

Supplementary Information

Polyvinylidene fluoride-Hyaluronic acid wound dressing comprised of ionic liquids for controlled drug delivery and dual therapeutic behavior

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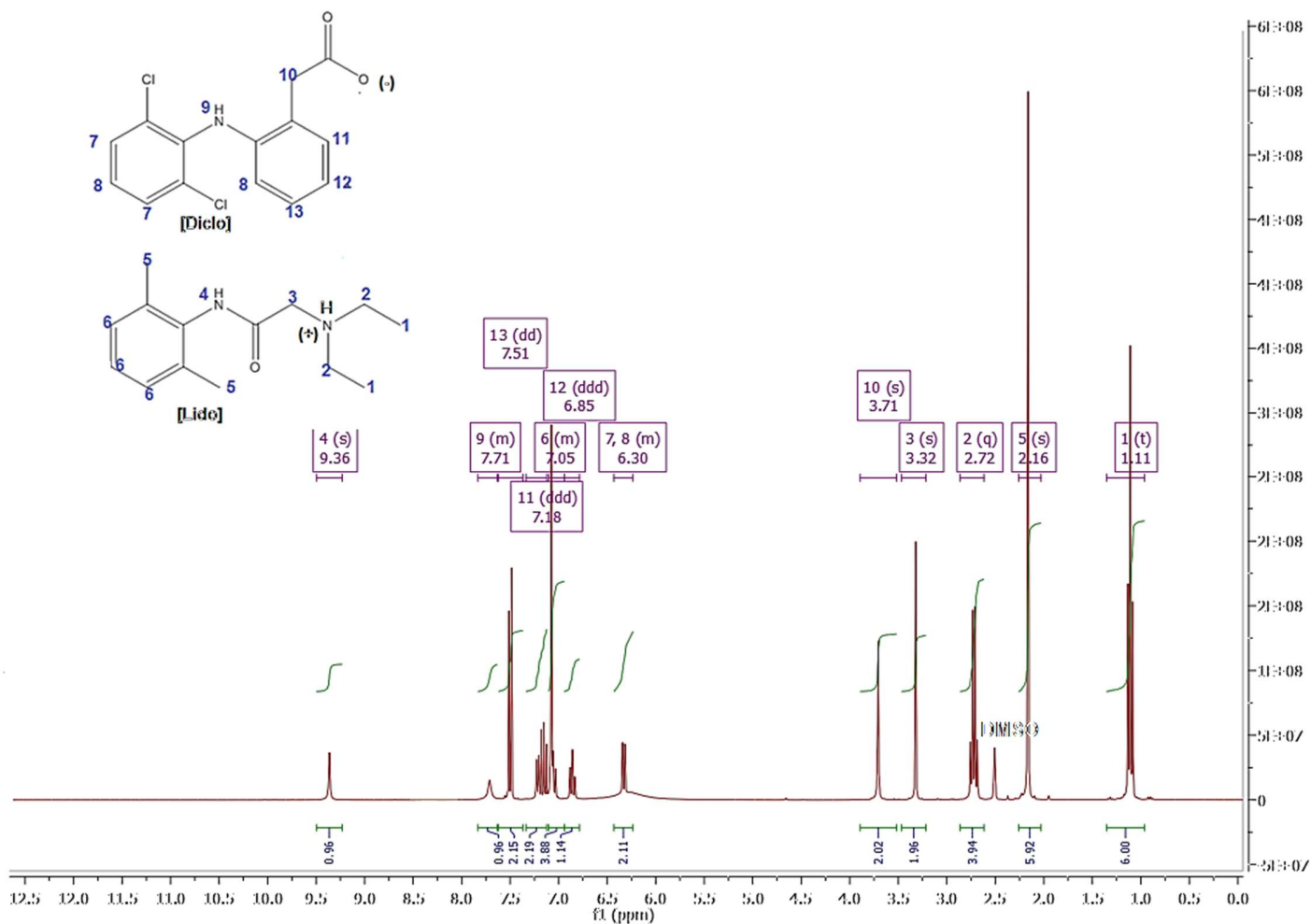
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maragfreire@ua.pt.

API-ILs Characterization:

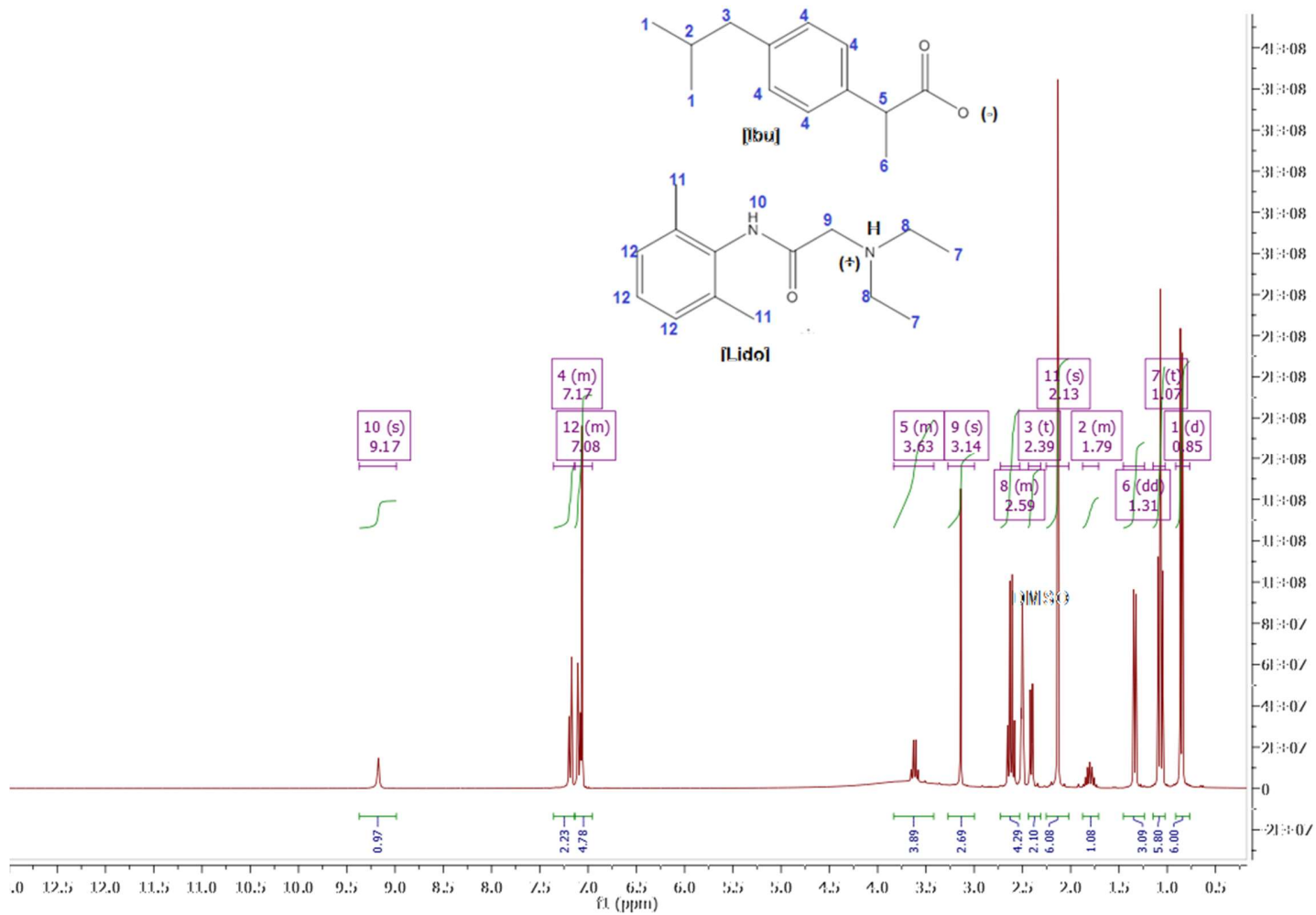
[Lido][Diclo] was prepared as a yellow viscous liquid. ^1H NMR (*d6*-DMSO, 300 MHz, [ppm]): δ 1.11 (t, $J = 7.2$ Hz, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.16 (s, 6H, $\text{C}=\text{C}-\text{CH}_3$, $\text{C}-\text{C}-\text{CH}_3$), 2.72 (q, $J = 7.1$ Hz, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.32 (s, 2H, $\text{NCH}_2\text{C}=\text{O}$), 3.71 (s, 2H, CCH_2COOH), 6.07 – 6.56 (m, 2H, $\text{ClCCH}=\text{CHCH}=\text{CCl}$, NCCHCHCH), 6.76 – 6.93 (m, 1H, $\text{CHCHCCH}_2\text{COOH}$), 6.94 – 7.31 (m, 3H, $\text{CH}_3\text{C}(\text{CH}_3)_3$), 7.13 – 7.20 (m, 1H, NCCHCHCH), 7.22 (dd, $J = 7.5$, 1.4 Hz, 1H, NCCHCH), 7.51 (dd, $J = 7.5$, 4.1 Hz, 2H, $\text{ClCCH}=\text{CHCH}=\text{CCl}$), 7.58 – 7.83 (s, 1H, CNHC), 9.36 (s, 1H, CONHC).

[Lido][Ibu] was prepared as a transparent viscous liquid. ^1H NMR (*d6*-DMSO, 300 MHz, [ppm]): δ 0.85 (d, $J = 6.6$ Hz, 6H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.07 (t, $J = 7.1$ Hz, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.31 (dd, $J = 14.0$, 7.1 Hz, 3H, CH_3CHCOO), 1.65 – 1.97 (m, 1H, CH_2CHCH_3), 2.13 (s, 6H, $\text{CH}=\text{CHCH}_3$, $\text{CH}-\text{CHCH}_3$), 2.39 (t, $J = 11.5$ Hz, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.55 – 2.72 (m, 4H, $\text{N}(\text{CH}_2)_2(\text{CH}_3)_2$), 3.14 (s, 2H, NHCOCH_2N), 3.34 – 3.89 (m, 1H, CH_3CHCOO), 7.07 (d, $J = 5.0$ Hz, 3H, $\text{CH}=\text{CHCHCH}_3$), 7.12 – 7.28 (m, 4H, C_6H_4), 9.17 (s, 1H, NH).

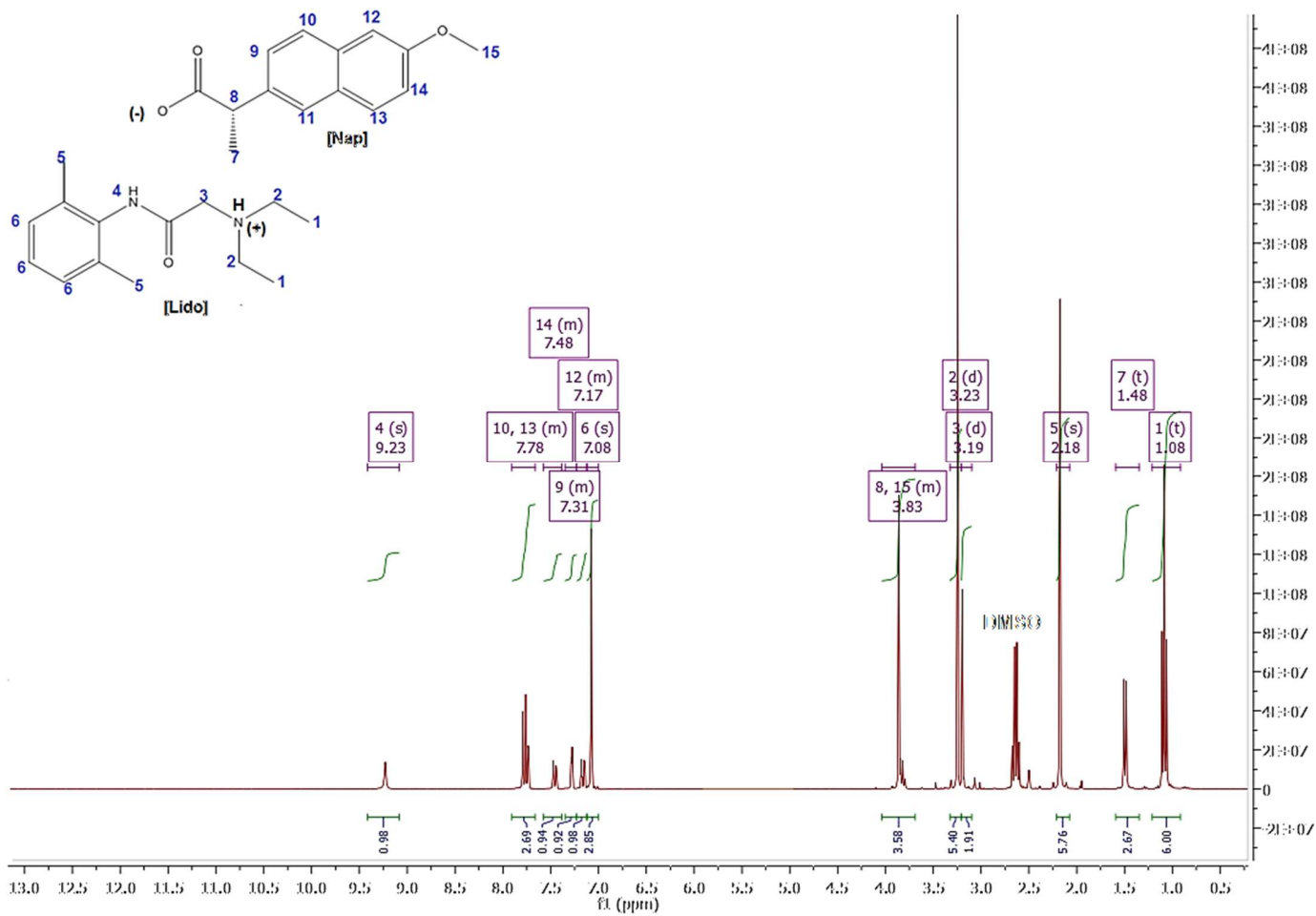
[Lido][Nap] was obtained as a transparent viscous liquid. ^1H NMR (*d6*-DMSO, 300 MHz, [ppm]): δ 1.08 (t, $J = 7.1$ Hz, 6H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.48 (d, $J = 7.1$ Hz, 3H, CHCH_3COOH), 2.16 (s, 6H, $\text{C}_6\text{H}_3(\text{CH}_3)_2$), 2.53 – 2.76 (m, 4H, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 3.19 (s, 2H, NHCOCH_2N), 3.77 (d, $J = 12.9$ Hz, 1H, CHCH_3COOH), 3.85 (d, $J = 7.4$ Hz, 3H, $\text{C}_6\text{H}_3\text{OCH}_3$), 7.07 (s, 3H, $\text{C}_6\text{H}_3(\text{CH}_3)_2$), 7.13 – 7.92 (m, 6H, $\text{CH}_3\text{CHC}_6\text{H}_3\text{C}_6\text{H}_3\text{OCH}_3$), 9.23 (s, 1H, $\text{NCH}_2\text{CONHC}_6\text{H}_3(\text{CH}_3)_2$).



(a)

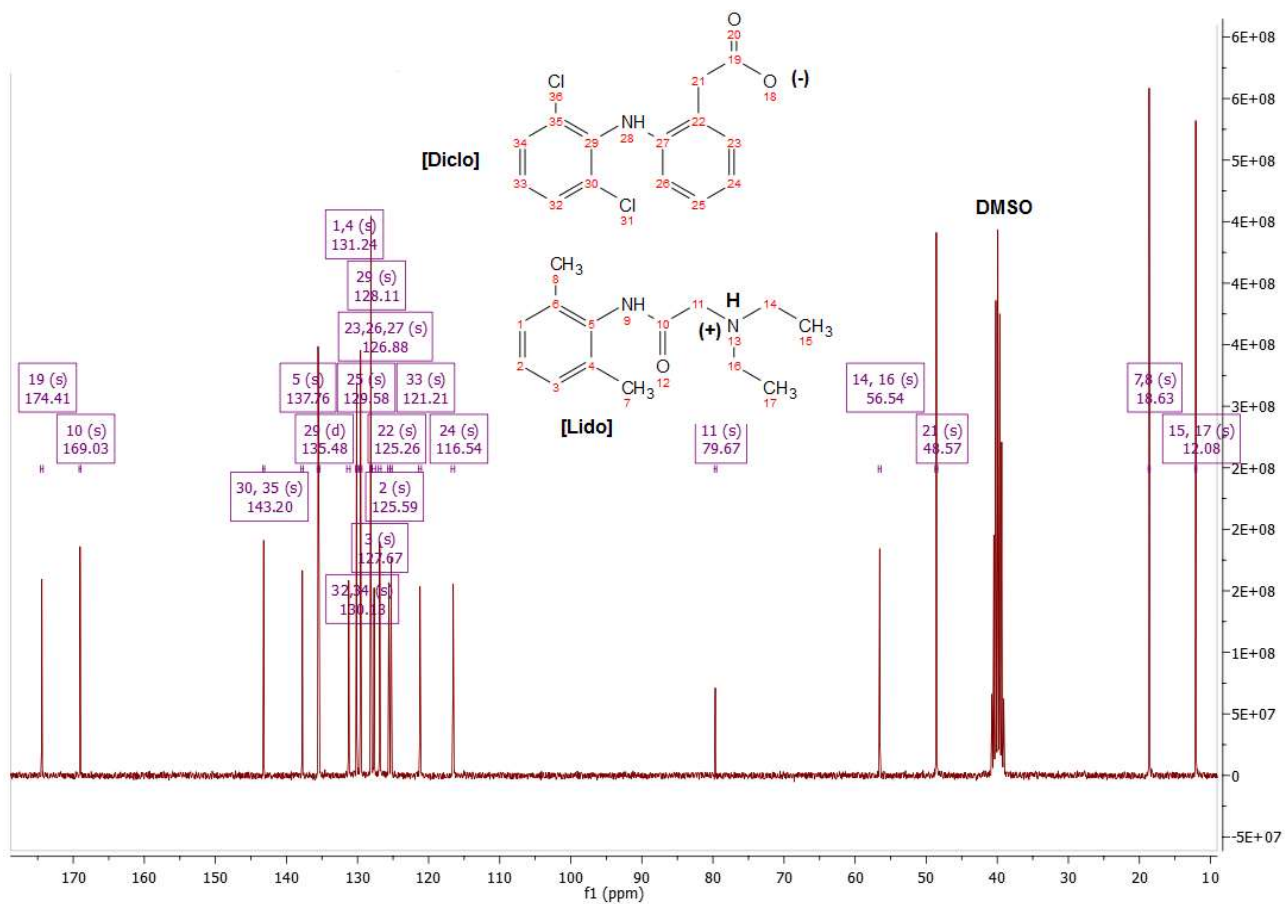


(b)

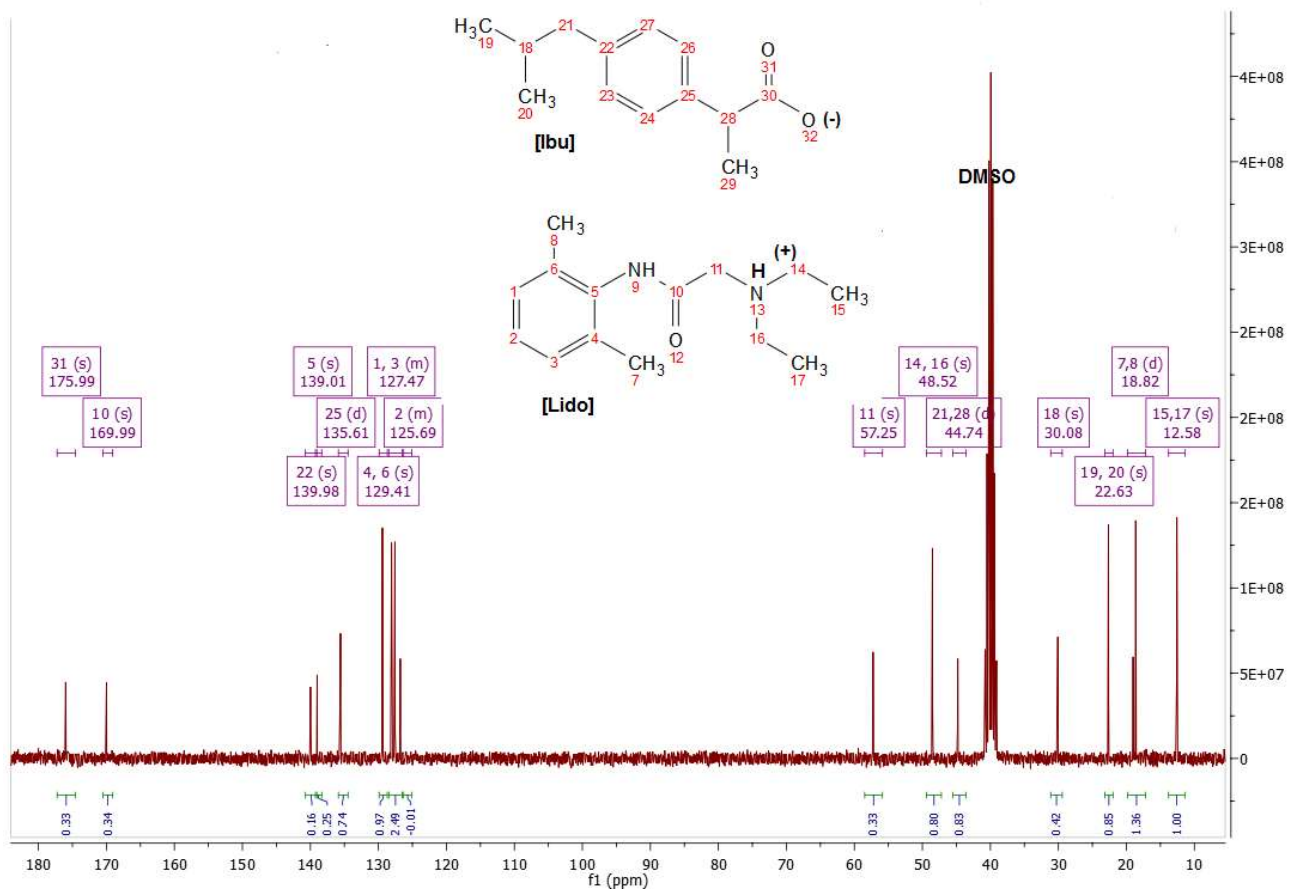


(c)

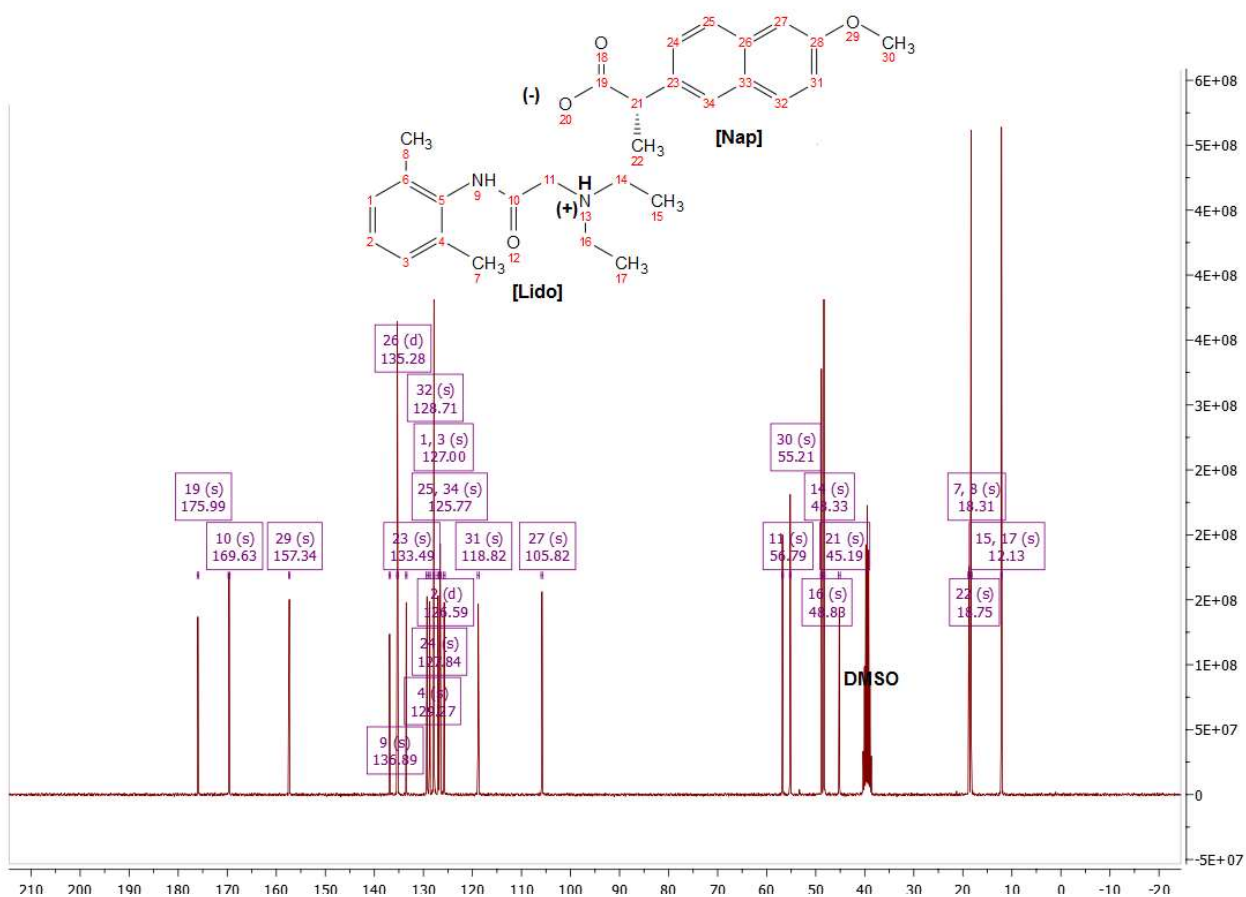
Figure S1. Chemical structure and ¹H NMR spectra of: (a) [Lido][Diclo], (b) [Lido][Ibu] and (c) [Lido][Nap].



(a)



(b)



(c)

Figure S2. Chemical structure and ¹³C NMR spectra of: (a) [Lido][Diclo], (b) [Lido][Ibu] and (c) [Lido][Nap].

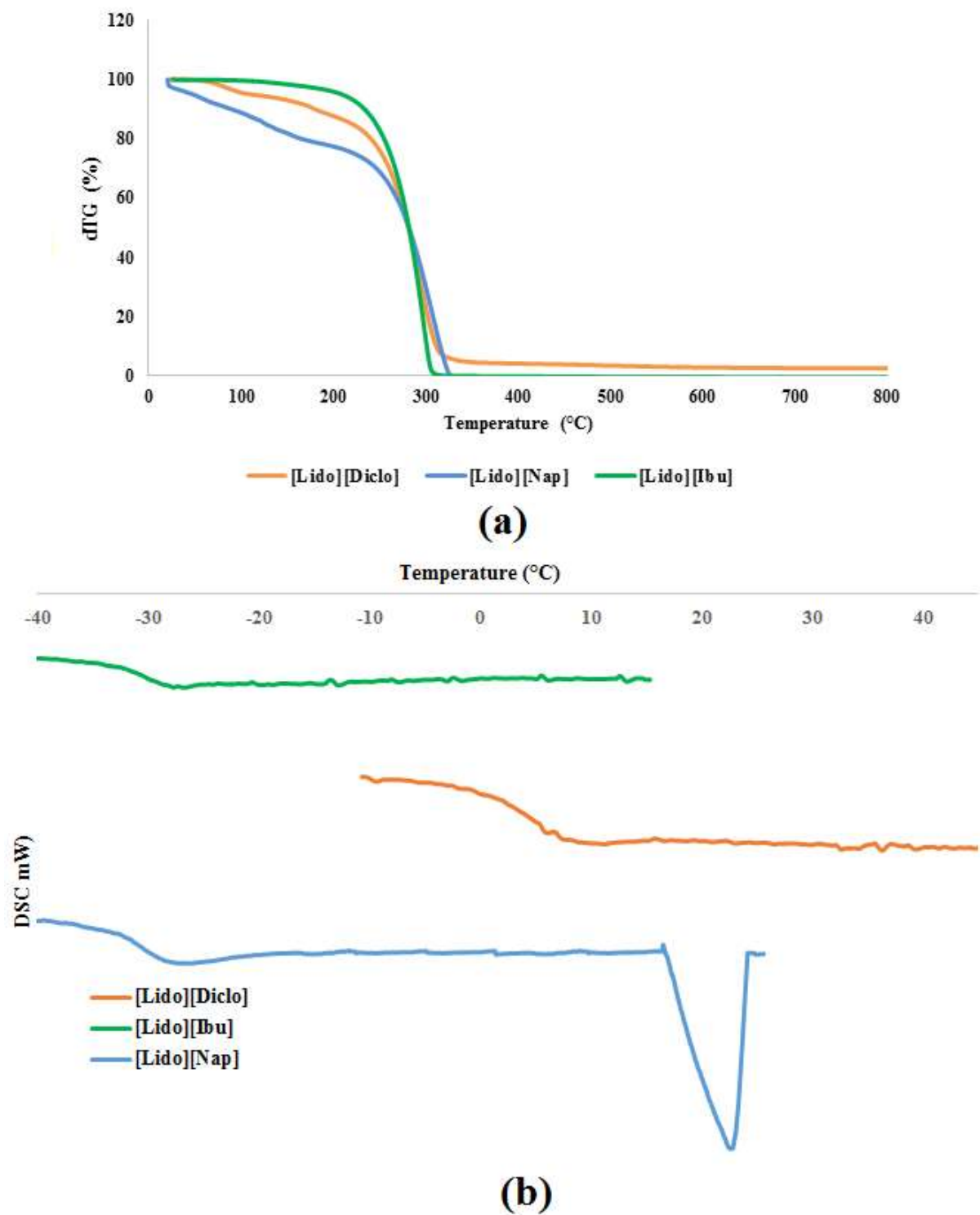


Figure S3. (a): TGA and (b) DSC of API-ILs.

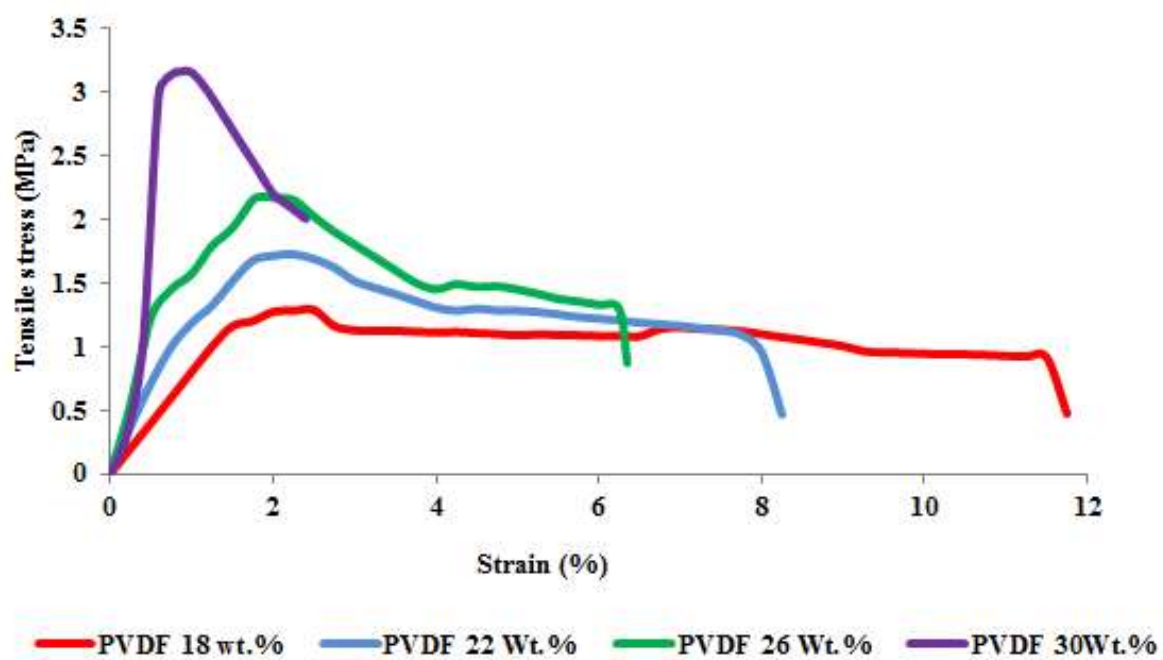


Figure S4. Stress-strain curves of PVDF membranes.

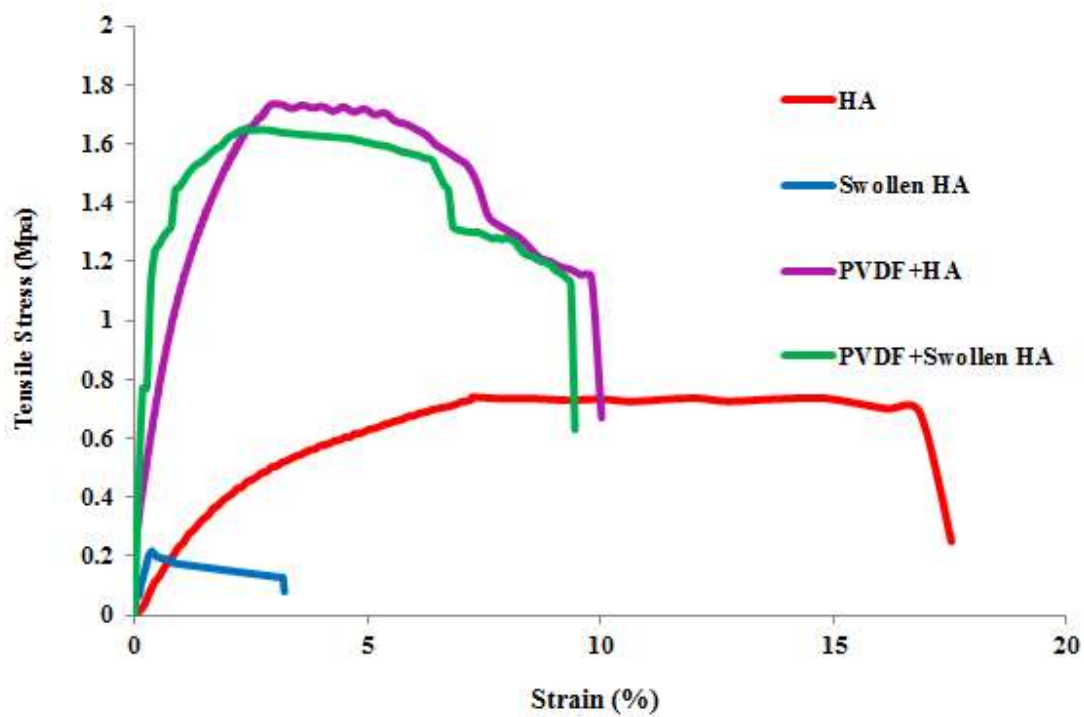


Figure S5. Stress- strain curves of HA and PVDF/HA membranes before and after swelling.

Table S1. API-ILs elemental analysis (C, N and H percentage weight fraction content).

API-IL	C	H	N
[Lido][Diclo]	62.75 ± 0.03	6.11 ± 0.02	7.87 ± 0.05
[Lido][Ibu]	72.99 ± 0.02	9.11 ± 0.04	6.12 ± 0.06
[Lido][Nap]	71.99 ± 0.05	7.56 ± 0.03	6.01 ± 0.04

Table S2. Water solubility of corresponding ions of API-ILs at 37 °C.

API-IL	Anion Solubility (mmol/mL) ± σ	Cation Solubility (mmol/mL) ± σ
[Lido][Ibu]	$(4.31 \pm 0.09) \times 10^{-2}$	$(4.06 \pm 0.04) \times 10^{-2}$
[Lido][Nap]	$(3.83 \pm 0.04) \times 10^{-2}$	$(3.75 \pm 0.01) \times 10^{-2}$
[Lido][Diclo]	$(3.841 \pm 0.004) \times 10^{-3}$	$(3.78 \pm 0.01) \times 10^{-3}$

Table S3. PVDF membranes API-IL uptake.

PVDF (wt. %)	Uptake ± σ (%)
18	13.2 ± 0.8
22	16.7 ± 0.5
26	12.1 ± 0.5
30	9.7 ± 0.8

Table S4. APIs and API-ILs release along time.

(Release±σ)%	API-IL			API			
Time (h)							
	[Lido][Ibu]	[Lido][Nap]	[Lido][Diclo]	Lido	Ibu	Nap	Diclo
1	20.34±0.03	18.36±0.04	15.64±0.02	50.43±0.02	15.47±0.03	11.50±0.05	10.11±0.02
2	33.45±0.02	30.44±0.04	26.94±0.05	63.76±0.06	22.82±0.04	18.46±0.03	17.62±0.03
4	43.76±0.05	37.54±0.02	35.65±0.03	75.21±0.04	23.85±0.03	20.18±0.03	17.98±0.04
6	49.10±0.02	46.87±0.05	41.99±0.04	80.44±0.04	24.46±0.04	21.97±0.05	18.01±0.03
12	53.36±0.02	51.27±0.04	46.68±0.03	80.56±0.03	24.87±0.05	22.04±0.04	18.33±0.03
24	74.51±0.02	71.25±0.03	67.75±0.03	80.81±0.01	25.01±0.01	22.14±0.02	18.86±0.02
48	81.57±0.01	78.45±0.02	70.14±0.01	80.97±0.02	25.45±0.03	22.19±0.02	18.90±0.01
72	88.39±0.02	83.43±0.03	73.67±0.03	81.16±0.01	25.77±0.02	22.23±0.02	18.92±0.02
96	91.35±0.01	85.55±0.02	77.23±0.02	81.25±0.01	25.98±0.01	22.25±0.01	18.94±0.01
120	91.35±0.01	85.56±0.01	78.33±0.01	81.25±0.01	26.78±0.01	22.26±0.01	18.95±0.01
144	91.35±0.01	85.56±0.01	78.34±0.01	81.25±0.01	26.78±0.01	22.26±0.01	18.95±0.01