Electronic Supplementary Material (ESI) for CrystEngComm
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Electronic Supporting Information (ESI)

Polymorphism in metformin embonate salt - recurrence of dimeric and tetrameric guanidinium-carboxylate synthons.

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Polymorph screen: Metformin embonate salt (ME) is soluble in methanol at 50-60°C. In water, its solubility is less at room temperature but increases with increase in temperature from RT to 50-60°C. ME has poor solubility in acetone, tetrahydrofuran, 1,4-dioxane, acetonitrile, iso propyl alcohol, aliphatic ethers and aliphatic hydrocarbon. The solvent in which ME salt has poor solubility are used as anti-solvent for precipitating the solid from the solution of ME in methanol and water. Following are the strategies adopted for polymorph screening. First, ME is directly used for crystallization in various solvents and solvent combinations using anti-solvents. Second, metformin base is converted to embonate salt by reacting with embonic acid. Third, crystallization of ME by fast evaporation of the solvent by rota-evaporation is employed. The solids obtained after fast evaporation were vacuum dried to remove any residual solvents. The analysis was done on 500mg input, Temp is dissolution temp for ME or metformin base, Volume is the amount of solvent taken for dissolving the components. The crystalline solids obtained under these crystallizations conditions were filtered, dried at 25-30°C and analyzed by powder X-ray diffraction. Melt-quenching technique could not be applied to the current system due to the chemical degradation of the sample immediately after melting.

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Table S1. Polymorph screening of metformin-embonate in various solvents, solvent combinations, anti-solvent additions, fast evaporation using rota-evaporation.

Solvent	Volume (ml)	Anti-solvent	Volume (ml)	Temperature	Form
Crystallization from Metformin Embonate salt					
Methanol	5	DIPE	10	60°C	I
Methanol	15	Ethyl acetate	50	77°C	I
Methanol	25	Dichloromethane	50	40°C	I
Methanol	8	Acetone	20	56°C	I
Methanol	10	Tetrahydrofuran	30	65°C	I
Methanol	10	1,4-dioxane	30	65°C	I
Ethanol	25	Hexane	25	75°C	I
Methanol	5	--	--	65°C	II
Water	14	--	--	70-75	II
Water	5	Methanol	2	75-80°C	II
Ethanol	15	Water	5	70°C	II
Crystallization from Metformin Base and Embonic acid					
Dichloromethane	30	----	----	25-30°C	I
Isopropyl alcohol	20	----	----	25-30°C	I
Acetonitrile	30	----	-----	60-65	I
Methanol	7	----	----	25-30°C	II
Rota evaporation method					
Ethanol	30	----	----	60-80°C	I
Methanol	20	----	----	60-80°C	I
Ethanol	30	Acetonitrile	20	60-80°C	I
Methanol	20	THF	20	60-80°C	Amorphous + traces of I
water	3	Isopropyl alcohol	40	60-80°C	Gummy liquid

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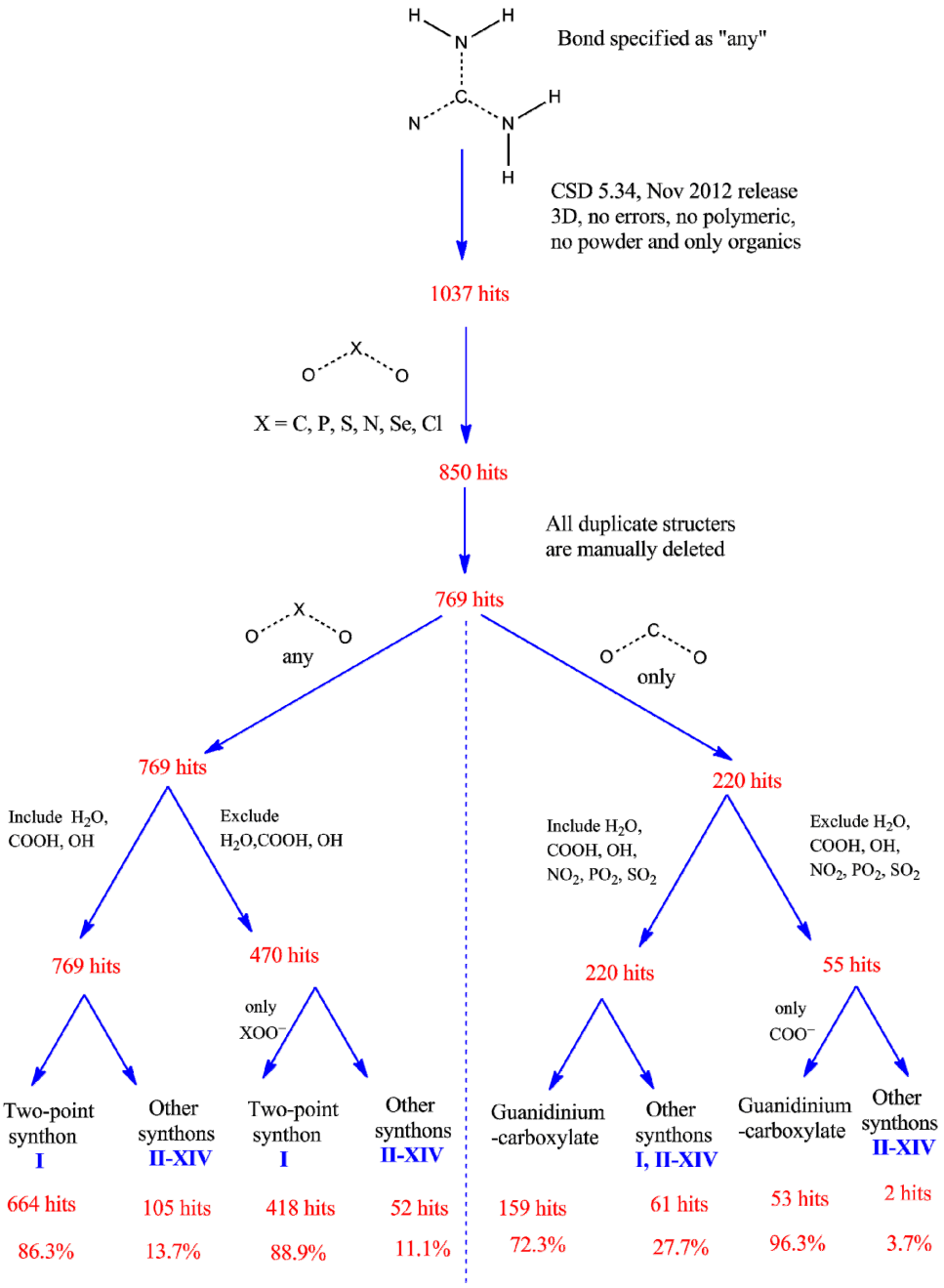

Scheme S1. CSD synthon analysis on guandine complexes with various acids. A schematic representation of the search queries used to obtain the hits is illustrated. The synthons exhibited by the guanidine acid complexes is summarized in scheme 3. The guanidine compelxes with any type of acids is shown on the left side and complexes with only carboxylic acids is shown on the right side.

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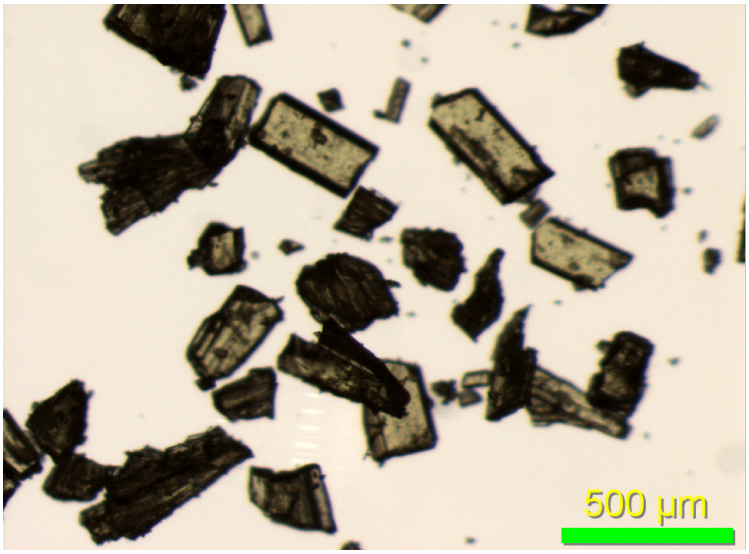
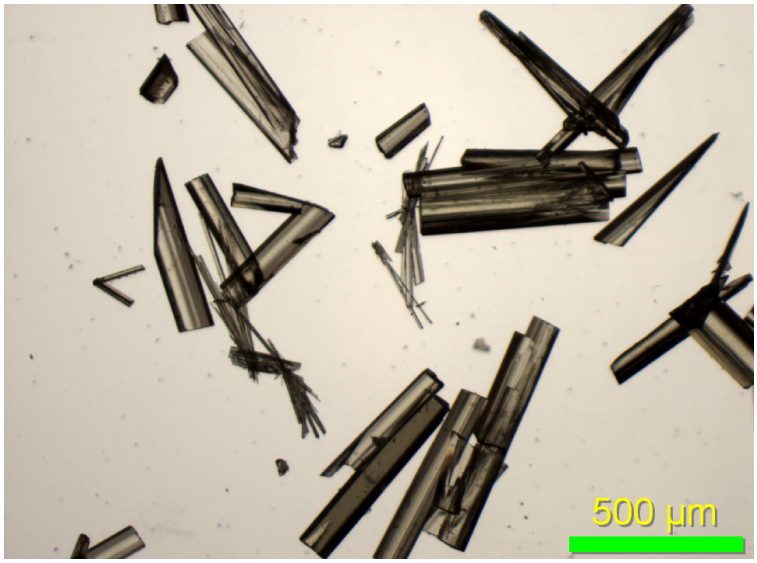


(a)



(b)

Figure S1. Crystal morphologies of metformin-embonate polymorphs. (a) Form I plates. (b) Form II needles.

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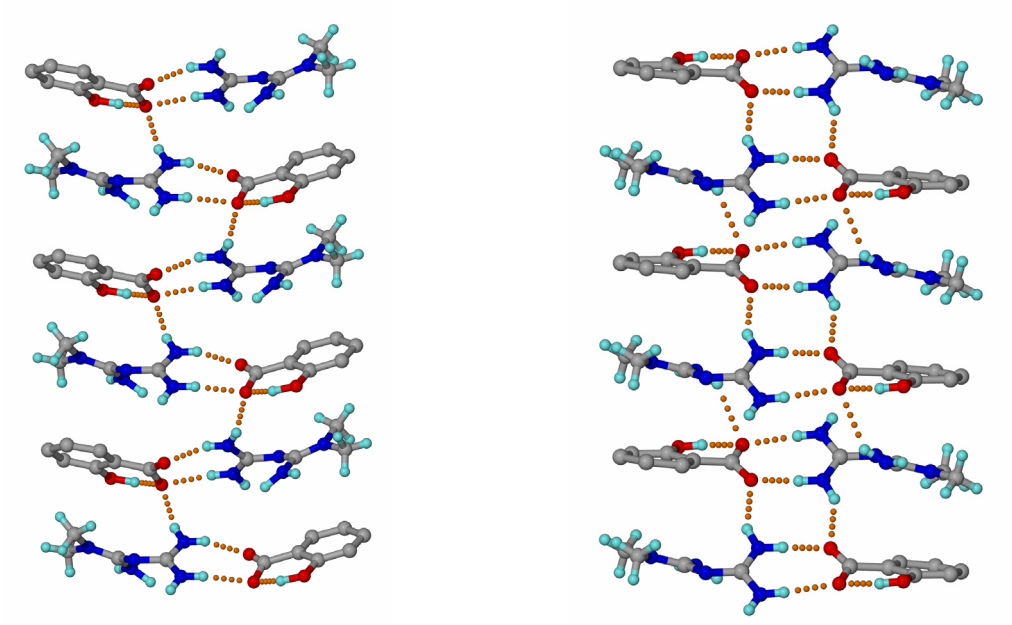
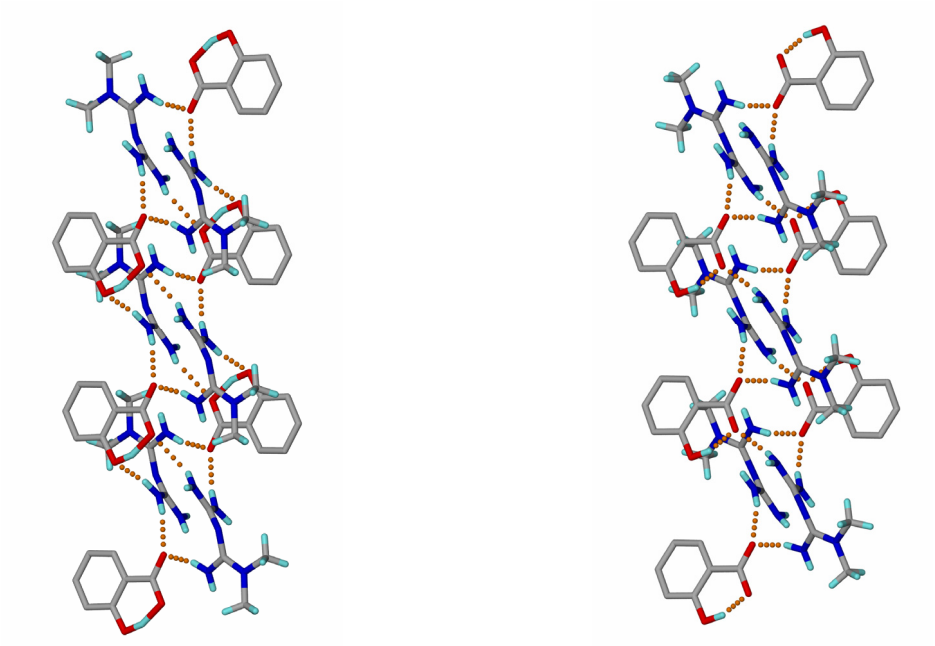


Form I Form II

Figure S2. Comparison of the dimer synthon propagation in polymorphs I and II.



Form I Form II

Figure S3. Comparison of the tetramer synthon propagation in polymorphs I and II

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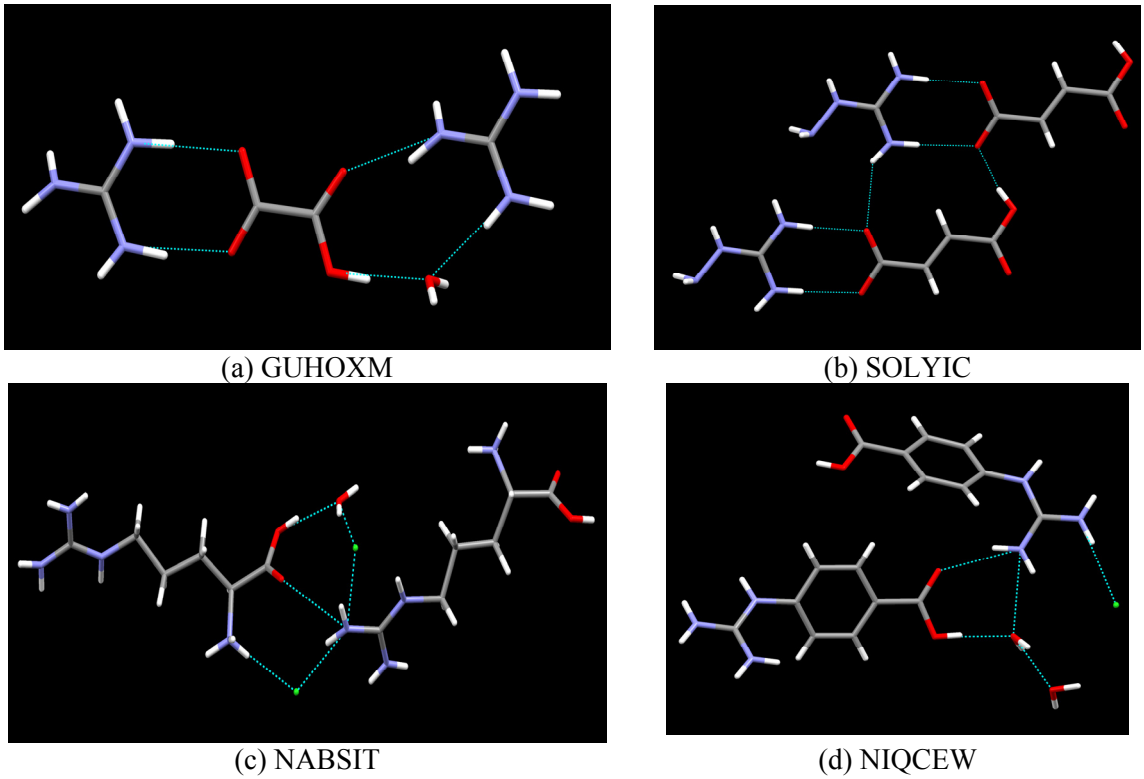

(a) GUHOXM (b) SOLYIC

(c) NABSIT (d) NIQCEW

Figure S4. Some representative guanidine acid complexes that contain carboxylic acid in its neutral form are shown. The examples are labeled with their CSD refcodes.[15] In refcodes GUHOXM and SOLYIC, the neutral COOH forms O-H…O interactions with water/carboxylate and N-H…O interactions with one of the donors of the guanidinium ion, however, it does not disrupt the dominant two-point motif between the guanidinium cation and carboxylate anion. In refcodes NABSIT and NIQCEW, the chloride ions disrupt the two-point motif.

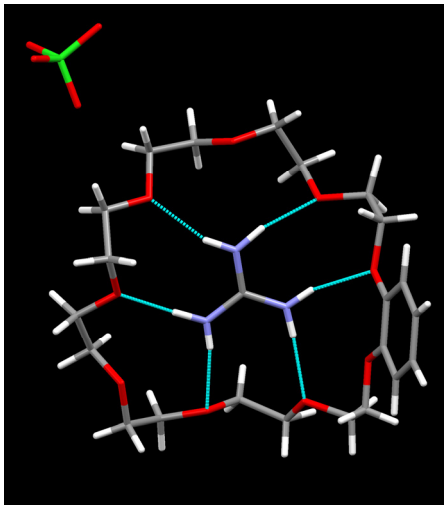

Figure S5. Inclusion complexes of guanidinium ion (refcode BAYXII).[15] It is encapsulated in the organic host frame work and is held to it by multi-point N-H…O hydrogen bonding.

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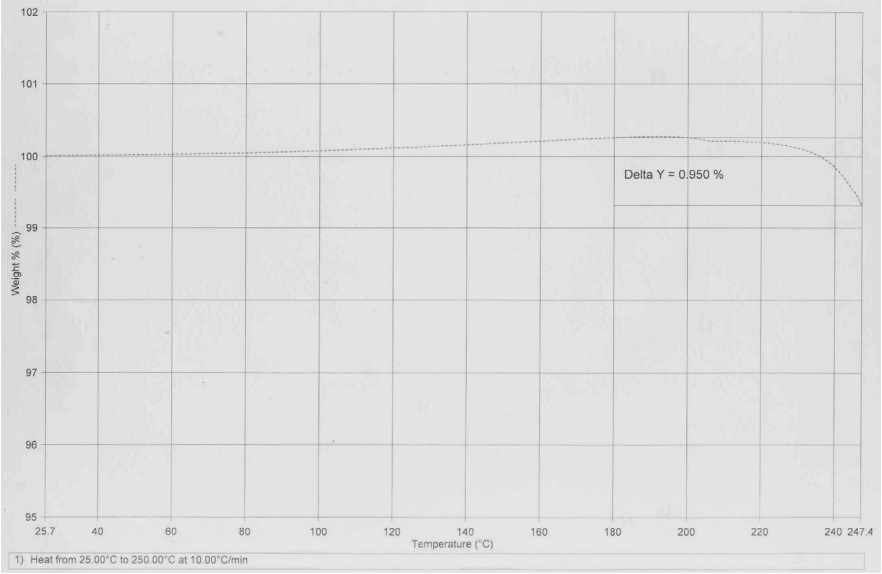
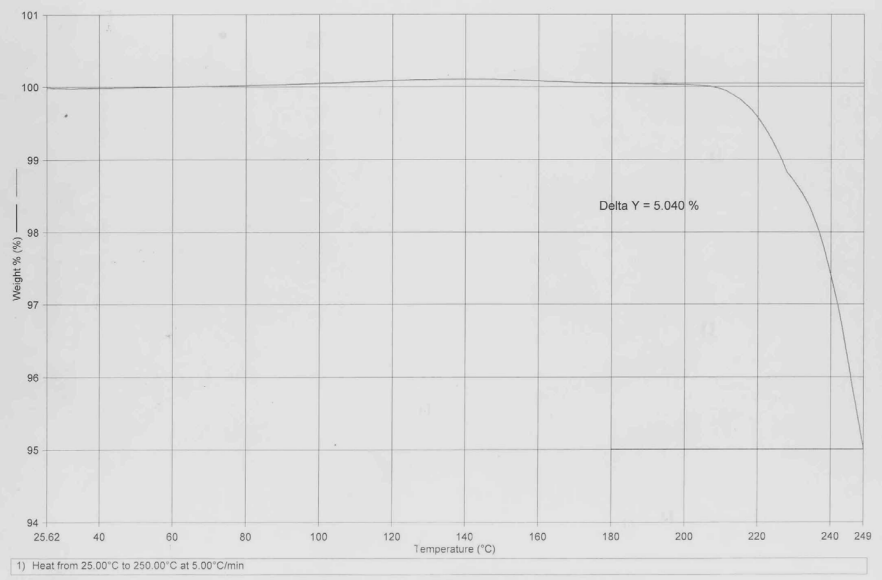


(a) TGA of form I



(a) TGA of form II

Figure S6. TGA experiments on metformin-embonate polymorphs. (a) Form I. (b) Form II. There is no weight loss before the melting event occurred indicating that samples are anhydrous. However, both forms start to show weight loss at the melting indicative of chemical degradation.

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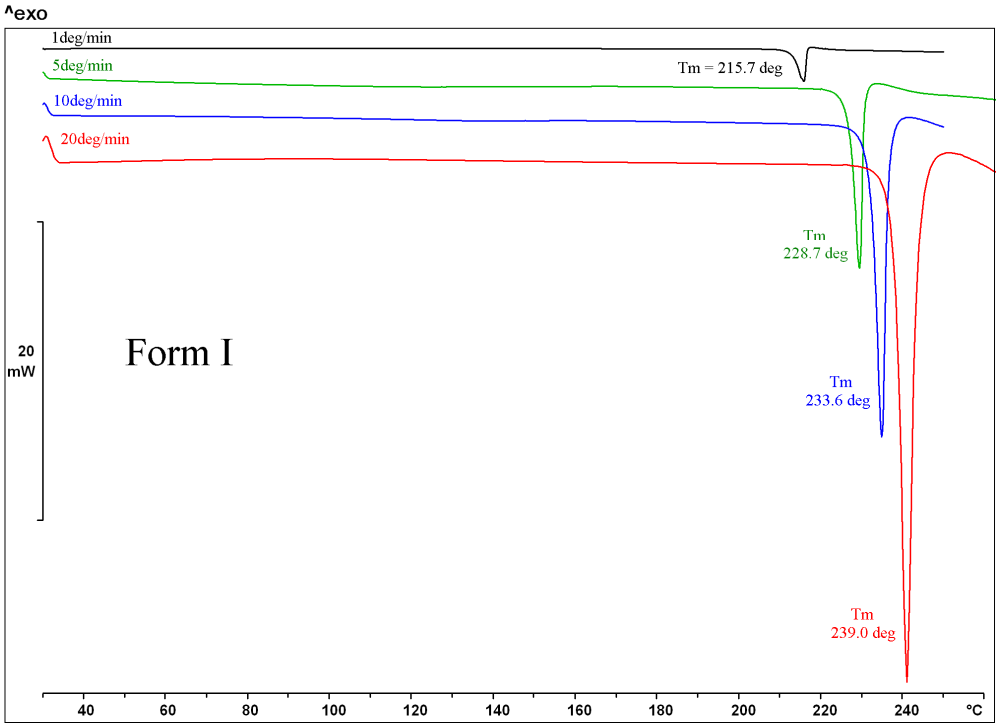
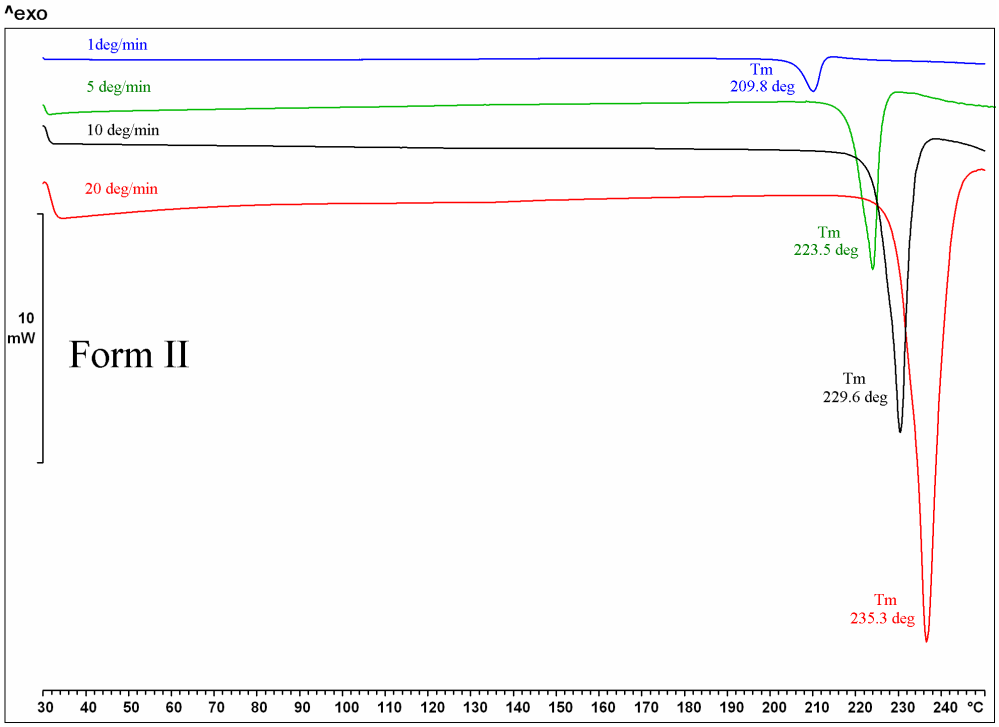


(a)



(b)

Figure S7. DSC scans on two polymorphs using different heating rates. (a) Form I. (b) Form II. With increase in heating rate, the melting point shifts to higher temperature. Form I consistently shows higher melting point compared to form II.

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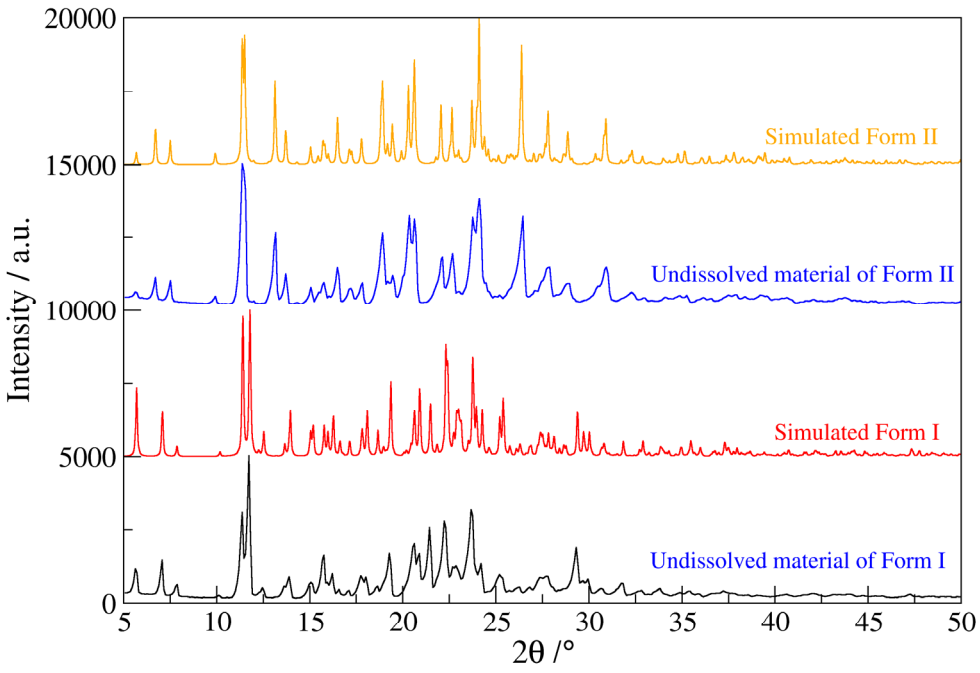

Figure S8. PXRD patterns of the undissolved polymorphic materials from the equilibrium solubility experiments in aqueous medium. Two different experiments are carried out separately on Form I and II, respectively. The undissolved materials were filtered and dried. The filtrate was used for estimating the concentrations of the material dissolved. The PXRD patterns of undissolved materials nicely match with the simulated patterns from their respective crystal structures indicating that both forms did not show any phase transformations during the equilibrium solubility experiments.

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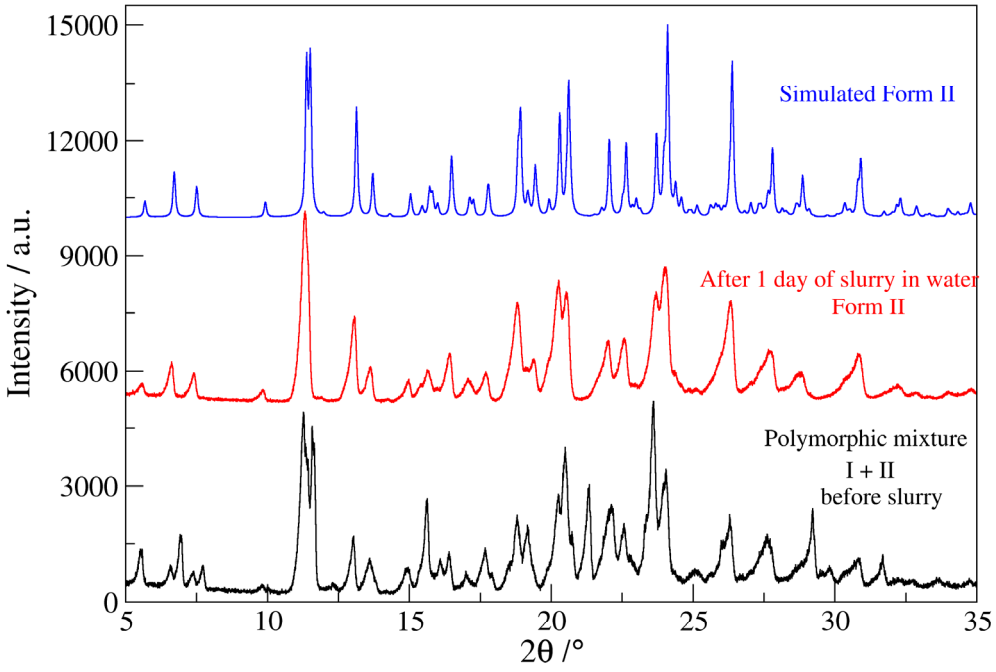

Figure S9. Results of the competitive slurry experiments. Equal weights of form I and form II (100mg each) were slurried for 1 day in 8mL of water. The undissolved material after 1 day of slurrying was filtered and dried. PXRD on the undissolved patterns indicated that polymorphic mixture converted to pure form II. Simulated pattern from form II crystal structure is shown for comparison.

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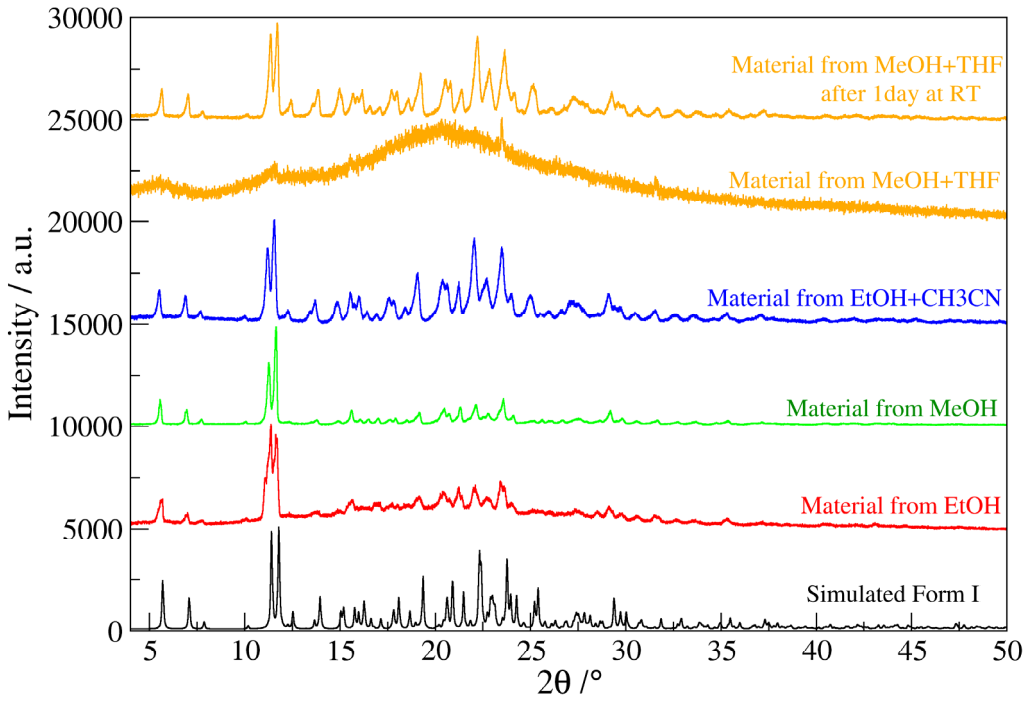

Figure S10. The metformin-embonate dissolved in various solvents was subjected to fast evaporation using the rotary evaporator. After the solvent evaporation, the material was vacuum dried. The resulting materials were characterized by PXRD to understand which form crystallizes in the fast evaporation method. Ethanol, Methanol, Ethanol + Acetonitrile combinations gave pure form I. Methanol + Tetrahydrofuran gave amorphous material with traces of form I. Upon storage of this material for 1 day at room temperature, amorphous material converted to pure form I. The simulated pattern from form I crystal is included for comparison.