An Overview of Solid Form Screening During Drug Development

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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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Definitions

- Polymorph
  - FDA: crystalline and amorphous forms as well as solvated and hydrated forms
  - Purists: crystalline forms with the same molecular composition (for example two anhydrous forms can be polymorphs, or two monohydrates can be polymorphs, but an anhydrate and a monohydrate can not be polymorphs)
  - How *polymorph* is used in journal articles and regulatory documents is important in understanding what is being said
- Solid form
  - Alternative to include all solid materials
    - Polymorphs, solvates, hydrates, amorphous, salts, cocrystals, amorphous dispersions

FDA definition: http://www.fda.gov/CDER/GUIDANCE/7590fnl.htm#_Toc167002781

Solid Forms

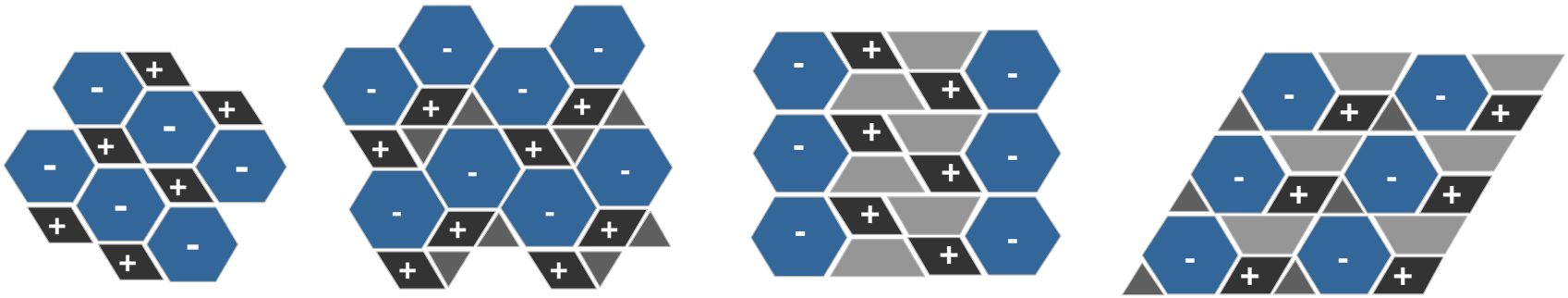
Classes of multicomponent molecular crystals

Neutral

Charged

Polymorphs

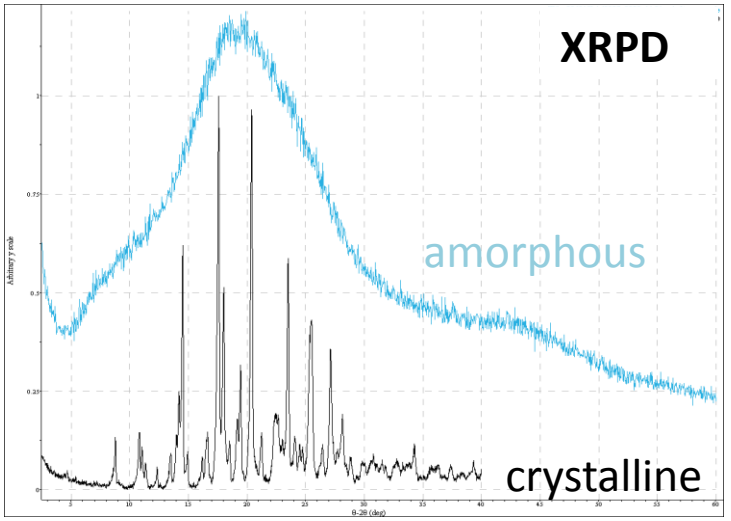
1. Homomeric
2. Hydrate/solvate
3. Cocrystal
4. Cocrystal hydrate



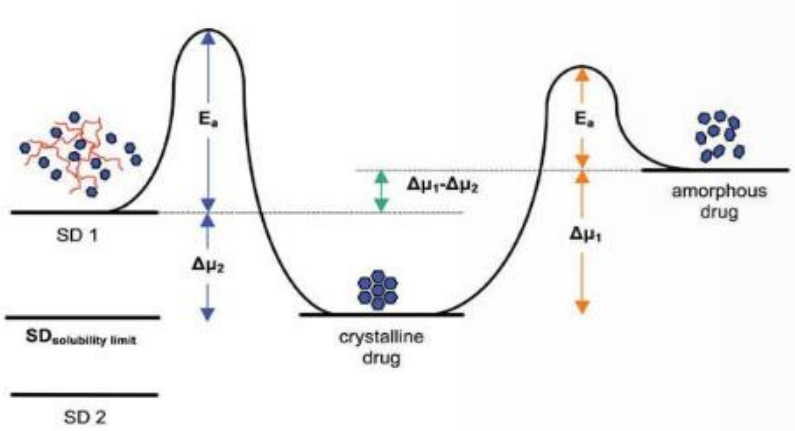
5. Salt
6. Salt hydrate/solvate
7. Salt cocrystal
8. Salt hydrate cocrystal

Amorphous

- Amorphous
  - No long range order
  - Do possess short range order
  - Less physically and chemically stable than crystalline materials
  - Higher dissolution than crystalline materials



- Amorphous solid dispersions
  - Amorphous drug with polymer
  - Polymer stabilizes amorphous drug
  - Results in better stability and higher dissolution

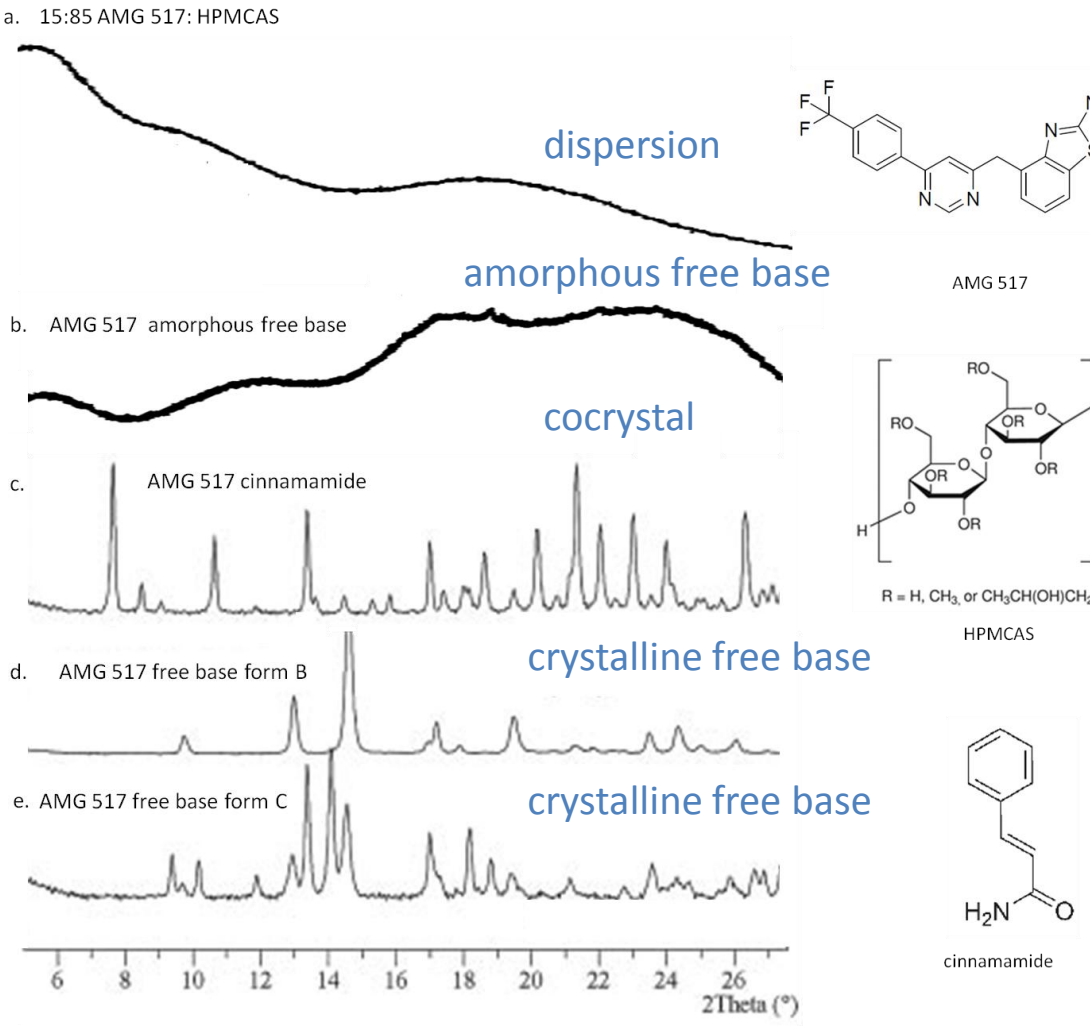


Schematic hypothetical energy cartoon showing the amorphous drug, crystalline drug, and several single phase amorphous solid dispersions (μ represents the chemical potential of the drug and E_a represents the activation energy barrier for crystallization).

Harmon et al. *AAPS Newsmagazine*, **2009**, *Sept*, 14-20

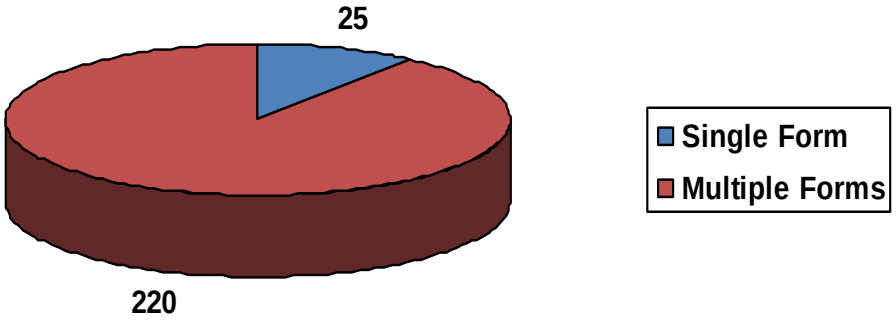
Form Characterization

- XRPD is front line technique to determine
  - Crystalline vs amorphous
  - Crystalline form
  - Changes in amorphous materials
- Once new patterns are found other techniques can be used to determine
  - Solvation state
  - Stoichiometry
  - Possible mixtures
  - Etc.



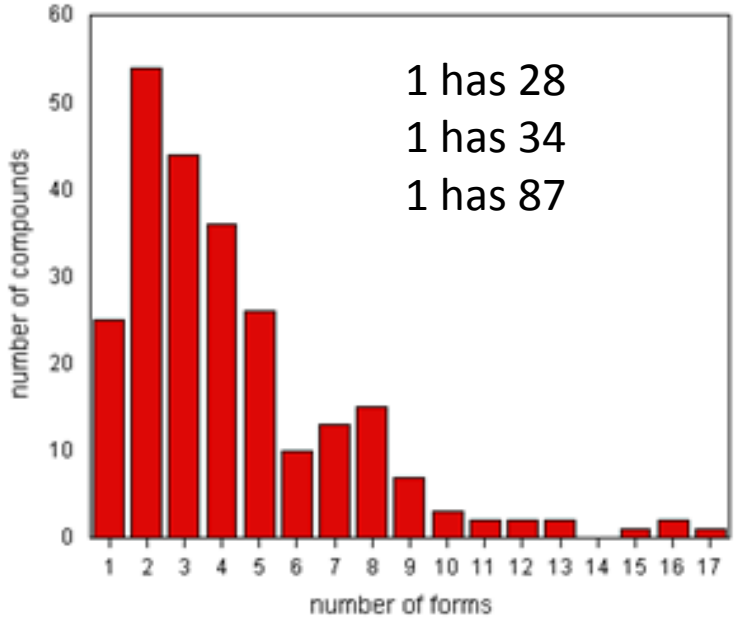
Stanton et al. *J. Pharm Sci*, **2010**, *99*, 3769-3778; Kennedy et al, *Mol Pharm*, **2008**, *5*, 981-993.

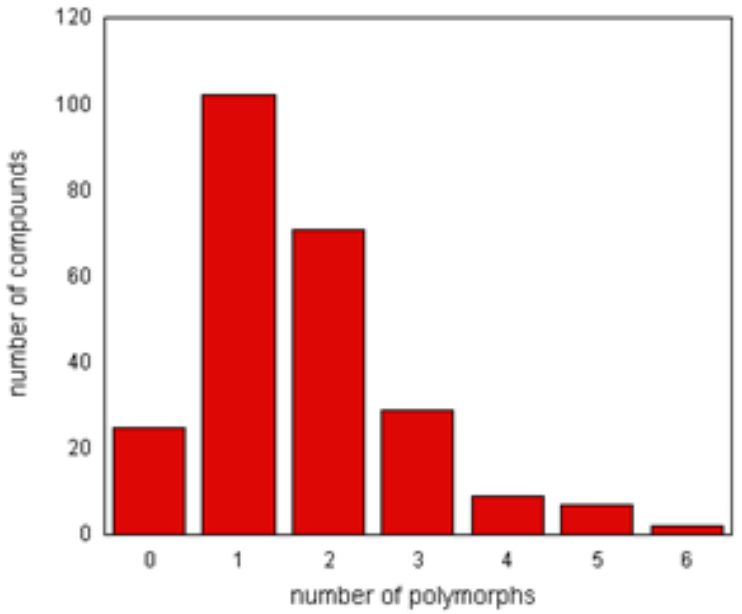
Why We Screen



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

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



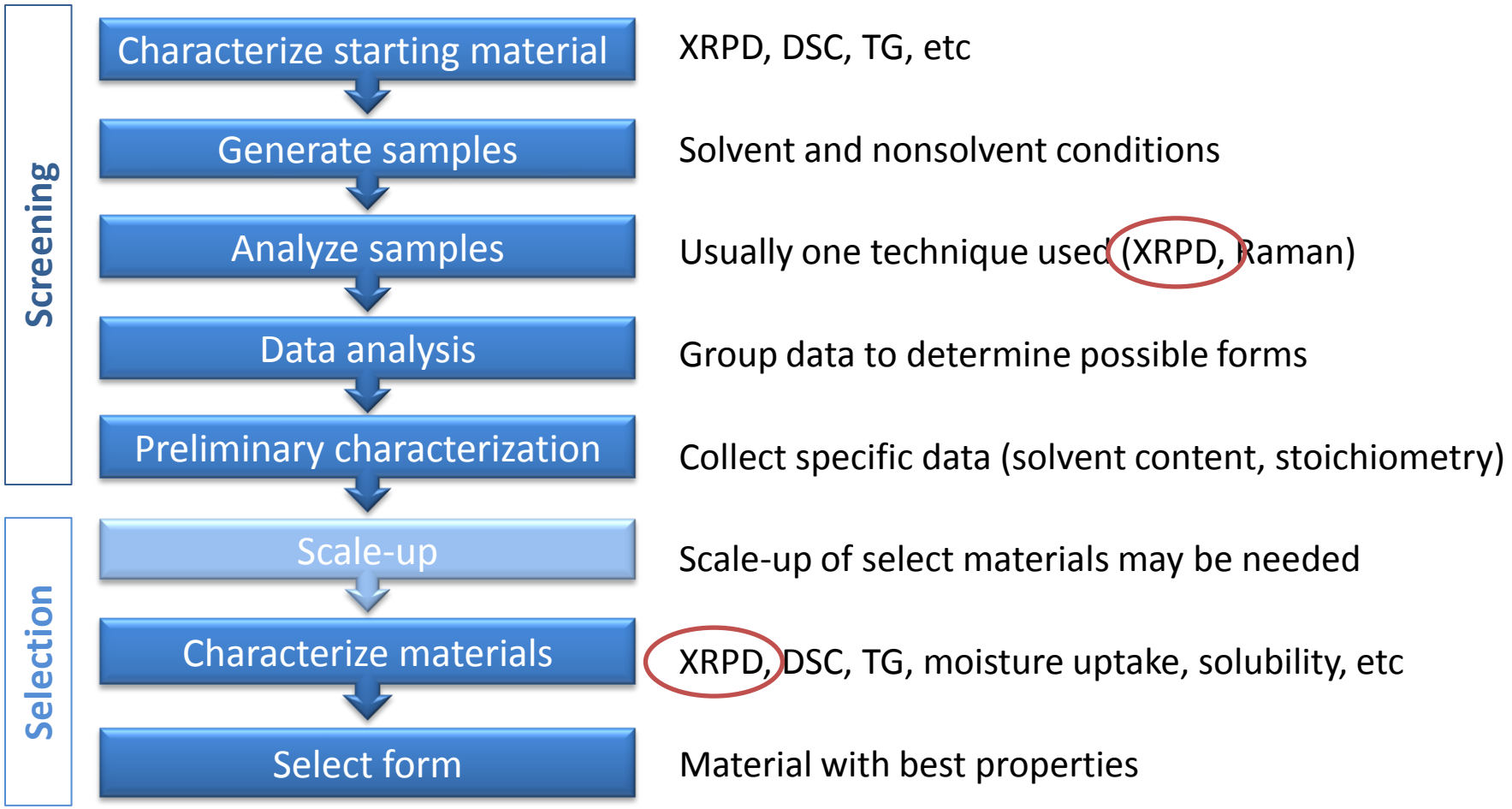


Stahly. *Cryst. Growth Des*, **2007**, *7*, 1007-1026

Form Screening vs Selection

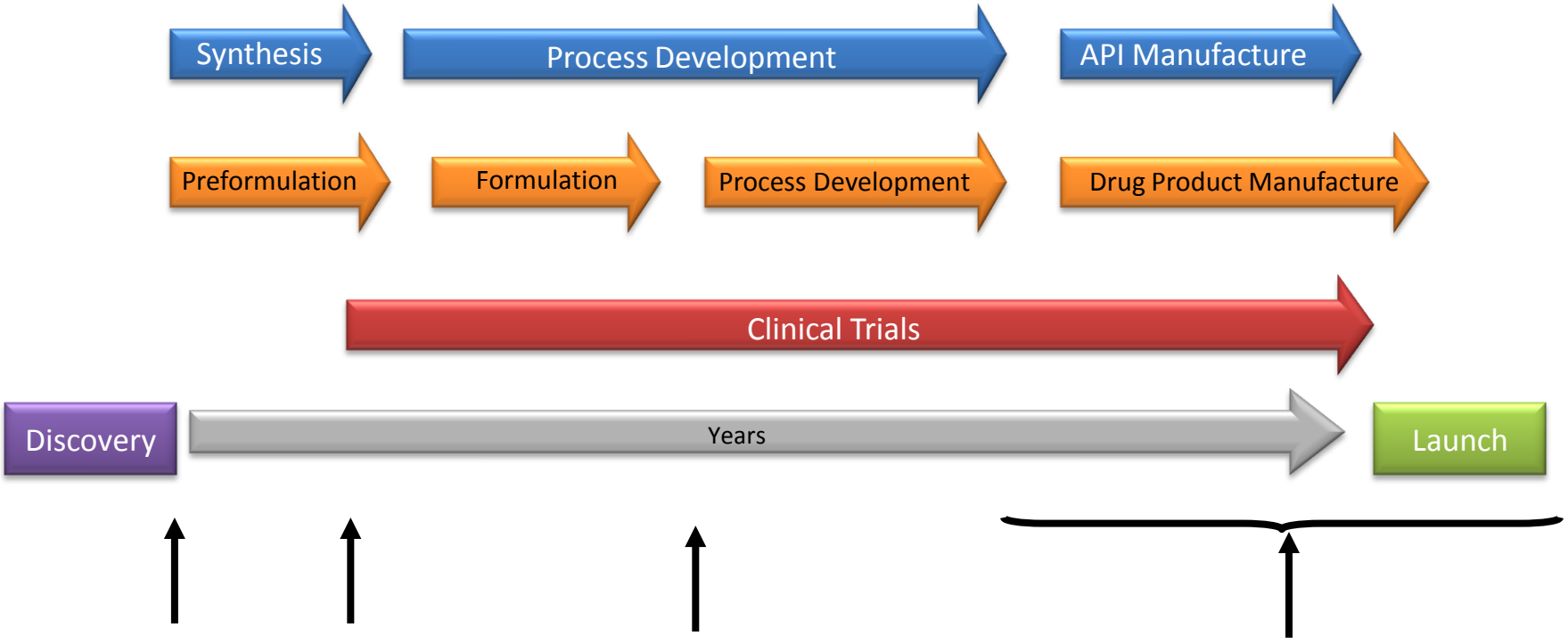
- Screening
  - Find possible forms under various conditions
  - Search for seeds/forms, *not a search for a process*
- Selection
  - Determine which form has the best properties for development
- Screen and selection are sometimes considered the same function
  - Not all forms found in a screen will be relevant when choosing a lead candidate (example- solvates)
  - However, knowing the possible forms will help in developing robust processes (API and drug product)

Screening and Selection

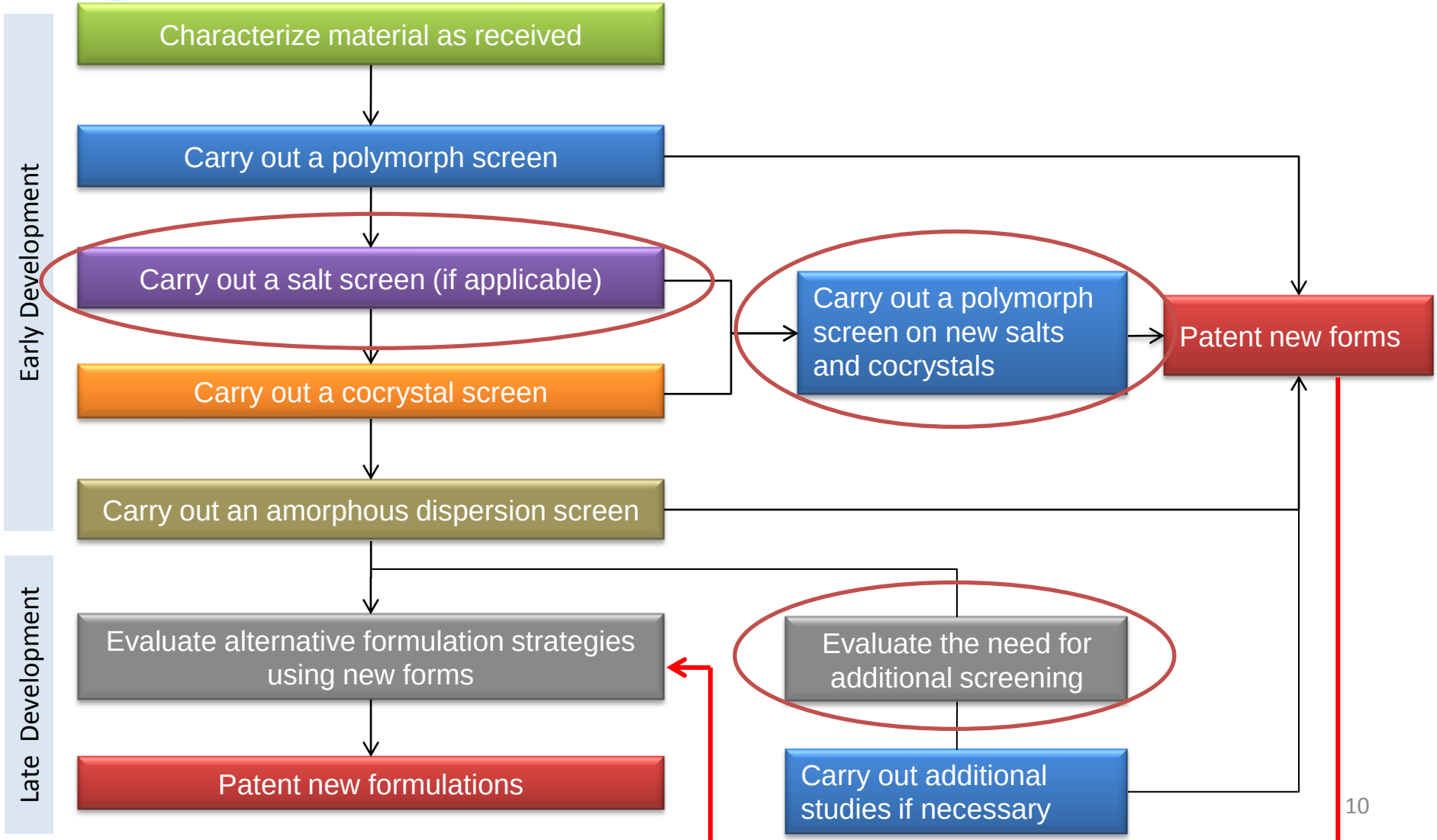


When to Screen

- Different screens can be performed at various stages of development
- Should have a good idea of form by end of Phase II meeting

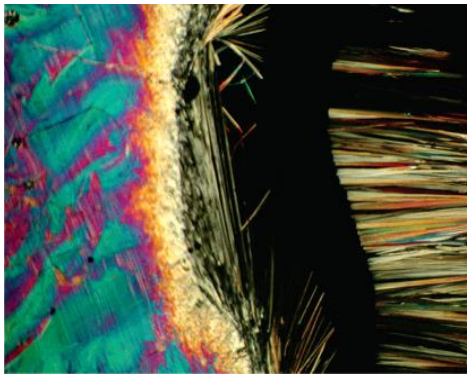


Screening Strategy



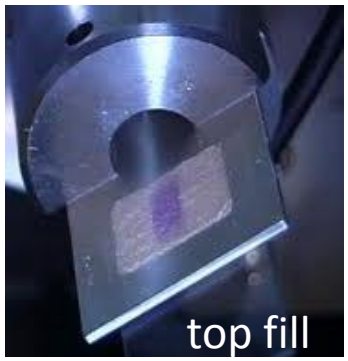
Manual Screens

- Salts, cocrystals, polymorphs, dispersions, amorphous
- Samples produced individually
- Solvent or solid methods used
- Solvent methods
  - Vials
    - Glass, silanized glass, acid or base washed, or polymer vials can be used
    - Check stability of plastic vials with various solvents
  - Capillaries, templates (polymers, gold, etc)
- Solid methods
  - Temperature or RH equilibration
  - Grinding, compression, sublimation
  - Cool from melt

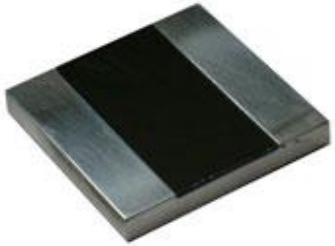


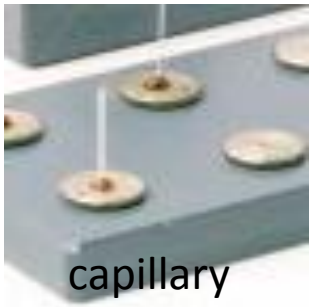
XRPD Sample Holders

- Large variety of sample holders available
- Can be specific to instrument or autosampler
- Need to maintain sample in random orientation
- Select a holder to accommodate the amount of sample produced

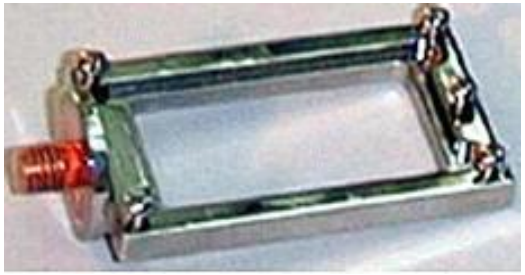

top fill


back fill

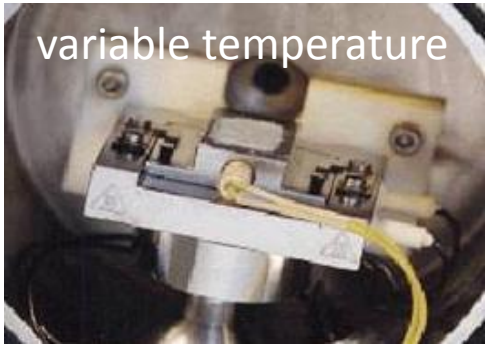

zero background


capillary


wire loop


transmission

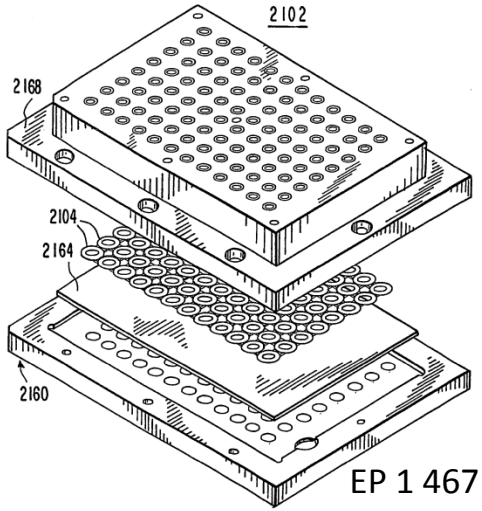

air tight


variable temperature


rotation

High Throughput Screens

- Screening
  - Usually done in an array with wells, tubes, or vials
  - Limited to solvent based methods
  - Limited crystallization conditions
  - Can generate large numbers of samples
- Analysis
  - XRPD instrument needs to be configured for plate
  - Issues with plate screens
    - Small sample size
    - Solid not always on bottom of vessel



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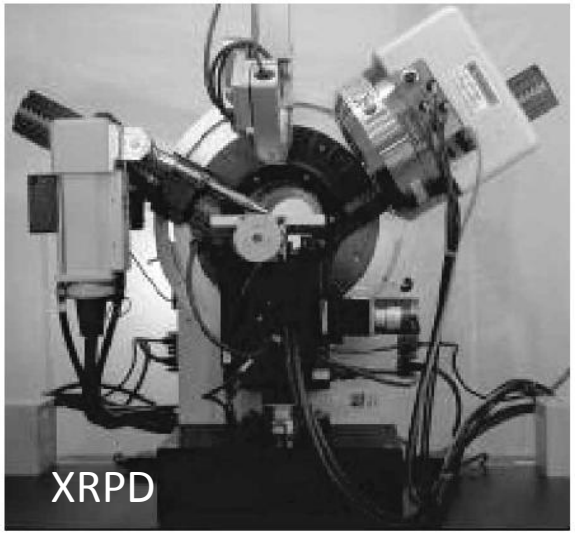
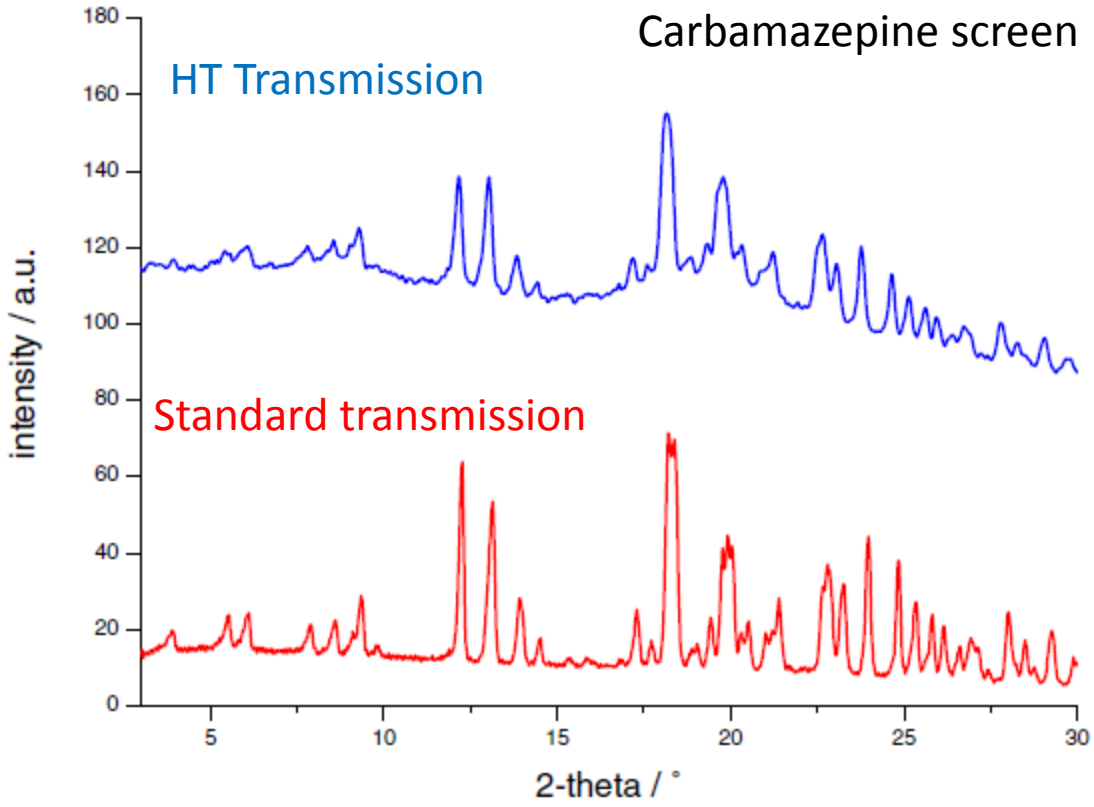


Storey et al. *Crystallography Rev.* **2004,** *10,* 45-56

XRPD Analysis

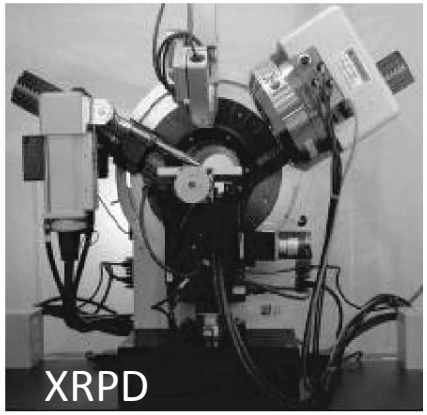
Issues with plate screens

- Small sample size
- Possible poor signal to noise ratio
- Broad peaks with variable shapes
- Strong background
- Preferred orientation

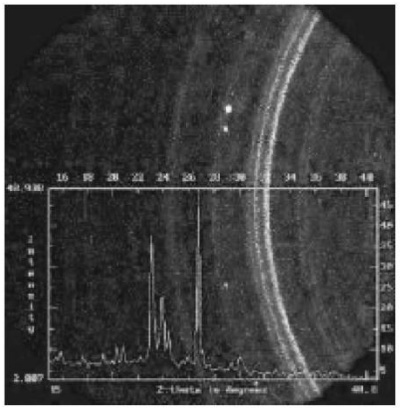


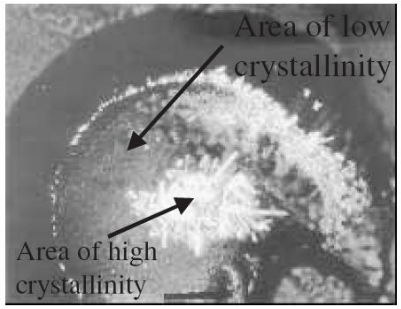
Wyttenback et al. *Pharm Res*. **2007**, *24*, 888-898

Analysis

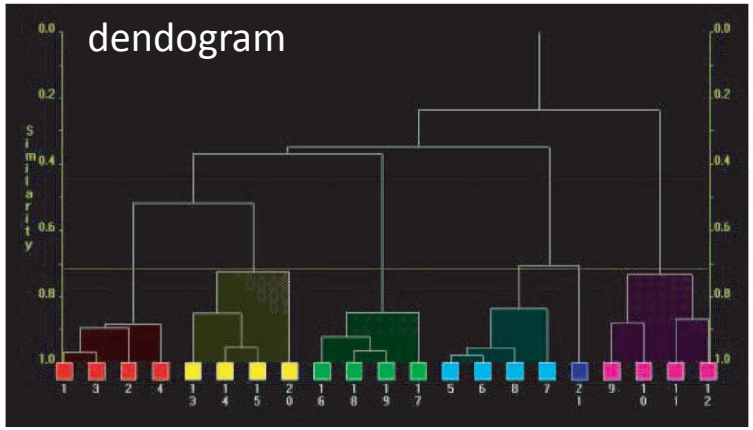


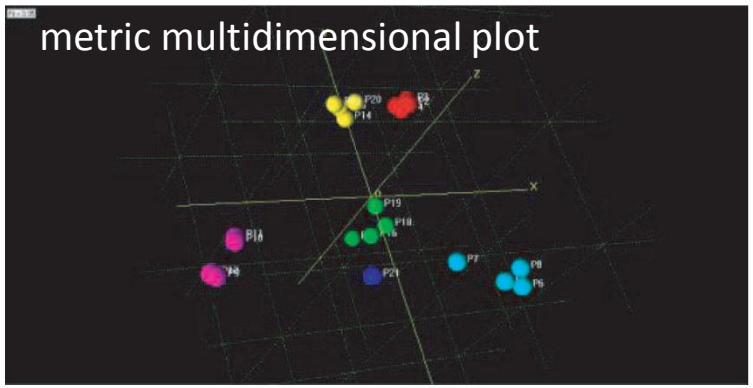
Sample Analysis
XRPD, IR, Raman

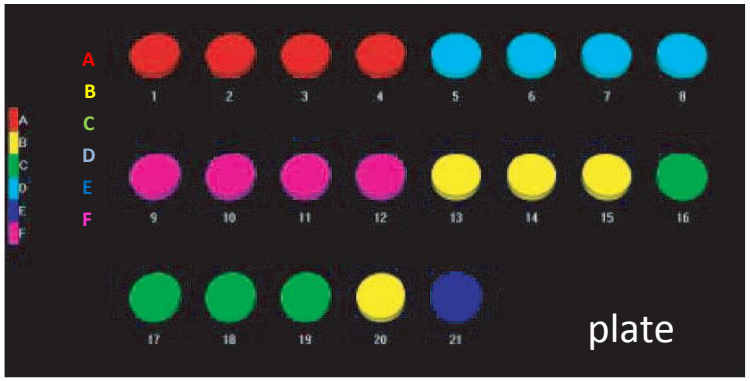




Data







Data Analysis

Storey et al. *Crystallography Rev.* **2004,** *10,* 45-56

Planning a screen

Variables to consider during crystallization/screening

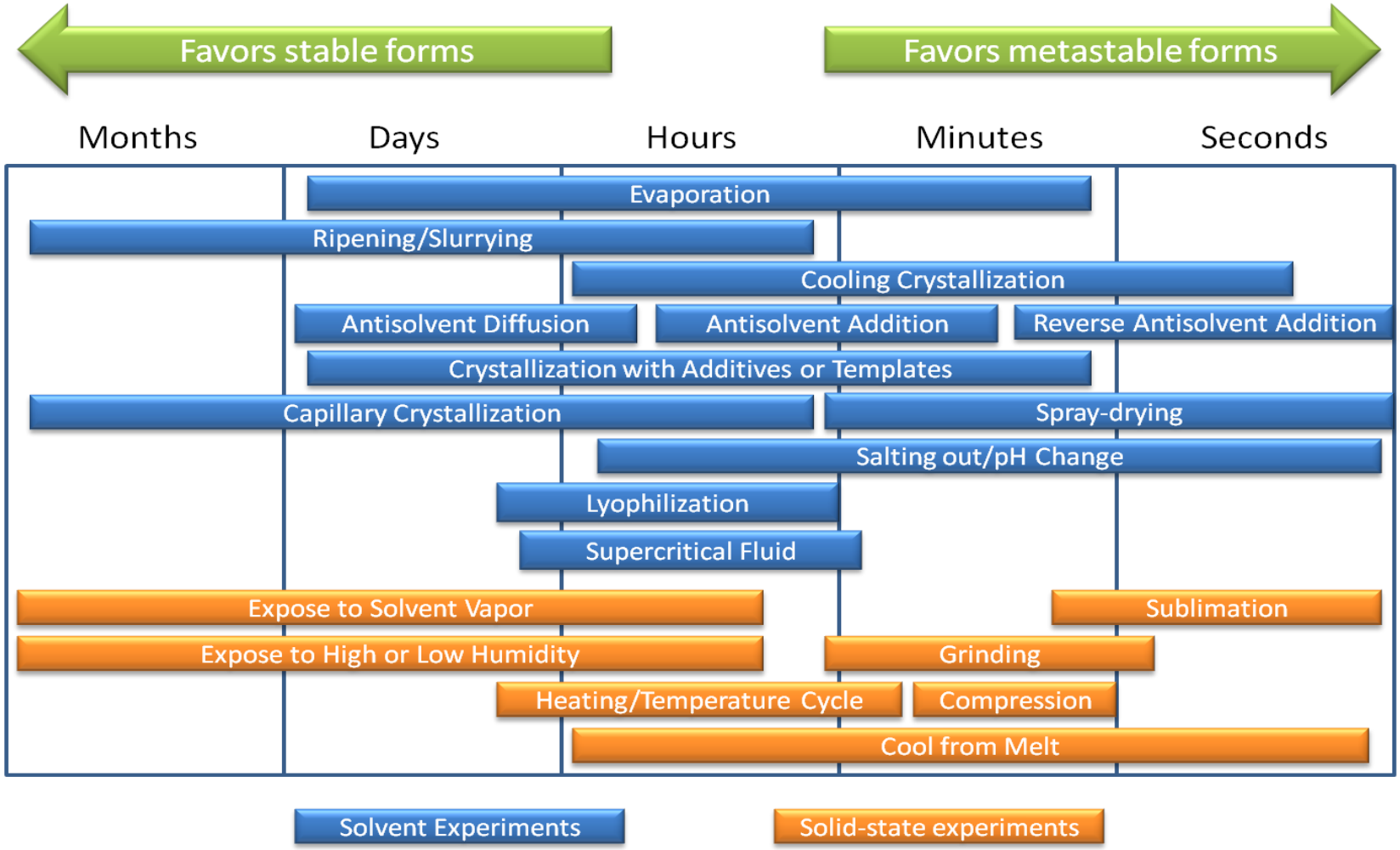
Crystallization composition and processing variables

Composition type		Process variables[a]				
Polymorph/ solvates	Salts/ co-crystals	Thermal	Anti-solvent	Evaporation	Slurry conversion	Other variables
▪ Solvent/ solvent combinations	▪ Counter-ion type	▪ Heating rate	▪ Anti-solvent type	▪ Rate of evaporation	▪ Solvent type	▪ Mixing rate
▪ Degree of supersaturation	▪ Acid/base ratio	▪ Cooling rate	▪ Rate of anti-solvent addition	▪ Evaporation time	▪ Incubation temperature	▪ Impeller design
▪ Additive type	▪ Solvent/ solvent combinations ▪ Order of addition	▪ Maximum temperature	▪ Temperature of anti-solvent addition	▪ Carrier gas	▪ Incubation time	▪ Crystallization vessel design (including capillaries, etc.)
▪ Additive concentration	▪ Degree of super-saturation ▪ Additive type and concentration ▪ pH ▪ Ionic strength	▪ Incubation temperature(s) ▪ Incubation time	▪ Time of anti-solvent addition	▪ Surface-volume ratio	▪ Thermal cycling and gradients	

[a] Applicable to all types of screens.

Morrissette et al. *Adv. Drug Delivery Rev*. **2004**, *56*, 275-300

Planning a Screen

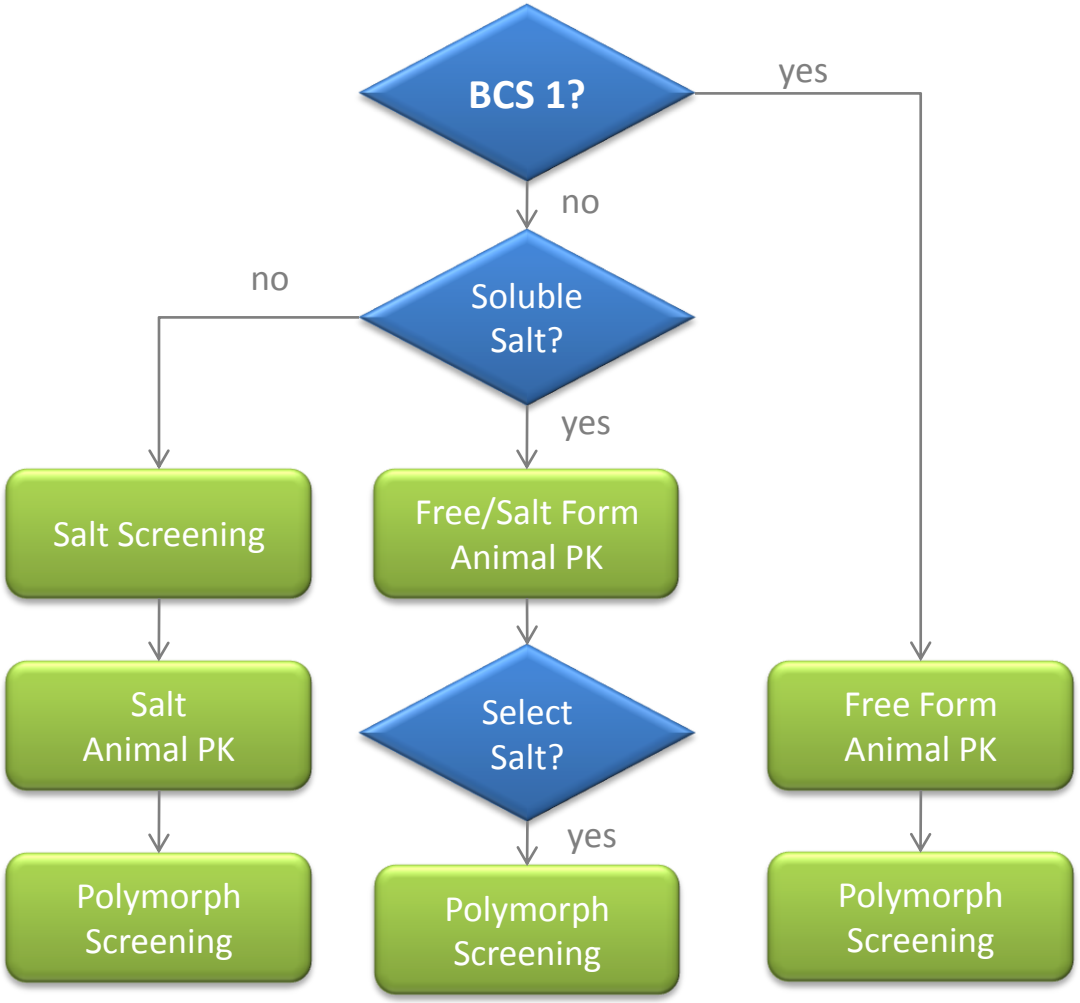


Adapted from Anderton. *Amer. Pharm. Rev.* **2007**, *10*, 34-40

Salt Screening Strategy

Early salt screens

- Can be based on BCS
- Not as crucial for BCS class 1 materials
- More important for classes 2 and 4



Soluble salt defined as enabling human dose soluble in 250 mL water

Ku. *Amer Pharm Rev*. **2010**, *13*, 22-30

Salt Development

- Requirements and selection process for each compound will be unique
- Variables that need to be considered when developing salts
  - solubility targeted
  - acceptable final form
  - dissolution
  - solubility of free compound
  - stability of free compound
  - melting point
  - dosage form to be developed
  - route of administration
  - loading in dosage form
  - amount of material available
  - previous experience with counterions
  - toxicology of counterions
  - etc

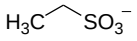
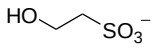
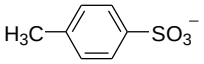
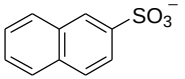
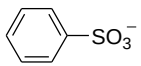
Properties related to form

Properties related to development

Counterion Selection

Consider size and shape of counterion and API

anions

chloride	Cl^-
bromide	Br^-
sulfate	SO_4^- $\left(HSO_4^=\right)$
nitrate	NO_3^-
phosphate	$H_2PO_4^-$ $\left(HPO_4^=\right)$
bicarbonate	HCO_3^-
mesylate	$CH_3SO_3^-$
esylate	
isethionate	
tosylate	
napsylate	
besylate	

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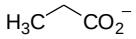
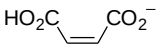
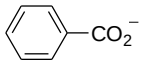
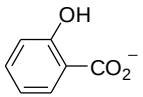
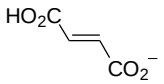
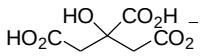
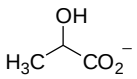
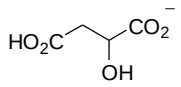
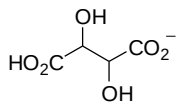
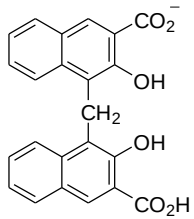
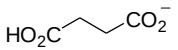
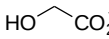
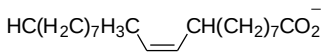
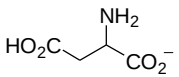
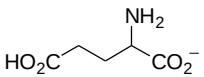
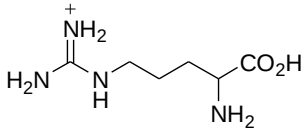
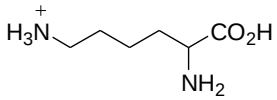
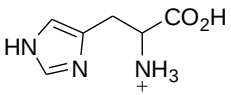
propionate	
maleate	
benzoate	
salicylate	
fumarate	
citrate	
lactate	
malate	
tartrate	

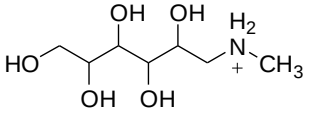
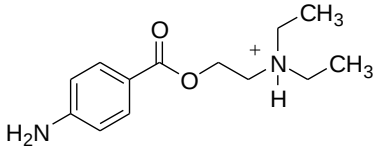
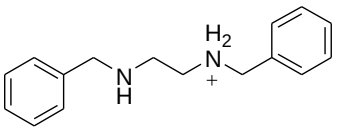
pamoate	
succinate	
glycolate	
hexanoate	$CH_3(CH_2)_4CO_2^-$
octanoate	$CH_3(CH_2)_6CO_2^-$
decanoate	$CH_3(CH_2)_8CO_2^-$
stearate	$CH_3(CH_2)_{16}CO_2^-$
oleate	
aspartate	
glutamate	

Counterion Selection

Not limited to inorganic counterions

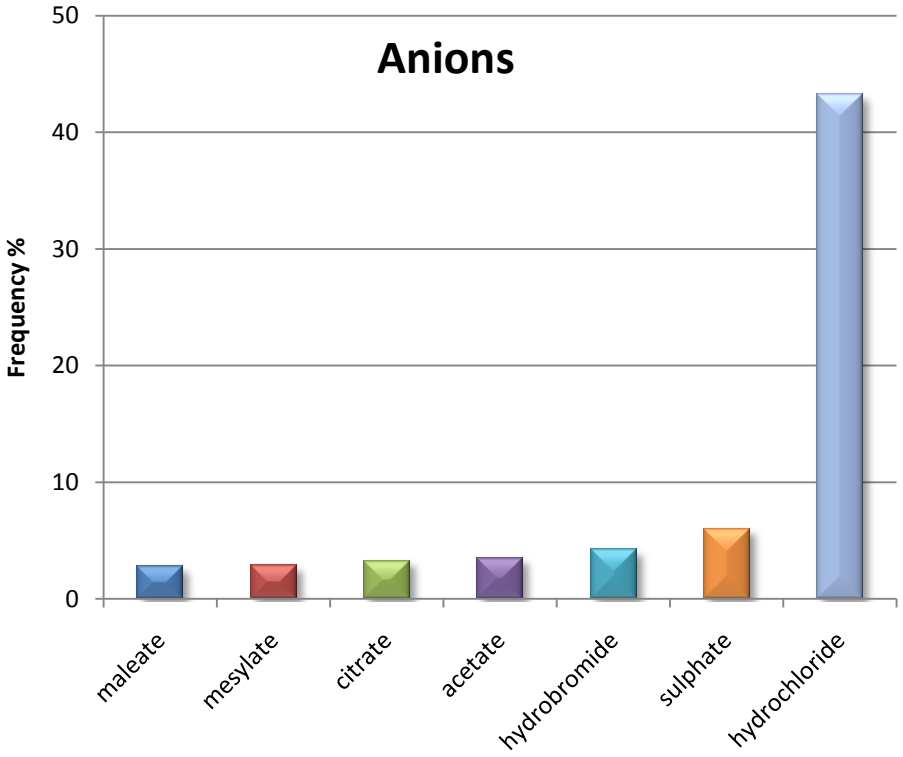
cations

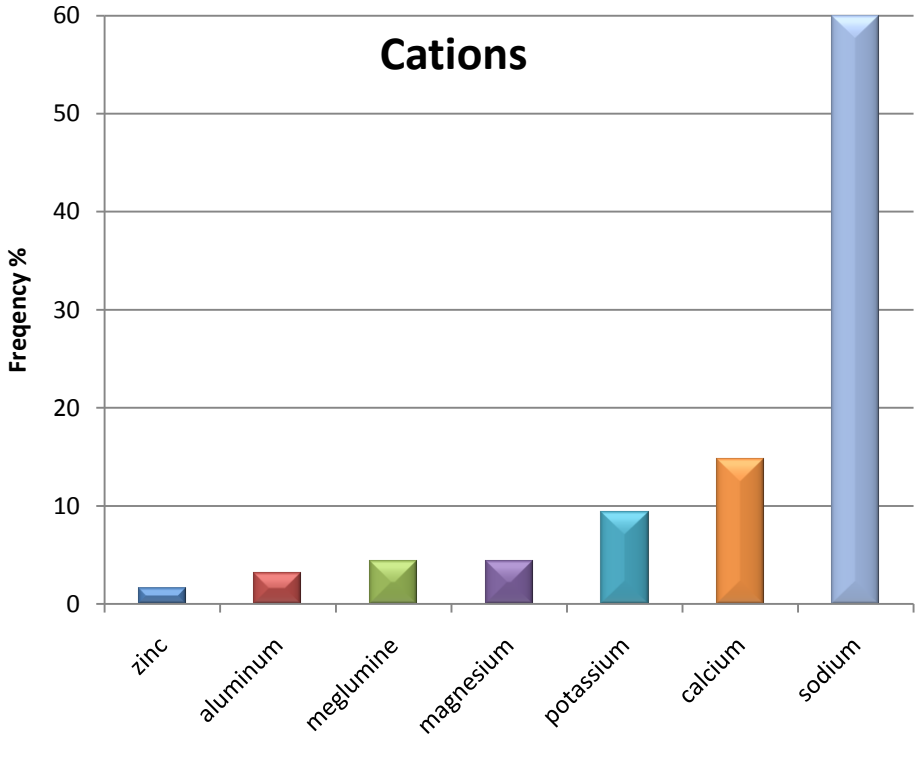
sodium	Na^+
potassium	K^+
calcium	Ca^{++}
magnesium	Mg^{++}
lithium	Li^+
zinc	Zn^{++}
aluminum	Al^{+++}
argenine	
lysine	
histidine	

triethylamine	$(CH_3CH_2)_3NH^+$
ethanolamine	$HOCH_2CH_2NH_3^+$
triethanolamine	$(HOCH_2CH_2)_3NH^+$
ethylenediamine	$H_2NCH_2CH_2NH_3^+$
choline	$HOCH_2CH_2N(CH_3)_3^+$
meglumine	
procaine	
benzathine	

Counterion Selection

Frequency of counterion in marketed products can be considered





Newman et al. Chapter 14. Salt and Cocrystal Form Selection in Preclinical Development Handbook. Wiley-Interscience, Hoboken. 2008, 455-481.

Counterion Selection

Frequency in dosage form can also be evaluated

- Will change over time

Distribution of Anions for API Used in Oral Dosage Forms

	overall (%)	pre-1982 (%)	1982–1986 (%)	1987–1991 (%)	1992–1996 (%)	1997–2001 (%)	2001–2006 (%)
acetate	0.9	0.6	7.7				
benzoate	0.3					2.5	
besylate	0.6	0.6			2.9		
bromide	4.1	5.2				5.0	8.7
chloride	56.6	55.8	65.4	79.2	65.7	45.0	34.8
chlortheophyllinate	0.3	0.6					
citrate	3.4	4.1			2.9	7.5	
ethandisulfonate	0.3	0.6					
fumarate	1.6	0.6		4.2	2.9	5.0	
gluconate	0.3	0.6					

Distribution of Anions for API Used in Injectable Dosage Forms

	overall (%)	pre-1982 (%)	1982–1986 (%)	1987–1991 (%)	1992–1996 (%)	1997–2001 (%)	2002–2006 (%)
acetate	5.8	2.3	5.0	26.3		14.3	16.7
besylate	1.4	0.8	5.0		5.0		
bromide	4.3	3.9	5.0	5.3	5.0	7.1	
camphorsulfonate	0.5	0.8					
chloride	53.4	54.3	60.0	42.1	55.0	50.0	50.0
chlortheophyllinate	0.5	0.8					
citrate	2.4	1.6	5.0		5.0		16.7
ethandisulfonate	0.5	0.8					
fumarate	0.5				5.0		
gluceptate	0.5	0.8					
gluconate	0.5	0.8					

Paulekuhn et al. *J Med Chem* **2007**, *50*, 6665-6672

Counterion Selection

pKa difference of 2 between API and counterion

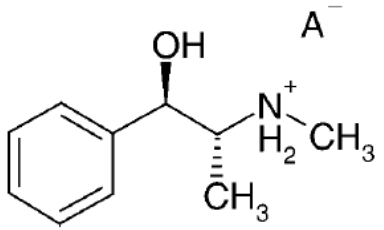
- Generally accepted for salt formation
  - Cocrystals possible if ignored
- pKa values can change significantly in different solvents
- Based on solution chemistry
  - Need to think about solubilities of solids

The pK_as of Selected Acids in Water and Methanol

Compound	pK_a Water	pK_a Methanol	ΔpK_a Water	ΔpK_a Methanol
Ephedrine	9.74	8.69	—	—
Acetic acid	4.76	9.63	4.98	−0.94
Benzoic acid	4.19	9.30	5.55	−0.61
Malonic acid	2.83, 5.70	7.66, 10.64	6.91, 4.04	1.03, −1.95
Fumaric acid	4.38	9.78	5.36	−1.09
Succinic acid	4.19, 5.61	9.14, 11.30	5.55, 4.13	−0.45, −2.61
L-tartaric acid	3.02	8.12	6.72	0.57

Black et al. *J Pharm Sci* **2007**, *96*, 1053-1068

Counterion Selection



Effect of Solvent on pKa

– 25 counterions used to make ephedrine slats

Carboxylic Acids	Dicarboxylic Acids	Hydroxy Acids	Inorganic Acids	Sulfonic Acids
Acetic	Adipic	Citric	Hydrochloric	Benzene sulfonic
Benzoic	Fumaric	D-(−)-gluconic	Nitric	1,2-Ethane disulfonic
Formic	Maleic	Glycolic	Phosphoric	Ethane sulfonic
Salicylic	Malonic	L-(−)-malic	Sulfuric	Methane sulfonic
Trichloroacetic	Succinic	L-(+)-tartaric	—	2-Naphthalene sulfonic
—	—	—	—	p-Toluene sulfonic

A Summary of all Crystallization Results

Acids	Water Results	Methanol Results	ΔpK_a Water	ΔpK_a Methanol
Strong Inorganic Sulfonic	9/10 crystalline	6/6 crystalline	8 to 12 units	2 to 6 units
Weak Carboxylic Dicarboxylic Hydroxy	8/15 crystalline including: 3 hydrates 4 conversions from an initial amorphous phase	0/9 crystalline	4 to 6 units	−2 to 1 units

Black et al. *J Pharm Sci* **2007**, *96*, 1053-1068

Counterion Selection

- Toxicity
  - Depends on molecule and daily dose
  - Will be different for short term vs chronic dosing
  - Toxic reaction products need to be considered
    - Methyl and ethyl formate esters associated with formic acid under certain conditions
    - Methyl methanesulfonate, a known mutagen, associated with methanesulfonic acid
      - Usually an issue when methanol is used as solvent

Salt Formation

- Solvent methods
  - Evaporation
  - Cooling
  - Antisolvent addition
  - Sonic slurry
  - Capillaries
- Number of parameters to investigate
  - Solvent, concentration/stoichiometry, cooling rates, evaporation rates
  - Manual or automated crystallization

- Solubilities
  - API and counterion/guest need to be soluble in same solvent or miscible solvents
- Try to get precipitation
  - reduce volume
  - cool solution
  - add anti-solvent (if known)
  - different ways of combining compounds
  - different temperatures
- Evaporations can result in physical mixture of materials rather than salt, or other unknown forms of free compound

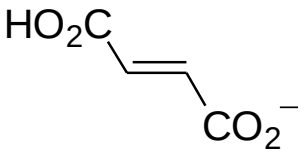
Salt Formation

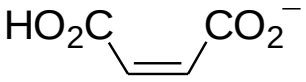
- A variety of less traditional methods are also available
  - binary melt (cocrystal formation as well)
  - grinding (cocrystal formation)/trituration
  - salt exchange
  - bubble gas (HCl, HBr) through solution
  - vapor diffusion
  - ion exchange resins
  - phase solubility (solubility as a function of pH)
  - precipitation of unwanted counterion first (ex. Silver salts used as counterion source and silver precipitated as silver iodide leaving desired anion)
- Try to get salts for evaluation or use process that is scaleable?

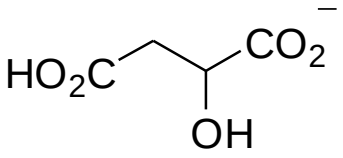
Newman and Stahly. *Form Selection of Pharmaceutical Compounds* in Handbook of Pharmaceutical Analysis. Marcel Dekkar: New York, 2002, 1-57

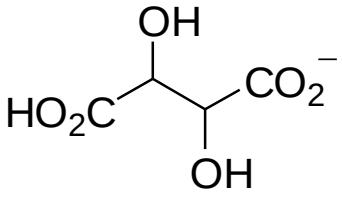
Salt Formation

- Different stoichiometries can be tried
  - more than one site on free compound
  - diacid counterion used (fumarate, malate, maleate, tartrate, etc)
- Control of stoichiometry may be an issue if pKa values are close

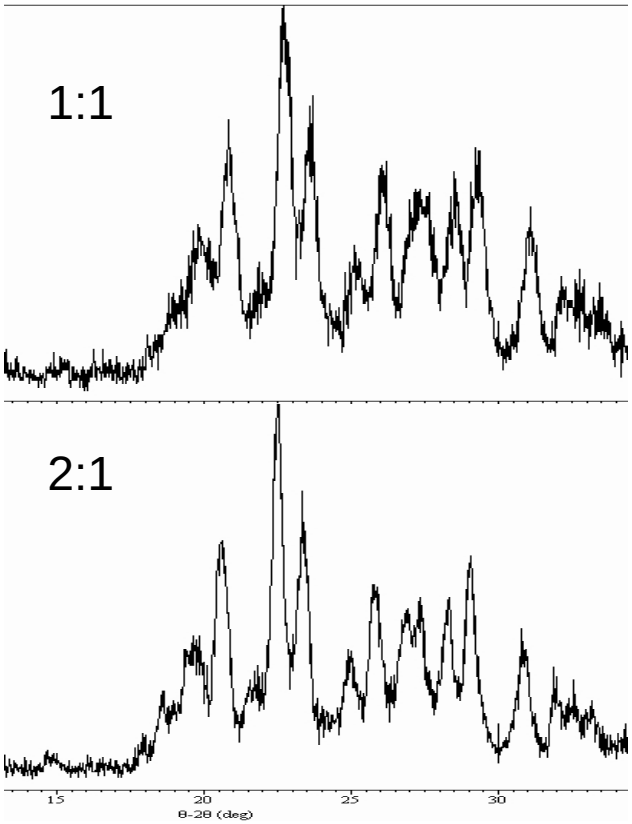








Characterization



- API with two basic sites
  - similar pK_a values
- HBr salt prepared with different molar ratios
  - Same XRPD pattern
  - Same elemental analysis
  - Different yields
- Favors formation of disalt

Element	*1:1 HBr:API*	*2:1 HBr:API*	*Expected Values for Disalt*
C	49.77	49.92	49.48
H	4.05	3.97	3.97
N	14.83	14.91	15.05
Br	28.86	29.20	28.63
	poor yield	good yield	

Newman et al. Chapter 14. Salt and Cocrystal Form Selection in Preclinical Development Handbook. Wiley-Interscience, Hoboken. 2008, 455-481.

Characterization

X-ray Powder Diffraction (XRPD)	Crystallinity Crystalline form	Crystalline pattern
Spectroscopy • Infrared (IR) • Raman • NMR	Interactions Crystalline form Mapping/imaging	Interactions between drug and counterion Stoichiometry
Thermal Methods •DSC (mDSC, HyperDSC) •Thermogravimetry (TG) •Hot Stage Microscopy	Melting point/Tg Form changes Volatile content	One melt Identify additional transitions
Moisture Sorption	Water uptake Form changes	Low water uptake

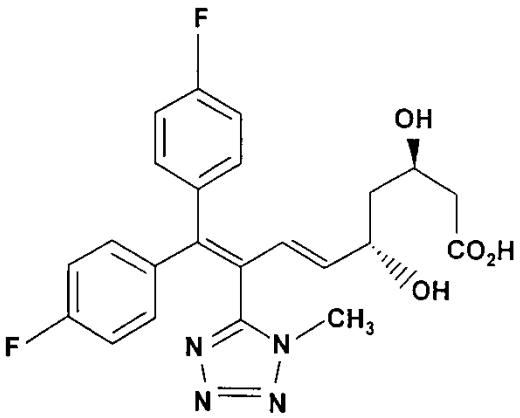
Solubility, stability, formulation

Evaluation

- Solubility in water
  - 0.1-10 mg/mL for solid oral dosage forms
  - ≥10 mg/mL for parenterals
- pH of aqueous solution
  - 3-10 for parenterals
- Melting point
  - >100 °C
- Hygroscopicity
  - Non-deliquescent at 60-75% RH
- Chemically and physically stable (excipient compatibility)
- Dissolution rate
- Crystal size, shape

Evaluation

Sodium 180431-03
Calcium 180431-04
Zinc 180431-05
Magnesium 180431-06
Potassium 180431-07
Lysine 180431-08
Arginine 180431-09

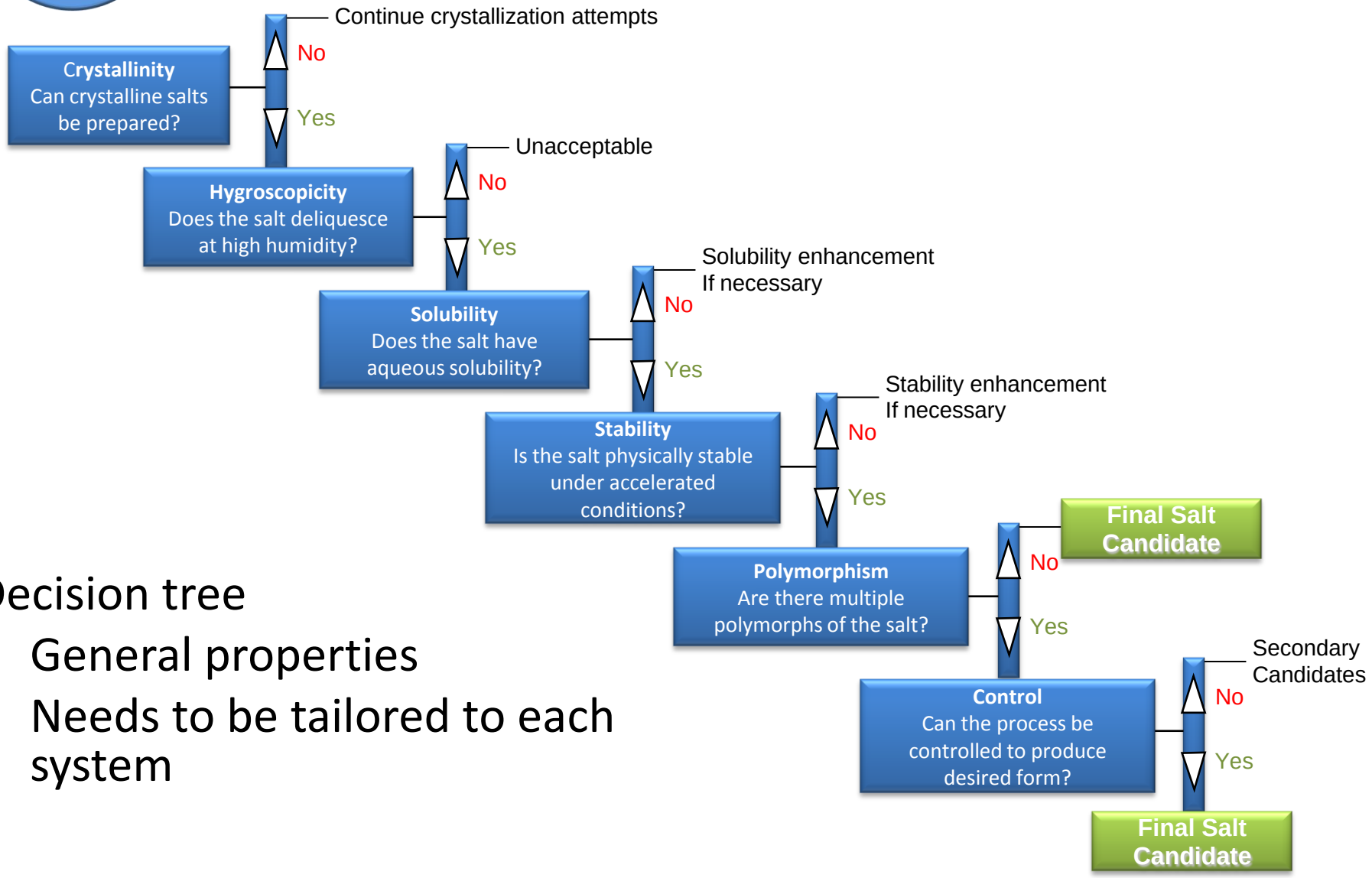


BMS 180431

Tier 1	Hygroscopicity (7 salts)
⬇	
Tier 2	Solubility/Crystal Changes (4 salts)
⬇	
Tier 3	Stability and Compatibility (1 salt and alternate)

Morris et al. *Int. J. Pharmaceutics* **1994**, *105*, 209

Salt Selection

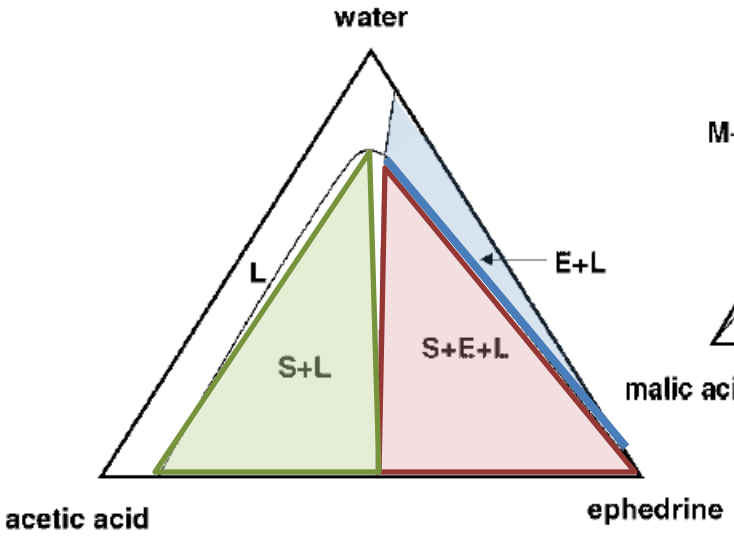


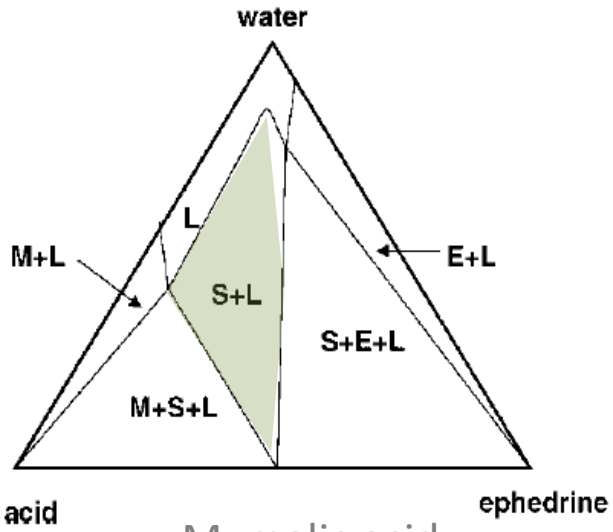
Decision tree

- General properties
- Needs to be tailored to each system

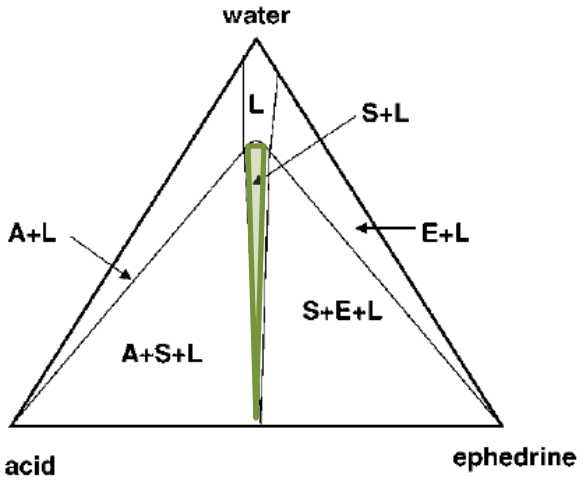
Crystallization

- Scale-up needs to be considered
- Ternary phase diagrams can be useful to determine concentrations





M: malic acid



A: adipic acid

E: ephedrine S: salt L: liquid

Black et al. *J Pharm Sci* **2007**, *96*, 1053-1068

Salt Screening

- A variety of salts are available
  - Salts, salt hydrates/solvates, salt cocrystals, salt cocrystal hydrates/solvates
- Salt screening can be used to find new salts
  - Solvent methods most common
  - Manual vs automated
- Characterization of salts needed
  - Form, protonation
- Scale-up can be an issue
- Salts can significantly alter properties of API
  - Melting point, solubility, stability, dissolution, bioavailability
- Salts can exhibit polymorphism- polymorph screen should be performed

Polymorph Screening

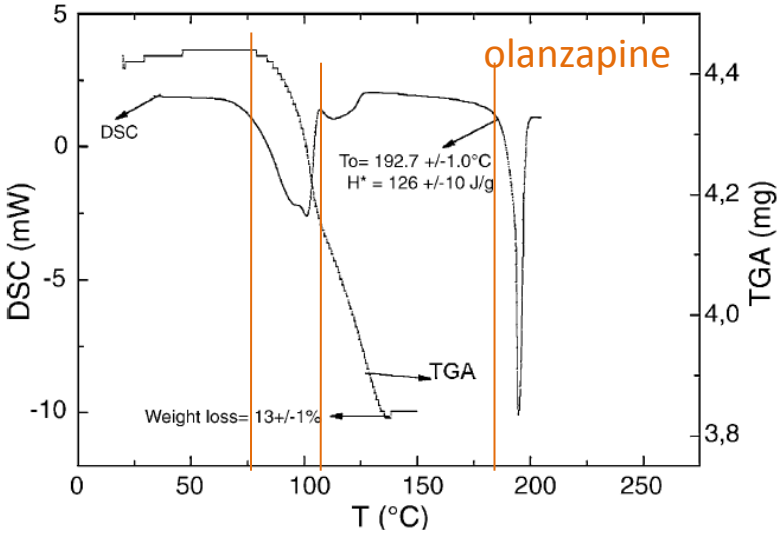
- *Search for seeds, not a search for a process*
  - Do not limit to Class III solvents
  - Do not limit to solvent experiments
  - Can gain information on crystallization process (example- solvate formation, slurry expts)
  - Can always use the initial crystals as seeds for a crystallization process
- Need to determine which forms are relevant to development
  - Anhydrates vs hydrates vs solvates
  - Initial goal is to find the most thermodynamically stable form
- *No screen can guarantee to find all forms*

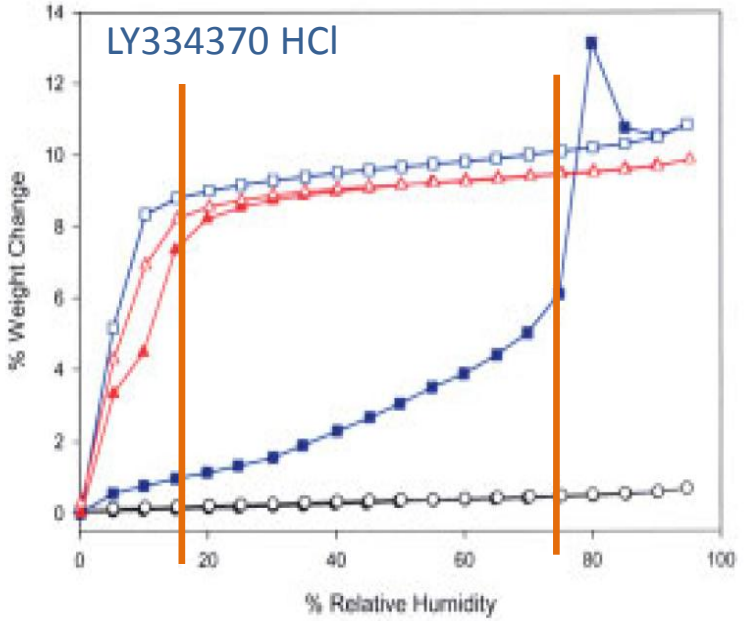
Sample Generation

- Solvent based methods can be employed based on solubility in various solvents
  - High solubility systems
    - High concentrations can result in gels/oils
    - Antisolvent additions, cooling experiments below supersaturation
  - Low solubility systems
    - Want to increase solubility or allow time for conversion
    - Slurry experiments, cooling crystallization from elevated temperature
    - Start with amorphous material to increase solubility
- Can tailor crystallization experiments to increase success

Sample Generation

- Nonsolvent methods can be tailored based on other properties/data
  - Heating/desolvation temperature based on TG loss
  - Heating/melting temperature based on DSC, hot stage data
  - Exposure to RH conditions based on water uptake data





Polla et al., *Int. J. Pharm*. **2005**, *301*, 33-40

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

Planning a Screen

Understand goal of screen and what information is needed

- For early screens want to know most stable form
- For later screens, may want additional information for processing or IP

Goal	Screen Type	Material
Determine propensity for polymorphism	preliminary	<0.5 g
Find thermodynamically stable form	stable form	1-2 g
Confirm the selected form can be produced with GMP material	focused	1-2 g
Find the best form for development	solid form selection	2-5 g
Widest experimental scope to find all possible forms	comprehensive	variable

Stahly. *Crystal Growth Des*. **2007**, *7,* 1007-1026

How Many Samples

Depends on

- Goal of screen and information needed
- Amount of material available
- Information already available (stability, solubility, etc)

Goal	Screen Type	Material	Number of Experiments
Determine propensity for polymorphism	preliminary	<0.5 g	tens
Find thermodynamically stable form	stable form	1-2 g	tens
Confirm the selected form can be produced with GMP material	focused	1-2 g	tens
Find the best form for development	solid form selection	2-5 g	hundreds
Widest experimental scope to find all possible forms	comprehensive	variable	thousands

Stable Form Screen

Stable Form Screen

- Targeted for early development to find the most stable form
- Small amount of compound needed (100-250 mg)
- Slurry experiments used (solvent mediated polymorphic transformation)

- Material suspended in diverse group of solvents for two weeks
- Solubility estimated using gravimetric method

Solvent	Dielectric constant (a measure of polarity)
Water	80.1
Nitromethane	39.4
N,N-Dimethylformamide (DMF)	36.7
Acetonitrile	36.6
Methanol	33.0
Ethanol	25.3
Acetone	20.7
2-Propanol (isopropyl alcohol, IPA)	20.3
2-Butanone (methyl ethyl ketone, MEK)	18.6
Tetrahydrofuran	7.5
1,2-Dimethoxyethane	7.3
Ethyl acetate	6.1
Chloroform	4.8
Methyl *t*-butyl ether	4.3
1,2-Xylene	2.6
Toluene	2.4
1,4-Dioxane	2.2
Hexanes	1.9

Miller et al. *Pharm. Dev. Technol*. **2005**, *10*, 291-297

Stable Form Screen

Pfizer Compound A

- Form I was initial form
- Transformation to more stable Form II observed
  - 6 out of 18 solvents in 2 days and 8 out 18 solvents in 2 weeks produced Form II
  - Dioxane solvate also found

Solvent	Solid form 2 days	Solid form 2 weeks	Solubility (mg/mL) 2 weeks
Hexanes	I	I	0.12±0.02
Water	I	I	0.13±0.01
1,2-Xylene	I	I	0.22±0.02
Toluene	I	II	0.62±0.04
Nitromethane	I	I	0.66±0.07
2-Propanol	I	I	0.99±0.10
Methyl *t*-butyl ether	I	II	1.36±0.04
Acetonitrile	I	I	1.41±0.01
Ethanol	I	I	2.02±0.09
Methanol	I	I	2.72±0.05
Ethyl acetate	II	II	3.42±0.07
Chloroform	II	II	6.04±0.12
Acetone	II	II	8.53±0.12
2-Butanone decomposition	I	I	13.3±0.7
1,4-Dioxane	Solvate	Solvate	17.3±0.3
1,2-Dimethoxyethane	II	II	18.7±0.4
Tetrahydrofuran	II	II	72.6±2.6
N,N-Dimethylformamide	II	II	282±3

Fastest tranfsormation at highest solubilities

Miller et al. *Pharm. Dev. Technol*. **2005**, *10*, 291-297

HTS

High throughput screening (HTS)

- Comparison of manual vs HTS
- Goal of screen was form diversity, not stable form
- 1500 experiments performed
  - 186 solids found after 7 days (13% hit rate)
  - After Raman clustering, 80 samples analyzed by XRPD

metric	traditional	HT mode
number of experiments	ca. 100	1500
time frame (weeks)	ca. 32	4
people requirement	ca. 2	1–2
amount of material used	>10 g	<5 g
number of crystalline forms found	9	18

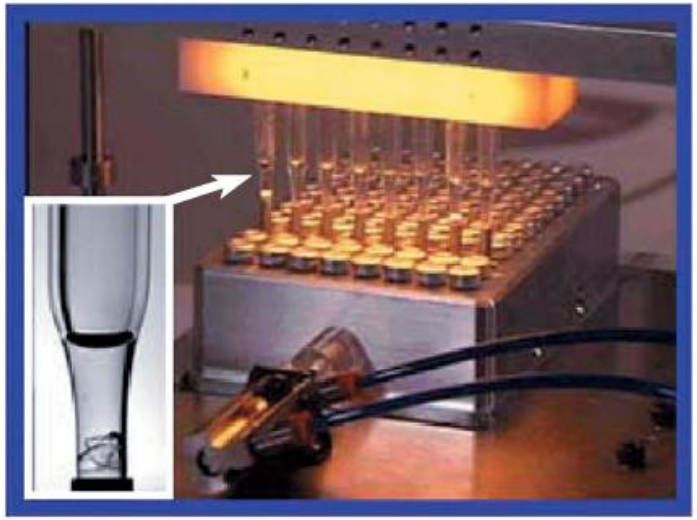
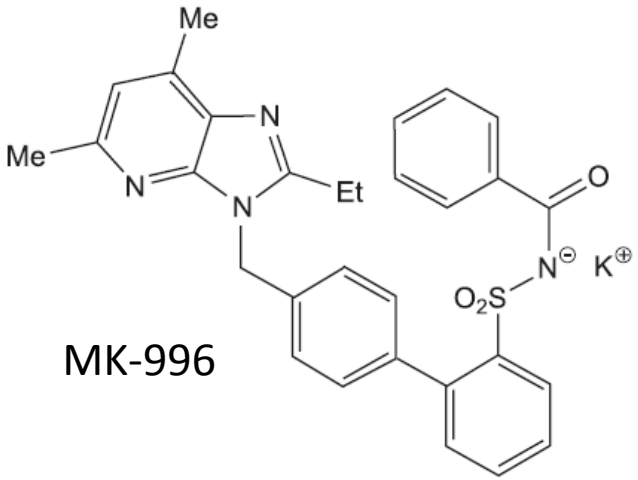


Photo of optical inspection station. (Inset shows close up of crystallization vessel that contains crystals.) (Courtesy of Trans-Form Pharmaceuticals, 2002.)



MK-996

Almarsson et al. *Cryst Growth Des.* **2003**, *3*, 927-933

HTS

- HTS screen found 18 forms
  - 13 new patterns
  - 5 previously known forms
- Screen did not find 4 previously known forms
  - Forms B and C (unsolvated), F, H
  - Form D was found in HTS. Original paper could not reproduce Form D after Form I was found.
- Form I originally chosen for development

form	peaks from powder pattern
A[a]	3.83, 7.21, 8.17, 10.53, 13.27, 13.81, 14.79, 15.23
D[a]	4.07, 8.15, 8.59, 9.59, 12.33, 13.45, 13.77, 15.73, 16.43, 18.61, 19.07, 24.21, 25.57
E[a]	3.75, 7.27, 8.19, 8.53, 10.15, 11.23, 13.39, 14.71, 15.55, 16.31, 17.91, 20.61, 23.51
G[a]	4.91, 5.79, 6.69, 9.03, 10.47, 13.43, 14.21, 15.45, 18.31, 20.13, 25.65
I[a]	3.81, 7.21, 8.10, 10.50, 11.41, 13.65, 14.71, 15.23, 18.23, 19.23, 19.59, 20.65, 21.55, 22.43, 24.03, 26.25
L	4.15, 7.49, 8.25, 9.23, 11.07, 12.33, 13.19, 15.01, 15.67, 17.79, 19.09, 20.83, 22.45, 23.85, 24.99, 25.49
M	3.67, 7.49, 9.97, 11.85, 13.87, 14.67, 20.45, 23.17, 26.23, 27.11, 28.49, 28.77
N	4.15, 4.45, 7.39, 7.91, 8.31, 8.95, 11.15, 12.49, 15.03, 15.51, 17.63, 20.85, 22.37, 23.93
O	4.21, 8.77, 13.99, 15.99, 16.61
P	4.25, 7.09, 7.53, 8.83, 9.65, 13.49, 14.83, 15.73 16.71, 17.51, 24.31, 25.39
H	3.81, 5.71, 7.91, 10.845 13.49, 15.23, 15.95, 18.25, 20.39, 24.05, 25.27, 26.41
Q	3.83, 4.71, 7.43, 8.17, 9.37, 10.35, 15.13, 17.93, 19.19, 24.07
R	4.21, 8.79, 10.13, 13.99, 15.95, 16.57, 19.63, 21.93, 24.23, 25.79
S	4.05, 4.88, 8.05, 13.85, 15.61, 24.09
T	3.77, 7.23, 8.51, 10.19, 10.57, 13.39, 14.69
U	6.95, 8.25, 9.95, 11.21, 11.83, 13.23, 14.55, 15.81, 16.55, 17.05, 17.83, 18.87, 20.39, 21.41, 23.15, 25.23, 26.27, 27.07, 28.87
V	3.67, 7.17, 7.51, 10.69, 15.05, 23.89
W	3.58, 4.35, 5.05, 8.91, 10.25, 14.04, 16.11, 16.67, 19.64, 24.47

a. Form reported in original paper: Jahansouz et al. *Pharm Dev. Technol*. **1999**,*4*,181-187

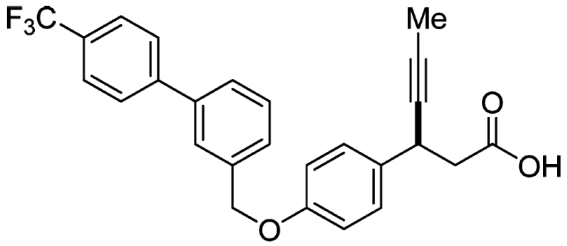
Almarsson et al. *Cryst Growth Des.* **2003**, *3*, 927-933

Polymorph Screens

- Need to understand the goal of the screen
  - most stable form, form diversity, change a specific property
- A variety of screens are possible
  - Manual, high throughput, etc
- Can tailor crystallization experiments to the properties of the molecules
  - Solubility for solvent based methods
  - Characterization data for solid experiments
- Multiple screens may be warranted throughout development

Case Study

AMG 837



- Treatment for type 2 diabetes
- Initially isolated as lysine salt
  - Poorly crystalline by XRPD
  - Hygroscopic above 65% RH
  - Difficult to scale up due to large volumes of solvent (>100 vol EtOH)
- Free acid investigated
  - Crystalline by XRPD
  - Poorly soluble (~0.5 mg/mL) and poor wettability
  - DSC showed low melting point of 80 C
  - Poor solution and solid-state stability
  - Benchtop polymorph screen conducted
    - Higher melting forms not identified
    - Samples usually thick oils and difficult to crystallize
- Salt screen performed to identify crystalline form with acceptable characteristics for development

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Case Study

- Ten counterions used
- Crystallization included
  - Evaporation, slurries, antisolvent addition

- Prioritized based on crystallization and information on counterions
  - Choline and sodium listed as high priority
- Counterion use in marketed products also considered

Counterion	XRPD Results	Priority	Comment
L-Arginine	---	---	
Calcium	Amorphous	Low	Amorphous
Choline	**Crystalline**	**High**	
Ethanolamine	Crystalline	Low	No marketed oral drugs identified
L-Histidine	---	---	
Magnesium	Amorphous	Low	Amorphous
Meglumine	---	---	
Potassium	Amorphous	Low	Amorphous
Sodium	**Crystalline**	**High**	
TRIS	Crystalline	Medium	Marketed products identified, counterion not employed for oral chronic use

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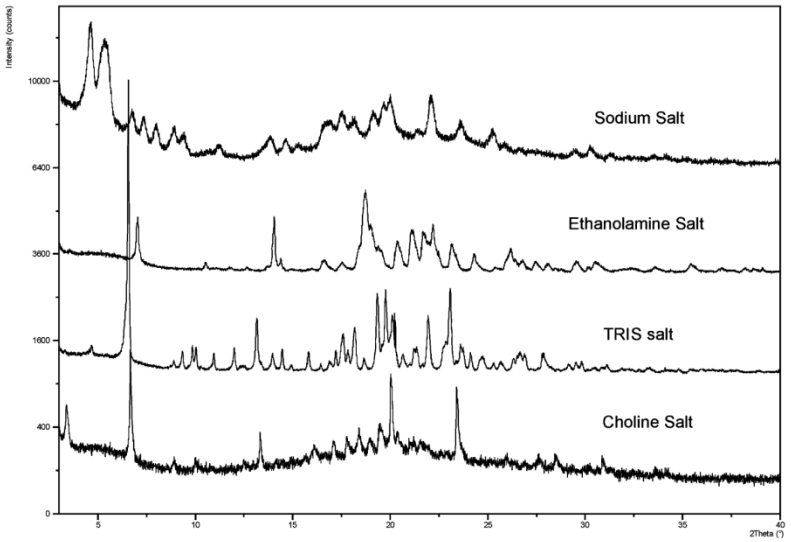
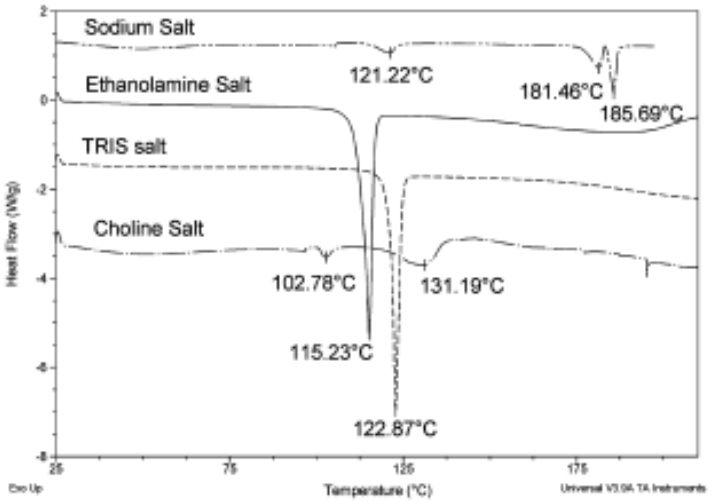
Case Study

- Salt Screen
  - Four crystalline hits identified
  - Ethanolamine and TRIS were considered second tier
  - Sodium had higher melting point than choline
  - Sodium salt chosen





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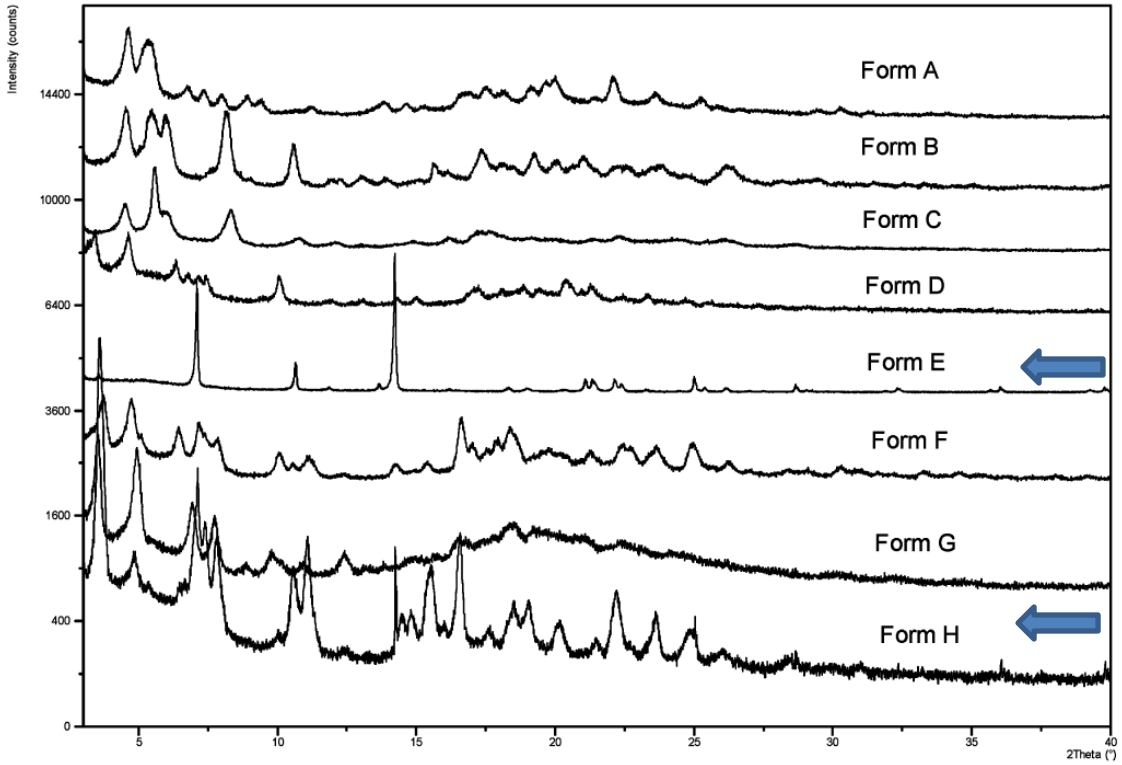
Case Study

- Full polymorph screen of sodium salt performed
  - Eight patterns observed
  - Forms E and H showed highest crystallinity



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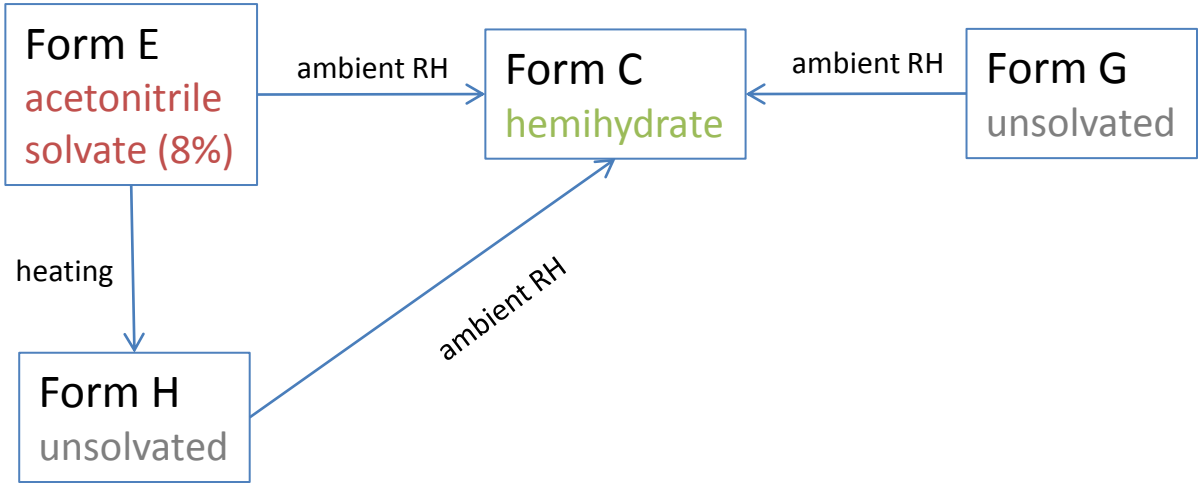
Case Study

- Four forms examined in more detail



- Form C chosen for further investigation
  - Found most often in screen
  - Solubility >100 mg/mL
  - Successfully scaled up for use as GLP and GMP material

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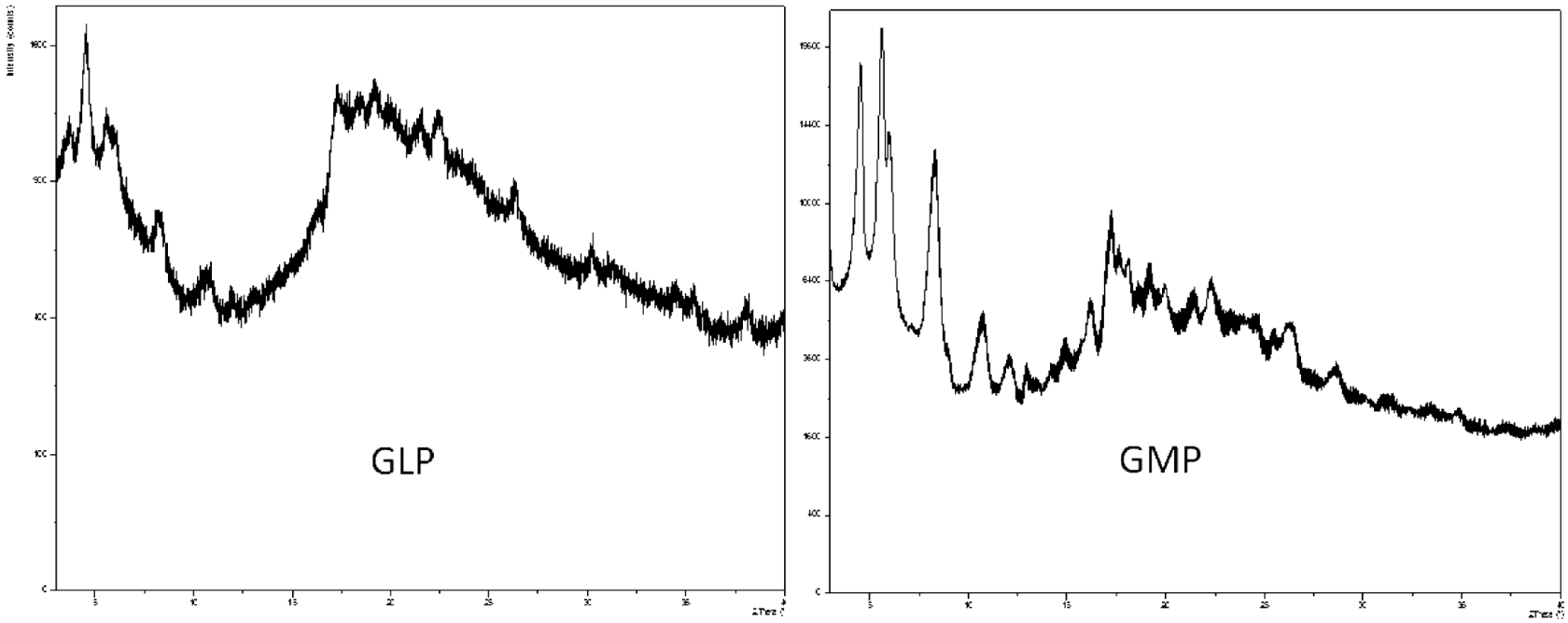
Case Study

- Successfully scaled up for use as GLP and GMP material
  - Produced Form E solvate then desolvated to Form C
  - GMP more crystalline than GLP material



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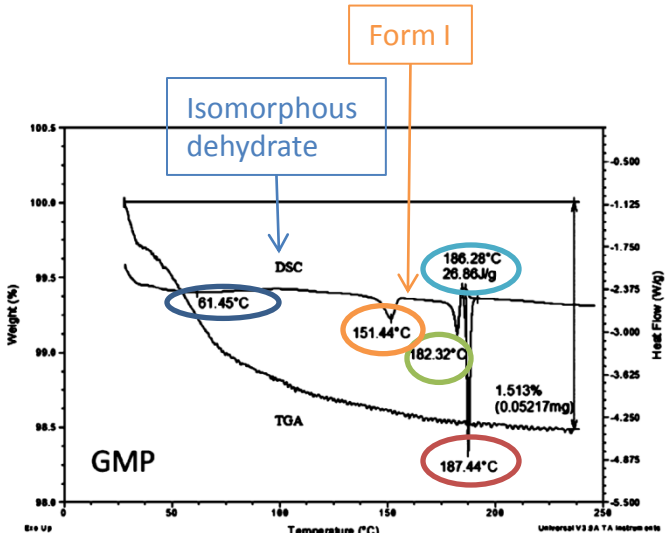
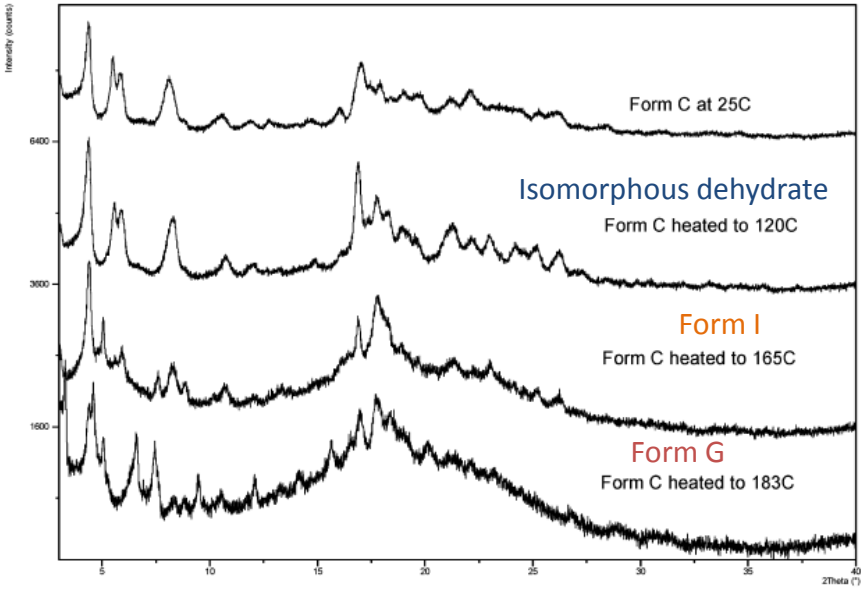
Case Study

- Form C exhibited multiple thermal transitions
  - Broad endo ~61 °C
  - Endos at ~ 151 and 182 °C
  - Exo ~ 186 °C
  - Major endo at 187 °C (melt of Form G)
- VT-XRPD performed
  - 120 °C
    - Slight changes to form isomorphous dehydrate
  - 165 °C
    - New form (Form I) which melts at 182 °C and recrystallizes
  - 183 °C
    - Form G which melts at 187 °C





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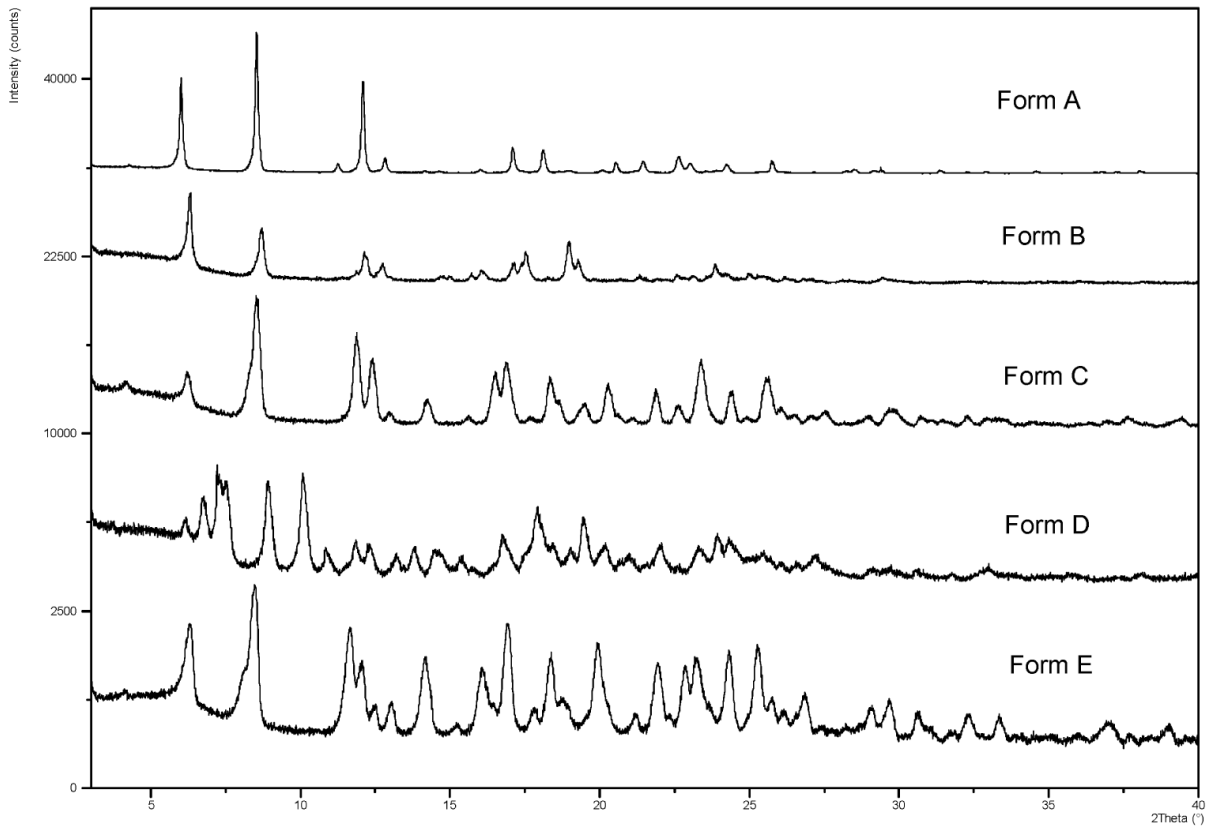
Case Study

- Form C showed mix of properties
  - Low crystallinity
  - Complicated DSC profile
  - Hygroscopic
  - Good short term physical stability at 68% RH, 60 C/26% RH, 60 C/50% RH
- Form C suitable for Phase I clinical trials
- Went back to original screen to find better candidate
- Sodium salt used to produce a crystalline hemicalcium salt
- Polymorph screen of calcium salt performed

Case Study

- Full polymorph screen conducted using both amorphous and crystalline calcium salt
- Five crystalline forms produced



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Case Study

- All forms contained solvent
- Characterization showed that none of the forms exhibited a true melt
  - Desolvation upon heating produced amorphous materials
  - Crystalline forms needed solvent to stabilize the crystal lattice

Form	Results	Comment
A	methanol solvate	solvate
B	dihydrate	**candidate**
C	dihydrate	**candidate**
D	isopropanol solvate	solvate
E	pentahydrate	Converted to Form C upon heating or exposure <55% RH

- Solubility used to determine thermodynamic stability of Forms B and C
  - Form B had lower solubility at 5, 21, and 40 °C
  - Form B was more stable form
  - Form B stable to small scale wet milling conditions to simulate wet granulation

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Case Study

- Both Form B calcium salt and Form C sodium salt were viable candidates
- A number of quality attributes were considered
- Calcium salt was recommended for product development

Comparison of the sodium salt form C and calcium salt form B

	sodium salt	calcium salt
hygroscopicity	hygroscopic	nonhygroscopic
crystallinity	poorly crystalline	crystalline
API stability	must be stored under refrigerated conditions and protected from light and humidity, and ambient humidity must be controlled on handling	stable ≥3 months at 40 °C/75% RH without desiccant
API manufacture	scalable	scalable, requires drying below 40 °C to avoid erosion of crystallinity due to dehydration
tablet manufacture	challenging to use wet granulation due to content uniformity concerns	feasible to use either wet granulation or dry process
solubility	high aqueous solubility (>100 mg/mL)	low aqueous solubility (0.003 mg/mL)
PK data	sodium salt solution and a calcium salt suspension (1 mg/kg dose) have a PK/BA profile similar to that in monkey	

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Case Study

- Summary
  - Initial salt screen performed due to unfavorable characteristics of free base
    - Low melt, poor stability, poor water solubility
    - Eleven counterions included in screen
      - Most yielded amorphous materials
      - Others not preferred due to lack of chronic oral use data and safety implications
      - Sodium salt moved forward
  - Second salt screen performed to improve properties
  - Calcium salts revisited based on crystallization of sodium salt
  - Polymorph screens performed on both sodium and calcium salts
      - 8 forms found for sodium, 5 forms found for calcium
  - Hemicalcium salt chosen for development based on properties
- More than one salt screen and more than one polymorph screen used to pick the best form during development
- Form matrix used for form selection

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What Have We Learned

- X-ray powder diffraction is a key characterization technique for screening and selection studies
- Screening is different from selection
- Polymorph and salt screens
  - Are a search for seeds and should cover a wide crystallization space including solvent and nonsolvent methods
  - Can be tailored to the information needed for compound development
  - Should use information already known on the compound
  - Can be performed at various points during development
- One screen will likely not give you all the form information on a compound
- Finding and characterizing forms early will help
  - In choosing the best form for development
  - To avoid processing conditions that could produce another form

Resources

Polymorph Screening

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