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LABORATORY NOTEBOOK

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NOTEBOOK PROCEDURE*

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1) Enter directly in this notebook all your objectives, ideas, experimental plans, experimental data, observations, calculations, *etc.* Do not put data on loose sheets and then transcribe them to this book

2) Make all entries in dark, indelible ink, preferably black, using a pen which creates an impression (*e.g.*, ballpoint)

3) All entries should be from a single author; entries by others should be clearly identified.

4) Erasures, whiting out, writing over, taping over, or pasting over are not permitted. Make corrections by lining out with a single line (do not obliterate entry), initialing, dating, and explaining.

5) All entries must be made in the notebook at the time of the experiment. The date of each recorded experiment must be entered in the notebook using a non-ambiguous Merck Standard format (*e.g.*, 15 Dec. 1997). Each day's entries must be signed and dated by the user immediately below the last entry The signature should include first name, initial, and surname (or what is commonly used by the investigator on legal documents); when multiple entries are made on different dates, each entry should be dated and signed.

6) Write on both left- and right-handed pages of the book. Include all observations, notes, references, quotations, discussions, calculations, sketches, *etc.*

7) In recording experiments, clearly identify by appropriate reference: starting materials, end products, protocols, controls, results, conclusion, cross-references, *etc.*

8) The record must be continuous so that no suspicion of interpolation, falsification, or amendment can be aroused. Accordingly, all entries must be made consecutively with no blank pages. Vacant spaces on a page should be marked out with a diagonal line or an "X", dated, and initialed. All entries related to previously numbered and paginated experiments must be designated by a reference in the margin.

9) Each page must be countersigned by someone not likely to be a co-inventor but who understands the significance of the recorded experiments. Countersigning should be done within one month, not to exceed three months, after the completion of the experiment.. ***NOTE:*** If the Standard Operating Procedure (SOP) for the experiment specifies the frequency of countersignature, countersignature should follow that SOP consistently (*e.g.*, if the SOP states that counter-signature will occur at the completion of each experiment, then it should occur one time at the end of each experiment; if the SOP states weekly countersignature will occur, then countersignature should be accomplished weekly). Any SOP developed by the laboratory for countersignature must also comply with the one month, not to exceed three month rule.

10) Any essential ancillary records such as photographs, computer printouts, spectra, graphs, memos, technical reports, *etc.* which may substantiate or validate your notebook should be referenced to the notebook number and page and be kept together as a reference to that notebook. A reference to the ancillary data should also be entered on the notebook page.

11) Complete a Table of Contents or index to enable ready access in the future by yourself or others. Pages are provided for this purpose in the front of the book. Index pages for unbound notebooks may be obtained from RI.

The records must be maintained in compliance with your written departmental procedure on keeping laboratory notebooks.

Complete instructions are* in MRL Policies, Procedures and Charters Manual, Policy 23, "Writing and Maintaining Laboratory Records", *available from Research Information, MRL.

October, 1999

Please sign this NB back in.

Thanks. A07-H04

J. Marencic
X4079
03 Jun 2010.

PS. Pager is down??

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TITLE: PURE CRYSTALLIZATION FROM WATER

OBJECTIVE: To determine characteristics of crystallization from water using brine as an antisolvent.

PROCEDURE:
- Dissolve 5g phosphate salt in 40 mL water.
- Make 20 mL of 35 weight % brine solution.
- Add brine to phosphate salt solution over 1 hour.
- Let age 1 hour.
- Vacuum filter. Submit samples for analysis.

RESULTS:
- Held supersaturation. Nucleated during aging step.
- Microscopy: Needles, about 300-400 μm length
- XRD: Not consistent with any other crystal forms
- AR to perform Cl and Na analysis, as well as phosphorus titration
- PSD: Mean = 88 μm 95% < 550 μm Bimodal

LOT #'S: PHOSPHATE SALT: Summit Flush Samples
NaCl: EM Science 41208139
Water: Distilled faucet

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TITLE: PURE CRYSTALLIZATION FROM DMSO

OBJECTIVE: To determine characteristics of phosphate salt crystallization in DMSO.

PROCEDURE:
- Isolate free base (8 g) in 80 mL of DMSO
- Place 4 g of phosphate salt with 2.38 g of H_3PO_4 85 weight % solution in 40 mL DMSO and stir at 250 rpm. (20°C)
- Add free base over 2 hours.
- Age 1 hour
- Vacuum filter and submit samples.

OBSERVATIONS:
- Heel dissolved!! Added ~~3.5~~ 5.5 g 3-FEB-2003 SHC more to act as "seed."
- Added 40 mL $MeCl_2$ to act as antisolvent.
- Not much growth.

LOT #'S:
PHOSPHATE SALT: Summix Flush Samples
FREE BASE: NB66839-42
AQUEOUS H_3PO_4: JT Baker V20812
DMSO: Aldrich

RESULTS:
- LCAP = 91.64 A% (58.14 A% at RRT = 0.14 → Solvent?)

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TITLE: PHOSPHATE SALT BREAK TO PRODUCE FREE BASE (RESULTS TO A.R.)

OBJECTIVE: To produce free base in THF for crystallization studies.

PROCEDURE:

- Same as TNB66839-37

DATA:

Phosphate Salt	(PS Recovered Solids)	= 51.70 g
KOH	(Aldrich B0107509)	= 17.2 g
NaCl	(EM Science 41208139)	= 9.3 g
Water		= 155 mL
THF	(Fisher 011510)	= 625 mL

Agitation = 350 rpm

Weight of First Water Cut = 114.7 g
Volume " " " " = 100 mL
Weight of First THF Cut = 661.2 g
Volume " " " " = 750 mL

Weight of Second Water Cut = 217.8 g
Volume " " " " = 190 mL
Weight of Second THF Cut = 609.2
Volume " " " " = 700 mL

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RESULTS (from A.R.):

First THF Cut = 58.84 g/L = 44.13 g FB
First Water Cut = 0.06 g/L = 0.006 g FB
Mass Balance = 44.136/41.673 = 106%
% Lost to Aqueous = 0.006/44.136 = .014%

2nd THF Cut = 61.46 g/L = ~~43.02~~ ~~37.44~~ g FB 5HC 6-FEB-2003
2nd Water Cut = 0.60 g/L = 0.114 g FB
Mass Balance = 43.134/41.673 = 103.5%
% Lost to Aqueous = .114/43.134 = 0.26.4%

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TITLE: PURE CRYSTALLIZATION FROM DMSO

OBJECTIVE: Determine crystal form obtained upon crystallization from pure DMSO.

PROCEDURE:

- Solvent Switch Free Base in THF (8 g F.B.) to DMSO (8 g F.B. in 100 mL Total Volume)
- Place 20 g phosphate Salt (Summix Flush Samples) in 40 mL DMSO at room temperature and stir at 250 rpm.
- Add 2.38 g 85 weight % H_3PO_4 (aq) to stirring heel (1.05 eq).
- Add f.b. solution over 2 hrs. (50 ml/hr)
- Let age 1 additional hour.
- Vacuum filter and submit samples.

RESULTS:

- 311 mg/g phosphate salt in mother liquors.
- XRD = Form II → solvated

Mean particle ≈ 5 μm

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TITLE: CRYSTALLIZATION FROM WATER USING NaH_2PO_4 SOLUTION AS ANTISOLVENT

OBJECTIVE: To crystallize L-715 Phosphate Salt directly from water using sodium phosphate solution as an antisolvent.

PROCEDURE:

- Dissolve 5 g phosphate salt (Summix Flush Samples) in 40 mL water (distilled).
- Dissolve 25 g NaH_2PO_4 in 65 g water. Place 20 mL of this solution in a syringe. SHC 6-FEB-2003
- Add salt solution at 10 mL/hr to solution of phosphate salt in water at room temperature at 250 rpm.
- Let age 1 additional hour after addition is complete.

RESULTS:

- XRD pattern similar to NB6683 9-45
- Crystal habit = 40 μm - 80 μm needles
- Na Content of wetcake = 1.1 weight %
- Solubility = 60 mg FB/g solution @ 20°C in H_2O

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TITLE: CRYSTALLIZATION FROM ISOAMYL ALCOHOL

OBJECTIVE: To crystallize L-715 phosphate salt through a reactive crystallization in Boamyl alcohol to produce either Form I or Form III directly.

PROCEDURE:

- Same as other reactive crystallizations
- Stir 2g phosphate salt (Summix Flush Samples) in 40 mL IAA (Sigma) for 1 hr. at room temperature at 250 rpm.
- Obtain 8 g Free Base in 65 mL total volume solution in IAA. Place in a syringe.
- Add 238 g 85 w% H_3PO_4 to heel.
- Add free base solution at 32.5 mL/hr
- Let age 1 hr after addition is complete.

RESULTS:

Filtrate = 0.515 mg 715-Phosphate Salt/g mL by HPLC

XRD = Form I + III (some amorphous)

Mean PSD = 48.8 μm 95% < 108.2 Unimodal

Lots of fines!!

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TITLE: CSA SALT-BREAK USING CSA-SALT ISOLATED BY S. RODGERS

OBJECTIVE: To run salt break using CSA-salt isolated by S. Rodgers.

PROCEDURE:

- Suspend 5 g CSA-salt in 60 mL THF
- Add 2 eq KOH dissolved in 15 mL 5 weight% brine.
- Stir at power #1.5 for 30 min.
- Let settle.
- Extract aqueous cut.
- Add 15 mL 20 weight% brine to THF cut and stir 30 min.
- Let settle.
- Keep THF cut w/ from base.

RESULTS/DATA:

CSA-salt (NB72772-103) = 4.999 g
THF (Fisher 011510) = 60 mL
KOH (Aeros B0107509) = 0.942 g (0.877 g target)
NaCl (EM Sci. 41208139) = 0.842 g (0.8 g target)
1st Water = 12.786 g (to make 15 mL Total)

1st Water Cut = 8.65 g (~ 8 mL)
1st THF Cut = 60.89 g (~ 68 mL)

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FOR BRINE WASH:

NaCl = 2.98 g
Water = 15.35 g (~17 mL total volume)

2nd Water Cut = 19.72 g (~20 mL)
2nd THF Cut = 51.25 g (~58 mL)

AR FB Concentration Results:

1st THF Cut = 58.84 g/L (4.00 g FB) → 126% Mass Balance
1st Water Cut = 0.06 g/L (.00048 g FB)
2nd THF Cut = 61.46 g/L (3.56 g FB) → 112% Mass Balance
2nd Water Cut = 0.60 g/L (.012 g FB)

Total Aqueous Losses = 0.392%

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TITLE: PHOSPHATE SALT BREAK TO PRODUCE FREE BASE FOR HYDROG STUDIES

OBJECTIVE: Produce free base in THF for use by Shane Krska in hydrog studies.

PROCEDURE:

- Same as NB66839-47

DATA:

- PHOSPHATE SALT (Summit Flush Samples) = 51.9 g
- THF (Acro's B0503074) = 620 ml
- KOH (Acros B0107509) = 17.21 g
- NaCl (EM Sci. 41208139) = 19.17 g
- 1st Water = 140.75 g (to make 155 ml Total)

FOR BRINE WASH:

NaCl = 29.90 g

Water = 140.90 g (to make 155 ml Total)

Weight of final THF Cut = 610.70 g (62.6 mg/g by HPLC)

Exact procedure duplicated to make second batch

Weight of 2nd Batch Final THF Cut = 647.17 g (60.8 mg/g)

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TITLE: PHOSPHATE SALT CRYSTALLIZATION FROM CSA-SALT BREAK

OBJECTIVE: To determine Rh rejection in final pure crystallization.

PROCEDURE:

- Prepare heel of phosphate salt (4.0 g) in 40 mL of EtOH.
- Dissolve 0.9 g Phosphoric Acid (85 weight %, 1.05 eq) in 20 mL EtOH.
- Obtain free base (NB 66839-52) in EtOH (3g FB in 20 mL total volume).
- Add phosphoric acid solution and free base solution simultaneously to heel at 6.67 mL/hr for each solution.
- Age 1 additional hour.
- Vacuum filter and dry wetcake in vacuum oven overnight at 40°C.
- Submit to T. Wang for Rh analysis.

RESULTS:

Rh = 4 ppm (compared to 20 ppm in CSA salt)

Na = 0.1 weight %

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TITLE: Polymorph Turnover in Isoamyl Alcohol

OBJECTIVE: To determine if wetcake from EtOH resuspended in isoamyl alcohol will result in Form I and/or III upon filtration.

PROCEDURE:

- Suspend 10 g of phosphate salt wetcake in EtOH (NB70223-181, wetcake from wet mill cycle #7) in 100 mL of isoamyl alcohol.
- Agitate in Morton Crystallizer @ 250 rpm for 4 hours.
- Vacuum filter.
- Submit wetcake for XRD analysis.

RESULTS:

XRD of EtOH wetcake = 4 hours Form II
TG of EtOH wetcake = 14% EtOH by weight
XRD of IAA wetcake = Form II and I (4 hours)
Mainly Form I with little Form III at 24 hrs.

NOTES:

- Submitted wetcake in IAA
- Also washed cake w/ n-hexane and submitted after partial drying
- Continue agitation overnight to obtain 24 hour results

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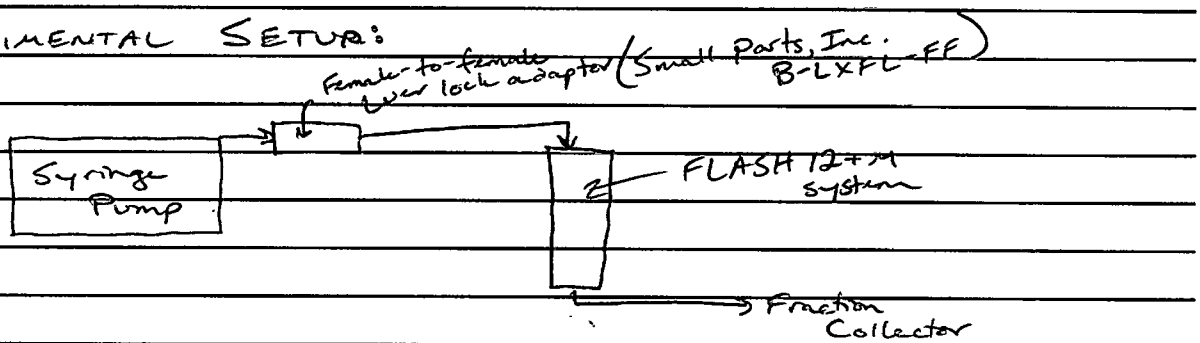
TITLE: INITIAL BREAKTHROUGH-CURVE OF Rh IN FLASH 12+M BIOTAGE C941 CARTRIDGE SYSTEM

OBJECTIVE: To determine Rh. breakthrough curve for FLASH 12+M system using cartridges packed with Ecosorb C941.

EXPERIMENTAL SETUP:



PROCEDURE:

- Pump 40 mL of neat methanol (Fisher 023375) through system @ 4 mL/min. 2 SHL 13-FEB-2003
- Attach hydrog crude stream. Pump total of 200 mL stream @ 4 mL/min, collecting fractions every 2.5 min (10 mL). 2 SHL 13-FEB-2003 NB70857-21
- Pump 40 mL of neat methanol to flush system @ 4 mL/min, collecting 10 mL fractions.
- Prepare samples for HPLC free base concentration calcs.
- 100 µL in 1.9 mL of DIW and then 8 mL of Trace Metal Grade Nitric Acid. Submit these to Tibay Wang for Rh analysis. 9 SHL 14-FEB-2003

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DATA:

DENSITY OF INLET STREAM:

WEIGHT: 1.6874 g (± .0005 g)

VOLUME: 2.0 mL @ 5HC 12-FEB-2003 (± 0.03 mL)

$\Delta D = \left(\left(\frac{\partial D}{\partial w}\right)^2 (\Delta w)^2 + \left(\frac{\partial D}{\partial v}\right)^2 (\Delta v)^2\right)^{1/2}$

DENSITY: 0.8437 g/mL ± 0.0127 g/mL

HPLC Vials:

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DATA for Free Base Concentration via HPLC

Sample Number	Inlet	1	2	3	4	5	6
Weight of Vial	18.2420			17.0756	17.0346	17.1346	17.3599
Vial + Diluent	30.4157			29.7595	29.8836	29.1670	29.7799
Vial+Dil+Sample	30.5130			29.8635	30.0026	29.2893	29.8820

Sample Number		7	8	9	10	11	12
Weight of Vial		17.0859	17.0790	17.3769	17.2860	16.9483	17.0432
Vial + Diluent		29.5016	29.6563	29.4651	28.5041	29.3555	29.8893
Vial+Dil+Sample		29.6336	29.7750	29.5577	28.6254	29.4668	30.0188

Sample Number		13	14	15	16	17	18
Weight of Vial		17.0904	17.1035	16.9779	16.9755	16.9812	17.3814
Vial + Diluent		27.7704	29.5934	27.2449	29.0261	28.6293	27.7943
Vial+Dil+Sample		27.8606	29.7171	27.3743	29.1370	28.7734	27.9038

Sample Number		19	20	21	22	23	24
Weight of Vial		17.1105	17.0527	16.8591	16.9716	17.1906	17.1595
Vial + Diluent		28.0161	28.7247	28.2477	27.6541	27.1560	27.4422
Vial+Dil+Sample		28.1393	29.8060	28.3823	27.7756	27.5141	27.9480

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RESULTS:

Freebase and Rh left in Spent Cartridge:

Fraction of Cartridge	Weight of Spent C-941	Weight of C-941 in FB study (3/4 mL MeOH) 64.9 ~~24.8~~ mg SHC 19-FEB 2003	Rh concentration
Top (1)	2.6366 g		
2	2.2387 g	90.6 mg	
3	1.7298 g	64.9 mg	
4	2.0143 g	65.9 mg	
5	1.9348 g	71.9 mg	

Sample	FB Conc. in Filtrate	FB Conc. on C-941
1	0.1464 mg/g	7.13 mg/g C-941
2	0.2445 mg/g	8.53 mg/g C-941
3	0.2456 mg/g	11.27 mg/g C-941
4	0.2930 mg/g	14.05 mg/g C-941
5	0.3762 mg/g	16.5 mg/g C-941

VOID FRACTION IN CARTRIDGE:

Weight of dry C-941 cartridge = 15.14 g

Weight of MeOH wet cartridge = 24.94 g

Volume of MeOH = (24.94 - 15.14) / .793 g/mL = 12.4 mL

Total Volume = 15 x π(.6)^2 = 16.96 mL

ε = 12.4/16.96 = 0.73

C-941 Particle Density: (.27)(16.96) / (4.5 mL) x 0.33 g/mL x 17 mL = 1.2 g/mL (John Weaver Biotage)

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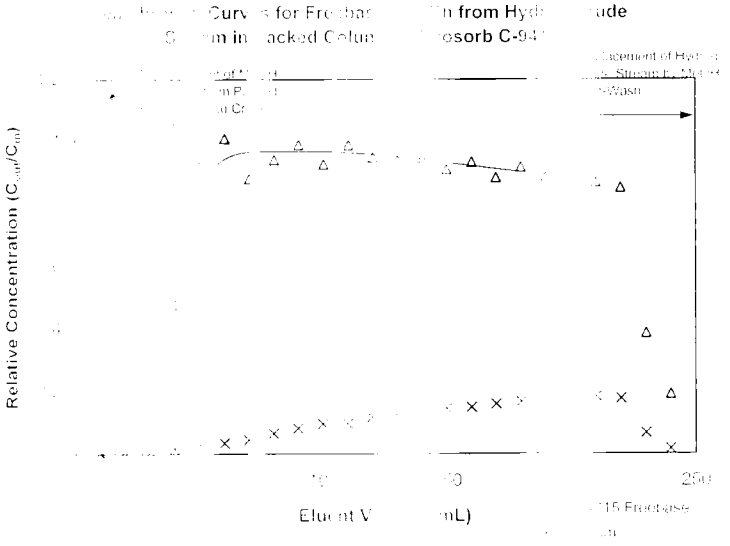
Sample Num	In	1	2	3	4	5	6
Weight		n/a		7.0756		17.1346	17.3599
Vial +		n/a		29.7595		29.167	29.7799
Vial+Dil		n/a		29.8635		29.2893	29.882
HPLC		0	1	0		7897.58	7025.07
Free Base		0	0	0		96.18917	105.5874
Rb Conc		0		0		2.31	2.86

Sample Num		7		9		11	12
Weight		0853	12	7.3769		16.9483	17.0432
Vial +		5016	29	9.4651		29.3555	29.8893
Vial+Dil		6336	28	29.5577		29.4668	30.0188
HPLC		2.195	75	412.89		7491.685	8085.5
Free Base		05598	0.8	3.3781		103.2634	99.28289
Rb Conc		6.74	8	6.71		7.92	9.68

Sample		13		15		17	18
Weight		0004	12	6.9779		16.9812	17.3814
Vial +		7781	28	7.2449		28.6293	27.7943
Vial+Dil		4668	24	7.3743		28.7734	27.9038
HPLC		7.174	72	58.785		9213.114	8141.551
Free Base		67459	0.9	5.10012		92.39472	85.87772
Rb Conc		4.5	1	11.99		13.2	13.75

Sample		19		21		23	24
Weight		1178	12	6.8591		17.1906	17.1595
Vial +		0181	29	8.2477		27.156	27.4422
Vial+Dil		1343	29	8.3823		27.5141	27.948
HPLC		2.0	1.5	48.312		11446.9	7682.27
Free Base		7.7	1	73382		40.44086	20.08083
Rb Conc		4.4		15.07		5.5	1.32



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TITLE: POLYMORPH TURNOVER IN MTBE

OBJECTIVE: Repeat NB66839-56 with MTBE to see if lower boiling non-solvating solvent results in polymorph turnover from Form II → I.

PROCEDURE:

- 5 g NB70223-181 EtOH wetcake agitated in 50 mL MTBE (Aldrich CA01162KO) overnight (~17 hours).
- Vacuum filter and submit wetcake for XRD analysis.

RESULTS:

- Still all Form II after 17 hours

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TITLE: KINETICS OF POLYMORPH TURNOVER IN ISOAMYL ALCOHOL

OBJECTIVE: To determine the kinetics of the polymorph turnover from Form II to Form I in isoamyl alcohol at 70°C.

PROCEDURE:

- Weigh 15 g of phosphate salt wetcake in EtOH (NB70223-181, 14 weight% EtOH, 100% Form II)
- Stir in 150 mL isoamyl alcohol at 70°C at 300 rpm.
- Take samples of resulting ISAA wetcake after 1 hr and 2 hrs.
- After 2 hours @ 70°C, cool down to 20°C in 30 min.. Stir another 2 hours and take sample. Let stir at 20°C 3 days and take final sample.

RESULTS: (XRD patters on following page)

Original EtOH wetcake = 100% Form II
1 hr ISAA wetcake = 100% Form I
2 hr " " = 100% Form I
4 days " " = 100% Form II

Conclusion: Reverted to Form II at 20°C due to ~2 weight% EtOH in system.

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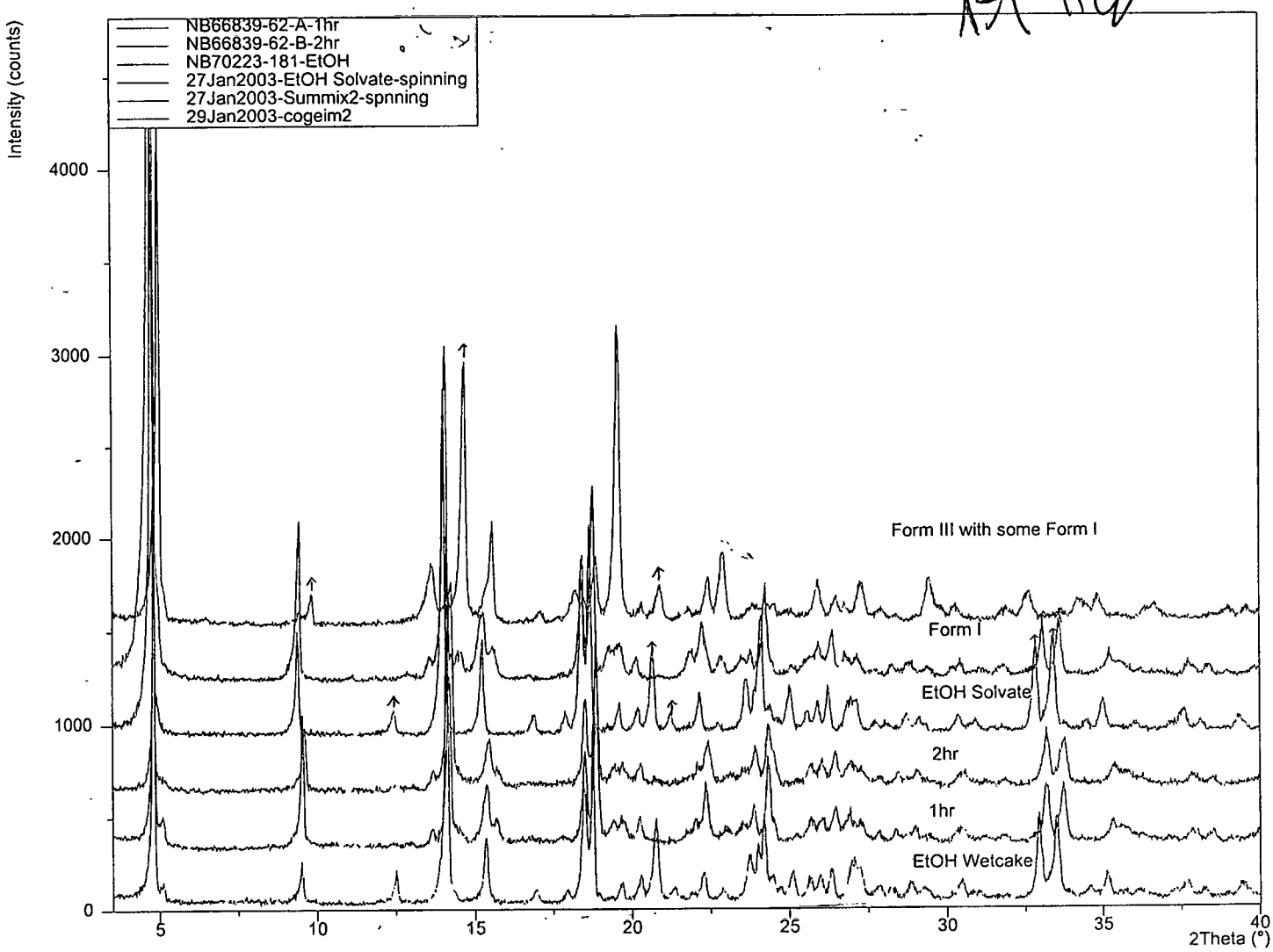

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TITLE: VISCOSITY OF HYDROG STREAM FOR PRESSURE DROP CALCS IN BIOTAGE CARTRIDGE

OBJECTIVE: To determine the viscosity of different hydrog crude stream concentrations for pressure drop calcs in Biotage system.

DATA:

RUSS Furlita unable to measure since solutions are not viscous enough.

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TITLE: Pure crystal Growth Kinetics IN ISOAMYL ALCOHOL

OBJECTIVE: To determine the growth kinetics of phosphate salt in isoamyl alcohol to facilitate crystal growth rather than nucleation in a reactive crystallization process.

PROCEDURE:

- Suspend 20 g of phosphate salt (PP81-2) in 200 g of isoamyl alcohol (ISAA, Aldrich) at 65°C with agitation.
- Take ~15 g of slurry, vacuum filter at room temp, and submit wetcake for XRD analysis after 1 hr in 65°C slurry (NB66839-65 sample to Phys. Meas.).
- Solvent switch free base from THF to ISAA. Resulting concentration in ISAA = 228 mg/g (HPLC) and KF = 890.
- Dilute 3 g 85 w% H_3PO_4 with 77 g ISAA.
- To mature heel, add 1 g FB "shot" (4.4 g FB solution) and what on ReactIR until signal stabalizes (~10-15 min.)
- Add "shot" of 1.05 eq H_3PO_4 (8 g of H_3PO_4 solution) and record decrease in FB concentration using ReactIR.

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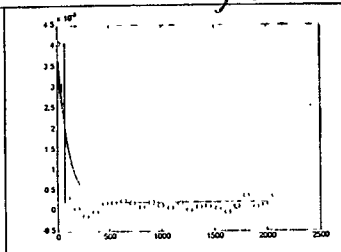
65801p295
Experiment 1
Seed: 20g milled L715 (ppb#2-2)
Solvent. 200g ISAA
Temp: 66.5 C

FB solution· 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

Addition· 4.4g FB solution to seedbed, then 8g H3PO4 solution (1.1 eq.)

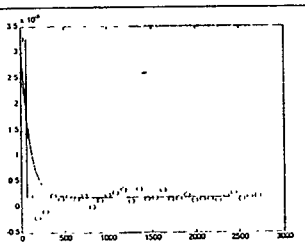
T1/2 = 70 sec.



65801p295
Experiment 2
Seed 20g milled L715 (ppb#2-2)
Solvent: 200g ISAA
Temp: 66.5 C

FB solution: 228mg/g in ISAA
H3PO4 solution· 3g 85% H3PO4 in 80g ISAA

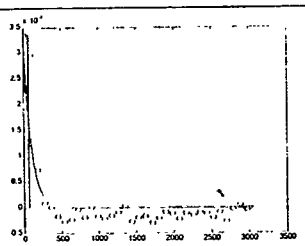
Addition: 8g H3PO4 solution to seedbed, then 4 4g FB solution (1:1 eq)
T1/2 = 67 sec



65801p296
Experiment 1
Seed: 20g milled L715 (ppb#2-2)
Solvent: 200g ISAA
Temp: 66 5 C

FB solution: 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

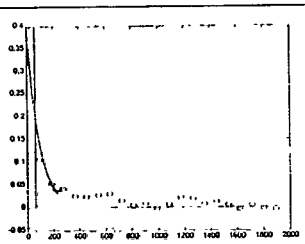
Addition 8.8g FB solution to seedbed, then 8g H3PO4 solution (2·1 eq)
T1/2 = 69 sec.



65801p296
Experiment 2
Seed. 20g milled L715 (ppb#2-2)
Solvent: 200g ISAA
Temp: 66.5 C

FB solution: 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

Addition· 16g H3PO4 solution to seedbed, then 4.4g FB solution (2:1 eq.)
T1/2 = 65 sec.



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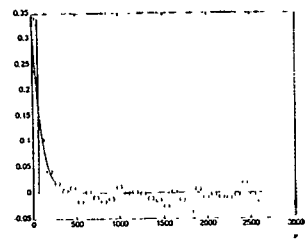
65801p296
Experiment 3
Seed: 20g milled L715 (ppb#2-2)
Solvent. 375g ISAA
Temp: 66 5 C

FB solution 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

Addition 4.4g FB solution to seedbed, then 8g H3PO4 solution (1:1 eq)

T1/2 = 67 sec.

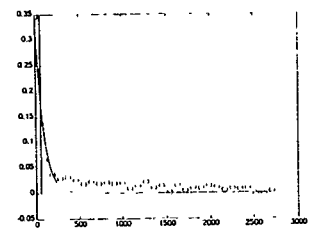


65801p297
Experiment 1
Seed: 20g milled L715 (ppb#2-2)
Solvent: 100g ISAA + 100 EtOH
Temp: 66.5 C

FB solution. 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

Addition: 4.4g FB solution to seedbed, then 8g H3PO4 solution (1:1 eq.)

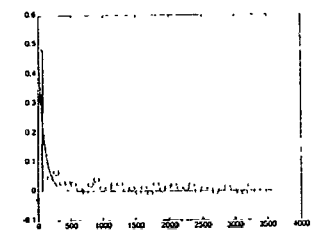
T1/2 = 60 sec.



65801p297
Experiment 2
Seed: 20g milled L715 (ppb#2-2)
Solvent: 100g ISAA + 100 EtOH
Temp. 66.5 C

FB solution: 228mg/g in ISAA
H3PO4 solution: 3g 85% H3PO4 in 80g ISAA

Addition: 8g H3PO4 solution to seedbed, then 4.4g FB solution (1.1 eq)
T1/2 = 65 sec.



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24-FEB-2003

Continued From: —

TITLE: REACTIVE CRYSTALLIZATION IN ISOAMYL ALCOHOL

OBJECTIVE: To obtain large phosphate salt crystals in a reactive crystallization in pure isoamyl alcohol.

PROCEDURE:

- Place 3 g Phosphate Salt (PPBI-2) in 30 mL ISAA (Aldrich). Place 50 g of 200 mg/g Freebase in ISAA with heat at 65 ~~20~~ °C (glycol bath).
- Age 30 min.
- Dissolve 2.97 g 85 wt% H_3PO_4 (1.05 eq) in 20 g of ISAA. Resulting solution is ~ 26 mL in volume.
- Add phosphoric acid solution to heel over 6 hours using a syringe pump (4.33 mL/hr).
- After addition, cool to 20°C in 30 min.
- Age at 20°C overnight

RESULTS:

- XRD revealed mix Form I and III in wetcake after aging @ 20°C (mainly Form I)
- ~~Fail~~ Mainly fines crystallized. Due to supersaturation levels too far above solubility level (outside metastable zone).
- Microscopic picture next page.

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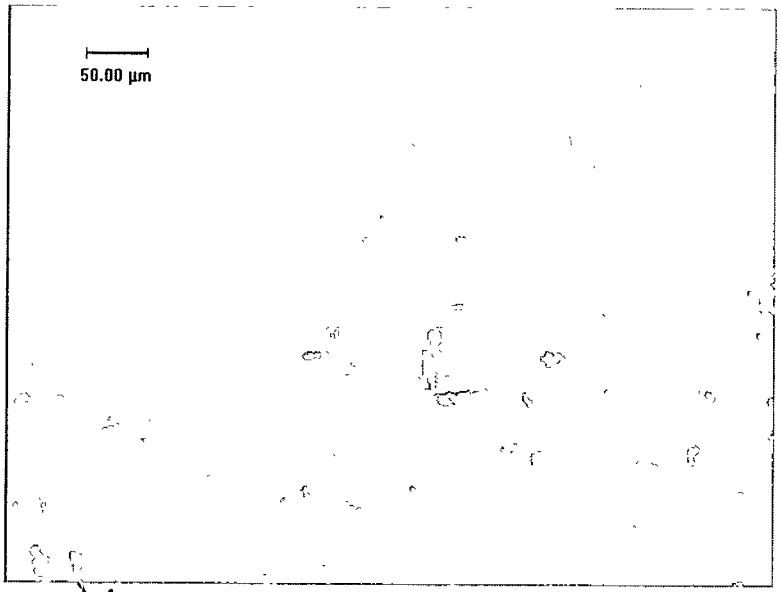

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24-FEB-2003

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TITLE: Solubility of phosphate salt in Isoamyl Alcohol

OBJECTIVE: To determine the solubility of L-224715 phosphate salt in isoamyl alcohol at several temperatures.

PROCEDURE:

- Place ~250 mg phosphate salt (Quintile Batch Reserve) in 5 mL vial.
- Add ~3 mL of ISAA
- Place 4 vials in 4 different temps (0°C, 25°C, 40°C, 60°) solubility blocks.
- Use in-line filter syringe and place filtrate directly in HPLC.

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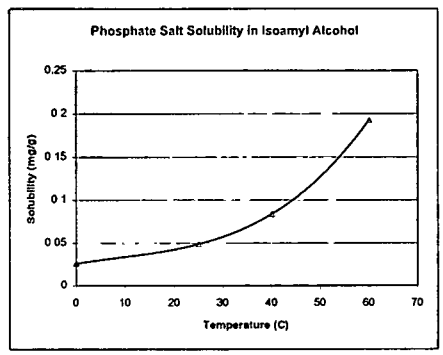
DATA:

60° C → 0.193 mg/g
40° C → 0.0839 mg/g
25° C → 0.0489 mg/g
0° C → 0.0262 mg/g



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Continued From: —

TITLE: STABILITY STUDY OF FREEBASE AND PHOSPHATE SALT IN ISAA

OBJECTIVE: To determine the stability of freebase and phosphate salt in ISAA @ 20°C and 70°C.

PROCEDURE:

(70°C Phosphate Salt)

- Slurry phosphate salt (Quintile Batch Rework) in Isoamyl Alcohol at 70°C using temp. controller and stir bar.
- Filter at time intervals and submit wetcake and filtrate for LCAP.

RESULTS:

- Large growth at RRT = 1.57 in ML. Probably olefin from decomposition product

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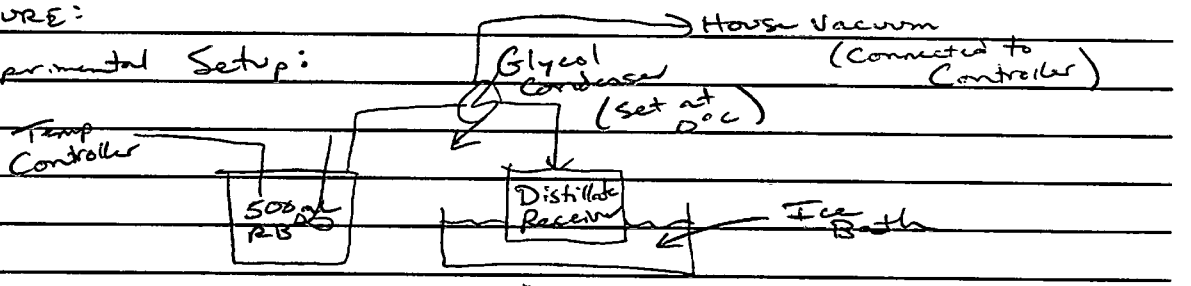
TITLE: Solvent Switch from Ethanol to Isoamyl Alcohol to promote polymorph transition

OBJECTIVE: To solvent switch a phosphate salt slurry in EtOH to ISAA to promote polymorph transition from Form II to Form I.

PROCEDURE:

Experimental Setup:



- Place 30 g of phosphate salt (NB70223-163) in RB
- Add 240 g of Denatured EtOH to RB
- Agitate at 250 rpm
- Set temp. controller to 50°C.
- Pull vacuum until boiling is observed
- Concentrate slurry in RB
- Add ISAA to return to original mass concentration
- Continue until turnover is observed.

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RESULTS:

STEP		Temp (C)	Pressure (torr)	EtOH Mass (g)	ISAA Mass (g)	Phosphate Salt Concentration (mg/g)	Mole% ISAA	Weight% ISAA	Crystal Form	Mean Particle Size (microns)	Crystal Habit
Add 240 g Denatured EtOH to 30 g Phosphate Salt (Mix Form I and Form III). Agitate 2 hrs. to solvate											
1	Start	50	225	240	0	111	0%	0%	Form II	50 00	Hexagonal (and Broken) Plates
	Finish	50	225	110	0	214	0%	0%	Form II	Undetermined	Hexagonal (and Broken) Plates
Add 110 g Isoamyl Alcohol											
2	Start	50	155	110	110	120	34%	50%	Form II	Undetermined	Hexagonal (and Broken) Plates
	Finish	50	120	70	110	143	45%	61%	Form II	Undetermined	Hexagonal (and Broken) Plates
Add 60 g Isoamyl Alcohol											
3	Start	50	115	70	170	111	56%	71%	Form II	Undetermined	Hexagonal (and Broken) Plates
	Finish	50	45	20	170	136	82%	89%	Form II	Undetermined	Hexagonal (and Broken) Plates
Add 50 g Isoamyl Alcohol											
4	Start	50	40	20	220	111	85%	92%	Form II	Undetermined	Hexagonal (and Broken) Plates
	Finish	50	22	4 5	220	118	96%	98%	Form I	45.53	Hexagonal (and Broken) Plates

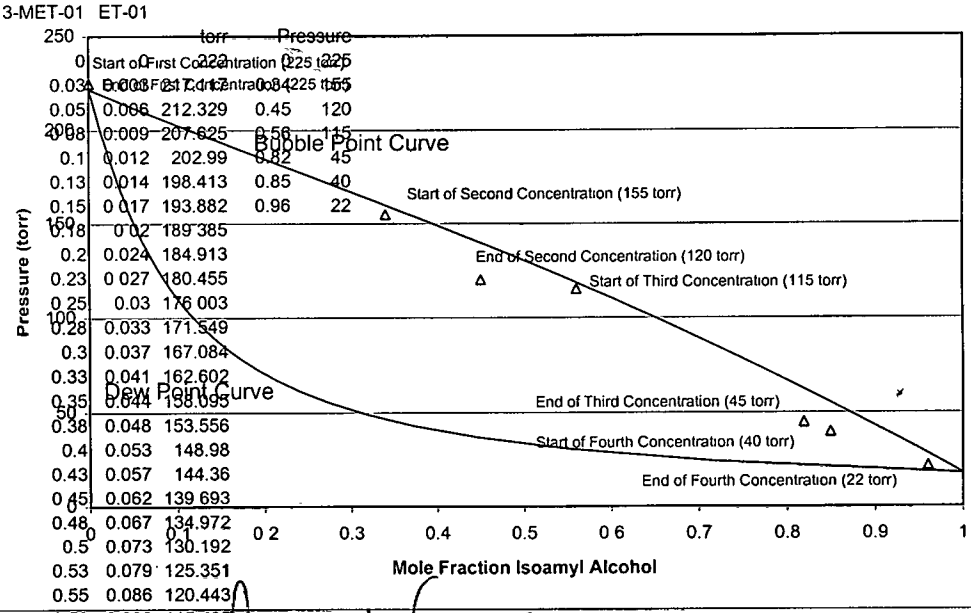
NOTE:

1 Ending solvent compositions in each step were determined by weighing the distillate, subtracting from the total weight of starting solvent, and estimating the mole fractions using a Pxy diagram produced using ASPEN. In each step, it was found that a negligible amount of ISAA was lost to the distillate, although this result is not entirely consistent with the Pxy diagram.

2. Mean particle size based on sonicated samples. Distribution was unimodal in all cases.

Pxy Diagram and Operating Points for Slurry Solvent Switch from Ethanol to Isoamyl Alcohol at 50°C

LIQUID OLEFRAC 3-MET-01	APOR FRAC ET-01	TOTAL PRES torr
0	0	222
0.03	0.003	217.112
0.05	0.006	212.329
0.08	0.009	207.625
0.1	0.012	202.99
0.13	0.014	198.413
0.15	0.017	193.882
0.18	0.02	189.385
0.2	0.024	184.913
0.23	0.027	180.455
0.25	0.03	176.003
0.28	0.033	171.549
0.3	0.037	167.084
0.33	0.041	162.602
0.35	0.044	158.095
0.38	0.048	153.556
0.4	0.053	148.98
0.43	0.057	144.36
0.45	0.062	139.693
0.48	0.067	134.972
0.5	0.073	130.192
0.53	0.079	125.351
0.55	0.086	120.443



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TITLE: REACTIVE CRYSTALLIZATION IN ISOAMYL ALCOHOL/ WATER SYSTEM AT 70°C

OBJECTIVE: To see if small amounts of water increases metastable zone and therefore promotes growth in ISAA instead of nucleation.

PROCEDURE:

- Place 3g phosphate salt (PPB1-2) in 100g heel (90g ISAA and 10g H_2O) at 70°C. (250 rpm agitation)
- Add 10g Free Base with 90g ISAA to phosphate salt heel.
- Add 3g 85 weight% H_3PO_4 to 47g of ISAA
- Add H_3PO_4 solution over 6 hrs. (60 mL/hr) to 70°C heel.
- After H_3PO_4 addition, cool to 20°C over 1 hr.
- Age at 20°C for 1 hr

OBSERVATIONS:

- Mixing not good in 250 mL Morton crystallizer. Use half of volume for future experiments.
- Microscope pictures taken 2 hrs into H_3PO_4 addition (NB66839-74A), 4 hrs into addition (-74B), and once batch reaches 20°C (-74C).

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RESULTS:

- XRD revealed mix Form I and III in final wetcake
- Microscopy revealed mix of agglomerates formed by dendritic growth with single crystals in background.

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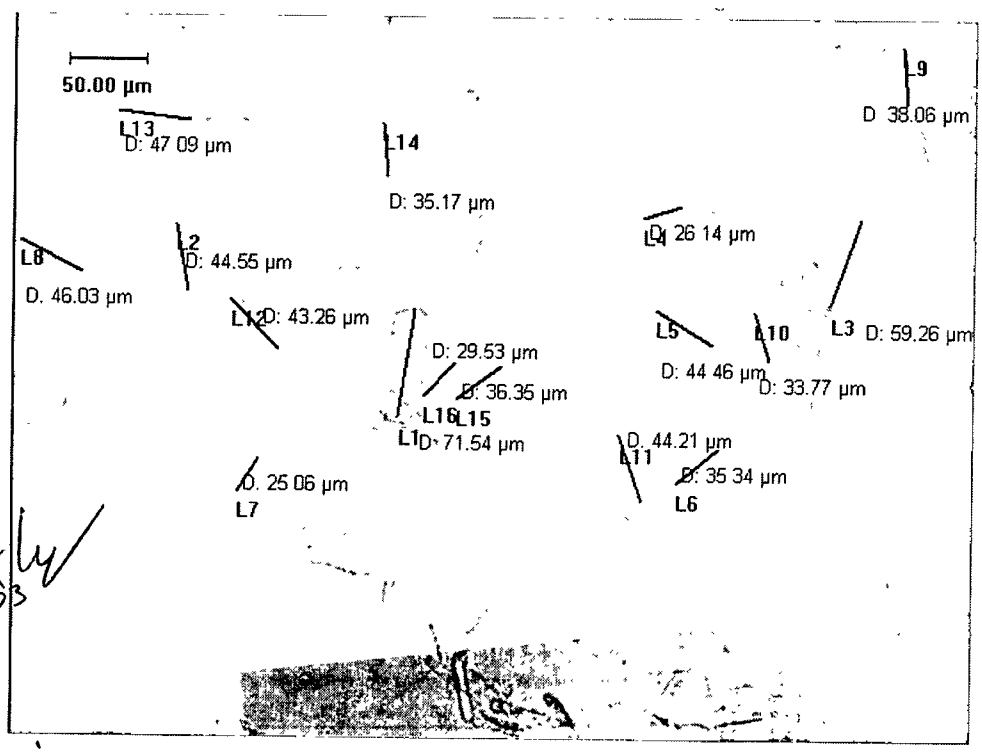
Dendritic Agglomerates



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Single xtals in background

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TITLE: REACTIVE CRYSTALLIZATION IN 95/5 ISOAMYL ALCOHOL/WATER AT 50°C.

OBJECTIVE: Repeat experiment NB66839-73 except perform at 50°C to reduce growth rate and prevent dendritic growth.

PROCEDURE:

- Place 1.5 g Phosphate Salt (PPB1-2) in 45 g ISAA and 5 g water at 50°C. (250 rpm agitation)
- Add 5g Free Base in 45g ISAA to phosphate salt heel.
- Dissolve 1.5 g 85 weight% H_3PO_4 in 23.5 g ISAA.
- Add H_3PO_4 solution to heel at 5 mL/hr (6 hour addition)
- After addition, age at 50°C for 30 min.
- Cool to 20°C over 1 hour.
- Age at 20°C overnight.
- Vacuum filter and submit samples.

OBSERVATIONS:

- Good Mixing.
- Microscope pictures taken:
  - NB66839-75A = 2 hours into addition
  - -75B = 4 hours into addition
  - -75C = End of H_3PO_4 addition

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RESULTS:

-XRD: mix Form I and III in final wetcake

-PSD: mv = 50 µm

-Microscopy: homogeneous small aglomeration of rods

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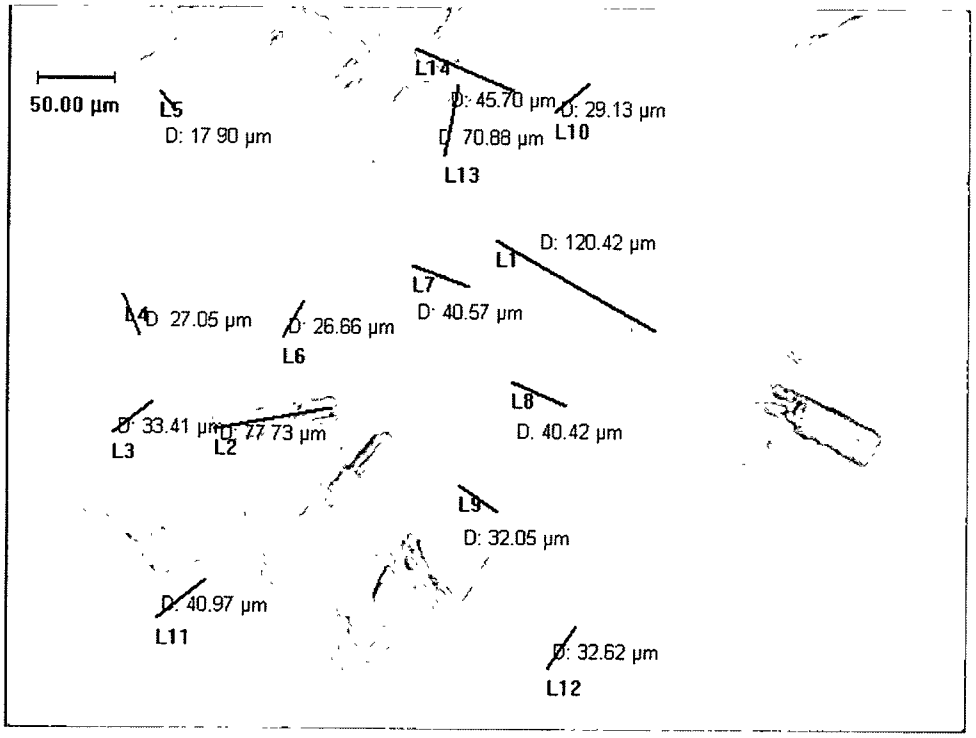

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TITLE: PHOSPHATE SALT BREAK IN ISOAMYL ALCOHOL/ WATER SYSTEM

OBJECTIVE: To determine the characteristics of performing a salt break in an ISAA/Water System.

PROCEDURE:

- Slurry phosphate salt (NB70223-163) in 12 L/kg ISAA (Aldrich TU11478DU).
- Add to slurry a solution of 3 eq KOH (Acros B0107509) in water to make 155 mL. (3 L/kg)
- Agitate @ 400 rpm for 30 mm @ room temp.
- Cut aqueous layer.
- Wash ISAA layer with 155 mL water.
- Cut wash.

DATA:

Phosphate Salt = 51.8 g
KOH = 17.2 g

1st Water Cut =	114.54 g	(~100 mL)
1st ISAA Cut =	594.03 g	(~700 mL)
2nd Water Cut =	142.85 g	(~145 mL)
2nd ISAA Cut =	594.75 g	(~695 mL)

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RESULTS =

Total Free Base = $51.8 \times \frac{407.3}{505.3} = 41.75$ g

1st Water = $\frac{768.16}{8000} = .096$ mg/g $\times$ 114.54 g = 11.0 mg

1st ISAA = $\frac{5695.14}{8000} \times \frac{(33.2445-17.0629)}{(33.2445-33.0792)} = 69.69$ mg/g $\times$ 594.03 g

= 41.4 g ⟹ 99.2% Mass Balance

2nd Water = $\frac{12242.9}{8000} = 1.53$ mg/g $\times$ 142.85 = 0.2 g FB

2nd ISAA = $\frac{6925.015}{8000} \times \frac{(31.9679-17.3085)}{(31.9679-31.7798)} = 67.5$ mg/g $\times$ 594.75 g

= 40.12 g FB ⟹ 96.5% Mass Balance

0.5% loss to aqueous cuts

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TITLE: BREAKTHROUGH CURVE ANALYSIS FOR Rh AND FREEBASE IN PACKED COLUMNS OF SN-B16 RESIN

OBJECTIVE: To obtain breakthrough curves for Rh and Freebase for a packed column of SN-B16 in the Biotage FLASH 12+M system. (Ref. NB66839-57)

APPARATUS:

See NB66839-57 for apparatus description.

PROCEDURE:

- Pump 40 mL of neat methanol (Fisher 023375) through cartridge at 4 mL/min as a pre-wash. Dispose eluent.
- Pump 400 mL of hydrog crude stream (~50 mg/g FB, ~65 $\mu g^{Rh}/g_{solution}$, Filtered >8 micron retained) at 4 mL/min, room temp. Collect fractions every 20 mL.
- Post-wash with 80 mL methanol at 4 mL/min, continuing to collect fractions.
- Use HPLC to determine Freebase concentration in fractions.
- Dilute 100 µL of each fraction with 1.9 mL DIW and 8 mL metal-grade nitric acid. Use atomic spectroscopy to determine Rh levels.

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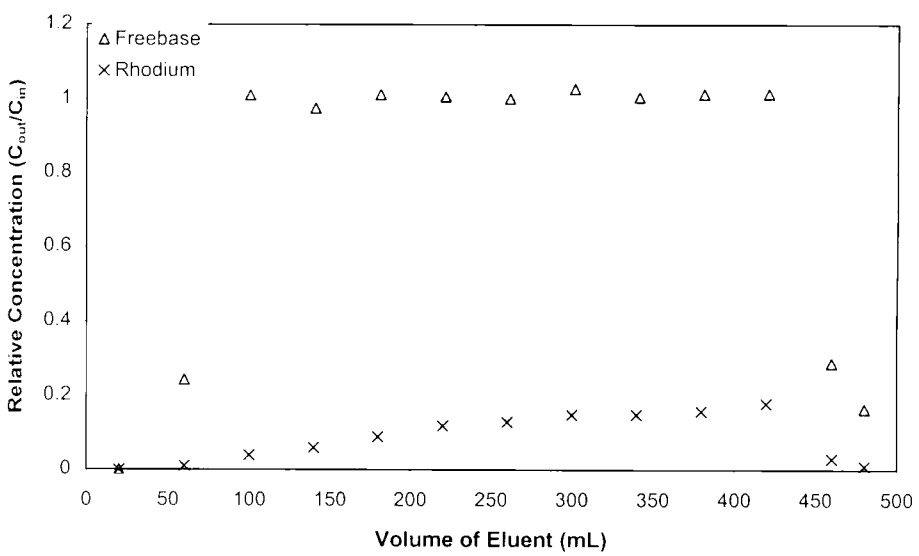
Volume	HPLC Area	Freebase Conc. mg/g	Relative Conc. Freebase		Rh (diluted)	Rh (microg/mL)	Relative Rh Conc.
20	0	0	0		0	0	0
60	1677.413	19.25225	0.243319		1	0.1	0.01
100	6966.545	79.95746	1.010542		4	0.4	0.04
140	6728.624	77.22675	0.97603		6	0.6	0.06
180	6979.89	80.11062	1.012478		9	0.9	0.09
220	6938.677	79.63761	1.0065		12	1.2	0.12
260	6905.271	79.25419	1.001654		13	1.3	0.13
300	7087.188	81.34212	1.028042		15	1.5	0.15
340	6932.89	79.57119	1.00566		15	1.5	0.15
380	6992.994	80.26102	1.014379		16	1.6	0.16
420	7002.313	80.36798	1.01573		18	1.8	0.18
460	1994.15	22.88755	0.289264		3	0.3	0.03
480	1139.291	13.07604	0.165261		1	0.1	0.01
Inlet	6893.87	79.12334	1		100	10	

Breakthrough Curves for Rh and Freebase Using Packed Column of SN-Bio



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Continued From: —

TITLE: REACTIVE CRYSTALLIZATION OF PHOSPHATE SALT FROM 95/5 ISOAMYL ALCOHOL/WATER AT 25°C

OBJECTIVE: To crystallize Form III directly by using a heel of 100% Form III and a reactive crystallization at 25°C

PROCEDURE:

- Place 2g of Form III wetcake (formed by slurrying Form I in 95/5 ISAA/water at room temp. for 6 days) with 33.3 g ISAA in 1 crystallizer at 25°C.
- Add free base in ISAA/Water (NB66839-77, KF: 65 mg/mL) (66.7 g total weight → ~5g F.B.; 5g H_2O) to heel.
- Dissolve 1.5 g 85 wt% H_3PO_4 in 23.5 g ISAA. Add to heel over 6 hours (5 mL/hr)

OBSERVATIONS:

- Heel dissolved. Due to excess KOH in NB66839-77 not removed since no solvent switch was needed.
- Upon adding more phosphate salt to heel, gelation occurred, possibly from excess K^+ or $H_2PO_4^-$ ions w/ free base at "low" temperatures.

CONCLUSIONS:

Need to remove excess KOH from Free base before running this crystallization!

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TITLE: CSA-SALT BREAK TO FOLLOW NEW IMPURITY THROUGH PURE STEP

OBJECTIVE: To perform CSA-Salt break on CSA-salt identified as having a higher level of a new impurity, and carry through to pure step.

PROCEDURE:

- Slurry 8 g CSA-Salt (3.74 g NB32452-89A with 4.27 g NB32452-89B) in 96 mL THF (Fisher 026782-12)
- Dissolve 1.4 g KOH (Acros B0107509) and 1.3 g NaCl (EM Sci. 41208139) in DIW to make 24 mL of solution
- Add KOH solution to CSA-salt slurry
- Agitate at 300 rpm for 30 min at room temp.
- Cut aqueous layer
- Wash THF layer with 5 g NaCl dissolved in DIW to make 24 mL solution by agitating at 300 rpm for 30 min.
- Cut aqueous layer. Gave freebase in THF to Mahmoud Kaba for further analysis.

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TITLE: CRYSTALLIZE PURE FORM III BY SELF-SEEDING PROCESS IN 95/5 ISAA/WATER AT ROOM TEMP

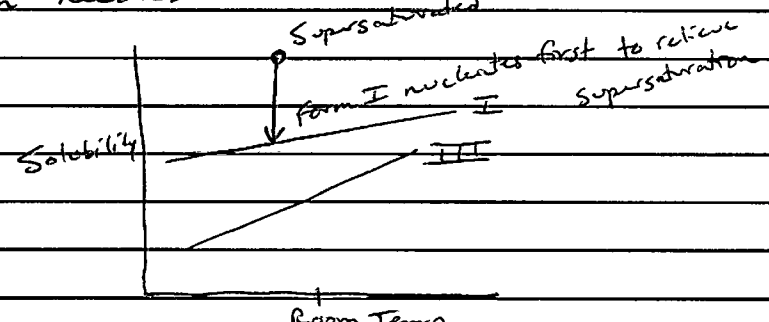
OBJECTIVE: To directly crystallize pure Form III without seed in order to use as seed in future crystallization studies.

PROCEDURE:

- Solvent switch freebase in THF from salt break to ISAA. Filter to remove salts that precipitate in solvent switch. Final solution (clear):
  FB: 125 mg/g
  Water: 6.84 mg/mL (by KF)
- Place 40 g of above solution in round bottom with stir bar and 55 g neat ISAA. → also 5 g DIW 6-MAR-2003 Stir at room temp.
- Dissolve 1.5 g 85 wt% H_3PO_4 in 23.5 g ISAA. Add to freebase solution over 6 hours.
- Age overnight with stirring.

RESULTS:

- Microscopy: 10-50 μm needles
- XRD: 100% Form I



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TITLE: CRYSTALLIZE PURE FORM III BY SELF-SEEDING IN 95/5 ISAA/WATER AT 40°C

OBJECTIVE: To directly crystallize Form III via Ostwald's Rule at 40°C.

PROCEDURE:

- Identical to NB66839-83, except perform crystallization at 40°C, and add H_3PO_4 over 4 hours.

RESULTS:

- 100% Form I by XRD
- Fines

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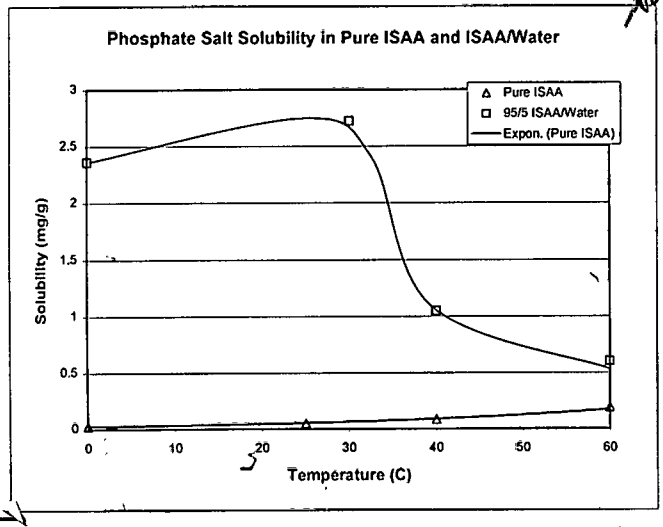
TITLE: PHOSPHATE SALT SOLUBILITY IN 95/5 ISOAMYL ALCOHOL / WATER

OBJECTIVE: To determine solubility of phosphate salt in 95/5 ISAA/Water as a function of temperature.

PROCEDURE:

- Place ~250 mg of phosphate salt (from Summix) in 4 separate vials
- Add 3.8 mL ISAA to each vial
- Add 200 µL H_2O (DIW) to each vial.
- Place in solubility blocks at different temperatures.

RESULTS:



Solubility decreases w/ temp. in 95/5 system since water is mainly in vapor phase at high temp.

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TITLE: CRYSTALLIZE PURE FORM III BY SEEDING AT ROOM TEMP

OBJECTIVE: To directly crystallize Form III in a reactive crystallization at room temperature using Pure Form III heel seed.

PROCEDURE:

- NB70223-153 phosphate salt was slurried in 95/5 ISAA/water for 1 day, and confirmed 100% Form III by XRD
- NB70223-153 vacuum filtered and partially dried under vacuum at room temp.
- 2.0 g of wetcake added to 5 g Freebase in 77 g ISAA + 20 g ISAA + 5 g DIW at room temp with agitation (rpm = 400)
- 1.5 g 85 wt% H_3PO_4 dissolved in 23.5 g ~~DIW~~ ISAA. Added to heel via syringe pump @ 5 mL/hr (6 hours) SHC 5-MAR-2003
- NOTE: Gelation of heel occurred almost immediately (see picture NB66839-86A). Dilute system with 100 g ISAA. Continue addition.

RESULTS:

- All fines
- 100% Form III by XRD (weakly diffracting)

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TITLE: PHOSPHATE SALT REACTIVE CRYSTALLIZATION IN 95/5 ISAA/H_2O @ 50°C to PRODUCE LARGE FORM I CRYSTALS

OBJECTIVE: To produce as large as possible Form I crystals in 95/5 ISAA/H_2O at 50°C.

PROCEDURE:

- Suspend 0.75 g Phosphate Salt (PPBI-12, mv = 12 μm) in 5 g Freebase dissolved in 90 g ISAA (solvent switched from THF, filtered, H_2O = 10 mg/mL by KF).
- Add 4.1 g DIW (since 0.9 g water added with Freebase stream) to heel at 50°C.
- Age at 50°C 30 min.
- Dissolve 1.5 g H_3PO_4 (85 wt%) in 23.5 g ISAA (30 mL Total Volume).
- Add H_3PO_4 solution to heel over 12 hours (2.5 mL/hr)
- Ramp temp to 20°C over 1 hour
- Age at 20°C overnight (~10 hours).
- Vacuum filter at room temperature.

RESULTS:

- Mother Liquor P.S. Conc. = 2.34 mg/g (Assuming 125 g ML → 4.2% Loss)

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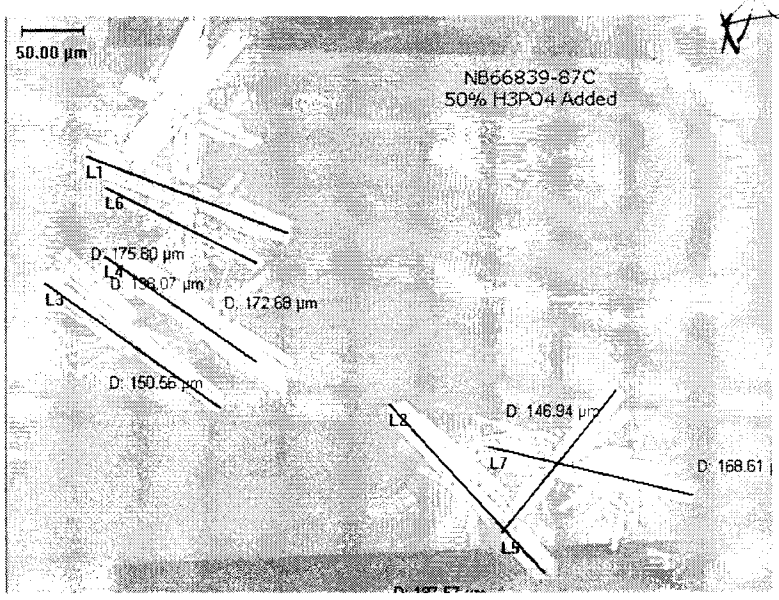

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Continued From: —

TITLE: REPEAT NB66839-87 AT 3x VOLUME WITH INLINE IR MEASUREMENT

OBJECTIVE: To determine how growth changes in a larger vessel for the phosphate salt fitted with in-line IR to watch free base disappearance in solution.

PROCEDURE:

- Charge 2.25 g PPB1-2 phosphate salt into 500 mL jacketed kettle fitted with IR probe.
- Slurry in 15 g Freebase, 270 g ISAA and 15 g DIW @ 50°C (400 rpm 11-MAR-2003)
- Dissolve 4.5 g H_3PO_4 (85 wt%) in ISAA to make 75 g Total (90 mL)
- Charge H_3PO_4 solution to heel at 7.5 mL/hr (12 hours), using IR to watch Freebase disappearance.
- Hold at 50°C for 3 hours after addition has ended.
- Keep slurry for cycling experiments.

RESULTS:

Mother Liquor P.S. Conc. = Undetermined

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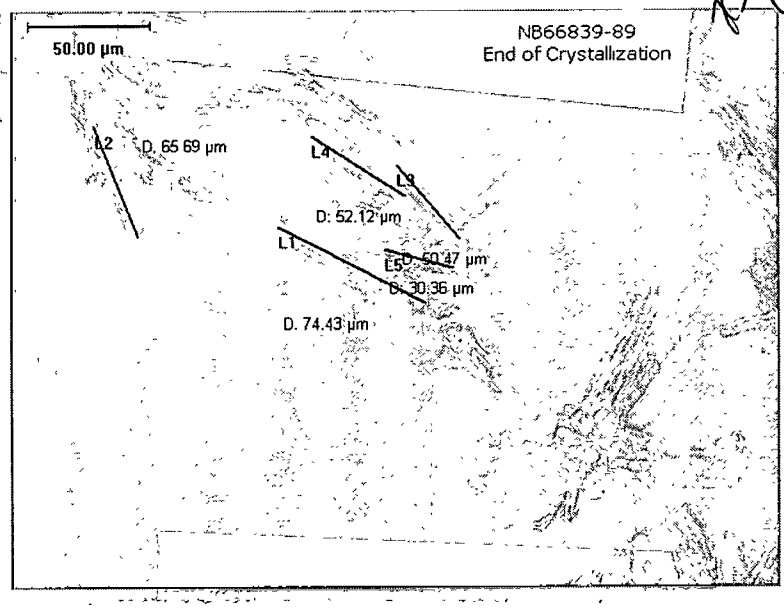

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TITLE: FRONT-RUN ISAA/H_2O CRYSTALLIZATION FOR YIELD DATA

OBJECTIVE: To determine typical yield for 50°C 95/5 ISAA/water phosphate salt crystallization finished at 10 L/kg.

PROCEDURE:

- Slurry 0.75 g phosphate salt (PPB1-2) in 3 g H_2O, 5 g FB and 50.75 g ISAA at 50°C in 250 mL Morton crystallizer. (250 rpm)
- Dissolve 1.5 g 85 wt% H_3PO_4 in 23.5 g ISAA.
- Add H_3PO_4 solution to heel at 2.5 mL/hr (12 hours)
- Hold at 50°C for 12 hours after addition has finished to "stress" yield. Cool to 20°C in 30 min

DATA:

0.7489 g PPB1-2 added

Freebase Addition:

Concentration in ISAA by HPLC:

Vial = 17.0853 g

Vial + Diluent = 33.2721 g

Vial + Dil. + Sample = 33.3556 g

HPLC Count = 7045.79 ⟹ 171.6 mg/g

Empty Beaker = 68.24 g

Beaker + FB = 96.78 g

Beaker after addition to heel = 68.63 ⟹ 28.15 g × .1716 = 4.83 g FB charged

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DATA (cont.):

- Amount of ISAA added = 28.15 g - 4.83 g = 23.32 g
- 27.15 g pure ISAA charged for total of 50.47 g
- 3 g H_2O charged

Final Heel Concentration:

0.7489 g Phosphate Salt

50.47 g ISAA

3.0 g H_2O

4.83 g Freebase

$$1.05 \text{ eq } 85 \text{ wt\% } H_3PO_4 = \frac{4.83}{407.3} \times 98 \text{ g/mol} \times \frac{1}{0.85} \times 1.05$$

$$= 1.436 \text{ g (1.5 g actually dissolved in 23.5 g ISAA)}$$

Tare Weights:

~~Dist~~ Mother Liquor Flask = 184.38 g

Filter = 117.55 g 12-MAR-2003

Mother Liquor + Flask = 275.18 g

Wetcake + Filter = 125.11 g

Drycake + Filter = 124.15 g

Theoretical PS = $0.7489 \text{ g} + (4.83 \text{ g})\left(\frac{505.3}{407.3}\right) = 6.74 \text{ g}$

Actual (Assuming Purity = 100%) = 124.15 - 117.55 = 6.6 g

Yield = 6.6/6.74 = **97.9% yield**

By HPLC, 0.101 g lost to ML's = $\frac{.101}{6.74}$ = **1.5% loss**

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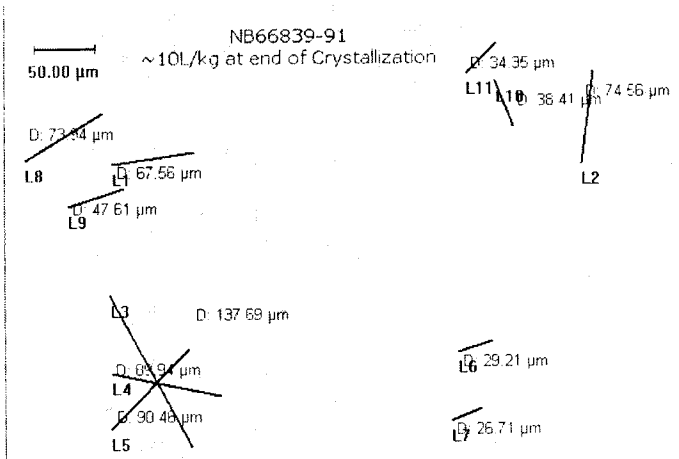

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TITLE: REACTIVE CRYSTALLIZATION IN 97/3 ISAA/WATER @ 50°C WITH 12:1 BATCH: HEEL RATIO

OBJECTIVE: To grow large crystals without agglomeration using ISAA/water reactive crystallization

PROCEDURE:

- Slurry 0.5 g PPB1-2 Phosphate Salt in 68 g ISAA, 5 g Freebase, 2.3 g DIW @ 50°C
- Dissolve 1.5 g 85 wt% H_3PO_4 in 6 g ISAA and 0.23 g DIW
- Using syringe pump, add H_3PO_4 solution to heel over 12 hours (0.667 mL/hr)
- Age at 50°C additional 10 hours after addition.
- Cool to 20°C over 1 hr.
- Age at 20°C 30 min.
- Vacuum Filter
- Dry at 70°C under full vacuum.

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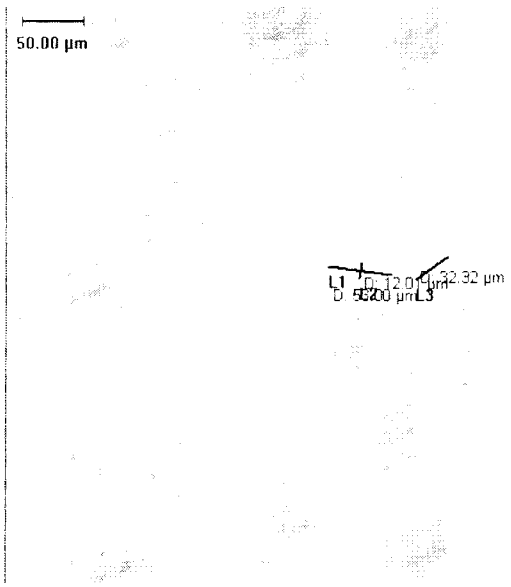

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TITLE: REACTIVE CRYSTALLIZATION IN 95/5 ISAA/Water AT 40°C WITH 8:1 BATCH: HEEL RATIO

OBJECTIVE: Control agglomeration by reducing temperature to decrease growth kinetics.

PROCEDURE:

- Slurry 0.75 g PPB1-2 Phosphate Salt in 68 g ISAA, 5 g Freebase and 3.8 g H_2O (DIW) @ 40°C
- Dissolve 1.5 g 85 wt% H_3PO_4 in 6 g ISAA and 0.4 g H_2O (DIW).
- Add H_3PO_4 solution to heel over 12 hours using a syringe pump (0.667 ml/hr).
- Age at 40°C 10 hours after addition
- Cool to 20°C over 1 hour
- Age at 20°C 30 min.
- Vacuum filter.
- Dry at 70°C under full vacuum.

OBSERVATIONS:

- Appears that Freebase "crashes out" about 1 hour into crystallization as a "web of needles." Stirring increased to 400 rpm to aide mixing.

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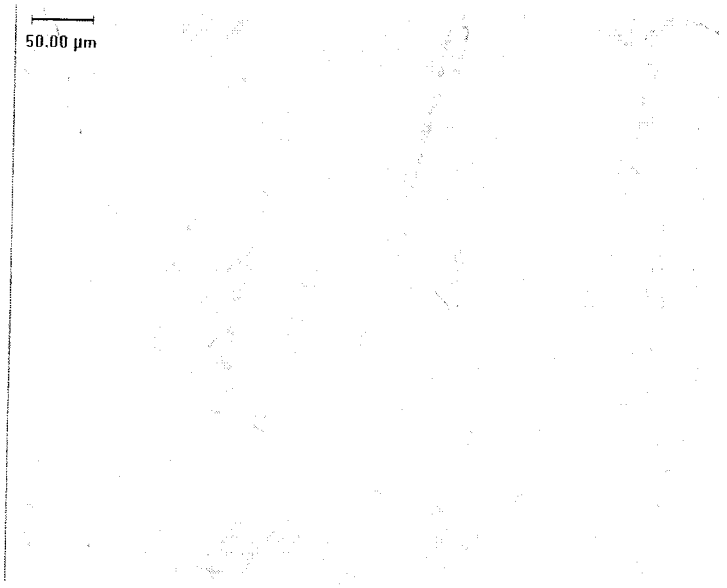

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TITLE: PHOSPHATE SALT BREAK TRACKING Na^+ and K^+ REJECTION

OBJECTIVE: To determine rejection of salts to individual cuts of salt break

PROCEDURE:

- Charge 51.7 g Phosphate Salt in 620 mL THF and slurry
- Dissolve 17.2 g KOH and 9.17 g NaCl in 140 mL DIW. Add solution to THF slurry.
- Agitate 30 min
- Settle and cut aqueous layer.
- Dissolve 30 g NaCl in 140 mL water, add to THF cut and agitate 30 min.
- Settle and cut aqueous layer.
- Submit samples to heavy metals lab for Na^+, K^+
- Submit samples to AR for Cl^- titration.

DATA:

Phosphate Salt (NB70223-163) = 51.70 g
KOH (Fisher 026214) = 17.13 g
NaCl (Fisher 028258) = 9.11 g

1st Cut

Water	THF
Beaker Tare = 110.25 g	Beaker Tare = 401.05 g
Beaker + Cut = 219.70 g (~90 mL)	Beaker + Cut = 1038.26 g (~676 mL)

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Brine Wash:

NaCl = 29.94 g

2nd Cut

Water	THF
Beaker Tare = 108.59 g	Beaker Tare = 399.64 g
Beaker + Cut = 306.28 g (~180 mL)	Beaker + Cut = 993.58 g (~620 mL)

RESULTS:

	Na^+	K^+
1st THF =	34 mg/L	142 mg/L
1st Water =	38,800 mg/L	110,800 mg/L
2nd THF =	157 mg/L	< 10 mg/L
2nd Water =	63,800 mg/L	2,200 mg/L

MASS BALANCE:

1st Cut = $9.11\ g\ NaCl \times \frac{23\ g\ Na^+}{58.5\ g\ NaCl} = 3.58\ g\ Na^+$

Sodium: THF = $34\ mg/L \times 0.675 = 0.023\ g\ Na^+$

Water = $38,800 \times 0.090 = 3.49\ g\ Na^+$ → 98.2% Mass Balance

0.65% of Sodium in THF, 99.35% in Water

Potassium: 11.94 g K^+ Total → 83.5% in Water, 0.8% in THF

2nd Cut = 29.94 g NaCl = 11.77 g Na^+ + 0.023 g Formed = 11.79 g

97.4% in Water, 0.8% in THF

Impossible to Exceed 0.2 weight % alkali phosphate salt crystallization.

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TITLE: PHOSPHATE SALT CRYSTALLIZATION IN 95/5 ISAA/WATER, 50°C, 1ST CYCLE

OBJECTIVE: Begin heel cycling experiments at low volumes.

PROCEDURE:

- Plan 0.75 g PPBI-2 in 250 ml Morton Crystallizer.
- Plan 5 g Fruebar, 68.25 g ISAA and 3.8 g DIW with PPBI-2 and slurry at 250 rpm and 50°C
- Dissolve 1.5 g 85 wt% H_3PO_4 in 6 g ISAA and 0.4 g DIW
- Add H_3PO_4 solution to heel over 12 hours (0.667 mL/hr).
- Age at 50°C ~10 hours after addition ended
- Cool to 20°C over 1 hour
- Age at 20°C for 3 hours.

OBSERVATIONS:

- Good slurry over entire addition

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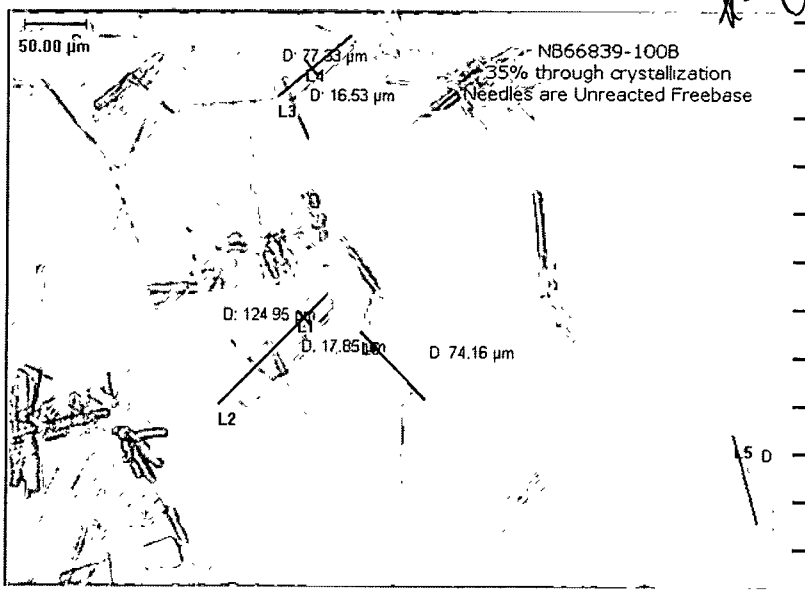

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TITLE: 2nd Cycle small scale heel cycling

OBJECTIVE: Continue small scale heel cycling experiments

PROCEDURE:

- Wetmill NB66839-100 using IKA "probe" at 4,000 min^{-1} for 1 min.
- Assuming 85 mg PS/g slurry NB66839-100, place 8.8 g wetmilled slurry (0.75g Solids, 7.65 g ISAA, 0.4 g DIW) in Morton Crystallizer.
- Add 5g Freebase, 60.6 g ISAA and 8.4 g DIW to slurry. Agitate at 240 rpm and 50°C.
- Dissolve 1.5g 85 w% H_3PO_4 in 6 g ISAA and 0.4g DIW.
- Add H_3PO_4 solution to heel over 12 hours (0.667 ml/hr)
- Age @ 50°C ~10 hours after addition completed.
- Cool to 20°C over 1 hour.
- Age at 20°C for 1 hour.

OBSERVATIONS:

- Freebase crashed out after ~ 10% H_3PO_4 added
- Addition continued. Good slurry after all H_3PO_4 added.

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Conclusions: Crystals were small rods and needles.
Pictures saved on CERD "Process" Folder.

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TITLE: 3rd Cycle of Small Scale Heel Cycling

OBJECTIVE: To run 3rd cycle in heel cycling experiment at small scale (93/7 ISAA/WATER)

PROCEDURE:

- Place unmilled NB66839-102 (8.8g Total slurry) in 250mL Morton crystallizer.
- Add 5g Freebase with 60.6g ISAA and 5.2g DIW (to make 7% water) to seed. Agitate at 250 rpm at 60°C.
- Dissolve 11.5g 85wt% H_3PO_4 in 6g ISAA and 0.56g DIW.
- Add H_3PO_4 solution to heel over 12 hours (0.667 mL/hr).
- Age at 60°C. 1 hour
- Cool to 20°C uncontrolled
- Let slurry sit over weekend.

OBSERVATIONS:

- Seed dissolved. Add another 2g NB66839-102.
- Seed dissolved again. Add another 2g NB66839-102.

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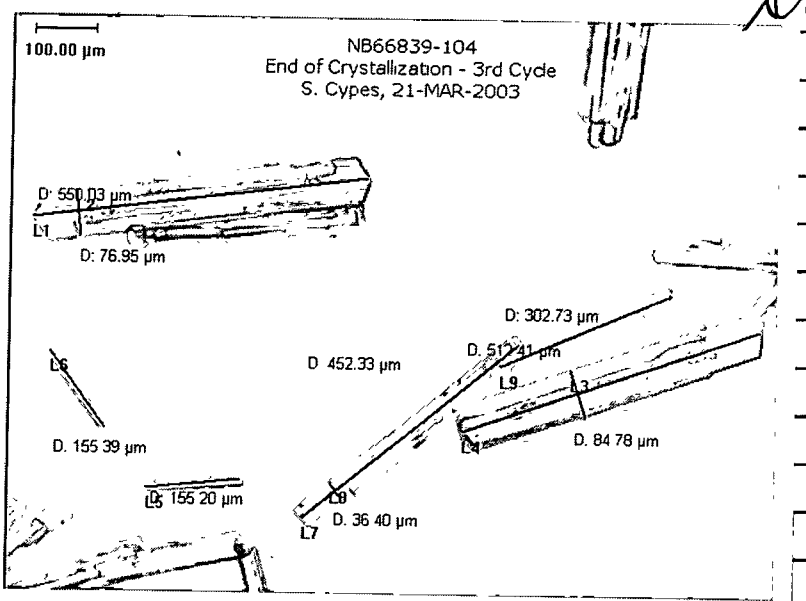

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TITLE: Large Scale 1st Cycle 95/5 ISAA/WATER PURGE CRYSTALLIZATION

OBJECTIVE: To perform heel cycling experiments on larger scale.

PROCEDURE:

- Wetmill NB66839-104 using IKA "probe" at max rpm for 1 min.
- Place 36 g of NB66839-104 slurry (Assume 85 mg PS/g slurry, 3 g solids, 30 g ISAA, 2.26 g DIW) in 500 ml Resin kettle fitted w/ FTIR
- Place 20 g FB (solvent switch part from THF and remainder from ISAA salt break NB66939-77) with 243 g ISAA and 12.94 g DIW with seed.
- Agitate heel at 450 rpm (tip speed = 1.2 m/s = min. of ST-30E in SSO) and batch temp of 60°C (jacket = 65°C).
- Dissolve 5.66 g 85 w% H_3PO_4 (1.00 eq) in 24 g ISAA and 1.6 g DIW
- Add H_3PO_4 solution to heel over 12 hours (2.75 ml/hr) measuring L-715 solution concentration w/ FTIR.
- Age at 60°C for 4 hours after addition.
- Cool to 20°C over 1 hour.
- Age at 20°C for 30 min.

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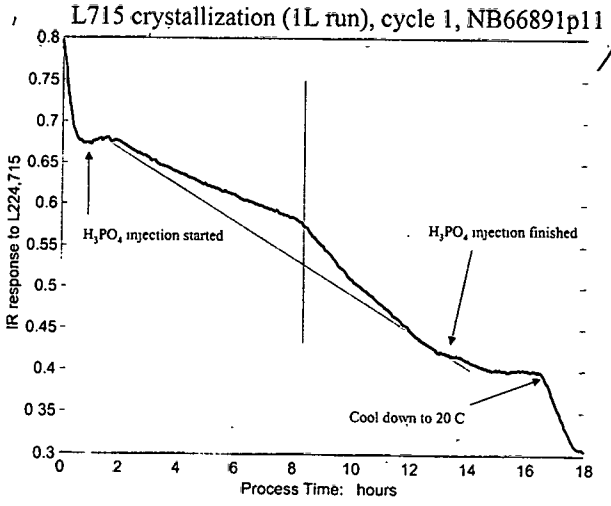
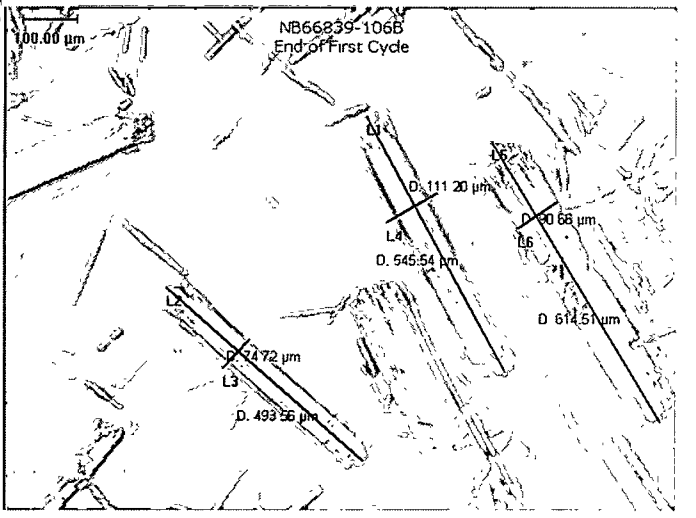


25-MAR-2003

Microscope Images

25-MAR-2003



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TITLE: LARGE SCALE, 2nd Cycle 95/5 ISAA/WATER AT 5:1 BATCH:HEEL RATIO

OBJECTIVE: To continue heel cycling experiment.

PROCEDURE:

- Based on first cycle's IR data, super saturation was not relieved quickly enough and nucleation therefore occurred. This can be fixed by either increasing the amount of surface area for growth, or slowing acid addition rate.
- Wetmill 62 g of slurry from 1st Cycle (NB66839-106) using "batch prolu wetmill" at 10,000 min^{-1} for 2 min.
- Charge wetmilled slurry to 500 mL crystallizer. (Contains 5 g Solids, 54 g ISAA, 2.85 g DIW)
- Charge 20 g Freebase, 243 g ISAA and 12.8 g DIW to heel. Stir at 450 rpm and 60°C.
- Dissolve 5.66 g 85 wt% H_3PO_4 (1.0 eq) in 22.6 g ISAA and 1.5 g DIW. Add over 12 hours (2.67 mL/hr) following IR response.
- Age at 60°C for ~10 hours after addition.
- Cool to 20°C over 1 hour
- Age at 20°C for 30 min.

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RESULTS:

Microscope Images:

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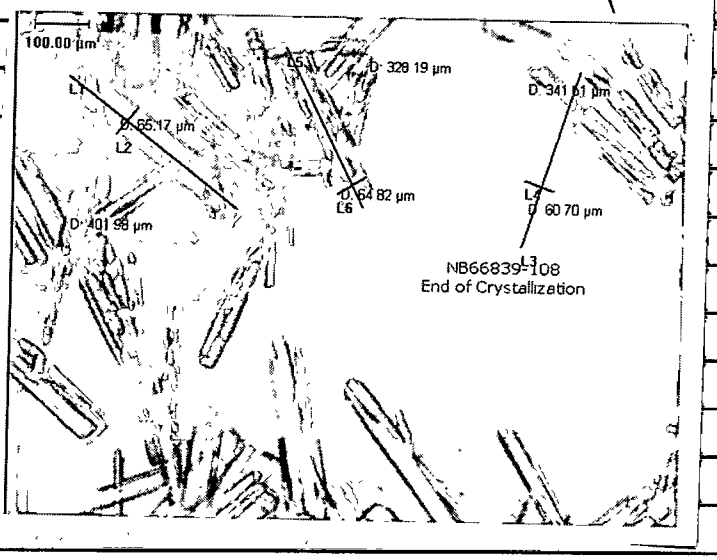

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TITLE: OHEL RUN OF REACTIVE CRYSTALLIZATION IN '95/5 ISAA/WATER

OBJECTIVE: To perform OHEL run of pure reactive crystallization in 95/5 ISAA/water in preparation for Lot 20 Rework in SSO

PROCEDURE:

- Obtain 5g Freebase by charging 76g of THF cut from salt break NB66839-98 into 500 mL Round Bottom
- THF removed by rotavap at 40°C and 280 mtorr.
- Added 11.5g Isoamyl Alcohol (Aldrich TU1147BDU) to resulting oil. Took Sample #10 and HPLC.
- Complete solvent switch using feed and bleed method with ISAA. Submit Sample #11 of final batch and HPLC.
- Submit Sample #12 of THF/Water/ISAA distillates.
- Resulting batch weighs 19.5g (~4.5g Freebase and 15g ISAA)
- Charge batch into 250 mL Morton Crystallizer.
- Dilute with 53g ISAA and 3.8g DIW.
- Charge 0.75g Phosphate Salt seed to crystallizer (PPB1-2).
- Dissolve 1.5g 85wt% H_3PO_4 in 6g ISAA and 0.4g DIW. Place in 50 mL syringe and add to heel over 12 hours at 60°C and 250 rpm agitation.
- Samples #13 and #14 taken of heel slurry before H_3PO_4 addition begun.

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- Age. final slurry at 60°C. ~ 8 hours after addition finished.
- Cool to 20°C over 1 hour.
- Age at 20°C for 30 min.
- Vacuum Filter. Submit Samples #15 and #16.
- Wash cake w/ 4 L/kg ISAA. Submit Samples #17 and #18.
- Dry at 70°C under full vac for 2 hours. Submit Sample #19.

RESULTS:

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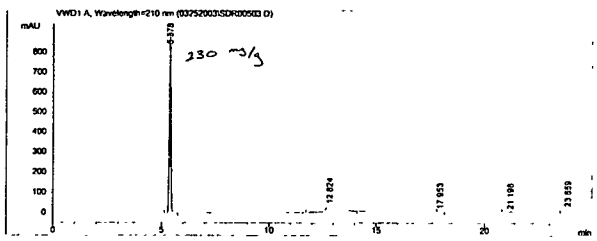
Data File C:\HPCHEM\HPLC5027\DATA\03252003\sdr00503.D Sample Name: NB66839-110
OHEL Run, Sample #10, ISAA + FB Concentrate, 400x dilut
ion

Injection Date : 3/25/03 2:44:48 PM Seq. Line : 4
Sample Name : NB66839-110 Vial : 1
Acq Operator : sdr Inj : 1
Inj Volume : 5 µl
Sequence File : C:\HPCHEM\HPLC5027\SEQUENCE\SDR20MAY.S
Method : C:\HPCHEM\HPLC5027\METHODS\L-715 M
Last changed : 3/4/03 12:01:16 PM by sdr
L-224-715 In-Process Method using Waters Symmetry C18 Column as developed by Process Research
April 2002



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1 VWD1 A, Wavelength=210 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.378	VB	0.0746	4301.11328	901.74915	77.2420
2	12.824	PB	0.4661	877.45636	26.92889	15.7579
3	17.953	VP	0.1088	13.52320	1.94464	0.2429
4	21.198	BB	0.3460	39.38500	1.70013	0.7073
5	23.859	BBA	0.2120	336.88242	21.32047	6.0499
Totals :				5568.36026	953.64327	

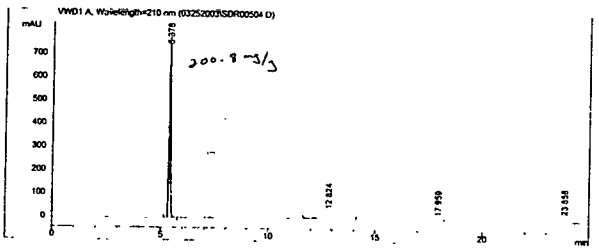
Results obtained with enhanced integrator!

*** End of Report ***

HPLC5027 3/25/03 3:07:04 PM sdr Page 1 of 1

Data File C:\HPCHEM\HPLC5027\DATA\03252003\sdr00504.D Sample Name: NB66839-110B
Sample #11, After solvent switch to ISAA, 400x dilution

Injection Date : 3/25/03 3:11:26 PM Seq. Line : 5
Sample Name : NB66839-110B Vial : 2
Acq. Operator : sdr Inj : 1
Inj Volume : 5 µl
Sequence File : C:\HPCHEM\HPLC5027\SEQUENCE\SDR20MAY.S
Method : C:\HPCHEM\HPLC5027\METHODS\L-715.M
Last changed : 3/4/03 12:01:16 PM by sdr
L-224-715 In-Process Method using Waters Symmetry C18 Column as developed by Process Research
April 2002



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: VWD1 A, Wavelength=210 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.378	VB	0.0742	3764.99683	794.97876	75.5331
2	12.824	PB	0.4657	871.10321	26.86242	17.4760
3	17.959	PP	0.1084	11.83345	1.70893	0.2374
4	23.858	BBA	0.2121	336.63037	21.29011	6.7535
Totals :				4984.56386	844.84022	

Results obtained with enhanced integrator!

*** End of Report ***

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Conclusions: All samples submitted (#10-#14 on 25-MAR-2003 and #15-#19 on 26-MAR-2003). No unusual observations noted during experiment.

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TITLE: LARGE SCALE, 3rd Cycle 95/5 ISAA/WATER AT 5:1 BATCH:HEEL RATIO

OBJECTIVE: To continue heel cycling experiment.

PROCEDURE:

- Wetmill NB66839-108 using IKA Ultra Turax T50 @ 10,000 min^{-1} for 5 min (Pictures taken w/ microscope).
- Place 59 g of wetmilled slurry in 500 ml crystallizer, with 20 g Freebase, 243.1 g ISAA, 12.8 g DIW. Agitate @ 450 rpm (Tip Speed = 1.2 m/s) and 60°C batch temperature.
- Wait for the freebase solution concentration to stabalize via TIR.
- Dissolve 5.66 g 85 wt% H_3PO_4 (1 eq) in 22.64 g ISAA and 1.5 g DIW.
- Using a syringe pump, add H_3PO_4 solution to heel over 12 hours (2.67 ml/hr)
- Age ~10 hours @ 60°C overnight.
- Filtered hot and submitted for PSD and XRD.

RESULTS:

XRD: Anamolous pattern on wetcake and 3.3 wt% LOD cake (after drying @ 70°C, full vac, 2 hours).

Monohydrate by TG, DSC, and XRD.

Drying: KF = 0.98% after 20 hours, KF = 0.4% after 72 hours

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Conclusions: no 3

Monohydrate: formic during heat cycling. Samples given to AR and Pharm R&D

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TITLE: Large Scale crystallization to produce phosphate salt monohydrate

OBJECTIVE: To produce the monohydrate phosphate salt for experimentation.

PROCEDURE:

- Dilute slurry of monohydrate NB66839-108 with ISAA to 2x final crystallization volume.
- Run slurry through IKA Pilot Labor for 50 recycles at 13,000 min^{-1}, ensuring temp. does not exceed 35°C.
- Place 118 g of slurry (5 g solids, 110 g ISAA, 2.8 g DIW) in 500 mL crystallizer at 60°C.
- Place 20 g of Fraction with 181 g ISAA and 13.6 g DIW in crystallizer @ 60°C. Agitate at 300 rpm and 60°C.
- Dissolve 5.66 g 85w% H_3PO_4 (1.00 eq) in 22.6 g ISAA and 1.5 g DIW.
- Add H_3PO_4 solution to hot over 12 hours (2.67 mL/hr).
- Shut off bath at end of addition.
- Let stir over weekend.
- Vacuum filter and dry at 70°C, Full Vac. for 2 hours.

RESULTS:

XRD confirms monohydrate. Batch given to Phys. Measurements.

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TITLE: IKA WETMILL STUDY OF NB66839-108

OBJECTIVE: To study wetmill effects on monohydrate phosphate salt using IKA Labor Pilot in UOps Lab.

PROCEDURE:

- Dilute final batch of NB66839-108 by 2x volume with Isoamyl Alcohol to fit on wetmill system
- Set bath temperature on vessel at -10°C.
- Attach vessel to IKA Labor Pilot and outlet of wetmill recycle back to vessel.
- Set wetmill speed to 13,000 min^{-1} with 3 superfine heads.
- Use draft of wetmill to produce flow. Flowrate ~100 mL/sec. according to calibration run by Ivan Lee.
- Take samples for PSD and microscopy after several recycle intervals.
- Make sure temp. of batch never exceeds 35°C. Stop mill and cool if temp. reaches 35°C.

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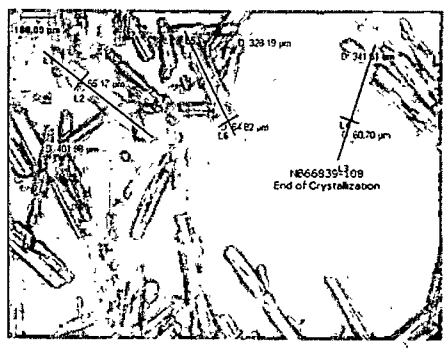
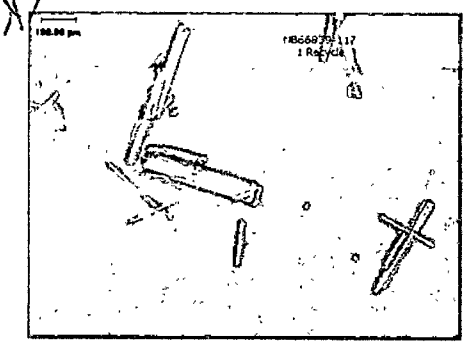
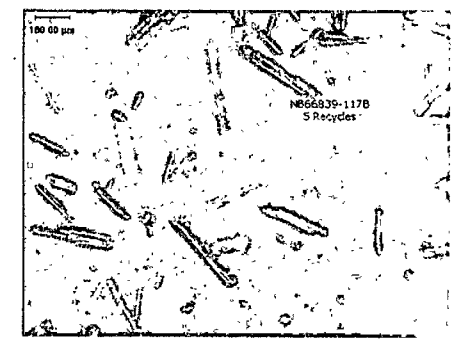
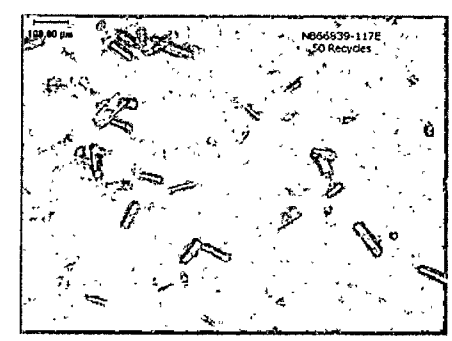
RESULTS:

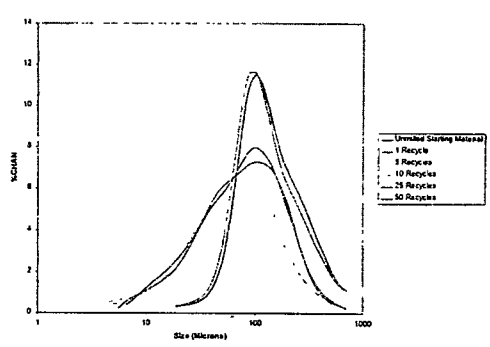


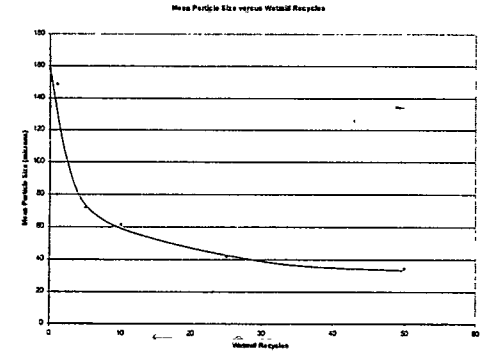






PSD Change versus Recycles on IKA Labor Pilot





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Ternary Plot

Solvent/100mg