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Supplementary Information

Modification of hygroscopicity and tabletability of L-carnitine by cocrystallization technique

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1. Tabletability test

Table S1 Tablet thickness (mm, n=3, mean ± SD), diameter (mm) and shape of MYR, LC salts and LC-MYR cocrystal obtained under different pressure.

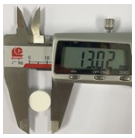
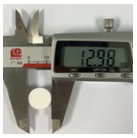
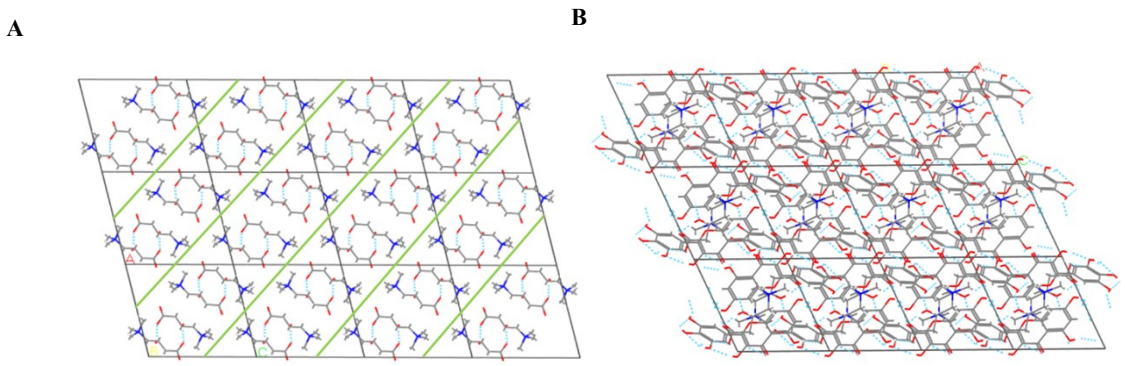
Sample	Pressure (Mpa)					
	50	75	100	125	150	175
MYR	 1.426±0.013	 1.379±0.024	 1.334±0.008	 1.291±0.012	 1.274±0.002	 1.236±0.005
LC fumarate	 1.593±0.015	 1.56±0.01	 1.523±0.012	 1.483±0.025	 1.43±0.026	 1.417±0.006
LC tartrate	 1.623±0.006	 1.61±0.04	 1.573±0.023	 1.553±0.035	 1.513±0.045	 1.543±0.015
LC-MYR cocrystal	 1.773±0.029	 1.677±0.006	 1.631±0.012	 1.601±0.021	 1.583±0.016	 1.562±0.011

Table S2 Powder true density of MYR, LC fumarate, LC tartrate and LC-MYR cocrystal (*n*=3, $\bar{X}$ ± SD)

Sample	Powder true density (g/cm^3)
MYR	1.4946±0.0045
LC fumarate	1.3198±0.0051
LC tartrate	1.359±0.0048
LC-MYR cocrystal	1.7897±0.0076
	(Calculated value from simulated crystal structure: 1.7975)

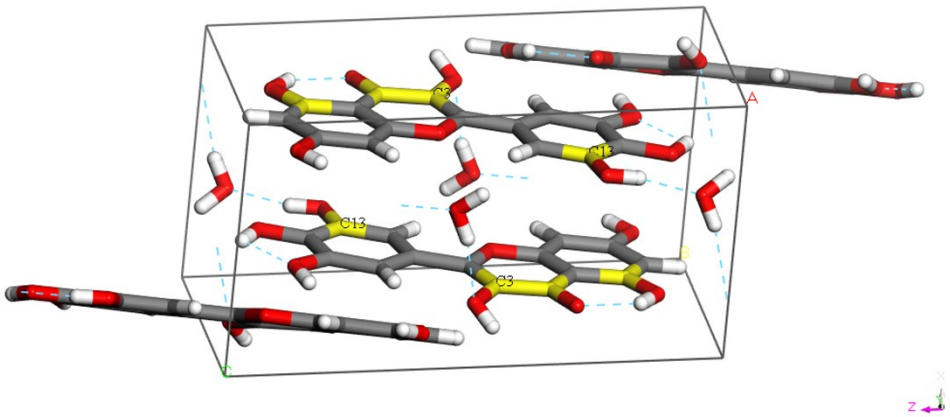
The higher true density of LC-MYC cocrystal can be interpreted based on its different crystal structure with LC. As shown in Fig. S1A, LC exhibited an obvious active slip system view along *b* axis (green line) while the slip system was absent in LC-MYR cocrystal and it had closer intermolecular distance due to the multiple 3D hydrogen bonding network (Fig. S1B). Slip planes are crystallographic planes that have the weakest inter-planar interactions in a given crystal, and are associated with the higher molecular density and the larger separation between adjacent planes[1, 2]. Thus, absence of slip planes in LC-MYR cocrystal offered a closer crystal packing, which conferred a dense crystalline structure and a higher density.

Fig. S1 Crystal packing patterns of (A) LC and (B) LC-MYR cocrystal viewed along the *b* axis



2. Thermal analysis

Fig. S2 Water molecules in one crystal cell of MYR monohydrate (Downloaded from the Cambridge Crystallographic Database, Deposition Number: 1409763)



D-H···A	D···A/ Å	H···A/ Å	D-H···A/ °
O-H (H_2O) ··· O3 (MYR)	2.969	2.196	153.496
O13-H (MYR) ··· O (H_2O)	2.665	1.890	152.764

3. Cocrystal structure simulation

Fig. S3 The measured powder X-ray diffraction patterns (blue), Rietveld refinements (red) and underneath the difference curves (black) of LC-MYR cocrystal. The green tick marks indicated reflection positions.

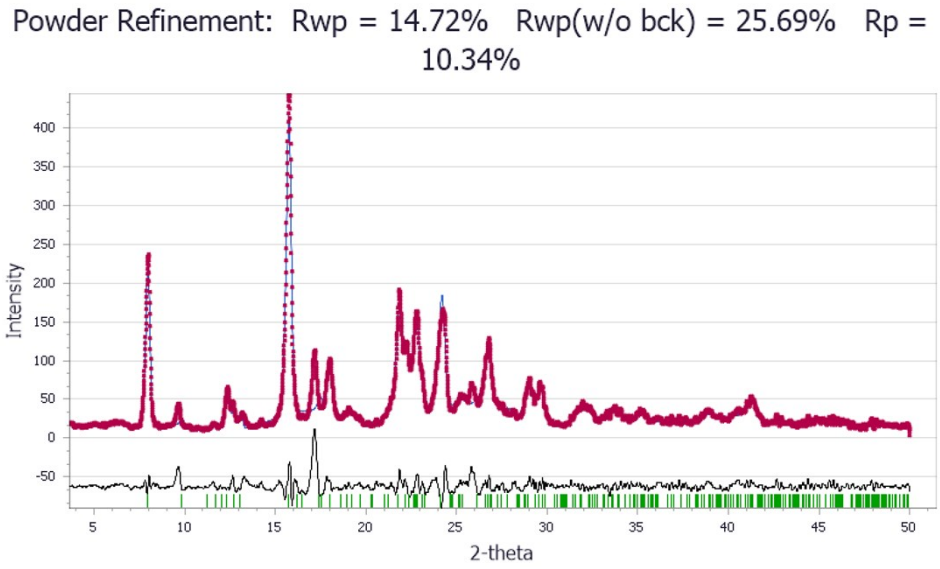


Fig. S4 Simulated LC-MYR cocrystal structure.

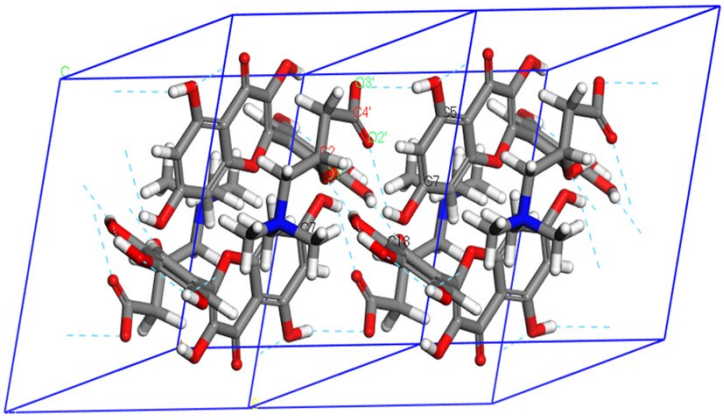


Table. S3 Crystallographic data of simulated LC-MYR cocrystal

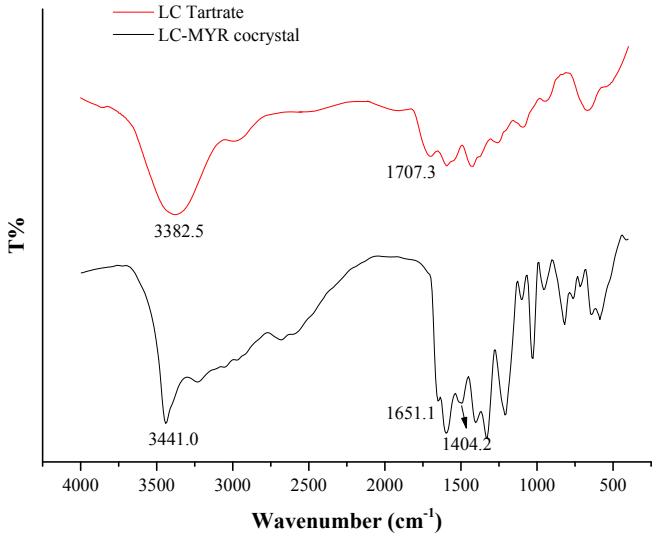
Item	LC-MYR cocrystal
Formula	$(C_{15}H_{10}O_8)\cdot(C_7H_{15}NO_3)$
Space group	$P\bar{1}$
Crystal system	Triclinic
a(Å)	12.0089
b(Å)	8.7926
c(Å)	14.0875
α(°)	83.976
β(°)	42.351
γ(°)	62.990
Volume (Å^3)	824.22
R_{wp}%	14.72 %

Table. S4 Hydrogen bond parameters for LC-MYR cocrystals

D-H···A	D···A/ Å	H···A/ Å	D-H···A/ °
O5-H (MYR) ··· O3′ (LC)	2.918	2.448	110.677
O7-H (MYR) ··· O2′ (LC)	2.794	2.367	107.650
O13-H (MYR) ··· O1′(LC)	2.746	1.974	141.083

4. FTIR analysis

Fig. S5 FT-IR spectra of LC-MYR cocrystal and LC tartrate



5. ^{13}C ss NMR Analysis

Table S5 Experimental ^{13}C CP/MAS chemical shifts in the MYR and LC spectra compared with the previous researches.

Molecules	C atoms	^{13}C Chemical Shifts/ppm	
		Experimental: This work	Literature [3,4]
MYR	C2	145.60	145.6
	C3	135.66	135.8
	C4	172.22	172.4
	C5	156.18	156.3
	C6	98.75	99.1
	C7	164.49	164.7
	C8	95.26	95.5
	C9	156.18	156.3
	C10	100.80	101.1
	C11	119.96	120.4
	C12	109.69	109
	C13	142.26	142.3
	C14	133.06	133.3
	C15	142.26	142.3
	C16	107.01	108.5
LC	C1′	69.67	71
	C2′	65.60	64.9
	C3′	47.06	43.8
	C4′	175.41	178.9
	C5′, C6′, C7′	51.32	54.9

The reported ^{13}C NMR of LC was obtained through liquid state NMR in D_2O.

6. Intrinsic dissolution testing

Methods

An improved method for IDR measurement was employed to perform the intrinsic dissolution rate (IDR) studies [5]. Briefly, 250 mg of MYR and LC-MYR cocrystal was compressed at a pressure of 75 MPa for 10 sec using a hydraulic press (4350L, Carver®, Wabash, USA). The resulting discs with a surface area of 1.3273 cm^2 were inserted into a molten beeswax-mold, in such a way that only one face could be in contact with dissolution medium. Because of the strong hygroscopicity of LC, PM could not be compressed to tablets at room temperature with 30% RH humidity condition. Therefore, the IDR of MYR in LC solution was performed with the method of dropping MYR tablets into the medium with dissolved specific amount of LC to assess the effect of physical mixed LC on MYR dissolution rate.

A USP II dissolution apparatus was applied in the intrinsic dissolution study. Dissolution tests (three replicates) were performed in 600 mL of pH 4.5 phosphate buffer saline (PBS 4.5) at 37 ^oC with the paddle rotating speed of 50 rpm. Three milliliters of aliquots were withdrawn at predetermined time points (5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210 and 240 min) and analyzed by the HPLC/UV method in “Stoichiometry determination of cocrystal” section. To evaluate the IDR of MYR, the cumulative amount dissolved per surface unit of the tablets was plotted against time. The slope of the linear region was taken as the intrinsic dissolution rate [6].

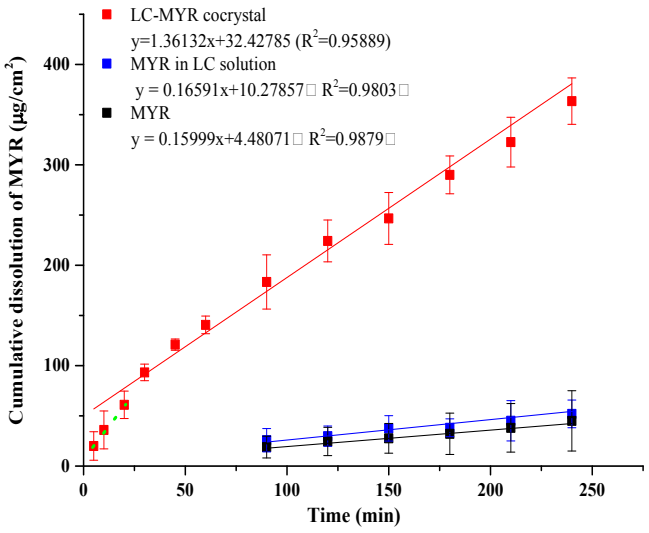
Result and discussion

As the intrinsic dissolution profiles (Fig. S6) shows, crystalline MYR, MYR in LC solution and LC-MYR cocrystal exhibited linear release profiles with IDR values of 0.1599, 0.16591

and 1.36132 $\mu g \cdot cm^{-2} \cdot min^{-1}$, respectively. MYR in medium containing LC exhibited similar IDR with MYR alone, which meant that LC could not improve the dissolution rate of MYR and consisted with the results in "Dissolution under non-sink condition" section. LC-MYR cocrystal showed a significant dissolution rate enhancement (8.5-fold) compared to pure MYR.

In addition, LC-MYR cocrystal showed the typical linear dissolution profile in the medium (R^2>0.95), while the first three points (5, 10, 20 min) slightly deviated from the IDR curve and the dotted line connected by the three points (green one) almost went through origin. During the dissolution process of the cocrystal, some small fragments fell from the surface of the tablet owing to the high hydrophilic LC-MYR cocrystal. The deviation might be attributed result from this phenomenon.

Fig. S6 Intrinsic dissolution profiles of LC-MYR cocrystal, MYR in LC solution and MYR in PBS 4.5 (n=3)



7. Effect of LC on the solubility of MYR

Excess powder of MYR was added into glass vials containing 3 mL of LC aqueous solution. The molar ratios of MYR to LC were 1:0.25, 1:0.5, 1:0.75, 1:0.9, and 1:1.5, respectively. Then the solutions were magnetically stirred for 24 h at 37 °C. The slurry was filtered through a 0.22 μm filter and then analyzed by HPLC/UV analysis. Each experiment was repeated in triplicate.

Table S6. Solubilities of MYR in LC aqueous solution with different molar ratios ($\bar{X}$ ± SD mg/mL, *n*=3)

Molar ratio	1:0.25	1:0.5	1:0.75	1:0.9	1:1.5
Solubility	2.43±0.03	2.36±0.11	2.28±0.32	2.39±0.06	2.34±0.12

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6. J. Zhang, D. Liu, Y. Huang, Y. Gao and S. Qian, i*nternational Journal of Pharmaceutics*, 2012, **436**, 311-317.