depicts the developed integrated process for NSAIDs removal from aqueous media, followed by the combined steps of NSAIDs removal and IL-rich phase recycling, thus ensuring the sustainability of the proposed process.

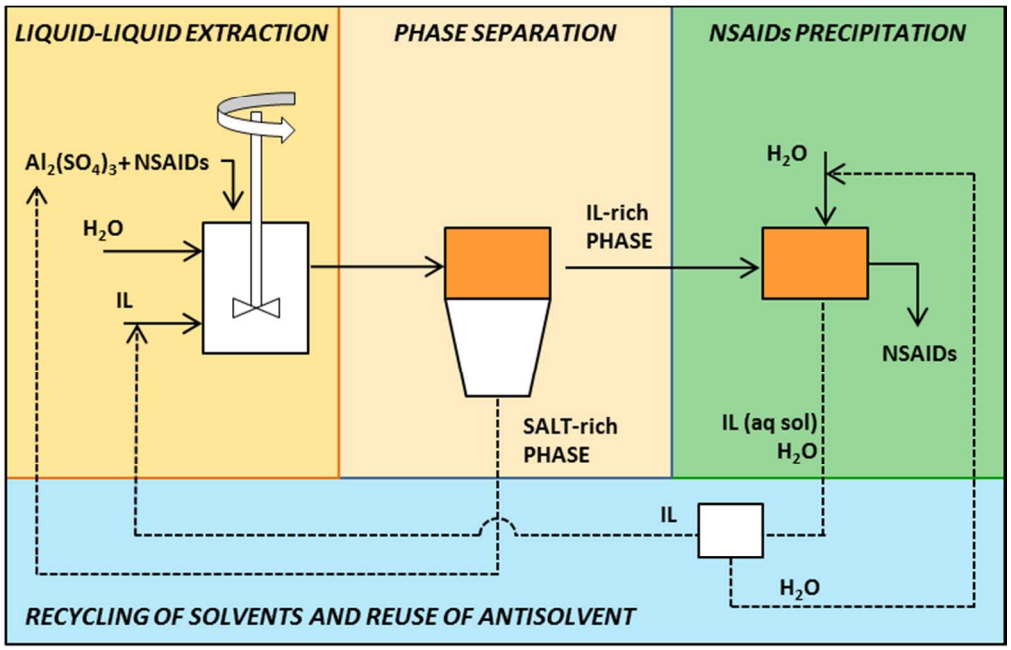



**Figure 5.** Representative scheme of the overall process for NSAIDs removal, comprising the NSAIDs recovery and IL recycling (bold lines and dashed lines represent the direct and indirect inputs, respectively).

## CONCLUSIONS

A novel method to remove NSAIDs, such as diclofenac, ibuprofen, naproxen and ketoprofen, from aqueous media was here proposed. ABS composed of $Al_2(SO_4)_3$ and ILs allow extraction efficiencies of NSAIDs up to 100% to be obtained in a single-step. Amongst the ILs investigated, phosphonium-based fluids display the best performance.

In addition to the high ability of IL-based ABS to extract an extensive number of compounds, the IL recycling and reuse remains an incomplete task within the scientific community dealing with these systems. Nevertheless, this step is crucial towards the development of greener and more sustainable and cost-effective IL-based processes. To overcome this main lacuna, an integrated process was proposed here and comprises: (i) the

NSAIDs removal from the aqueous media; (ii) the NSAIDs recovery from the IL-rich phase by induced precipitation; and (iii) the IL recovery and reuse. Based on the high hydrophobic nature of NSAIDs, a proper choice of an anti-solvent, namely water which stands amongst the greener solvents, was used in order to precipitate NSAIDs and to "clean" the IL-rich phase, in which recovery percentages of NSAIDs up to 91% were obtained in a single-step. The IL was then recovered (more than 94 wt%) and reused in 4 consecutive cycles, contributing to the sustainability of the proposed process and with no losses on the ABS extraction performance.

The proposed integrated process represents an improvement towards the use of IL-based ABS comprising the recyclability of the system and contributing to a circular economy, while demonstrating the relevant potential of these systems to remove pharmaceutical drugs from aqueous media and by unlocking new doors to the treatment of aqueous streams/effluents.

**Supporting Information**. Initial composition and weight fraction percentages (wt%) of ionic liquid ([IL]) + aluminium sulfate ([salt]) + water at the coexisting phases of each ABS; extraction efficiencies for the diclofenac sodium salt, ibuprofen, naproxen and ketoprofen; pH values of the IL-rich phases; and speciation curves and log$K_{ow}$ values of all NSAIDs.

AUTHOR INFORMATION

**Corresponding Author**

*E-mail address: maragfreire@ua.pt; Tel: +351-234-401422; Fax: +351-234-370084;

## Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## ACKNOWLEDGMENT

This work was developed in the scope of the project CICECO-Aveiro Institute of Materials (Ref. FCT UID/CTM/50011/2013), financed by national funds through the FCT/MEC and co-financed by FEDER under the PT2020 Partnership Agreement. Hugo F. D. Almeida and Isabel M. Marrucho acknowledge FCT for doctoral grant SFRH/BD/88369/2012 and the 2012 FCT Investigator Program, respectively.

## REFERENCES


1. Daughton, C. G. and Ternes, T. A. Pharmaceuticals and personal care products in the environment: agents of subtle change? *Environ. Health Perspect.*, **1999**, *107*, 907-938.
2. United Nations Environmental program (UNEP) classification at http://www.unep.org/ (Accessed on January 2017).
3. Boyd, G. R. and Grimm, D. A. Occurrence of Pharmaceutical Contaminants and Screening of Treatment Alternatives for Southeastern Louisiana. *Ann. N. Y. Acad. Sci.*, **2001**, *948*, 80-89.
4. Drewes, J. E., Heberer, T., Rauch, T. and Reddersen, K. Fate of Pharmaceuticals During Ground Water Recharge. *Ground Water Monit. R.*, **2003**, *23*, 64-72.
5. Odendaal, C., Seaman, M. T., Kemp, G., Patterton, H. E. and Patterton, H.-G. An LC-MS/MS based survey of contaminants of emerging concern in drinking water in South Africa. *S. Afr. J. Sci.*, **2015**, *111*, 160-165.
6. Fischer, K., Fries, E., Körner, W., Schmalz, C. and Zwiener, C. New developments in the trace analysis of organic water pollutants. *Appl. Microbiol. Biotechnol.*, **2012**, *94*, 11-28.
7. Zhang, Y., Habteselassie, M. Y., Resurreccion, E. P., Mantripragada, V., Peng, S., Bauer, S. and Colosi, L. M. Evaluating Removal of Steroid Estrogens by a Model Alga as a Possible Sustainability Benefit of Hypothetical Integrated Algae Cultivation and Wastewater Treatment Systems. *ACS Sustain. Chem. Eng.*, **2014**, *2*, 2544-2553.

8. Halling-Sørensen, B., Nors Nielsen, S., Lanzky, P. F., Ingerslev, F., Holten Lützhøft, H. C. and Jørgensen, S. E. Occurrence, fate and effects of pharmaceutical substances in the environment- A review. *Chemosphere*, **1998**, *36*, 357-393.

9. Salgado, R., Noronha, J. P., Oehmen, A., Carvalho, G. and Reis, M. A. M. Analysis of 65 pharmaceuticals and personal care products in 5 wastewater treatment plants in Portugal using a simplified analytical methodology. *Water Sci. Technol.*, **2010**, *62*, 2862-2871.

10. Maja, D., Alg-Göran, D. and Elzbieta, P. Low concentrations of high priority' : Pharmaceutical and personal care products (PPCPs); Occurrence and removal at wastewater treatment plants. *Vatten*, **2006**, *62*, 139-148.

11. Lindberg, R. H., Östman, M., Olofsson, U., Grabic, R. and Fick, J. Occurrence and behaviour of 105 active pharmaceutical ingredients in sewage waters of a municipal sewer collection system. *Water Res.*, **2014**, *58*, 221-229.

12. Murray, K. E., Thomas, S. M. and Bodour, A. A. Prioritizing research for trace pollutants and emerging contaminants in the freshwater environment. *Environmental Polluti.*, **2010**, *158*, 3462-3471.

13. Kasprzyk-Hordern, B., Dinsdale, R. M. and Guwy, A. J. The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. *Water Res.*, **2009**, *43*, 363-380.

14. Okuda, T., Kobayashi, Y., Nagao, R., Yamashita, N., Tanaka, H., Tanaka, S., Fujii, S., Konishi, C. and Houwa, I. Removal efficiency of 66 pharmaceuticals during wastewater treatment process in Japan. *Water Sci. Technol.*, **2008**, *57*, 65-71.

15. Pal, A., Gin, K. Y.-H., Lin, A. Y.-C. and Reinhard, M. Impacts of emerging organic contaminants on freshwater resources: Review of recent occurrences, sources, fate and effects. *Sci. Total Environ.*, **2010**, *408*, 6062-6069.

16. Chan, A., Salsali, H. and McBean, E. Heavy Metal Removal (Copper and Zinc) in Secondary Effluent from Wastewater Treatment Plants by Microalgae. *ACS Sustain. Chem. Eng.*, **2014**, *2*, 130-137.

17. Wilkinson, J. L., Hooda, P. S., Barker, J., Barton, S. and Swinden, J. Ecotoxic pharmaceuticals, personal care products, and other emerging contaminants: A review of environmental, receptor-mediated, developmental, and epigenetic toxicity with discussion of proposed toxicity to humans. *Crit. Rev. Env. Sci. Tec.*, **2016**, *46*, 336-381.

18. aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A. and Küster, A. Pharmaceuticals in the environment—Global occurrences and perspectives. *Environ. Toxicol. Chem.*, **2016**, *35*, 823-835.

19. de Voogt, P., Janex-Habibi, M.-L., Sacher, F., Puijker, L. and Mons, M. Development of a common priority list of pharmaceuticals relevant for the water cycle. *Water Sci. Technol.*, **2009**, *59*, 39-46.

20. Rahman, M. F., Yanful, E. K. and Jasim, S. Y. Endocrine disrupting compounds (EDCs) and pharmaceuticals and personal care products (PPCPs) in the aquatic environment: implications for the drinking water industry and global environmental health. *J. Water Health*, **2009**, *7*, 224-243.

21. Castiglioni, S., Bagnati, R., Fanelli, R., Pomati, F., Calamari, D. and Zuccato, E. Removal of Pharmaceuticals in Sewage Treatment Plants in Italy. *Environ. Sci. Technol.*, **2005**, *40*, 357-363.

22. Almeida, B., Oehmen, A., Marques, R., Brito, D., Carvalho, G. and Barreto Crespo, M. T. Modelling the biodegradation of non-steroidal anti-inflammatory drugs (NSAIDs) by activated sludge and a pure culture. *Bioresource Technol.*, **2013**, *133*, 31-37.

23. Tran, N. H., Urase, T. and Ta, T. T. A Preliminary Study on the Occurrence of Pharmaceutically Active Compounds in Hospital Wastewater and Surface Water in Hanoi, Vietnam. *CLEAN – Soil, Air, Water*, **2014**, *42*, 267-275.

24. Kosma, C. I., Lambropoulou, D. A. and Albanis, T. A. Investigation of PPCPs in wastewater treatment plants in Greece: Occurrence, removal and environmental risk assessment. *Sci. Total Environ.*, **2014**, *466–467*, 421-438.

25. Yargeau, V., Lopata, A. and Metcalfe, C. Pharmaceuticals in the Yamaska River, Quebec, Canada. *Water Qual. Res. J. Can.*, **2007**, *42*, 231-239.

26. Ortiz de García, S., Pinto Pinto, G., García Encina, P. and Irusta Mata, R. Consumption and occurrence of pharmaceutical and personal care products in the aquatic environment in Spain. *Sci. Total Environ.*, **2013**, *444*, 451-465.

27. Santos, J. L., Aparicio, I., Callejón, M. and Alonso, E. Occurrence of pharmaceutically active compounds during 1-year period in wastewaters from four wastewater treatment plants in Seville (Spain). *J. Hazard. Mater.*, **2009**, *164*, 1509-1516.

28. Rosal, R., Rodríguez, A., Perdigón-Melón, J. A., Petre, A., García-Calvo, E., Gómez, M. J., Agüera, A. and Fernández-Alba, A. R. Occurrence of emerging pollutants in urban wastewater and their removal through biological treatment followed by ozonation. *Water Res.*, **2010**, *44*, 578-588.

29. Heberer, T. Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. *Toxicol. Lett.*, **2002**, *131*, 5-17.

30. Vieno, N. and Sillanpää, M. Fate of diclofenac in municipal wastewater treatment plant - A review. *Environ. Int.*, **2014**, *69*, 28-39.

31. Dias-Ferreira, C., Valente, S. and Vaz, J. Practices of pharmaceutical waste generation and discarding in households across Portugal. *Waste Manag. Res.*, **2016**, *34*, 1006-1013.

32. GWRC Pharmaceuticals and personal care products in the water cycle. An international review. London, UK., **2004**.

33. Jones, O. A. H., Voulvoulis, N. and Lester, J. N. Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. *Water Res.*, **2002**, *36*, 5013-5022.

34. Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D. and Snyder, S. A. Pharmaceuticals and Endocrine Disrupting Compounds in U.S. Drinking Water. *Environ. Sci. Technol.*, **2009**, *43*, 597-603.

35. Zhou, J. L., Zhang, Z. L., Banks, E., Grover, D. and Jiang, J. Q. Pharmaceutical residues in wastewater treatment works effluents and their impact on receiving river water. *J. Hazard. Mater.*, **2009**, *166*, 655-661.

36. Suarez, S., Lema, J. M. and Omil, F. Pre-treatment of hospital wastewater by coagulation–flocculation and flotation. *Bioresource Technol.*, **2009**, *100*, 2138-2146.

37. Ternes, T. A., Stüber, J., Herrmann, N., McDowell, D., Ried, A., Kampmann, M. and Teiser, B. Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? *Water Res.*, **2003**, *37*, 1976-1982.

38. Westerhoff, P., Yoon, Y., Snyder, S. and Wert, E. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. *Environ. Sci. Technol.*, **2005**, *39*, 6649-6663.

39. Khan, S., Wintgens, T., Sherman, P., Zaricky, J. and Schafer, A. Removal of hormones and pharmaceuticals in the advanced water recycling demonstration plant in Queensland, Australia. *Water Sci. Technol.*, **2004**, *50*, 15-22.

40. Albertsson, P. A. Partition of Cell Particles and Macromolecules. 3rd ed., Wiley, New York, **1986**.

41. Zaslavsky, B. Y. Aqueous Two-Phase Partitioning. Marcel Dekker, Inc., New York, **1994**.

42. Pereira, J. F. B., Ventura, S. P. M., e Silva, F. A., Shahriari, S., Freire, M. G. and Coutinho, J. A. P. Aqueous biphasic systems composed of ionic liquids and polymers: A platform for the purification of biomolecules. *Sep. Purif. Technol.*, **2013**, *113*, 83-89.

43. Li, F.-W., Xu, L.-W. and Xia, C.-G. Polymer-supported palladium–nickel bimetallic hydroxycarbonylation of styrene under aqueous–organic two-phase system. *Appl. Catal. A*, **2003**, *253*, 509-514.

44. Gutowski, K. E., Broker, G. A., Willauer, H. D., Huddleston, J. G., Swatloski, R. P., Holbrey, J. D. and Rogers, R. D. Controlling the Aqueous Miscibility of Ionic Liquids: Aqueous Biphasic Systems of Water-Miscible Ionic Liquids and Water-Structuring Salts for Recycle, Metathesis, and Separations. *J. Am. Chem. Soc.*, **2003**, *125*, 6632-6633.

45. Freire, M. G., Claudio, A. F. M., Araujo, J. M. M., Coutinho, J. A. P., Marrucho, I. M., Lopes, J. N. C. and Rebelo, L. P. N. Aqueous biphasic systems: a boost brought about by using ionic liquids. *Chem. Soc. Rev.*, **2012**, 4966-4995.

46. Welton, T. Room-Temperature Ionic Liquids. Solvents for Synthesis and Catalysis. *Chem. Rev.*, **1999**, *99*, 2071-2084.

47. Gaune-Escard, M. and Seddon, K. R. Molten Salts and Ionic Liquids: Never the Twain? John Wiley: Hoboken, N.J., **2010**.

48. Rogers, R. D. and Seddon, K. R. Ionic Liquids - Solvents of the Future? *Science*, **2003**, *302*, 792-793.

49. Conceicao, L. J. A., Bogel-Lukasik, E. and Bogel-Lukasik, R. A new outlook on solubility of carbohydrates and sugar alcohols in ionic liquids. *RSC Adv.*, **2012**, *2*, 1846-1855.

50. Pereira, J. F. B., Lima, A. S., Freire, M. G. and Coutinho, J. A. P. Ionic liquids as adjuvants for the tailored extraction of biomolecules in aqueous biphasic systems. *Green Chem.*, **2010**, *12*, 1661-1669.

51. Domínguez-Pérez, M., Tomé, L. I. N., Freire, M. G., Marrucho, I. M., Cabeza, O. and Coutinho, J. A. P. (Extraction of biomolecules using) aqueous biphasic systems formed by ionic liquids and aminoacids. *Sep. Purif. Technol.*, **2010**, *72*, 85-91.

52. Han, J., Wang, Y., Kang, W., Li, C., Yan, Y., Pan, J. and Xie, X. Phase equilibrium and macrolide antibiotics partitioning in real water samples using a two-phase system composed of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate and an aqueous solution of an inorganic salt. *Microchim. Acta*, **2010**, *169*, 15-22.

53. Han, J., Wang, Y., Yu, C.-l., Yan, Y.-s. and Xie, X.-q. Extraction and determination of chloramphenicol in feed water, milk, and honey samples using an ionic

liquid/sodium citrate aqueous two-phase system coupled with high-performance liquid chromatography. *Anal. Bioanal. Chem.*, **2011**, *399*, 1295-1304.

54. Jiang, Y., Xia, H., Yu, J., Guo, C. and Liu, H. Hydrophobic ionic liquids-assisted polymer recovery during penicillin extraction in aqueous two-phase system. *Chem. Eng. J.*, **2009**, *147*, 22-26.

55. e Silva, F. A., Sintra, T., Ventura, S. P. M. and Coutinho, J. A. P. Recovery of paracetamol from pharmaceutical wastes. *Sep. Purif. Technol.*, **2014**, *122*, 315-322.

56. e Silva, F. A., Caban, M., Stepnowski, P., Coutinho, J. A. P. and Ventura, S. P. M. Recovery of ibuprofen from pharmaceutical wastes using ionic liquids. *Green Chem.*, **2016**, *18*, 3749-3757.

57. Khopkar, S. M., Environmental Pollution Monitoring and Control, New Age International Ltd. , **2004**.

58. Neves, C. M. S. S., Freire, M. G. and Coutinho, J. A. P. Improved recovery of ionic liquids from contaminated aqueous streams using aluminium-based salts. *RSC Adv.*, **2012**, *2*, 10882-10890.

59. Merchuk, J. C., Andrews, B. A. and Asenjo, J. A. Aqueous two-phase systems for protein separation: Studies on phase inversion. *J. Chromatogr. B Biomed. Sci. Appl.*, **1998**, *711*, 285-293.

60. Drug Bank - Open Data Drug & Drug Target Database at http://www.drugbank.ca (Accessed on October 2016).

61. Claudio, A. F. M., Neves, M. C., Shimizu, K., Canongia Lopes, J. N., Freire, M. G. and Coutinho, J. A. P. The magic of aqueous solutions of ionic liquids: ionic liquids as a powerful class of catanionic hydrotropes. *Green Chem.*, **2015**, *17*, 3948-3963.

62. ChemSpider - The free chemical database at www.chemspider.com (Accessed on October 2016).

63. Sangster, J. log$K_{ow}$ - a databank of evaluated octanol-water partition coefficients Sangster Research Laboratories, Montreal, **1993**.

64. Avdeef, A., Box, K. J., Comer, J. E. A., Hibbert, C. and Tam, K. Y. pH-Metric logP 10. Determination of Liposomal Membrane-Water Partition Coefficients of Ionizable Drugs. *Pharm. Res.*, **1998**, *15*, 209-215.

65. Shahriari, S., Neves, C. M. S. S., Freire, M. G. and Coutinho, J. A. P. Role of the Hofmeister Series in the Formation of Ionic-Liquid-Based Aqueous Biphasic Systems. *J. Phys. Chem. B*, **2012**, *116*, 7252-7258.

66. Bridges, N. J., Gutowski, K. E. and Rogers, R. D. Investigation of aqueous biphasic systems formed from solutions of chaotropic salts with kosmotropic salts (salt-salt ABS). *Green Chem.*, **2007**, *9*, 177-183.

67. Louros, C. L. S., Cláudio, A. F. M., Neves, C. M. S. S., Freire, M. G., Marrucho, I. M., Pauly, J. and Coutinho, J. A. P. Extraction of Biomolecules Using Phosphonium-Based Ionic Liquids + $K_3PO_4$ Aqueous Biphasic Systems. *Int. J. Mol. Sci.*, **2010**, *11*, 1777-1797.

68. Atefi, F., Garcia, M. T., Singer, R. D. and Scammells, P. J. Phosphonium ionic liquids: design, synthesis and evaluation of biodegradability. *Green Chem.*, **2009**, *11*, 1595-1604.

69. Bradaric, C. J., Downard, A., Kennedy, C., Robertson, A. J. and Zhou, Y. Industrial preparation of phosphonium ionic liquids. *Green Chem.*, **2003**, *5*, 143-152.

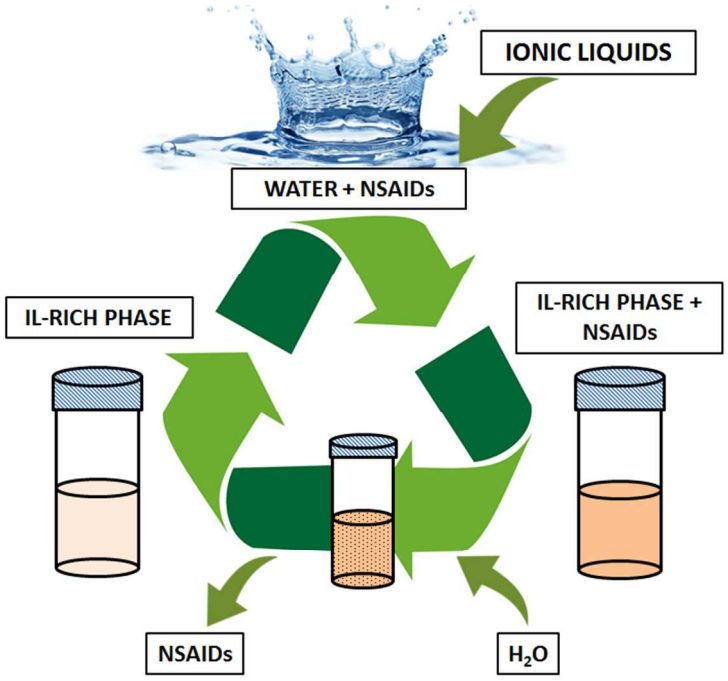
70. Smith, K. B., Bridson, R. H. and Leeke, G. A. Solubilities of Pharmaceutical Compounds in Ionic Liquids. *J. Chem. Eng. Data*, **2011**, *56*, 2039-2043.

71. Faria, R. A. and Bogel-Łukasik, E. Solubilities of pharmaceutical and bioactive compounds in trihexyl(tetradecyl)phosphonium chloride ionic liquid. *Fluid Phase Equilibr.*, **2015**, *397*, 18-25.

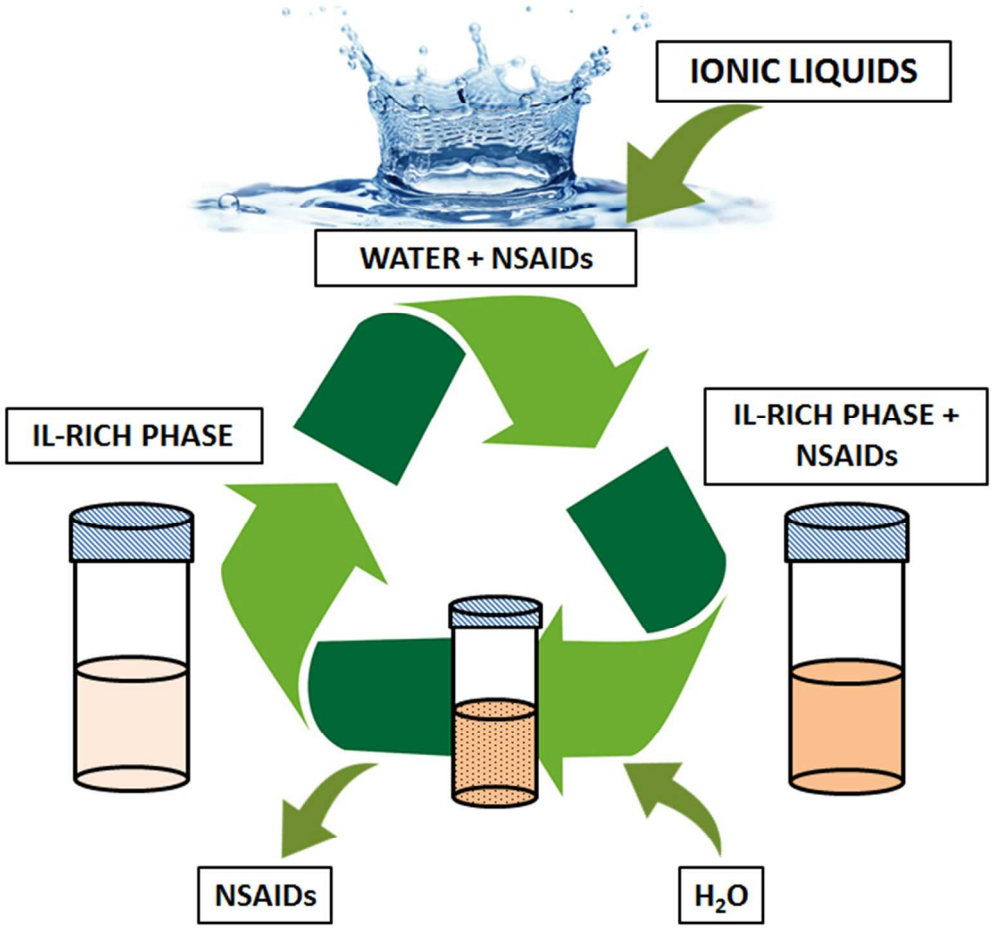
72. Forte, A., Melo, C. I., Bogel-Łukasik, R. and Bogel-Łukasik, E. A favourable solubility of isoniazid, an antitubercular antibiotic drug, in alternative solvents. *Fluid Phase Equilibr.*, **2012**, *318*, 89-95.

73. Wilms, D. A. and Van Haute, A. A., Primary Flocculation of Wastewater With $Al_2(SO_4)_3$ and $NaAlO_2$ Salts Recuperated from Spent Aluminium Anodising Baths, Elsevier, **1984**, *23*, 213-220.

## Table of Contents Graphic and Synopsis




Recyclable ionic-liquid-based aqueous biphasic systems allow the one-step removal of persistent pollutants from aqueous environments.




Reusable ionic-liquid-based aqueous biphasic systems allow the one-step removal of persistent pollutants from aqueous environments

250x236mm (72 x 72 DPI)