Supporting Information

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

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Table S1. General information of the pills used as real matrices in this study; identification and content of the NSAIDs , name of the medicine, list of excipients and MA holder [information available on the website of the Portuguese National Authority of Medicines and Health Products (INFARMED, I.P.) - www.infarmed.pt].

API	***Medicine name*** **(NSAIDs content)**	**Excipients**	**MA holder**
NAP	*Naproxeno Generis* (naproxen 250 mg)	Magnesium stearate, microcrystalline cellulose, colloidal silica, povidone	Generis Farmacêutica, Amadora, Portugal
KET	*Profenid Retard* (ketoprofen 200 mg)	Tablet core: calcium hydrogen phosphate dihydrate, hydroxyethyl cellulose, magnesium stearate Coating: cellulose acetate phthalate, ethyl phthalate	Sanofi Aventis, Porto Salvo, Portugal
IBU	*Brufen* (ibuprofen 200 mg)	Microcrystalline cellulose, crosslinked sodium carboxymethylcellulose, lactose monohydrate, colloidal silica dioxide, sodium lauryl sulfate, magnesium stearate, hypromellose (hydroxypropyl methylcellulose) 2910, hypromellose 2910, talc and titanium dioxide	Abbott Laboratórios, Amadora, Portugal

Table S2. Validation parameters for the HPLC-DAD analytical method.

	Ibuprofen	**Naproxen**	**Ketoprofen**
Retention Time (min)	16.48[a]	12.73	12.27
Concentration range (µg.mL^{-1}) Minimum of 6 concentrations	10 – 750[a] *0.05 - 50*	10 - 750 *0.05 - 50*	10 - 750 *0.05 - 50*
Injection volume (µL)	10[a] *25*	10 *25*	10 *25*
Wavelength (nm)	230[a] *230*	270 *245*	270 *245*
R^2	0.9999[a] *1.0000*	1.0000 *1.0000*	1.0000 *1.0000*
Linearity range (µg.mL^{-1})	10-750[a] *0.5-50.00*	10-750 *0.05-50.00*	10-750 *0.10-50.00*
LOQ	10[a] *0.50*	10 *0.05*	10 *0.10*
LOD	1[a] *0.20*	1 *0.02*	1 *0.05*
Accuracy intra-day (%)	83.1-101.0[a] *92.9-101.6*	80.5-104.9 *98.2-112.6*	83.0-99.5 *89.2 - 100.5*
Accuracy inter-day (%)	88.7-109.7[a]	87.2-109.3	81.9-114.3
Precision intra-day (RSD, %)	0.15-3.00[a] *0.70-4.00*	0.04-1.73 *0.20-1.90*	0.02-0.50 *0.10-2.00*
Precision inter-day, (%)	0.01-1.93[a]	0.00-0.64	0.00-0.14

[a] Values taken from *e Silva, F. A.; Caban, M.; Stepnowski, P.; Coutinho, J. A. P.; Ventura, S. P. M. Recovery of ibuprofen from pharmaceutical wastes using ionic liquids.* Green Chem. ***2016,*** 18*, 3749-3757. DOI: 10.1039/c6gc00261g.*

Table S3. Tie-lines (TLs) and corresponding values of tie-line lengths (TLLs) information for the IL-based ABS at 25 (±1) °C utilized in the NSAIDs extraction.

ABS	$[IL]_T$ [a]	$[salt]_T$ [b]	$[water]_T$ [c]	$[IL]_M$ [d]	$[salt]_M$ [e]	$[IL]_B$ [f]	$[salt]_B$ [g]	$[water]_B$ [h]	TLL
$[N_{4444}]Cl$ + citrate buffer (pH 7)	68.44	1.74	29.82	29.76	30.11	0.65	51.46	47.89	84.07
[BzCh]Cl + citrate buffer (pH 7)	58.34	7.72	33.94	34.88	30.05	8.95	54.73	36.32	68.18
$[C_4mim]Cl$ + citrate buffer (pH 7)	51.05	8.13	40.82	29.93	29.93	7.82	52.75	39.43	62.13
	55.21	6.01	38.78	33.02	28.12	7.23	53.81	38.96	67.73
	55.62	5.82	38.55	35.25	26.64	5.72	56.82	37.46	71.35
$[C_4mim]Cl$ + citrate buffer (pH 8)	52.27	7.91	39.81	29.95	30.04	7.10	52.69	40.22	63.60
$[C_4mim]Cl$ + potassium citrate tribasic (pH ≈9)	52.95	7.17	39.88	30.10	29.94	6.25	53.72	40.03	65.94

[a] Weight fraction composition (in wt%) of IL in the top phase. | [b] Weight fraction composition (in wt%) of salt in the top phase. | [c] Weight fraction composition (in wt%) of water in the top phase. | [d] Weight fraction composition (in wt%) of IL in the biphasic mixture. | [e] Weight fraction composition (in wt%) of salt in the biphasic mixture. | [f] Weight fraction composition (in wt%) of IL in the bottom phase. | [g] Weight fraction composition (in wt%) of salt in the bottom phase. | [h] Weight fraction composition (in wt%) of water in the bottom phase.

Table S4. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using the ABS composed of 30 wt% of $[C_4mim]Cl$ + 30 wt% of potassium citrate buffer (pH 7), and with distinct NSAIDs contents (in mg NSAID *per* g ABS).

NSAID content / (mg NSAID *per* g ABS)	**1**	**2**	**4**
Ibuprofen			
EE_{NSAID} **± σ, %**	86.7 ± 1.3	87.9 ± 0.7	97.8 ± 2.9
R_T **± σ, %**	98.2 ± 0.1	98.8 ± 0.0	99.2 ± 0.3
Naproxen			
EE_{NSAID} **± σ, %**	90.4 ± 2.6	98.1 ± 2.3	92.8 ± 6.9
R_T **± σ, %**	98.2 ± 0.1	98.5 ± 0.0	98.7 ± 0.7
Ketoprofen			
EE_{NSAID} **± σ, %**	93.7 ± 4.0	91.9 ± 0.1	99.2 ± 3.5
R_T **± σ, %**	98.7 ± 0.1	98.9 ± 0.1	99.1 ± 0.5

Table S5. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using distinct IL-based ABS.

IL	**[C_4mim]Cl**	**[N_{4444}]Cl**	**[BzCh]Cl**
Ibuprofen			
EE_{NSAID} ± σ, %	97.8 ± 2.9	88.8 ± 8.4	90.1 ± 6.6
R_T ± σ, %	99.2 ± 0.3	100	100
Naproxen			
EE_{NSAID} ± σ, %	92.8 ± 6.9	84.9 ± 5.6	86.6 ± 8.5
R_T ± σ, %	98.7 ± 0.7	100	99.8 ± 0.0
Ketoprofen			
EE_{NSAID} ± σ, %	99.2 ± 3.5	90.2 ± 9.6	99.6 ± 7.9
R_T ± σ, %	99.1 ± 0.5	100	99.6 ± 0.0

Table S6. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using the ABS composed of 30 wt% of $[C_4mim]Cl$ + 30 wt% of potassium citrate buffer at distinct temperatures (±1 °C) and pH 7.

Temperature (°C)	**15**	**25**	**35**	**45**
Ibuprofen				
EE_{NSAID} **± σ, %**	90.0 ± 2.4	97.8 ± 2.9	91.5 ± 2.2	91.3 ± 0.5
R_T **± σ, %**	97.8 ± 0.5	99.2 ± 0.3	99.2 ±0.1	99.3 ±0.0
Naproxen				
EE_{NSAID} **± σ, %**	91.2 ± 2.0	92.8 ± 6.9	92.5 ± 0.4	96.4 ± 2.2
R_T **± σ, %**	97.4 ± 0.9	98.7 ± 0.7	99.1 ± 0.1	99.2 ± 0.0
Ketoprofen				
EE_{NSAID} **± σ, %**	94.5 ± 1.6	99.2 ± 3.5	94.8 ± 1.0	100
R_T **± σ, %**	97.7 ± 0.7	99.1 ± 0.5	99.3 ± 0.1	99.4 ± 0.1

Table S7. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using ABS composed of 30 wt% of $[C_4mim]Cl$ + 30 wt% of potassium citrate buffer or potassium citrate tribasic, at distinct pH values.

pH	**7**	**8**	**≈9**
Ibuprofen			
$EE_{NSAID} \pm \sigma$, %	97.8 ± 2.9	94.2 ± 4.8	85.1 ± 3.8
$R_T \pm \sigma$, %	99.2 ± 0.3	99.0 ± 0.2	99.1 ± 0.2
Naproxen			
$EE_{NSAID} \pm \sigma$, %	92.8 ± 6.9	91.7 ± 0.8	86.5 ± 0.6
$R_T \pm \sigma$, %	98.7 ± 0.7	98.8 ± 0.3	99.0 ± 0.2
Ketoprofen			
$EE_{NSAID} \pm \sigma$, %	99.2 ± 3.5	95.3 ± 3.9	89.1 ± 0.8
$R_T \pm \sigma$, %	99.1 ± 0.5	99.1 ± 0.2	99.1 ± 0.3

Table S8. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using the ABS composed of $[C_4mim]Cl$ + potassium citrate buffer (pH 7) at variable mixture compositions (in wt%)/TLLs.

($[IL]_M$, $[Salt]_M$) / (wt%) ***TLL***	**(30, 30)** ***62.13***	**(33, 28)** ***67.73***	**(35, 26.5)** ***71.35***
Ibuprofen			
EE_{NSAID} ± σ, %	97.8 ± 2.9	85.6 ± 3.7	80.3 ± 2.6
R_T ± σ, %	99.2 ± 0.3	98.2 ± 1.4	99.4 ± 0.2
Naproxen			
EE_{NSAID} ± σ, %	92.8 ± 6.9	86.5 ± 3.1	82.5 ± 3.0
R_T ± σ, %	98.7 ± 0.7	98.1 ± 1.4	99.4 ± 0.2
Ketoprofen			
EE_{NSAID} ± σ, %	99.2 ± 3.5	93.0 ± 1.2	85.1 ± 2.9
R_T ± σ, %	99.1 ± 0.5	99.0 ± 0.8	99.4 ± 0.2

Table S9. Comparison between the proposed stability study protocol and the original OECD 111e one.

Parameter	OECD 111e	Present protocol
Purpose	Estimating hydrolysis as abiotic degradation path in environment.	Determining ILs' influence on the stability of drugs in extraction processes.
Test substance application	Compounds with good solubility in water are required.	Compounds with good solubility in water are not mandatory. It will depend upon compounds' solubility in IL enriched matrix.
Concentration of tested compound	10^{-2} to 10^{-3} M for environmental conditions (≤10^{-6} M).	Not confined. Similar concentrations to those instilled by the extraction process are preferable.
Temperature	50 °C	Temperature at which the IL-based ABS was conducted. Other temperatures may be included if a temperature effect study is targeted.
Time of incubation	5 days (preliminary test)	5 days
Sample pH	4, 7 and 9	pH at which the IL-based ABS was conducted. Other pH values may be included if a pH effect study is targeted.
Buffer solution	CLARK and LUBS, Citrate buffers of KOLTHOFF and VLEESCHHOUWER, Borate and phosphate mixtures of SÖRENSEN	Buffer (or salt) used as phase-forming agent in the ABS. Also samples without salt addition may be included to control salt effect on analyte stability.
Sub-samples taking time	t_0 and after 5 days.	St_0 (control) and after 5 days (St_{25} and St_{50}).

Table S10. Extraction efficiencies (EE_{NSAID}, %) and recovery toward the top phase (R_T, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using the IL-TPP investigated.

	[C_4mim]Cl	**[N_{4444}]Cl**	**[BzCh]Cl**
Ibuprofen			
EE_{NSAID} ± σ, %	92.3 ± 5.1	89.8 ± 5.1	86.3 ± 5.5
R_T ± σ, %	97.8 ± 0.7	100	99.8 ± 0.1
Naproxen			
EE_{NSAID} ± σ, %	86.6 ± 5.0	89.7 ± 3.1	84.9 ± 3.9
R_T ± σ, %	97.8 ± 0.3	100	99.7 ± 0.0
Ketoprofen			
EE_{NSAID} ± σ, %	99.5 ± 6.2	83.8 ± 7.7	86.8 ± 4.1
R_T ± σ, %	98.1 ± 0.3	100	98.3 ± 1.0

Table S11. Isolation efficiencies (IE_{NSAID}, %) plus the corresponding standard deviations (σ) of the three target NSAIDs obtained using the distinct approaches based on the precipitation with an antisolvent.

Ratio of top phase and antisolvent volume	IE_{IBU} **± σ, %**	IE_{NAP} **± σ, %**	IE_{KET} **± σ, %**
Citric acid aqueous solution at 25 wt%			
1:4	78.7 ± 2.2	79.1 ± 3.0	-
Aluminium sulphate aqueous solution at 15 wt%			
1:4	-	-	76.2 ± 1.8
1:6	-	-	80.9 ± 0.7
1:8	-	-	83.4 ± 4.0
1:10	-	-	87.1 ± 0.2
1:12	-	-	87.9 ± 0.3

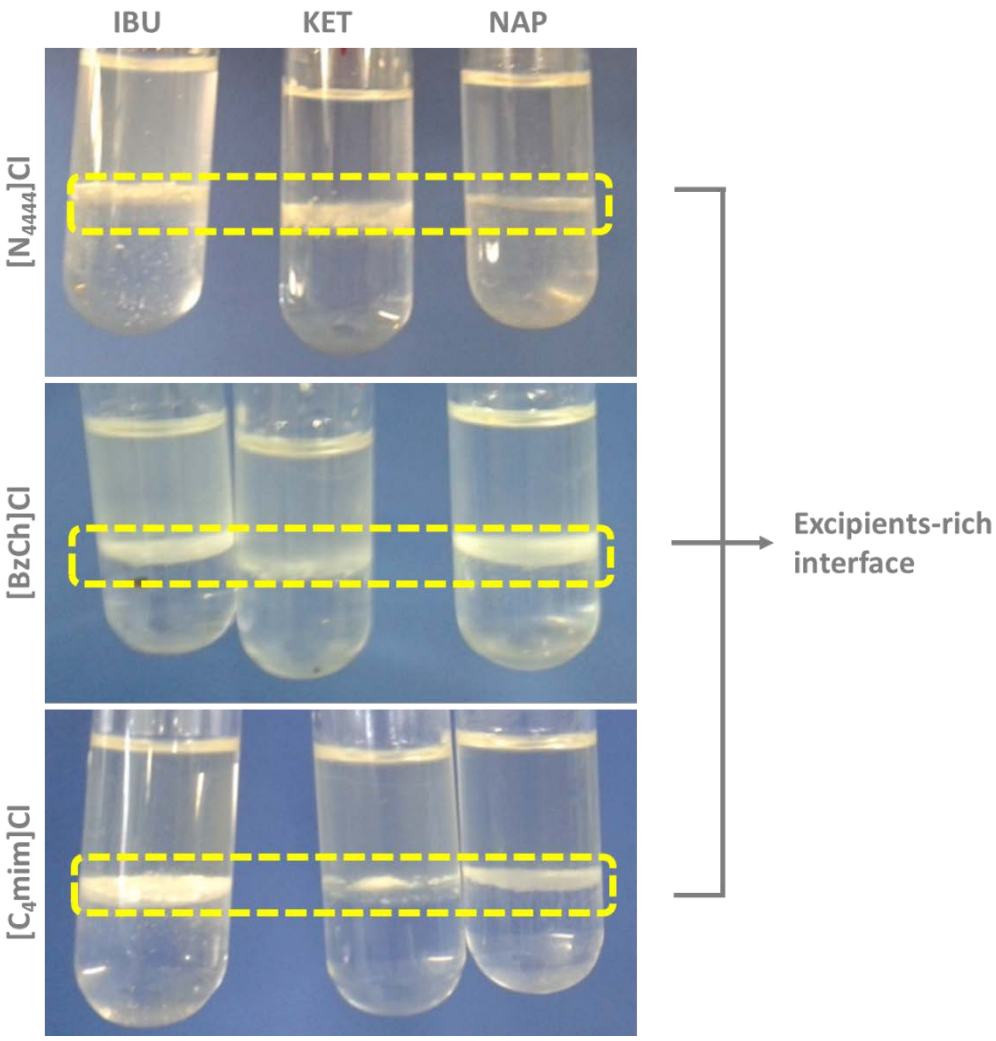

Figure S1. Visual appearance of IL-based TPP developed in the present study for the recovery of active ingredients, namely ibuprofen (IBU), ketoprofen (KET) and naproxen (NAP) from solid state pills.