

Article

Recovery of non-steroidal anti-inflammatory drugs from wastes using ionic liquid-based three-phase partitioning systems

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ACS Sustainable Chem. Eng., **Just Accepted Manuscript** • DOI: 10.1021/acssuschemeng.7b03216 • Publication Date (Web): 13 Feb 2018Downloaded from <http://pubs.acs.org> on February 15, 2018**Just Accepted**

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ABSTRACT

Aiming at outlining new strategies for the valorization of solid pharmaceutical wastes as viable alternatives to incineration, this work proposes the use of ionic liquids-based three phase partitioning (IL-based TPP) systems. Ibuprofen, naproxen and ketoprofen, all belonging to the class of non-steroidal anti-inflammatory drugs (NSAIDs), were adopted as model compounds. An integrated process has been conceptualized based on three steps: 1 - extraction and purification of NSAIDs using the IL-based TPP systems; 2 - drug isolation by precipitation with antisolvents; 3 - recycle and reuse of the solvents. With the optimization of steps 1 and 2 as objects of this investigation, aqueous biphasic systems (ABS) composed of three distinct ILs (tetrabutylammonium chloride, 1-butyl-3-methylimidazolium chloride and benzyldimethyl(2-hydroxyethyl)ammonium chloride) and potassium citrate buffer were studied. The corresponding IL-based TPP systems were further applied in the purification of each NSAID, and different antisolvents (citric acid aqueous solutions for ibuprofen and naproxen and aluminium sulphate aqueous solutions for ketoprofen) were evaluated as precipitating agents to isolate each drug. The success of the process developed is demonstrated by the extraction efficiencies higher than $83.8 \pm 7.7 \%$ attained in step 1 and isolation efficiencies higher than $76.2 \pm 1.8 \%$ in step 2. The stability of the three NSAIDs in IL-based aqueous matrices was additionally checked by using a protocol adapted from the OECD guidelines. The economic efficiency and environmental benignity of the process herein developed is underlined, based not only on the low cost of the solvents chosen, but also on the possibility of recycling and reusing the phase-forming components and anti-solvents employed.

KEYWORDS

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3 Ionic Liquid, Three-phase partitioning system, Pharmaceutical wastes, Recovery, Non-steroidal
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5 anti-inflammatory drugs
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10 INTRODUCTION

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13 The huge amount of pharmaceutical wastes produced and their impact upon environment and
14 human health accompany the increasing consumption of medicines worldwide.¹ The current
15 disposal of outdated or unwanted medicines comprises incineration or land disposal,^{2, 3} which
16 fail to fulfill the entire set of guidelines imposed by the Green Chemistry principles.⁴ Actually,
17 not only the high environmental footprint and costs of these processes contribute for their low
18 sustainability,² but also the complete destruction of their main active ingredients of commercial
19 interest. If only 10% of the active ingredient of an expired drug is no longer active according to
20 the regulatory bodies,⁵ the remaining 90% are currently being lost by incineration or land
21 disposal. Considering the lack of strategies of enhanced economic profitability,^{6, 7}
22 pharmaceutical wastes are still treated as hazardous substances and, thus, poorly valorised.
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37 Under this scenario, and during the last years, pharmaceutical wastes are being increasingly
38 foreseen as valuable pharmaceutically active ingredient sources. Actually, these active
39 ingredients recovered could be used in a wide range of applications in the chemical industry,
40 namely as starting materials for other chemicals or as industrial or commercial standards, to
41 mention a few. Since our first work, where the recovery of paracetamol from wastes using
42 ammonium halide-based aqueous biphasic systems (ABS) was successfully achieved,⁸ other
43 approaches followed. The design of an integrated process based on ABS composed of ionic
44 liquids (ILs) regarding the recovery and isolation of the antidepressant amitriptyline
45 hydrochloride was established.⁹ Then, a simpler approach for the purification of ibuprofen was
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3 proposed by playing with the enhanced solvency power of ILs and the hydrotropic action of the
4 citrate-based salt in a solid-liquid extraction.¹⁰ In fact, a considerable spectrum of drugs
5 (analgesic, anti-inflammatory and antidepressant) possessing different properties (isoelectric
6 points and water solubility) was already studied. Integrated processes comprising the efficient
7 purification and isolation of the active ingredients by the adequate selection of the best solvents
8 and polishing agents were optimized and the balance of the molecular-level interactions leading
9 to boosted performances was disclosed. Assuming the specificity of each pharmaceutical
10 compound and the plethora of active ingredients with commercial interest that can be recovered
11 from wastes, ILs in aqueous media allowed us to finely tune the extraction processes.⁸⁻¹⁰

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25 The ILs unique properties¹¹⁻¹³ along with their high degree of structural tunability¹⁴ and the
26 countless options of chemicals (salts, polymers, surfactants, amino-acids and carbohydrates)
27 which can be combined with them to form ABS,¹⁵ called the attention towards these systems.
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29 Moreover, ABS provide simple implementation, easy scalability and enhanced
30 biocompatibility.¹⁶ Progresses on the understanding of IL-based ABS formation have been
31 achieved and insights into their specific design have been disclosed, as recently reviewed.^{15, 17, 18}
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33 On the search for more sustainable IL-based ABS,¹⁹ the application of ILs of natural origin (*e.g.*
34 cholinium-based cations with amino-acids or carboxylic acids as the anion^{20, 21}) over those of
35 aromatic nature and organic salts (citrate-based, *e.g.* ²²) instead of inorganic ones was envisaged.
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37 Applying more benign ABS made of cholinium-based ILs and either salts, polymers or
38 surfactants, new ways for recovering purer antibiotics and anti-inflammatory drugs from their
39 raw matrices have been proposed.²³⁻²⁵ Despite the IL-based ABS advantages, the
40 purification/polishing of the target compounds and IL recycling routes are seldom studied.¹⁵
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3 The highly aqueous-rich environment of IL-based ABS along with the interfacial partition of
4 targeted compounds in three phase partitioning (TPP) systems has originated a novel separation
5 platform, the IL-based TPP systems.²⁶ While conventional TPP resorts to organic solvents,²⁷ the
6 introduction of ABS improve the process biocompatibility. Moreover, IL-based TPP are able to
7 keep all the ABS advantages with an extra degree of operational simplicity linked to the
8 purification stage, where the formation of an interface enriched in target compounds or
9 contaminants in a purer state occurs.²⁶ IL-based TPP has been successfully applied in the one-
10 step purification of several biomolecules, particularly proteins and amino-acids, showing some
11 advantages when compared with the common ABS and IL-ABS.^{26, 28-30} In a series of works
12 devoted to IL-based TPP systems, Alvarez-Guerra and collaborators^{26, 28, 29} recovered up to 99%
13 of lactoferrin from waste streams and defined some efficient ways of recycling and reusing the
14 IL. Chiral IL-based TPP systems find also application in enantiomeric separations. As shown by
15 Wu et al.,³⁰ under optimized conditions, it was possible to tune the partition of the two
16 enantiomeric forms of phenylalanine. The L-enantiomer precipitates in the interface, while the
17 D-enantiomer partitions to the IL-rich phase.

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39 This work aims at the optimization and implementation of a new process for the purification of
40 non-steroidal anti-inflammatory drugs (NSAIDs) from wastes taking into account the IL-based
41 ABS characteristics, but instead using IL-based TPP systems. The spectrum of active ingredients
42 (ibuprofen, naproxen and ketoprofen, used as model NSAIDs) and of technologies available is
43 here extended. ABS composed of three different ILs conjugated with the potassium citrate buffer
44 were used to perform the partition studies of the model NSAIDs. Beyond the investigation of the
45 IL's impact on the ABS extraction performance, other operational conditions were studied [*viz.*
46 NSAID content, temperature, pH and tie-line length (TLL)]. Meanwhile and using the
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3 characteristics of the systems under study, the development of IL-based TPP systems was
4 investigated. Thus, to recover ibuprofen, naproxen and ketoprofen directly from their waste-
5 based matrices in a single-step (where the excipients are eliminated at the liquid-liquid interface),
6 the IL-TPP systems were optimized. At the end, these IL-based TPP were integrated in a process,
7 where the isolation (*i.e.* polishing) of the three drugs is contemplated. The stability of the three
8 NSAIDs in ILs or ILs + salts aqueous solutions was also assessed through the implementation of
9 a new protocol adapted from OECD guidelines. Thus, this work allowed the development and
10 optimization of an alternative and efficient process for the recovery of drugs from
11 pharmaceutical wastes, transversal to other active ingredients and more complex waste
12 mixtures/solutions. Moreover, the process allowed inferring on the suitability of the IL-TPP
13 technology, not solely centered on its performance but also addressing the target molecule
14 integrity.

EXPERIMENTAL SECTION

Materials. NSAIDs standards for ketoprofen (CAS number 22071-15-4) (≥ 98 %; Sigma-Aldrich, China), naproxen (CAS number 22204-53-1) (≥ 97 %; Sigma-Aldrich, USA) and ibuprofen (CAS number 15687-27-1) (≥ 98 %; Sigma-Aldrich, China) were purchased from Sigma-Aldrich. The corresponding pills were acquired in a local pharmacy (Aveiro, Portugal), being their specifications (*viz.* NSAIDs' content and the excipients' profile) shown in Table S1 from Supporting Information. The ILs tested were tetrabutylammonium chloride [N₄₄₄₄]Cl (97 %, Sigma-Aldrich), 1-butyl-3-methylimidazolium chloride, [C₄mim]Cl (99 %, IoLiTec, Ionic Liquids Technology) and the benzyldimethyl(2-hydroxyethyl)ammonium chloride [BzCh]Cl (97 %, Fluka). Depicted in Figure 1 are the NSAIDs and ILs chemical structures along with the abbreviations adopted. Citric acid monohydrate C₆H₈O₇•H₂O (100 %) was from Fisher-Scientific, potassium citrate tribasic monohydrate C₆H₅K₃O₇•H₂O (99 %) was supplied by Acros Organics and aluminium sulphate hexadecahydrate Al₂(SO₄)₃•16H₂O (≥ 95 %) was purchased at Sigma-Aldrich.

For the HPLC-DAD mobile phase, ammonium acetate NH₄C₂H₃O₂ ($\geq 99.99\%$; Sigma-Aldrich, Japan), acetic acid (≥ 99.99 %; Sigma-Aldrich, USA), acetonitrile (HPLC gradient grade; HiPerSolv CHROMANORM) and ultrapure water (treated with a Mili-Q 185 water apparatus) were used. Syringe filters (0.45 μ m of pore size; Specanalitica, Portugal) and membrane filters (0.22 μ m; Sartorius Stedim Biotech, Germany) were applied in the filtration steps.

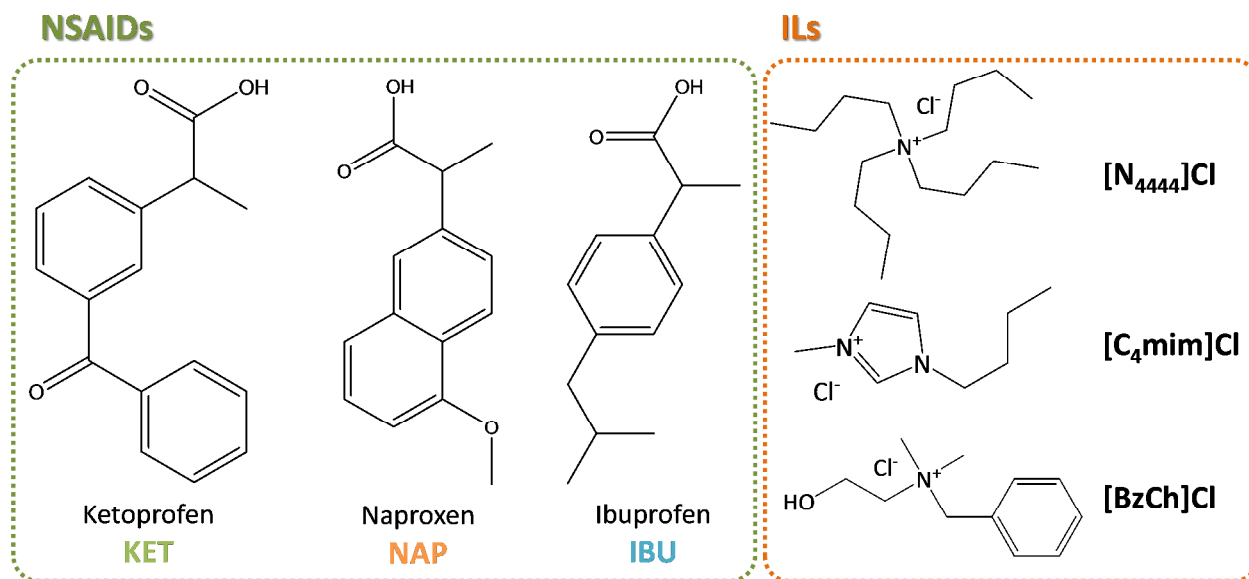


Figure 1. Chemical structures and abbreviations of the studied NSAIDs and ILs.

NSAIDs partitioning optimization studies using IL-based ABS. ABS composed of ILs with potassium citrate buffer were evaluated in what regards their ability to extract NSAIDs from pharmaceutical wastes. The corresponding ternary phase diagrams can be found in literature,^{8, 31, 32} these being considered when selecting the compositions of the ABS and calculating the corresponding tie-lines (TLs) and TLLs. The TLs were determined through the Asenjo and collaborators³³ method, which was already adopted and validated by our research group for IL-based ABS.^{8, 31, 32} TLLs are the Euclidean distance between the top and bottom phase compositions.

The influence of several operational conditions was assessed, namely IL structure, NSAID content, temperature, pH and TLL. The ABS preparation was carried by weighing the appropriate amounts of each component and NSAID according to Table 1. NSAIDs were added to the ABS (5 g of total mass) as a mixture composed of equal amounts of ibuprofen, ketoprofen and naproxen standard powders (at final contents of each NSAID of approximately 1, 2 and 4 mg

per g of ABS). The systems were vigorously stirred and placed at the desired temperature at least during 18 hours to reach equilibrium and to achieve the complete partition of the NSAIDs. In order to obtain the distinct pH values evaluated during the ABS optimization studies, potassium citrate buffer at pH 7 and 8, prepared according to tabulated values,²² was used, while pH 9 was afforded by the use of potassium citrate tribasic.

After the appearance of two clear phases, their separation was carried followed by the measurement of their weight and volume. In the end, these systems resulted in one IL-rich and one salt-rich phase as the top and bottom layers, respectively. At least three repetitions of each system were performed. Both the top and bottom phases were analyzed by HPLC-DAD after filtration using syringe filters of 0.45 μm pore (to remove suspended solids) and appropriate dilution: for the top phase, 25 times in a mixture of water:ACN (70:30, v/v), 5 times in water was the dilution adopted for the salt-rich layers (three injections per sample). In order to evaluate the extractive performance of these systems, two parameters were calculated, namely the extraction efficiency of each NSAID (EE_{NSAID} , %) – eqn. 1 – and their recovery toward the IL-rich (top) phase (R_T , %) – eqn. 2.

$$EE_{NSAID}, \% = \frac{[NSAID]_T \times V_T}{m_0} \times 100 \quad (1)$$

$$R_T, \% = \frac{[NSAID]_T \times V_T}{[NSAID]_T \times V_T + [NSAID]_B \times V_B} \times 100 \quad (2)$$

$[NSAID]_T$ and $[NSAID]_B$ are the concentrations of each NSAID (ibuprofen, naproxen or ketoprofen) found in the top and bottom phases, V_T and V_B are the volumes of the top and bottom phases and m_0 is the mass of each NSAID initially added in the ABS preparation. Both EE_{NSAID} (%) and R_T (%) are reported as the average values with the corresponding standard deviations.

Table 1. Conditions studied and approximate mass fraction compositions (in weight percentage) used during the ABS optimization studies.

Operational condition	IL	Salt	NSAIDs / content (mg per g of ABS)	pH	$T (\pm 1) / (^{\circ}\text{C})$	100 × mass fraction composition / (wt%)		
						IL	Salt	Water
IL structure	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
	[BzCh]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	35	30	35
	[N ₄₄₄₄]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
NSAID content	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	1	7	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	2	7	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
Temperature	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	15	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	35	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	45	30	30	40
pH	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	8	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇	4	≈9	25	30	30	40
TLL	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	30	30	40
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	33	28	39
	[C ₄ mim]Cl	C ₆ H ₅ K ₃ O ₇ /C ₆ H ₈ O ₇	4	7	25	35	26.5	38.5

Recovery of NSAIDs from pharmaceutical wastes.

i) NSAIDs extraction by applying IL-based TTP systems. When applying the IL-based ABS to the pills, the extraction of each NSAID was performed separately in a single-step, *i.e.* the non-soluble excipients settled in the interface allowing their separation from the target active ingredients – IL-based TPP. Their visual appearance is depicted in Figure S1 in Supporting Information. The mass of each pill containing the NSAID was determined taking into account the total mass of NSAID present in the grinded pill and excluding that of excipients (data verified in the medicine flyers). So, using *Naproxeno Generis* ($\approx 25\%$ of excipients) and *Brufen* ($\approx 25\%$ of excipients) pills, 20 mg of naproxen and ibuprofen was added (4 mg *per g* of ABS), whereas for *Profenid Retard* ($\approx 61\%$ of excipients due to the prolonged release character of this medicine) the addition of 10 mg of ketoprofen was done (2 mg *per g* of ABS). During the phase separation, the excipients-rich interface was discarded. All the remaining procedure and calculations were the same as those adopted throughout the NSAIDs partitioning optimization studies using IL-based ABS.

ii) NSAIDs isolation through precipitation. NSAIDs isolation from the IL-rich phase was conducted through precipitation with antisolvents, namely citric acid and aluminium sulfate aqueous solutions. From the three distinct types of ABS investigated, the one composed of ≈ 30 wt% of $[C_4mim]Cl$, 30 wt% of salt and 40 wt% of water containing the same amounts of pills aforementioned was elected. It should be stressed that with *Profenid Retard* the pills quantities were doubled in order to facilitate this task. In a first attempt, aqueous solutions of citric acid at 25 wt% were added in ratios of top phase volume to volume of antisolvent of 1:4 (given the conditions tested in our previous work¹⁰). Due to the impossibility of precipitating ketoprofen with citric acid aqueous solutions, an aqueous solution of aluminium sulfate at 15

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3 wt% was instead employed in a broader range of ratios (1:4, 1:6, 1:8, 1:10 and 1:12). After the
4 addition of the antisolvent, a precipitate was formed, which induced a turbidity into the resulting
5 solution. This was then filtrated using syringe filters with the concentration of the target NSAID
6 remaining in solution determined using HPLC-DAD. Triplicates were consistently done,
7 allowing determining the average isolation efficiencies of each NSAID (IE_{NSAID} , % - eqn. 3) and
8 the corresponding standard deviations (σ).
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$$18 \quad IE_{NSAID}, \% = 100 - \left(\frac{m_{NSAID}^{Antisolv}}{m_{NSAID}^T} \times 100 \right) \quad (3)$$

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23 In eqn. 3, $m_{NSAID}^{Antisolv}$ and m_{NSAID}^T denote the mass of NSAID present in the filtered phase after the
24 addition of the antisolvent and that initially existing in the top phase, respectively.
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28 **NSAIDs stability in ILs and IL-salt aqueous solutions.** A protocol for stability assessment was
29 carried based on the OCDE 111e guideline and further applied to the analysis of the impact of
30 the IL structure, media pH, salt presence/absence and temperature of incubation impact on the
31 NSAIDs stability. Four sets of experiments were conducted as described on Table 2, always with
32 aqueous solutions composed of 45 wt% of IL, [C₄mim]Cl, [BzCh]Cl or [N₄₄₄₄]Cl. The first three
33 sets comprised aqueous solutions in presence of potassium citrate buffer at pH \approx 5 or 7 (the same
34 source for preparation guidelines as that aforementioned was consulted²²) and potassium citrate
35 tribasic monohydrate, representing a pH of circa 9, at 5 wt% of salt composition. These
36 compositions were adopted in order to mimic the IL-rich phase of an ABS. No salt was added in
37 the fourth set of experiments. In all tests, a total of \approx 3 mg of each NSAID was dissolved in 3 g
38 of aqueous solution, and stirred for 1 hour. Each sample was divided into three portions: one
39 taken at the beginning of experiments without any treatment (St_0) and the remaining two
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3 incubated in the dark at 25 or 50 (± 1) °C for five days (St_{25} and St_{50} , respectively). At the end,
4 these samples were analyzed by HPLC-DAD following the procedure of filtration previously
5 described, adequate dilution in water:ACN (70:30, v/v) and injection. The relative stability
6 (St_{NSAID} , in percentage) was calculated as the ratio between the NSAID peak areas in St_{25} or St_{50}
7 and that in St_0 sample times 100.
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15 **NSAIDs quantification.** Similar chromatographic conditions as those reported in our previous
16 work were used.¹⁰ The liquid chromatograph HPLC Elite LaChrom (VWR Hitachi) consisted of
17 a diode array detector (DAD) 1-2455, column oven 1-2300, auto-sampler 1-2200 and pump 1-
18 2130. The analytical column used was purchased from Merck and it was composed of a sorbent
19 LiChrospher 100 RP-18 (5 μ m) and cartridge LiChroCART 250-4 HPLC-Cartridge. Both the pre-
20 column, in a special holder, and the main column possess the same type of stationary phase. The
21 aqueous phase (A) contained 5 mM of ammonium acetate and was adjusted to pH 4.02 by adding
22 acetic acid. Then, 5% of the ACN was added. Phase A was filtrated using membrane filters and
23 further degassed in an ultrasound bath. The organic phase (B) contained the gradient grade ACN
24 and it was degassed by ultrasonication. The separation was carried out using a gradient elution
25 mode, according to the following program: 0 - 4 min 30% of B, 4-11 min from 30 to 60% of B,
26 11-18 min 60% of B, 18-21 min from 60 to 30% of B, 21-24 min 30% of B, using flow rate 1
27 mL.min⁻¹. The column temperature was adjusted to 27 °C and the autosampler to 25 °C. DAD
28 was set to measure the spectrum from 200 to 400 nm and three specific wavelengths: 230 nm for
29 ibuprofen and 245 or 270 nm for ketoprofen and naproxen depending on the sample type, as
30 detailed in Table S2 from Supporting Information. The injection volume was 10 μ L or 25 μ L if
31 the sample was the top or bottom phase, respectively.
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3 The instrumental validation was based on an external standard method. Two instrumental
4 calibration curves were determined. Stock mixtures of the three NSAIDs at 1 mg.mL⁻¹ in ACN,
5 further submitted to serial dilutions, were prepared for validation purpose. Accuracy was
6 determined by comparison of the real concentrations of the NSAIDs and the values determined
7 by the equipment. Precision corresponds to the relative standard deviations between injections.
8 Accuracy and precision were determined in intra- and inter-day modes. The limit of
9 quantification was the lowest concentrations of analytes used in the calibration curves, with a
10 precision < 5 % and accuracy between 80-120%. The limit of detection was established using a
11 signal/noise (S/N) ratio of 3. The quantification method and validation for ibuprofen at the
12 higher concentration range was already reported in a previous work.¹⁰ All the details regarding
13 the validation parameters are shown in Table S2 from Supporting Information.
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29 **pH measurements.** The pH of the potassium citrate buffers and phase A of the HPLC mobile
30 phase were measured using an HI 9321 Microprocessor pH meter equipment (Hanna
31 Instruments) at 25 (±1) °C and within ± 0.02 pH units.
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41 RESULTS AND DISCUSSION

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44 The applicability of IL-based TPP systems to the purification of ketoprofen, ibuprofen and
45 naproxen from pharmaceutical wastes was here studied. Firstly, an optimization study using
46 commercial standards of each NSAID and testing the parent IL-based ABS was carried out.
47 Then, the capability to directly extract and refine these NSAIDs from real matrices, *i.e.* solid
48 state pills, in a single step by applying the IL-based TPP was assessed. As previously mentioned,
49 IL-based TPP systems use the same systems as IL-based ABS.²⁶ Taking this into account, all
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3 information on the TLs used in the first part of this work is provided in Table S3 in Supporting
4 Information, namely the weight fraction composition (in wt%) of each compound composing the
5 biphasic mixture and the coexisting phases, as well as the TLLs.
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11 The optimization studies were centered on assessing the influence of the ILs nature, temperature,
12 pH and TLL upon the partition of the three NSAIDs in ABS. Three structurally different ionic
13 compounds were tested, [N₄₄₄₄]⁺Cl⁻, [BzCh]⁺Cl⁻ and [C₄mim]⁺Cl⁻, allowing screening distinct
14 physical, chemical and biological properties. These were selected based on our previous know-
15 how on designing extraction approaches applying ILs¹⁵ to purify drugs.^{8, 10} At the same time that
16 the anion structure was kept simplistic offering benefits from an operational and economic point
17 of view, the range of cations elected allows inspecting distinct partition environments (due to
18 their distinct hydrophobic nature).³¹ Moreover, and according to the well-established acute
19 toxicity levels,³⁴ all ILs are non-toxic towards the marine bacteria *Vibrio fischeri* (EC₅₀ of 519
20 mg.L⁻¹, 1498 mg.L⁻¹ and 472 mg.L⁻¹ for [C₄mim]⁺Cl⁻, [BzCh]⁺Cl⁻ and [N₄₄₄₄]⁺Cl⁻, respectively³⁵⁻³⁷).
21
22 Also, all bearing the cheap Cl⁻ anion and two being quaternary ammonium-based, the ILs here
23 elected may be considered as cost-effective.³⁸ The highly biodegradable character²² and wide
24 application in the pharmaceutical industry³⁹ of citrate-based salts encouraged the citrate buffer
25 use as phase-forming component. Moreover, it was also previously shown that the combined use
26 of this triad of ILs with citrate buffer in aqueous solution enhanced the solubilization of
27 ibuprofen in water in comparison to water itself, thus yielding good extraction efficiencies.¹⁰
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29 This fact allowed the use of high amounts (i.e. *circa* 20 mg in 5 g of total mass) of these
30 NSAIDs, which are characterized by a low water solubility ([IBU] = 21 mg L⁻¹; [NAP] = 15.9
31 mg L⁻¹; [KET] = 51 mg L⁻¹ – values at 25 °C)⁴⁰, to perform the partition studies. This was
32 confirmed for all the NSAIDs here tested with experiments performed using the system based on
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[C₄mim]Cl and potassium citrate buffer at pH 7. Actually, for the NSAID amounts tested at *circa* 1 and 2 mg of each NSAID *per g* of ABS the results yielded similar EE_{NSAID} and R_T values, respectively, $93.7 \pm 4.0 \% < EE_{KET} < 99.2 \pm 3.5 \%$, $90.4 \pm 2.6 \% < EE_{NAP} < 92.8 \pm 6.9 \%$ and $86.7 \pm 1.3 \% < EE_{IBU} < 97.8 \pm 2.9 \%$ and $R_T > 98.2 \pm 0.1 \%$ (*cf.* Figure 2 and Table S4 in Supporting Information). This feature overcomes the limitation of ABS application when large amounts of waste are applied and the target active ingredient possesses a low solubility in water. The results exposed and discussed below suggest that it was possible to extract large amounts of NSAIDs, well above their saturation in water, with EE_{NSAID} and R_T higher than 80 % and 97 %, respectively.

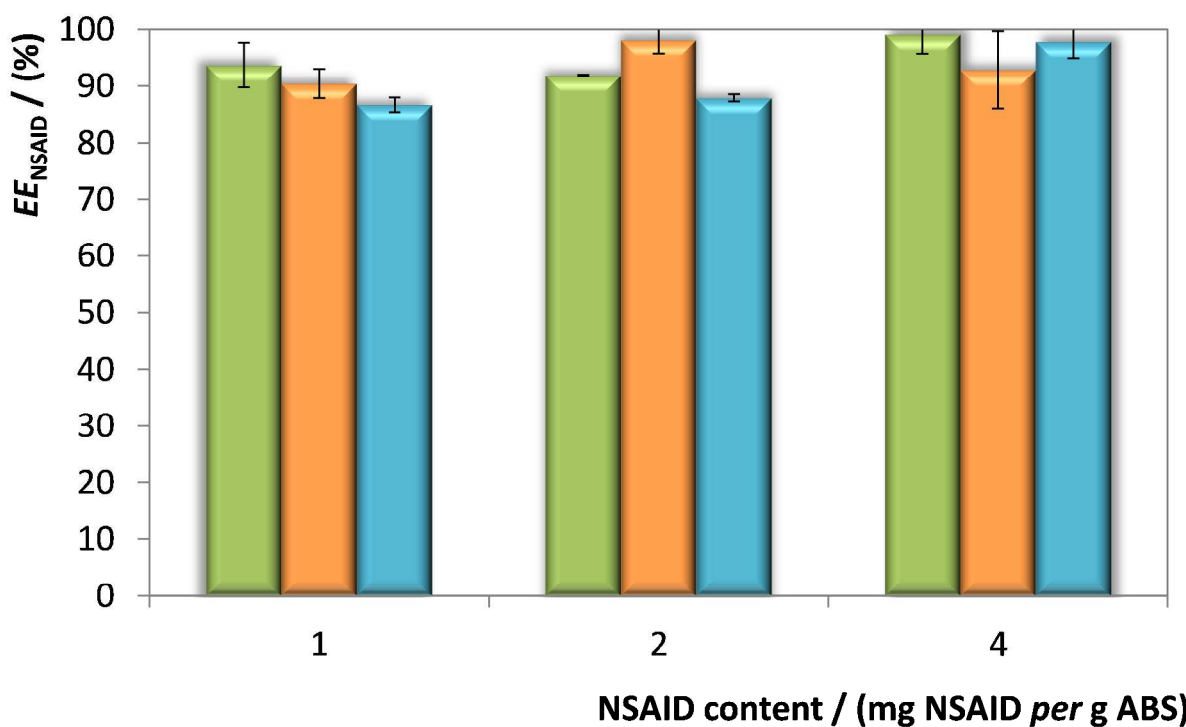


Figure 2. Impact of NSAIDs content on the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green bars), naproxen (orange bars) and ibuprofen (blue bars) using ABS composed of 30 wt% of [C₄mim]Cl and 30 wt% of potassium citrate buffer at pH 7.

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3 **NSAIDs partition studies using IL-based ABS.** The parameters determined to evaluate the
4 extraction performance of the IL-salt ABS employed, namely the extraction efficiency for each
5 NSAID (EE_{NSAID} , %) and the recovery towards the top phase (R_{T} , %) are reliable indicators to
6 measure the success of the process here developed. The graphical representation of the
7 relationship between EE_{NSAID} calculated for the three NSAIDs and distinct IL-based ABS are
8 depicted in Figure 3, while the detailed numerical results, for both EE_{NSAID} and R_{T} , are given in
9 Table S5 in Supporting Information. In general, EE_{NSAID} values were higher than 80 %, showing
10 the capacity of the studied IL-salt-based ABS to concentrate the NSAID in just one phase. In
11 fact, the EE_{NSAID} vary from 90.2 ± 9.6 % to 99.6 ± 7.9 %, 84.9 ± 5.6 % to 92.8 ± 6.9 %, and 88.8
12 ± 8.4 % to 97.8 ± 2.9 %, for ketoprofen, naproxen and ibuprofen, respectively.

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27 The partition in these IL-based ABS results from a complex set of interactions between the
28 NSAIDs and the phase-forming components, i.e. the interactions of “NSAIDs-ILs”, “NSAIDs-
29 citrate” and/or “NSAIDs-water”. At first glance, the preferential migration of the NSAIDs to the
30 top (IL-rich) phase can be easily explained by their octanol-water partition coefficient values –
31 Log P (3.97 for ibuprofen, 3.12 for ketoprofen and 3.18 for naproxen).⁴¹ These parameters
32 indicate the NSAIDs affinity for more hydrophobic environments ($\log P > 0$). Hydrophobic
33 interactions were shown to play a significant role in the partition behaviour of other molecules in
34 IL-based ABS, namely proteins^{42, 43} and other drugs.^{9, 44} This tendency is corroborated by
35 recoveries to the top phase higher than 97.8 ± 0.3 % for all NSAIDs (Table S5 in the Supporting
36 Information). Actually, these pharmaceutical active ingredients have similar structures and
37 characteristics leading to similar extraction efficiencies using any of the IL-salt-based ABS under
38 investigation.

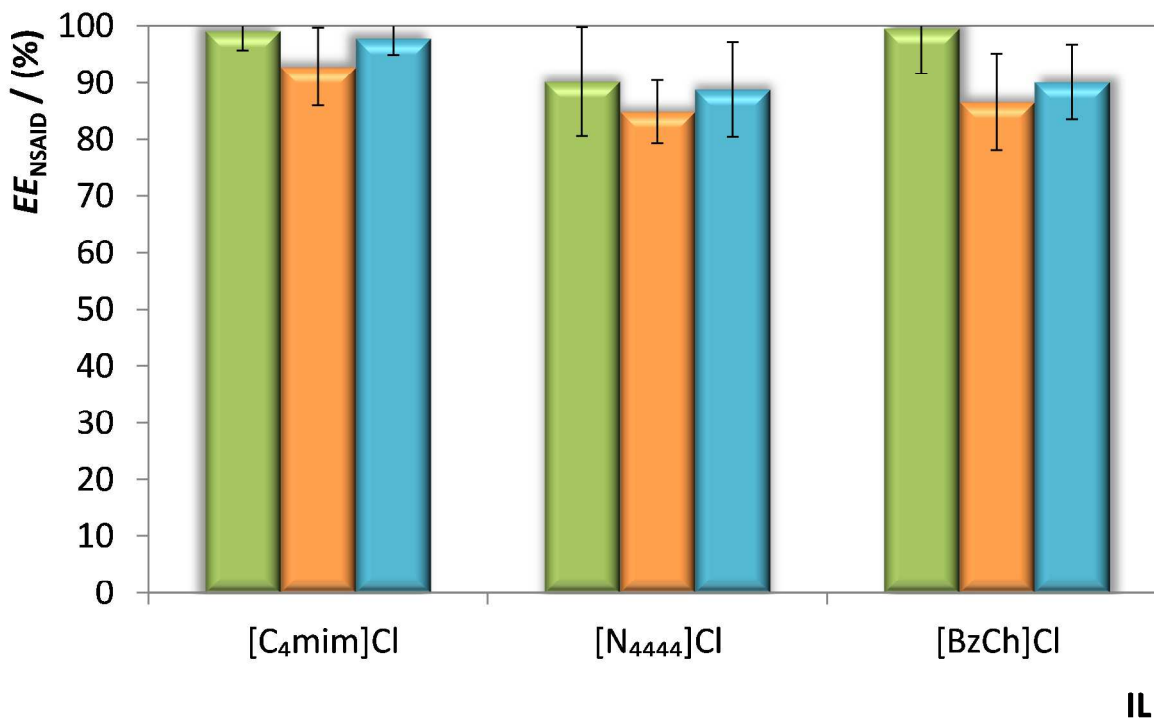
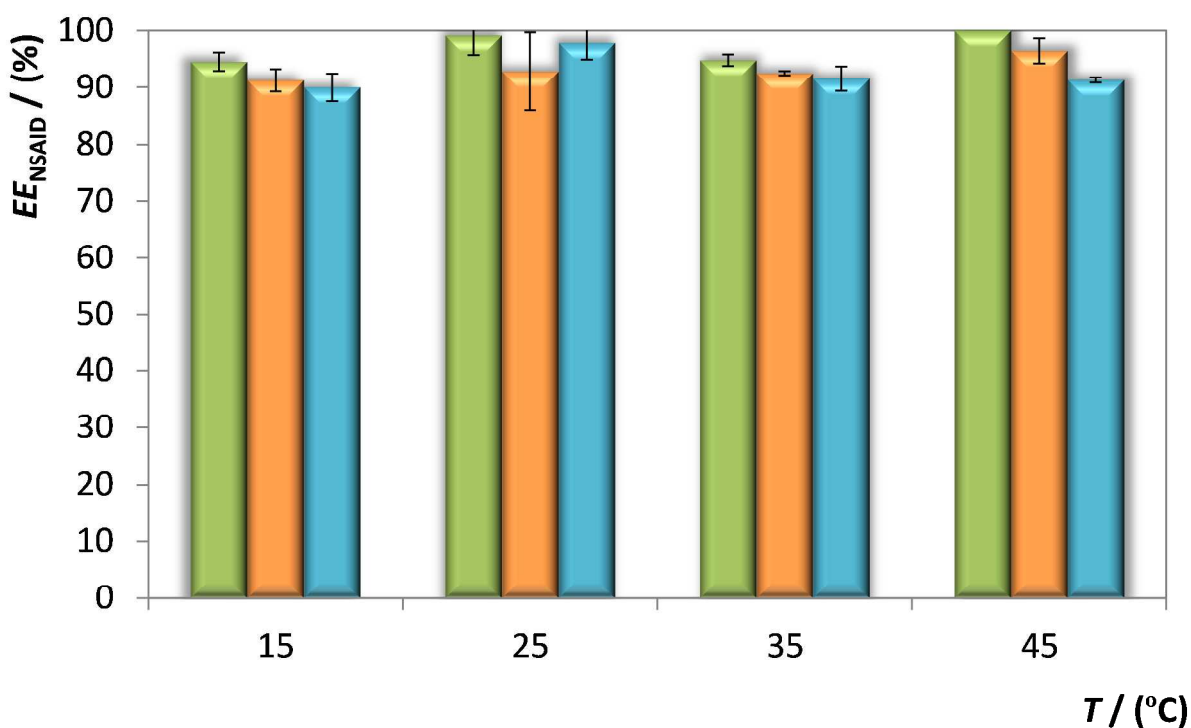


Figure 3. Impact of IL structure on the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green bars), naproxen (orange bars) and ibuprofen (blue bars) using ABS composed of 30 wt% or 35 wt% of IL and 30 wt% of potassium citrate buffer.

In order to gain further details on the operational conditions affecting the extraction of NSAIDs using IL-based ABS, temperature, pH and TLL were also studied. As all IL-based ABS evaluated yielded similar performances, the system containing [C₄mim]Cl was considered to assess the impact of such conditions. Figures 4 to 6 show the effects obtained for the extraction efficiencies of the three NSAIDs, being the detailed numerical data presented in Tables S6 to S8 in Supporting Information. The conclusion emerging from the results obtained reveals that temperature, pH and TLL, although having distinct effects on the migration of NSAIDs in

[C₄mim]Cl-based ABS, do not drastically influence their migration affinity, as represented by the data of $EE_{\text{NSAID}} > 80.3 \pm 2.6 \%$ and $R_T > 97.4 \pm 0.9 \%$.

Temperature, varied between 15 °C and 45 °C with intervals of 10 °C, was shown to have a marginal effect on the extraction of ibuprofen, ketoprofen and naproxen (*cf.* Figure 4 and Table S6 in Supporting Information). A diversified scenario is found in literature, where the temperature may lead to either null (as here) or significant (positive/negative) impacts on the extraction performance of IL-based ABS depending on the operational conditions under study (e.g. IL, target molecule, phase formers pair, among others).⁴⁵⁻⁴⁹ Due to the negligible temperature impact found and the possibility of minimizing energetic and operational costs, the room temperature was further maintained.



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3 **Figure 4.** Impact of temperature on the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green
4 bars), naproxen (orange bars) and ibuprofen (blue bars) using ABS composed of 30 wt% of
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6 [C₄mim]Cl and 30 wt% of potassium citrate buffer.
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14 The pH effect was also evaluated by selecting potassium citrate buffer at pH 7 and 8 along with
15 potassium citrate tribasic at pH \approx 9. A wider range of pH was not studied due to the weak ability
16 of the [C₄mim]Cl-based ABS to undergo phase separation at pH lower than 7.⁵⁰ It is well-known
17 that electrostatic interactions triggered by pH changes may display significant impacts in the
18 partition of ionizable solutes, allowing the control of their migration patterns.⁵¹⁻⁵⁴ However, this
19 profile is highly dependent on the molecules addressed, in particular for NSAIDs, as unveiled by
20 Almeida et al.^{55, 56} Using IL-based ABS containing either aluminium sulphate (pH \approx 2.4 – 2.9) or
21 potassium citrate tribasic (pH \approx 9), the authors showed that regardless of the pH, a major
22 partition of the NSAIDs to the most hydrophobic (IL-rich) phase occurs. So, the same happened
23 in this work, for which the preferential migration of the NSAIDs to the IL-rich phase was
24 constantly observed ($EE_{NSAID} > 85.1 \pm 3.8$ % and $R_T > 98.7 \pm 0.7$ %). As depicted in Figure 5
25 (detailed data is presented in Supporting Information as Table S7), higher pH values lead to
26 slightly poorer extraction efficiencies, mostly when potassium citrate tribasic (pH \approx 9) is used.
27 Since the charge of the three NSAIDs is kept constant and negative within the pH range
28 evaluated, no major differences are observed for the migration of NSAIDs to the IL-rich phase
29 (99.2 ± 3.5 % $> EE_{KET} > 89.1 \pm 0.8$ %; 92.8 ± 6.9 % $> EE_{NAP} > 86.5 \pm 0.6$ % and 97.8 ± 2.9 % $>$
30 $EE_{IBU} > 85.1 \pm 3.8$ %). Considering the 10% of maximum variation of the extraction efficiency
31 values, pH 7 was maintained in further studies.
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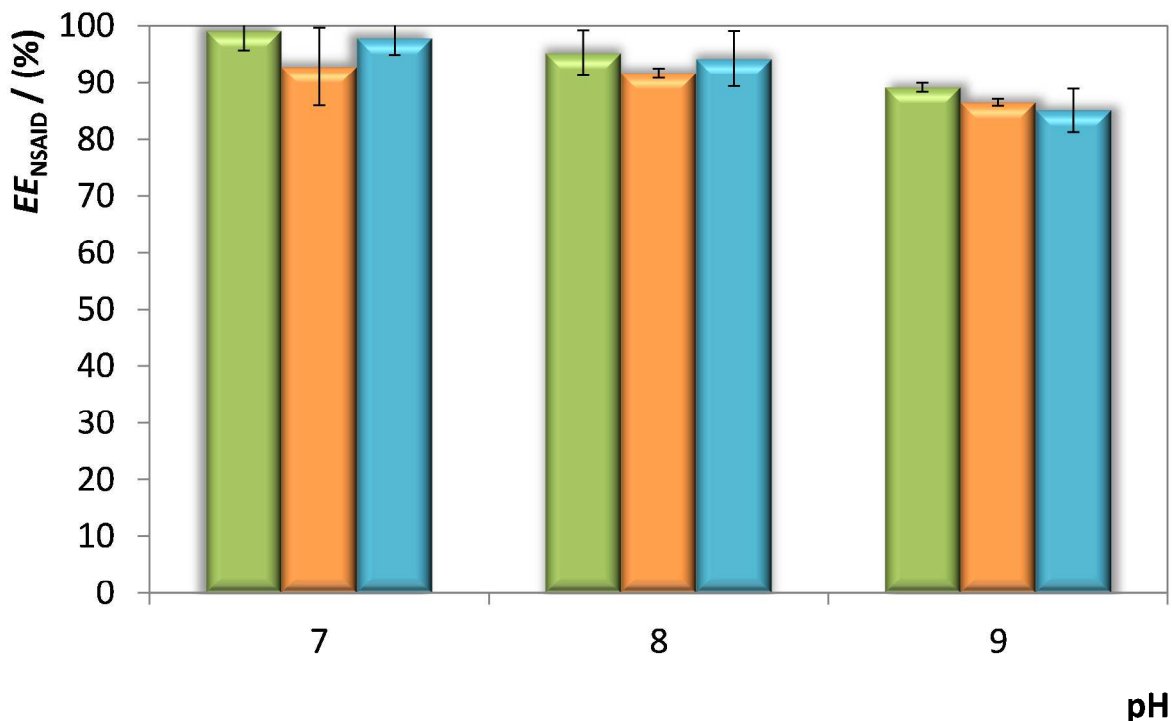


Figure 5. Impact of pH on the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green bars), naproxen (orange bars) and ibuprofen (blue bars) using ABS composed of 30 wt% of $[C_4mim]Cl$ and 30 wt% of potassium citrate buffer (pH 7 and pH 8) or potassium citrate tribasic salt (pH ≈ 9).

Finally, the TLL influence on the NSAIDs partition was assessed by varying the compositions of $[C_4mim]Cl$ and potassium citrate buffer at pH 7 (30 wt%/30 wt%, 33 wt%/28 wt% and 35 wt%/26.5 wt%). The shortest the TLL is, the lowest are the amounts of IL and salt present in both phases and the highest are the water contents (*cf.* Table S3 in Supporting Information). The evaluation of such a parameter allowed inferring on the role of $[water]_T$ on the NSAIDs partition. By increasing the TLL, under the conditions tested (IL = $[C_4mim]Cl$, salt = potassium citrate buffer, NSAID content = 4 mg *per* g of ABS, pH = 7 and $T = 25$ °C), *circa* 20% decline in the

NSAIDs extraction efficiency was verified. In other words, the higher the $[\text{water}]_T$, the higher the EE_{NSAID} ($99.2 \pm 3.5 \% > EE_{\text{KET}} > 85.1 \pm 2.9 \%$, $92.8 \pm 6.9 \% > EE_{\text{NAP}} > 82.5 \pm 3.0 \%$ and $97.8 \pm 2.9 \% > EE_{\text{IBU}} > 80.3 \pm 2.6 \%$) – see Figure 6 (the detailed data is also presented in Supporting Information as Table S8). This allowed concluding that slightly lower amounts of IL can be used to maximize the recovery of the NSAIDs.

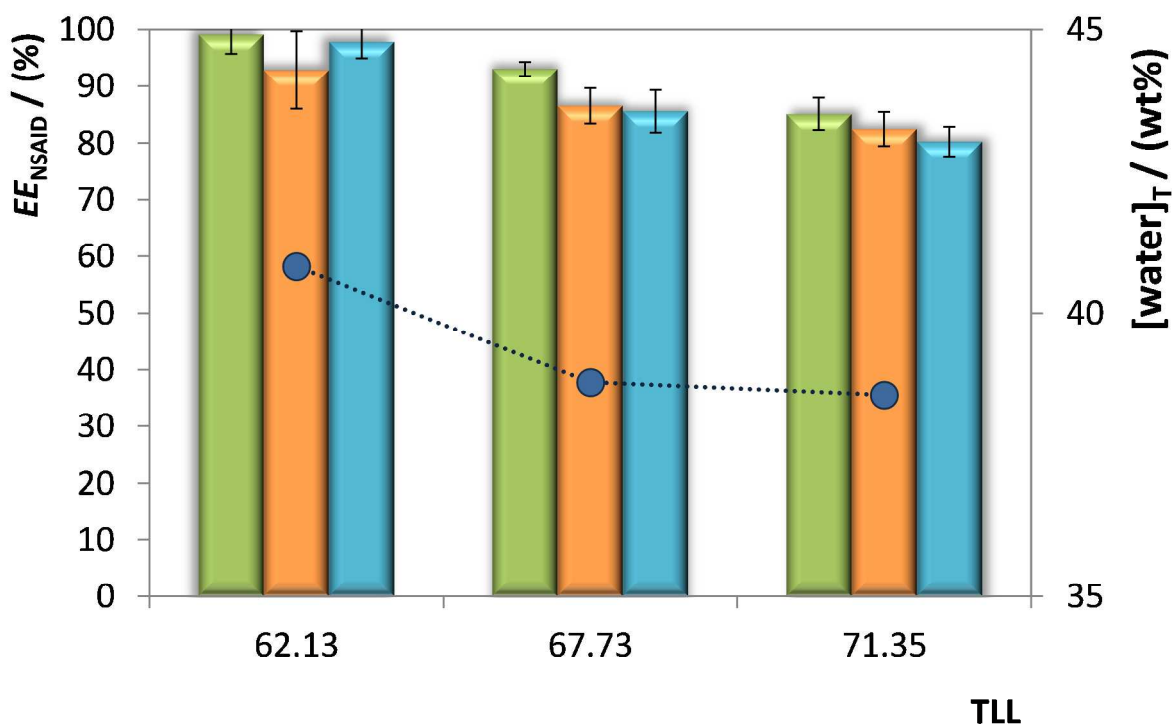


Figure 6. Impact of TLL on the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green bars), naproxen (orange bars) and ibuprofen (blue bars) using ABS composed of variable amounts of $[\text{C}_4\text{mim}]\text{Cl}$ and potassium citrate buffer at pH 7. The weight fraction of water present in the top phase ($[\text{water}]_T$, wt%) is also shown (circles connected by the dashed line).

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3 **Insights into the stability of NSAIDs in IL- and IL-salt-based aqueous matrices.** In a
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5 scenario where three NSAIDs are successfully extracted and recovered from wastes to be further
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7 used for other applications, their chemical stability is a matter of great concern to assure the
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9 quality of the final product. It should therefore be assumed that the chemical environment
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11 afforded by the IL enriched (top) phase, *i.e.* a milieu made of IL and water bearing tiny amounts
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13 of citrate buffer salt (Table S3 in Supporting Information), must guarantee no degradation or by-
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15 product formation. Actually, if in the case of biomolecules such as proteins, their greater
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17 susceptibility to stability or activity losses prompts detailed studies,^{43, 57-59} in the case of simpler
18
19 and synthetic molecules this issue has been disregarded. In this sense, a stability protocol adapted
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21 from the OECD guidelines was used to test the NSAIDs stability. This test was adopted due to its
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23 simplicity and adequacy of the parameters (temperature, energy, UV radiation and pH)
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25 evaluated, when compared with other possible options, e.g. Stability Testing of Active
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27 Substances and Pharmaceutical Products from the World Health Organization (WHO) or the
28
29 Q1A(R2) Stability Testing of New Drug Substances and Products from the Food and Drugs
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31 Administration (FDA). The protocol used in this work was compared with the original from
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33 OECD (111e) in Table S9 in Supporting Information, thus leading to a simpler way of
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35 determining the chemicals stability in aqueous matrices of ILs. Taking into account the TLs
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37 determined (Table S3 in Supporting Information) aqueous solutions containing 45 wt% of each
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39 IL and 5 wt% of salt were used to mimic the top phase environment allowing a direct
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41 comparison between systems. Bringing together the four sets of experiments it was possible to
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43 carefully assess the impact of IL structure, pH, salt and temperature of incubation on the
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45 NSAIDs stability.
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3 The mean values of relative stability with standard deviations for the three NSAIDs under all the
4 described conditions are reported in Table 2. It is clear that the set of NSAIDs did not lose
5 stability during the five days of experiments, independently of their chemical structure, IL
6 structure, pH, temperature or salt presence. Remarkable stability values consistently higher than
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12 93.4 ± 0.1 % were achieved.
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15 In spite of the limited solubility of these NSAIDs in water, the results obtained attest their
16 stability in this solvent. This results from the fact that their simple structure lacks easily
17 dissociated functional groups, *e.g.* esters and amides.⁶⁰ Furthermore, ketoprofen was proven to
18 be more stable in neutral than in acidic conditions,⁶¹ whilst ibuprofen was prone to lose its
19 stability only in acidic conditions.⁶² This evidence may explain the slight loss of stability of
20 ibuprofen in presence of potassium citrate buffer at pH 5 (*cf.* Table 2). These results point IL-
21 salt-based ABS as mild routes for the extraction of these NSAIDs from pharmaceutical wastes,
22 contrarily to what is being reported in literature about the photo-, bio- and ultrasonic degradation
23 of naproxen, ibuprofen and ketoprofen.⁶³⁻⁷⁰
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Table 2. Mass fraction compositions (in wt%) of the matrices adopted to study the stability of the three NSAIDs along with the conditions tested and percentage stabilities (St_{NSAID} , %) plus the corresponding standard deviations (σ).

IL	Salt	[IL] / (wt%)	[Salt] / (wt%)	[water] / (wt%)	T (± 1) / ($^{\circ}\text{C}$)	St_{IBU} / (%)	St_{NAP} / (%)	St_{KET} / (%)
<i>1st set</i>								
[C ₄ mim]Cl		45	5	50	25	100	100	100
					50	100	98.2 \pm 0.8	100
[N ₄₄₄₄]Cl	Potassium citrate buffer (pH 5)	45	5	50	25	97.6 \pm 1.4	98.6 \pm 2.9	100
					50	93.4 \pm 0.1	100	100
[BzCh]Cl		45	5	50	25	100	100	100
					50	100	99.1 \pm 2.5	99.0 \pm 2.2
<i>2nd set</i>								
[C ₄ mim]Cl		45	5	50	25	100	100	99.1 \pm 2.7
					50	99.8 \pm 0.7	99.8 \pm 0.2	99.3 \pm 3.8
[N ₄₄₄₄]Cl	Potassium citrate buffer (pH 7)	45	5	50	25	96.9 \pm 1.6	98.8 \pm 2.1	98.8 \pm 1.6
					50	98.2 \pm 1.1	100	100
[BzCh]Cl		45	5	50	25	100	99.2 \pm 1.8	100
					50	100	98.3 \pm 2.3	99.1 \pm 2.3
<i>3rd set</i>								
[C ₄ mim]Cl		45	5	50	25	100	99.1 \pm 4.4	99.4 \pm 1.9
					50	99.2 \pm 0.9	98.7 \pm 4.3	97.9 \pm 4.0
[N ₄₄₄₄]Cl	Potassium citrate tribasic (pH \approx 9)	45	5	50	25	100	99.1 \pm 1.0	100
					50	98.4 \pm 1.1	97.3 \pm 0.3	100
[BzCh]Cl		45	5	50	25	100	98.4 \pm 2.8	100
					50	100	96.1 \pm 4.5	100

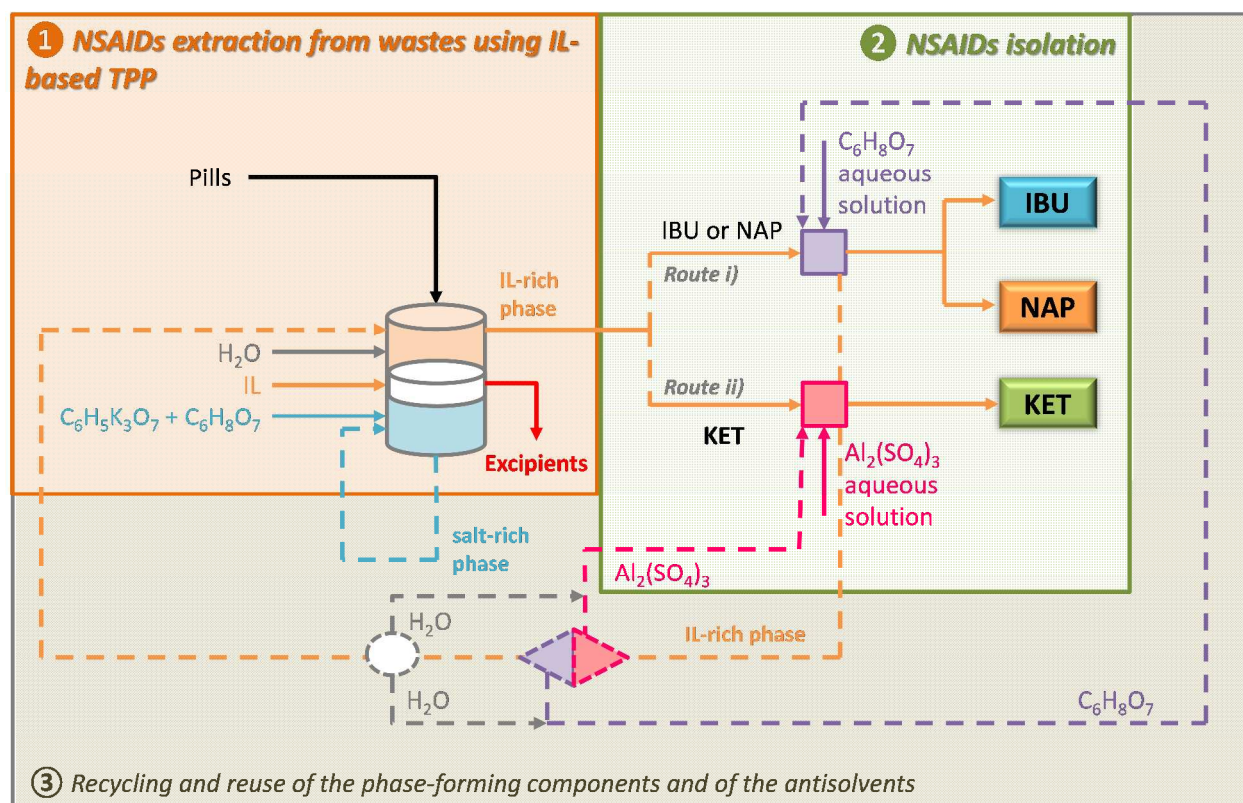
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4th set

5	[C ₄ mim]Cl	45	0	55	25	100	100	100
6					50	100	100	100
7					25	100	98.8 ± 1.5	99.4 ± 0.3
8	[N ₄₄₄₄]Cl -	45	0	55	50	98.7 ± 2.4	100	100
9					25	100	100	100
10	[BzCh]Cl	45	0	55	50	100	100	100
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3 **NSAIDs recovery from pharmaceutical wastes using IL-based TPP.** IL-based ABSs
4 exhibited a very good ability to extract the three target NSAIDs while preserving their chemical
5 stability. They will thus serve as useful tools to conceptualize an integrated process of NSAIDs
6 purification envisaging the pharmaceutical wastes valorization. Based on a similar approach to
7 that followed by IL-based ABSs, TPP constituted by the same triad of neoteric solvents were
8 further employed as a way of simultaneously extracting NSAIDs (IL-rich phase) and separating
9 the excipients (interface). The extraction in a one-step by IL-based TPP was attempted (*step 1*),
10 and an antisolvent-like isolation strategy for the three drugs was further investigated (*step 2*).
11 Figure 7 provides a schematic representation of the conceptual process proposed. Although not
12 studied in the present work, the recycling and reuse of both ABS components and antisolvents
13 (*step 3*) was also represented as it is considered essential for the economic and environmental
14 sustainability of the process.^{71, 72}



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3 **Figure 7.** Schematic representation of the integrated process of NSAIDs purification (step 1) and
4 isolation (step 2), including a hypothetical recycling of both the ABS components and the
5 antisolvents employed (step 3). Route i) represents the approach adopted for ibuprofen and
6 naproxen isolation while Route ii) depicts the strategy developed for the ketoprofen isolation.
7 Dashed lines were used for the hypothetical routes of recycling and reusing the solvents and
8 antisolvents.
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20 *Step 1: Application of IL-based TPP systems to purify the NSAIDs.* The results
21 presented in Figure 8 (for more details see Table S10 in Supporting Information) pinpoint the
22 remarkable performance of IL-based TPP in the single-step extraction and purification of
23 ibuprofen, ketoprofen and naproxen from their pharmaceutical matrices. Despite the slightly less
24 effective extraction efficiencies obtained from the solid state pills when compared with those
25 obtained with the model systems (*cf.* Figure 3), it should be pointed out that successful
26 performances were also attained using the IL-TPP systems ($EE_{NSAID} \geq 84.9 \pm 3.9\%$). R_T values
27 higher than $97.8 \pm 0.3\%$ (Table S10 in the Supporting Information) corroborate such evidence.
28 However, it should be noticed that EE_{NSAID} values lower than 100 % do not necessarily indicate
29 the preferential NSAIDs partition, but can represent some losses of the drugs to the excipient-
30 rich interface formed. In this work, no significant interferences were detected, due to the nature
31 of the excipients present in the pills and the conditions defined for the quantification method. As
32 examples, the ethyl phthalate composing the pill containing ketoprofen (Table S1 in Supporting
33 Information) was checked in the top (IL-rich) phase, and its presence was not detected in the
34 chromatograms. The cellulose-derivative excipients, despite their potential dissolution by ILs⁷³,
35 were also eliminated as contaminants because at 25 °C (the temperature of the extraction
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process), ILs may only cause the cellulose to be wet.⁷⁴ Finally, the titanium dioxide that, despite its high affinity for ILs (or top-IL-rich phase),⁷⁵ has a limited solubility in water and was also discarded as main contaminant. Thus, the main bulk of excipients settle in the interface due to its low-solubility in the water/aqueous phases of ABS.

The design of these IL-based TPP systems allowed the purification of each NSAID under study by the exclusion of the excipients that settled on the interface of the IL-salt-based ABS. This allowed the purification of ketoprofen, ibuprofen and naproxen in a single-step. These results suggest that IL-salt-based TPP systems are a suitable approach for the recovery of active ingredients from pharmaceutical wastes.

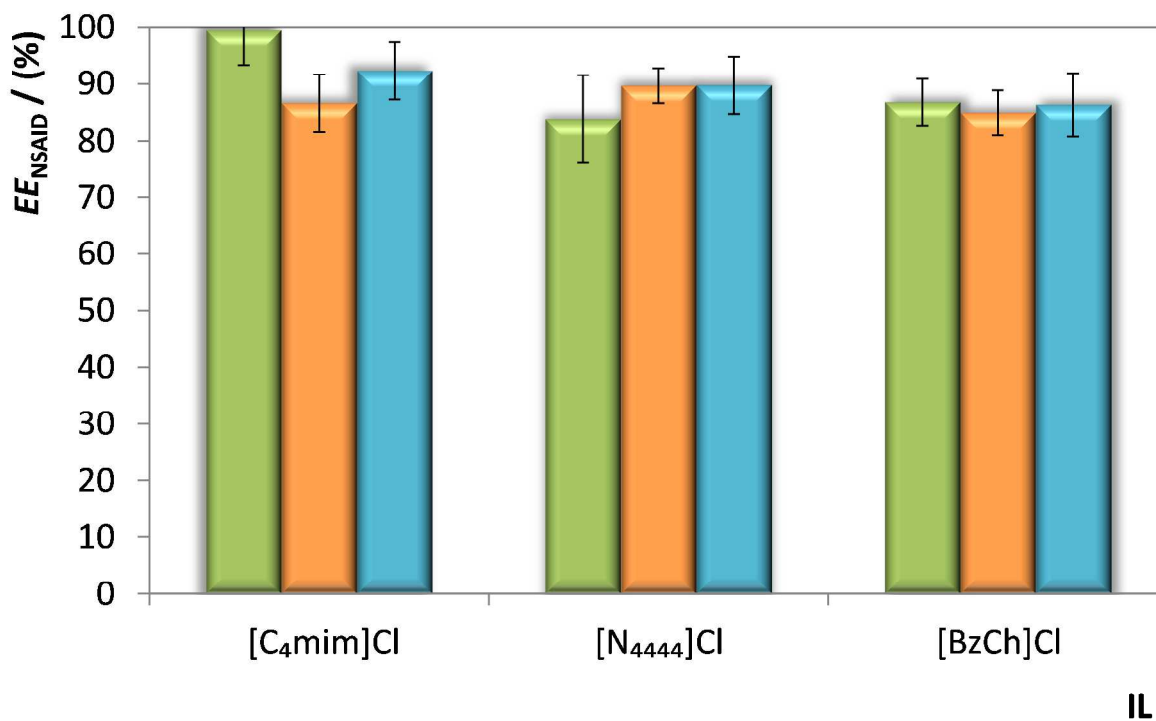


Figure 8. Results obtained for the extraction efficiency (EE_{NSAID} , %) of ketoprofen (green bars), naproxen (orange bars) and ibuprofen (blue bars) from pharmaceutical pills using IL-based TPP systems.

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3 **Step 2: Isolation of NSAIDs from IL-salt-based ABS through precipitation with**
4 **antisolvents.** High extraction performances were obtained when the separation of the three
5 NSAIDs from the real waste-based matrix was attempted. Envisaging the industrial potential of
6 this process, an isolation strategy to remove the phase formers was defined. Precipitation through
7 the addition of an antisolvent was the approach selected due to its simple operation and
8 scalability.⁷⁶ Although equivalent extraction parameters were gauged, the ABS composed of
9 [C₄mim]Cl was selected as the most efficient (*cf.* Figure 8). Due to the distinct solubility in water
10 of each NSAID,⁴⁰ specific precipitation agents were selected. The results are represented in
11 Figure 9 and in Table S11 in Supporting Information (mean values and standard deviations).
12 Initially, citric acid aqueous solutions at 25 wt% were selected as the ideal antisolvent due to the
13 good isolation results attained of 78.7 ± 2.2 % and 79.1 ± 3.0 % for ibuprofen and naproxen,
14 respectively. Moreover, using this antisolvent, the introduction of additional species was
15 avoided, which simplifies the process.¹⁰ It seems here that the combined action of water and
16 citric acid is ruling the precipitation phenomena: if on one hand both ibuprofen and naproxen are
17 practically insoluble in water,⁴⁰ on the other hand both are acidic drugs (pKa of 4.91 for
18 ibuprofen and 4.15 for naproxen⁴¹) having their solubility enhanced at higher pH values due to
19 ionization.^{77, 78}

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43 Since ketoprofen did not precipitate in the same conditions, it was necessary to develop a
44 different strategy for its isolation. Aluminium sulphate aqueous solutions were studied and a
45 broader range of top phase and antisolvent volume ratios was tested, namely 1:4, 1:6, 1:8, 1:10
46 and 1:12. The reason behind this choice was the strong “salting-out” effect and high acidic
47 character of this salt.⁷⁹ It was confirmed to work well as a precipitation agent leading to isolation
48 efficiencies from 76.2 ± 1.8 % to 87.9 ± 0.3 %, depending of the volume of antisolvent added.
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Besides the ketoprofen limited solubility in water and pKa value (4.45⁴¹), changes in the ionic strength and species in the media by the introduction of aluminium sulphate also hampered the “ketoprofen-IL-citrate buffer-water” interactions thus leading to ketoprofen precipitation. This result is in agreement with that observed for the isolation of ibuprofen from an IL + citrate buffer aqueous solution by the addition of potassium chloride.¹⁰ Important to be highlighted is the fact that the NSAIDs content remaining in solution (21 % of either ibuprofen or naproxen and around 12 % of ketoprofen) after the precipitation can be recycled to *step 1*. The target NSAID content at the feed stream will enlarge, thus improving the isolation in *step 2* up to a point where the amount of NSAID is the same as that recovered in each cycle.

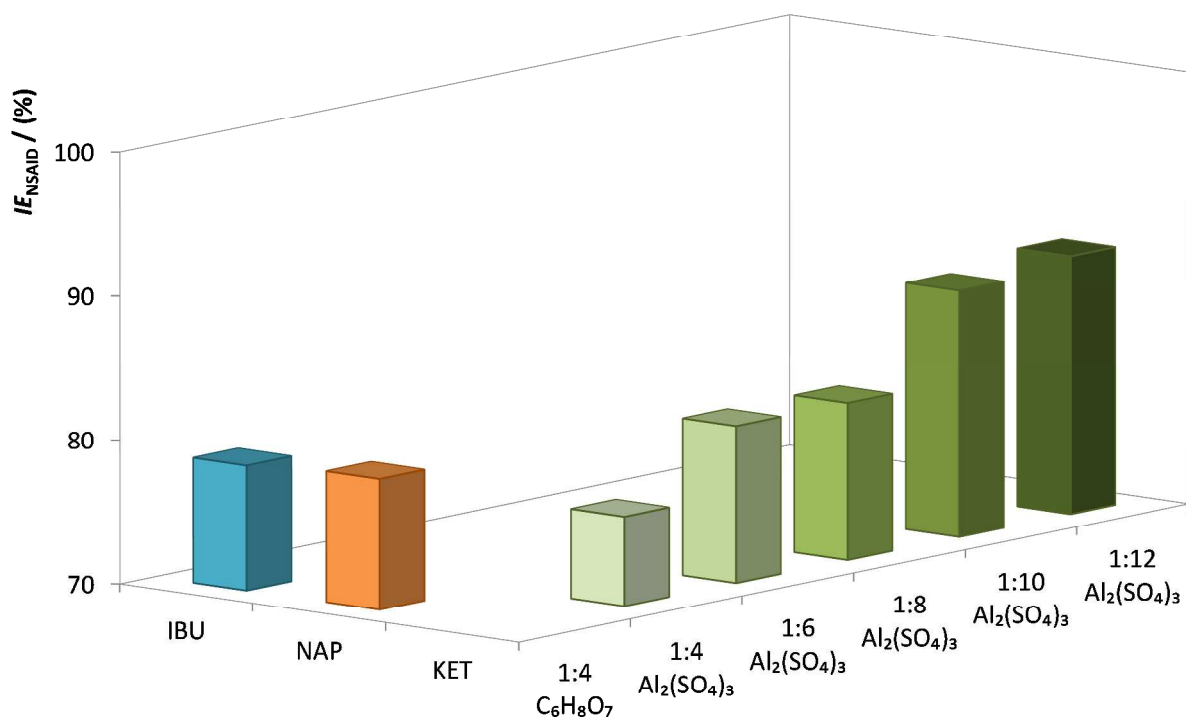


Figure 9. Results obtained for the isolation efficiency (IE_{NSAID} , %) of each NSAID using distinct antisolvents.

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3 The process herein conceptualized (Figure 7) represents another step towards the creation of a set
4 of effective technologies for the recovery of NSAIDs from pharmaceutical matrices. The
5 sustainability of the proposed process is proved when compared to others reported in literature.
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7 Some processes aimed at recovering naproxen,⁸⁰ ketoprofen⁸¹ and ibuprofen⁸² from
8 pharmaceutical formulations, e.g. suppositories, topical creams and tablets. Even though
9 speeding up the recovery process, the use of microwave-assisted methods (e.g. microwave
10 irradiation of 2450 MHz)^{80, 81} and/or high temperatures (≥ 35 °C,⁸² 65 °C⁸¹ and 70 °C⁸⁰) generate
11 high energetic inputs. In all three works, the use of volatile organic solvents, such as methanol,⁸⁰
12 acetone⁸¹ and alkanes⁸² as part of the extraction solvent constrained the safety and benignity of
13 the processes developed. Instead, in this work, volatile organic solvents were replaced by benign
14 ILs in aqueous environment with no additional energetic costs arising from neither irradiation
15 nor heating. Yet, the use of ILs as a way to improve the green credentials of NSAIDs processing
16 is not new. 1-ethyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide for example,
17 further abbreviated as [C₂mim][NTf₂], was evaluated as a crystallization solvent for ibuprofen
18 and naproxen.⁸³ [C₂mim][NTf₂] was able to solubilize naproxen at elevated temperatures (≈ 125
19 °C), while failing to solubilize ibuprofen independently of the temperature used.⁸³ Recently, our
20 group developed a simple process to recover ibuprofen,¹⁰ replacing the use of volatile organic
21 solvents by an IL aqueous solution and operating under ambient conditions. However, this
22 approach is not the most adequate when more complex waste mixtures/solutions are used and,
23 consequently, when more than one active ingredient needs to be simultaneously recovered and
24 separated from the excipients.
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3 Compared to the process developed in the present work, and also some other previously
4 published by us,¹⁰ such approaches are not as flexible as ours for the different NSAIDs, require
5 more expensive and less biocompatible ILs and utilize harsh temperature/pressure conditions.
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11 CONCLUSIONS

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15 An alternative approach for the purification of three NSAIDs, namely ibuprofen, naproxen and
16 ketoprofen, was here designed by applying IL-based TPP systems. Three steps were
17 contemplated in the conceptual integrated process proposed: a **step 1** of extraction and
18 purification of the target drugs using IL-based TPP systems, a **step 2** aimed at the isolation (*i.e.*
19 polishing) of each target compound by antisolvent induced precipitation, and a **step 3** of
20 recycling and reuse of the solvents employed. After the **step 1** of optimization using pure
21 standards, where ABS composed of ILs and the potassium citrate buffer revealed a very good
22 capability to extract the three NSAIDs from real solid wastes ($84.9 \pm 5.6 \% < EE_{NSAID} < 99.6 \pm$
23 7.9%), IL-based ABS were transformed into TPP systems allowing the interfacial separation of
24 the main contaminants (*i.e.* pills' excipients). A single-step purification process was proposed
25 with extraction efficiencies on the range ($83.8 \pm 7.7 \% < EE_{NSAID} < 99.5 \pm 6.2 \%$). The isolation
26 of each of three NSAIDs was attempted by precipitation with antisolvents. Two distinct
27 strategies were outlined: one for naproxen and ibuprofen using citric acid aqueous solutions (to
28 maintain the species in solution) and other for ketoprofen isolation employing aluminium
29 sulphate aqueous solutions. Isolation efficiencies of $76.2 \pm 1.8 \%$ were attained with the
30 possibility of being recycled to **step 1**. Additionally, problems associated with possible stability
31 losses in IL-rich media were mitigated, since ibuprofen, ketoprofen and naproxen have been
32 proven to be stable in these processing conditions. A sustainable and efficient alternative route
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3 for the recovery of drugs from pharmaceutical wastes transversal to other active ingredients was
4 developed in this work, opening the opportunity for further application to more complex systems
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6 or matrices other than pills.
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10 ASSOCIATED CONTENT

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14 **Supporting Information.** General information of the pills used in this study as real matrices,
15 validation parameters for the HPLC-DAD analytical method, tie-lines data and detailed
16 extraction and isolation data of the three NSAIDs studied.
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32 ACKNOWLEDGMENTS

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35 This work was developed within the scope of the project CICECO-Aveiro Institute of Materials,
36 POCI-01-0145-FEDER-007679 (FCT Ref. UID/CTM/50011/2013), financed by national funds
37 through the FCT/MEC and when appropriate co-financed by FEDER under the PT2020
38 Partnership Agreement. The authors acknowledge FCT for the financial support from the
39 doctoral scholarship SFRH/BD/94901/2013 granted to F.A. e Silva. S.P.M. Ventura
40 acknowledges FCT/MEC for a contract under *Investigador FCT* 2015 contract number
41 IF/00402/2015.
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52 The authors are also grateful to the financial support from the European Social Fund as a part of
53 the project "Educators for the elite - integrated training program for PhD students, post-docs and
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3 professors as academic teachers at the University of Gdansk" within the framework of the
4
5 Human Capital Operational Programme, Action IV, is also acknowledged. This work was
6
7 supported by a STSM Grant (Ref. COST-STSM-CM1206-27298) from COST Action CM1206
8
9 (EXIL – Exchange on Ionic Liquids). This publication reflects the views only of the authors, and
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11 the funder cannot be held responsible for any use which may be made of the information
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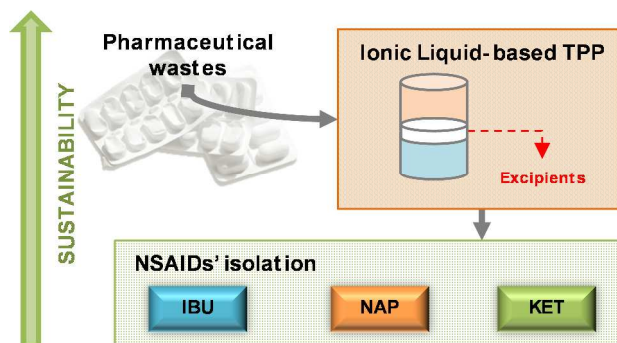
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Ionic liquid-based three phase partitioning systems represent efficient and sustainable routes for the recovery of valuable drugs from pharmaceutical wastes.