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Supporting Information

Mechanochemical Synthesis of Aspirin Nanocrystals for Pharmaceutical Applications

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1) Neat ground experiment

Neat grinding (without solvent) reduced the crystal size but resulted in a mix of ~200 nm spherical and ~3200 nm spike-like particles, indicating poor uniformity.

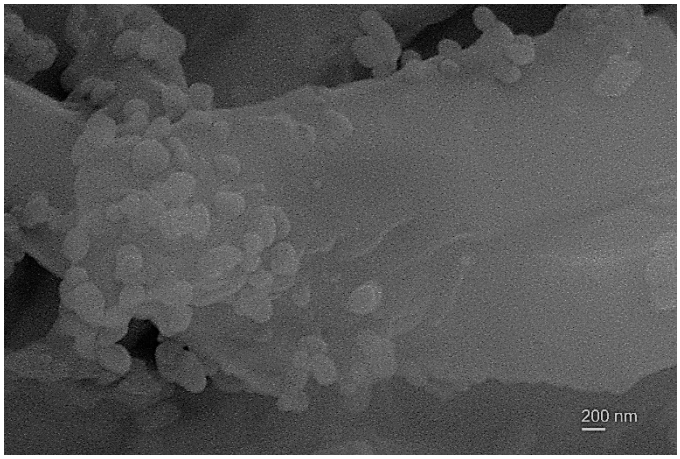

Figure: S1. SEM images of Aspirin crystals neat grind 60min,30Hz, RT 29°C.

2) FTIR analysis

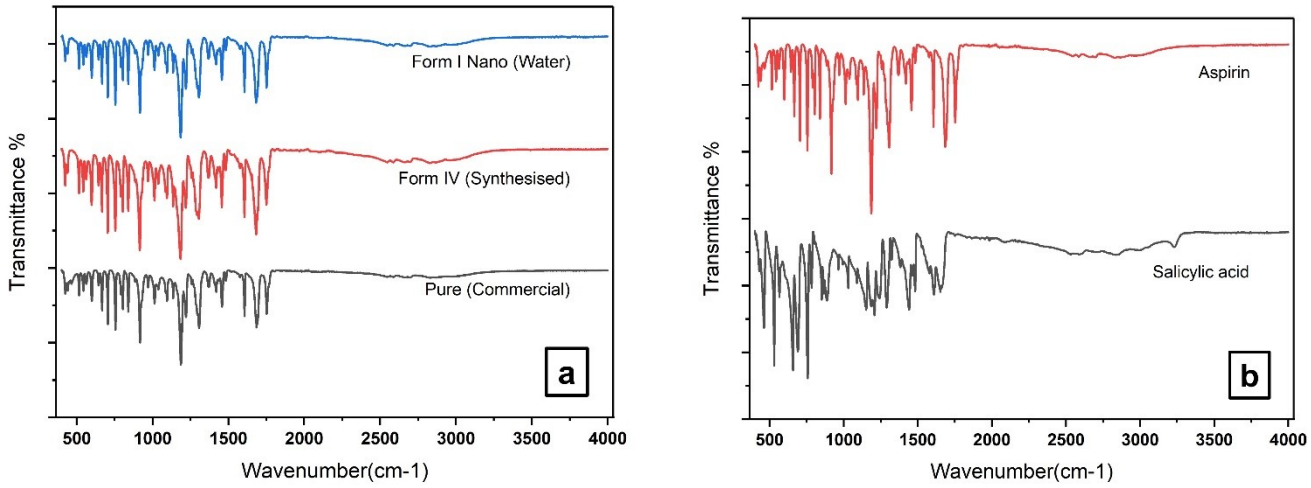

Figure: S2. FTIR spectrum of Aspirin (a) pure aspirin Form IV synthesised and Form I commercial, grind with water 30 min, 50 µL, 30 Hz, RT 29 °C [Nano product] (b) pure Aspirin and Salicylic acid.

3) TGA analysis

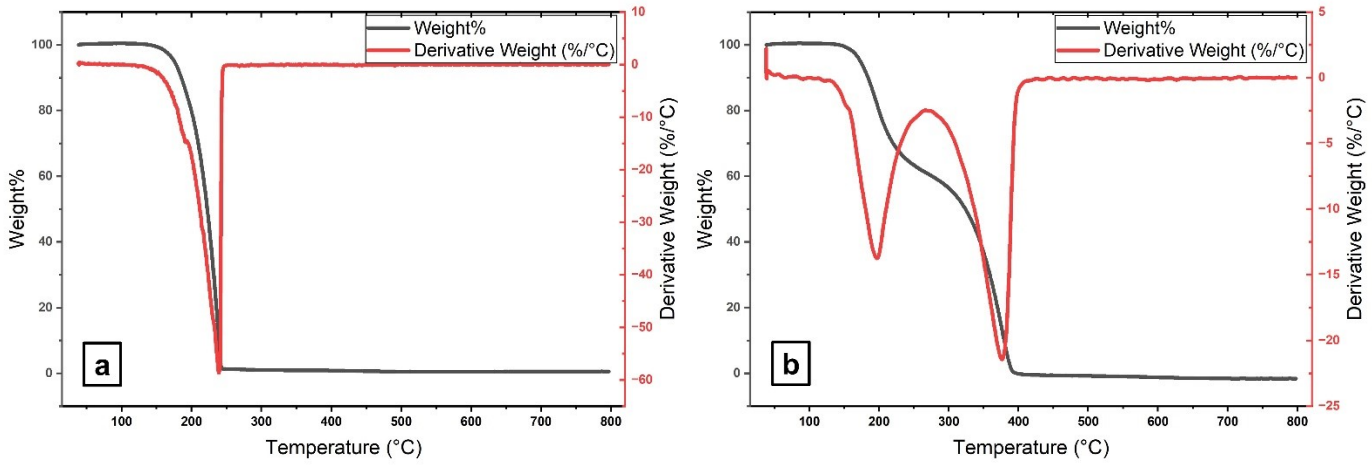

Figure: S3. TGA Analysis profiles for (a) Salicylic acid (b) Aspirin (Synthesised).

4) PXRD analysis of synthesised aspirin Form IV after 60 days

According to PXRD Pattern aspirin Form IV stable up to 60 days.

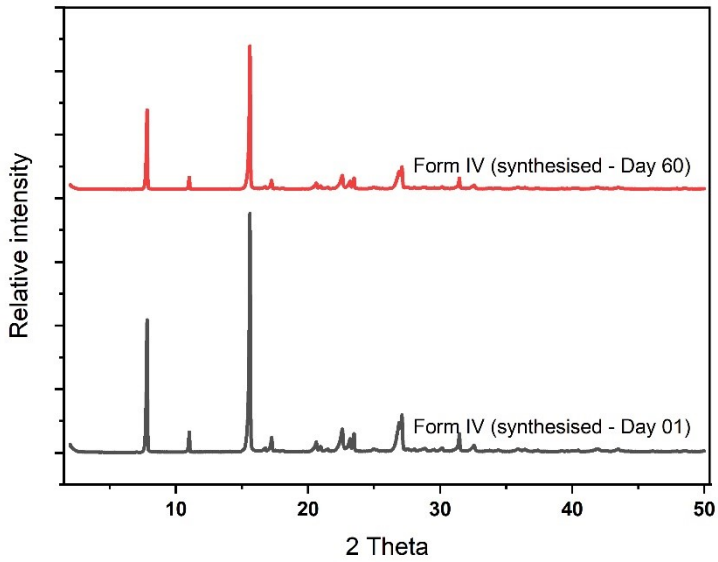

Figure: S4. X-ray powder diffraction patterns of form IV chemically synthesised, after 60 days.

5) Aspirin solubility test

Table: S1. Aspirin solubility data for tested organic solvents.

Solvent	Formula	Aspirin solubility(mg/mL) at ~27 °C	Solvent Type
Cyclohexane	C_6H_{12}	~0.01–0.05 insoluble	Non-polar
Hexane	C_6H_{14}	~0.005–0.02 insoluble	Non-polar
Toluene	C_7H_8	3.52	Non-polar
Tetrahydrofuran (THF)	C_4H_8O	521.25	Polar Aprotic (borderline)
Dichloromethane	CH_2Cl_2	59.33	Polar Aprotic (borderline)
Acetone	C_3H_6O	119.2	Polar Aprotic
Acetonitrile	C_2H_3N	119.43	Polar Aprotic
Ethanol	C_2H_6O	375	Polar Protic
Water	H_2O	5.23	Highly Polar Protic

6) Calibration curve for quantitative analysis in the aspirin release study

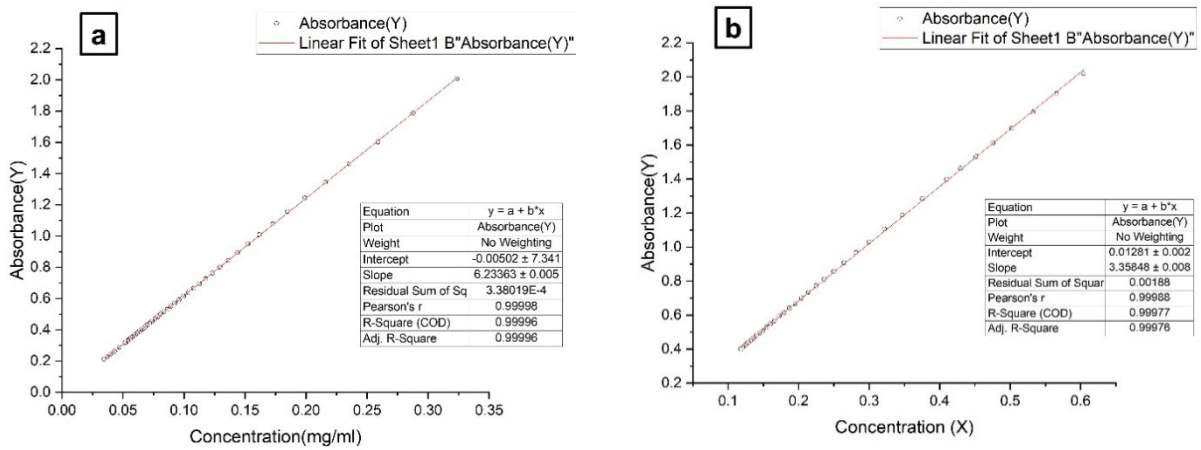

Figure: S5. Calibration curves for quantitative analysis in the aspirin release study (a) pH 1.2 (b) pH 6.8.

7) Ferric Chloride colorimetric analysis of aspirin

The presence of unreacted salicylic acid in the synthesized aspirin was evaluated using a ferric chloride ($FeCl_3$) colorimetric test, which is based on the formation of a coloured complex between ferric ions and phenolic hydroxyl groups. Since acetylation of salicylic acid eliminates the free phenolic –OH group, pure aspirin does not produce a colour response, whereas residual salicylic acid yields a characteristic violet coloration. The appearance of a violet or purple coloration indicated the presence of residual salicylic acid due to complex formation with Fe^{3+} ions, while the absence of any visible colour change confirmed successful acetylation and the formation of aspirin with negligible salicylic acid contamination in our synthesised aspirin. This assay was employed as a rapid qualitative method to confirm the completeness of the aspirin synthesis prior to further characterization.

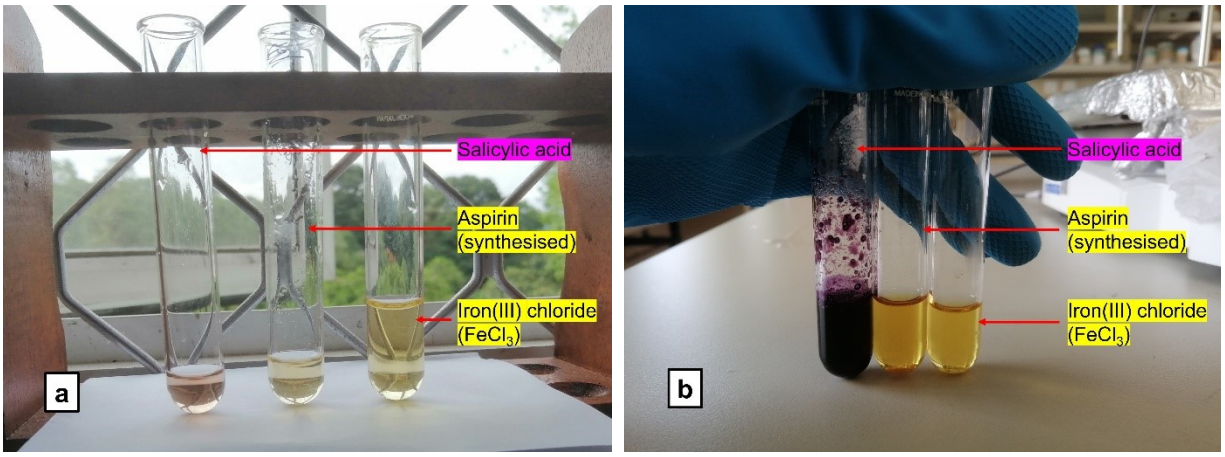

Figure: S6. Colorimetric analysis of aspirin (a) Low concentration (b) High concentration.

8) Comparison of the liquid assisted grinding (LAG) PXRD with the initial experimental PXRD

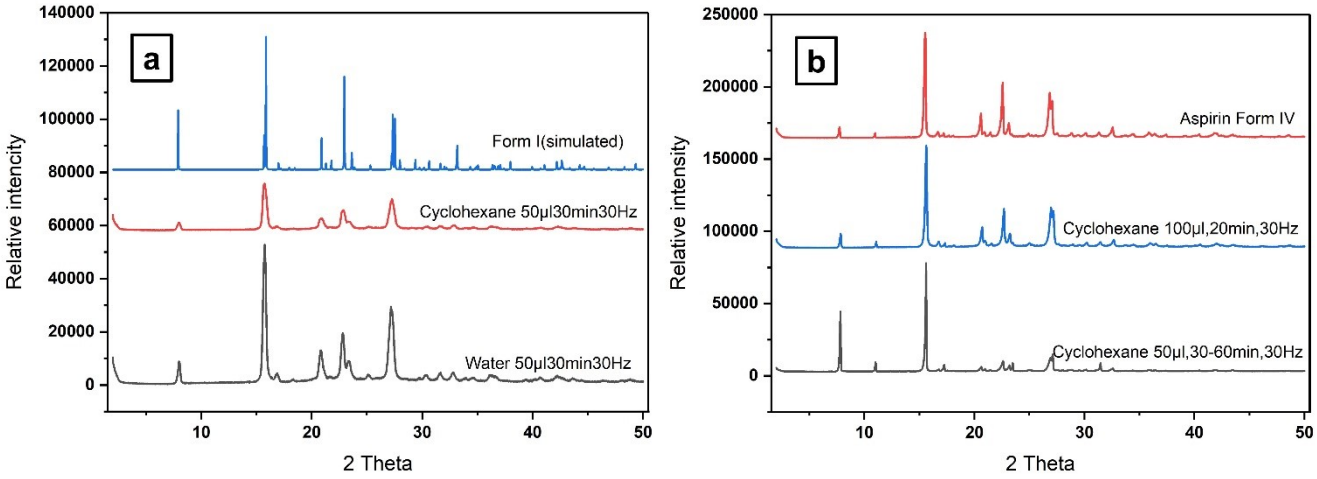

Figure: S7. X-ray powder diffraction patterns of Aspirin (a) form I simulated (CSD_CIF_ACSALA02), grind with cyclohexane 30min,50µL,30Hz, RT 29°C and water 30min,50µL,30Hz, RT 29°C (b) Form IV (synthesised), grind with cyclohexane 20min,100µL,30Hz,RT 29°C and grind with cyclohexane more than 30min up to 60 min,50µL,30Hz, RT 29°C