SUPPORTING INFORMATION

Competitive mechanochemical solvate formation of theophylline in the presence of miscible liquid mixtures

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List of abbreviations: anhydrous theophylline (**theo**); theophylline monohydrate (**theo:h2o-mh**); theophylline monosolvate (**theo:pyr-ms**); theophylline sesquisolvate (**theo:pyr-ss**); water:2-pyrrolidone (**h2o:pyr**) mixtures.

Contents

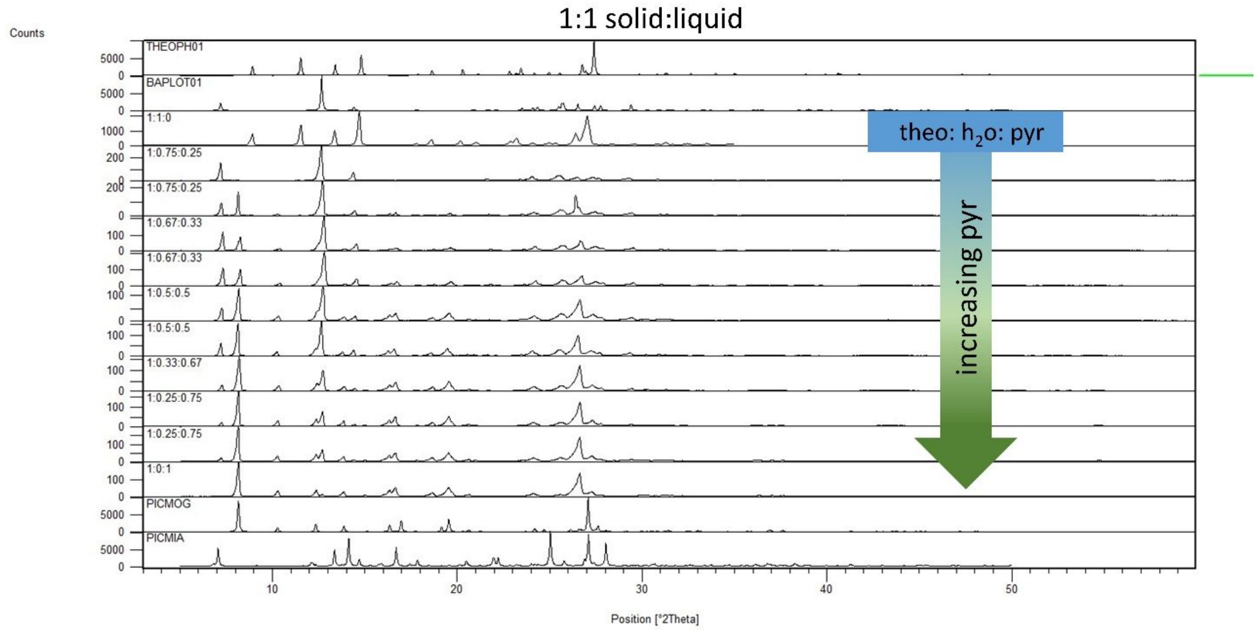

Figure S1. PXRD pattern of **1:1 solid:liquid** (molar ratio) set compared to theophylline pure solid phases (anhydrous BAPLOT01 , monohydrate THEOPH01, monosolvate PICMOG, sesquisolvate PICMIA), with indication of **theo:h$_2$o:pyr** molar ratio used in each sample.

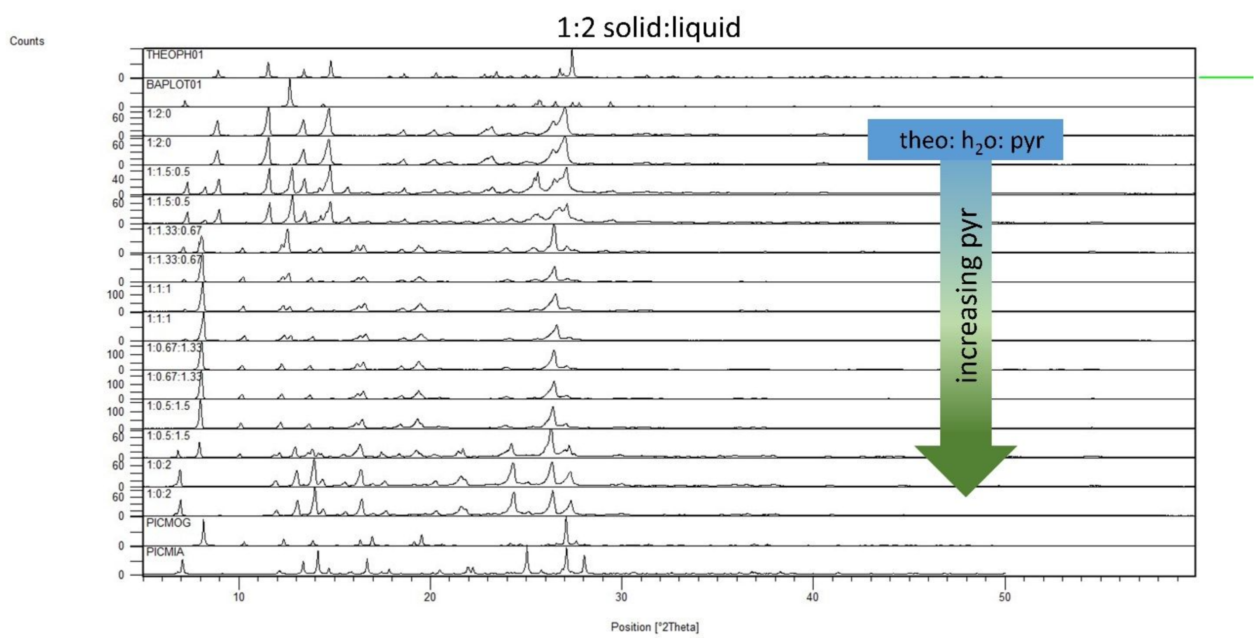

Figure S2. PXRD pattern of **1:2 solid:liquid** (molar ratio) set compared to theophylline pure solid phases (anhydrous BAPLOT01 , monohydrate THEOPH01, monosolvate PICMOG, sesquisolvate PICMIA), with indication of **theo:h$_2$o:pyr** molar ratio used in each sample.

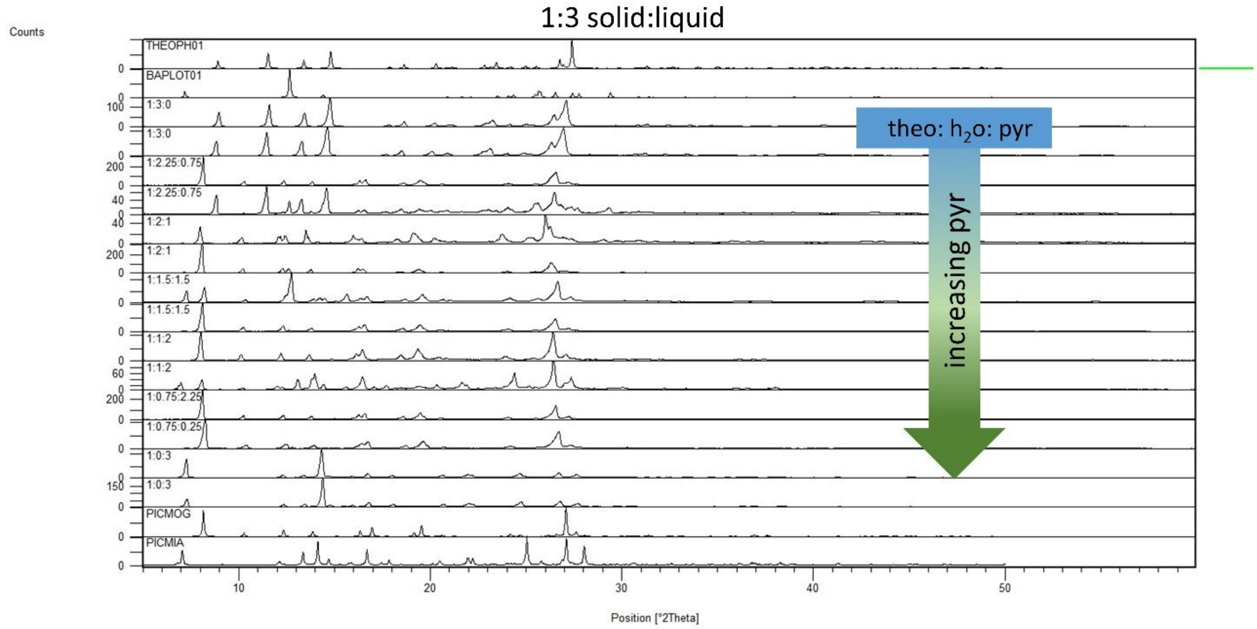

Figure S3. PXRD pattern of **1:3 solid:liquid** (molar ratio) set compared to theophylline pure solid phases (anhydrous BAPLOT01 , monohydrate THEOPH01, monosolvate PICMOG, sesquisolvate PICMIA), with indication of **theo:h_2o:pyr** molar ratio used in each sample.

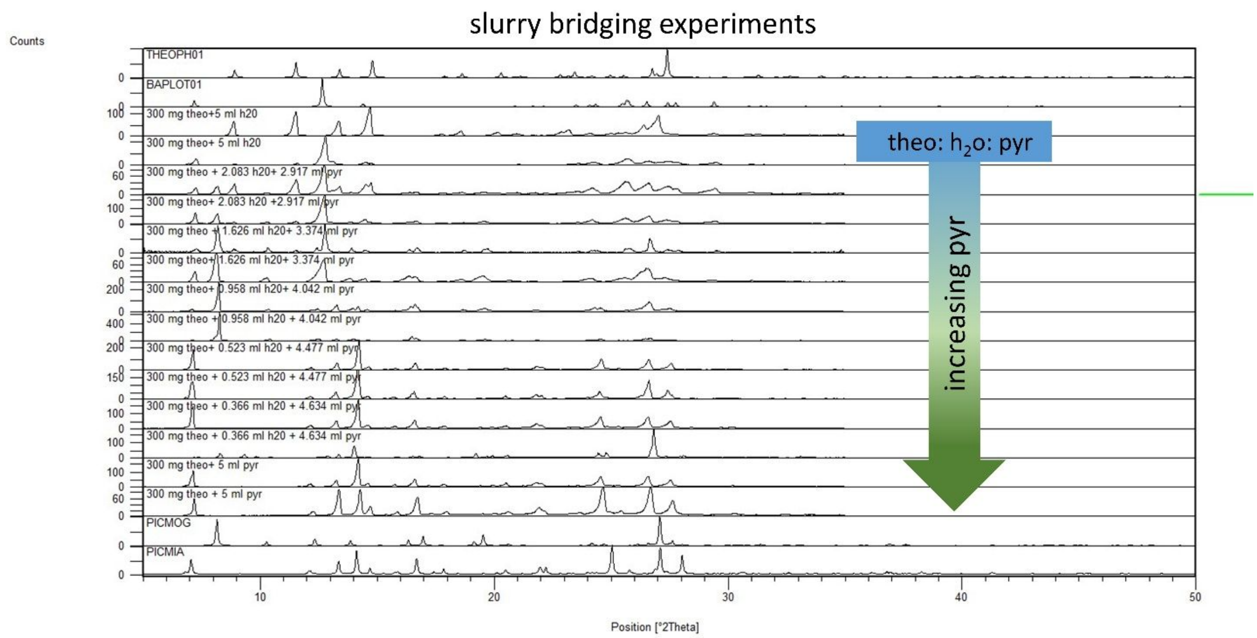

Figure S4. PXRD pattern of **slurry bridging experiments** compared to theophylline pure solid phases (anhydrous BAPLOT01, monohydrate THEOPH01, monosolvate PICMOG, sesquisolvate PICMIA), with indication of **theo:h_2o:pyr** ratio used in each sample.

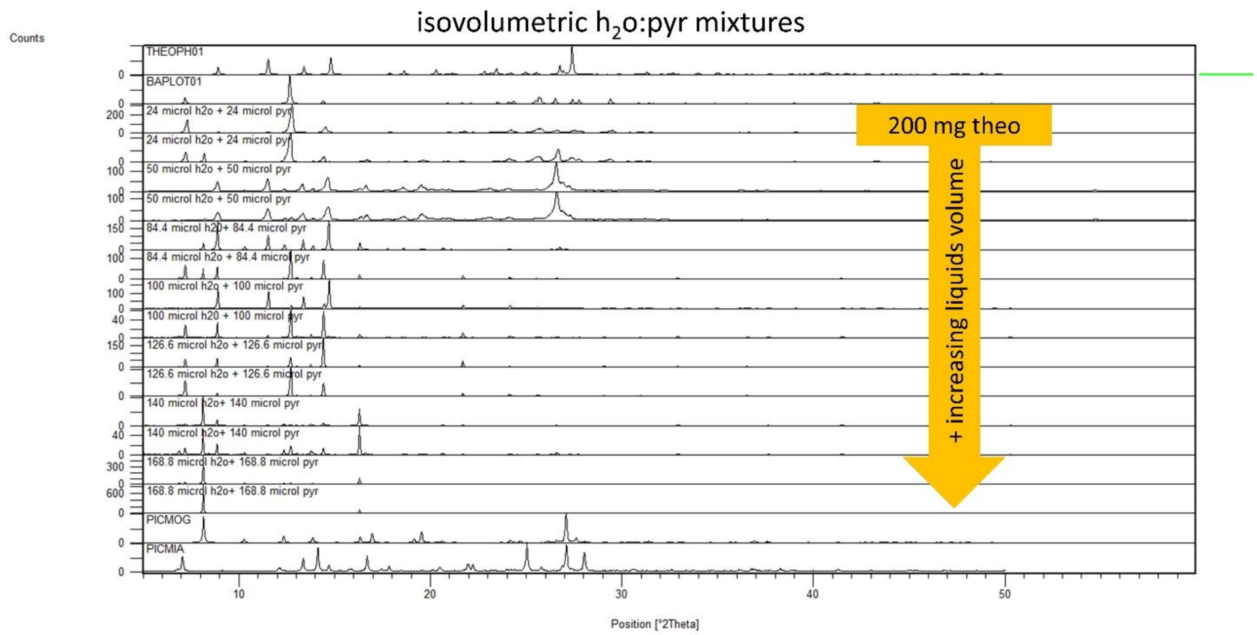

Figure S5. PXRD pattern of the series 2 (isovolumetric mixtures) compared to theophylline pure solid phases (anhydrous BAPLOT01, monohydrate THEOPH01, monosolvate PICMOG, sesquisolvate PICMIA), with indication of **theo:h_2o:pyr** ratio used in each sample.

In situ measurement of sample temperature during grinding

The temperature inside the jar upon grinding was measured by means of the Thermojar system in the same conditions as the routine experiments (1h no stop grinding, 25 Hz, 200 mg solid, same void volume) and this information was correlated to the solvent boiling points. Even if the jar material is different (Thermojar system is based on PMMA jars whilst the common jars are stainless steel jars), our previous studies demonstrated that the temperature difference between the two materials during grinding is less than 5°C (Zanolla et al., 2019). The statistical analysis (conducted comparing average temperature values at 10, 20, 30, 40, 50, 60 min) revealed no significant difference in the detected temperatures between the 3 analyzed samples (**theo** neat ground, **theo** plus 20 µl or 84 µl liquid), meaning that, in accordance to previous findings, the sample temperature is influenced by process conditions rather than sample composition. The registered temperature rise was a ramp from ambient temperature to 35°C in 1h time, with the trend depicted in Figure S6.

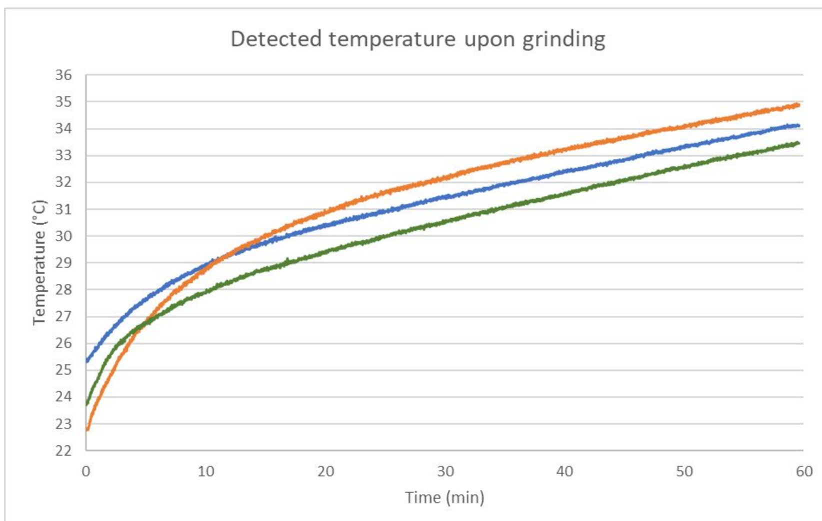

Figure S6. Temperature profiles upon grinding (each curve represents the means of 3 samples); the blue alone (mean S.D.=2.9)- blue line; **theo** plus 20 µl h_2o (S.D.=4.05)- orange line; **theo** plus 84.4 µl h_2o (S.D.=3.5) -green line.

Theophylline dissolution tests in h_2o and pyr

Dissolution profiles are reported in Figures S7. It can be immediately noticed that the amount of **theo** dissolved after 1h in **h_2o** (81 ±4.36%) is much greater than that dissolved in **pyr** (63±5.9%). Another difference is the trend of the dissolution profiles: **theo** dissolution in **h_2o** reaches a plateau in 6 min while **theo** concentration in **pyr** increases over time/temperature. Due to the higher expected **theo** solubility in **pyr**, these results are somewhat surprising. In 1h dissolution time (the same time as the grinding) the viscosity of **pyr**, much higher than **h_2o** (Table S4), probably hinders the dissolution process of **theo** increasing the viscosity of the diffusion layer where the passage in solution takes place. As the temperature increases, the viscosity of **pyr** decreases, which may be another reason for the increase in concentration of dissolved theophylline as time (and temperature) increases. A statistically significant difference between **theo** dissolution in the 2 liquids was attested by the similarity factor of f_2=29.76.

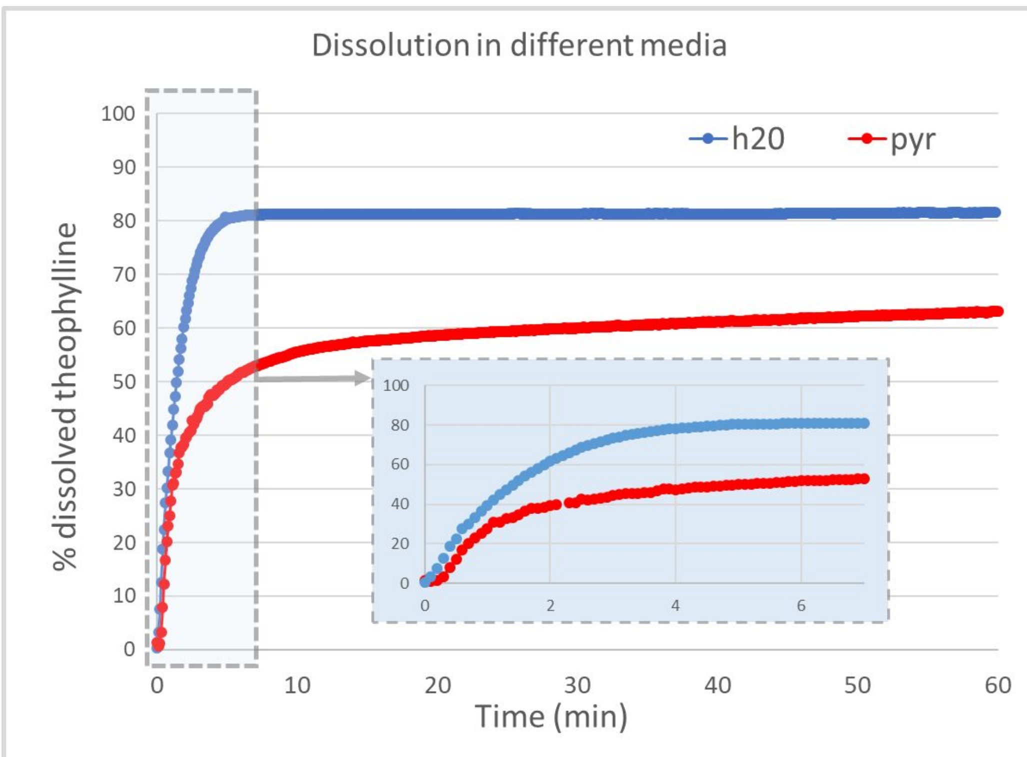

Figure S7. **theo** dissolution profiles in different media: **h_2o** (blue) and **pyr** (red), conducted varying temperature from 22 to 35°C during 1h analysis.
In the green frame, the first 6.5 min profiles are zoomed.

Physical stability of theo:h_2o-mh, theo:pyr-ms and theo:pyr-ss

theo:h_2o-mh, theo:pyr-ms, theo:pyr-ss were mechanochemically synthesized (see paragraph 2.2.4), stored at ambient temperature in a desiccator and physical stability of the 3 multicomponent solid phases was assayed by means of PXRD analyses (conditions reported in paragraph 2.3.1) over a period of 3 months.

theo:h_2o-mh sample (obtained by mechanochemistry) appeared to be stable in ambient temperature, as visible in Figure S8.

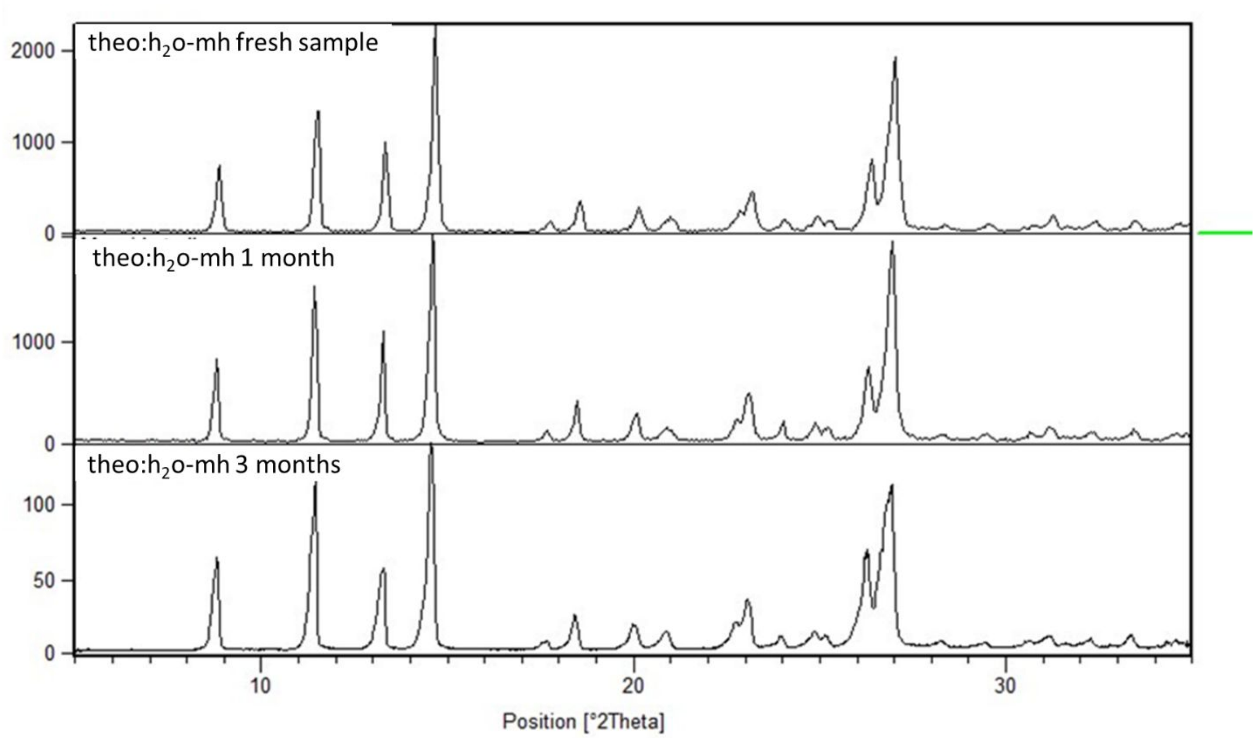

Figure S8: **theo:h_2o-mh** PXRD pattern: fresh sample, after 1 month and after 3 months.

Conversely, **theo:pyr-ms** shows a partial desolvation and the appearance in the PXRD pattern of anhydrous **theo** signal since the first month (e.g. 7.2°; 12.66° 2θ), as visible in Figure S9.

theo:pyr-ss is stable for the 3 months of analysis, as visible in Figure S10. The superior sesquisolvate stability compared to the **theo:pyr-ms** agrees with literature data (Hasa et al., 2019).

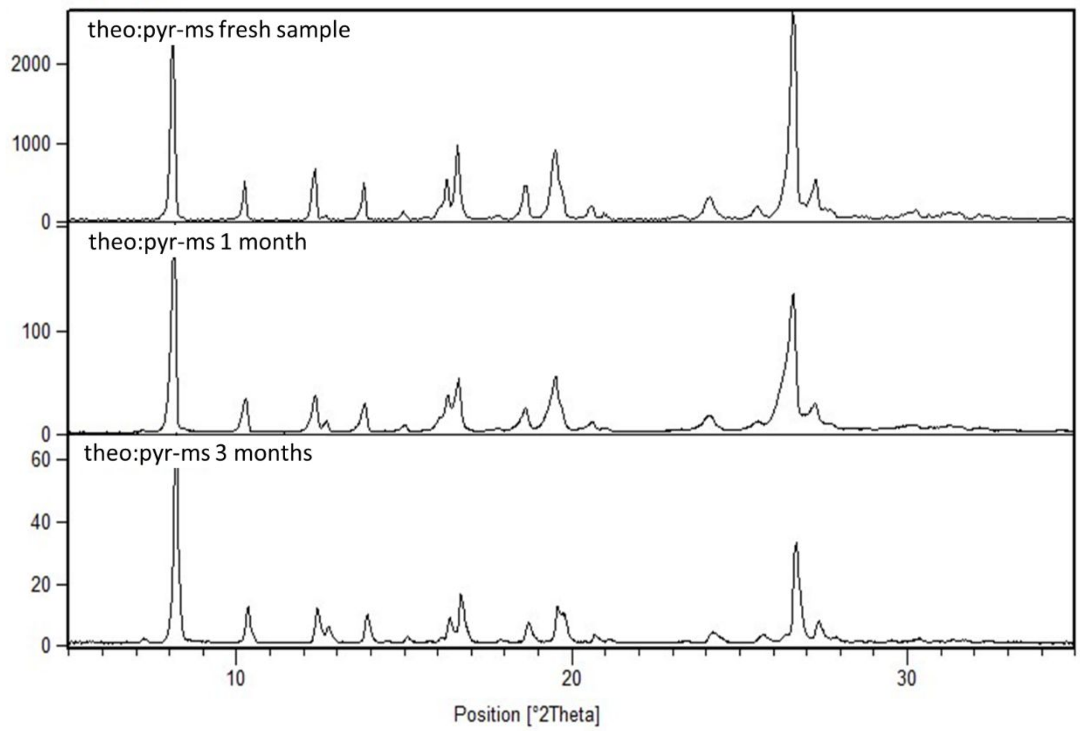

Figure S9: theo:pyr-ms PXRD pattern: fresh sample, after 1 month and after 3 months.

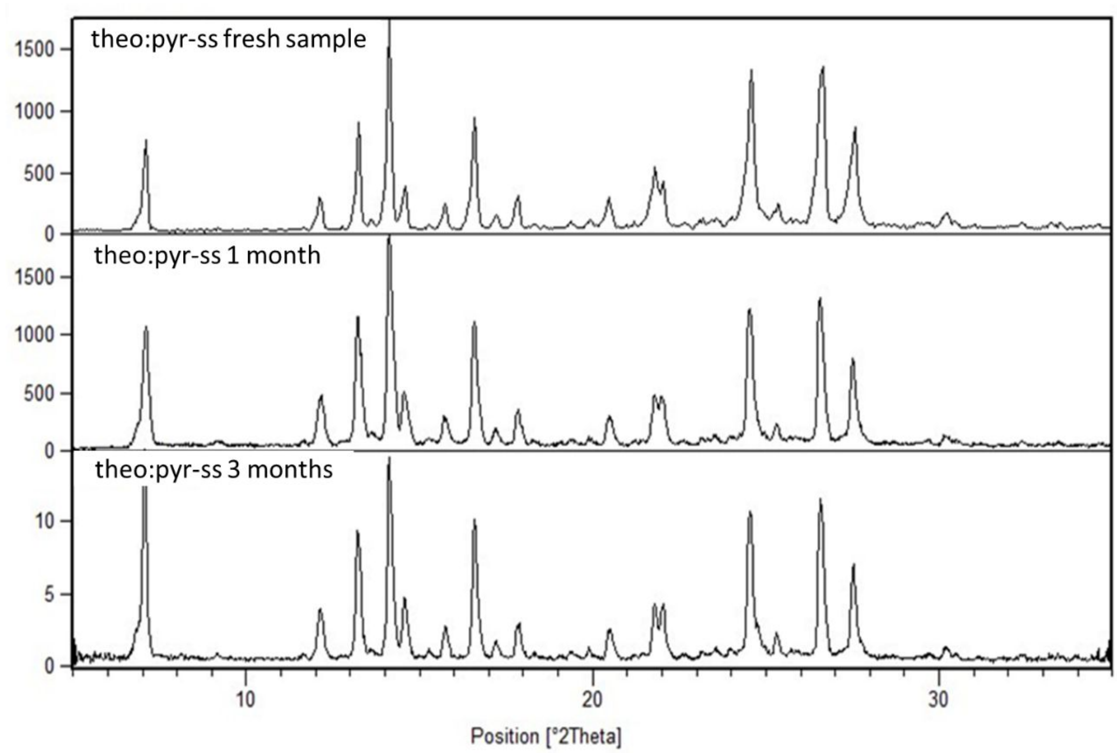

Figure S10: **theo:pyr-ss** PXRD pattern: fresh sample, after 1 month and after 3 months.

Table S1. Overview of the interconversion experiments with 200 mg preformed hydrate or solvate forms in the presence of **equimolar mixtures of solvents** (the added solvent is enough to give origin to a different multicomponent form).

starting solid (200 mg)	Added moles of equimolar liquid mix		a_w	Expected outcome
	h_2o	**pyr**		
theo:h_2o-mh (0.001 theo moles)	0.001 moles (18 µl)	0.001 moles (76.7 µl)	0.8553	theo:pyr-ms
theo:h_2o-mh (0.001 theo moles)	0.0016 moles (28.5 µl)	0.0016 moles (120 µl)	0.8524	theo:pyr-ss
theo:pyr-ms (0.0008 theo moles)	0.0007 moles (13.6 µl)	0.00075 moles (57.3 µl)	0.7012	theo:h_2o-mh
theo:pyr-ss (0.0007 theo moles)	0.0007 moles (11.7 µl)	0.0007 moles (49.4 µl)	0.5208	theo: h_2o-mh
theo:pyr-ms (0.0008 theo moles)	0.00045 moles (8.2 µl)	0.00045 moles (34.4 µl)	0.6169	theo:pyr-ss

Table S2. Overview of the interconversion experiments with 200 mg pre-formed hydrate or solvate forms in the presence of **isovolumetric mixtures of solvents** (the added solvent is enough to give origin to a different multicomponent form).

starting solid (200 mg)	Added moles of isovolumetric liquid mix		a_w	Expected outcome
	h_2o	**pyr**		
theo:h_2o-mh (0.001 theo moles)	0.0042 moles (76.7 µl)	0.001 moles (76.7 µl)	0.8553	theo:pyr-ms
theo:h_2o-mh (0.001 theo moles)	0.0067 moles (120 µl)	0.0014 moles (120 µl)	0.8694	theo:pyr-ss
theo:pyr-ms (0.0008 theo moles)	0.0008 moles (13.6 µl)	0.0002 moles (13.6 µl)	0.8023	theo:h_2o-mh
theo:pyr-ss (0.0007 theo moles)	0.00065 moles (11.7 µl)	0.00015 moles (11.7 µl)	0.5923	theo:h_2o-mh
theo:pyr-ms (0.0008 theo moles)	0.00018 moles (34.4 µl)	0.00048 moles (34.4 µl)	0.8503	theo:pyr-ss

Table S3. Overview of Rietveld refinement results (as weight fractions) for each experiment performed in this study.

									Rietveld Refinement - Weight fractions / %								
Exp	Type	Time	Frequency	THEO form	mg	H2O : 2-PYR	H2O (µl)	2-PYR (µl)	Theophylline			Theophylline hydrate		2-pyr sesquisolvate		2-pyr monosolvate	
1:1 solid: liquid									*Rwp / %*	*Value*	*Error*	*Value*	*Error*	*Value*	*Error*	*Value*	*Error*
	LAG	60 min	25 Hz	FORM II	200	1:0	20.00	0.00	18.06	99.21	0.56	0.59	0.30	0.12	0.38	0.09	0.29
	LAG	60 min	25 Hz	FORM II	200	1:0	20.00	0.00	20.30	9.12	0.27	89.61	0.48	0.36	0.35	0.91	0.26
	LAG	60 min	25 Hz	FORM II	200	1:0	20.00	0.00	18.77	98.91	0.61	0.78	0.33	0.28	0.42	0.02	0.31
	LAG	60 min	25 Hz	FORM II	200	1:0	20.00	0.00	19.44	3.84	0.23	94.60	0.47	0.28	0.34	1.28	0.27
	LAG	60 min	25 Hz	FORM II	200	0.75: 0.25	15.00	21.00	25.75	25.76	0.50	47.49	0.63	0.00	0.47	26.75	0.55
	LAG	60 min	25 Hz	FORM II	200	0.75: 0.25	15.00	21.00	27.51	68.61	0.70	1.19	0.36	0.00	0.53	30.21	0.58
	LAG	60 min	25 Hz	FORM II	200	0.67:0.33	13.40	27.80	25.21	65.79	0.77	0.00	0.48	0.00	0.60	34.21	0.63
	LAG	60 min	25 Hz	FORM II	200	0.67:0.33	13.40	27.80	28.04	62.83	0.84	0.00	0.53	0.79	0.67	36.38	0.72
	LAG	60 min	25 Hz	FORM II	200	0.50:0.50	10.00	42.20	56.38	62.83	1.64	0.00	1.06	0.79	1.23	36.38	1.42
	LAG	60 min	25 Hz	FORM II	200	0.50:0.50	10.00	42.20	22.23	43.55	0.51	0.00	0.36	0.00	0.39	56.45	0.55
	LAG	60 min	25 Hz	FORM II	200	0.33:0.66	6.60	56.50	20.53	27.43	0.42	0.00	0.21	0.00	0.37	72.57	0.50
	LAG	60 min	25 Hz	FORM II	200	0.25:0.75	5.00	63.30	20.56	19.99	0.37	0.00	0.19	0.00	0.33	80.01	0.48
	LAG	60 min	25 Hz	FORM II	200	0.25:0.75	5.00	63.30	19.89	17.55	0.35	0.00	0.19	0.00	0.33	82.45	0.46
	LAG	60 min	25 Hz	FORM II	200	0:1	0.00	84.40	20.78	2.33	0.21	0.00	0.21	0.00	0.32	97.67	0.43
1:2 solid: liquid																	
	LAG	60 min	25 Hz	FORM II	200	2:0	40.00	0.00	19.87	0.67	0.31	98.09	0.49	0.00	0.30	1.24	0.25
	LAG	60 min	25 Hz	FORM II	200	2:0	40.00	0.00	18.31	0.87	0.31	97.60	0.48	0.00	0.29	1.52	0.24
	LAG	60 min	25 Hz	FORM II	200	1.5:0.5	30.00	42.00	30.66	24.08	0.64	65.02	0.89	3.48	0.71	7.41	0.61
	LAG	60 min	25 Hz	FORM II	200	1.5:0.5	30.00	42.00	28.69	28.83	0.65	57.57	0.84	4.50	0.71	9.10	0.56
	LAG	60 min	25 Hz	FORM II	200	1.34:0.66	26.8	55.6	24.60	97.74	1.12	0.81	0.61	1.21	0.75	0.23	0.60
	LAG	60 min	25 Hz	FORM II	200	1.34:0.66	26.8	55.6	23.83	32.29	0.60	0.02	0.52	0.00	0.52	67.69	0.74
	LAG	60 min	25 Hz	FORM II	200	1.34:0.66	26.8	55.6	31.22	69.10	1.08	1.46	0.70	0.01	0.90	29.43	0.81
	LAG	60 min	25 Hz	FORM II	200	1.34:0.66	26.8	55.6	23.66	21.55	0.46	0.00	0.42	0.00	0.42	78.45	0.64
	LAG	60 min	25 Hz	FORM II	200	1:1	20.00	84.4	27.77	22.16	0.60	0.00	0.38	0.00	0.65	77.84	0.82
	LAG	60 min	25 Hz	FORM II	200	1:1	20.00	84.4	22.66	8.17	0.33	0.00	0.44	0.00	0.39	91.83	0.63
	LAG	60 min	25 Hz	FORM II	200	1:1	20.00	84.4	24.36	49.63	0.77	0.00	0.61	0.00	0.67	50.37	0.77
	LAG	60 min	25 Hz	FORM II	200	1:1	20.00	84.4	23.43	9.95	0.36	0.00	0.45	0.00	0.43	90.05	0.66
	LAG	60 min	25 Hz	FORM II	200	1:1	20.00	84.4	23.05	11.52	0.39	0.00	0.47	0.00	0.46	88.48	0.69
	LAG	60 min	25 Hz	FORM II	200	0.66:1.34	13.2	113.00	20.58	0.01	0.17	0.00	0.23	0.00	0.35	99.98	0.46
	LAG	60 min	25 Hz	FORM II	200	0.66:1.34	13.2	113.00	22.07	0.00	0.47	0.00	0.25	0.00	0.36	100.00	0.64
	LAG	60 min	25 Hz	FORM II	200	0.5:1.5	10.00	126.6	22.90	0.00	0.51	0.00	0.50	0.00	0.40	100.00	0.82
	LAG	60 min	25 Hz	FORM II	200	0.5:1.5	10.00	126.6	39.69	0.00	1.25	0.00	1.04	46.96	1.66	53.04	1.71
	LAG	60 min	25 Hz	FORM II	200	0:2	0.00	168.8	31.56	0.00	0.70	1.67	0.66	94.99	1.16	3.34	0.71
	LAG	60 min	25 Hz	FORM II	200	0:2	0.00	168.8	29.05	0.00	0.59	2.46	0.57	93.63	1.00	3.91	0.63
1:2 solid: liquid																	
	LAG	60 min	25Hz	FORM II	200	3:0	60.00	0.00	29.10	0.28	0.43	98.55	0.68	0.00	0.41	1.17	0.36
	LAG	60 min	25Hz	FORM II	200	3:0	60.00	0.00	19.58	0.26	0.27	97.91	0.41	0.07	0.24	1.77	0.21
	LAG	60 min	25Hz	FORM II	200	2.25:0.75	45.00	63.3	25.55	1.44	0.57	0.00	0.31	0.00	0.43	98.55	0.77
	LAG	60 min	25Hz	FORM II	200	2.25:0.75	45.00	63.3	27.78	32.80	1.03	54.04	1.09	1.30	0.77	11.87	0.71
	LAG	60 min	25Hz	FORM II	200	2.01:0.99	40.2	83.5	37.27	24.83	1.79	1.33	1.01	0.00	1.81	73.84	2.29
	LAG	60 min	25Hz	FORM II	200	2.01:0.99	40.2	83.5	32.22	13.92	0.58	0.00	0.38	0.00	0.63	86.08	0.85
	LAG	60 min	25Hz	FORM II	200	1.5:1.5	30.00	126.6	28.99	40.88	0.92	0.00	0.47	0.00	0.95	59.12	1.03
	LAG	60 min	25Hz	FORM II	200	1.5:1.5	30.00	126.6	19.99	1.70	0.23	0.00	0.49	0.00	0.43	98.30	0.68
	LAG	60 min	25Hz	FORM II	200	0.99:2.01	19.8	169.6	18.17	0.00	0.49	0.00	0.51	0.00	0.40	100.00	0.82
	LAG	60 min	25Hz	FORM II	200	0.99:2.01	19.8	169.6	23.44	0.00	0.54	0.00	0.63	74.53	0.88	25.47	0.66
	LAG	60 min	25Hz	FORM II	200	0.75:2.25	15.00	189.8	21.69	0.00	0.45	0.00	0.44	0.00	0.36	100.00	0.72
	LAG	60 min	25Hz	FORM II	200	0.75:2.25	15.00	189.8	22.95	1.86	0.24	0.00	0.48	0.00	0.43	98.14	0.67
	LAG	60 min	25Hz	FORM II	200	0:3	0.00	253.2	43.98	6.97	0.86	0.00	2.02	91.65	2.54	1.37	1.63
	LAG	60 min	25Hz	FORM II	200	0:3	0.00	253.2	43.22	9.07	1.21	0.00	2.69	89.34	3.33	1.59	2.17
Slurry bridging																	
	SLURRY	7 days	/	FORM II	300	1:0	5 ml	0.00	25.77	3.53	0.55	95.19	0.73	0.38	0.39	0.89	0.31
	SLURRY	7 days	/	FORM II	300	1:0	5 ml	0.00	24.72	82.83	0.82	13.88	0.55	3.29	0.61	0.00	0.42
	SLURRY	7 days	/	FORM II	300	0.75:0.25	2.083 ml	2.917 ml	31.32	58.40	1.11	27.79	0.93	2.04	0.81	11.76	0.82
	SLURRY	7 days	/	FORM II	300	0.75:0.25	2.083 ml	2.917 ml	22.56	65.03	0.67	5.58	0.44	0.00	0.52	29.39	0.54
	SLURRY	7 days	/	FORM II	300	0.66:0.33	1.626 ml	3.374 ml	43.24	39.91	1.79	3.32	1.35	0.60	2.15	56.17	2.07
	SLURRY	7 days	/	FORM II	300	0.66:0.33	1.626 ml	3.374 ml	23.12	37.76	0.59	0.00	0.31	0.00	0.55	62.24	0.67
	SLURRY	7 days	/	FORM II	300	0.50:0.50	0.958 ml	4.042 ml	34.55	1.04	0.83	0.11	0.55	36.81	1.12	62.04	1.22
	SLURRY	7 days	/	FORM II	300	0.50:0.50	0.958 ml	4.042 ml	44.14	0.53	1.14	0.01	0.71	26.03	1.47	73.44	1.73
	SLURRY	7 days	/	FORM II	300	0.33:0.66	0.523 ml	4.477 ml	36.36	0.00	0.71	0.00	0.74	99.83	1.25	0.17	0.71
	SLURRY	7 days	/	FORM II	300	0.33:0.66	0.523 ml	4.477 ml	40.26	0.00	0.84	0.00	0.92	96.27	1.39	3.73	0.72
	SLURRY	7 days	/	FORM II	300	0.25:0.75	0.366 ml	4.634 ml	34.82	0.00	0.73	0.00	0.78	99.59	1.26	0.41	0.68
	SLURRY	7 days	/	FORM II	300	0.25:0.75	0.366 ml	4.634 ml	62.12	4.53	2.69	18.13	4.61	45.96	5.13	31.37	4.73
	SLURRY	7 days	/	FORM II	300	0:1	0.00	5 ml	31.24	0.00	0.78	0.00	0.86	99.79	1.41	0.21	0.79
	SLURRY	7 days	/	FORM II	300	0:1	0.00	5 ml	34.69	0.00	1.00	0.45	1.07	95.65	1.62	3.90	0.81
Isovolumetric h2o: 2-pyr mixtures																	
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	20.00	20.00	25.33	90.47	0.79	7.81	0.48	1.44	0.61	0.28	0.34
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	20.00	20.00	25.51	73.89	0.71	2.31	0.43	0.00	0.52	23.80	0.53
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	84.4	84.4	64.41	1.62	1.70	85.38	3.61	0.00	1.93	13.00	2.91
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	84.4	84.4	55.92	78.59	3.06	2.55	1.36	0.13	2.12	18.74	2.41
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	168.8	168.8	41.92	11.21	1.04	1.84	0.80	0.00	1.11	86.95	1.58
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	168.8	168.8	45.33	2.78	0.69	0.00	0.69	0.00	1.10	97.22	1.43
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	168.8	168.8	58.03	2.99	0.87	0.00	1.94	0.00	1.61	97.01	2.59
	LAG	90 min	25Hz	FORM II	200	V h_2o=V 2-pyr	168.8	168.8	40.82	9.15	1.02	0.00	1.38	0.00	1.30	90.85	1.99
	LAG	120 min	25Hz	FORM II	200	V h_2o=V 2-pyr	168.8	168.8	48.44	72.99	3.32	0.00	1.96	4.17	2.04	22.84	2.74
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	126.6	126.6	69.36	89.56	7.39	6.54	4.01	3.67	3.99	0.24	5.70
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	50.00	50.00	28.18	1.04	0.28	63.15	0.90	0.32	0.66	35.49	0.81
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	50.00	50.00	25.55	3.88	0.36	60.70	0.87	0.02	0.72	35.40	0.78
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	100.00	100.00	69.28	21.49	4.35	78.46	7.89	0.00	5.15	0.05	7.04
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	100.00	100.00	60.57	89.72	4.92	10.19	2.05	0.00	2.86	0.09	4.13
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	140.00	140.00	56.98	14.17	1.78	4.41	1.74	0.00	2.27	81.42	2.93
	LAG	60 min	25Hz	FORM II	200	V h_2o=V 2-pyr	140.00	140.00	56.63	32.42	2.51	1.18	1.78	0.00	2.72	66.40	3.15
preformed solvates/hydrate plus individual solvents				**starting sample**													
	LAG	15 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	24.40	10.80	0.45	0.01	0.60	0.00	0.56	89.20	0.85
	LAG	15 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	16.55	30.88	0.42	1.14	0.37	0.00	0.37	67.98	0.52
	LAG	30 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	38.47	0.11	0.56	3.24	0.87	0.00	1.35	96.65	1.66
	LAG	30 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	41.20	1.87	0.55	1.08	1.29	0.00	1.21	97.05	1.81
	LAG	60 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	24.54	3.75	0.31	10.25	0.54	0.00	0.45	85.99	0.71
	LAG	60 min	25Hz	MONOHYDRATE	200	0:1	0.00	76.7	20.82	3.45	0.24	0.00	0.22	0.00	0.34	96.55	0.46
	LAG	15 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	28.51	0.03	0.33	0.00	0.78	0.00	0.64	99.97	1.06
	LAG	15 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	20.96	0.00	0.47	0.00	0.48	0.00	0.39	100.00	0.78
	LAG	30 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	34.24	1.33	0.95	0.00	1.04	0.00	0.83	98.67	1.62
	LAG	30 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	31.60	1.58	0.80	0.00	0.83	0.00	0.67	98.42	1.32
	LAG	60 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	28.27	0.00	0.72	0.00	0.78	0.00	0.62	100.00	1.22
	LAG	60 min	25Hz	MONOHYDRATE	200	0:1.58	0.00	120.00	20.96	0.00	0.47	0.00	0.49	0.00	0.37	100.00	0.78
	LAG	30 min	25Hz	MONOSOLVATE	200	1:0	13.6	0.00	44.44	45.53	1.77	0.00	2.23	0.00	2.18	55.47	2.63
	LAG	30 min	25Hz	MONOSOLVATE	200	1:0	13.6	0.00	43.09	51.80	1.97	0.02	1.73	0.00	1.74	48.19	1.92
	LAG	60 min	25Hz	MONOSOLVATE	200	1:0	13.6	0.00	33.54	0.03	0.31	0.00	0.76	0.00	0.63	99.97	1.04
	LAG	60 min	25Hz	MONOSOLVATE	200	1:0	13.6	0.00	40.59	0.05	1.07	0.00	1.61	0.00	1.51	99.95	2.45
	LAG	30 min	25Hz	SESQUISOLVATE	200	1:0	11.7	0.00	22.82	0.55	0.18	0.00	0.43	0.00	0.36	99.45	0.59
	LAG	30 min	25Hz	SESQUISOLVATE	200	1:0	11.7	0.00	41.98	1.74	0.51	0.00	1.34	0.00	1.26	98.26	1.88
	LAG	60 min	25Hz	SESQUISOLVATE	200	1:0	11.7	0.00	23.71	0.00	0.65	0.00	0.70	1.17	0.72	98.83	1.19
	LAG	60 min	25Hz	SESQUISOLVATE	200	1:0	11.7	0.00	28.27	0.00	0.72	0.00	0.78	0.00	0.62	100.00	1.22
	LAG	30 min	25Hz	MONOSOLVATE	200	0:1.58	0.00	34.4	32.00	0.82	0.60	0.04	0.79	99.14	1.98	0.00	1.74
	LAG	30 min	25Hz	MONOSOLVATE	200	0:1.58	0.00	34.4	32.88	0.00	1.15	0.00	1.59	99.47	3.15	0.53	2.47
	LAG	60 min	25Hz	MONOSOLVATE	200	0:1.58	0.00	34.4	26.23	0.00	0.54	0.00	0.73	100.00	1.14	0.00	0.68
	LAG	60 min	25Hz	MONOSOLVATE	200	0:1.58	0.00	34.4	31.74	0.00	0.76	0.00	1.02	99.41	1.82	0.59	1.30
preformed solvates/hydrate plus isolumetric liquid mixtures				**starting sample**			**H2O (µl)**	**2-PYR (µl)**									
	LAG	30 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	76.7	76.7	58.47	52.62	3.64	46.71	3.50	0.67	3.11	0.00	2.60
	LAG	30 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	76.7	76.7	51.48	95.43	3.70	3.40	1.38	1.07	2.05	0.09	2.95
	LAG	60 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	76.7	76.7	17.34	0.00	0.34	98.47	0.55	0.00	0.35	1.52	0.28
	LAG	60 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	76.7	76.7	55.02	72.34	3.96	27.13	2.41	0.00	2.43	0.54	3.98
	LAG	30 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	120.00	120.00	61.61	87.92	6.19	12.04	2.91	0.00	4.02	0.04	4.80
	LAG	30 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	120.00	120.00	51.16	86.61	2.78	0.60	1.31	1.03	2.07	11.77	1.82
	LAG	60 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	120.00	120.00	55.93	85.47	4.84	1.87	1.98	0.00	2.96	12.66	3.84
	LAG	60 min	25Hz	MONOHYDRATE	200	Vh2o=V2-pyr	120.00	120.00	62.79	82.71	7.18	15.18	3.45	0.37	4.73	1.74	6.05
	LAG	30 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	13.6	13.6	43.61	0.84	0.67	0.00	1.83	0.00	1.73	99.16	2.59
	LAG	30 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	13.6	13.6	44.83	3.31	0.72	0.00	1.63	0.00	1.54	96.69	2.29
	LAG	60 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	13.6	13.6	33.54	0.03	0.31	0.00	0.76	0.00	0.63	99.97	1.04
	LAG	60 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	13.6	13.6	35.43	3.65	0.79	0.00	0.77	0.00	0.62	96.35	1.23
	LAG	30 min	25Hz	SESQUISOLVATE	200	Vh2o=V2-pyr	11.7	11.7	42.10	0.00	1.15	0.83	1.53	50.26	1.83	48.91	1.82
	LAG	30 min	25Hz	SESQUISOLVATE	200	Vh2o=V2-pyr	11.7	11.7	42.86	1.47	0.90	0.00	1.24	47.19	1.57	51.33	1.60
	LAG	60 min	25Hz	SESQUISOLVATE	200	Vh2o=V2-pyr	11.7	11.7	33.13	0.00	1.16	0.00	1.19	0.00	1.25	100.00	2.08
	LAG	60 min	25Hz	SESQUISOLVATE	200	Vh2o=V2-pyr	11.7	11.7	36.66	2.08	1.31	0.01	1.76	4.20	1.60	93.72	2.60
	LAG	30 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	34.4	34.4	68.02	17.00	1.96	0.00	1.95	0.54	1.99	82.46	2.99
	LAG	30 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	34.4	34.4	56.97	12.44	1.33	0.00	1.53	0.01	1.53	87.55	2.30
	LAG	60 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	34.4	34.4	33.85	16.75	0.74	0.00	0.88	0.01	0.81	83.24	1.22
	LAG	60 min	25Hz	MONOSOLVATE	200	Vh2o=V2-pyr	34.4	34.4	50.81	8.77	1.06	0.00	1.15	0.00	1.15	91.23	1.82
preformed solvates/hydrate plus equimolar liquid mixtures				**starting sample**			**H2O (µl)**	**2-PYR (µl)**									
	LAG	30 min	25Hz	MONOHYDRATE	200		18.00	76.7	68.42	98.56	4.47	0.00	2.77	0.00	3.06	1.43	1.85
	LAG	30 min	25Hz	MONOHYDRATE	200		18.00	76.7	66.12	99.93	4.80	0.00	2.28	0.00	2.51	0.07	3.40
	LAG	60 min	25Hz	MONOHYDRATE	200		18.00	76.7	42.56	16.64	0.96	0.21	0.82	0.00	0.76	83.14	1.32
	LAG	60 min	25Hz	MONOHYDRATE	200		18.00	76.7	57.07	26.24	1.39	0.90	1.01	0.00	1.06	72.86	1.72
	LAG	30 min	25Hz	MONOHYDRATE	200		28.5	120.00	43.83	51.44	2.08	0.00	1.89	0.00	1.90	48.56	2.03
	LAG	30 min	25Hz	MONOHYDRATE	200		28.5	120.00	44.98	33.66	1.97	0.01	2.44	0.00	2.41	66.33	2.78
	LAG	60 min	25Hz	MONOHYDRATE	200		28.5	120.00	40.79	15.04	1.65	0.47	2.04	0.00	1.73	84.49	2.77
	LAG	60 min	25Hz	MONOHYDRATE	200		28.5	120.00	44.91	3.74	6.39	9.40	5.71	0.00	4.46	86.85	8.84
	LAG	30 min	25Hz	MONOSOLVATE	200		13.6	57.3	34.98	3.77	0.73	0.00	1.83	63.73	2.12	32.50	1.86
	LAG	30 min	25Hz	MONOSOLVATE	200		13.6	57.3	28.06	0.00	0.55	0.01	0.87	68.55	1.16	31.44	0.97
	LAG	60 min	25Hz	MONOSOLVATE	200		13.6	57.3	29.34	0.00	0.68	1.20	0.88	98.26	1.82	0.53	1.47
	LAG	60 min	25Hz	MONOSOLVATE	200		13.6	57.3	31.74	0.00	0.76	0.00	1.02	99.41	1.82	0.59	1.30
	LAG	30 min	25Hz	SESQUISOLVATE	200		11.7	49.4	32.00	0.82	0.60	0.04	0.79	99.14	1.98	0.00	1.74
	LAG	30 min	25Hz	SESQUISOLVATE	200		11.7	49.4	26.23	0.00	0.54	0.00	0.73	100.00	1.14	0.00	0.68
	LAG	60 min	25Hz	SESQUISOLVATE	200		11.7	49.4	43.71	0.00	4.15	0.00	5.07	86.80	6.90	13.20	4.00
	LAG	60 min	25Hz	SESQUISOLVATE	200		11.7	49.4	32.88	0.00	1.15	0.00	1.59	99.47	3.15	0.53	2.47
	LAG	30 min	25Hz	MONOSOLVATE	200		8.2	34.4	42.56	0.00	0.57	0.00	1.49	5.90	1.49	94.10	2.11
	LAG	30 min	25Hz	MONOSOLVATE	200		8.2	34.4	25.86	0.00	0.40	0.00	0.53	78.72	0.85	21.28	0.69
	LAG	60 min	25Hz	MONOSOLVATE	200		8.2	34.4	25.66	0.00	0.55	0.00	0.66	81.39	0.98	18.61	0.70
	LAG	60 min	25Hz	MONOSOLVATE	200		8.2	34.4	25.19	0.51	0.55	0.00	0.66	74.99	0.94	24.50	0.71

Table S4. Solvent physico-chemical parameters.

	pyr	**h_2o**
Molecular weight (g/mol)	85.10	18.02
Boiling point (°C)[a]	245	100
Theophylline solubility (mg/ml)	N.R.	8.4[b]
Theophylline dissolution (%)[c] (after 1h, dynamic temperature conditions)	63.0±5.9	81.0 ±4.4
Viscosity (cP) a 25°C[a]	13.3	1.0
Superficial tension (dyne/cm)[a]	40.7	77.1
Wettability towards anhydrous theophylline (contact angle°)[c]	43.8±10.6	41.1±5.4
Density (g/cm^3)[a]	1.12	1

[a] (Lide, 1994),[b] (Bustamante et al., 2011), [c]experimental data