Screening and selective preparation of polymorphs by fast evaporation method: A case study of aspirin, anthranilic acid and niflumic acid

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Experimental Method:

FT-IR Spectroscopy (KBr): Fourier transmission infrared spectra of the solids were obtained using a Fourier–transform infrared spectrometer (PerkinElmer 502 or SHIMADZU FTIR-8400S). KBr samples (2 mg in 20 mg of KBr) were prepared and 5 scans were collected at 4 cm^{-1} resolution for each sample. The spectra were measured over the range of 4000-400 cm^{-1}.

Powder X-Ray Diffraction (PXRD): The PXRD patterns were collected on a Rigaku SmartLab with a Cu Kα radiation (1.540 Å). The tube voltage and amperage were set at 40 kV and 50 mA respectively. Each sample was scanned between 5 and 50° 2θ with a step size of 0.02°. The instrument was previously calibrated using a silicon standard.

Differential Scanning Calorimetry (DSC): DSC was conducted on a Mettler-Toledo DSI1 STAR^e instrument. Accurately weighed samples (4-6 mg) were placed in hermetically sealed aluminium crucibles (40 µL) and scanned in the range of 30 °C to 300 °C at a heating rate of 5 °C/min under a dry nitrogen atmosphere (flow rate 80 mL/min). The data were managed by STAR^e software.

Thermo Gravimetric Analysis: TGA was performed on a Mettler-Toledo TGA/SDTA 851^e instrument. Approximately 6-8 mg of the sample was added to an aluminium crucible and heated from 30 to 350 °C at a rate of 10 °C/min under continuous nitrogen purge.

Table S1. Conditions used at rotary evaporator for the preparation of aspirin (ASP) polymorphs. In all the milligram scale batches, 200 mg of ASP (1.1101 mmol; Sigma-Aldrich) was dissolved in suitable solvents (30-40 mL) for preparing the polymorphs. The weight of ASP used in the large scale batches was 2 gm (11.1014 mmol; in ca. 300-400 mL of solvent).

Solvent/No of attempts	**Pressure (mbar) (± 5)**	**Temperature of water bath (°C) (± 3)**	**Revolution Speed of r.b. flask (rpm)**	**Polymorph Obtained**
Acetone	400	50	130	Form I
DCM	800	50	130	Form I
CH_3CN	180	50	130	Form I
MeOH	300	50	130	Form I
EtOH	250	50	130	Form I
THF	250	50	130	Form I
Ether	992	50	130	Form I
EA	250	50	130	Form I
Isopropanol	130	50	130	Form I
CH_3NO_2	90	50	130	Form I
Acetone/1	50	**10**	130	Form I
Acetone/2	60	**2**	130	Form I
Acetone/3	100	**10**	130	Form I
DCM/1	125-70	**10**	130	Form II
DCM/2	125-70	**10**	130	Form II
DCM/3	125-70	**10**	130	Form II
DCM/4	125-70	**2**	130	Form II
DCM/5	125-70	**2**	130	Form II
Ether	300	**10**	130	Form II
CH_3CN	38	**10**	130	Form I

MeOH	45	**10**	130	Form I
EtOH	35	**10**	130	Form I
THF	70	**10**	130	Form I
EA	50	**10**	130	Form I
Isopropanol	50	**10**	130	Form I
CH_3NO_2	50	**10**	130	Form I

Table S2. Conditions used at rotary evaporator for the preparation of anthranilic acid (AA) polymorphs. In all the milligram scale batches, 400 mg of AA (0.2916 mmol; Sigma-Aldrich) was dissolved in suitable solvents (30-40 mL) for preparing the polymorphs. The weights of AA used in the large scale batches were 2 gm (14.5836 mmol; in ca. 300-400 mL of solvent) and 5 gm (36.459 mmol; in ca. 550 mL of solvent).

Solvent/No of attempts	**Pressure (mbar) (± 5)**	**Temperature of water bath (°C) (± 3)**	**Revolution Speed of r.b. flask (rpm)**	**Polymorph Obtained**
H_2O	100	60	130-225	Form I
DCM	800	50	130	Form II
CH_3CN	180-210	50	130	Form II
$CHCl_3$	550	50	130	Form II
Isopropanol	100	50	130	Form II
MeOH	400	50	130	Form II
EtOH	580	50	130	Form II
CH_3NO_2	110-125	50	130	Form II
Dioxan	90	60	130	Form II
DMF	50-18	70	130-200	Form II

Table S3. Conditions used at rotary evaporator for the preparation of niflumic acid (NFA) polymorphs. In all the batches 100 mg of NFA (0.5487 mmol; Sigma-Aldrich) was dissolved in suitable solvents (30-40 mL) for preparing the polymorphs.

Solvent/No of attempts	**Pressure (mbar) (± 5)**	**Temperature of water bath (°C) (± 3)**	**Revolution Speed of r.b. flask (rpm)**	**Polymorph Obtained**
MeOH	300	50	130	Form I
CH_3CN	180	50	130	Form I
THF	250	50	130	Form I
Acetone	400	50	130	Form I
CH_3NO_2	90	50	130	Form I
EA	250	50	130	Form I
DCM	800	50	130	Form I
EtOH	200	50	130	Form II
Isopropanol	130	50	130	Mixture of Form I & Form II

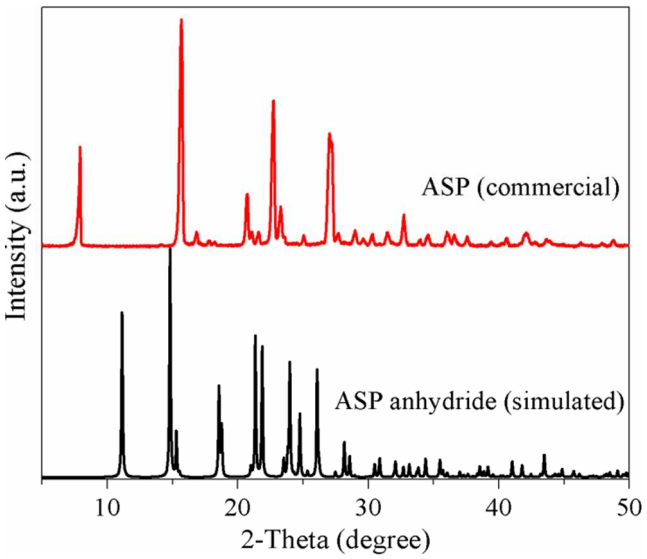
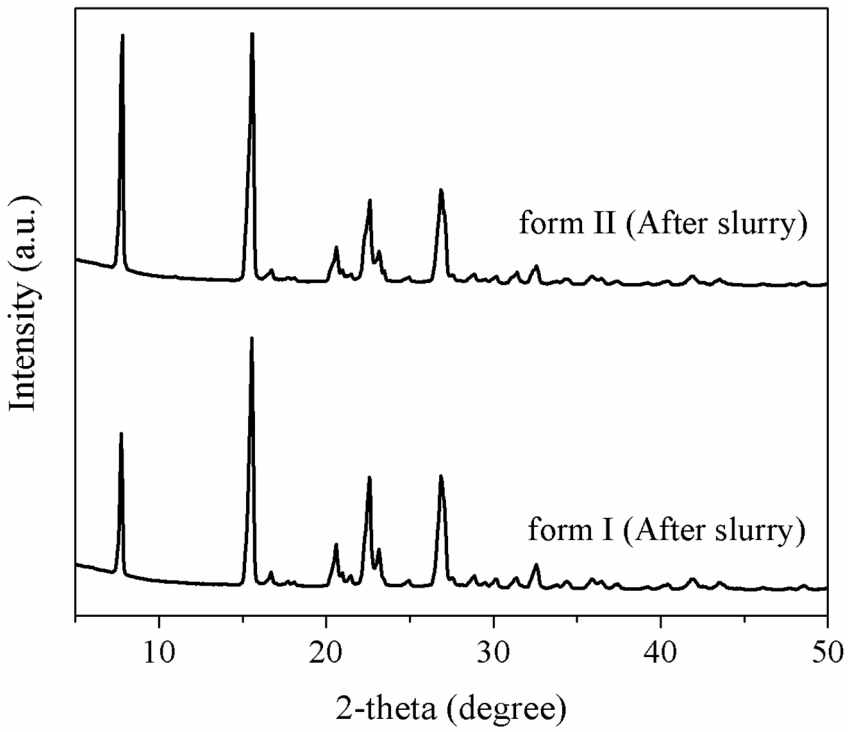
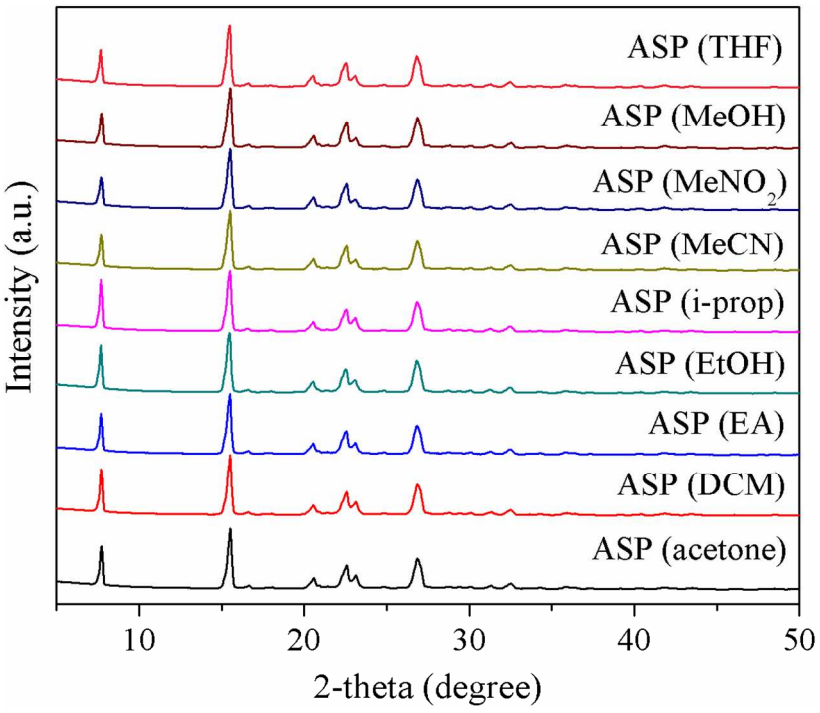


Figure S1: PXRD patterns of the simulated aspirin (ASP) anhydride and the commercial ASP (Aldrich). Note that the PXRD of the commercial ASP sample has no detectable ASP anhydride impurities (or far less than 1%).

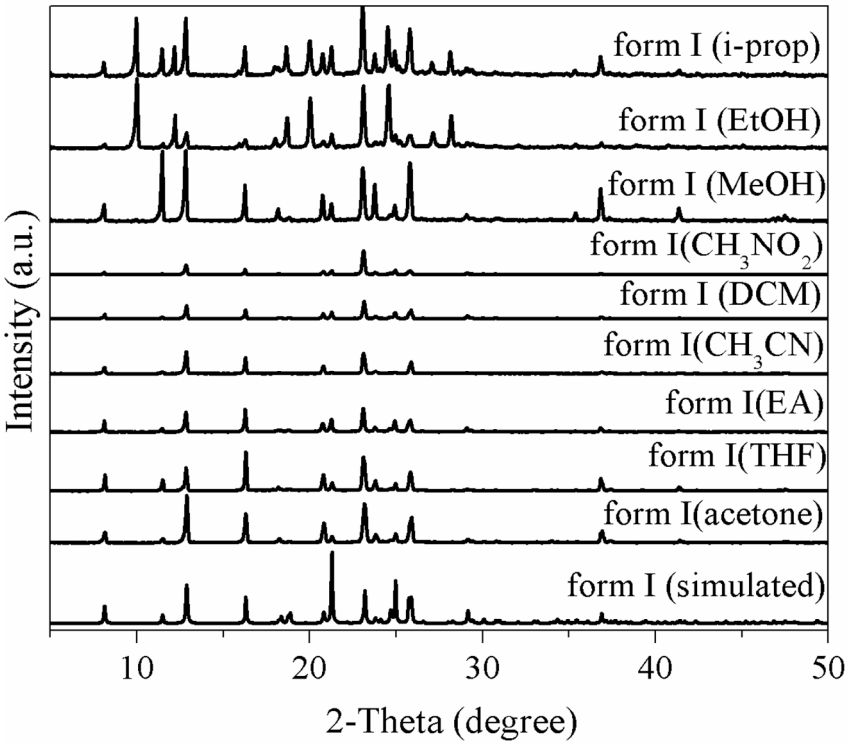


(a)

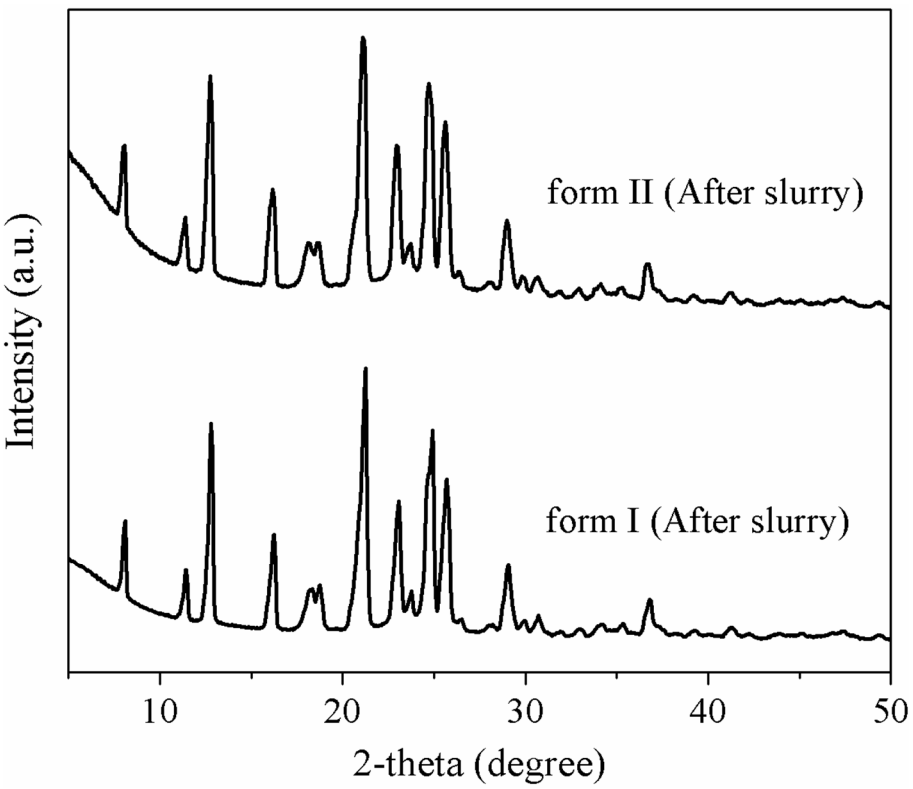


(b)

Figure S2: (a) PXRD patterns of the aspirin forms I and II after the slurry experiments (48 hr) from water in that the form II converts to form I, while the form I remains stable. This confirms the metastable nature of the form II. (b) PXRD patterns of the aspirin solids obtained from liquid assisted grinding (LAG) confirm the formation of only aspirin form I.

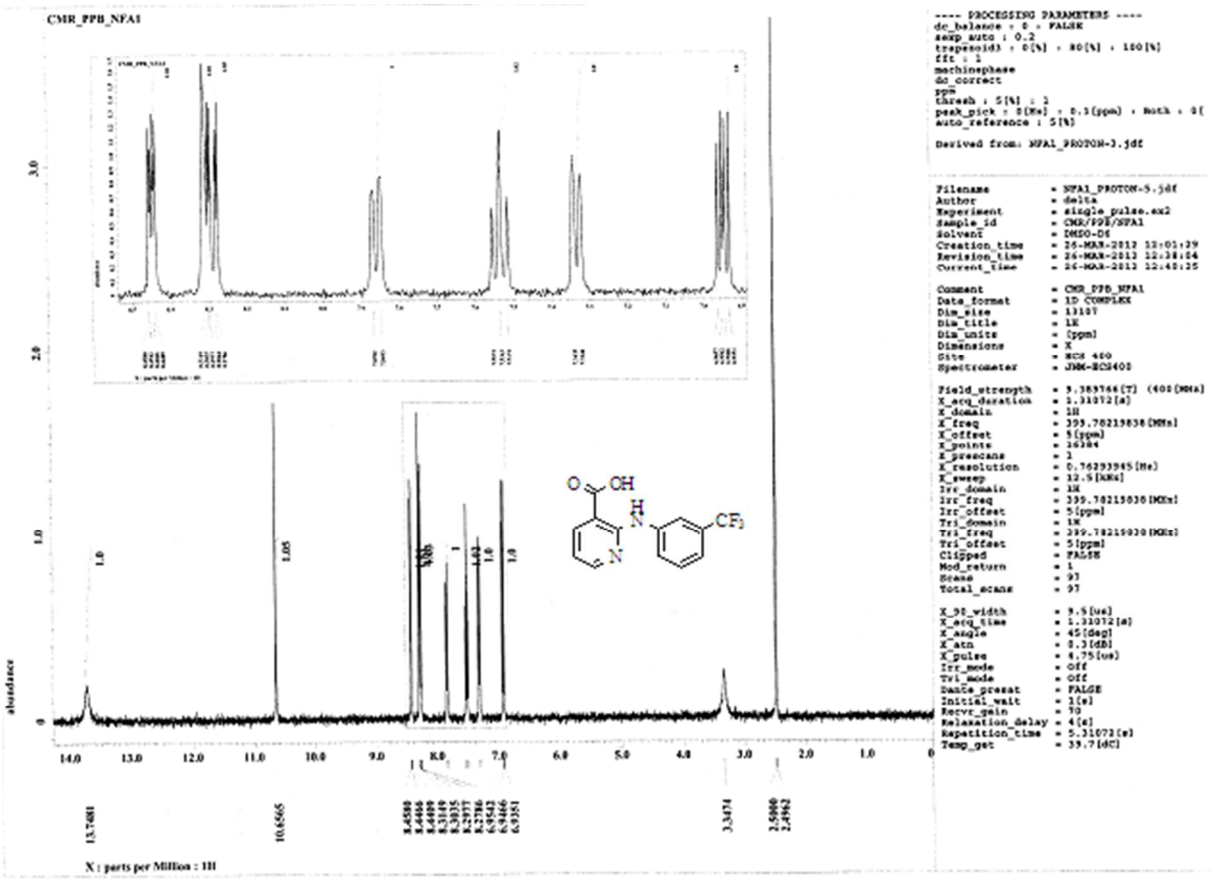


(a)

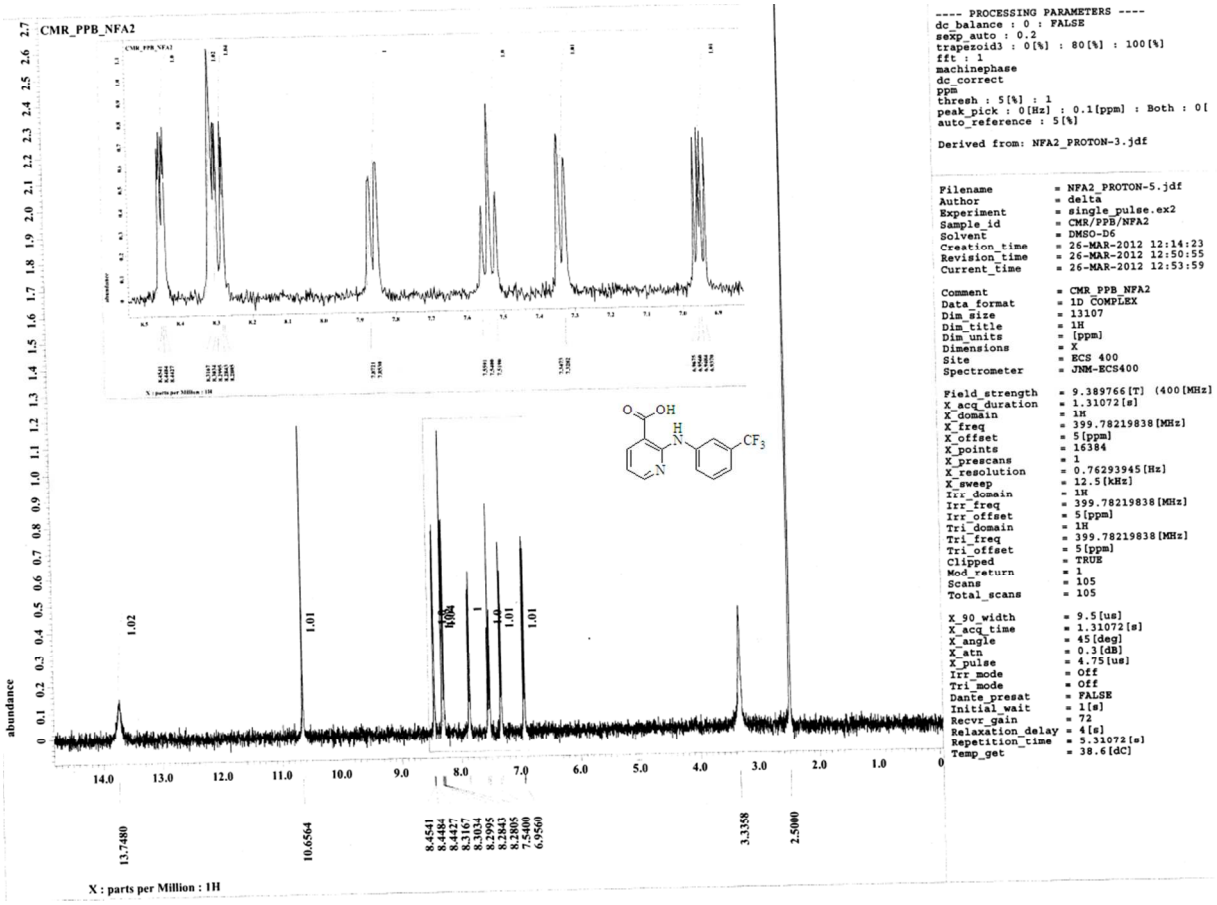


(b)

Figure S3: (a) PXRD patterns of the niflumic acid solids obtained by FE method from different solvents. The PXRD pattern of the new polymorph (Form II) obtained from EtOH is distinct from the known form I, obtained from the rest of the solvents. (b) PXRD patterns of the NFA, after slurry experiments to show the conversion of form II to form I, and unchanged form I.

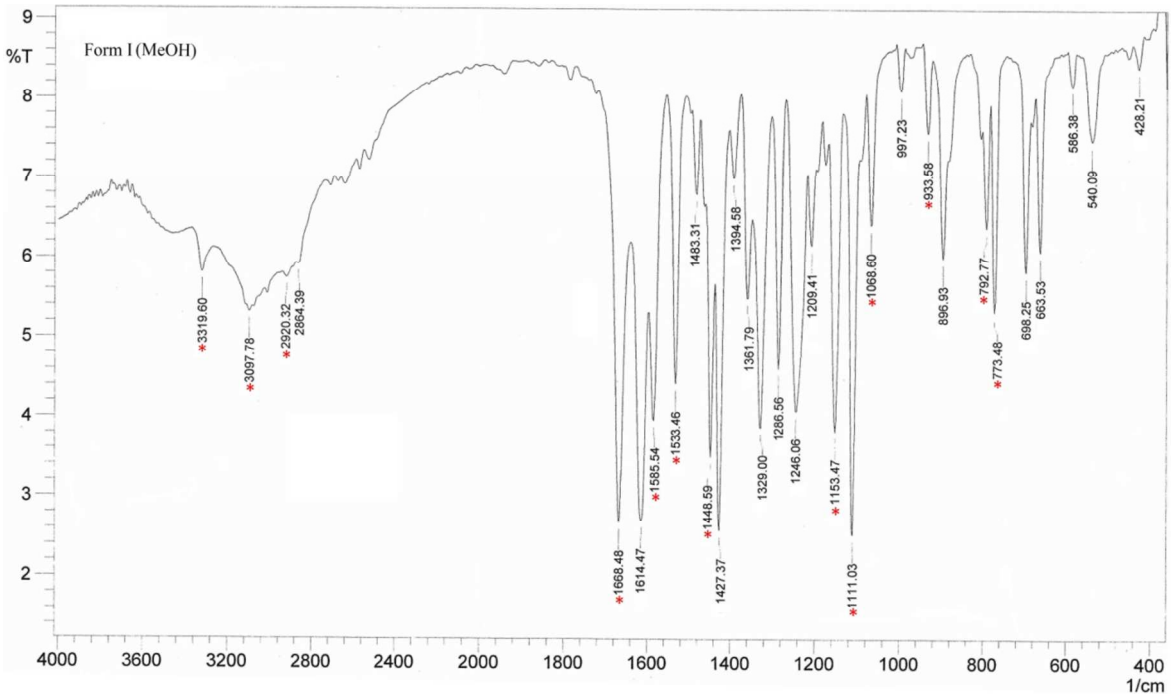

CMR_PPB_NFA1
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
aexp_auto : 0.2
trapezoid3 : 0[%] : 80[%] : 160[%]
fft : 1
machinephase
dc_correct
ppm
thresh : 5[%] : 1
peak_pick : 0[Hz] : 0.1[ppm] : Both : 0[
auto_reference : 5[%]
Derived from: NFA1_PROTON-3.jdf
Filename = NFA1_PROTON-5.jdf
Author = delta
Experiment = single_pulse.ex2
Sample_id = CMR/PPB/NFA1
Solvent = DMSO-D6
Creation_time = 26-MAR-2013 11:01:29
Revision_time = 26-MAR-2013 12:38:54
Current_time = 26-MAR-2013 12:40:35
Comment = CMR_PPB_NFA1
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = NCS 400
Spectrometer = JNM-ECS400
Field_strength = 9.389766[T] (400[MHz])
X_acq_duration = 1.31072[s]
X_domain = 1H
X_freq = 399.78219838[MHz]
X_offset = 5[ppm]
X_points = 26384
X_prescans = 1
X_resolution = 0.76293945[Hz]
X_sweep = 12.5[kHz]
Irr_domain = 1H
Irr_freq = 399.78219838[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 399.78219838[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 97
Total_scans = 97
X_90_width = 9.5[us]
X_acq_time = 1.31072[s]
X_angle = 45[deg]
X_atn = 3.3[dB]
X_pulse = 6.75[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 70
Relaxation_delay = 4[s]
Repetition_time = 5.31072[s]
Temp_get = 39.7[dC]
abundance
X : parts per Million : 1H

(a)

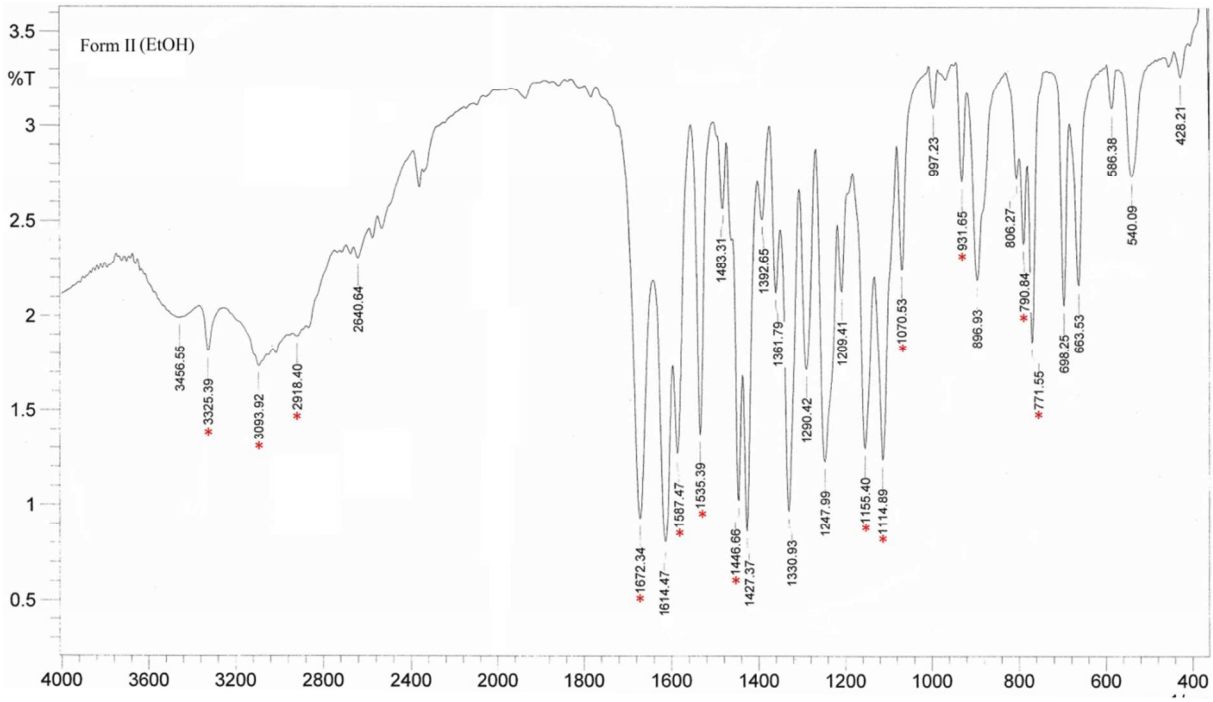


(b)

Figure S4. ^{1}H-NMR from DMSO-d_6 for niflumic acid (a) form I solid obtained from MeOH and (b) form II obtained from EtOH by FE method. Note that the ^{1}H-NMR of the FE products show no chemical change to NFA, hence the distinct PXRD pattern of the solid from EtOH must be due to the formation of a new NFA solid form II.



(a)



(b)

Figure S5. IR spectra of niflumic acid (a) form I obtained from MeOH and (b) form II obtained from EtOH by FE method. The representative peaks that distinguish new form II, form the known form I, are marked with '*'.