Exploring Solubility of Novel Lamotrigine Drug-Drug Salts: The Role of pH and Structural Variability

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Table S1. The hydrogen bonds in LAM-NFA, LAM-MFA, LAM-DFA, and LAM-FFA salts.

Salts	D	H	A	d (D-A) / Å	D-H-A / °
LAM-FFA	N2	H2	O3 (1-X, +Y, +Z)	2.625	166.4
	N4	H4B	O4 (1-X, +Y, +Z)	2.781	175.0
	N5	H5A	N3 (-X, 1-Y, 2-Z)	2.957	179.1
	N6	H6	O3	2.638	129.0
LAM-DFA	N2	H2	O2 (1+X, +Y, +Z)	2.554	171.4
	N4	H4	O1 (1+X, +Y, +Z)	2.864	174.8
	N4	H4B	O3 (1-X, 1-Y, -Z)	2.954	165.0
	N5	H5A	N3 (1-X, 1-Y, 1-Z)	2.919	169.2
	N5	H5B	O3 (+X, +Y, 1+Z)	2.850	146.3
	N6	H6	O2	2.792	156.9
	N8	H8	O4	2.554	168.4
	N10	H10A	O3	2.933	172.8
	N11	H11B	O1 (1+X, +Y, +Z)	2.803	148.7
	N12	H12A	O4	2.801	152.8
LAM-MFA	N2	H2	O2 (-X, 1-Y, 1-Z)	2.591	153.4
	N4	H4B	O3(1+X, +Y, +Z)	2.819	124.9
	N5	H5A	O3 (1-X, 1-Y, 1-Z)	2.985	163.6
	N5	H5B	O1 (-X, 1-Y, 1-Z)	2.891	165.9
	N6	H6	O1	2.665	134.2
	O3	H3	O2 (-X, 1-Y, 1-Z)	2.829	151.7
LAM-NFA	N2	H2	O1	2.601	136.0
	N4	H4A	O2 (1-X, 1-Y, 1-Z)	2.702	168.9
	N6	H6A	O1 (1-X, 1-Y, 1-Z)	2.758	169.4
	N6	H6B	O2S (2-X, 1-Y, 1-Z)	2.979	163.8
	N7	H7B	O2S	2.771	133.2
	O1S	H1S	O2 (1-X, -Y, 1-Z)	2.787	167.5
	O2S	H2S	O1S (1+X, 1+Y, +Z)	2.666	174.5

Table S2. Calibration curves and R-squared of LAM, FFA, DFA, MFA, NFA in solubility

experiments

	Calibration curve	R^2
LAM	y = 7.30x	1
FFA	y = 17194x	1
DFA	y = 8221.80x	1
MFA	y = 17784x	0.999
NFA	y = 22.79x	1

Table S3. Solubility results of LAM and its salts

Compounds	Solubility (μg/mL)									
	pH 1.2	SD	pH 3.0	SD	pH 5.0	SD	pH 6.8	SD	Water	SD
LAM	3578.2 3290.9 3304.2	162.2	4894.7 4935.8 5351.3	252.6	974.4 1051.6 1028.6	39.6	268.8 269.2 264.6	2.5	266.0 263.0 255.3	5.5
LAM-FFA	3861.2 3181.9 3861.2	392.2	2760.3 2602.1 3299.4	365.6	192.2 350.0 407.7	111.5	124.7 124.6 123.4	0.7	49.8 48.3 51.1	1.4
LAM-DFA	3114.5 3135.7 3107.3	14.8	5325.6 5273.5 5562.2	153.9	1018.0 1091.6 1053.6	36.8	168.9 151.3 149.9	10.6	162.1 161.8 161.7	0.2
LAM-MFA	1788.8 1793.6 2204.1	238.4	3529.8 3031.0 3299.4	249.6	737.7 1024.8 997.4	158.4	205.5 220.4 222.2	9.2	232.3 232.7 233.6	0.7
LAM-NFA	3193.4 3209.9 3190.9	10.3	4546.6 4361.1 4333.1	116.0	1071.0 1046.8 1057.5	12.1	268.2 268.7 266.7	1.1	208.0 204.0 204.3	2.2

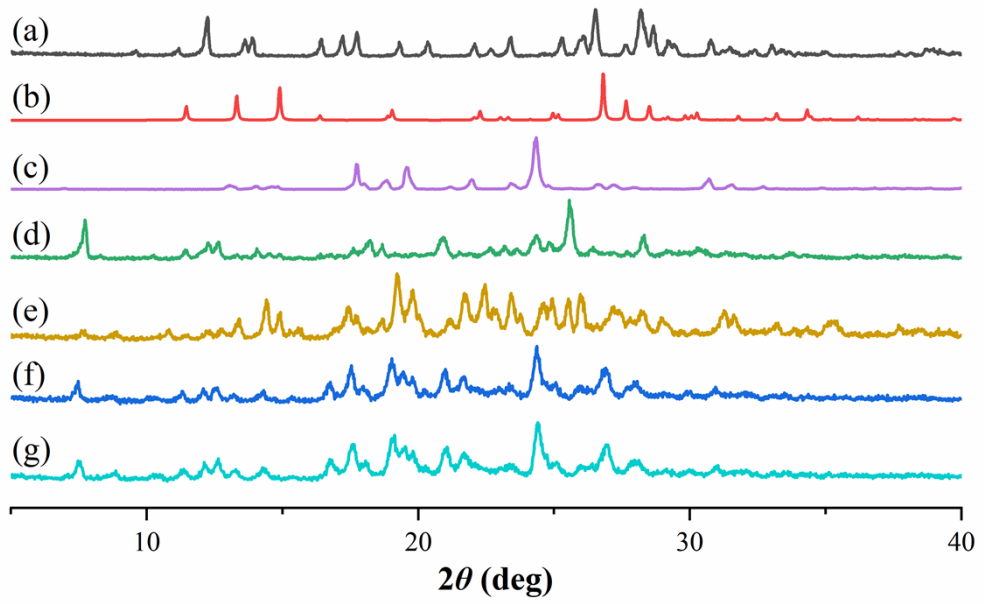

Fig. S1. Phase transformation analysis of LAM and LAM-FFA salts after solubility using PXRD (a): LAM, (b): LAM monohydrate, (c): FFA, (d): LAM-FFA, (e): LAM-FFA in pH = 1.2 buffer solution (f): LAM-FFA in pH = 6.8 buffer solution; (g): LAM-FFA in water

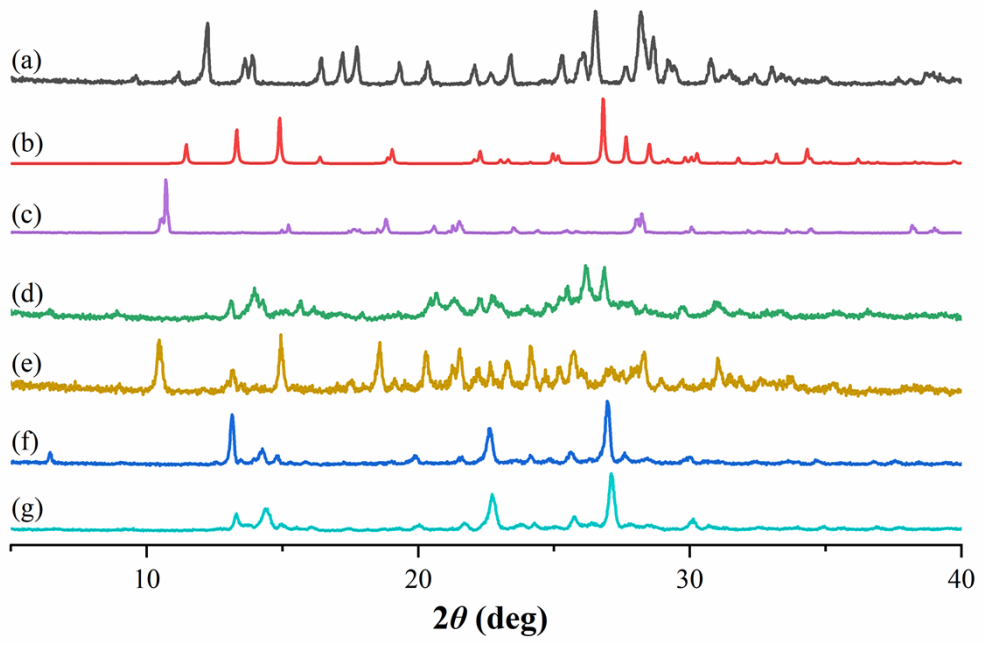

Fig. S2. Phase transformation analysis of LAM and LAM-DFA salts after solubility using PXRD (a): LAM, (b): LAM monohydrate, (c): DFA, (d): LAM-DFA, (e): LAM-DFA in pH = 1.2 buffer solution (f): LAM-DFA in pH = 6.8 buffer solution; (g): LAM-DFA in water

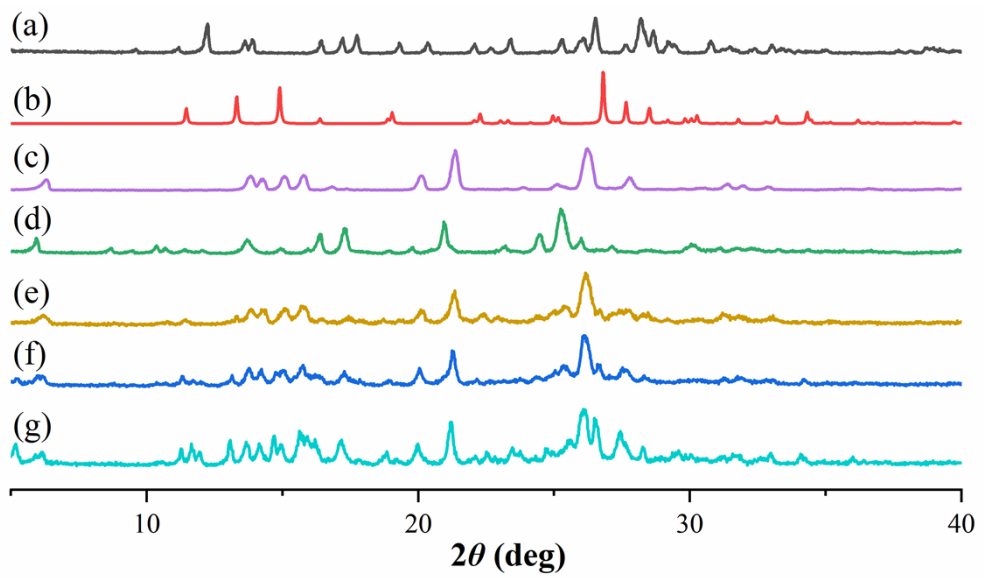

Fig. S3. Phase transformation analysis of LAM and LAM-MFA salts after solubility using PXRD (a): LAM, (b): LAM monohydrate, (c): MFA, (d): LAM-MFA, (e): LAM-MFA in pH = 1.2 buffer solution (f): LAM-MFA in pH = 6.8 buffer solution; (g): LAM-MFA in water

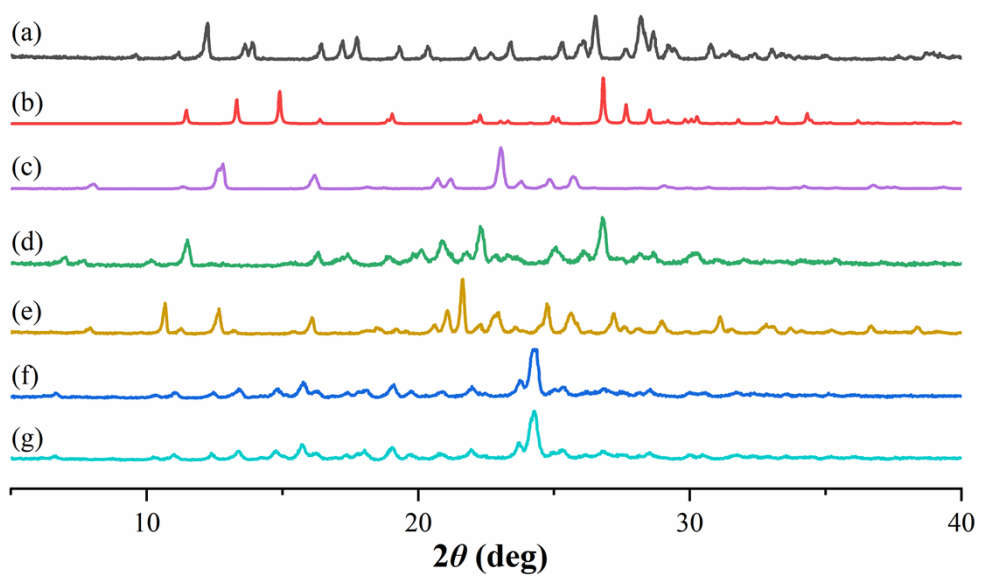

Fig. S4. Phase transformation analysis of LAM and LAM-NFA salts after solubility using PXRD (a): LAM, (b): LAM monohydrate, (c): NFA, (d): LAM-NFA, (e): LAM-NFA in pH = 1.2 buffer solution (f): LAM-NFA in pH = 6.8 buffer solution; (g): LAM-NFA in water

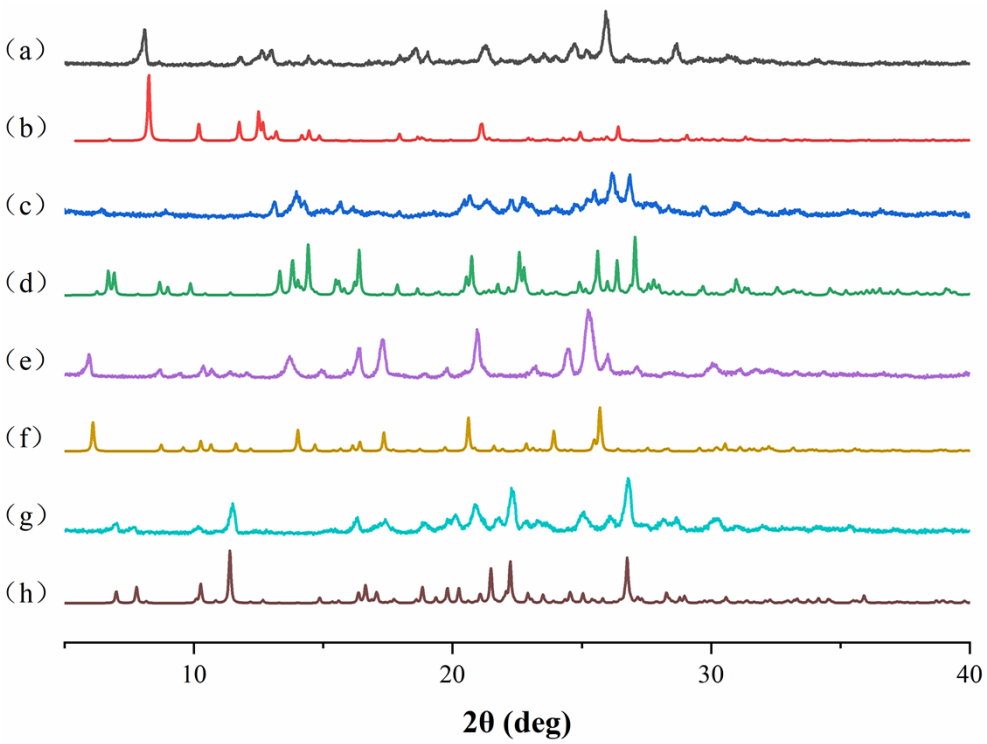

Fig. S5. Experimental and simulated PXRD of LAM salts. (a): experimental PXRD of LAM-FFA; (b): simulated PXRD of LAM-FFA; (c): experimental PXRD of LAM-DFA; (d): simulated PXRD of LAM-DFA; (e): experimental PXRD of LAM-MFA; (f): simulated PXRD of LAM-MFA; (g): experimental PXRD of LAM-NFA; (h): simulated PXRD of LAM-NFA

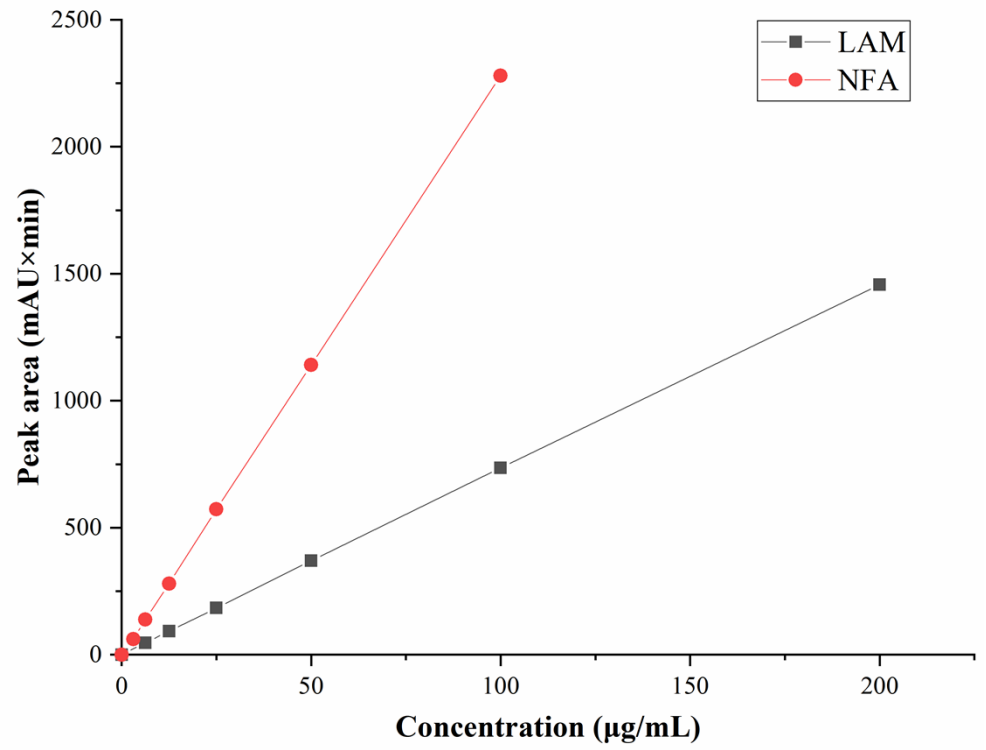

Fig. S6. Calibration curves for HPLC measurement of LAM and NFA in solubility experiments

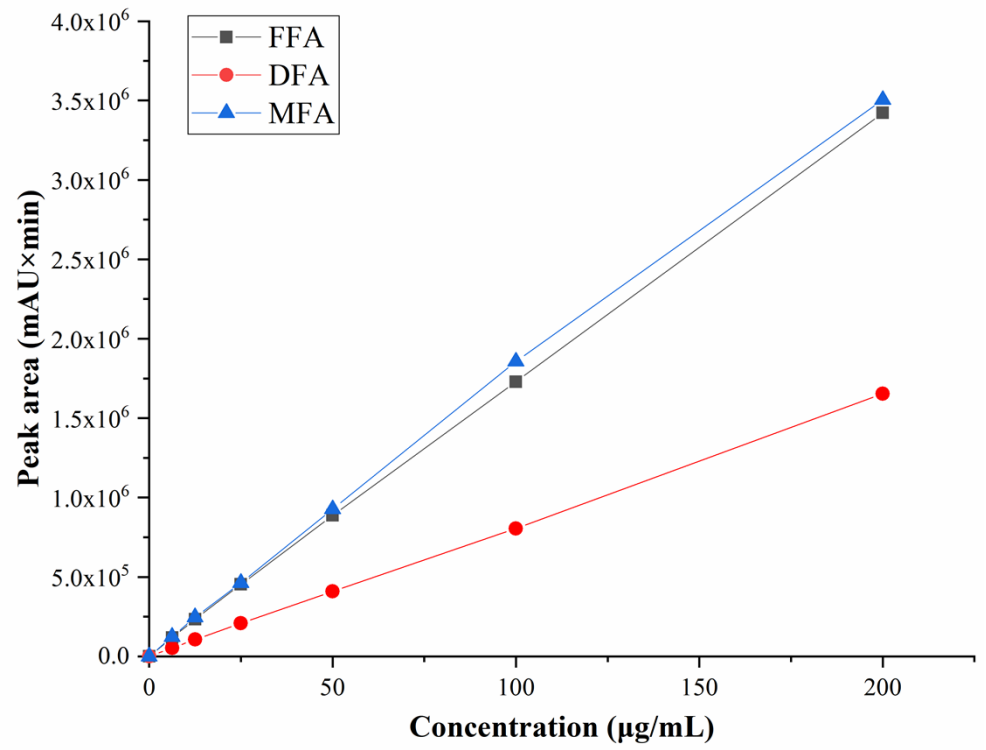

Fig. S7. Calibration curves for HPLC measurement of FFA, DFA and MFA in solubility experiments