Electronic Supplementary information

Solid State Thermomechanical Engineering of High-Quality Pharmaceutical Salts via Solvent Free Continuous Processing

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1. Screw Configuration

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<th>C4</th>
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Fig. S1.1†: Complete screw profile showing the order of the Conveying (C), Kneading (K) and Discharge (D) zones

Fig. S1.2†: Screw configuration for Kneading zone 1
Fig. S1.3†: Screw configuration for Kneading zone 2

Fig. S1.4†: Screw configuration for Kneading zone 3

Fig. S1.5†: Screw configuration for the Conveying zones
Fig. S1.6†: Screw configuration for the Discharge zone

2. Particle Size and Morphology
**Fig. S2.1†.** Particle size distribution of the feed materials for both mixtures used in ssTME and LAG processing.

**Fig. S2.2 †:** SEM images of bulk KTZ (Left) and CFX (Right)
Fig. S2.3 †: SEM images of KTZ-OA salts and CFX-MA salts produced via LAG

3. Thermal Analysis
Fig. S3.1†. DSC thermogram of KTZ – OA and CFX – MA physical mixture.

4. PXRD analysis

Fig. S4.1†. PXRD analysis of KTZ-OA salts taken from each individual conveying and kneading zone within the twin-screw extruder, showing the cocrystals transformation
Fig. S4.2†: PXRD analysis of CFX-MA salts taken from each individual conveying and kneading zone within the twin-screw extruder, showing the cocrystals transformation pathway.

R-Values:
\[ R_{\text{exp}}: 4.73 \quad R_{\text{wp}}: 8.74 \quad R_{p}: 6.69 \quad \text{GOF: 1.85} \]
\[ R_{\text{exp}}: 6.05 \quad R_{\text{wp}}: 11.18 \quad R_{p}: 9.14 \quad \text{DW: 0.64} \]

Fig. S4.3†: Rietveld refinement of the PXRD data for the KTZ OA ssTME, where the measured pattern is represented with blue line, the simulated pattern with the red line and the difference pattern in grey. Refinement values displayed.
R-Values:

Rexp : 4.79    Rwp : 6.78     Rp  : 5.23   GOF : 1.42
Rexp`: 5.74    Rwp`: 8.13     Rp` : 6.50   DW  : 1.03

Fig. S4.4†: Rietveld refinement of the PXRD data for the KTZ OA LAG, where the measured pattern is represented with blue line, the simulated pattern with the red line and the difference pattern in grey. Refinement values displayed.

R-Values

Rexp : 7.70    Rwp : 16.17    Rp  : 12.66  GOF : 2.10
Rexp`: 8.31    Rwp`: 17.45    Rp` : 13.87  DW  : 0.50

Quantitative Analysis - Rietveld

Phase 1  : "CFX MA Polymorph 2"          99.048 %
Phase 2  : "CFX MA Polymorph 1"          0.952 %

Fig. S4.5†: Rietveld refinement of the PXRD data for the CFX MA ssTME, where the measured pattern is represented with blue line, the simulated pattern with the red line and the difference pattern in grey. Refinement values displayed.
R-Values

Rexp : 11.73   Rwp : 20.34   Rp : 15.96   GOF : 1.73
Rexp' : 14.17   Rwp' : 24.57   Rp' : 19.65   DW : 0.70

Quantitative Analysis - Rietveld

Phase 1 : "CFX MA Polymorph 2"    99.001 %
Phase 2 : "CFX MA polymorph 1"    0.999 %

Fig. S4.6†: Rietveld refinement of the PXRD data for the CFX MA LAG, where the measured pattern is represented with blue line, the simulated pattern with the red line and the difference pattern in grey. Refinement values displayed.

5. Release Studies
**Fig. S5.1†:** Dissolution profiles of bulk CFX and CFX-MA salt synthesised by ssTME and LAG.

**Fig. S5.2†:** Dissolution profile for the KTZ-OA physical blend at pH 4.4.

**Fig. S5.3†:** Dissolution profile for the CFX-MA physical blend at pH 6.8.
Fig. S5.4†: Dissolution profile for the CFX-MA physical blend at pH 1.2