Electronic Supplementary Information:

Polymorphism of Chlorpropamide on Liquid-Assisted Mechanical Treatment: Choice of Liquid and Type of Mechanical Treatment Matter

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1. PREPARATION OF β-CHLORPROPAMIDE

The method developed for formation of β-CPA requires crystallisation of α-CPA under well-controlled temperature conditions. Slight deviations from the desired temperature (*ca* 61 ^{0}C) can introduce large quantities of additional phases, primarily α-CPA, as by-products, Figure S1.

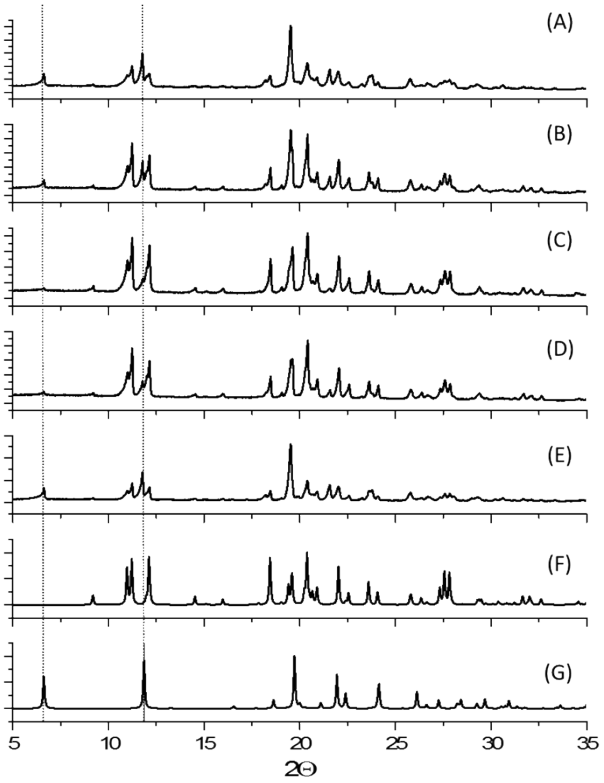

Fig S1: XRPD patterns for the formation of β-CPA, after heating α-CPA to (A) 40 °C, (B) 60 °C, (C) 65 °C, (D) 70 °C, and (E) 80 °C. Simulated patterns are given for (F) β-CPA and (G) α-CPA. The major peaks of α-CPA are indicated with a dotted line.

2. HUMIDITY STABILITY

To test the stability of the two metastable CPA polymorphs to humidity, a sample of each was stored under a *ca* 90% relative humidity atmosphere, Figure S2. In both samples, conversion to the α-phase was observed in less than a week.

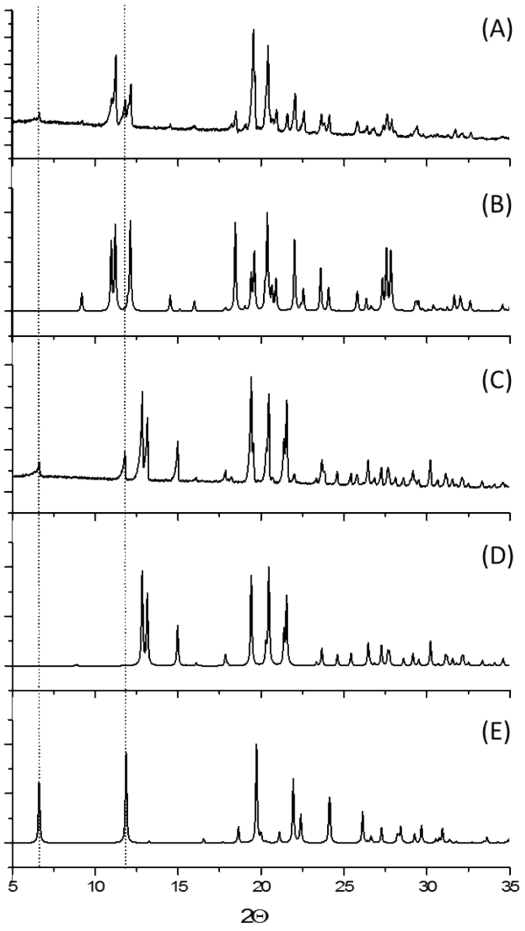

Fig S2: XRPD for humidity tests of CPA polymorphs. XRPD are given for (A) β-CPA stored RH *ca* 9 days, (B) simulated XRPD for β-CPA, (C) ε-CPA stored RH *ca* 90% for 4 days, (D) simulated XRPD for ε-CPA, and (E) simulated XRPD for α-CPA. Dashed lines are given as visual guides of major peaks.

3. DRY MANUAL GRINDING

It has been previously demonstrated that the sorption of atmospheric moisture can result in inadvertent liquid assisted grinding. Thus, it was important to investigate the effects of ambient atmosphere on the transformation of CPA on grinding. In ambient atmosphere, manual grinding of β-CPA led to traces of α-CPA in only 30 minutes, Figure S3. Instead, when manual grinding was performed in a dry box, with relative humidity of < 10 %, no signs of the α-CPA phase were found. Similarly, grinding ε-CPA under ambient atmospheric conditions led to complete conversion to the thermodynamics α-CPA, while grinding in a dry box with relative humidity of < 10% shows only traces of α-CPA after 30 minutes of grinding, Figure S4. It is therefore clear that CPA polymorphism is another example of inadvertent liquid assisted grinding, and that the CPA transformation is the result of a liquid assisted process. It is interesting to observe the more rapid conversion of ε-CPA than β-CPA, even under nearly dry atmosphere. This suggests either notable differences in hygroscopicity between the polymorphs, or notably lower kinetics to dissolution in the atmospheric moisture.

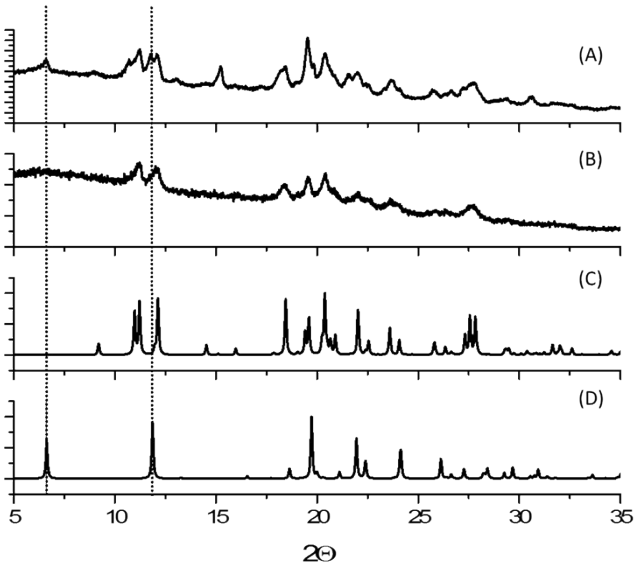

Fig S3: XRPD for dry grinding of β-CPA. XRPD are given for (A) dry grinding in atmosphere, (B) dry grinding in a glove box. Simulated patterns given for (C) β-CPA and (D) α-CPA. Dashed lines are given as visual guides of major peaks.

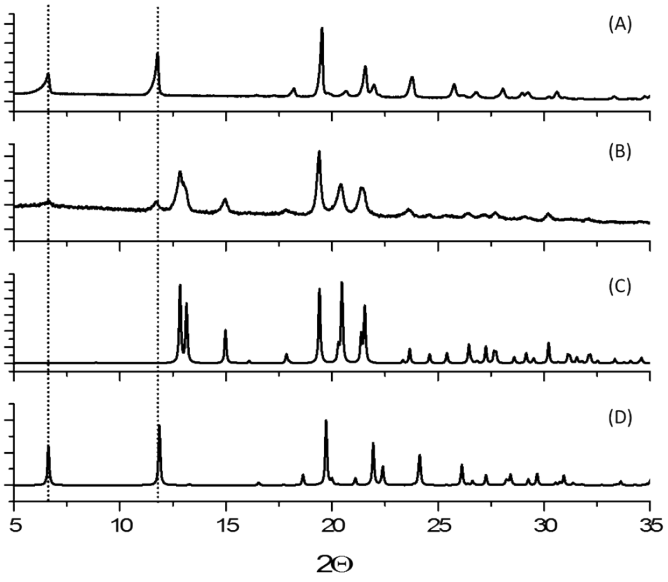

Fig S4: XRPD for dry grinding of ε-CPA. XRPD are given for (A) dry grinding in atmosphere, (B) dry grinding in a glove box. Simulated patterns given for (C) ε-CPA and (D) α-CPA. Dashed lines are given as visual guides of major peaks.

4. MANUAL GRINDING – LIQUID ASSISTED GRINDING

Unlike dry grinding, the addition of liquid greatly accelerated conversion of CPA. When grinding β-CPA in the presence of ethanol, chloroform or toluene, a complete conversion from β- to α-CPA was observed in < 30 minutes, Figure S5. However, on grinding in the presence of heptane, a mixture of the α- and δ-form is generated. Rietveld refinement, Figure S5, suggests formation larger quantities of the α-phase than the δ-form, at *ca* 70 mol% and 30 mol%, respectively. The formation of larger

quantities of α-CPA is likely a by-product of grinding in atmospheric moisture, following evaporation of heptane.

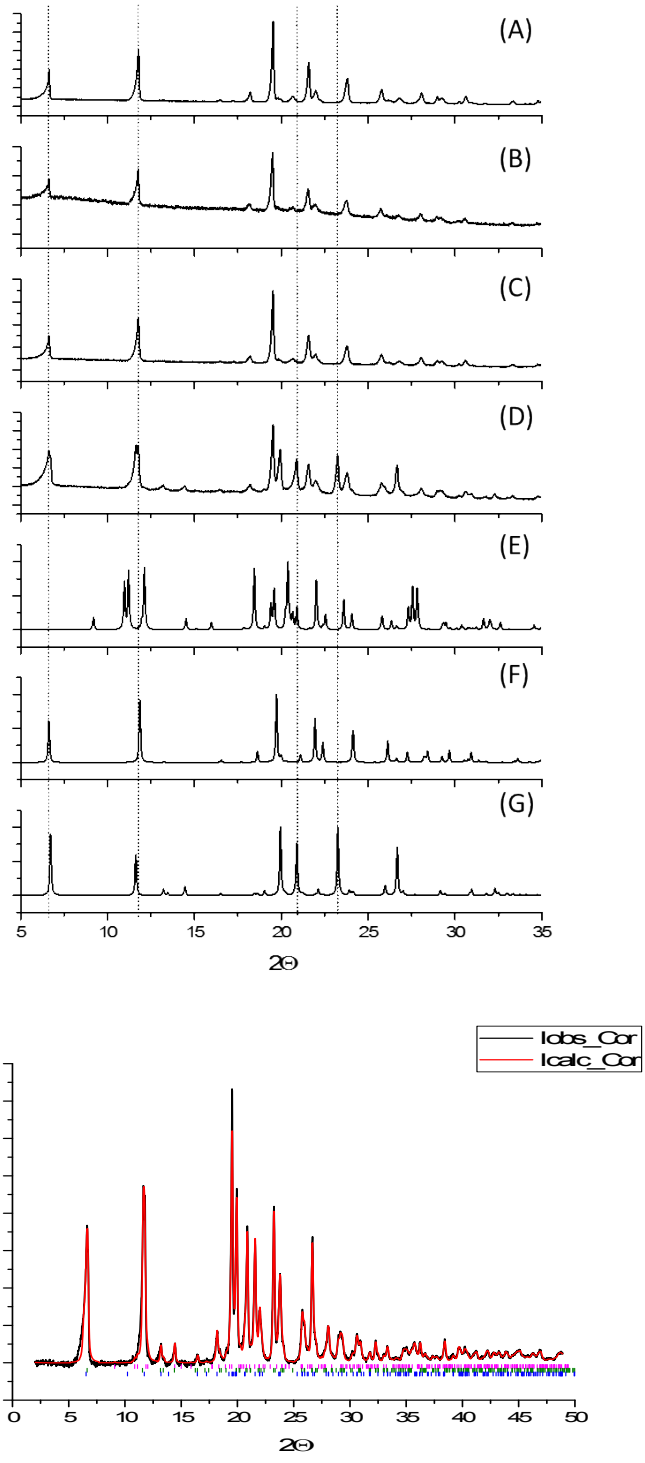

Fig S5: XRPD patterns resulting from manual grinding of β-CPA. (Top) Experimental XRPD are provided for (A) grinding 30 minutes in ethanol, (B) grinding 15 minutes in chloroform, (C) grinding 25 minutes in toluene, and (D) grinding 15 minutes in heptane. Simulated XRPD are provided for (E) β-CPA, (F) α-CPA, and (G) δ-CPA. Dashed lines are given as visual guides of major peaks. (Bottom) Rietveld refinement for grinding β-CPA 15 minutes in heptane (pattern (D)). Experimental patterns

are shown in black, and calculated pattern in red. The position of simulated Bragg reflections are given for β-CPA (pink), α-CPA (blue) and δ-CPA (green). Refined quantities show *ca* 70 mol% α-CPA, 30 mol% δ-CPA, with only traces of β-CPA.

Grinding of ε-CPA in the presence of small traces of solvent, ethanol, chloroform, toluene and heptane all led to conversion to the α-phase, Figure S6. However, we note residual quantities of ε-CPA in the case of grinding with heptane. In contrast to grinding of β-CPA (Figure S5), no traces of δ-CPA were observed on grinding ε-CPA with heptane. This may indicate unique reactivity of the two polymorphs, or may be in part due to longer grinding times for ε-CPA. However, given the volatility of heptane, we note that all traces can be expected to have disappeared by 15 minutes of manual grinding. We further note that all previous transformations observed on neat grinding occur slowly (Section 3). Thus, we do not expect complete loss of any δ-CPA within 15 minutes of dry grinding.

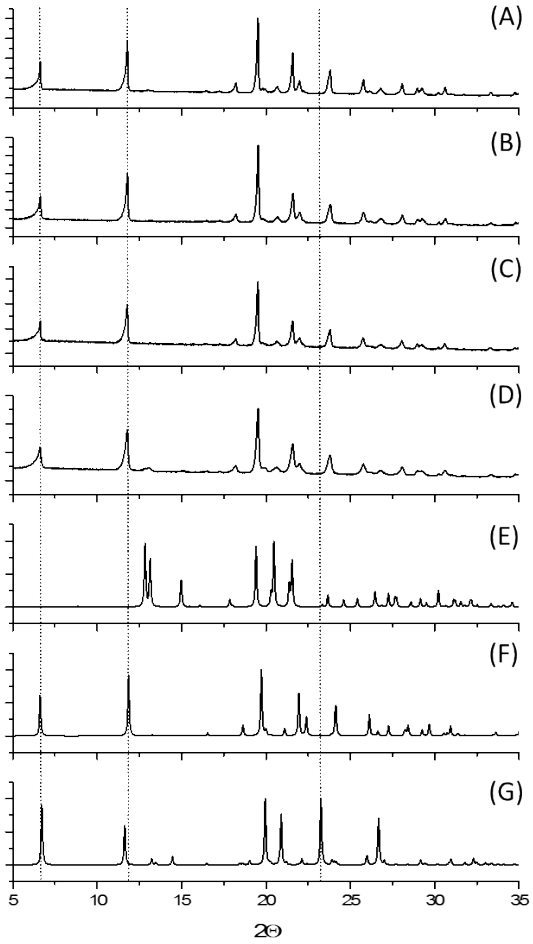

Fig S6: XRPD patterns resulting from manual grinding of ε-CPA. Experimental XRPD are provided for (A) grinding 30 minutes in ethanol, (B) grinding 30 minutes in chloroform, (C) grinding 30 minutes in toluene, and (D) grinding 30 minutes in heptane. Simulated XRPD are provided for (E) ε-CPA, (F) α-CPA, and (G) δ-CPA. Dashed lines are given as visual guides of major peaks.

5. RESTRICTED IMPACT – LIQUID ASSISTED GRINDING

Pure samples ~~of each~~ of β-CPA were subjected to restricted impact treatment, both dry and in a series of LAG solvents, Figure S7. Even after an hour of treatment under dry atmosphere, the restricted impact of a dry sample of β-CPA contained a mixture of β- and α-CPA. We note that the Bragg peak at *ca* 2θ=15° does not correspond to a known phase of CPA, nor does that at *ca* 2θ=10^0. Due to notable peak broadening associated with the dry impact treatment, it is difficult to determine the origin of these peaks. In stark contrast, the restricted impact treatment of β-CPA in the presence of ethanol, chloroform or toluene resulted in complete conversion to α-CPA in < 30 minutes. In the case of restricted impact with heptane, the resulting powder appears to be a mixture of β- and δ-CPA.

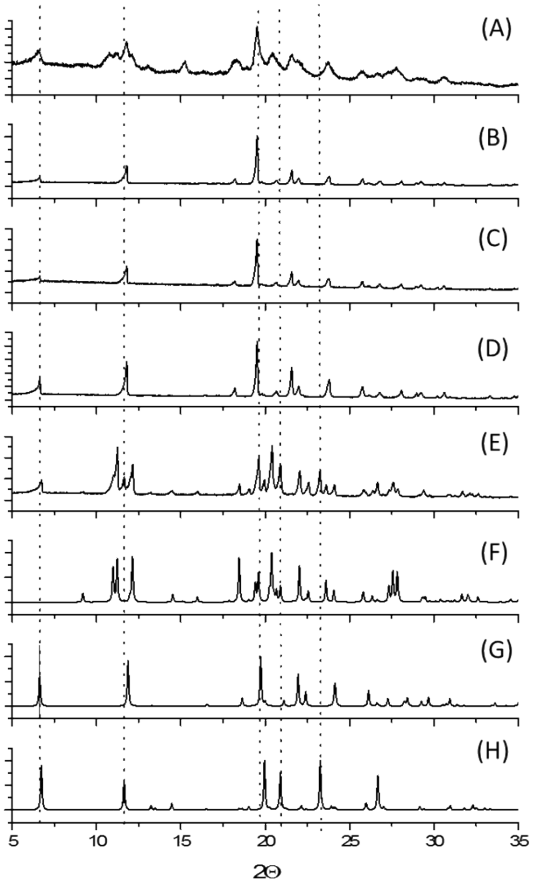

Fig S7: XRPD patterns resulting from restricted impact of β-CPA. Experimental XRPD are given for (A) dry impact for 60 minutes, (B) 30 min impact in ethanol, (C) 10 minute impact in chloroform, (D) 20 minute impact in toluene, and (E) 20 minute impact in heptane. Simulated XRPD are given for (F) β-CPA, (G) α-CPA and (H) δ-CPA. Dashed lines are given as visual guides of major peaks.

On prolonged impact in the presence of heptane, the conversion of β-CPA to the δ-polymorph was found to increase until a nearly pure phase was obtained, Figure S8.

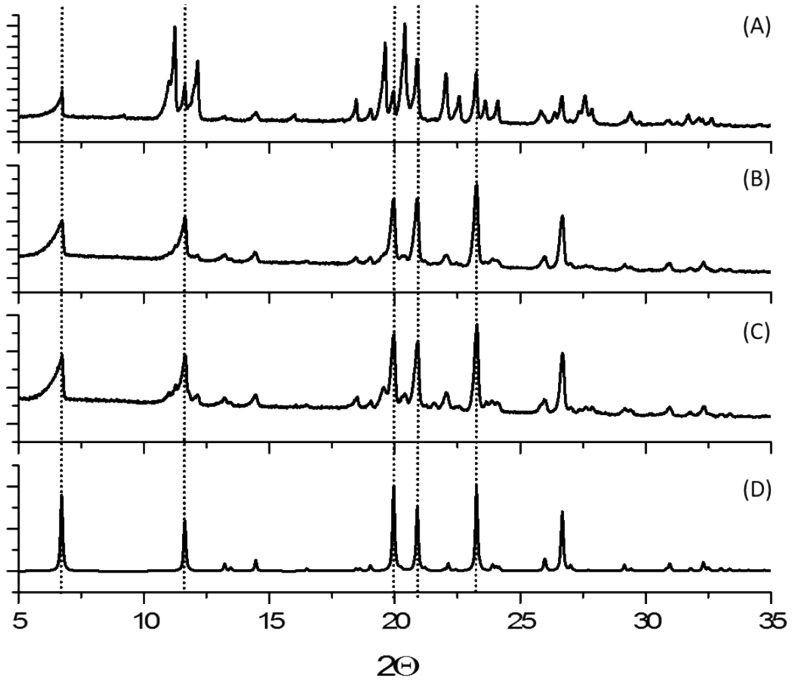

Fig S8: XRPD patterns resulting from restricted impact of β-CPA. Experimental XRPD are given for (A) 20 minute impact in heptane, (B) 30 minute impact in heptane, (C) 60 minute impact in heptane. Each experiment performed from a new powder sample. The simulated XRPD is given for (D) δ-CPA. Dashed lines are given as visual guides of major peaks.

Restricted impact treatment of a pure sample of ε-CPA displays a similar effect, Figure S9. In the presence of a small quantity of ethanol, chloroform or toluene, a full conversion to the α-phase is observed in < 30 minutes. However, when subjected to restricted impact in the presence of heptane, only traces of the conversion are found. Due to the similarities in XRPD patterns of the α- and δ-phases, it is difficult to unambiguously identify the nature of the trace phase on restricted impact with heptane. However, the existence of a dominant peak at *ca* 2θ=23° in some patterns does suggest it to be the δ-phase, Figure S10. This peak is not present in all runs, and suggests conversion to both the α- and δ-phases may be possible. Control between these two forms is the subject of further investigation. The slightly different impact timings of the two patterns displayed in Figure S10 is unlikely to cause conversion of δ- to α-CPA, given that dry impact leads to no conversion, and prolonged impact of the δ-phase in Figure S8 does not lead to its conversion to the α-form.

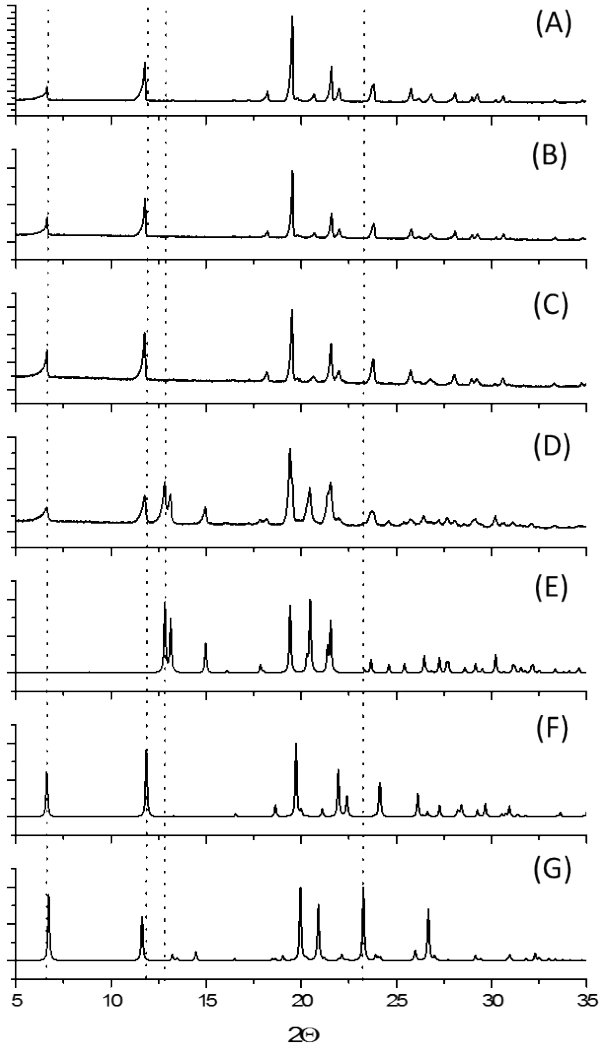

Fig S9: XRPD patterns resulting from restricted impact of ε-CPA. Experimental XRPD are given for (A) 30 min impact in ethanol, (B) 20 minute impact in chloroform, (C) 35 minute impact in toluene, and (D) 45 minute impact in heptane. Simulated XRPD are given for (E) ε-CPA, (F) α-CPA and (G) δ-CPA. Dashed lines are given as visual guides of major peaks. Dashed lines are given as visual guides of major peaks.

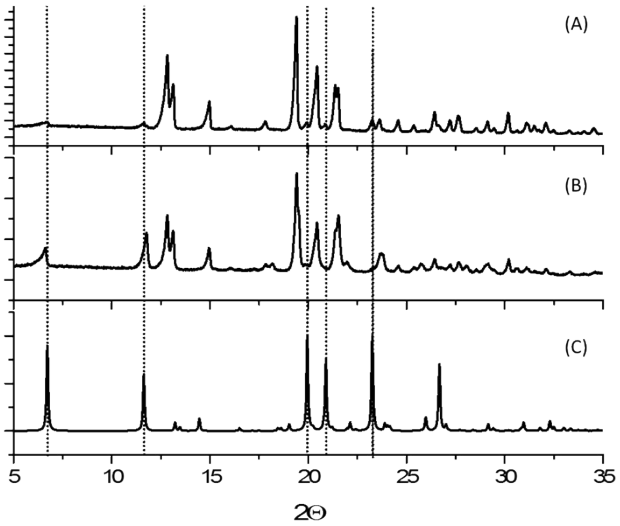

Fig S10: XRPD patterns resulting from restricted impact of ε-CPA. Experimental XRPD are given for (A) 30 minutes restricted impact in heptane and (B) 45 minute restricted impact in heptane. Simulated XRPD is given for (C) δ-CPA. Dashed lines are given as visual guides of major peaks.

6. SHEAR MECHANICAL TREATMENT – LIQUID ASSISTED GRINDING

To compare the effects of different types of mechanical treatment on the polymorphism of CPA, pure samples of β- and ε-CPA were subjected to pure shear treatment, in the presence of small quantities of the same liquids used for restricted impact.

When β-CPA was subject to shear in the presence of ethanol, chloroform or toluene, conversion to α-CPA was observed in < 30 minutes, Figure S11. Interestingly, though, shear in the presence of heptane led to what appears to be conversion to pure γ-CPA. This is both different than what is observed for the other solvents, *and* is different than what is observed when β-CPA is ground manually (in open atmosphere) or subjected to restricted impact treatment in the presence of the same solvent. The origin of this difference is not yet known, primarily the differences between manual grinding and the model shear device, but may lay in the evaporation conditions (comparing open atmosphere to a sealed shear device), or the amount of pressure imposed on the sample (and thus intensity of shear). This phenomenon requires further investigation.

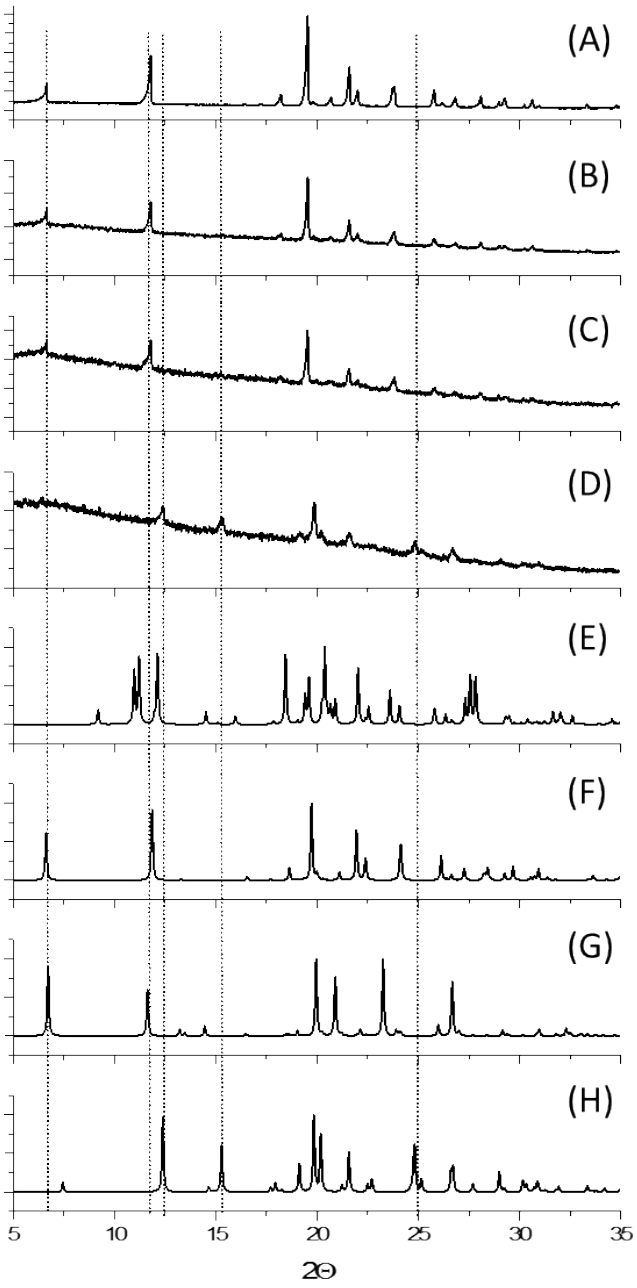

Fig S11: XRPD patterns for β-CPA samples, exposed to shear treatment. Experimental XRPD are given for shear treatment (A) 35 mins in ethanol, (B) 15 mins in chloroform, (C) 35 mins in toluene, and (D) 30 mins heptane. Simulated patterns are given for (E) β-CPA, (F) α-CPA, (G) δ-CPA, and (H) γ-CPA. Dashed lines are given as visual guides of major peaks.

In contrast to the shear treatment of β-CPA, shear of ε-CPA in all tested solvents leads to conversion to the stable α-phase, Figure S12. This is consistent with findings from manual grinding, where all solvents also led to this same conclusion. This highlights the complex reactivity of various polymorphs to liquid assisted grinding, and suggests unique reaction paths in mechanochemistry, depending on the starting polymorph.

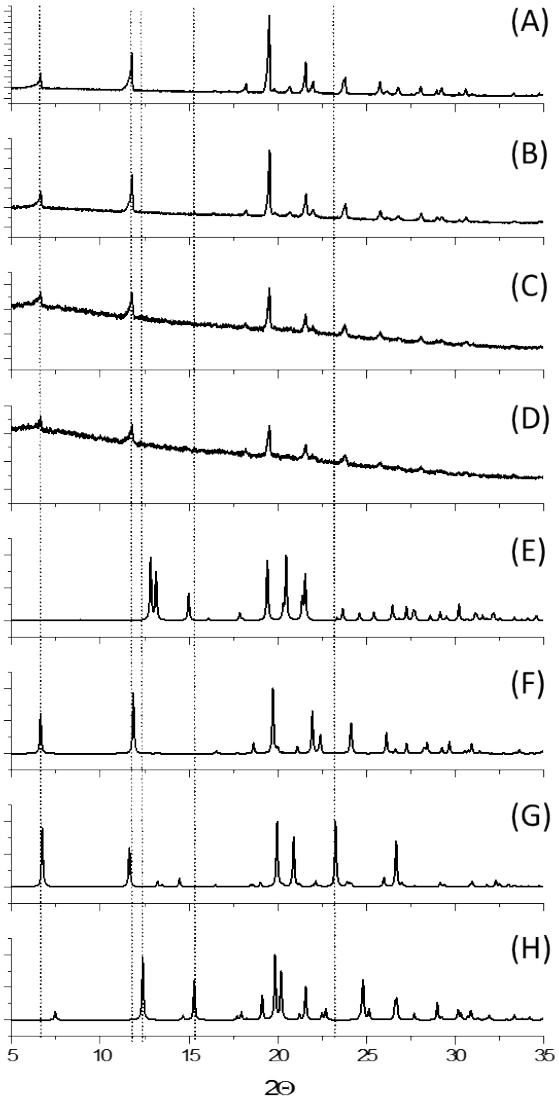

Fig S12: XRPD patterns for ε-CPA samples, exposed to shear treatment. Experimental XRPD are given for shear treatment (A) 30 mins in ethanol, (B) 25 mins in chloroform, (C) 35 mins in toluene, and (D) 45 mins heptane. Simulated patterns are given for (E) ε-CPA, (F) α-CPA, (G) δ-CPA, and (H) γ-CPA. Dashed lines are given as visual guides of major peaks.