Electronic Supplementary Information

Improved Monitoring of Aqueous Samples by the Concentration of Active Pharmaceutical Ingredients using Ionic-Liquid-based Systems

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Determination of Tie-Lines (TLs) and Tie-Line Lengths (TLLs)

The specific composition of each phase in equilibrium was determined based on the initial mixture composition and on the weight of each phase, using the following equations (eqs. (1) – (4)) with four unknown values ($[IL]_{IL}$, $[IL]_{salt}$, $[salt]_{IL}$, $[salt]_{salt}$): [1]

$$[\mathrm{IL}]_{\mathrm{IL}} = \mathrm{A}\exp[(\mathrm{B}\times[\mathrm{salt}]_{\mathrm{IL}}^{0.5}) \quad (\mathrm{C}\times[\mathrm{salt}]_{\mathrm{IL}}^{3})] \tag{1}$$

$$[\mathrm{IL}]_{\mathrm{salt}} = \mathrm{A}\exp[(\mathrm{B}\times[\mathrm{salt}]_{\mathrm{salt}}^{0.5}) \quad (\mathrm{C}\times[\mathrm{salt}]_{\mathrm{salt}}^{3})] \tag{2}$$

$$[\mathrm{IL}]_{\mathrm{IL}} = \frac{[\mathrm{IL}]_{\mathrm{M}}}{\alpha} \quad \frac{1-\alpha}{\alpha}\times[\mathrm{IL}]_{\mathrm{salt}} \tag{3}$$

$$[\mathrm{salt}]_{\mathrm{IL}} = \frac{[\mathrm{salt}]_{\mathrm{M}}}{\alpha} \quad \frac{1-\alpha}{\alpha}\times[\mathrm{salt}]_{\mathrm{salt}} \tag{4}$$

where IL, salt and M are the ionic-liquid-rich phase, the salt-rich phase and the mixture, respectively. [IL] and [salt] correspond to the weight fraction percentage of ionic liquid and salt, respectively, and α is the ratio between the weight of the ionic-liquid-rich phase and the total mass of the mixture.

For the calculation of the tie-line length (TLL), the following equation was used:

$$\mathrm{TLL} = \sqrt{([\mathrm{salt}]_{\mathrm{IL}} \quad [\mathrm{salt}]_{\mathrm{salt}})^2 + ([\mathrm{IL}]_{\mathrm{IL}} \quad [\mathrm{IL}]_{\mathrm{salt}})^2} \tag{5}$$

where IL and salt represents the ionic-liquid-rich phase and salt-rich phase, respectively. [IL] and [salt] correspond to the weight fraction percentage of ionic liquid and salt, as described before.

Extraction and concentration of APIs using IL-based ABS

Table S.I. 1. Weight fraction percentage (wt%) of each compound in the coexisting phases of the ABS investigated.

	Fluoroquinolones					
	Weight fraction percentage / wt%					
Ionic Liquid	**$[IL]_{salt}$**	**$[salt]_{salt}$**	**$[IL]_M$**	**$[salt]_M$**	**$[IL]_{IL}$**	**$[salt]_{IL}$**
$[P_{4444}]Cl$	2.7	40.3	40.2	18.8	66.5	3.8
$[N_{4444}]Cl$	1.9	46.4	39.8	18.8	62.8	2.1
$[C_4C_1pip][Cl$	3.1	58.9	40.1	18.9	51.9	6.1
$[C_4C_1pyr]Cl$	5.6	54.1	40.0	18.9	53.1	5.5
$[C_4C_1im]Cl$	9.1	48.9	39.9	18.8	49.9	8.9
$[C_8C_1im]Cl$	12.7	44.4	39.9	18.7	46.9	12.2
$[C_4C_1im]Br$	4.6	43.1	39.9	18.9	63.7	2.7
$[C_4C_1im][SCN]$	0.0	34.7	40.1	19.0	87.4	0.5
$[C_4C_1im][N(CN)_2]$	0.1	40.6	39.8	18.9	71.9	1.4
$[C_4C_1im][CF_3SO_3]$	1.1	34.2	40.1	19.0	85.7	1.2
	Non-steroidal anti-inflammatory drugs					
	Weight fraction percentage / wt%					
Ionic Liquid	**$[IL]_{salt}$**	**$[salt]_{salt}$**	**$[IL]_M$**	**$[salt]_M$**	**$[IL]_{IL}$**	**$[salt]_{IL}$**
$[P_{4444}]Cl$	2.8	40.1	40.0	18.9	66.7	3.7
$[N_{4444}]Cl$	2.1	45.9	40.0	18.9	64.0	1.9
$[C_4C_1pip][Cl$	3.1	58.8	39.8	18.9	51.6	6.2
$[C_4C_1pyr]Cl$	2.9	61.4	40.1	18.9	51.0	6.4
$[C_4C_1im]Cl$	9.6	48.2	40.0	18.9	51.1	8.2
$[C_8C_1im]Cl$	11.9	45.6	40.0	18.8	47.2	12.0
$[C_4C_1im]Br$	4.4	43.6	40.0	18.9	63.4	2.7
$[C_4C_1im][SCN]$	0.1	34.6	40.1	19.0	87.6	0.4
$[C_4C_1im][N(CN)_2]$	0.0	43.3	39.8	18.8	67.3	1.5
$[C_4C_1im][CF_3SO_3]$	1.0	34.3	40.0	19.0	85.4	1.0

Table S.I. 2. Tie-line length (TLL), pH of the IL-rich phase (pH_{IL}), and extraction efficiencies of the studied fluoroquinolones ($\%EE_{FQs}$), and corresponding standard deviations (σ).

Ciprofloxacin			
Ionic Liquid	**TLL ± σ**	**pH_{IL} ± σ**	**$\%EE_{FQs}$ ± σ**
$[P_{4444}]Cl$	73.3 ± 0.3	8.52 ± 0.04	99.80 ± 0.39
$[N_{4444}]Cl$	75.5 ± 0.3	9.91 ± 0.06	99.37 ± 0.73
$[C_4C_1pip][Cl$	72.7 ± 1.1	9.51 ± 0.03	99.29 ± 0.59
$[C_4C_1pyr]Cl$	68.9 ± 1.3	9.31 ± 0.01	98.82 ± 0.23
$[C_4C_1im]Cl$	58.1 ± 1.3	9.08 ± 0.02	99.28 ± 0.43
$[C_8C_1im]Cl$	47.4 ± 0.6	7.37 ± 0.01	99.29 ± 0.37
$[C_4C_1im]Br$	71.5 ± 0.2	8.23 ± 0.02	93.06 ± 1.96
$[C_4C_1im][SCN]$	93.8 ± 0.5	7.59 ± 0.03	62.72 ± 0.22
$[C_4C_1im][N(CN)_2]$	81.8 ± 0.0	9.14 ± 0.01	98.13 ± 0.32
$[C_4C_1im][CF_3SO_3]$	90.8 ± 1.1	8.04 ± 0.04	61.33 ± 2.58
Norfloxacin			
Ionic Liquid	**TLL ± σ**	**pH_{IL} ± σ**	**$\%EE_{FQs}$ ± σ**
$[P_{4444}]Cl$	73.3 ± 0.3	8.61 ± 0.04	98.35 ± 3.29
$[N_{4444}]Cl$	76.2 ± 0.5	9.95 ± 0.09	99.36 ± 0.72
$[C_4C_1pip][Cl$	70.7 ± 1.1	9.52 ± 0.01	93.62 ± 0.52
$[C_4C_1pyr]Cl$	67.5 ± 0.1	9.28 ± 0.02	98.84 ± 0.16
$[C_4C_1im]Cl$	58.7 ± 0.4	9.08 ± 0.02	99.16 ± 0.25
$[C_8C_1im]Cl$	45.9 ± 1.0	7.37 ± 0.01	98.96 ± 0.40
$[C_4C_1im]Br$	71.9 ± 0.0	8.14 ± 0.02	95.32 ± 2.24
$[C_4C_1im][SCN]$	93.5 ± 0.6	7.50 ± 0.05	62.83 ± 0.87
$[C_4C_1im][N(CN)_2]$	80.8 ± 0.0	9.12 ± 0.04	96.62 ± 0.20
$[C_4C_1im][CF_3SO_3]$	90.4 ± 0.9	7.50 ± 0.01	58.83 ± 0.83
Enrofloxacin			
Ionic Liquid	**TLL ± σ**	**pH_{IL} ± σ**	**$\%EE_{FQs}$ ± σ**
$[P_{4444}]Cl$	72.7 ± 0.4	8.22 ± 0.03	97.28 ± 0.78
$[N_{4444}]Cl$	75.9 ± 0.1	9.78 ± 0.00	99.44 ± 1.13
$[C_4C_1pip][Cl$	71.0 ± 0.6	9.72 ± 0.04	99.35 ± 0.31
$[C_4C_1pyr]Cl$	58.2 ± 0.0	9.15 ± 0.02	99.55 ± 0.35
$[C_4C_1im]Cl$	60.1 ± 0.3	9.52 ± 0.04	99.66 ± 0.68
$[C_8C_1im]Cl$	46.0 ± 0.6	7.39 ± 0.01	99.35 ± 0.31
$[C_4C_1im]Br$	72.2 ± 0.1	8.57 ± 0.01	97.57 ± 1.87
$[C_4C_1im][SCN]$	93.9 ± 1.0	7.59 ± 0.03	95.16 ± 0.63
$[C_4C_1im][N(CN)_2]$	82.6 ± 0.0	9.15 ± 0.03	99.60 ± 0.11
$[C_4C_1im][CF_3SO_3]$	90.1 ± 0.8	7.98 ± 0.13	90.89 ± 2.42

Table S.I. 3. Tie-line length (TLL), pH of the IL-rich phase (pH_{IL}), and extraction efficiencies of the studied non-steroidal anti-inflammatory drugs ($\%EE_{NSAIDs}$), and corresponding standard deviations (σ).

Ionic Liquid	TLL ± σ	pH_{IL} ± σ	$\%EE_{NSAIDs}$ ± σ
	Diclofenac		
$[P_{4444}]Cl$	73.5 ± 0.3	9.55 ± 0.06	99.55 ± 0.81
$[N_{4444}]Cl$	76.0 ± 0.1	9.90 ± 0.04	99.71 ± 0.70
$[C_4C_1pip][Cl$	72.4 ± 1.3	9.51 ± 0.03	99.65 ± 0.16
$[C_4C_1pyr]Cl$	70.6 ± 3.6	9.56 ± 0.01	99.21 ± 0.69
$[C_4C_1im]Cl$	57.7 ± 1.7	8.72 ± 0.02	97.65 ± 2.82
$[C_8C_1im]Cl$	48.8 ± 0.8	7.38 ± 0.01	99.22 ± 0.38
$[C_4C_1im]Br$	71.8 ± 0.6	8.35 ± 0.02	96.16 ± 2.44
$[C_4C_1im][SCN]$	93.7 ± 0.4	7.68 ± 0.03	97.42 ± 2.46
$[C_4C_1im][N(CN)_2]$	80.0 ± 1.3	9.33 ± 0.01	95.61 ± 0.85
$[C_4C_1im][CF_3SO_3]$	90.1 ± 0.8	7.90 ± 0.04	96.41 ± 2.66
	Naproxen		
Ionic Liquid	**TLL ± σ**	**pH_{IL} ± σ**	**$\%EE_{NSAIDs}$ ± σ**
$[P_{4444}]Cl$	76.1 ± 0.1	9.19 ± 0.04	95.44 ± 2.96
$[N_{4444}]Cl$	78.9 ± 0.1	9.20 ± 0.10	99.75 ± 0.01
$[C_4C_1pip][Cl$	71.2 ± 1.2	9.52 ± 0.01	95.65 ± 2.57
$[C_4C_1pyr]Cl$	70.3 ± 1.7	9.58 ± 0.02	98.21 ± 1.50
$[C_4C_1im]Cl$	67.4 ± 0.5	8.74 ± 0.02	97.98 ± 1.86
$[C_8C_1im]Cl$	47.4 ± 0.7	7.36 ± 0.01	99.34 ± 0.24
$[C_4C_1im]Br$	75.7 ± 0.1	8.45 ± 0.03	92.32 ± 5.33
$[C_4C_1im][SCN]$	93.6 ± 0.7	7.62 ± 0.05	83.14 ± 1.31
$[C_4C_1im][N(CN)_2]$	82.4 ± 0.1	9.29 ± 0.04	93.10 ± 6.50
$[C_4C_1im][CF_3SO_3]$	90.3 ± 0.8	7.84 ± 0.01	96.06 ± 1.72
	Ketoprofen		
Ionic Liquid	**TLL ± σ**	**pH_{IL} ± σ**	**$\%EE_{NSAIDs}$ ± σ**
$[P_{4444}]Cl$	72.9 ± 0.5	9.76 ± 0.03	92.63 ± 4.53
$[N_{4444}]Cl$	77.5 ± 2.0	9.59 ± 0.00	99.52 ± 0.25
$[C_4C_1pip][Cl$	71.0 ± 0.6	9.72 ± 0.04	98.96 ± 0.94
$[C_4C_1pyr]Cl$	71.4 ± 0.9	9.58 ± 0.02	98.09 ± 1.82
$[C_4C_1im]Cl$	60.5 ± 1.0	8.79 ± 0.04	97.33 ± 4.31
$[C_8C_1im]Cl$	45.9 ± 0.6	7.39 ± 0.01	93.65 ± 1.91
$[C_4C_1im]Br$	71.6 ± 0.1	8.37 ± 0.01	94.46 ± 5.12
$[C_4C_1im][SCN]$	93.8 ± 1.1	7.70 ± 0.33	95.32 ± 3.84
$[C_4C_1im][N(CN)_2]$	80.4 ± 0.7	9.34 ± 0.03	96.53 ± 1.54
$[C_4C_1im][CF_3SO_3]$	90.0 ± 0.7	7.86 ± 0.13	85.33 ± 8.14

Table S.I. 4. Initial mixture composition (wt%), percentage extraction efficiencies of ciprofloxacin and diclofenac (%EE_{FQs} and % EE_{NSAIDs}, respectively) and tie-line length (TLL), with corresponding standard deviations (σ).

IL	***Ciprofloxacin***							
	Weight fraction percentage / wt%						**TLL ± σ**	**% EE_{FQs} ± σ**
	$[IL]_{salt}$	**$[salt]_{salt}$**	**$[IL]_M$**	**$[salt]_M$**	**$[IL]_{IL}$**	**$[salt]_{IL}$**		
	2.8	43.5	39.8	15.1	55.2	3.4	65.82 ± 0.17	99.75 ± 0.29
$[N_{4444}]Cl$	1.9	46.4	39.9	18.8	63.3	2.0	77.51 ± 0.28	99.37 ± 0.73
	0.5	53.7	39.9	24.1	71.5	1.0	87.64 ± 0.35	99.77 ± 0.27

IL	***Diclofenac***							
	Weight fraction percentage / wt%						**TLL ± σ**	**% EE_{NSAIDs} ± σ**
	$[IL]_{salt}$	**$[salt]_{salt}$**	**$[IL]_M$**	**$[salt]_M$**	**$[IL]_{IL}$**	**$[salt]_{IL}$**		
	3.3	41.5	40.2	14.8	56.4	3.1	65.51 ± 0.66	99.26 ± 0.51
$[N_{4444}]Cl$	1.8	46.0	40.1	18.9	64.2	1.9	76.40 ± 0.17	99.71 ± 0.70
	0.7	51.8	40.3	24.3	73.9	0.8	89.18 ± 0.77	99.32 ± 0.82

Table S.I. 5. Percentage extraction efficiencies of ciprofloxacin and diclofenac (%EE_{FQs} and % EE_{NSAIDs}, respectively) with corresponding standard deviations (σ), initial mixture composition (wt %) and concentration factor (CF).

Ciprofloxacin				
IL	**Weight fraction percentage / wt%**		**%EE_{FQs} ± σ**	**CF**
	$[IL]_M$	**$[salt]_M$**		
$[N_{4444}]Cl$	39.92	24.14	99.8 ± 0.3	0.6
	24.35	35.07	99.7 ± 0.4	1.1
	13.98	42.52	99.7 ± 0.5	2.0
	8.07	46.54	99.5 ± 0.8	3.3
	2.99	49.85	99.7 ± 0.4	9.0
	0.53	51.74	99.9 ± 0.2	1084.5
Diclofenac				
IL	**Weight fraction percentage / wt%**		**%EE_{NSAIDs} ± σ**	**CF**
	$[IL]_M$	**$[salt]_M$**		
$[N_{4444}]Cl$	40.11	24.35	99.3 ± 0.8	0.7
	24.38	35.12	99.6 ± 0.7	1.1
	14.01	42.50	99.4 ± 0.8	2.1
	8.02	46.53	99.0 ± 0.8	3.3
	3.02	50.03	99.1 ± 1.2	8.0
	0.53	51.74	99.9 ± 0.2	1164.4

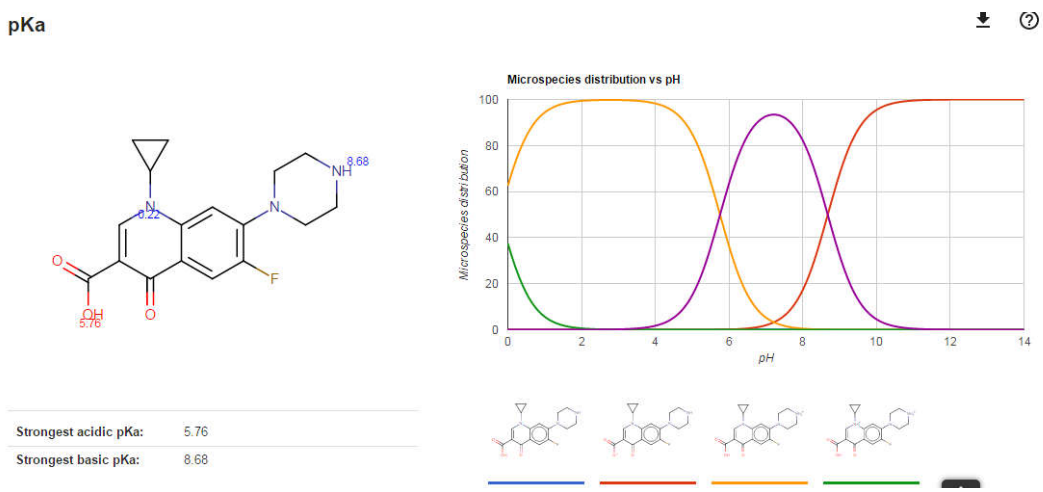


Figure S.I. 1. Speciation profile of ciprofloxacin as a function of the pH.[3]

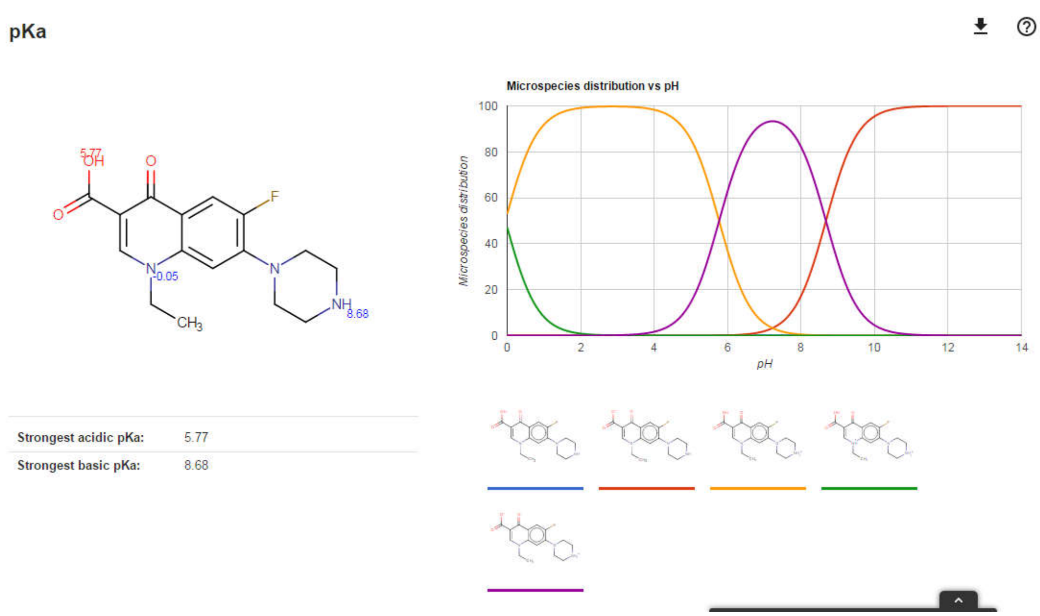


Figure S.I. 2. Speciation profile of norfloxacin as a function of the pH.[3]

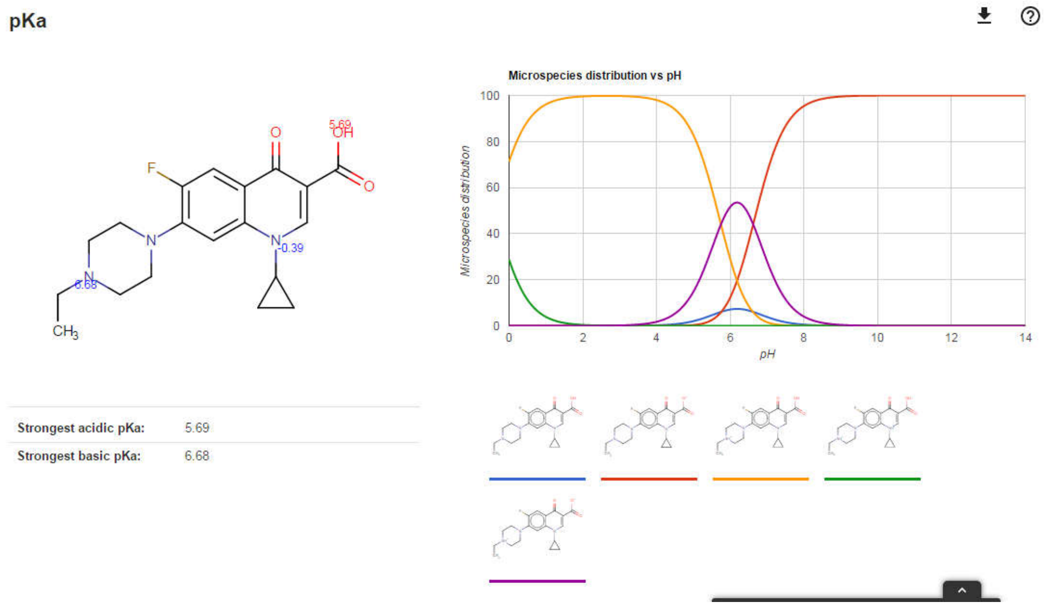


Figure S.I. 3. Speciation profile of enrofloxacin as a function of the pH.[3]

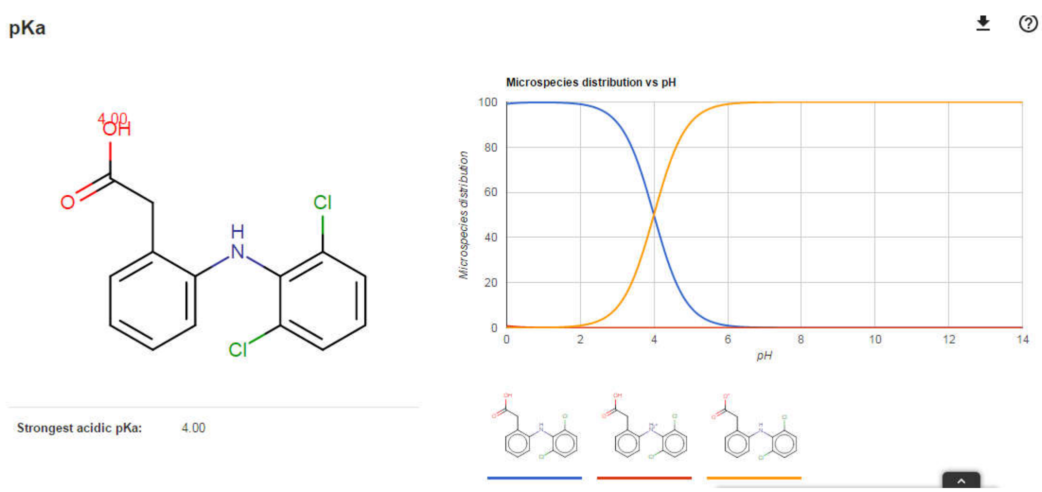


Figure S.I. 4. Speciation profile of diclofenac as a function of the pH.[3]

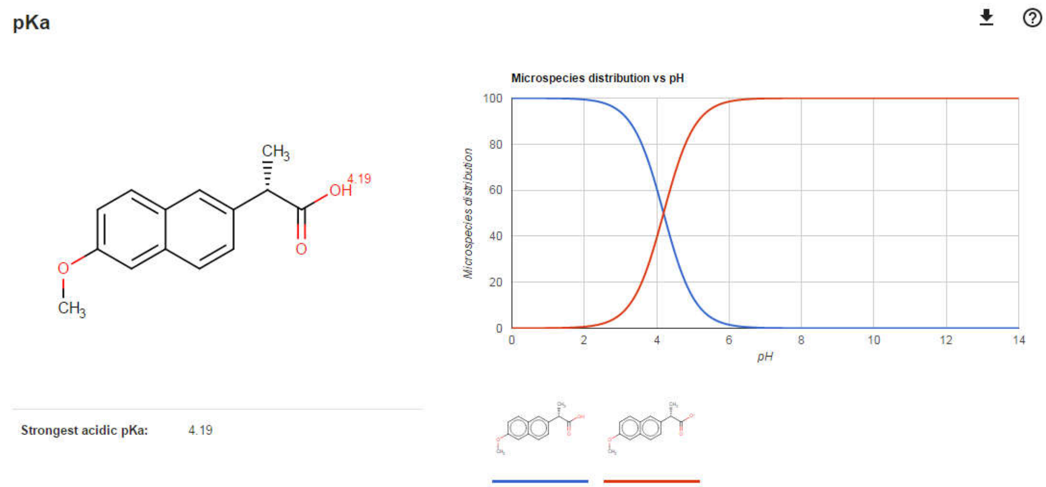


Figure S.I. 5. Speciation profile of naproxen as a function of the pH.[3]

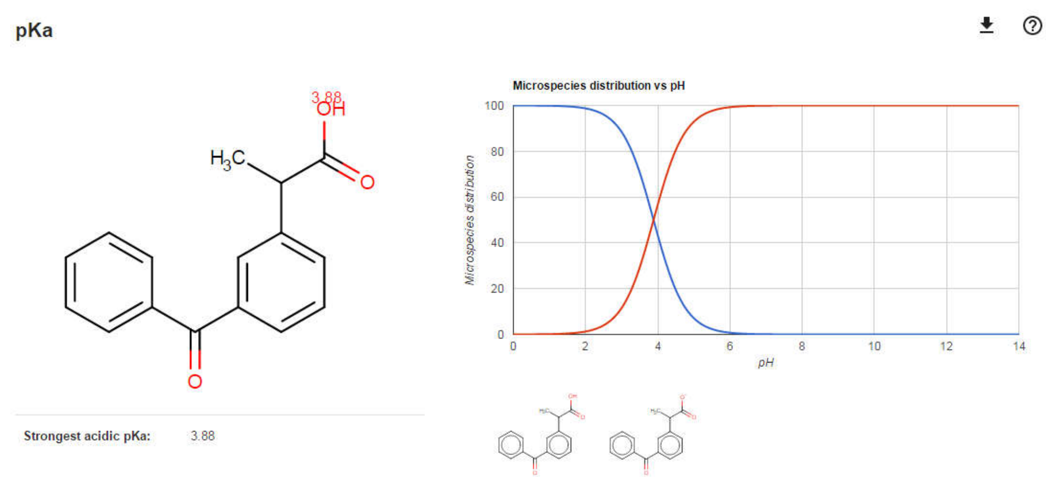


Figure S.I. 6. Speciation profile of ketoprofen as a function of the pH.[3]

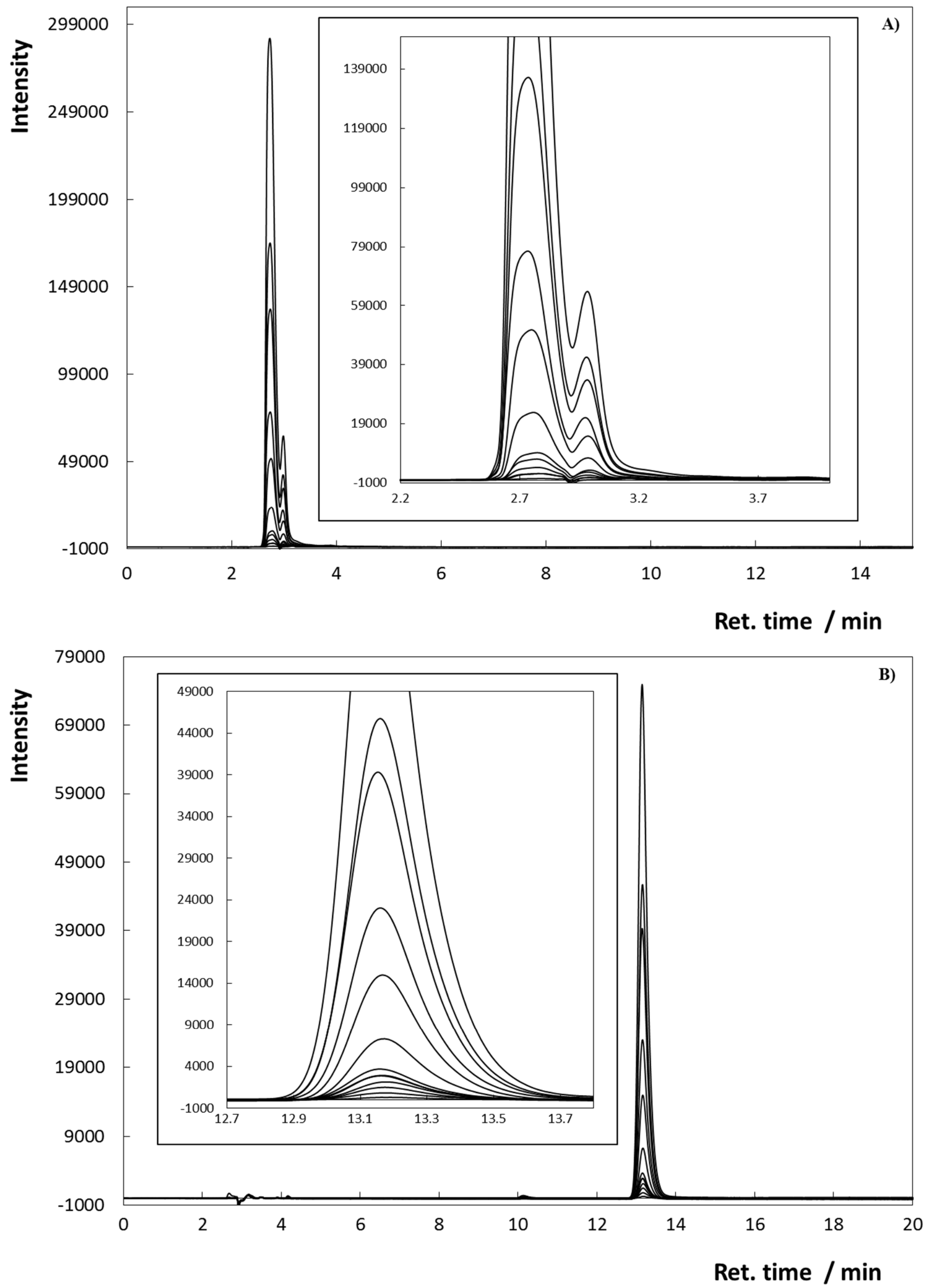
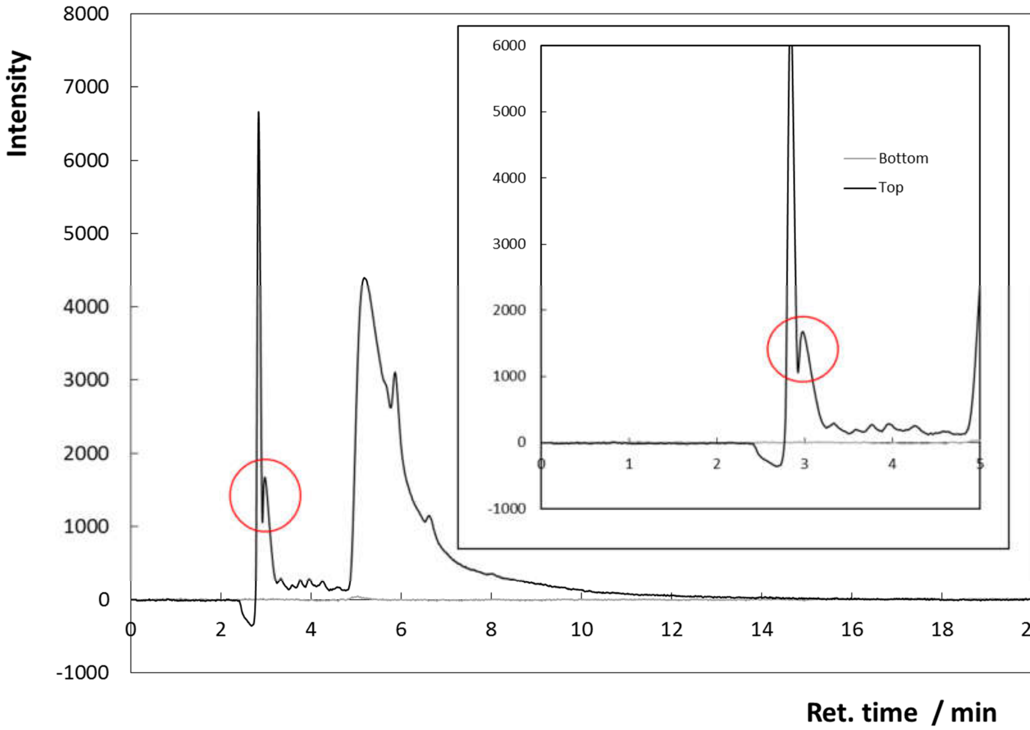


Figure S.I. 7. HPLC-UV chromatograms of (A) ciprofloxacin and (B) diclofenac at different concentrations at 278 nm and 275 nm, respectively. The concentrations used were in the range of 0.0002 to 0.0500 $g.L^{-1}$.



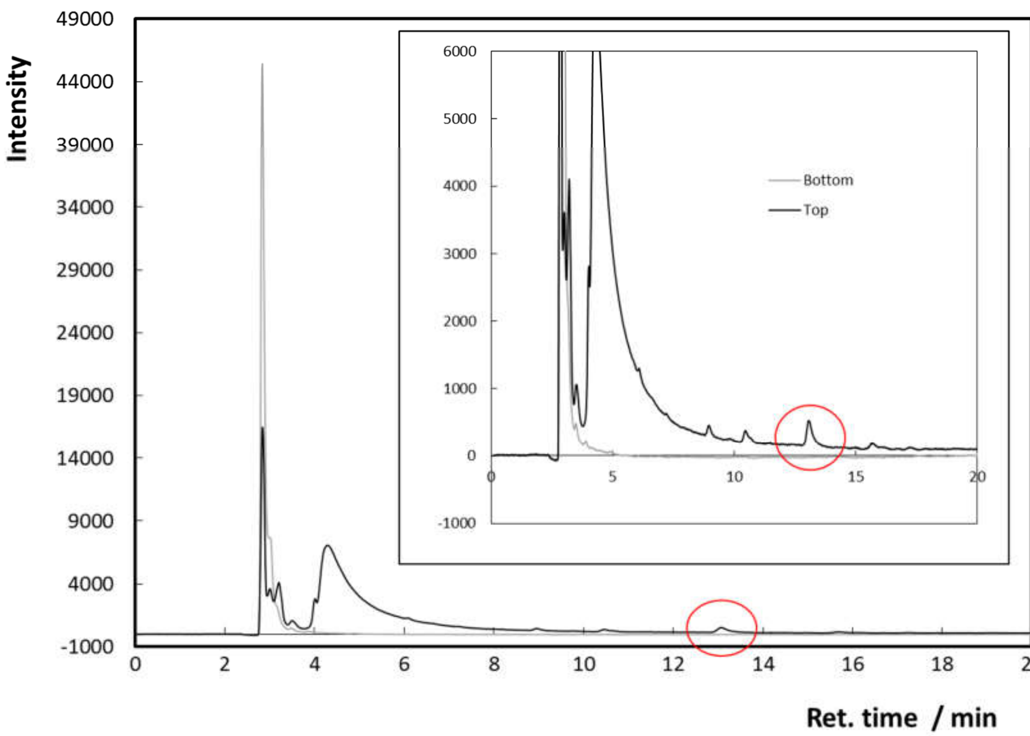


Figure S.I. 1. HPLC-UV chromatograms after the ABS concentration step with model systems (distilled water) containing (A) ciprofloxacin and (B) diclofenac at 278 nm and 275 nm, respectively. Circles are representative of ciprofloxacin and diclofenac.

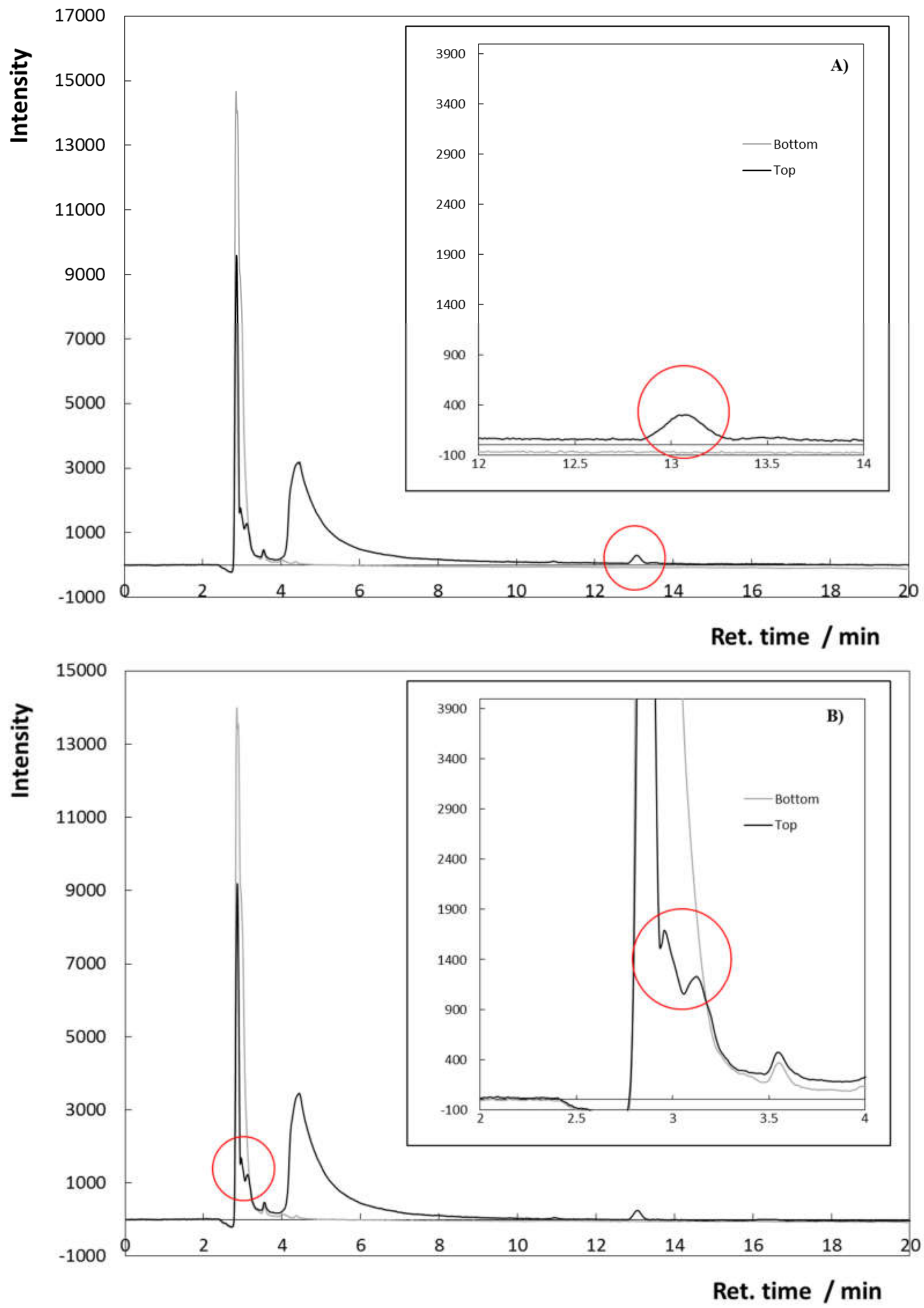


Figure S.I. 9. HPLC-UV chromatograms after the ABS concentration step with model systems/distilled water containing a mixture of (A) ciprofloxacin and (B) diclofenac at 278 nm and 275 nm, respectively. Circles are representative of ciprofloxacin and diclofenac.

References

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2 A. M. Ferreira, J. A. P. Coutinho, A. M. Fernandes and M. G. Freire, *Separation and Purification Technology*, 2014, **128**, 58-66.
3 ChemSpider - The free chemical database at www.chemspider.com (Accessed on October 2015)).