Solid-Form Screening and Selection: Challenges and Strategies of Difficult Molecules

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Catalent Pharma Solutions

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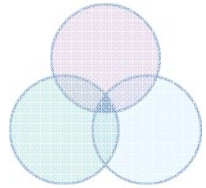
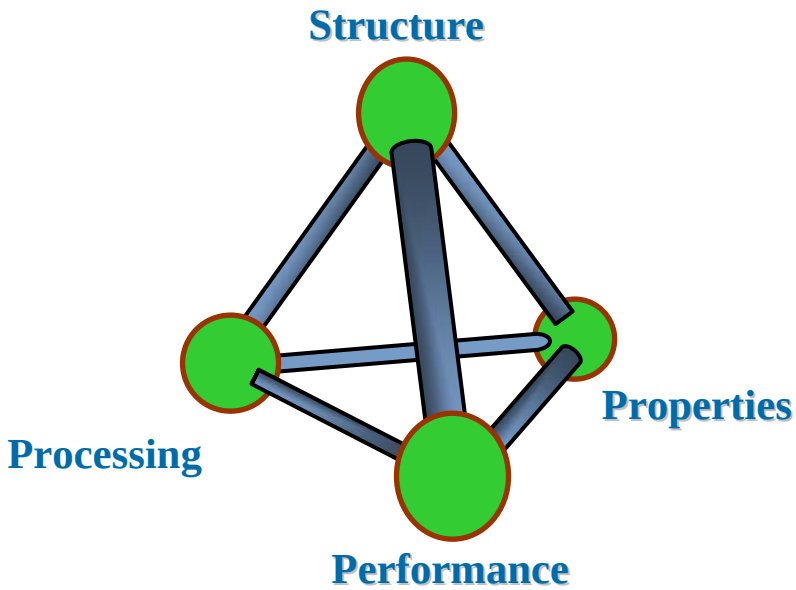
Objectives



- Pharmaceutical impact
- HT solid-state form screening and selection processes
- Can Raman spectroscopy differentiate ALL solid-forms of an API?
- Salt screening strategies to crystallize highly soluble and difficult to crystallize compound
- Polymorph screening and selection of highly polymorphic compounds/salts

Pharmaceutical Impact of Solid-State Forms

- Manufacturing Processes
  - API purification and isolation
  - Drug product (dosage form)
- Material Properties
  - Solubility (bioavailability)
  - Stability (chemical and physical)
  - Physical properties
- Product Performance
  - Efficacy
  - Safety
  - Shelf life
- Regulatory & IP
  - CMC
  - Patents

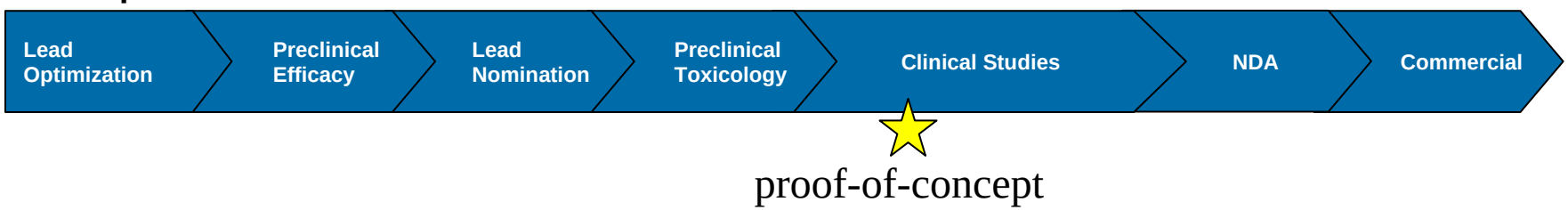


- C. Sun, *J. Pharm. Sci*. **2008,** *97*, 2855.
- G. Zografi, *AAPS/FDA Workshop on Evolving Science and Technology in Physical Pharmacy and Biopharmaceutics,* Baltimore, **May 2009.**

Fit-for-Purpose

- **Risks related to target and mechanism viability, toxicolology (tolerance, safety), efficacy, etc.**
- **Portfolio considerations**
- **Financial considerations**
- **Timeline considerations**

Development Timeline



P.Y. Chen, D. Igo, *Drug Dev. & Delivery*. **2011,** 11(1), pp.38-40.

Salt & Polymorph Screening: Timing and Scope

Solid-Form Screening

- 50-1000 crystallization experiments
- Yields uncertain (a few crystals to ~mg)
- Diverse range of solvent properties (e.g., viscosity, boiling point)
- Salts and crystal-form differentiation

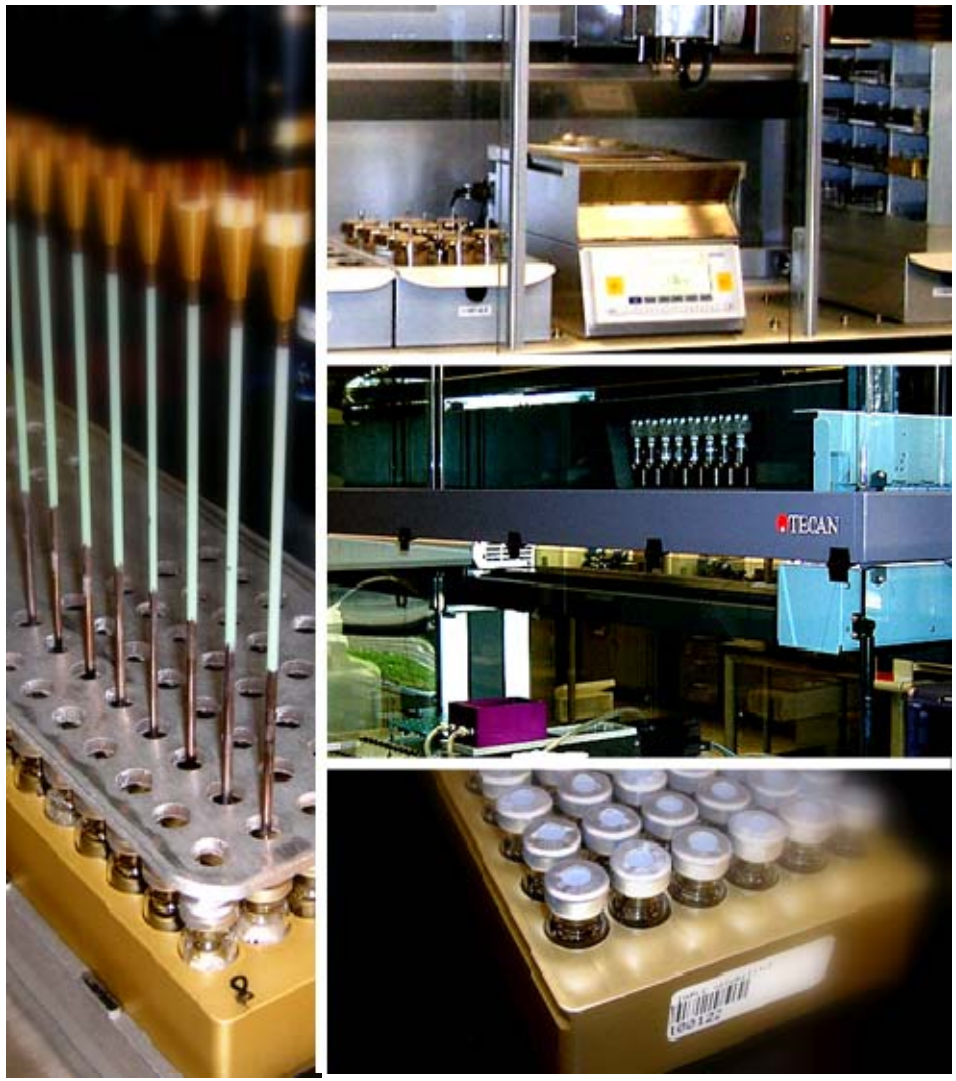
- Material limitations (1~5 g)
- Fast-to-decision (~1 month)

Development Timeline

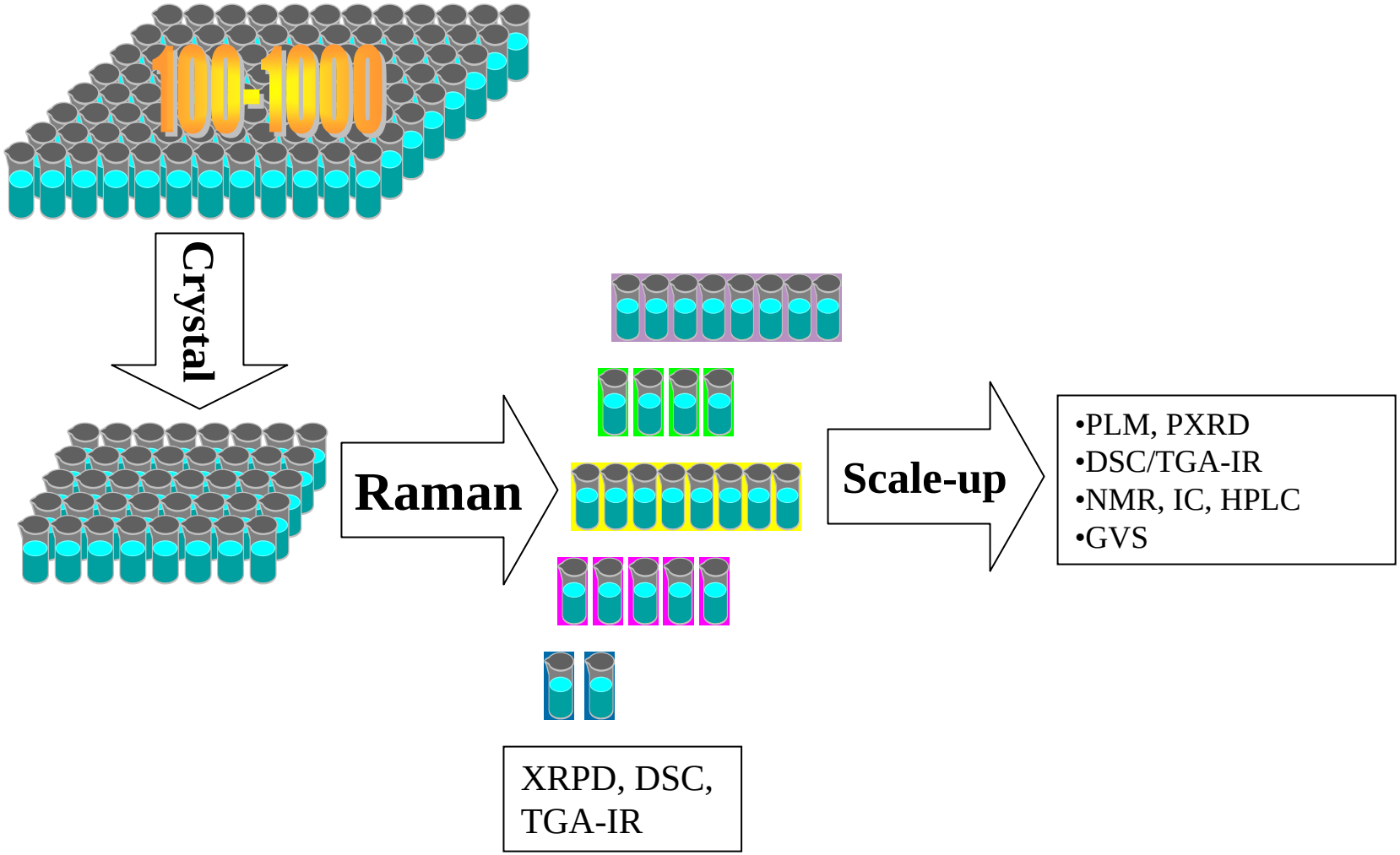
Optiform™ Technologies

- **High-throughput platform for salt, crystal-form, and cocrystal screening**
- **Developed and refined over the past ten years**
- **Applied to more than 500 compounds, spanning from early stage lead compounds through launched products**

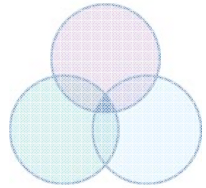
Filtration and Analysis Plate



Tiered Analytical Strategy



PXRD vs. Raman



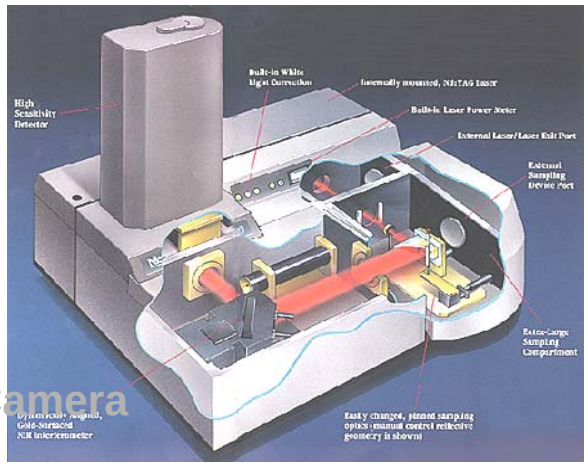
- PXRD
  - Gold standard
  - Sensitivity & sample size
  - Sample presentation
  - Data quality and interpretation (resolution, preferred orientation)
- Raman
  - Sample presentation
  - High sensitivity with small samples (single crystal)
  - Chemical information
  - Can Raman differentiate different crystals forms reliably?

Dispersive vs. FT-Raman

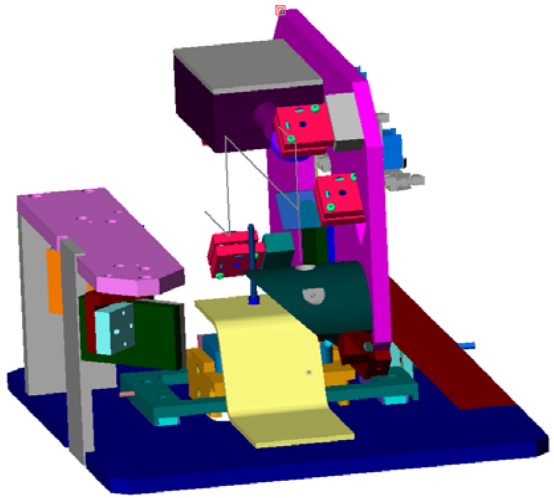
- Dispersive Raman Microscope
  - Better sensitivity (single crystal)
  - Microscope (μm laser spot) → Orientation effect
  - System stability and calibration introduce larger spectral variation
  - Local heating and fluorescence
- FT-Raman
  - Lower sensitivity with small samples (<50 μg)
  - Great spectral reproducibility (HeNe laser reference, < 0.1 cm^{-1})
  - Larger laser spot (50 μm ~ 1 mm)
  - Less fluorescent interference (1064 nm)

- Igo, D.; Chen, P. in *Application of Vibrational Spectroscopy in the Pharmaceutical Research and Development*, Ed. Pivonka, D.; Chalmers, J. and Griffiths, P., John Wiley & Sons, 2007, pp. 293-308.
- B.T. Bowie, D.B. Chase, P. R. Griffiths, Appl. Spectrosc. 54, 164A & 200A (2000).

FT-Raman Spectroscopy

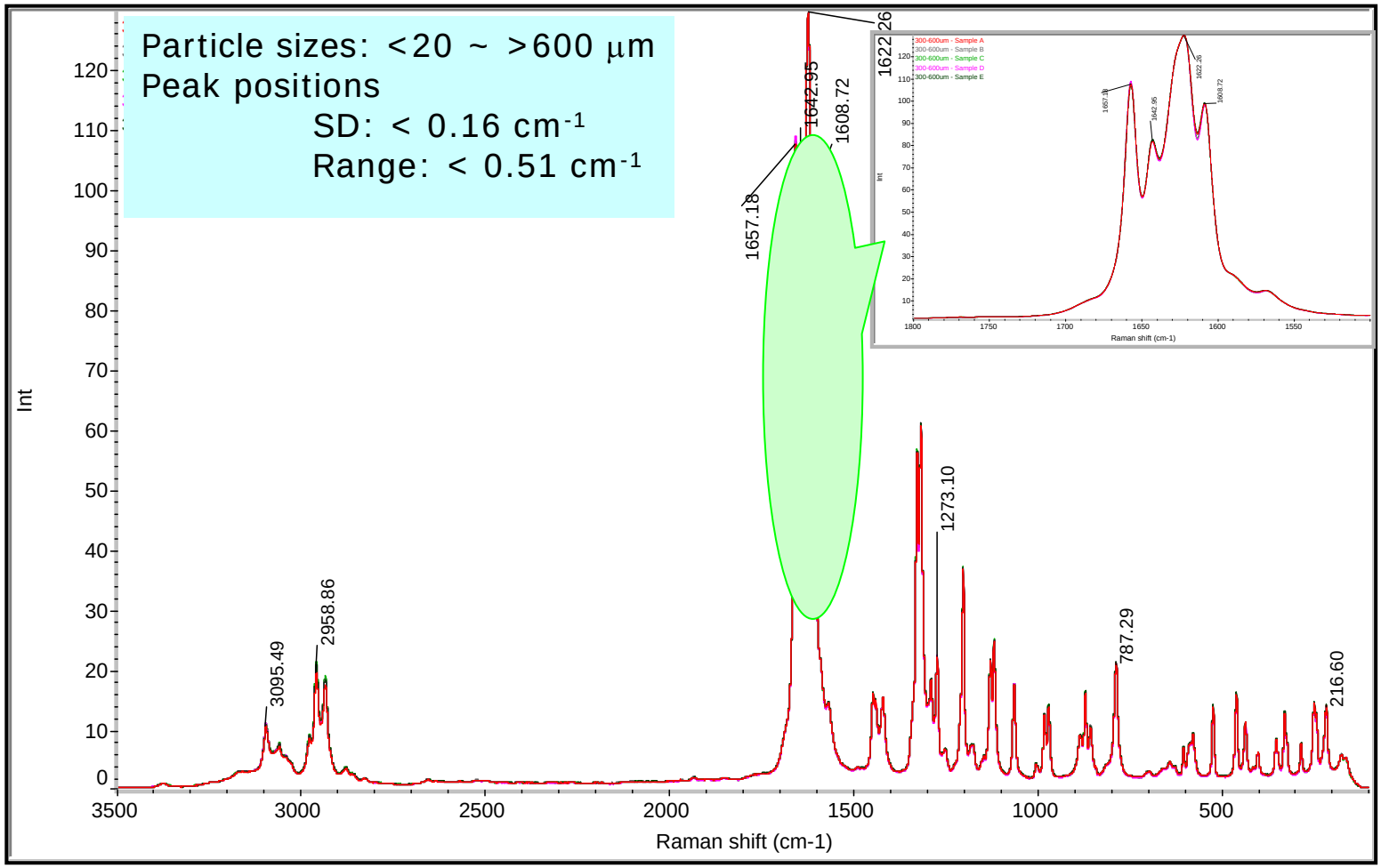


Camera



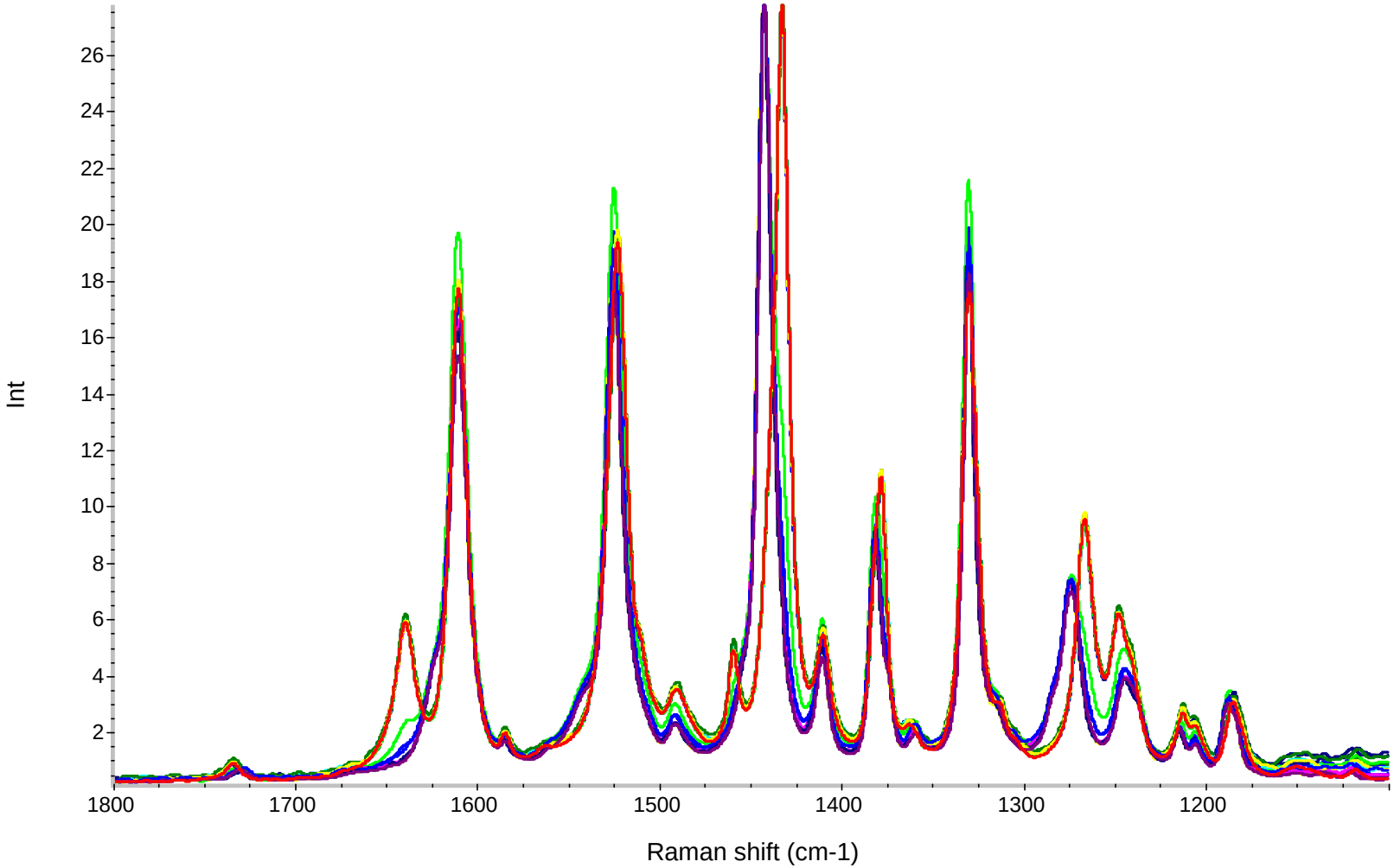
XYZ stage

FT-Raman Spectra of Compound A

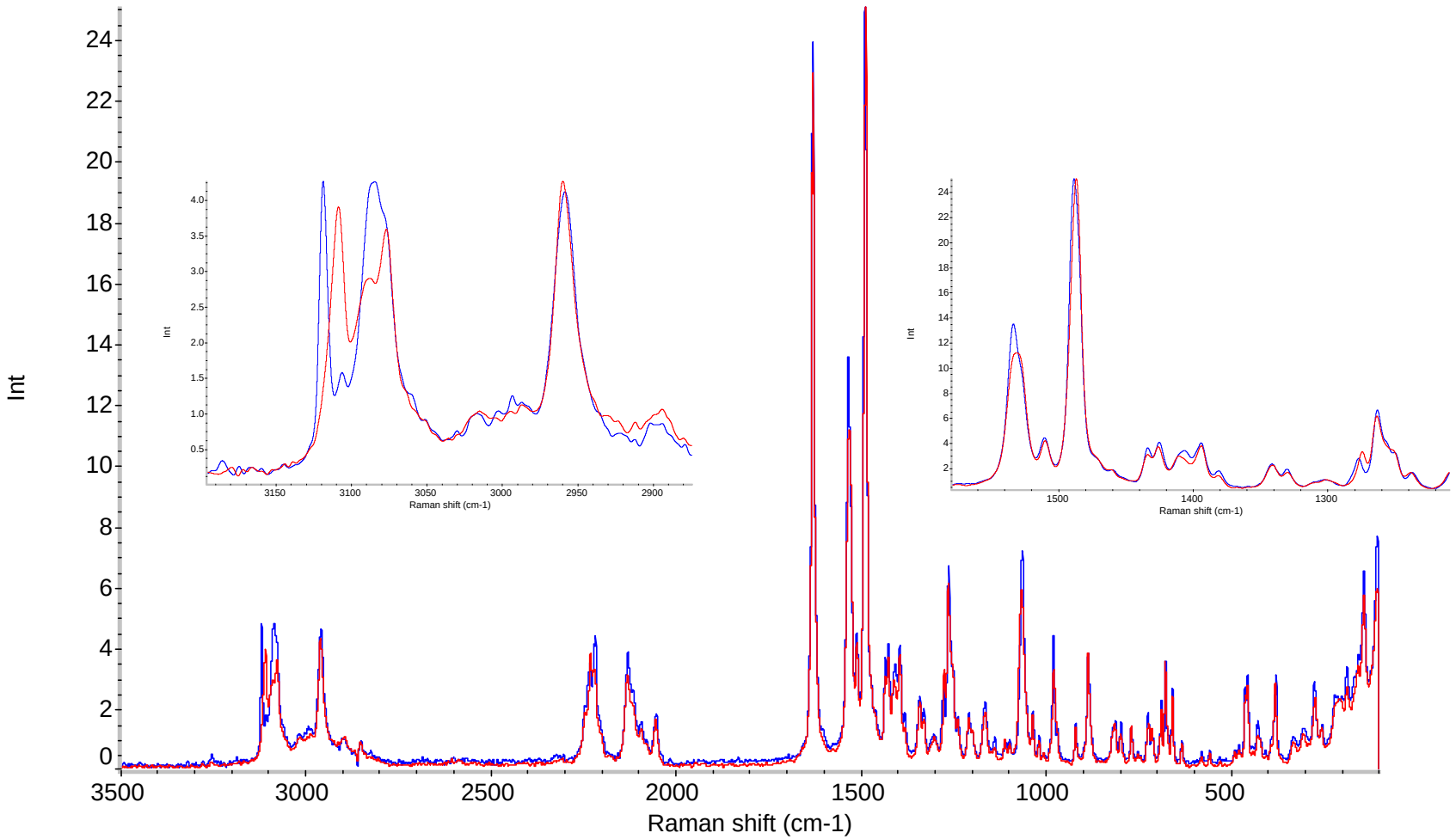


- S.M. Mehrens, U.J. Kale, X. Qu, *J. Pharm. Sci*. 94, 1354 (2005).

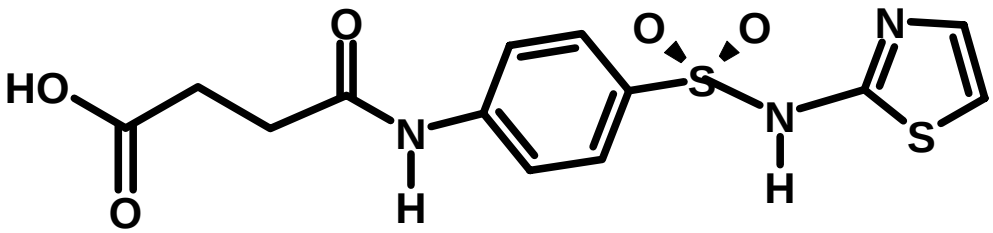
Compound B: Samples from Screening



Compound C: Two Different Polymorphs



Succinylsulfathiazole (SST)



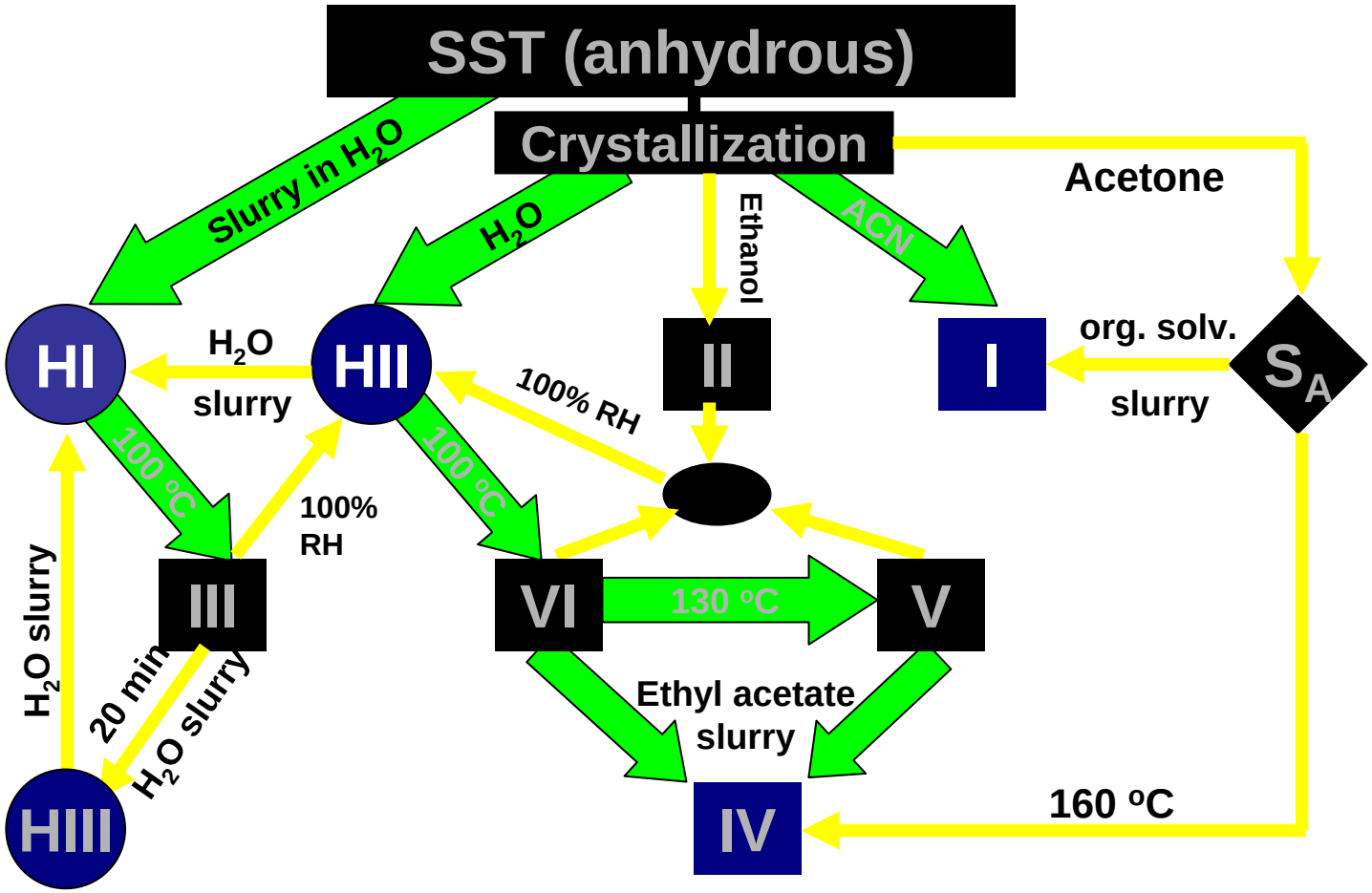
Six anhydrous polymorphs

Three polymorphic monohydrates

Solvates (acetone, 1-butanol)

A. Burger and U. J. Grieβer, Sci. Pharm. 57, 293-305 (1989)

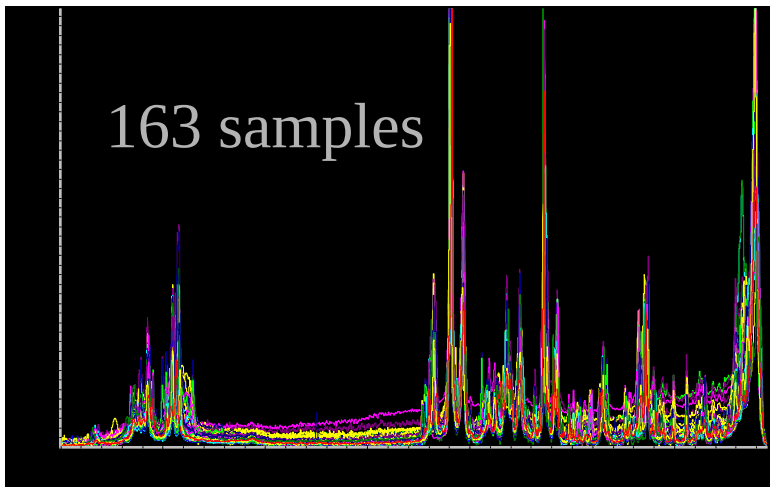
Inter-conversion Chart of SST

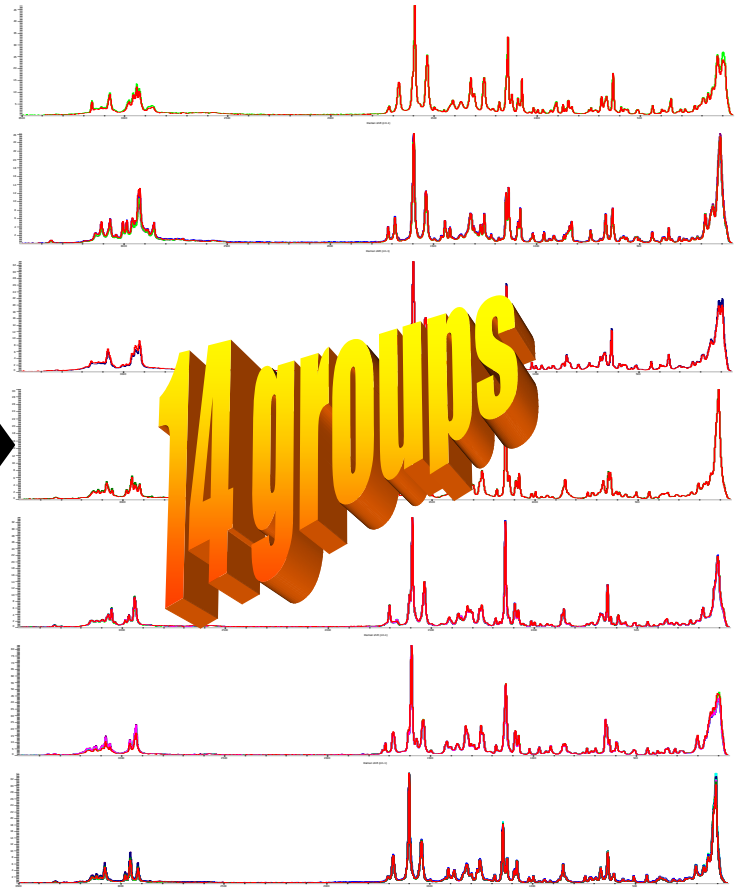


A. Burger, U.L. Grieβer, *Eur. J. Pharm. Biopharm*. 37, 118-124 (1991)

S.R. Burns; R.R.Pfeiffer; J.G. Stowell, *Solid-State Chemistry of Drugs*, 2nd Ed. p.171

Overlaid Spectra of All SST Samples





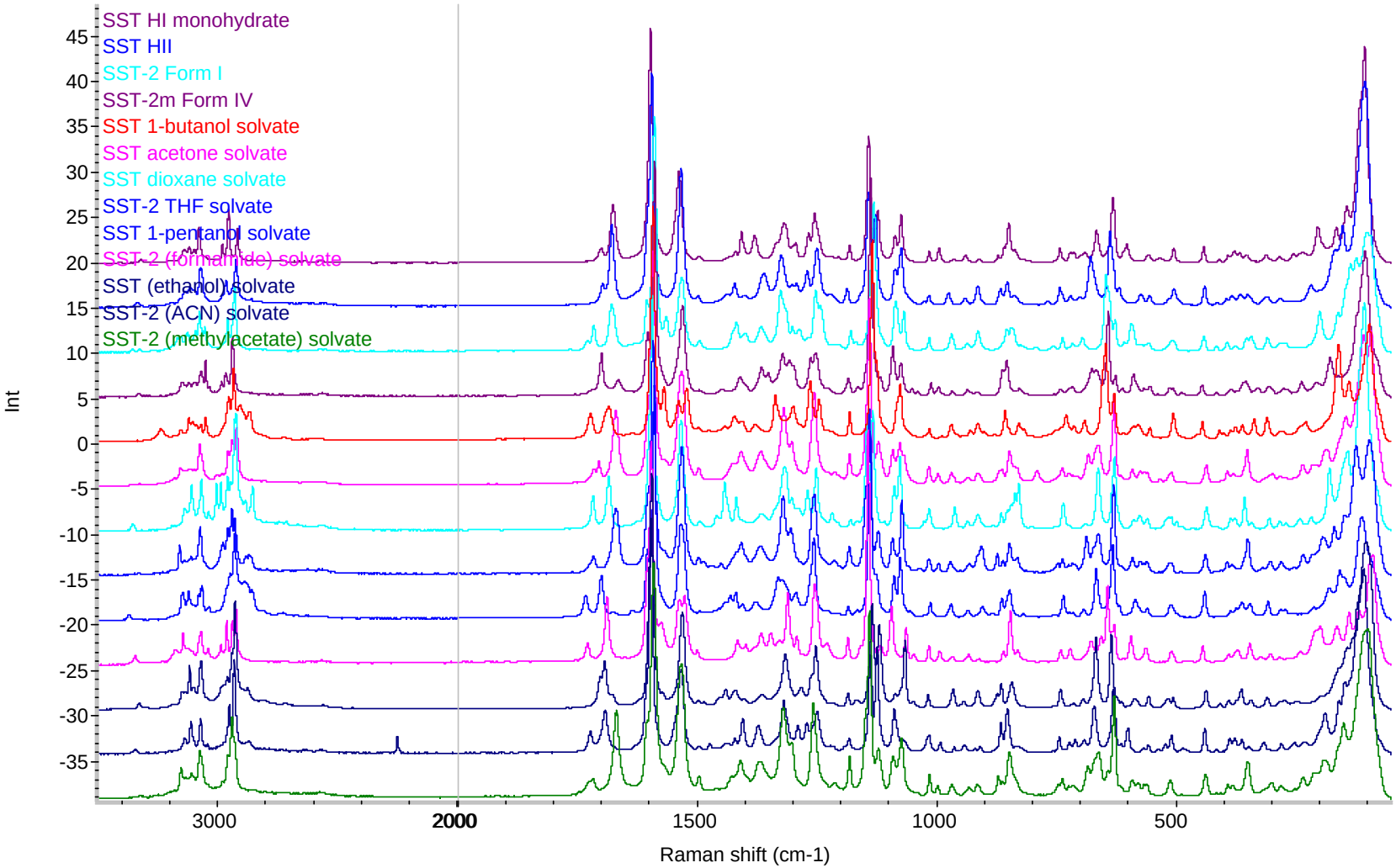
Temp. Cycling - 88

Fast Evaporation - 30

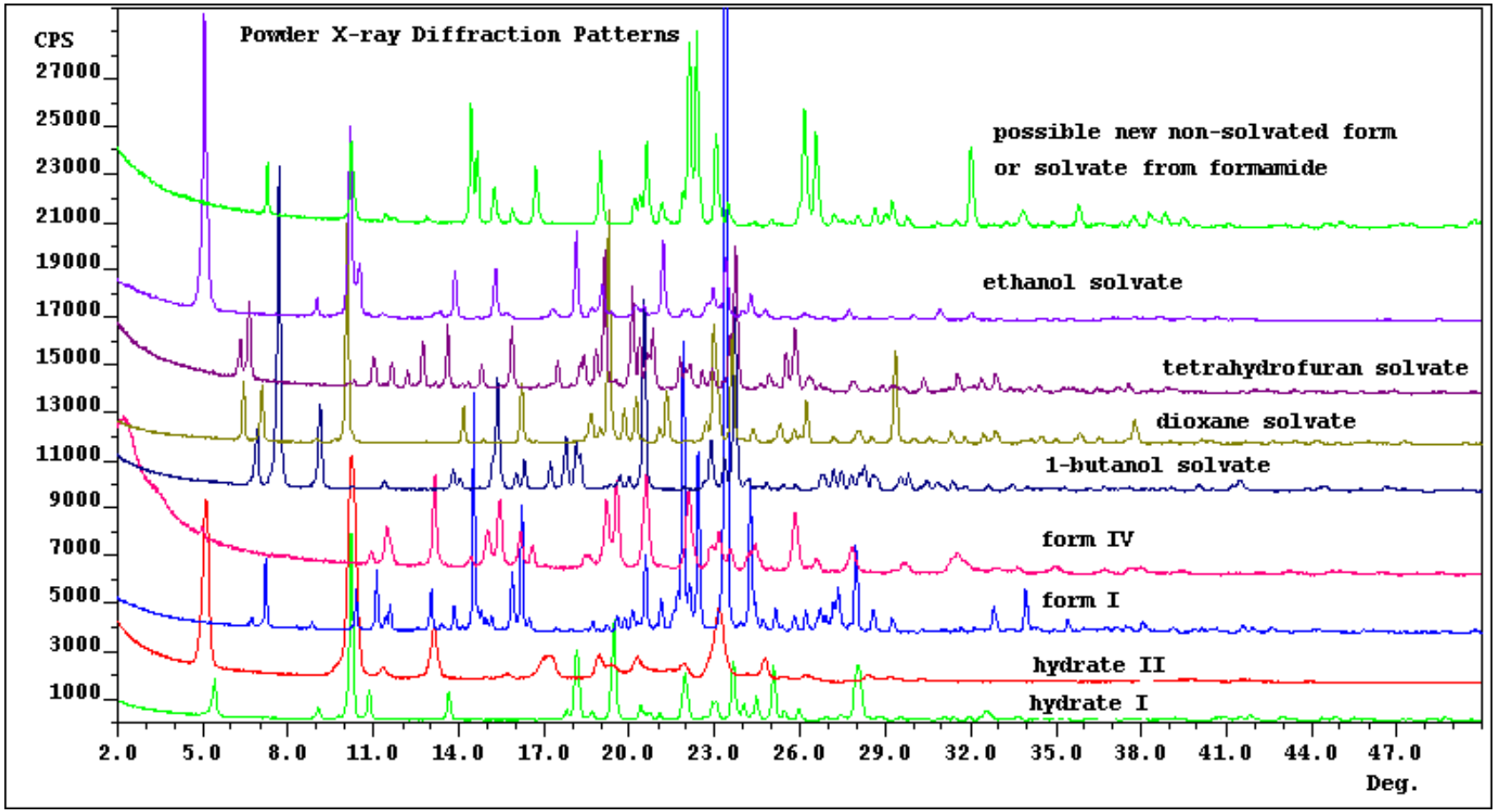
Slow Evaporation - 39

Cooling - 6

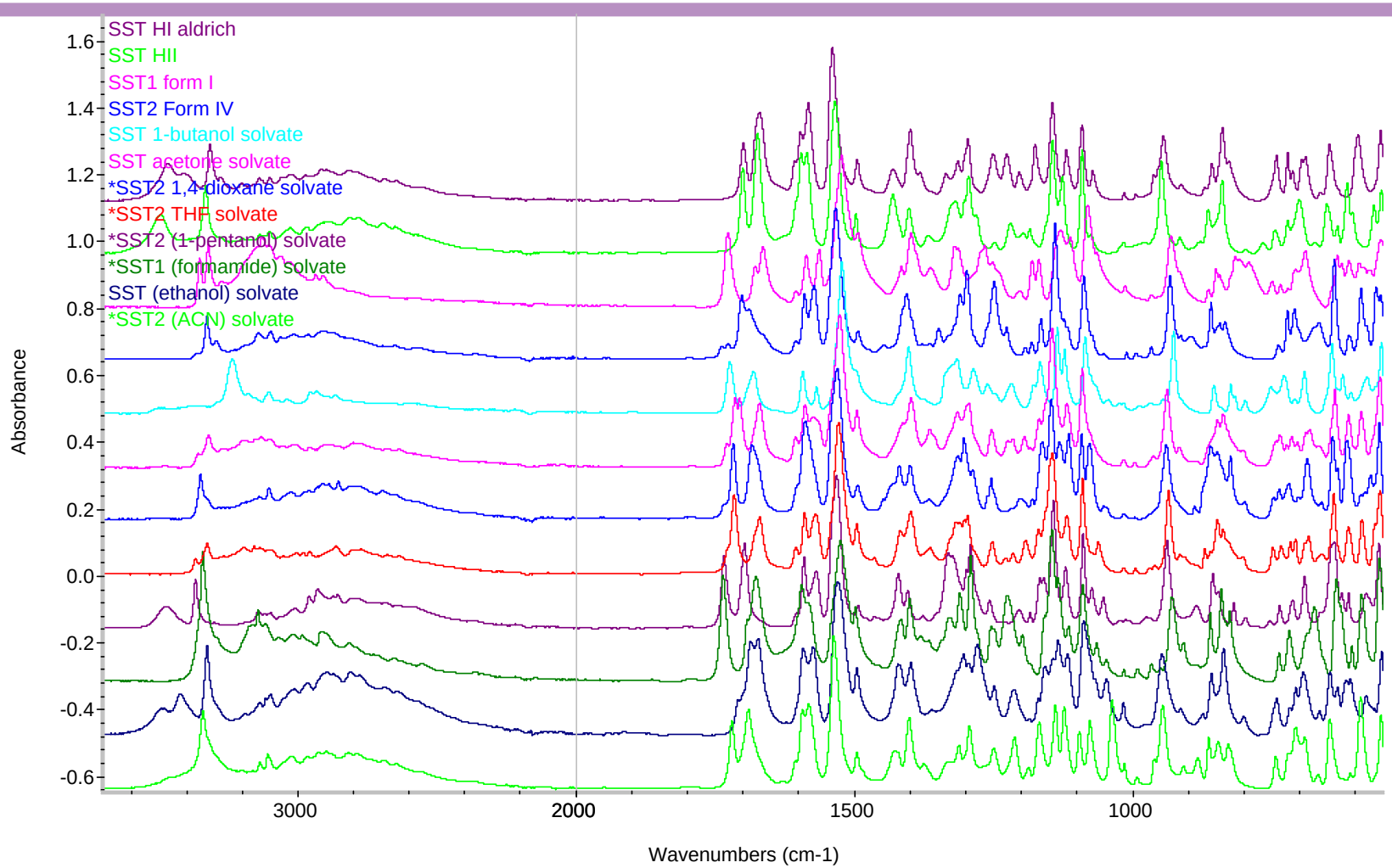
SST - Raman Spectra of Unique Groups



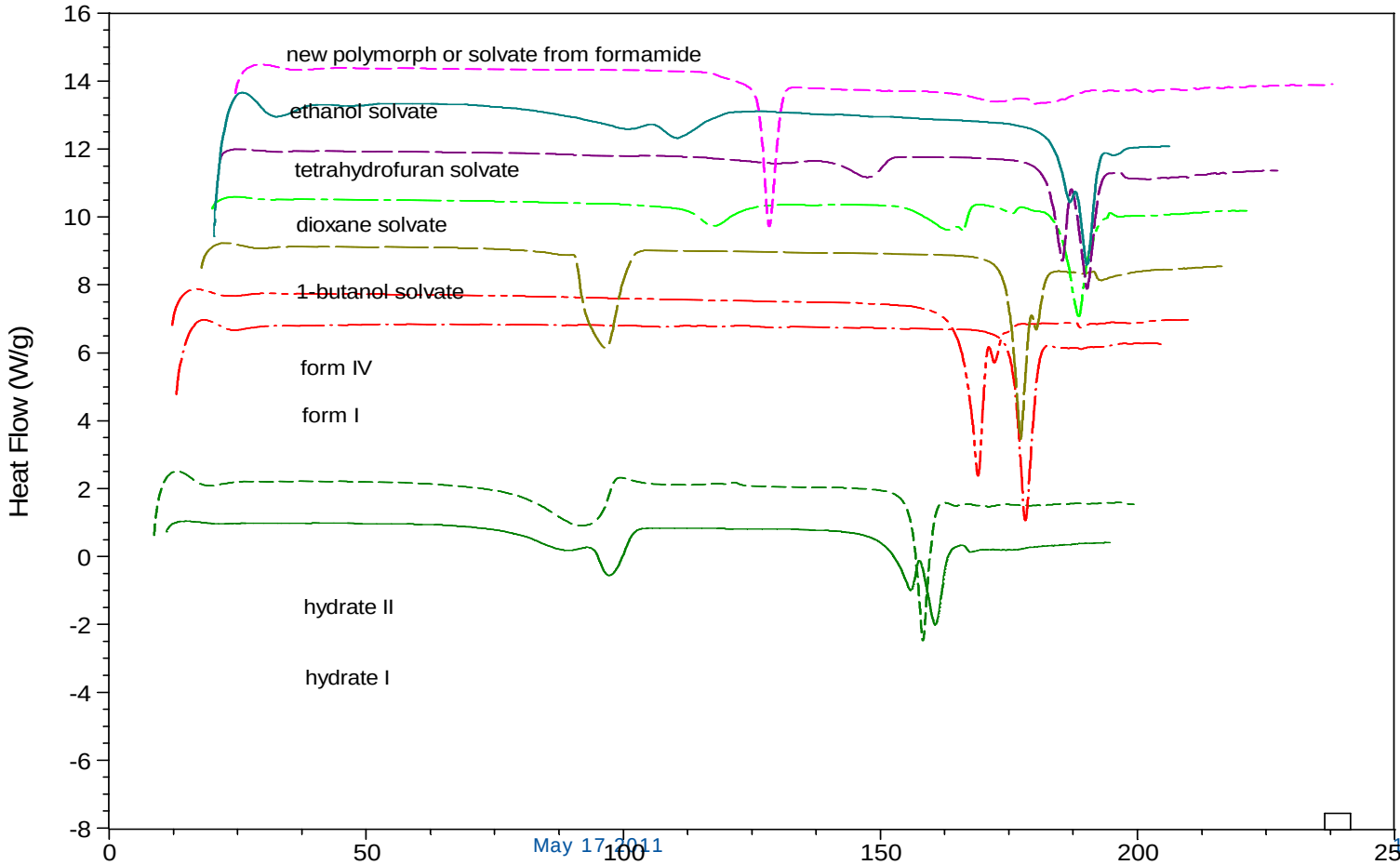
SST - XRD Patterns of Unique Groups



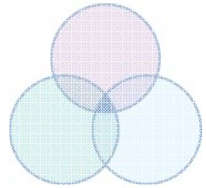
SST - IR Spectra of Unique Groups



SST - DSC of Unique Groups



Case Study #1: Improve Solubility and Polymorphism



Project Background

- MW: ~ 600
- high dose (100-400 mg IR tablet/capsule)
- pKa = 5.2 (acyl sulfonamide)

Free-acid (FA)

- Two polymorphs
- Practically insoluble
- Poor exposure (<1%F in dog)

Na Salt

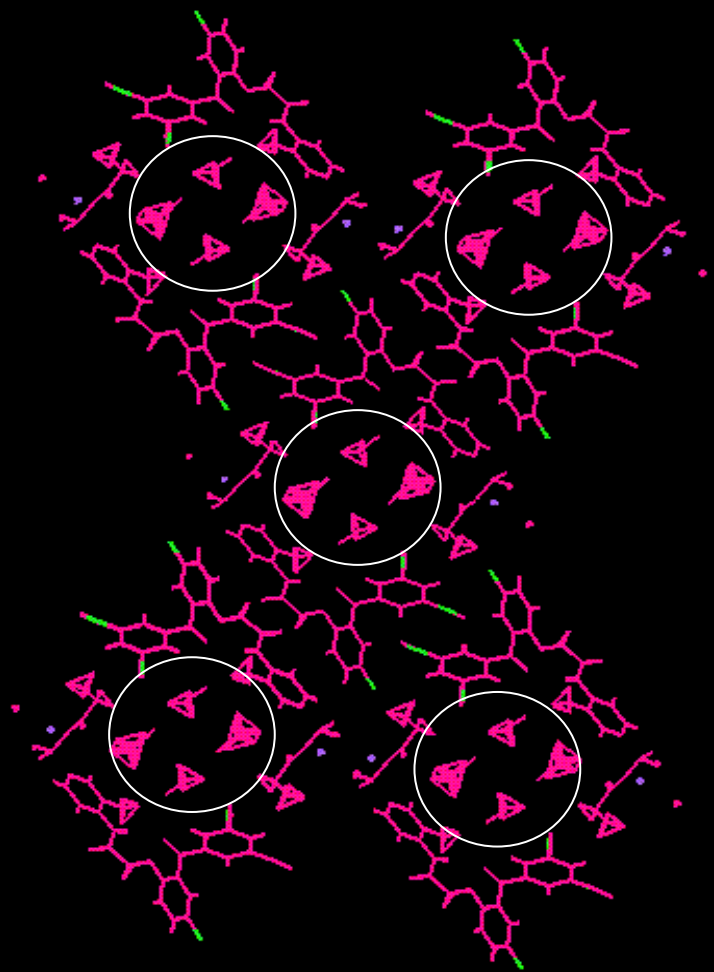
- Good aqueous solubility and exposure (30%F in dog)
- 19 crystal forms (anhydrate, hydrate, many solvates)
- Preparation of the “anhydrous” form in large scale was not feasible due to channel solvate formation (Form 9).
- Residual solvent in the channel solvate was extremely difficult to remove.

Case Study#1:Single Crystal Structure of Na Salt

Channel solvate

- **residual solvents**
- **hygroscopic**

First campaign batch was dried at 65 ^{o}C for 3 days!



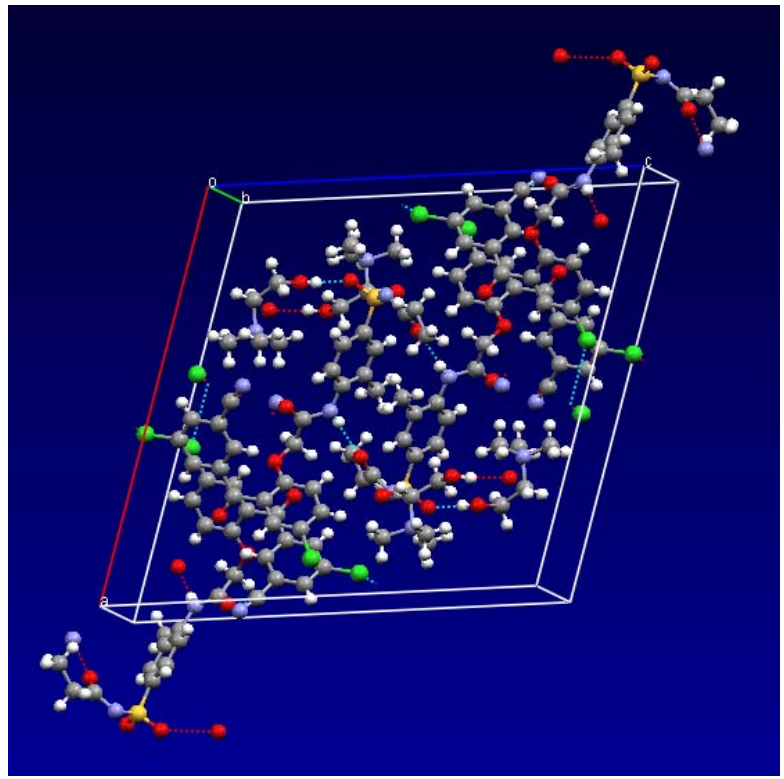
Case Study#1: Salt & Polymorph Screening

Salt Screening & Evaluation

- Crystalline K^+, Mg^{++}, Ca^{++}, choline, ethanolamine salts
- K^+, Mg^{++}, Ca^{++}, and ethanolamine salts have complicated polymorphism and/or poor aqueous solubilities/PK

Choline Salt is the Optimal Salt

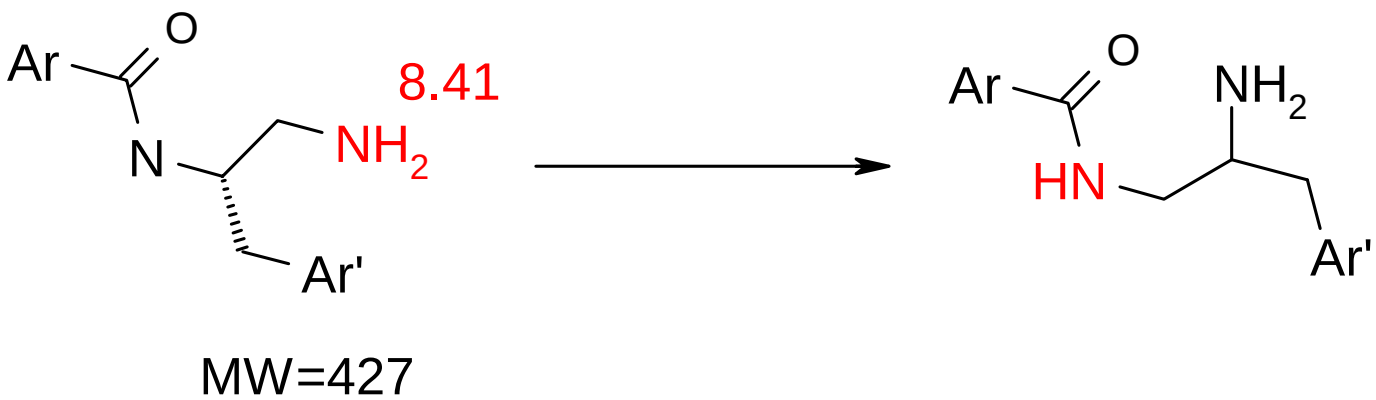
- Aqueous solubility (60 mg/mL)
- Bioavailability (60% in dog)
- Polymorph – 1 (mp ~180C)
- Non-hygroscopic
- Good stability



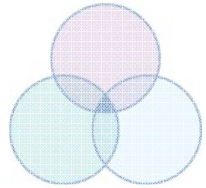
Case Study#2 – Improve Crystallinity and Chemical Stability

Project background

- Aggressive timeline (FTIH start in <9 months)
- Highly soluble
- No crystalline form
- Improve chemical stability w/strong acid salts



Case Study#2 – Improve Crystallinity and Chemical Stability



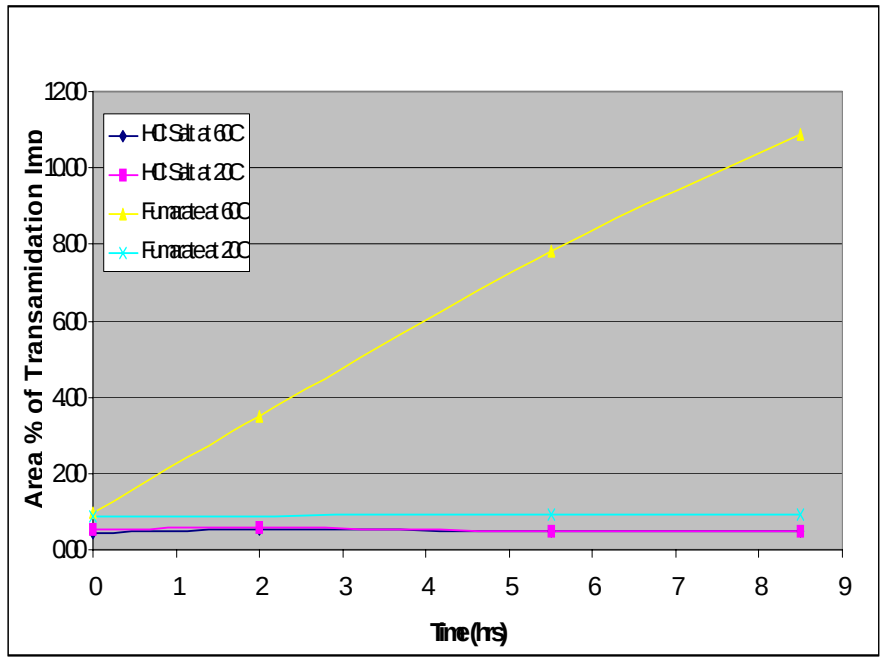
HT salt screen identified two crystalline salts:

- Acetate salt is unstable & eliminated quickly
  - mp ~ 136 C
  - Loss of acetic acid starts ~ 80°C on TGA-IR
  - Loss of acetic acid when dried at 50°C overnight.
- Fumarate salt (mp ~ 180°C) was supplied to support DRF studies
  - Good phys. prop. & solubility
  - Risks associated with the fumarate salt
    - Acyl migration
    - Poor solubility of fumaric acid (CD)
    - Potential API and DP stability (Michael addition)

Case Study#2 – Crystallinity and Chemical Stability

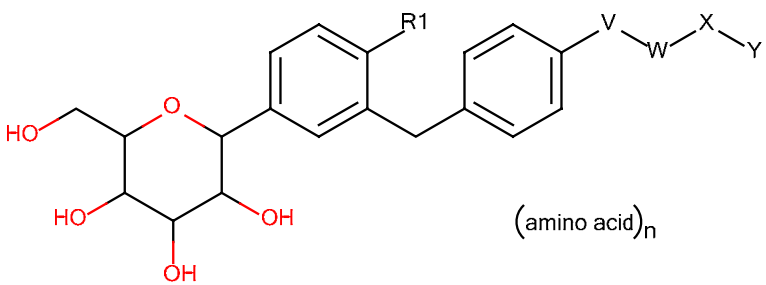
Carefully designed manual expts crystallized HCl salt

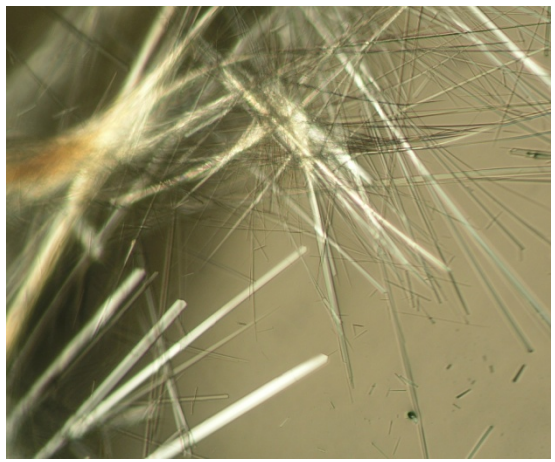
- Good phys. prop. (mp ~ 211°C)
- A single anhydrous form
- Good solubility in bio-relevant media (~80 mg/mL)
- No acyl migration and Micheal addition risks



Case Study#3: Co-crystal to Improve Crystallinity

- Sodium-dependent glucose cotransporter (SGLT) inhibitor
- Highly soluble
- Difficult to crystallize
- Cocrystals to confer crystallinity and improve mp.



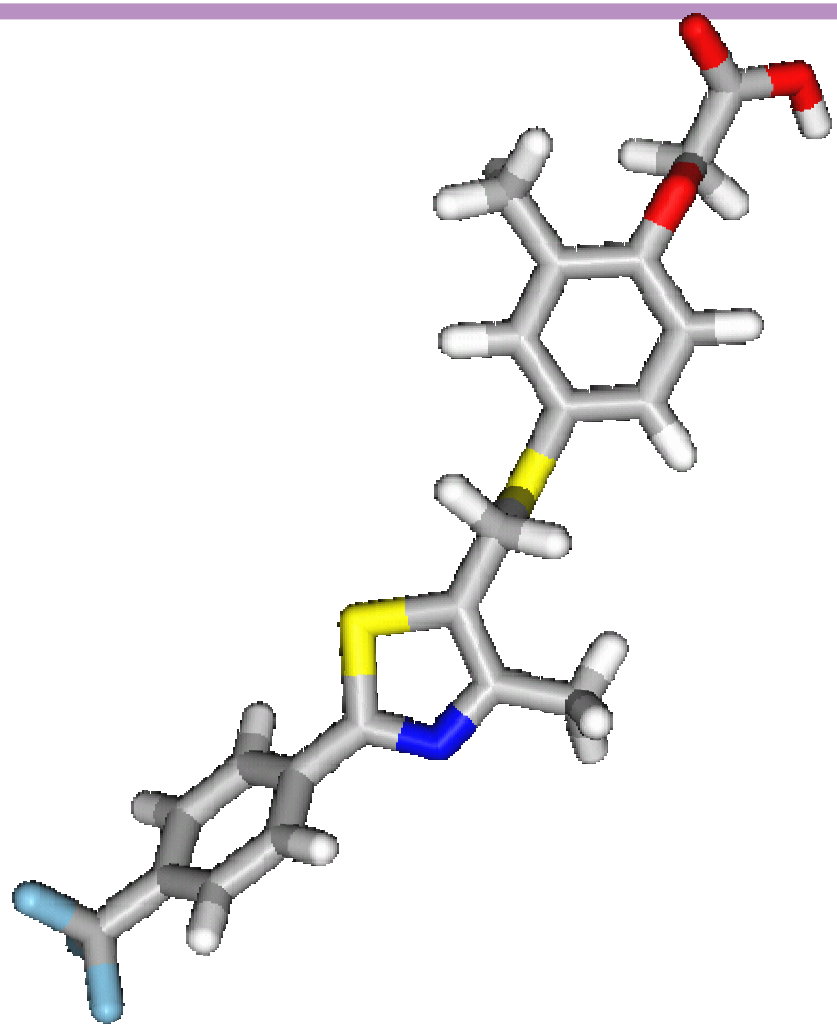


Patent: US2010/0222599A1

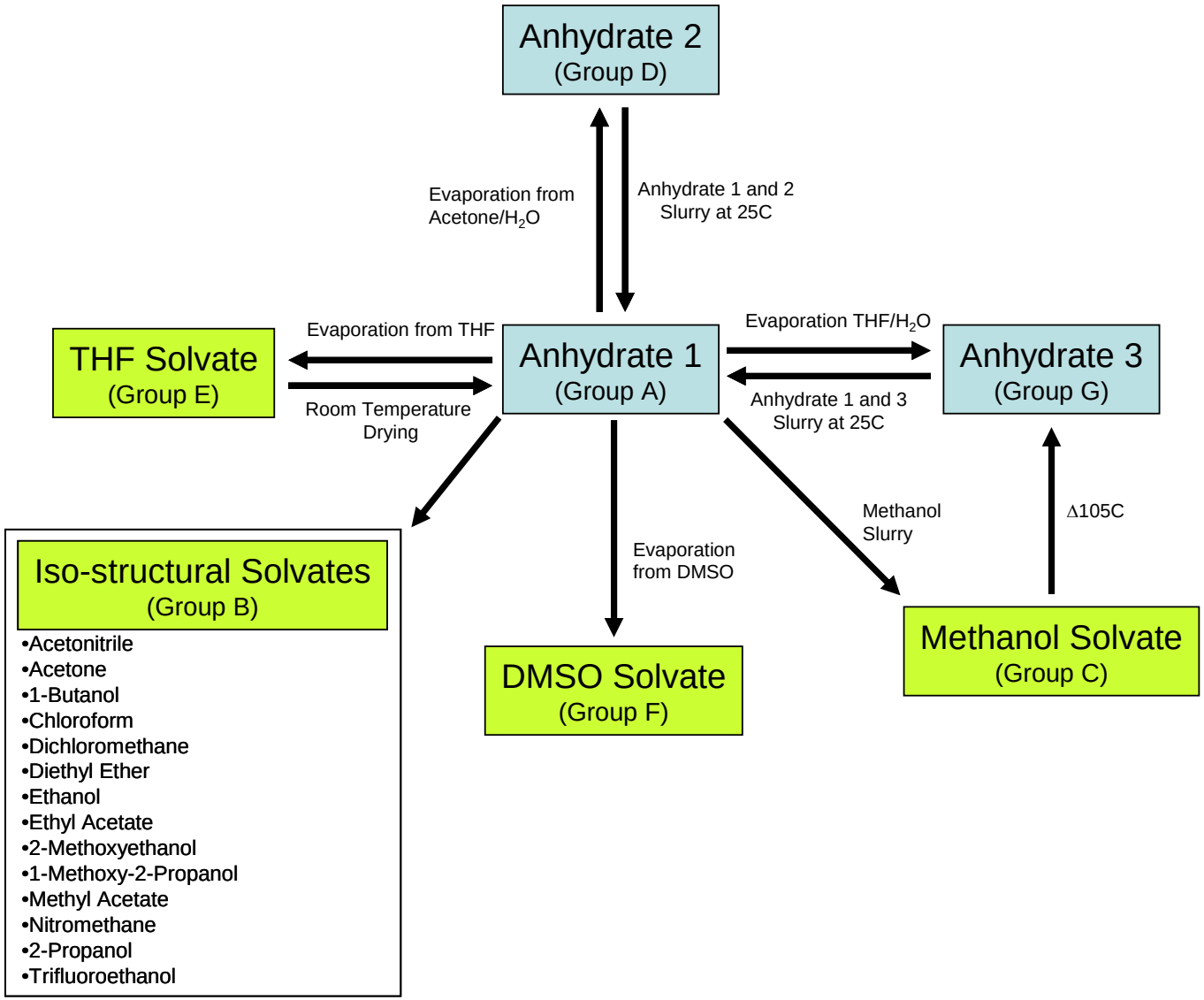
Case Study#4: Polymorphism of Opt0802

Objective: Examine form space of an API with moderate flexibility and MW

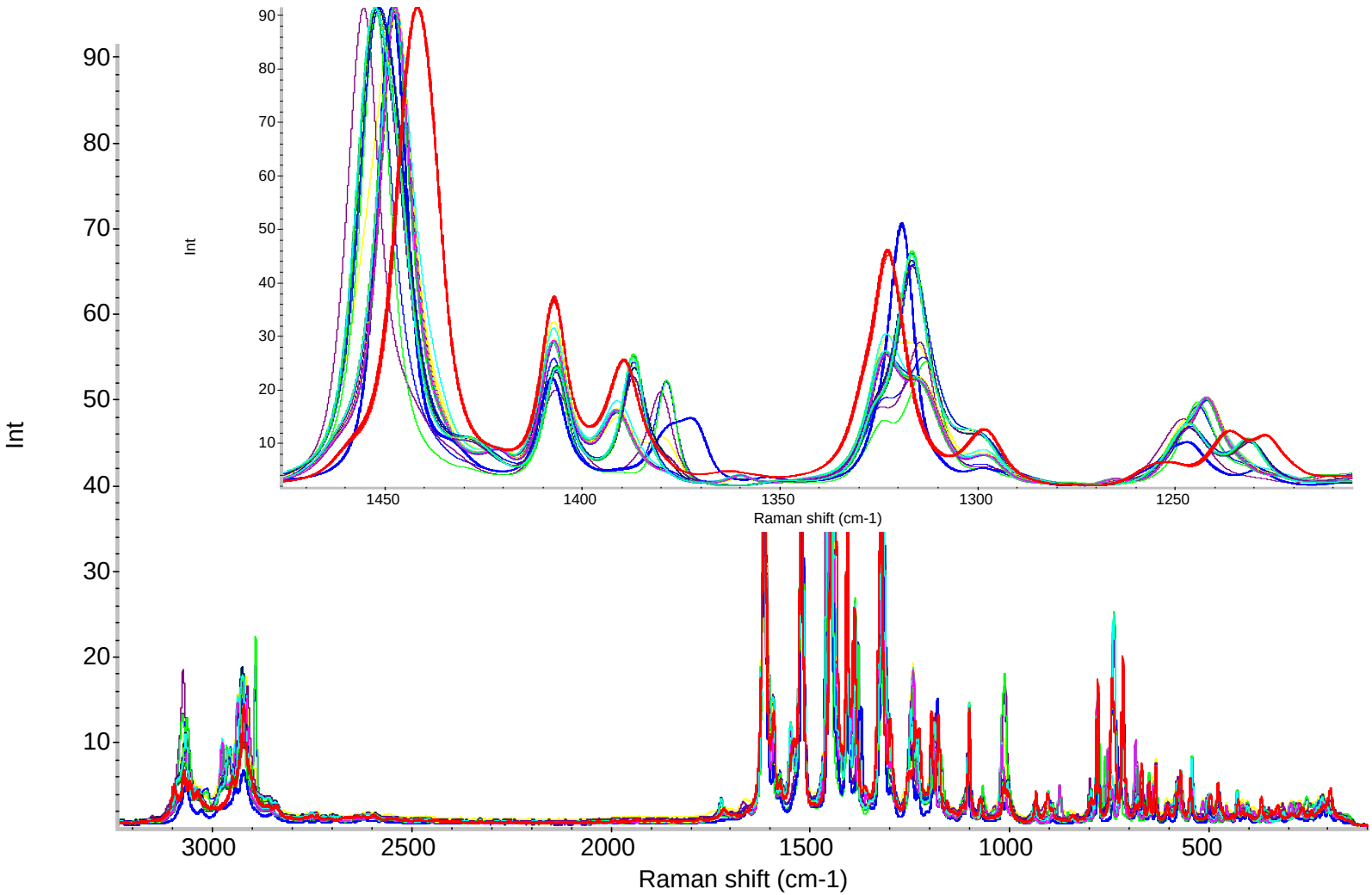
- API has several heteroatoms that can act as H-bond donors and acceptors thus propensity for polymorphism is expected to be high
- Screen was performed using 48 solvent systems and three crystallization modes (thermal treatments/temperature-cycling, evaporation, rapid cooling)



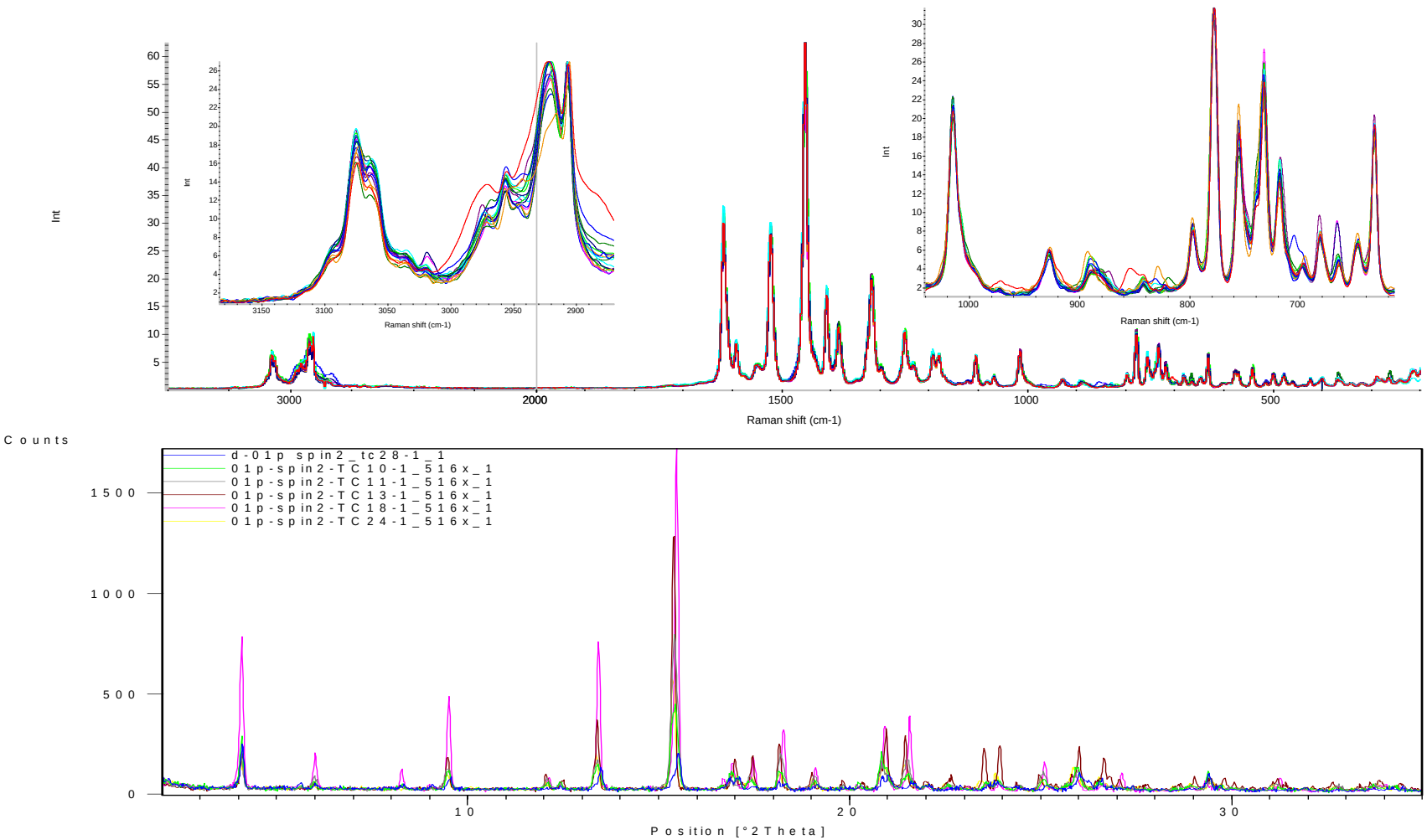
Case Study#4: Polymorphism of Opt0802



Case Study#4: FT-Raman Spectra of Opt0802

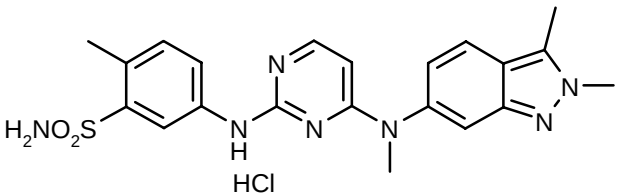


Case Study#4: Iso-structural Solvates of Opt0802



- L.Yu, S.M. Reutzel, G.A. Stephenson, PSTT, 1, 118-127 (1998)

Case Study#5: Complicated Polymorphism of GW786034B (Pazopanib)



Votrient®, Pazopanib

- **28 solid-state forms**
- **Polymorph control**
- **Data Analyses**

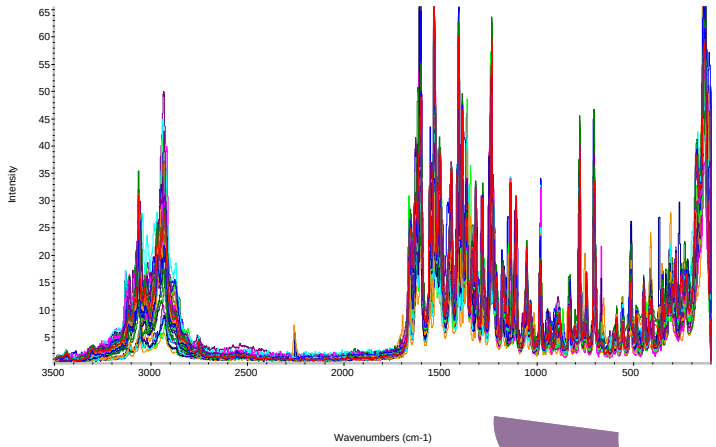
Class	Description	Comments
Anhydrates	Anhydrate 1	MP= 290°C w/decomposition
	Anhydrate 2	MP= 216°C, then recrys. to Anhydrate 1
Hydrates	Monohydrate	3.8% water content (monohydrate)
	Dihydrate	8.2% water content (dihydrate)
Solvates	Acetone, MeOH (1) , EtOH, 2-butanone	1:1 stoichiometry; Desolvates to Anhydrate 2 (heat to ~150°C)
	1-Propanol, cyclohexanone, DMSO, Chloroform, DMF, 1-Methyl 2-pyrrolindone	1:1 stoichiometry; Desolvates to Anhydrate 1 (heat to ~150°C)
	ethylene glycol, chlorobenzene, MeOH (2), MIBK, THF	non-stoichiometric; Desolvates to Anhydrate 1 (heat to ~150°C)
	1,4 dioxane	0.5:1 (solvent:API) stoichiometry; Desolvates to Anhydrate 1 (heat to ~150°C)
	Acetonitrile Solvate	nonstoichiometric; forms desolvated solvate heated to 150°C, then conversion to Anhydrate 1 heated to 200°C
Others	Desolvated ACN solvate	structurally similar to ACN solvate
	Dehydrated Dihydrate	structurally similar to dihydrate

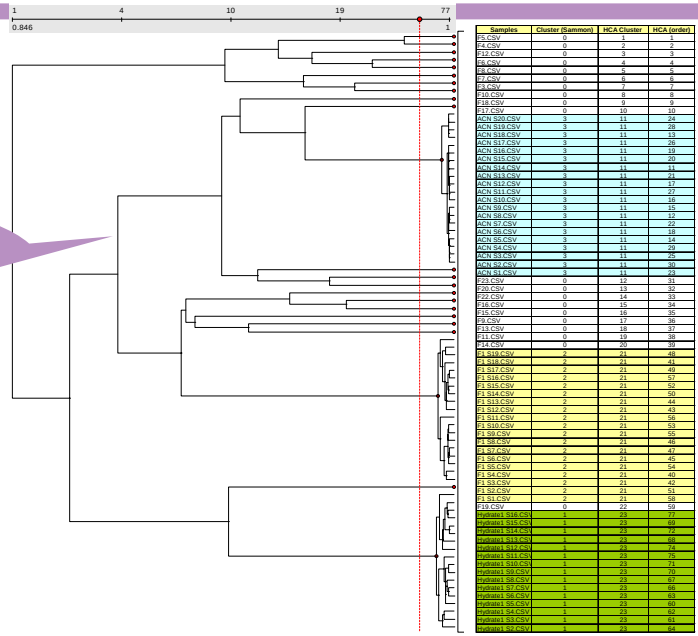
"Utilization of FT-Raman Spectroscopy to Unravel the Complicated Polymorphism of GW786034B (Pazopanib)" P.Chen*, D. Igo, L. Katrincic, R. Couch; 2009 FACSS Meeting, Louisville, KY, Oct. 19-22, 2009.

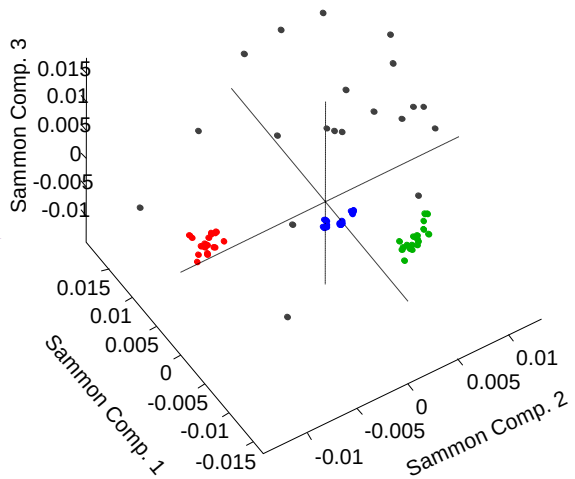
Case Study#5: Unsupervised Clustering Analyses

Hierarchical Cluster Analysis

FT-Raman Data





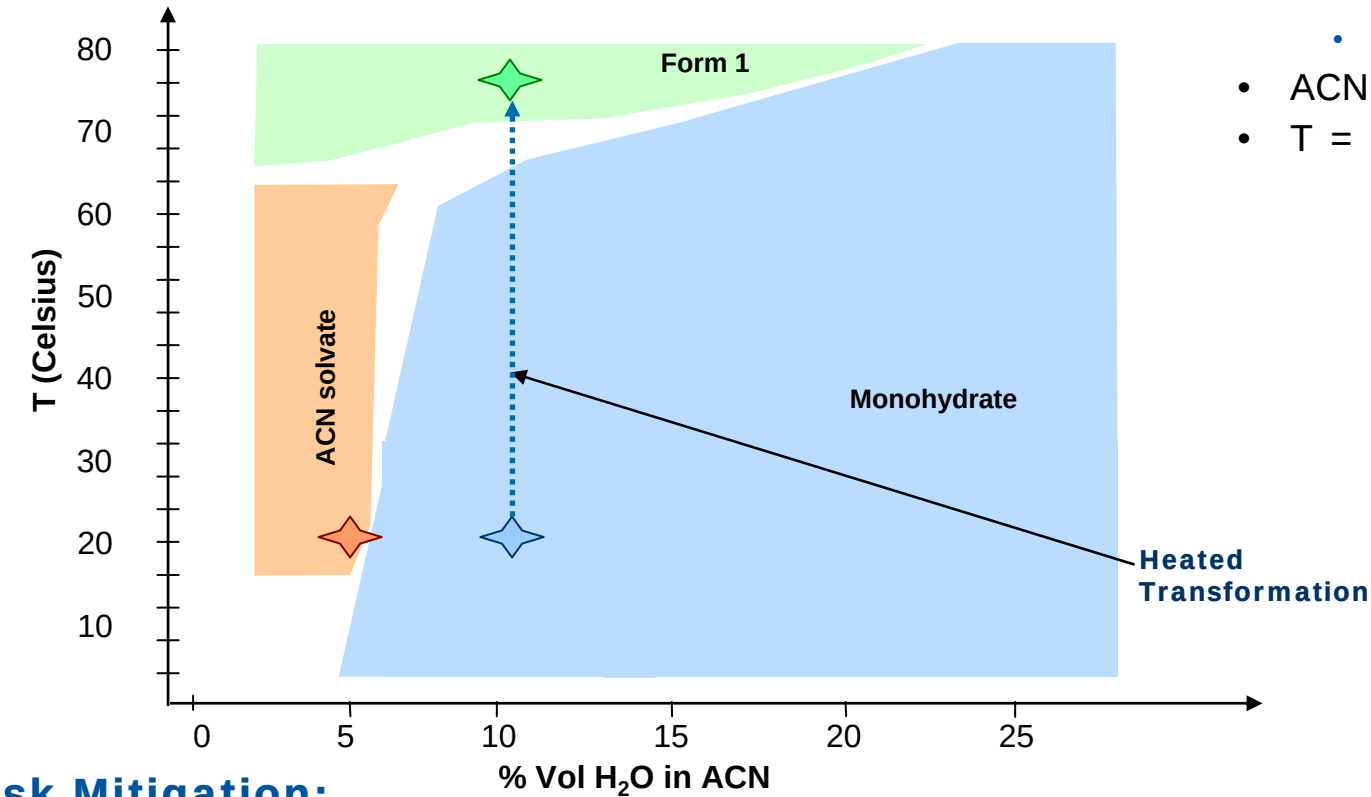


"Utilization of FT-Raman Spectroscopy to Unravel the Complicated Polymorphism of GW786034B (Pazopanib)" P.Chen*, D. Igo, L. Katrincic, R. Couch; 2009 FACSS Meeting, Louisville, KY, Oct. 19-22, 2009.

Case Study#5: Final API Crystallization Process

Situation:

- Stable ACN solvate discovered
- Current process: 5%aq. ACN (water addition)



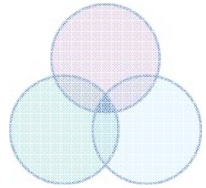
Risk assessment:

- Process-Relevant Forms:
  - Form 1
  - Monohydrate
  - ACN Solvate
- ACN/water mixtures
- T = 0-80°C

Risk Mitigation:

- Heated transformation of monohydrate in 10% aq. ACN

Concluding Remarks



- Solid-form selection is a critical development activity for small-molecule drug candidates.
- HT screening is valuable & effective in most cases, but some difficult molecules will require careful design and control of crystallization, and nucleation aid such as seeding with crystals of a structurally similar compound.
- Raman spectral differences between different solid-forms of an API are relatively small, and appears throughout the entire spectral range.
- All solid-state forms of an API can be differentiated with the appropriate Raman spectrometers and sampling parameters.
  - Spectral quality (S/N, resolution, minimal background)
  - Spectral reproducibility (better than 1 cm^{-1})
- FT-Raman is nearly ideal for solid-form screening & routine characterization.

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