Electronic Supplementary information

Significantly improving the solubility of non-steroidal anti-inflammatory drugs in deep eutectic solvents for potential nonaqueous liquid administration

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ESI1. Experimental section

1.1 Materials

All chemicals and reagents were of analytical reagent grade and used without further purification. HPLC-grade methanol was purchased from Tedia Company Inc (Ohio, USA). HPLC-grade water was obtained with a Milli-Q system (Millipore, Bedford, MA, USA). Aspirin was bought from Alfa Aesar (MA, USA). Acetaminophen was obtained from Sigma-Aldrich (MO, USA). Ketoprofen, naproxen and ibuprofen were bought from TCI (Shanghai, China).

1.2 Preparation of DESs for dissolving NSAIDs

DESs were prepared following the method described by Abbot et al.[1] In a typical procedure, both the hydrogen bond donor (HBD) and acceptor (HBA) molecules were mixed and heated between 80℃and 110℃ at selected mole ratios with constant stirring until homogenous liquids were formed. If the mixture formed turbid liquid after heating for 3h at 110℃, it indicated that the HBA and HBD could not form a DES at selected ratio. After preparation, the DESs were dehydrated by incubating with 3Å molecular sieves for several days before drug solubility experiments.

1.3 Dissolution of NSAIDs in DESs, and HPLC analysis

Solubility tests were carried out by saturating different DESs with an excess of the tested drug in a bottle with a cap, stirring at 300 rpm and 37℃ for 24 h. The suspension was then centrifuged at 10,000 rpm for 30 min. Triplicate samples of the supernatant were diluted with HPLC mobile phase to the linear range of the standard curves. The diluted solutions were analyzed using a Waters 2695 HPLC system (Waters Corp., Milford, Massachusetts, USA) equipped with an ODS-BP-C18 column (4.6 mm×200 mm, 5 μm; Dalian Elite Analytical Instruments Co., Ltd, Dalian, China) at wavelength of 220 nm for aspirin and ibuprofen, 263 nm for acetaminophen, ketoprofen and naproxen. Analyses were run at a flow rate of 0.5 mL/min with mobile phase mixtures of 40% (v%) methanol+60% (v%) 5 mmol/L ammonium acetate solution for aspirin and acetaminophen, 75% (v%) methanol+25% (v%) 5 mmol/L ammonium acetate solution for ketoprofen and naproxen, 40% (v %) methanol+60% (v%) phosphate solution with the volume ratio of phosphate to water of 247/3 for ibuprofen. The column temperature was maintained at 25℃, and the injection volume was 10μL. The concentrations of the dissolved drugs were calculated by the standard curves for 5 drugs.

1.4 Thermal stability of aspirin dissolving in DES, water and DES/water mixture

Aspirin was taken as an example to investigate the thermal stability of drug dissolving in DESs. 5 mL DES (choline chloride: 1, 2-propanediol, 1:2) was transferred to a clean vial containing a stir bar. The vial was immersed in an oil bath heated to 80°C, and the DES was stirred at 300 rpm until its temperature reached 80°C. Then, 2.5 mg of aspirin was added to the DES with stirring to ensure the aspirin completely

dissolved in a short time. Sampling was taken at a certain time interval, and the residual concentration of aspirin in DES was analyzed by HPLC. Similar procedures were used to investigate the thermal stability of aspirin in deionized water and water-DES mixture (1:1, v/v).

ESI2. Other supporting tables and figures

Table S1 DESs prepared for dissolving NSAIDs

Entry	Abbreviation	Hydrogen bond acceptor	Hydrogen bond donor	Molar ratio	Appearance at 45℃
First group					
1	ChCl-G	Choline chloride	Glycerol	1:2	Clear liquid
2	ChCl-EG	Choline chloride	Ethylene glycol	1:2	Clear liquid
3	ChCl-P	Choline chloride	1, 2-Propanediol	1:2	Clear liquid
4	ChCl-B	Choline chloride	1, 3-Butanediol	1:2	Initially formed a clear liquid, then crystals separated out
5	ChCl-X	Choline chloride	Xylitol	1:1	Viscous liquid
6	ChCl-DS	Choline chloride	D-Sorbitol	1:1	Viscous liquid
7	ChCl-DG	Choline chloride	D-glucose	1:1	Transparent gel
8	ChCl-DF	Choline chloride	D-Fructose	1:1	Transparent gel
9	ChCl-S	Choline chloride	Sucrose	1:1	Unable to form a liquid
10	ChCl-M	Choline chloride	Maltose	4:1	Unable to form a liquid
11	ChCl-DM	Choline chloride	D-Mannose	5:2	Unable to form a liquid
12	ChCl-GA1	Choline chloride	Glutaric acid	1:1	Clear liquid
13	ChCl-GA2	Choline chloride	Glycolic acid	1:1	Clear liquid
14	ChCl-MA1	Choline chloride	Malonic acid	1:1	Clear liquid
15	ChCl-OA	Choline chloride	Oxalic acid	1:1	Clear liquid
16	ChCl-MA2	Choline chloride	Malic acid	1:1	Viscous liquid
17	ChCl-LA1	Choline chloride	Levulinic acid	1:2	Clear liquid
18	ChCl-LA2	Choline chloride	Lactic acid	1:1	Clear liquid
19	ChCl-CA	Choline chloride	Citric acid	1:1	Viscous liquid
20	ChCl-TA	Choline chloride	L-(+)-Tartaric acid	2:1	Viscous liquid
21	ChCl-GA3	Choline chloride	Glutamic acid	1:2	Unable to form a liquid
22	ChCl-MA3	Choline chloride	Maleic acid	1:1	Unable to form a liquid
23	ChCl-U	Choline chloride	Urea	1:2	Clear liquid
Second group					
24	EAC-EG	Ethylammonium chloride	Ethylene glycol	1:2	Clear liquid
25	EAC-P	Ethylammonium chloride	1,2-Propanediol	1:2	Clear liquid
26	EAC-GA	Ethylammonium chloride	Glutaric acid	1:1	Initially formed a clear liquid, then crystals separated out
27	EAC-MA	Ethylammonium chloride	Malonic acid	1:1	Initially formed a clear liquid, then crystals separated out
28	EAC-LA1	Ethylammonium chloride	Levulinic acid	1:2	Clear liquid
29	EAC-LA2	Ethylammonium chloride	Lactic acid	1:1	Clear liquid
30	EAC-U	Ethylammonium chloride	Urea	1:2	Initially formed a clear liquid, then crystals separated out

31	TPAB-EG	Tetrapropylammonium bromide	Ethylene glycol	1:2	Initially formed a clear liquid, then crystals separated out
32	TPAB-P	Tetrapropylammonium bromide	1, 2-Propanediol	1:2	Clear liquid
33	TPAB-GA	Tetrapropylammonium bromide	Glutaric acid	1:1	Viscous liquid
34	TPAB-MA	Tetrapropylammonium bromide	Malonic acid	1:1	Unable to form a liquid
35	TPAB-LA1	Tetrapropylammonium bromide	Levulinic acid	1:2	Clear liquid
36	TPAB-LA2	Tetrapropylammonium bromide	Lactic acid	1:1	Initially formed a clear liquid, then crystals separated out
37	TPAB-U	Tetrapropylammonium bromide	Urea	1:2	Unable to form a liquid
38	BE-EG	Betaine	Ethylene glycol	1:2	Initially formed a clear liquid, then crystals separated out
39	BE-P	Betaine	1,2-Propanediol	1:2	Initially formed a clear liquid, then crystals separated out
40	BE-GA	Betaine	Glutaric acid	1:1	Unable to form a liquid
41	BE-MA	Betaine	Malonic acid	1:1	Unable to form a liquid
42	BE-LA1	Betaine	Levulinic acid	1:2	Clear liquid
43	BE-LA2	Betaine	Lactic acid	1:1	Clear liquid
44	BE-U	Betaine	Urea	1:2	Initially formed a clear liquid, then crystals separated out
45	ChBt-EG	Choline bitartrate	Ethylene glycol	1:2	Unable to form a liquid
46	ChBt-P	Choline bitartrate	1,2-Propanediol	1:2	Unable to form a liquid
47	ChBt-GA	Choline bitartrate	Glutaric acid	1:1	Unable to form a liquid
48	ChBt-MA	Choline bitartrate	Malonic acid	1:1	Unable to form a liquid
49	ChBt-LA1	Choline bitartrate	Levulinic acid	1:2	Clear liquid
50	ChBt-LA2	Choline bitartrate	Lactic acid	1:1	Transparent gel
51	ChBt-U	Choline bitartrate	Urea	1:2	Transparent gel

Table S2 The solubility of different NSAIDs in several neat DESs and the latters' physicochemical parameters

DESs	Viscosity (cP)	pH	E_{NR}	β	π*	Solubility (mg/mL)				
						Aspirin	Acetaminophen	Ketoprofen	Naproxen	Ibuprofen
ChCl-LA1	117	2.19	49.2	0.575	1.00	135.03±0.19	278.96±3.20	192.85±3.62	31.67±0.40	78.69±0.93
ChCl-G	194	5.78	49.6	0.408	1.24	42.48±0.81	140.33±2.58	11.13±0.12	3.69±0.04	3.82±0.03
ChCl-EG	33.5	7.00	50.5	0.480	1.19	138.96±2.11	287.01±4.01	81.99±1.07	20.68±0.52	24.29±0.18
ChCl-U	386	9.93	49.7	0.351	1.31	147.90±2.23	169.66±1.98	61.00±0.74	15.46±0.11	4.5±0.01
ChCl-MA1	1110	0.280	47.7	0.527	1.01	126.29±2.06	266.25±2.44	60.99±0.31	21.98±0.21	25.87±0.13
BE-LA1	451	4.68	51.1	0.485	0.984	149.82±0.96	212.10±1.92	329.06±4.42	76.64±0.72	280.17±2.68

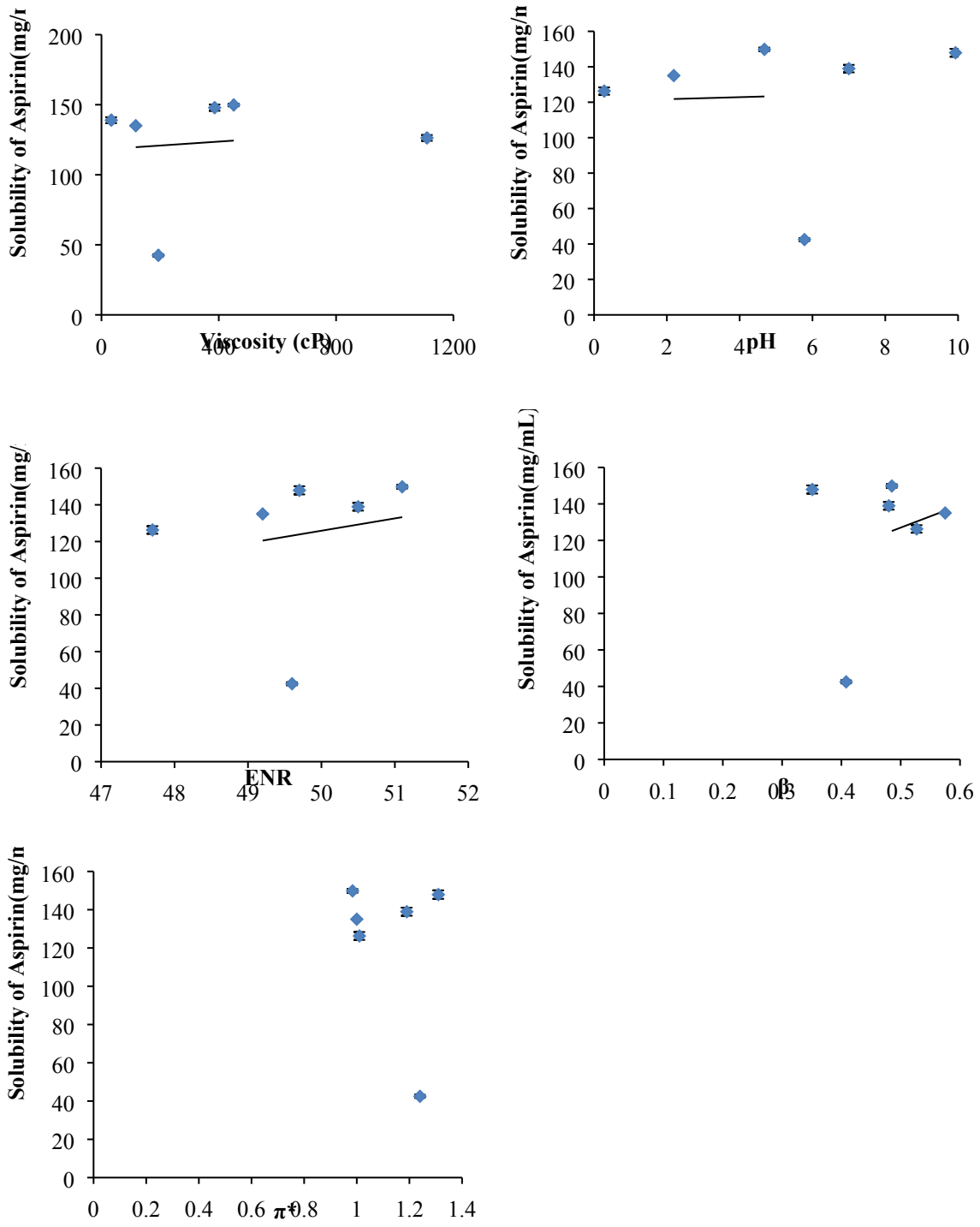

Figure S1. Attempts to correlate the aspirin solubility in DESs with the latter's characteristics. (a) viscosity, (b) pH, (c) E_{NR}, (d) βviscosity, and (e) π*. The dependences obtained for acetaminophen, ketoprofen, naproxen and ibuprofen were qualitatively similar to those for Aspirin and equally devoid of any discernible correlations.

Reference:

1. A. P. Abbott, D. Boothby, G. Capper, D. L. Davies, R. K. Rasheed, Journal of the American Chemical Society, 2004, **126**, 9142-9147.