Drug Product Characterization: What Solid Form is in My Formulation?

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Solid Forms

Classes of multicomponent molecular crystals

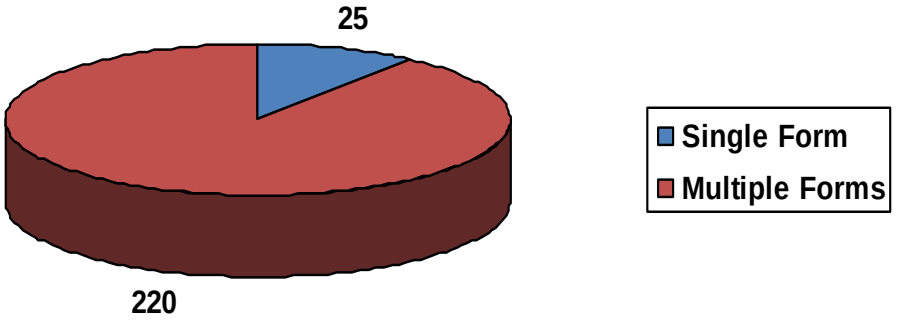
Neutral

Charged

Polymorphs

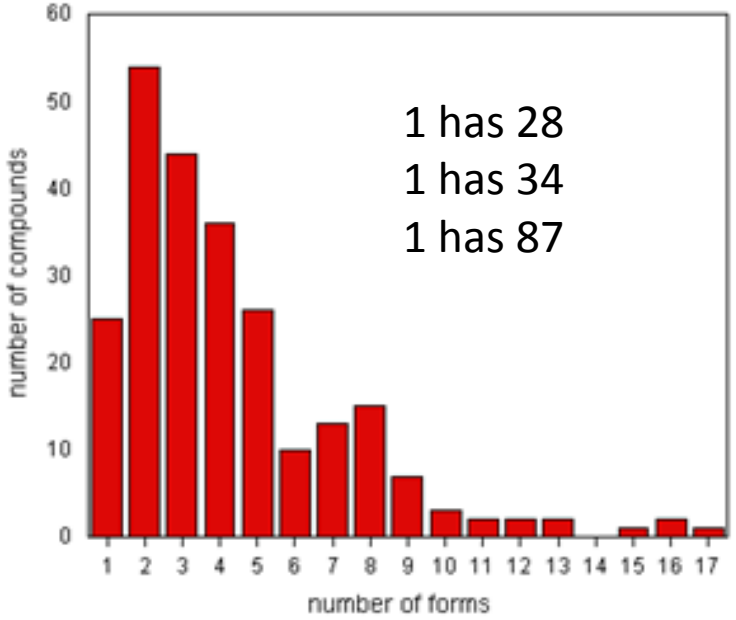
1. Homomeric
2. Hydrate/solvate
3. Cocrystal
4. Cocrystal hydrate
5. Salt
6. Salt hydrate/solvate
7. Salt cocrystal
8. Salt hydrate cocrystal

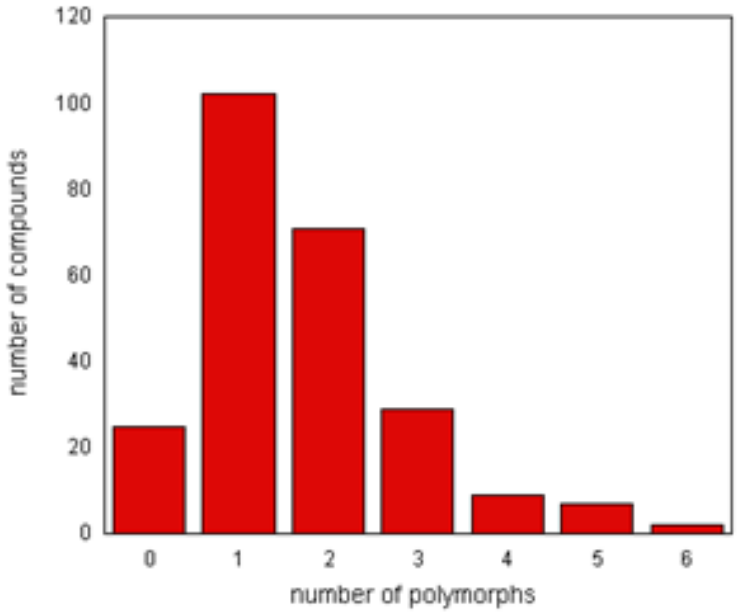
Solid Forms



89% of compounds screened resulted in multiple forms (based on 245 screens)

- includes 10 steroids, 7 peptide-based structures, 5 cephalosporins, 4 organometallics, 2 macrolide antibiotics

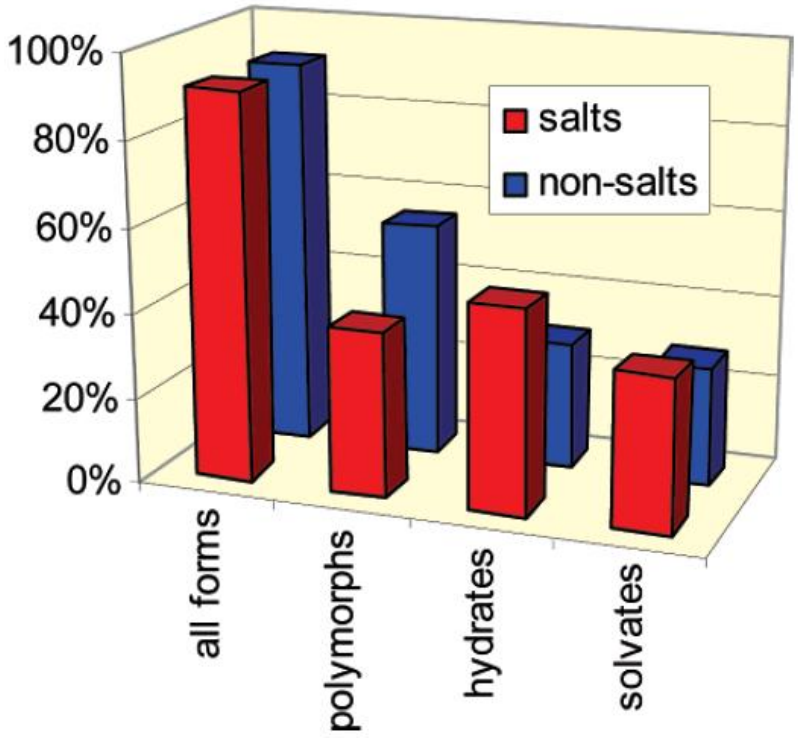




Stahly. *Crystal Growth & Design.* **2007**, *7*, 1007-1026

Solid Forms

- Propensity to produce different forms not significantly different for salts and non-salts
- Need more data on cocrystals



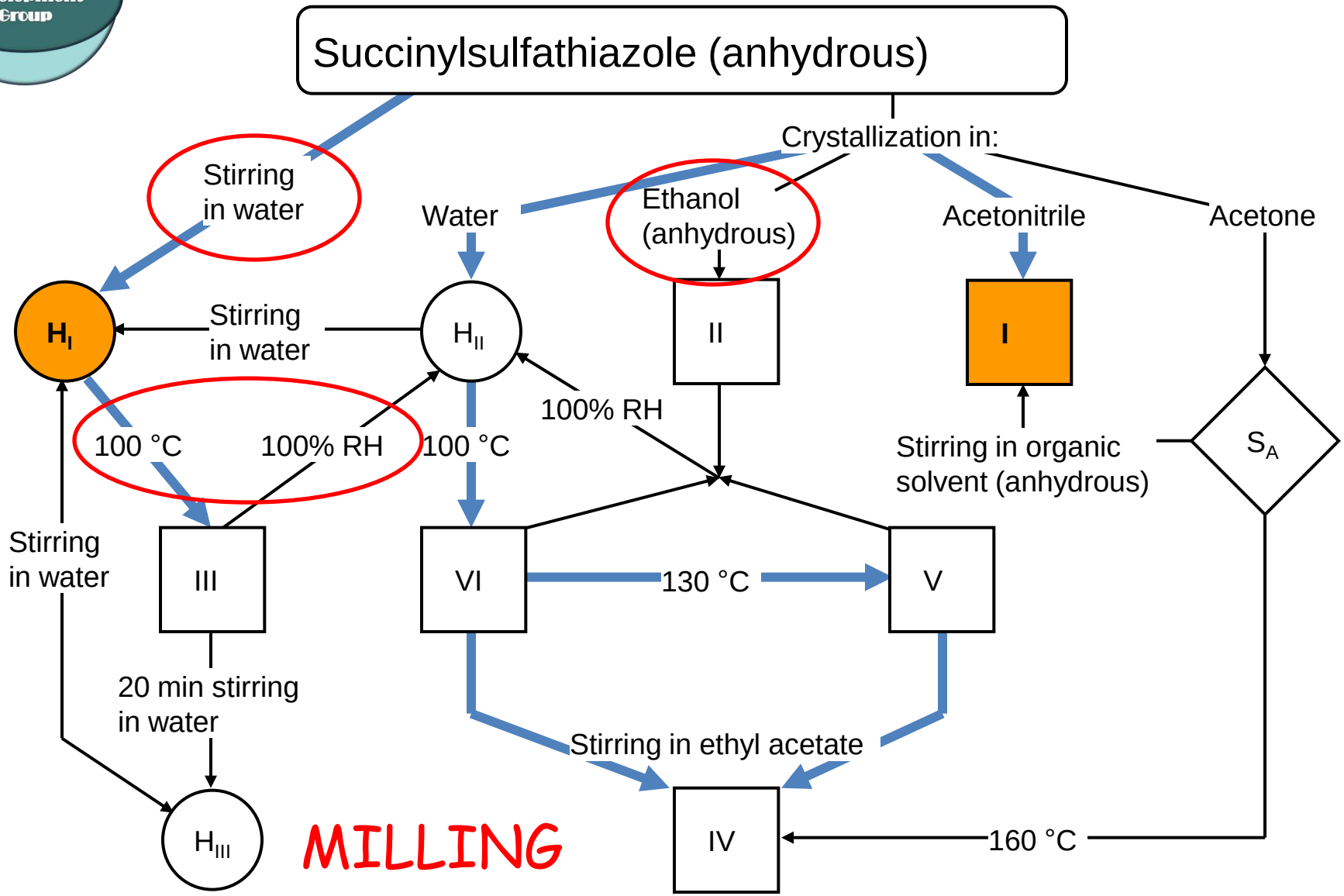
Percentages of Forms from Polymorph Screening

	all compounds [count (%)]	salts [count (%)]	non-salts [count (%)]
multiple forms[a]	220 (89)	86 (91)	116 (91)
multiple crystalline forms[b]	200 (82)	77 (81)	105 (82)
polymorphs[c]	118 (48)	37 (39)	71 (55)
hydrates	94 (38)	46 (48)	38 (30)
solvates	78 (32)	34 (36)	36 (28)
noncrystalline	118 (48)	51 (54)	55 (43)
total compounds	245	95	128

[a] Crystalline polymorphs, hydrates, and solvates plus noncrystalline forms. [b] Crystalline polymorphs, hydrates, and solvates. [c] Crystalline polymorphs.

Stahly. *Crystal Growth & Design.* **2007**, *7*, 1007-1026

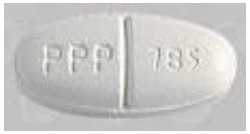
Solid Forms



A. Burger and U. J. Griesser. *Eur. J. Pharm. Biopharm*. **1991**, *37*, 118-124.

Drug Products

- Tablets
- Capsules
- Solutions
- Suspensions
- Intravenous (IV)
- Soft gel capsules



- Inhalers
- Implants/stents
- Suppositories
- Patches
- Emulsions
- Depot
- Other

Interference from excipients is major issue for drug products

Liquid Dosage Forms

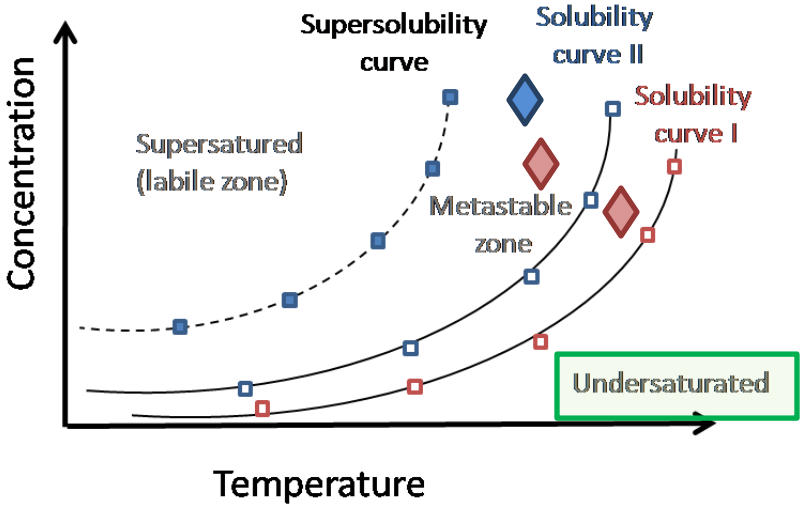
- Solution
  - Solid is dissolved in liquid, usually with other excipients
  - Can be exposed to elevated temperatures during manufacture
- Suspension
  - Solid is suspended in liquid, usually with other excipients
- Reconstituted Solutions
  - Solid is freeze-dried, usually with excipients
  - Solid is usually amorphous
  - Liquid added at later time to make solution
- Can be exposed to elevated temperature during stability studies, shipping, storage

http://www.lorrainespharmacy.com/compounding/oral.htm

http://www.vetter-pharma.com/vcc/lyo/lyo1

Liquid Dosage Forms

- Excipients added such as thickeners, preservatives, buffer agents, sweeteners, etc
- Solution
  - Drug is dissolved in formulation vehicle
  - Concentration should be below equilibrium solubility of form in vehicle to prevent crystallization



- Suspension
  - Drug is suspended in formulation vehicle
  - Even with low solubility formulations, drug can dissolve and recrystallize over time
  - Most stable form usually used to prevent recrystallization

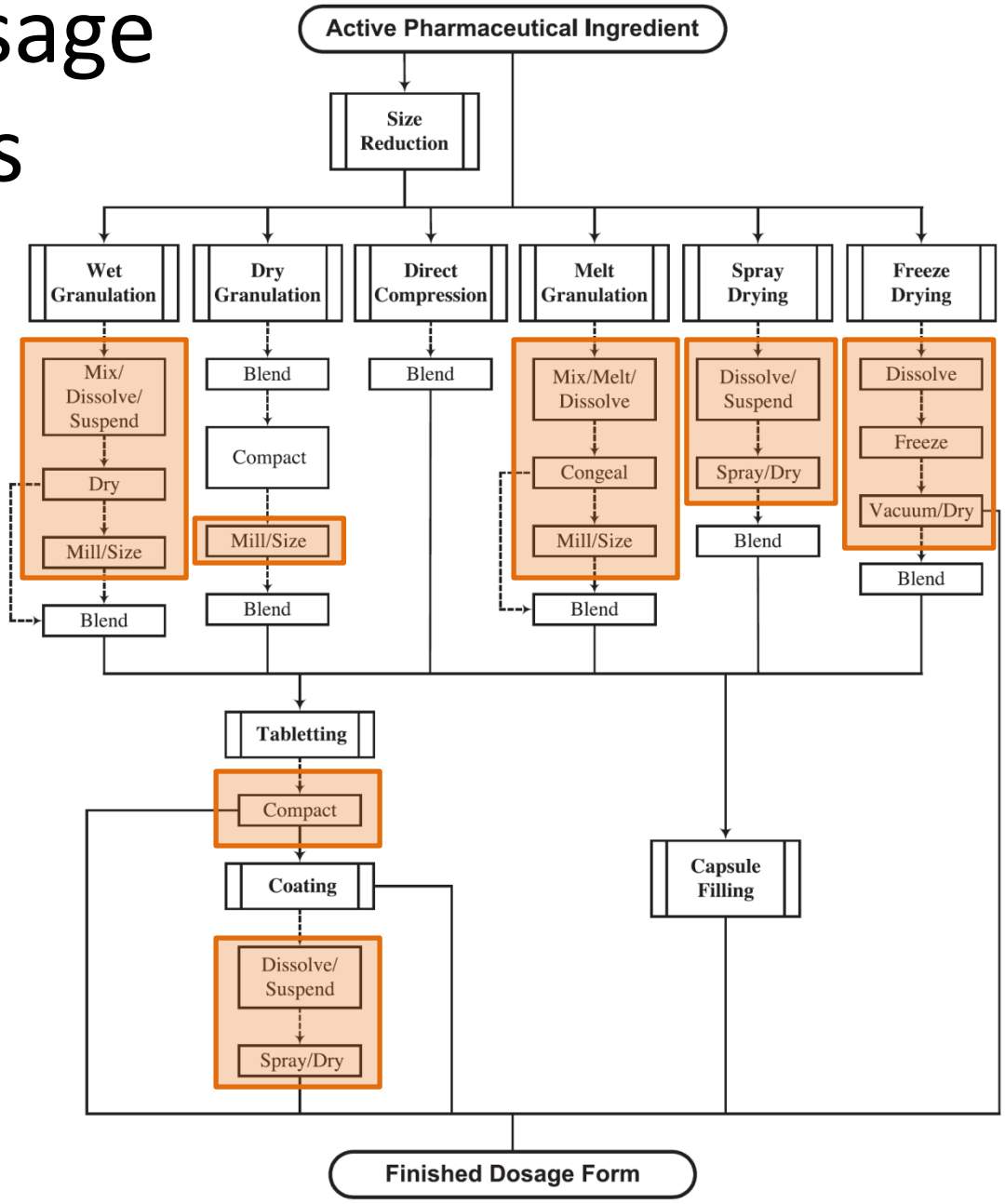
Solid Dosage Forms

- Solid mixed with excipients (disintegrants, flow aids, etc)
  - Wet granulation
    - Mix solids with water or solvent
    - Dry solids
    - Mill to produce powder
  - Dry granulation/direct compression
    - Mix solids dry
- Put into capsules or pressed into tablets
  - Exposure to RH during capsule filling
  - Compression into tablets
- Tablets may be coated
  - Exposed to coating solutions
- Will be exposed to elevated temperature and RH during stability studies, shipping, storage

Kaletra

Solid Dosage Forms

- Form changes can occur
  - Mixed/dissolved/ suspended in solvent
  - Drying
  - Milling
  - Compaction
  - RH exposure
- Changes can occur with both drug substance and excipients
- Can have interactions between drug substance and excipients that cause form changes



Zhang et al. *Adv Drug Delivery Rev*. **2004**, *56*, 371-390

Process Induced Transformations

- Can involve one component or more
- Can be solid-solid or solid-liquid-solid
- Can happen with compound, excipient, or both

Types of the most important phase transitions during processing of pharmaceuticals[a]

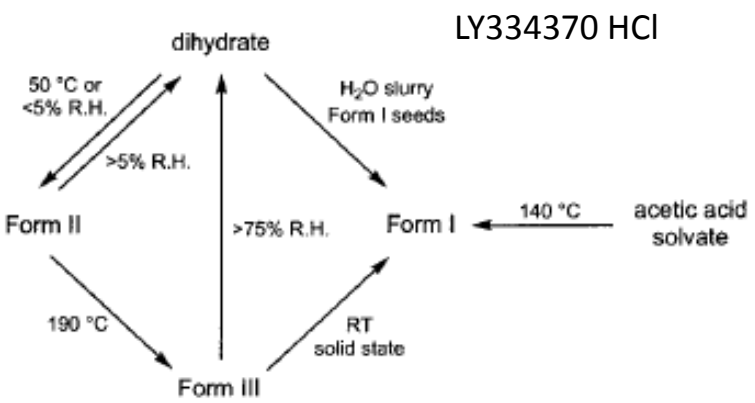
Basic process	State of aggregation	Specific process
Transformations (one component)	Solid–solid	Polymorphic transformations
		Crystallization of the amorphous form and vice versa
	Solid–liquid–solid	Incongruent melting (melting followed by crystallization of a more stable form)
		Solution mediated polymorphic transformations
Physical interactions (multicomponent)	Solid–solid	Eutectic reaction
	Solid–liquid–solid	Formation of a molecular compound or a solid solution (including solvate formation) **cocrystals, salts**
	Solid–solid or Solid–liquid–solid	Hydrate formation in humid air
Physical decompositions (multicomponent)	Solid–solid or Solid–liquid–solid	Desolvation **dissociation**

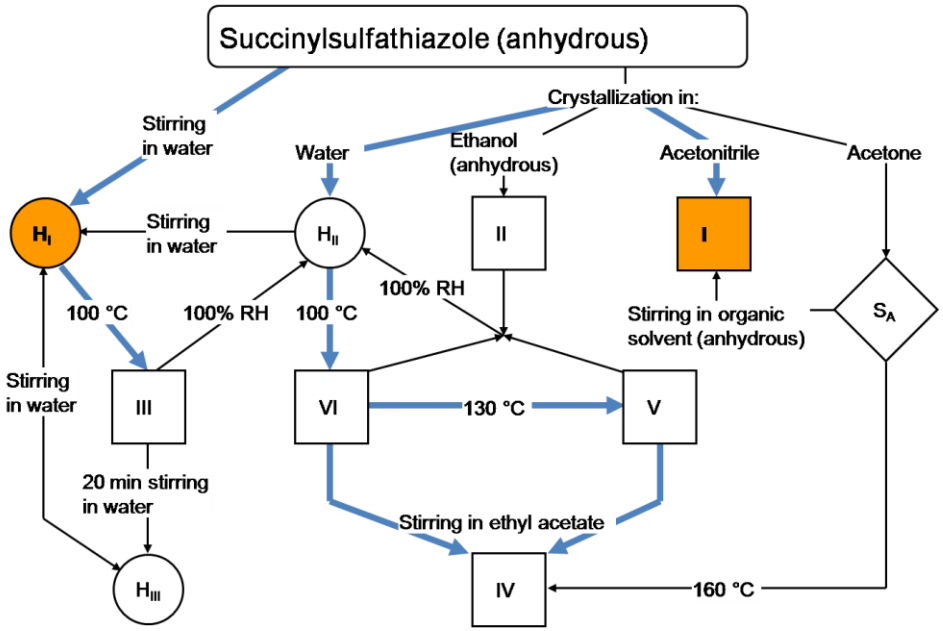
[a] Does not consider chemical changes.

Morris et al. *Adv Drug Delivery Rev*. **2001**, *48*, 91-114

Formulation Plan

- Process induced phase transformations can be anticipated based on screening and preformulation studies
- Use your road maps





Reutzel-Edens et al. *J. Pharm. Sci.* **2003**, *92*, 1196-1205

A. Burger and U. J. Griesser. *Eur. J. Pharm. Biopharm*. **1991**, *37(2)*, 118-124.

Formulation Plan

Transformations can be controlled and circumvented by selecting the appropriate process

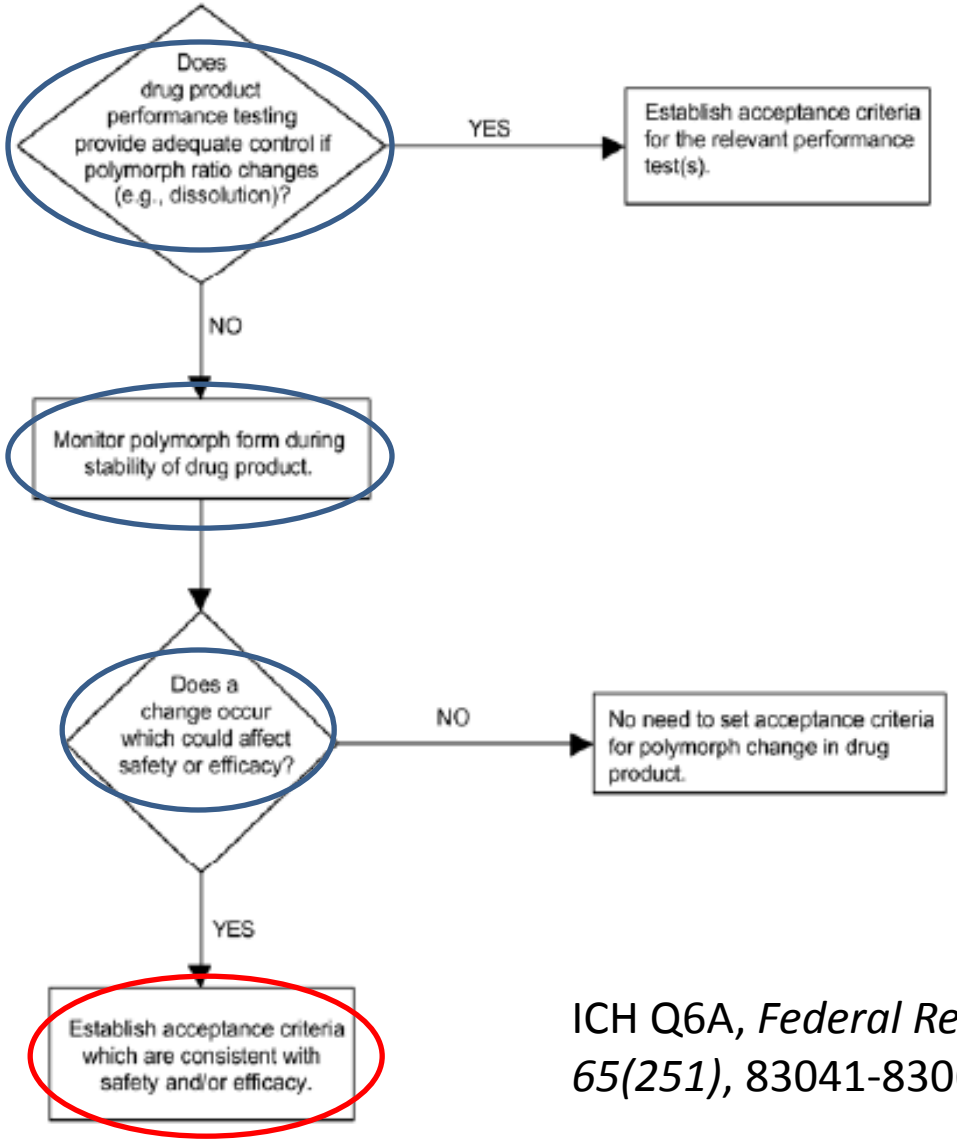
Issue	Possible Process
Solid is sensitive to moisture or solvent	Use dry or melt granulation
Undesirable transition during milling	Use melt granulation through melt extrusion if drug is thermally stable Control particle size during crystallization
Undesirable transition during compression	Use capsules instead of tablets
Enantiotropic form conversion upon heating	Maintain drying temperature below the transition temperature
Undesirable form conversion on surface during film coating	Minimize or eliminate solid-liquid interactions by applying a seal coat of low viscosity or use organic solvent-based polymer with rapid evaporation

Zhang et al. *Adv Drug Delivery Rev*. **2004**, *56*, 371-390

Regulatory

3.

Drug Product



ICH Q6A, *Federal Register,* **2000**, *65(251)*, 83041-83063.

Characterization Methods

X-ray Powder Diffraction (XRPD)	Crystallinity Crystalline form	Sampling (PO) Specificity Particle size
Spectroscopy • Infrared (IR) • Raman • SS NMR	Interactions Crystalline form Mapping/imaging	Sampling Specificity Particle size Beam size Data collection times
Thermal Methods •DSC (mDSC, HyperDSC) •Thermogravimetry (TG) •Hot Stage Microscopy	Melting point/Tg Form changes Volatile content	Sampling Specificity Particle size Scan rate Dynamic techniques
Moisture Sorption	Water uptake Form changes	Sampling Initial corrections

Qualitative vs Quantitative

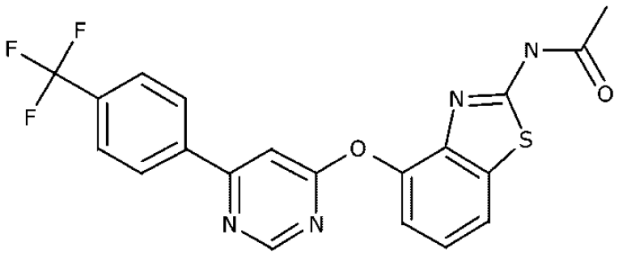
- When multiple forms are known:
  - need test/assay to show control of process
  - assay can be qualitative or quantitative
  - can be an issue in API and drug product
- Different levels of use and validation through out development
  - Early development: qualitative/visual
  - Late development: increase level of validation
- Univariate vs multivariate and chemometric approaches

Summary of quantitative methods

Quantitative method	Scope of assay	Result
Limit test	A limit of detection for a technique is determined (such as 2%)	Result is specified as '<2% Form B present'
Specification assay	An assay limit is determined for a technique (such as 95%)	Result is specified as '>95% Form A present'
Full quantitative method	A minimum quantifiable limit (MQL) (such as 2%) and linear range (such as 2–25%) is determined	'X% of Form B' if within the quantitation range of 2–25% or '<2% Form B' if below MQL or '>25% Form B' if above linear range

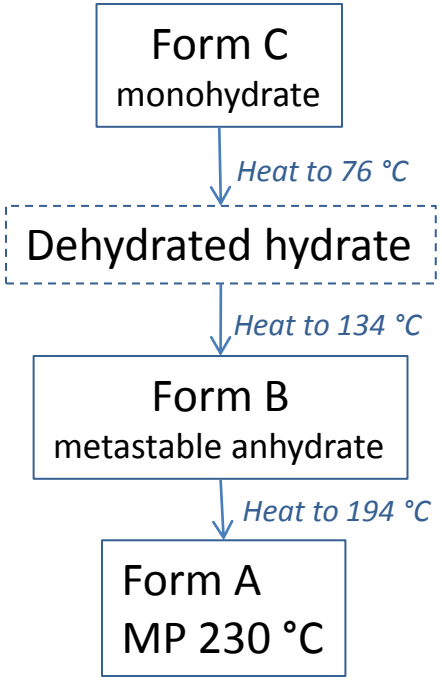
Newman and Byrn, *Drug Discovery Today*, **2003**, *8*, 898-905

Solution



AMG517

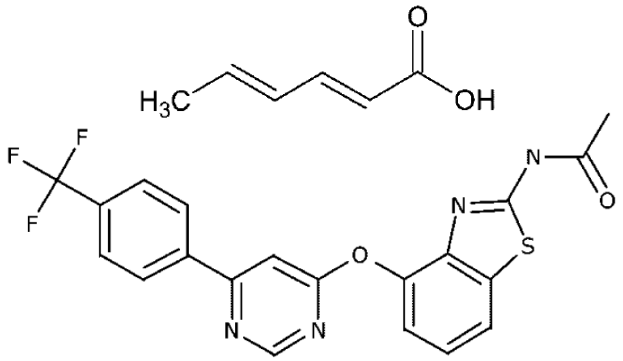
- Number of crystalline forms found for free base
- Numerous solvates also isolated
- Several crystalline salts prepared
  - Disproportionated in aqueous solution
  - Resulting pH was low and acid mediated cleavage occurred at ether bond
- Form A selected for early development
  - Insoluble in water
- A suspension in 10% (w/v) Pluronic F108® in OraPlus ® (unadjusted pH ~4 for all concentration levels)

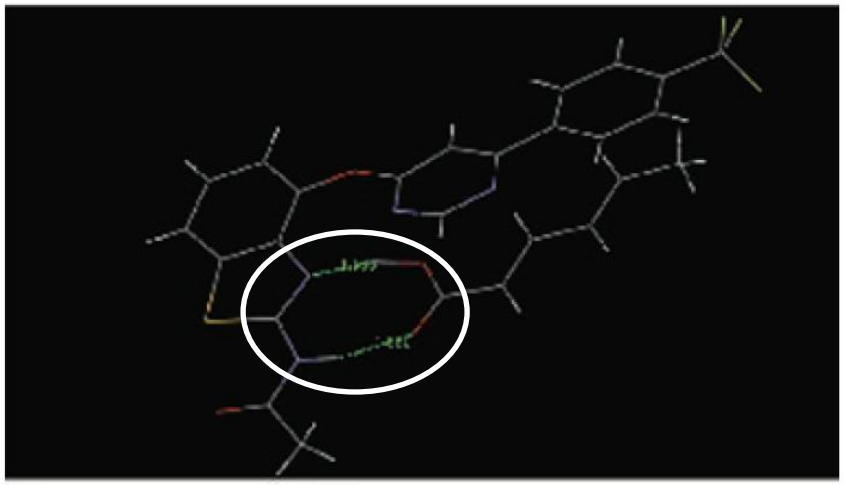


Bak et al. J Pharm Sci. 2008, 97, 3942-3956.

Solution

- At high doses, found solubility limited absorption
  - Due to new solid form in suspension
- OraPlus® contains 0.1% sorbic acid as a preservative
- New form was 1:1 AMG517:sorbic acid cocrystal
- Found 12 additional cocrystals in subsequent studies
- Know what is in your solutions
  - can also happen with buffers





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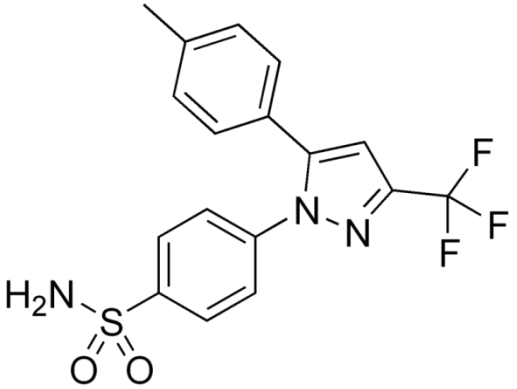
Suspension



- Celecoxib
  - Three unsolvated forms (I, II III)
  - Form III thermodynamically stable form at RT
  - Two solvates: N,N-dimethyl acetamine and N,N-dimethyl formamide (DMF)
- Suspension formulation made with Form III

Representative Formulations of Celecoxib Suspensions

	% w/w					
Ingredient	Lot A	Lot B	Lot C	Lot D	Lot E	Lot F
Celecoxib	1.77	1.20	1.77	1.77	1.77	1.77
HPMC 2910 USP 15	4	4	5	5	2.5	5
PEG 400	4.13	2.9	4.13	4.13	4.13	4.13
Polysorbate 80	1	1	1	1	0.5	0
PVP K90	0	1	0	2	1	2
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2
Citric acid	1.31	1.31	1.31	1.31	1.31	1.31
Sodium citrate	1.11	1.11	1.11	1.11	1.11	1.11
Sucrose	30	30	0	30	15	0
Tutti frutti flavoring	0	0	0.05	0.05	0.05	0.05
DI water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Lu et al. *J Pharm Sci*. **2006**, *95*, 305-317

Suspension

HPMC and PVP dispersed in water with agitation

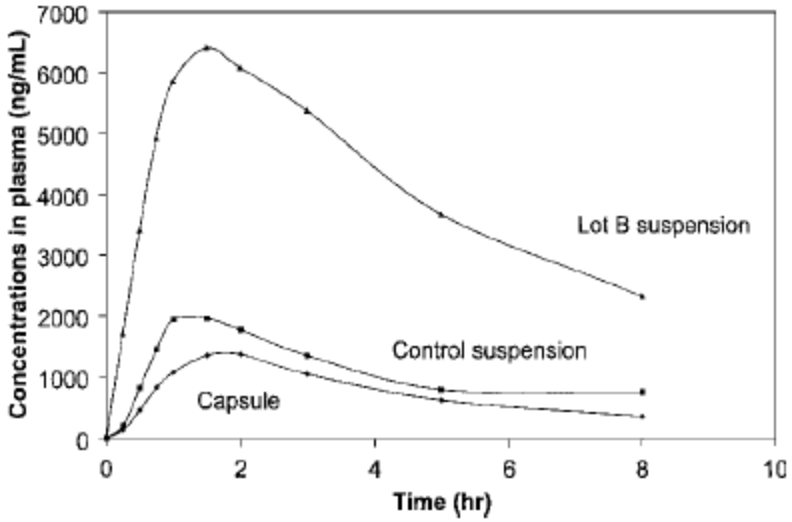
PEG 400 solution made with celecoxib (10-30%) and polysorbate 80 added with stirring

Precipitation

Add sucrose and other excipients
Stir 10-30 min
Homogenization 3-5 min if needed

Suspension formulation

Lot B showed significant increase in bioavailability in animals compared to capsules and control formulation (Form III with different excipients)

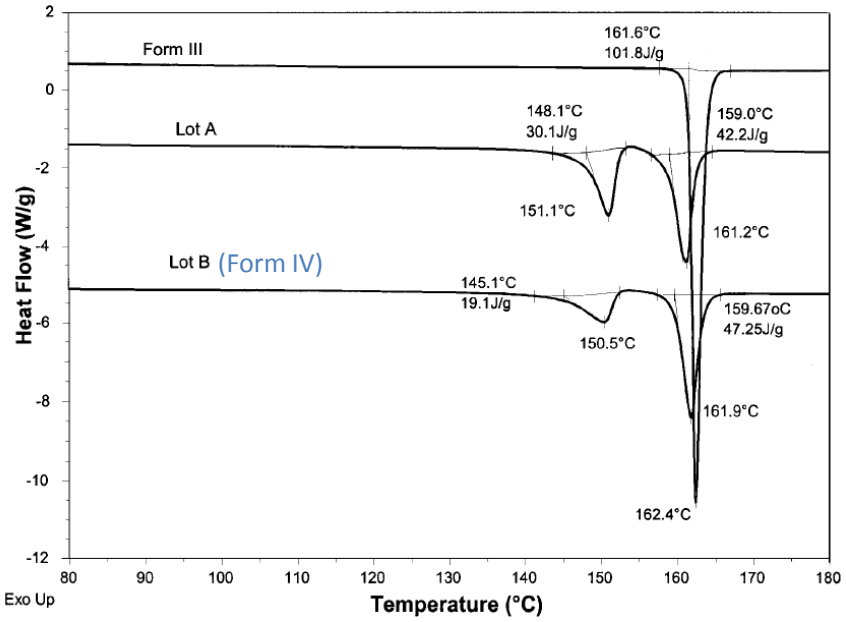


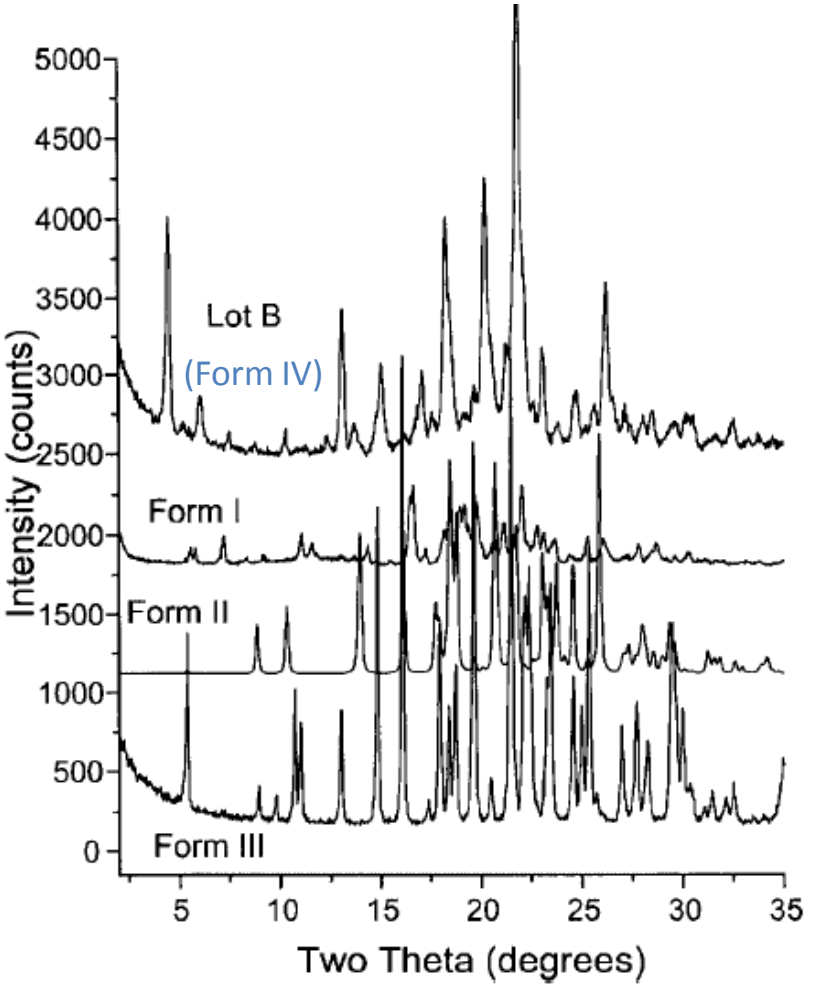
Pharmacokinetic profiles of the celecoxib suspensions and the capsule in dogs ($n = 6$).

Lu et al. *J Pharm Sci*. **2006**, *95*, 305-317

Suspension

- XRPD showed Lot B contained a new form of celecoxib (Form IV)
- Upon heating, Form IV melts and converts to Form III
- IPA slurry with Forms III and IV show Form III is more stable at RT



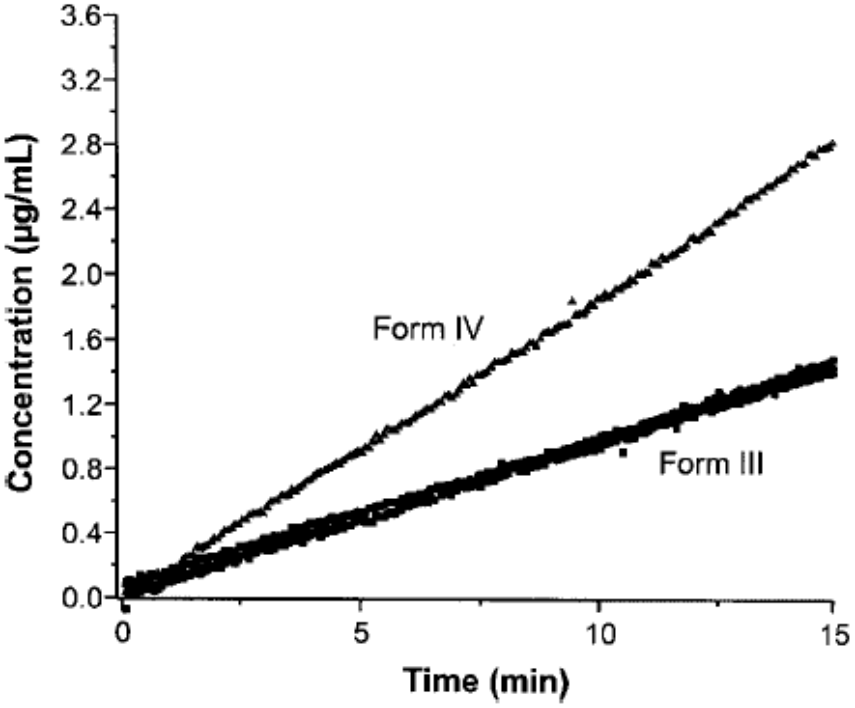


Powder X-ray comparison of the precipitated celecoxib Lot B to the three known crystal forms of celecoxib.

Lu et al. *J Pharm Sci*. **2006**, *95*, 305-317

Suspension

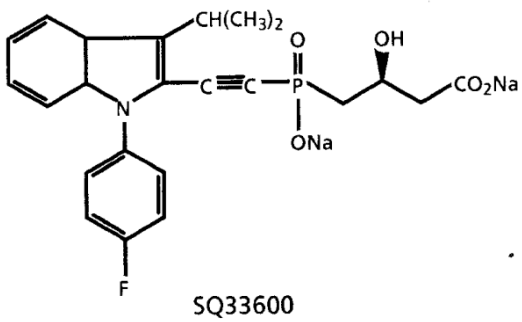
- Metastable Form IV produced from formulation process
- Found concentrations and ratio of HPMC and Polysorbate 80 were critical to the generation of Form IV
- Form IV is 2-3X more soluble than Form III
- Formulations with Form IV are stable at 40 °C for at least 6 months and at 25 °C for at least 16 months
- Possible to stabilize metastable Form IV in suspension and achieve higher bioavailability
- Processing conditions and excipients can affect form; excipients can stabilize forms



Rotating disk dissolution for Form IV and Form III of celecoxib.

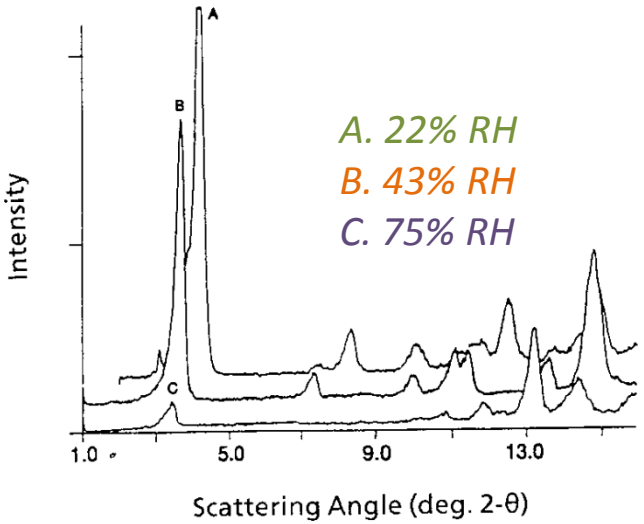
Lu et al. *J Pharm Sci*. **2006**, *95*, 305-317

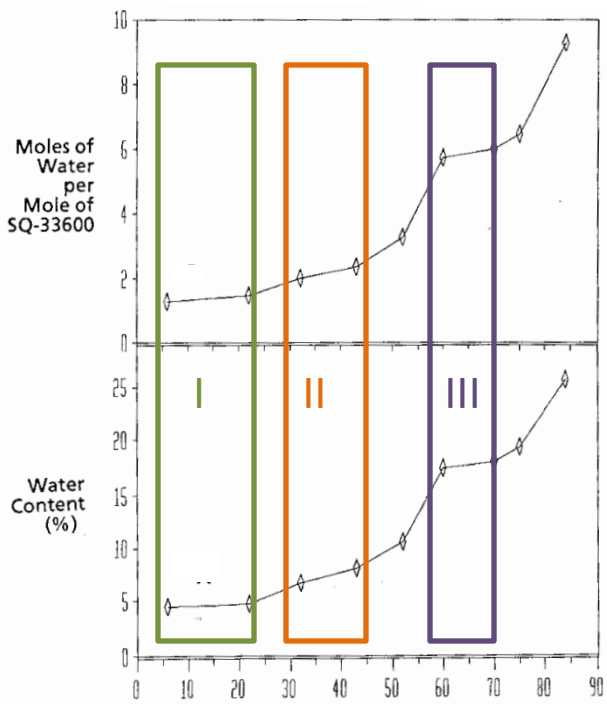
Early Formulation

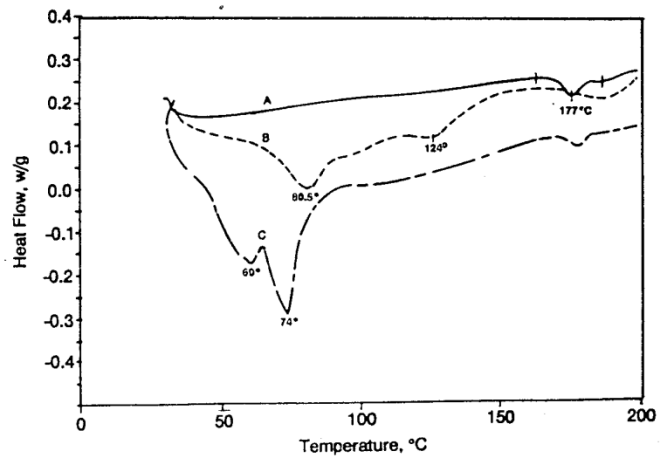


SQ33600

- SQ33600
- HMG-CoA reductase inhibitor
- Aqueous solubility 300 mg/mL
- Hygroscopic
- Form dependent on RH
  - Type I (<22% RH)
  - Type II (33-52% RH)
  - Type III (60-75% RH)
  - Semisolid (>84% RH)



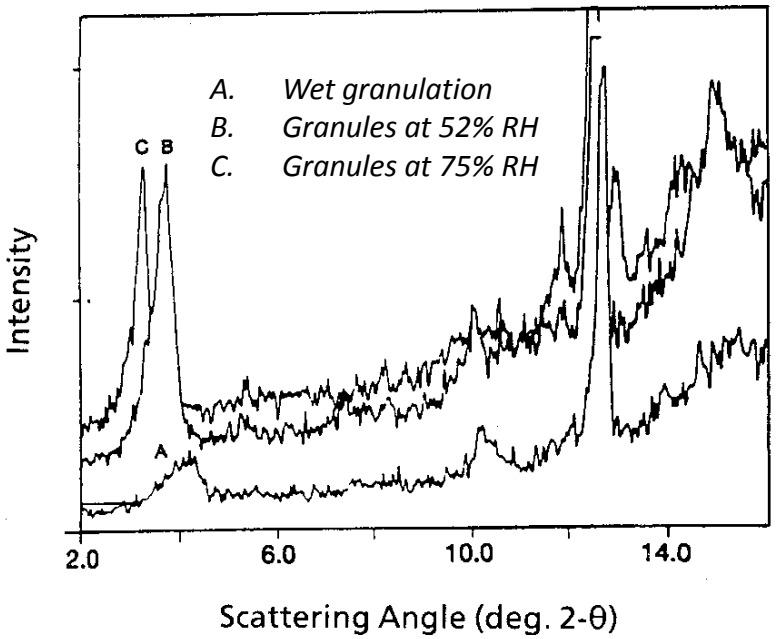




Morris et al. *Int J Pharm* **1994**, *108,* 195-206

Early Formulation

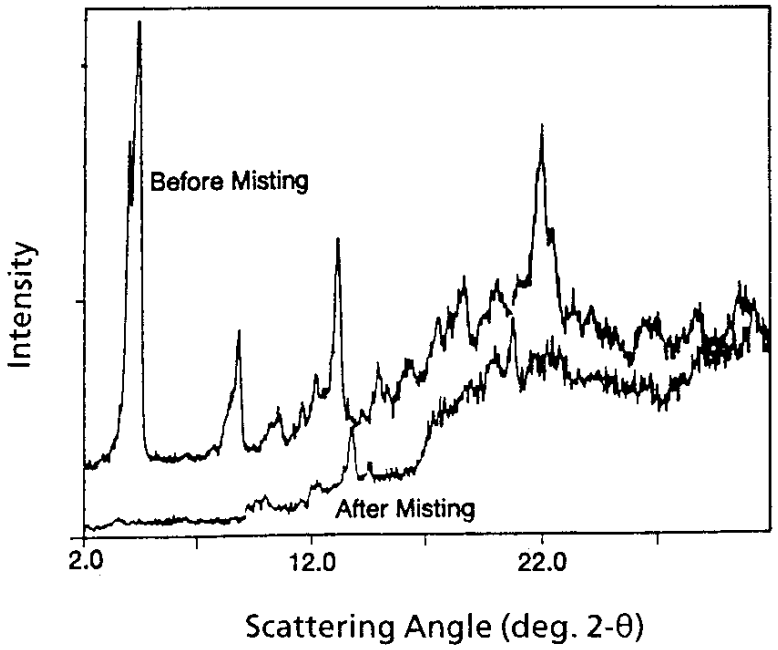
- Capsules and tablets prepared by wet granulation and dry blending
  - Clinical formulations: 1:10 and 1:15 drug:excipient
  - Prototype formulation: 1:2.8 drug:excipient
- Dry blend showed no change in crystallinity
- Wet granlulation resulted in mostly amorphous drug
- Dry blend adopted for clinical supplies with special packaging



Morris et al. *Int J Pharm* **1994**, *108,* 195-206

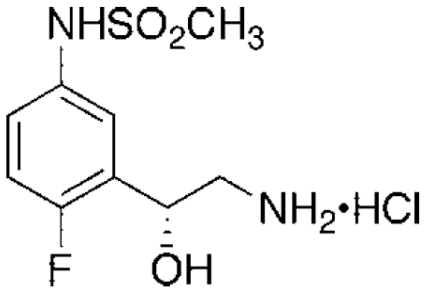
Early Formulation

- Possible changes at surface investigated by misting surface of compact with water
  - Converted to amorphous or semisolid phase
  - Suggests that all forms would convert in dissolution media and produce the same profile
- Understand the affect of water on forms



Morris et al. *Int J Pharm* **1994**, *108,* 195-206

Granulation



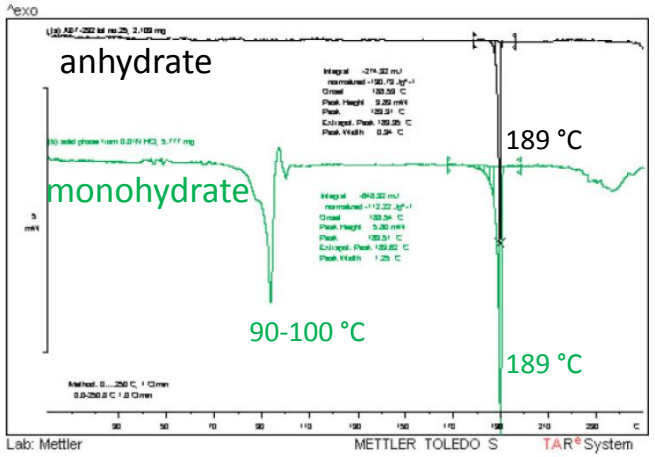
- Abbott-232
  - Investigated for relief of stress urinary incontinence
  - Preformulation studies showed it was
    - Highly water soluble
    - Chemically stable
    - Compatible with range of standard excipients, except lactose and silicon dioxide
    - Stable in solution and to light
    - Stable in solid state for 10 mos at 40 °C/75% RH
    - Highly potent

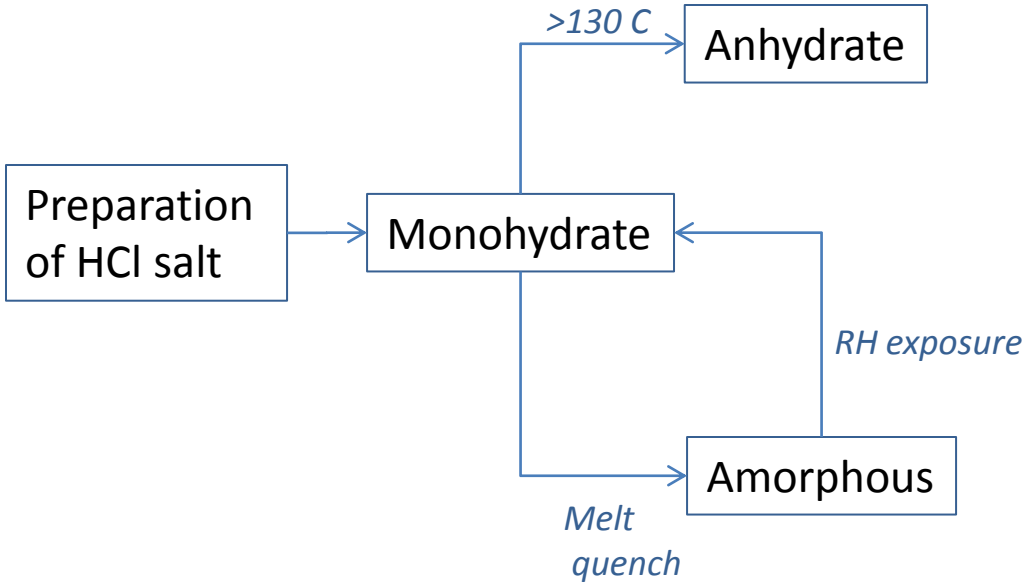
Wardrop et al. *J Pharm Sci*. **2006,** *95*, 2380-2392.

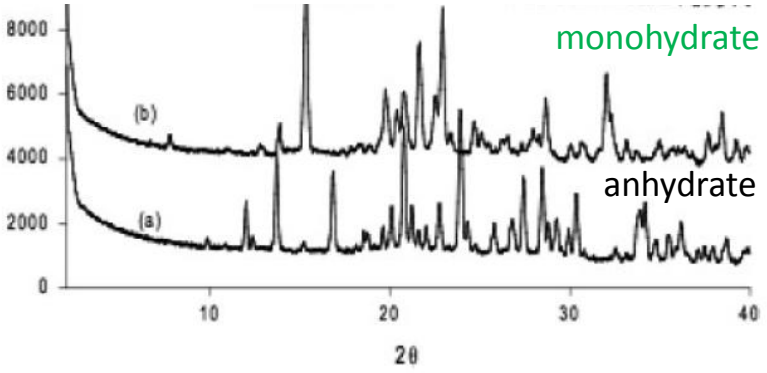
Granulation

Abbott-232

- Three solid forms found
  - Anhydrate
  - Monohydrate
  - Amorphous form







Wardrop et al. J Pharm Sci. 2006, 95, 2380-2392.

Granulation

- Since the drug was highly potent, low doses (1-2%) needed for clinical studies
  - Wet granulation and direct compression used to make immediate release (IR) and extended release (ER) tablets

Abbott-232 Immediate Release Tablet Formulations

	Wet Granulation (% w/w)	Direct Compression (% w/w)
Abbott-232	1.0	1.0
Pre-gelatinized starch	5.0	—
Sodium starch glycolate	4.0	4.0
Mannitol	84.5	—
Avicel pH 101	5.0	—
Avicel pH 102	—	55.3
Fujicalin		37.2
Magnesium stearate	0.5	2.5
Total tablet weight (mg)	100.0	100.0

Abbott-232 Extended Release Tablet Formulations

Matrix Tablet—Wet Granulation		Multi-Unit Reservoir Tablet—Direct Compression	
Ingredient	(% w/w)	Ingredient	mg/Tablet
		Tablets:	
Abbott-232	1.0	Abbott-232	0.50
HPMC K15M	30.0	Avicel pH 102[a]	2.50
Carbopol 974P	15.0	Fujicalin[a]	21.38
Avicel PH 101	20.0	Magnesium stearate	0.62
Mannitol, USP	33.0		
Magnesium stearate	1.0	Tablet weight	25.00 mg
		Coating[b]:	Solids as % aquacoat
		Aquacoat	N/A
		Triethylcitrate	35.00%
		HPMC 2910 USP 15cp	20.00%

[a]Represents a ratio of 20:75.5 Avicel pH 102: Fujicalin.
[b]Total coating (solids) weight gain up to 30% tablet weight, solution is 13% solids.

Wardrop et al. *J Pharm Sci*. **2006**, *95*, 2380-2392.

Granulation

IR Granulation processes

Wet Granulation

Excipients passed through 40 mesh screen and bag blended

↓

Dry mix charged into high shear mixer

↓

Granulated with Abbott-232 solution and additional water

↓

Dried

↓

Milled with impact mill

↓

Lubricated with magnesium stearate in diffusion blender

↓

Compressed with rotary compressing machine

Direct Compression

Abbott-232 screened through 200 mesh screen

↓

Bag blended with Avicel, Fujicalin, sodium starch glycolate

↓

Layered with remaining excipients into V-blender

↓

Mixed for 30 min

↓

Magnesium stearate added and mixed for 10 min

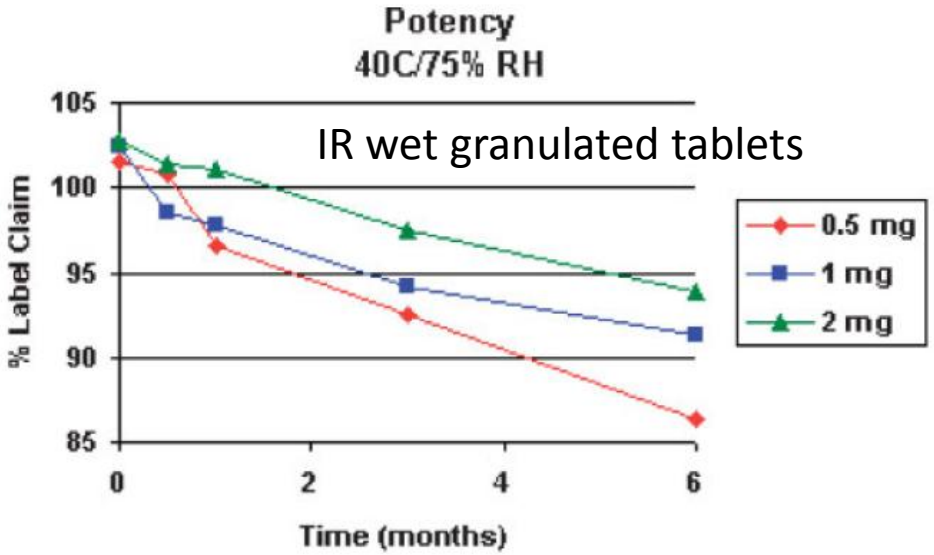
↓

Compressed with rotary compressing machine

Wardrop et al. *J Pharm Sci*. **2006**, *95*, 2380-2392.

Granulation

- Accelerated stability showed wet granulated material not as stable as direct compression formulation



Accelerated Stability Results for Abbott-232 IR Tablets, 1 mg, Prepared by Wet Granulation and Direct Compression

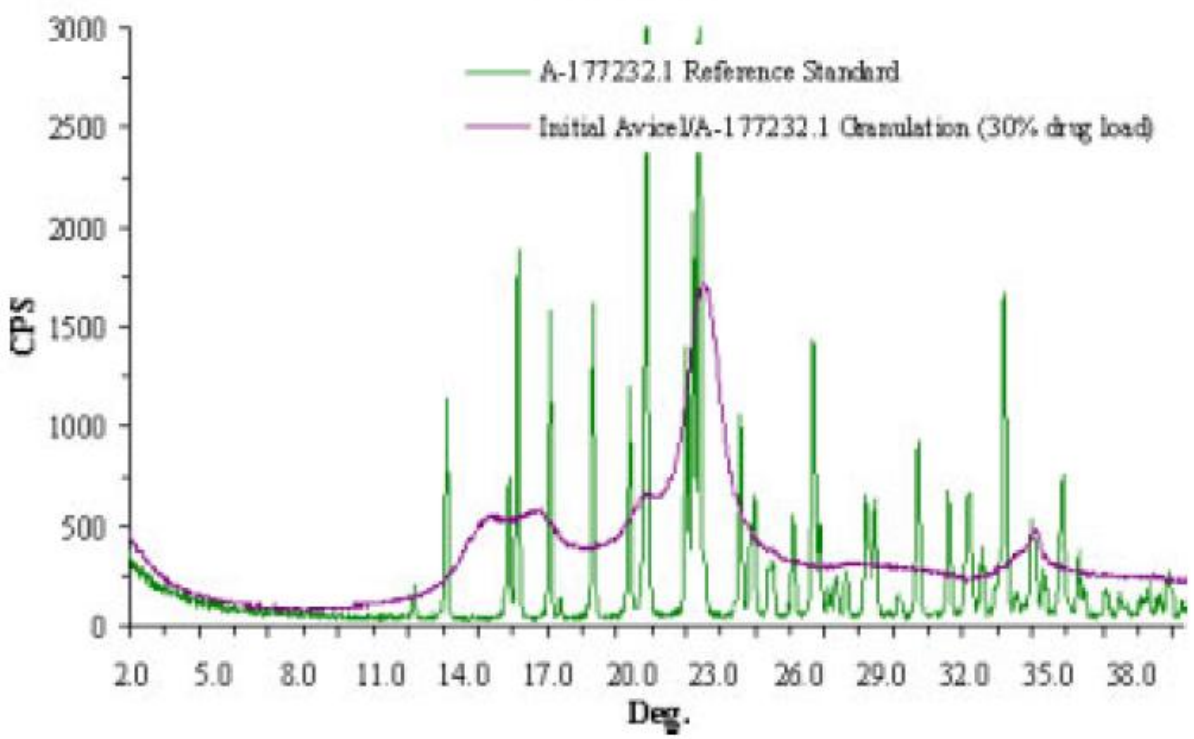
40°C/75% RH	Wet Granulation		Direct Compression	
Time (weeks)	Potency (% LC)	Related Substances (% w/w)	Potency (% LC)	Related Substances (% w/w)
1	102.4	0.30	100.5	0.32
4	97.4	1.02	100.2	0.37

Wardrop et al. *J Pharm Sci*. **2006**, *95*, 2380-2392.

Granulation

Prepared batch at 30% loading to investigate instability

- XRPD showed that Abbott-232 was amorphous
- Amorphous material less chemically stable than crystalline

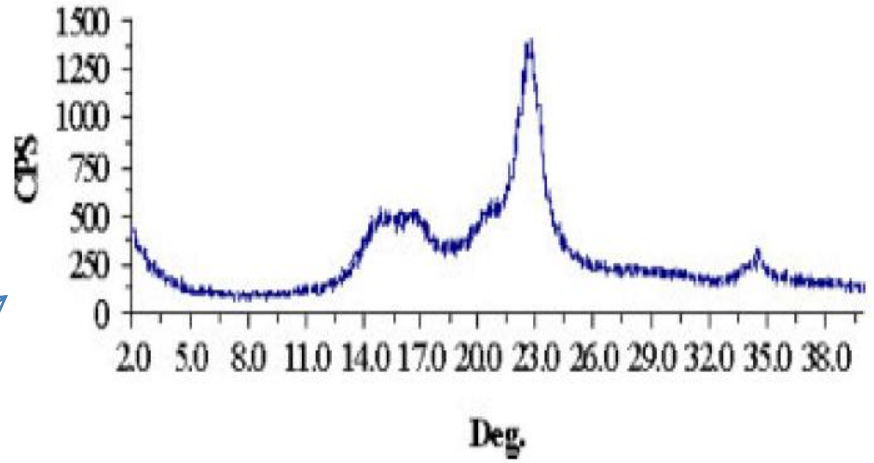


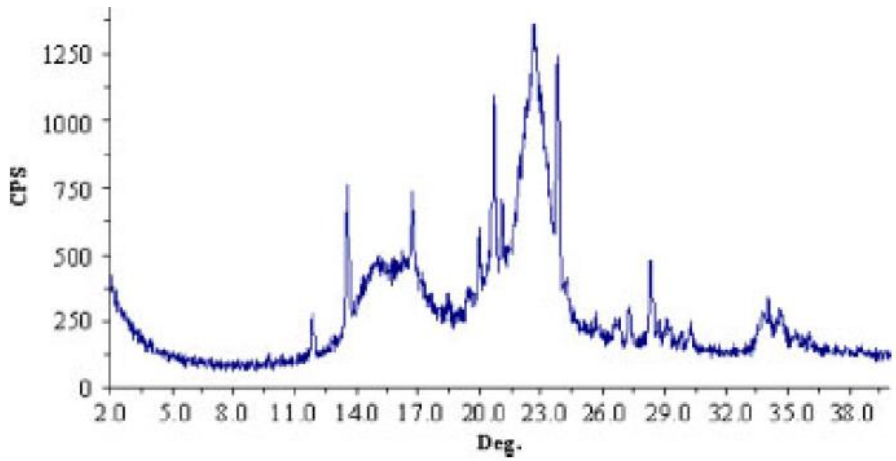
Wardrop et al. *J Pharm Sci*. **2006**, *95*, 2380-2392.

Granulation

Amorphous formulation

- Stable in capped bottle for 5 mos at ambient RH
- Unstable after 1 mo at 40 °C/75% RH

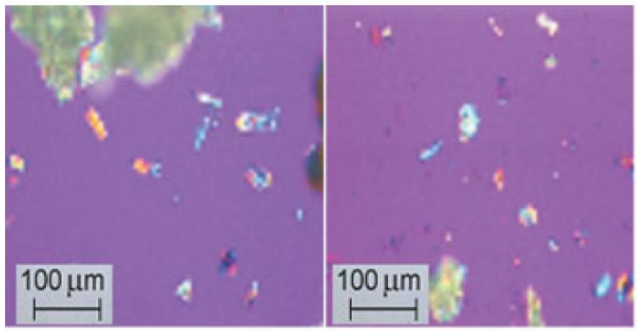




Wardrop et al. *J Pharm Sci*. **2006**, *95*, 2380-2392.

Granulation

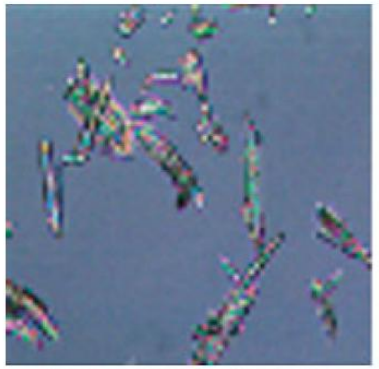
- Switched to direct compression formulation
- Monitored crystal form by optical microscopy
  - Anhydrate form can be distinguished in formulation
  - Other techniques could not be used due to low loading (1%)
- Direct compression gave desired stability
- Understand the changes in form during your process; may need to do perform targeted studies at higher concentrations to understand changes



Abbott-232 IR Dry Blend

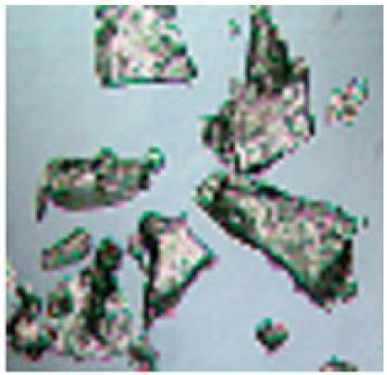
A: Before Compression B: After Compression, Crushing

Direct compression blend



Abbott-232 (anhydrate)
Crystalline

Abbott-232 (anhydrate)
Amorphous



Abbott-232 (monohydrate)
Crystalline

Pure Forms

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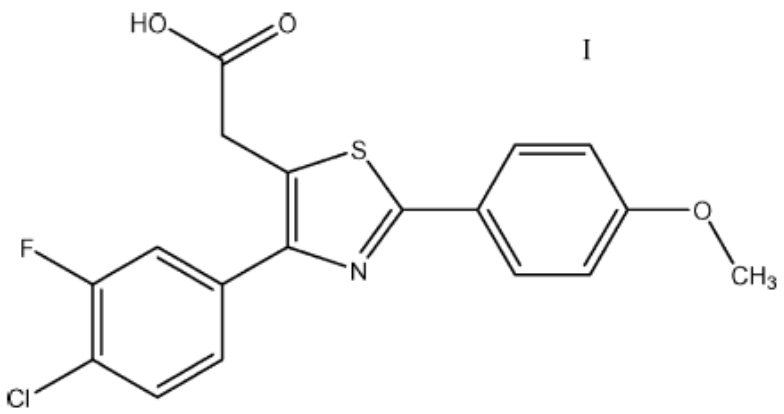
Case Study

- Compound 1 being developed for treatment of overactive bladder
- Aqueous equilibrium solubility 0.07 mg/mL
- Comprehensive polymorph screen resulted in two anhydrous forms (Forms 1 and 2)
- Salt screening did not result in any developable salts



I

pKa 3.66

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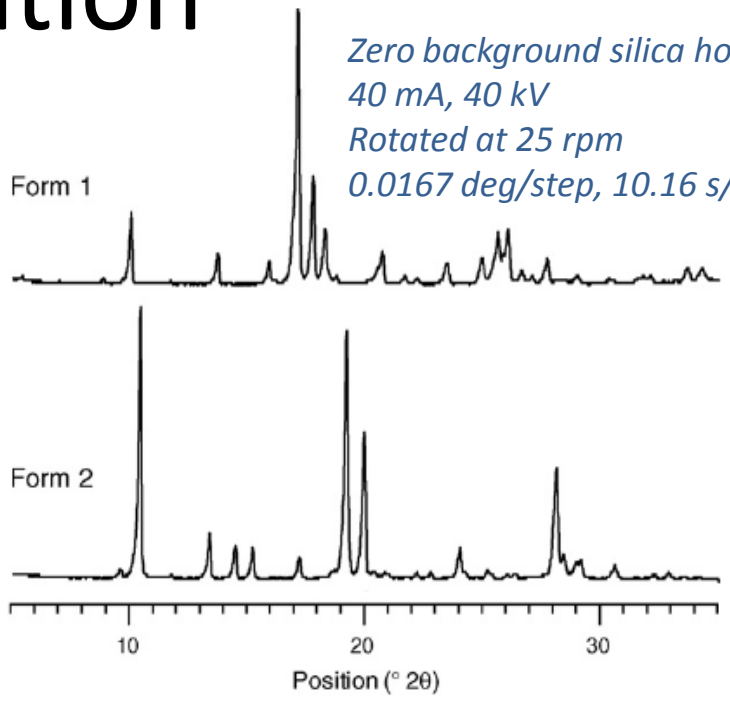
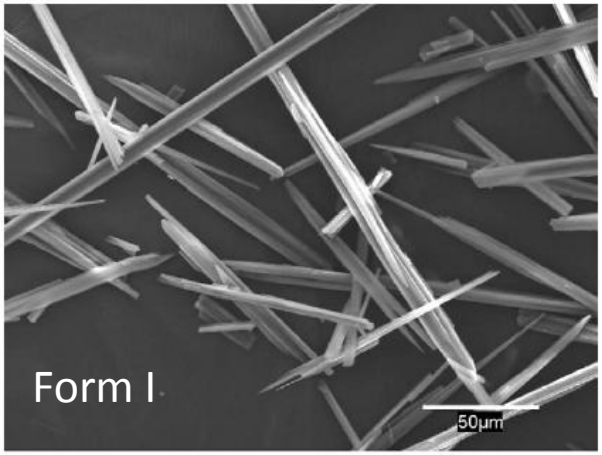
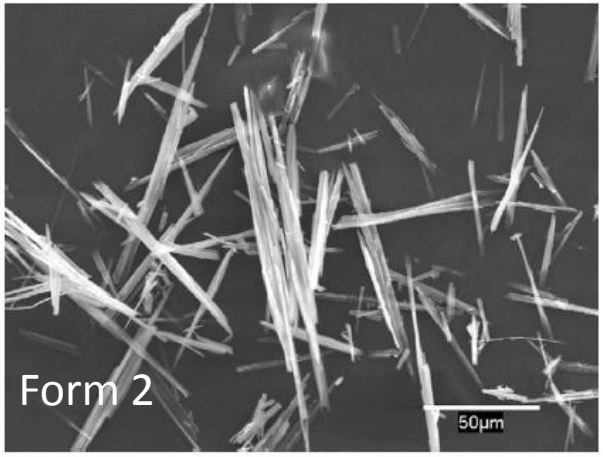
Characterization

- XRPD showed distinct peaks for each form
- SEM showed needle morphology for both forms



Zero background silica holder
40 mA, 40 kV
Rotated at 25 rpm
0.0167 deg/step, 10.16 s/step





Backscatter mode
15 kV beam

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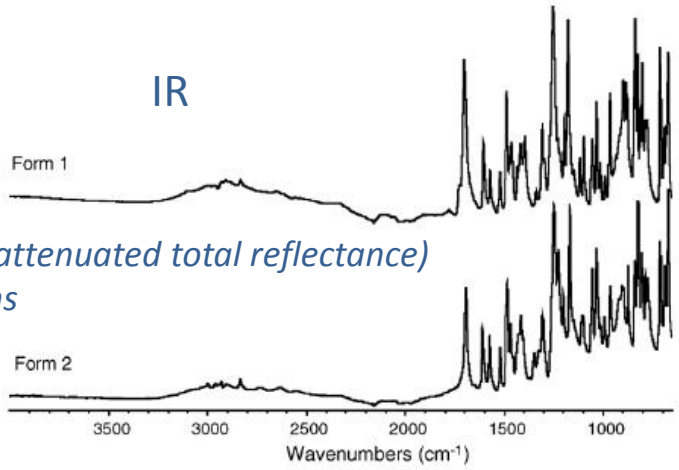
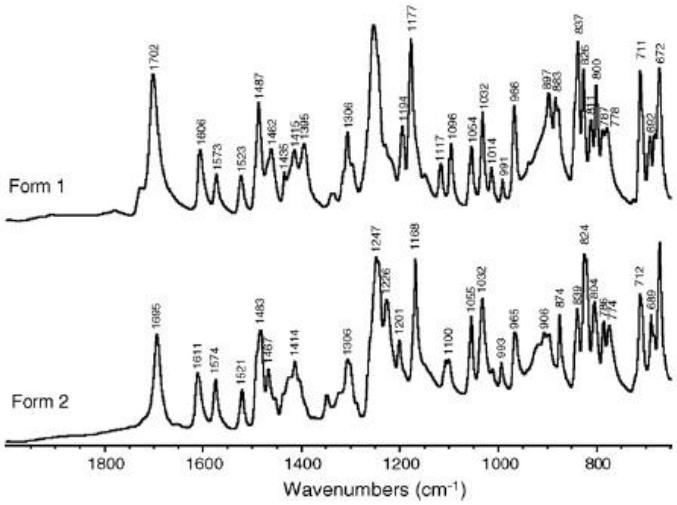
Characterization

Unique IR and Raman spectra were observed

IR

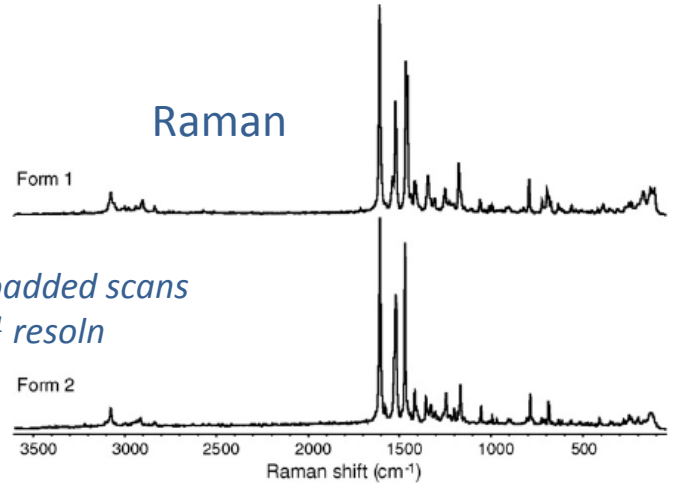
DATR (diamond attenuated total reflectance)
64 coadded scans
4 cm^{-1} resoln

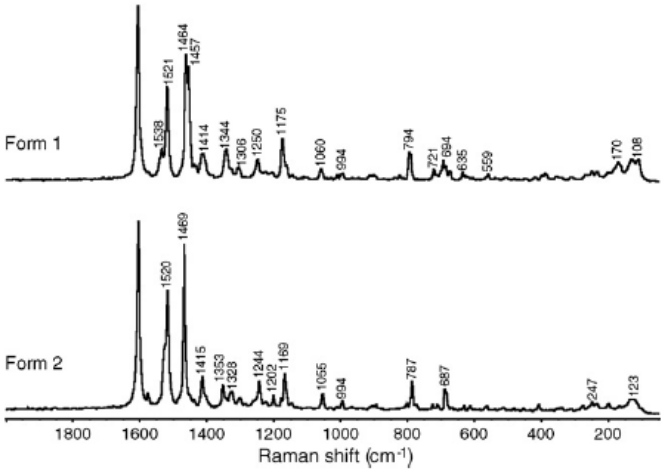




Raman

pellet
128 coadded scans
4 cm^{-1} resoln





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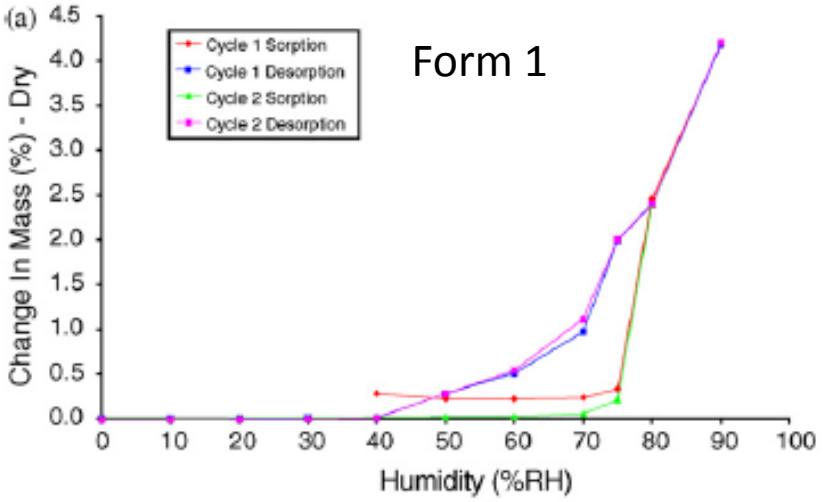
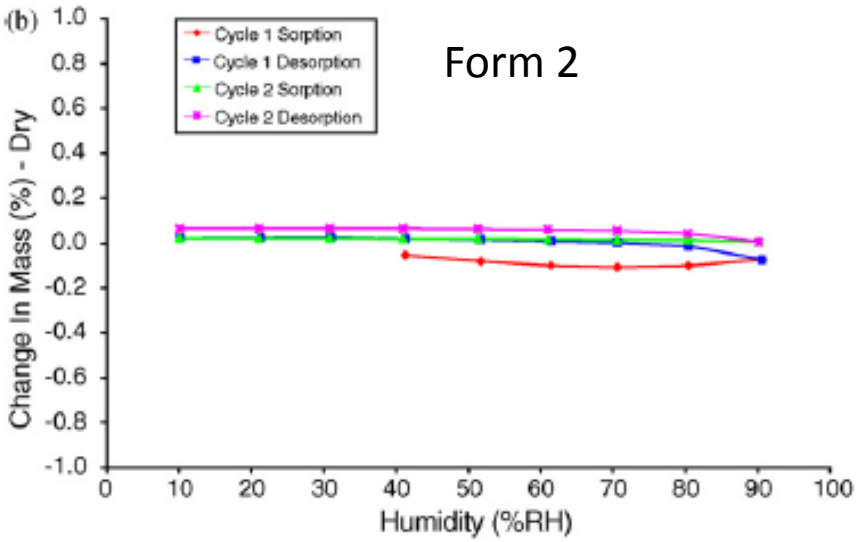
Characterization

- Water isotherms show that Form 1 will take up more water than Form 2
- Handling conditions would need to be monitored for Form 1





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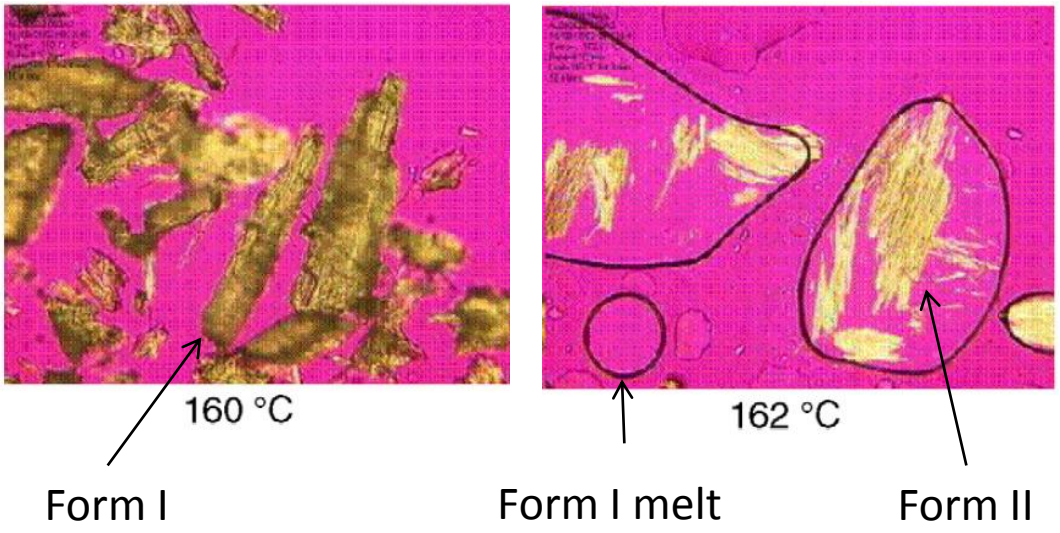
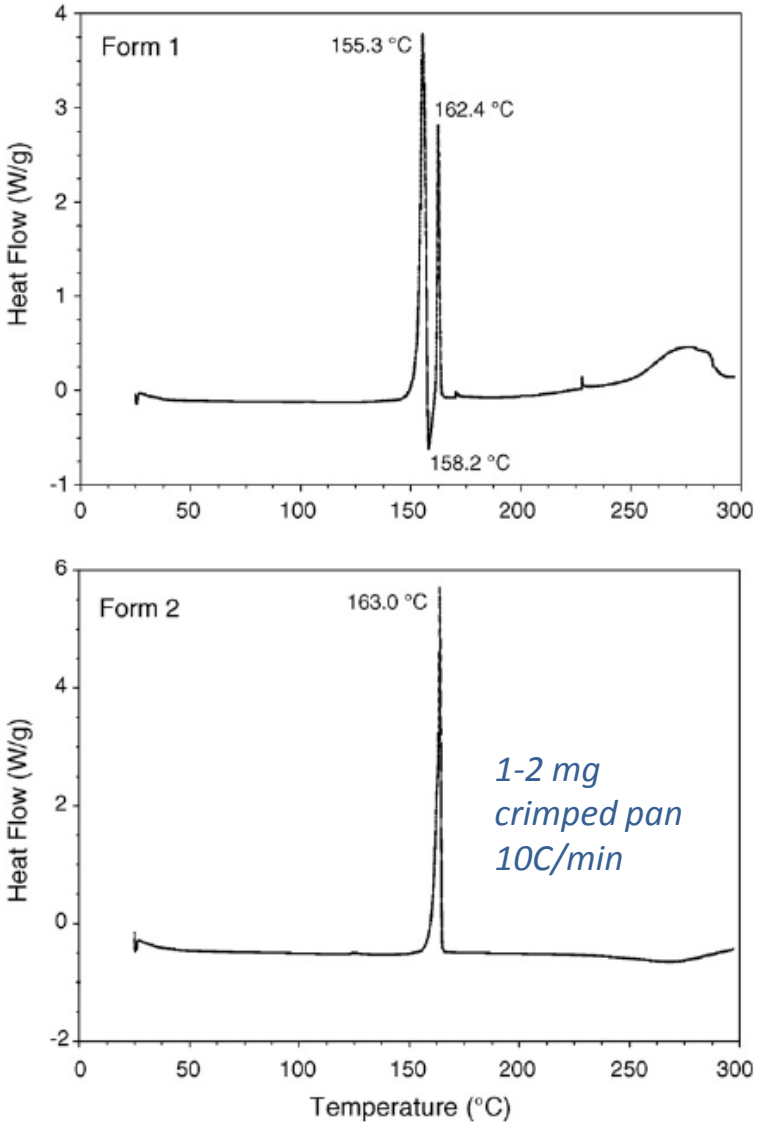
Characterization

DSC and hot stage microscopy show that Form 1 melts and recrystallizes to Form 2





Form	Solubility RT (mg/mL)	Solubility 43°C (mg/mL)
1	10.6	20
2	13.3	16

acetonitrile

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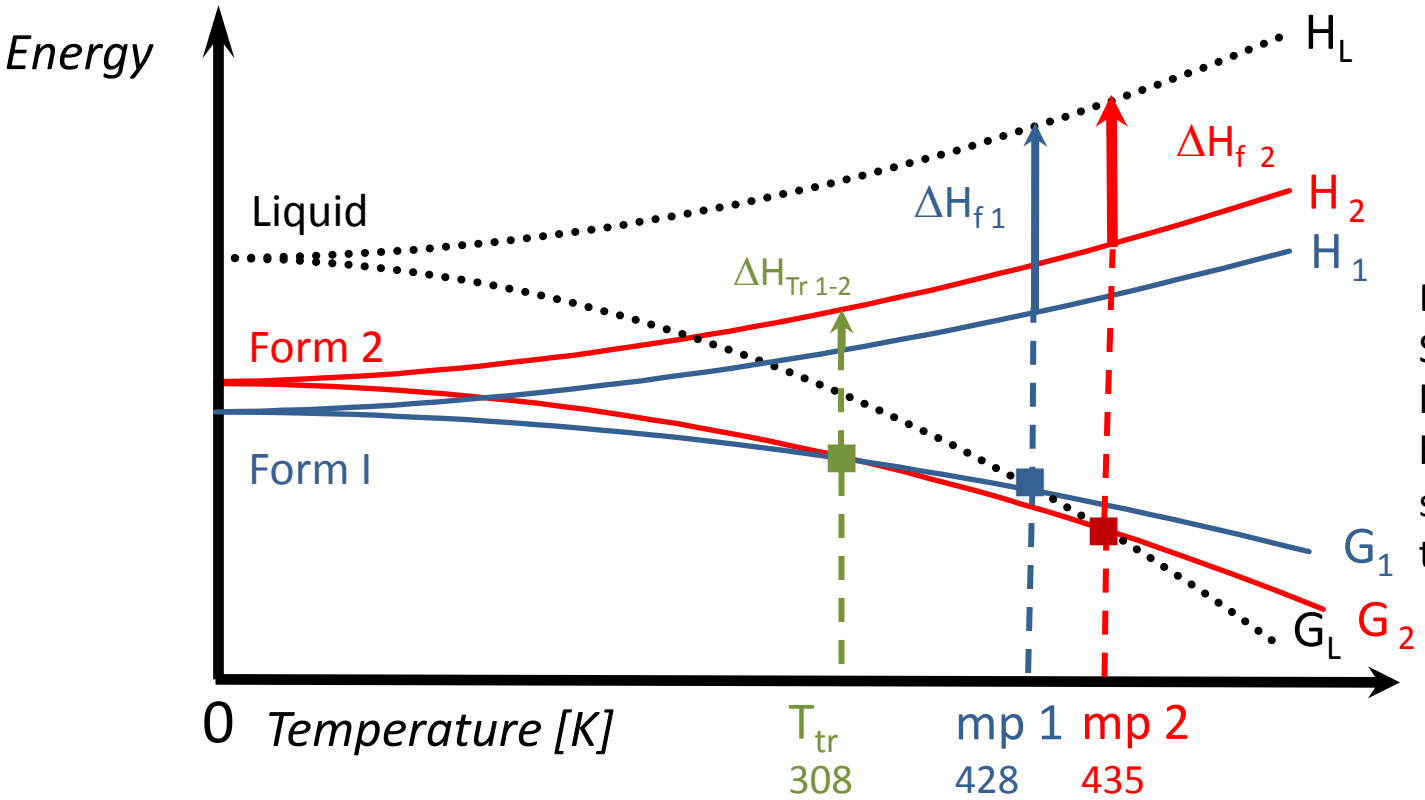
Stability

Temperature	Form
23.2	1
29.8	1
32.0	1
36.5	2
41.3	2
48.0	2

ethyl acetate
6 days
XRPD and DSC data

Enantiotropic system

- Form 1 is stable below 32°C
- Form 2 is stable above 36.5°C
- Transition temperature of 35°C



Enantiotropic system: Stable form at RT has lower melting point and higher heat of fusion; stability determined by transition temperature

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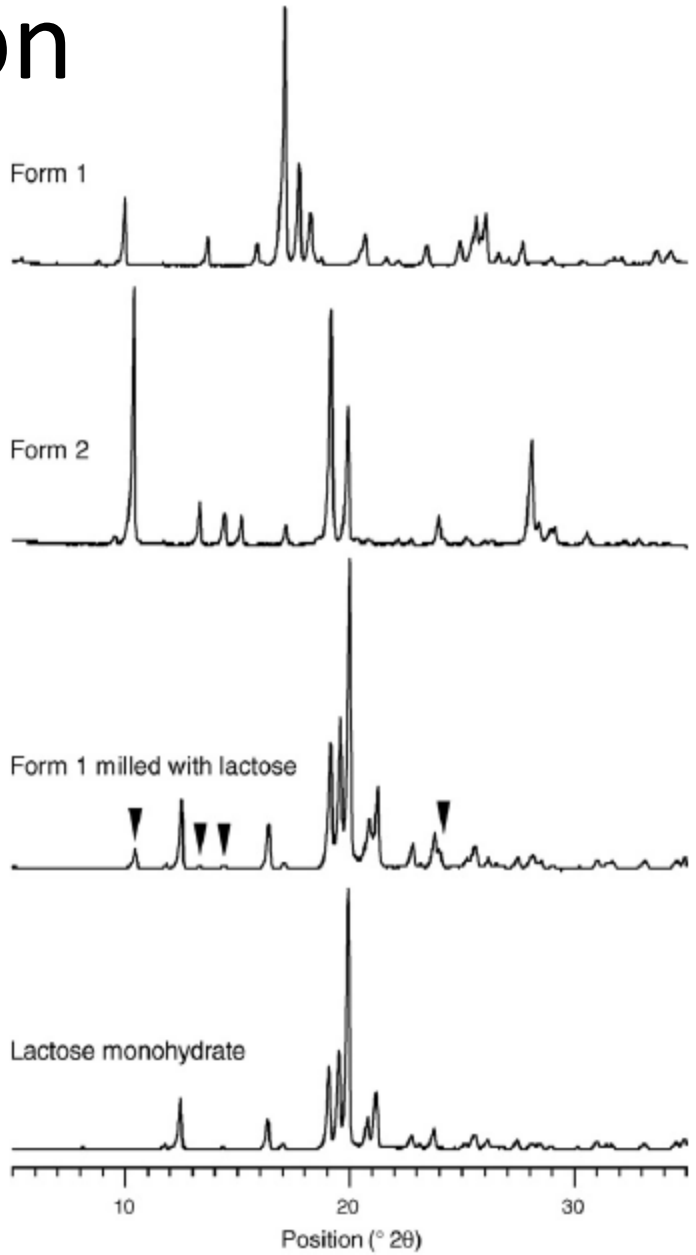
Formulation

Multistep dry-blending

- Mill drug with lactose monohydrate to reduce particle size and improve flow properties
- Form 1 converts to Form 2 during milling

Component	Percent (w/w)
Drug	8.3
Lactose monohydrate	61
Microcrystalline cellulose	24
Crosscarmellose sodium	3
Magnesium stearate	1

307.5 mg film coated tablet
300 mg of blend
Additional mass from film coating



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Form Selection

Form 2 was chosen for development even though it wasn't the stable form at RT

- Milling and hygroscopicity were important
- Showed that Form 2 was stable for 1 year under stability conditions

Criteria	Form 1	Form 2
Thermodynamic stability at RT	√	X
Milling stability	X	√
Chemical stability	√	√
Physical stability 20C/65% RH and 40C/75% RH (1yr)	√	√
Flow properties	X	√
Hygroscopicity	X	√
Ease of processing	X	√

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API Quantitation

- IR was used for API quantitation
  - May be a regulatory specification and need to be transferred to manufacturing sites; IR commonly onsite for chemical identification
  - DATR-IR benefits from rapid, simple sample preparation and minimal instrument to instrument variability
  - Multivariate approach using Partial Least Squares (PLS) employed
    - 1450-1420, 1360-1330, 1240-1215, 1190-1155, 820-775 cm-1
  - Standards: 10,25,50,75, and 90% Form 1 mixed with Form 2
  - Standards analyzed in triplicate
  - Correlation coefficient (R2) of 0.991, low root mean square error of calibration (RMEC) of 4.88%
  - Lower limit 5% Form 1; minimum quantifiable limit 10%
  - Limits confirmed with XRPD and SSNMR
  - Used for batch analysis and stability testing

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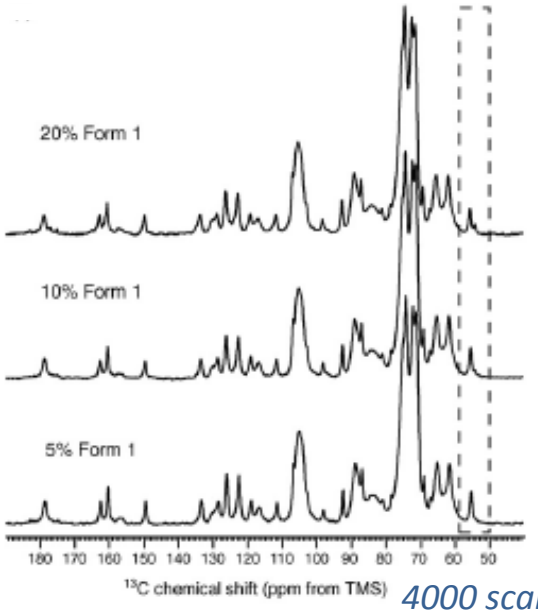
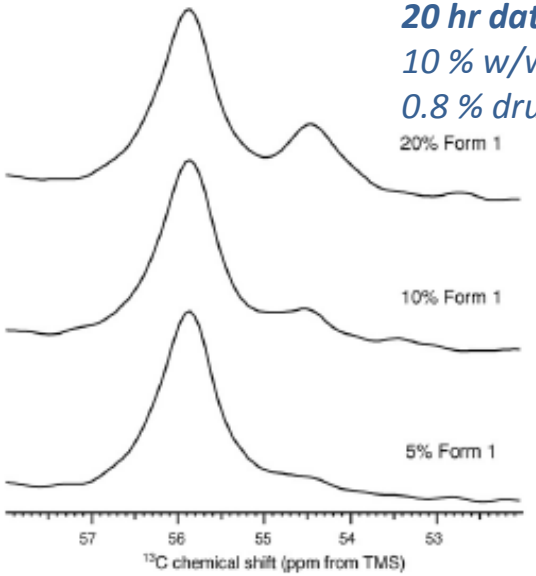
Drug Product Quantitation

- Highest strength tablet 8.1% w/w drug
- IR and Raman did not have needed sensitivity
- XRPD had significant overlap with Form 1 and excipients; Form 2 did not show significant overlap
- ^{13}C SSNMR had sufficient sensitivity and resolution
  - Limit test method developed



4000 scans
20 hr data acquisition
10 % w/w LOD
0.8 % drug



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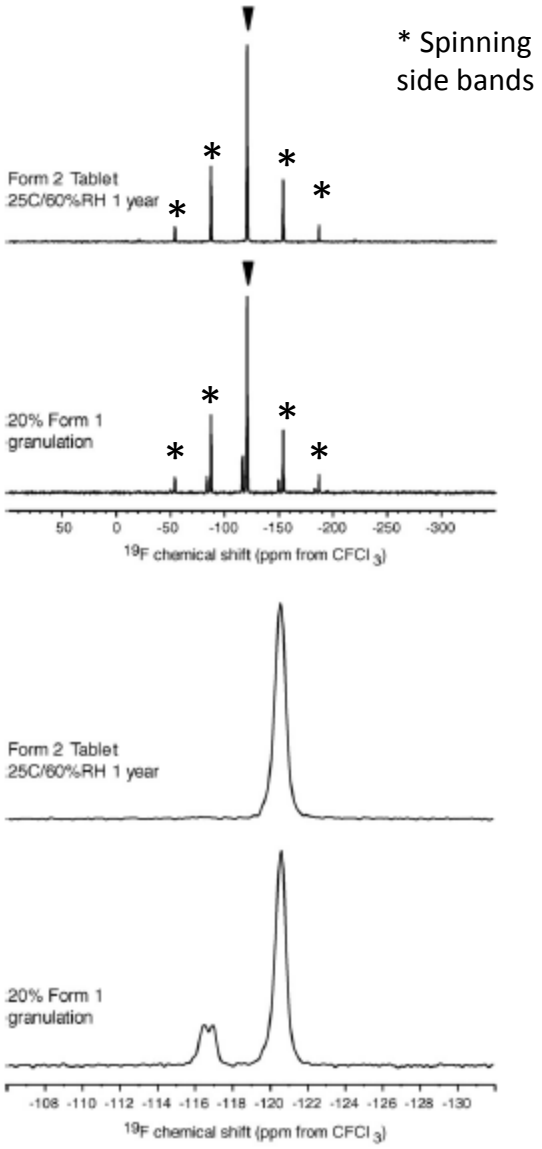
Drug Product Quantitation

- Improved method developed with ^{19}F NMR
  - ^{19}F more sensitive than ^{13}C
  - Reduces long analysis times
  - Transfer to other sites may be limited
- Limit of detection of ^{19}F method 1.5% w/w Form 1
  - Absolute detection limit 0.12% w/w Form 1
  - 4.2 hr acquisition time
- Can be used for lower dose tablets
  - 0.3% w/w drug in tablets (1 mg drug in 300 mg tablets)



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Case Study

- Understand and characterize your API before doing formulation development
- Metastable forms can be chosen if risks are considered
- Understand what properties you need/want for formulation
- Test key processing steps to determine change in form
- Development of analytical testing requires more than just specificity (testing sites, excipient interference, loading, sensitivity, etc)

What Have We Learned

- Characterization is a key component to successful formulation development
- A variety of characterization methods are available to analyze the form in drug products
- Characterization can involve qualitative or quantitative determination of forms
- Most processes can change the crystal form of the drug substance or excipients
- Formulation development must be linked with known forms, properties, formulation processes, etc
- Consider what other components are in the formulation and how the process may affect the solid
  - Crystalline to amorphous, amorphous to crystalline, salt/cocrystal formation, eutectics, etc
- May need small scale experiments to understand changes or determine operating parameters for process/forms
- Make sure your solid form fits your dosage form

Why Do We Care

- A change in form can result in property changes
  - Dissolution, bioavailability, physical stability, chemical stability, hardness, etc
- Property changes in the drug product can lead to failed batches
- Understanding the relationship between forms and form changes upon processing will help develop robust product manufacturing and decrease the number of failed batches
- Good characterization of the forms in drug products will result in better regulatory and IP documentation

Resources

- Over view: *Solid-State Chemistry of Drugs*, 2nd edition, S. R. Byrn, R. R. Pfeiffer, and J. G. Stowell, SSCI, Inc, West Lafayette, IN 1999.
- Overview: Newman et al. *Drug Discovery Today* **2003**, *8*, 898-905.
- Overview: Zhang et al. *Adv. Drug Delivery Rev*. **2004**, *56*, 371-390.
- XRPD chemometrics: Moore et al. *J Pharm Biomedical Analysis* **2009**, *49*, 619-626.
- Raman: Taylor et al. *J. Pharm Sci*, **2000**, *89*, 1342-1353.
- Thermal: Giron et al. *J. Therm Analysis*, **1997**, *48*, 473-483.
- NMR: Tishmack et al. *J Pharm Sci,* **2003**, *92*, 441-474.
- NIR imaging: Reich. *Adv Drug Delivery Rev,* **2005**, *57*, 1109-1143.
- Terahertz: Zeitler et al. *J Pharm Pharmacol*. **2007**, *59*, 209-223.
- Thermal conductivity: Sanders et al. *J. Microscopy*, **2000**, *198*-77-81.
- Quantitation: Stephenson et al. *Adv Drug Delivery Rev*. **2001**, *48*, 67-90.
- Reactivity: Byrn and Newman. *Adv. Drug Delivery Rev.* **2001**, *48*, 115-136.

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