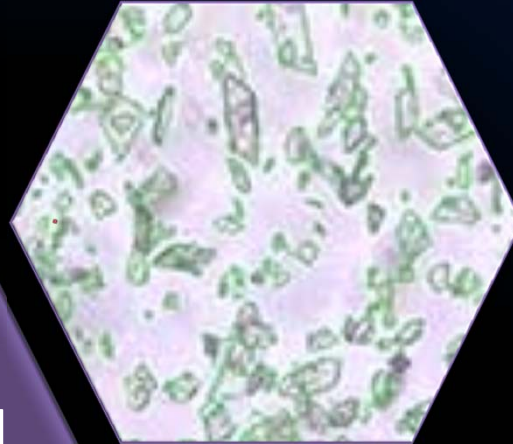


# Does Particle Size Matter? Yes or No

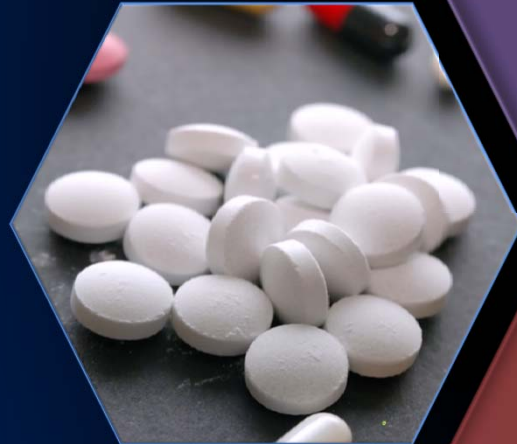
Mick Hurrey Ph.D.



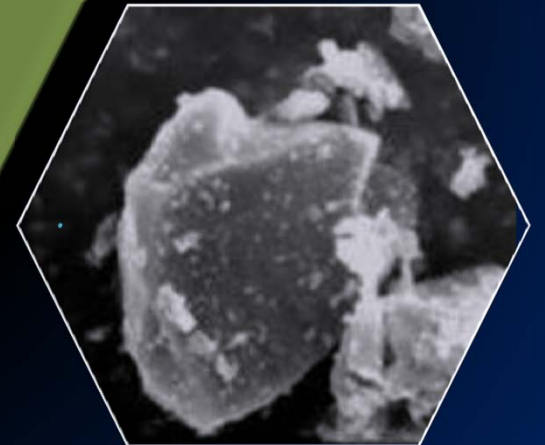
Pharmaceutical  
Materials



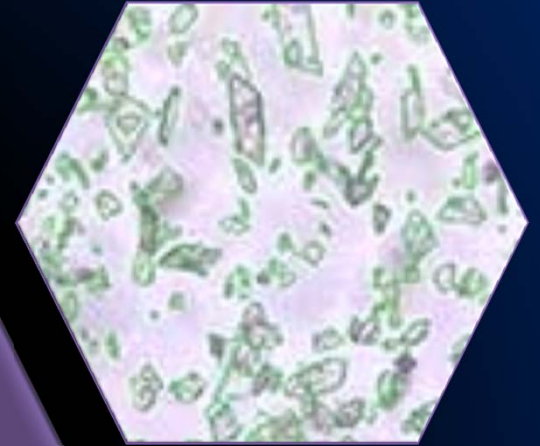
The Right Spec



Particle Effects  
on  
Performance

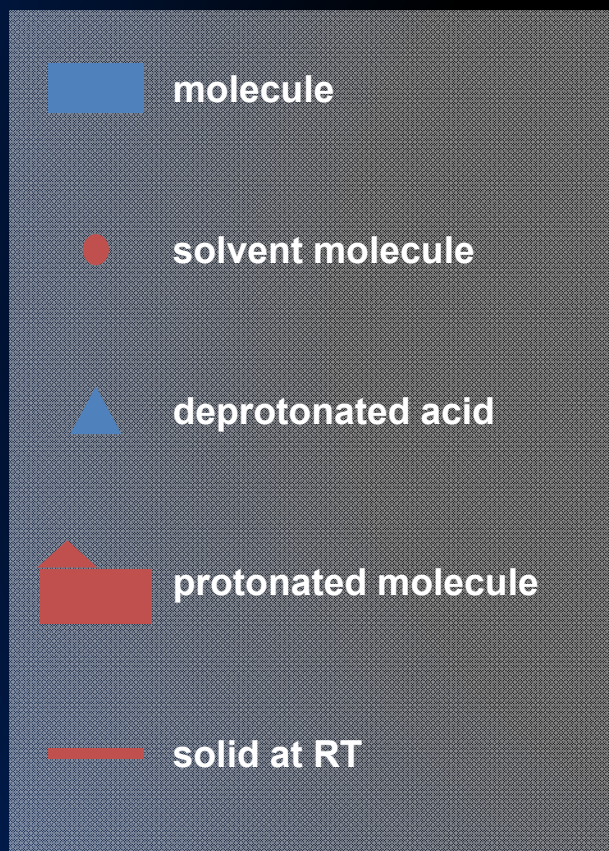
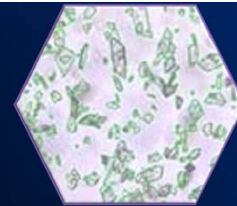


# Pharmaceutical Materials

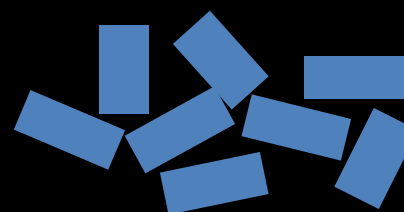




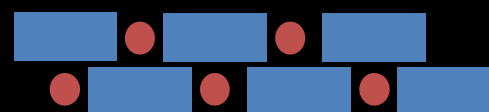
# Types of Pharmaceutical Materials



Polymorphs



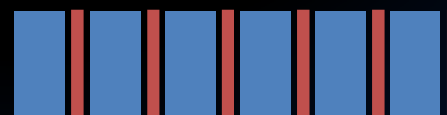
Amorphous



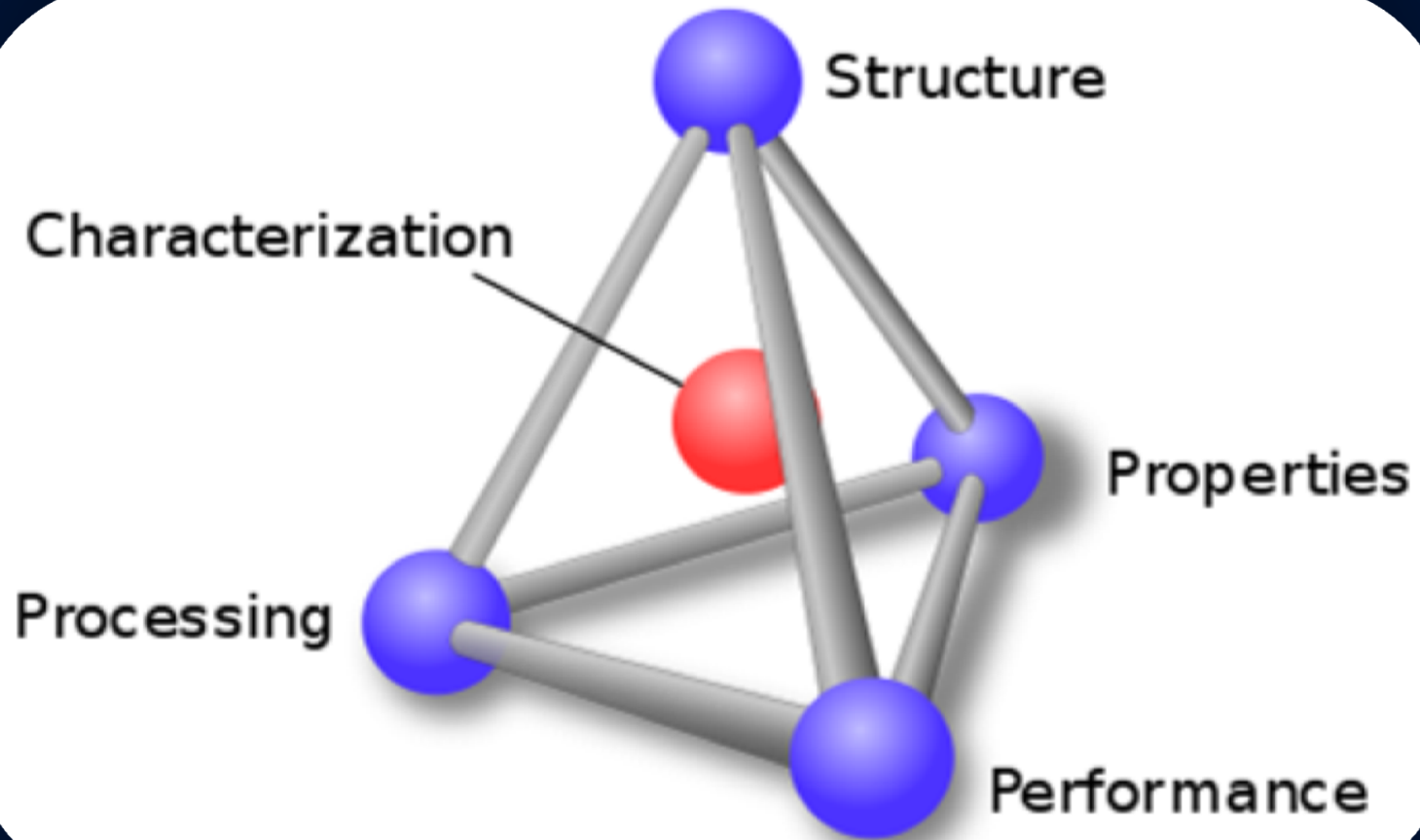
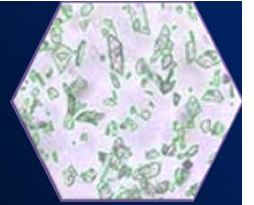
Solvate



Salt



Co-Crystal



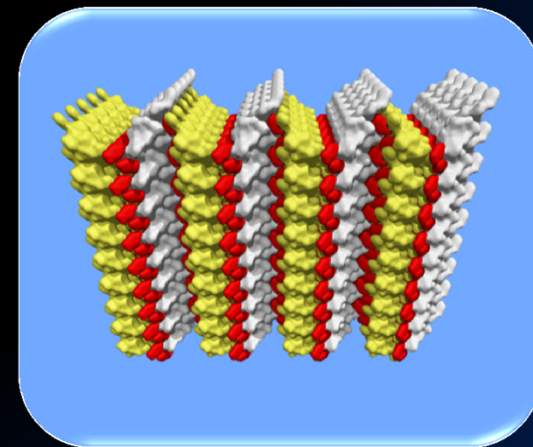
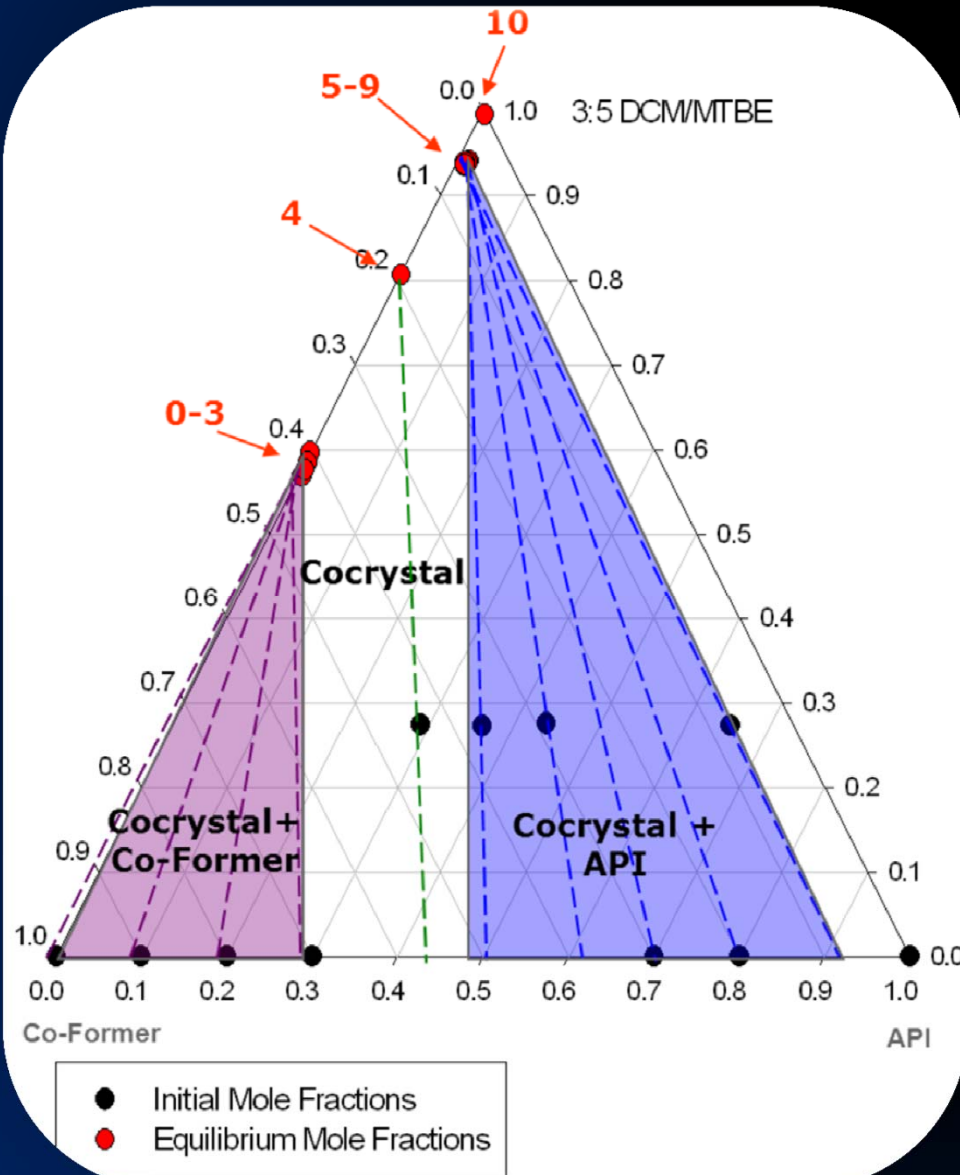
# Structure



Crystallization Process

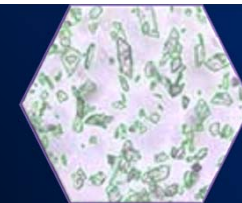
Form Control

Phase Mapping

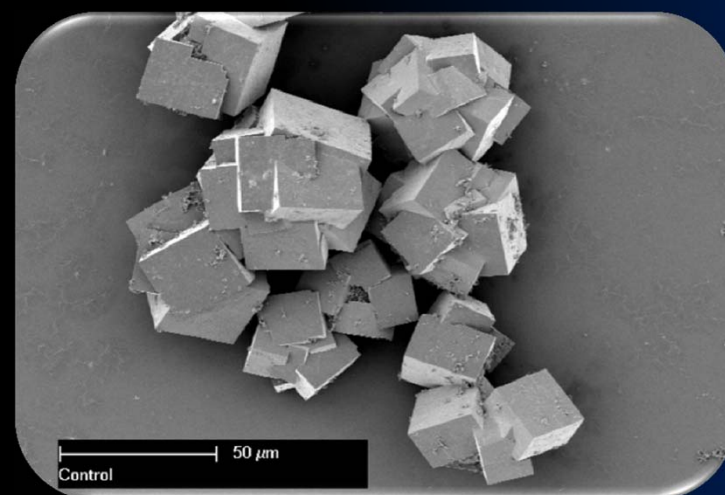


Crystal Structure

# Properties

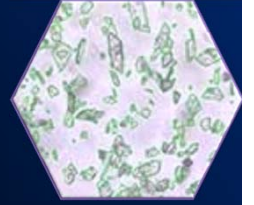


Parameter	Compound 1
Molecular Weight	817.97g/mol
Melting Point (°C)	188°C ( $\Delta H = 94\text{J/g}$ )
clogP	4.5 (neat form)
pKa	4.58, 9.23 (calculated)
FESSGF <00> Solubility	0.614mg/mL at 120min
Bulk Density	0.25mg/mL
Particle Size / Morphology / Surface Area	75 $\mu\text{m}$ (d50, dry LLS) / small square plates / 1m <sup>2</sup> /g
API scale up	1.2kg by crystallization
Hygroscopicity	0.4%w/w at 95%RH

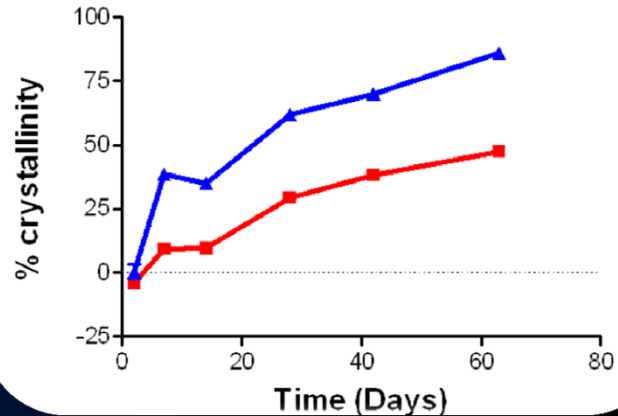




# Processing



Crystallization Kinetics of Unseeded SDD  
at 40°C/100%RH

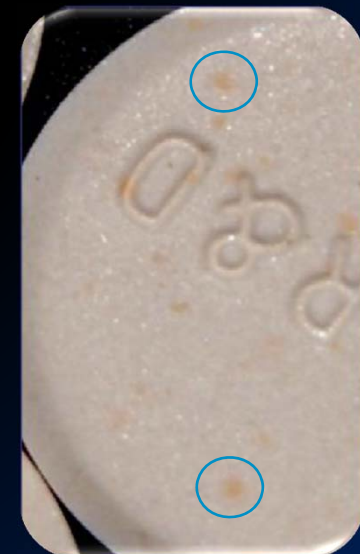


Meta-stable Form Analysis

Powder Properties

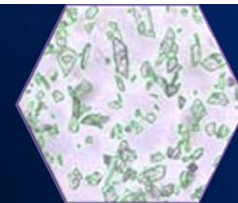
Unknown Identification

Food	Chemical Stability	Physical Stability
Applesauce	☑Up to 3hr	☑Up to 1hr
Orange Juice	☑Up to 3hr	☑Up to 1hr
Banana Puree	☑Up to 3hr	☑Up to 1hr
Vanilla Pudding	☑Up to 3hr	☑Up to 1hr
Strawberry Jam	☑Up to 3hr	☑Up to 1hr
Whole/Chocolate Milk	☑Up to 3hr	☑Less than 4% in 1hr
Whole Milk Yogurt	☑Up to 3hr	☑Less than 4% in 1hr
Nutella	☑Up to 3hr	☒Crystallizes after 5 hrs





# Solid Phase Characterization



X-Ray Diffraction:  
Structure and Form

(HORIBA XGT-7200 X-ray Analytical Microscope)

Light Scattering:  
Particle Size

(HORIBA LA-960 Laser diffraction Analyzer)

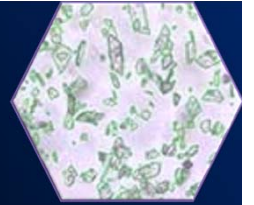


Calorimetry:  
Thermodynamics

Vapor Sorption:  
Hygroscopicity

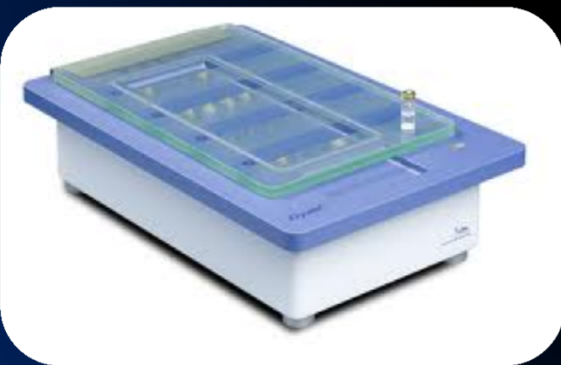
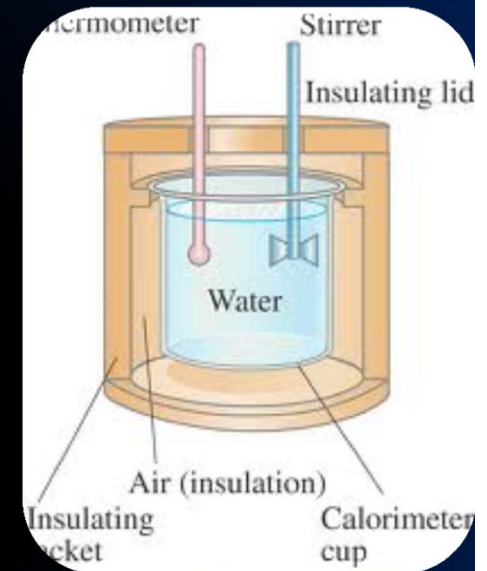


# Characterization in Media



Dissolution:  
Kinetics

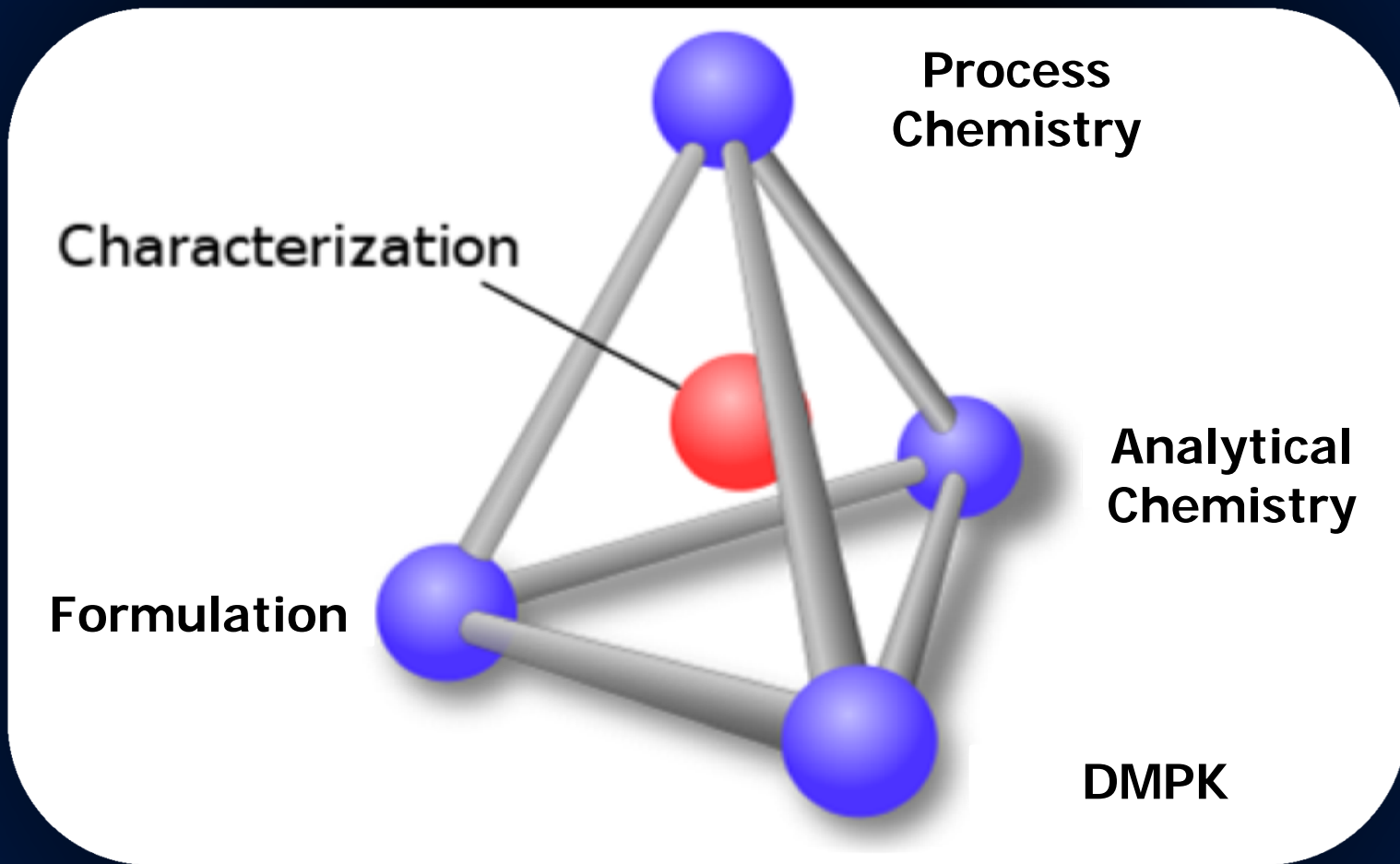
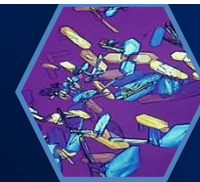
Solution Calorimetry:  
Thermodynamics



Turbidity:  
Process Space

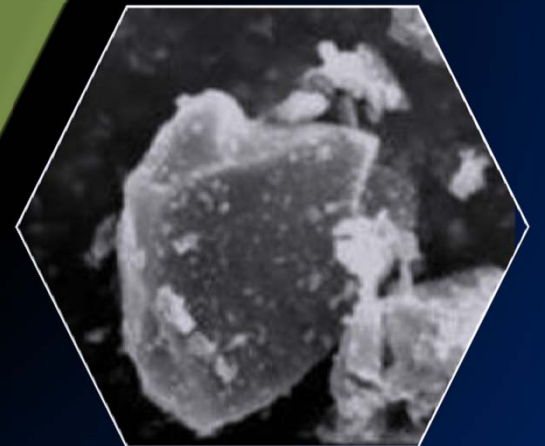
Spectroscopy:  
Form Control



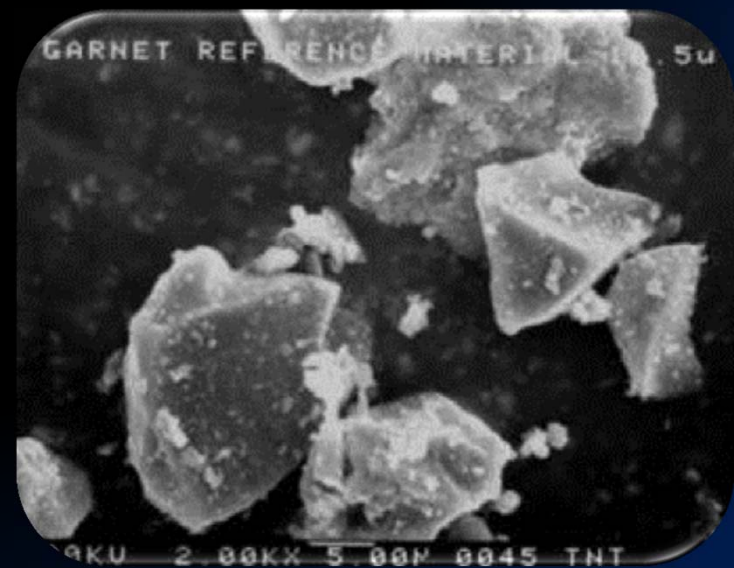
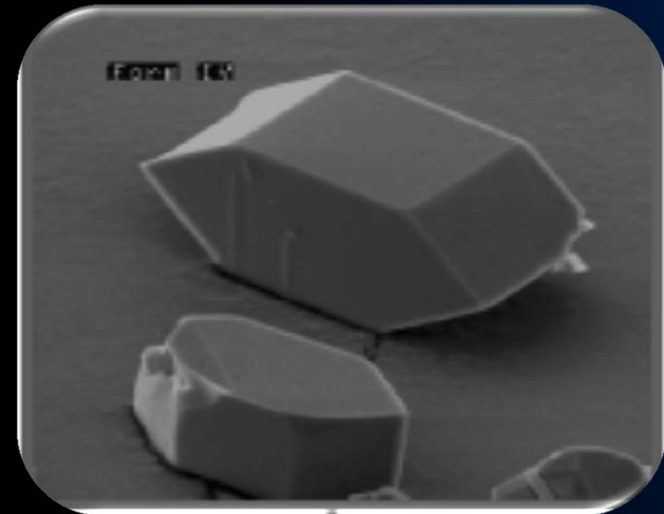
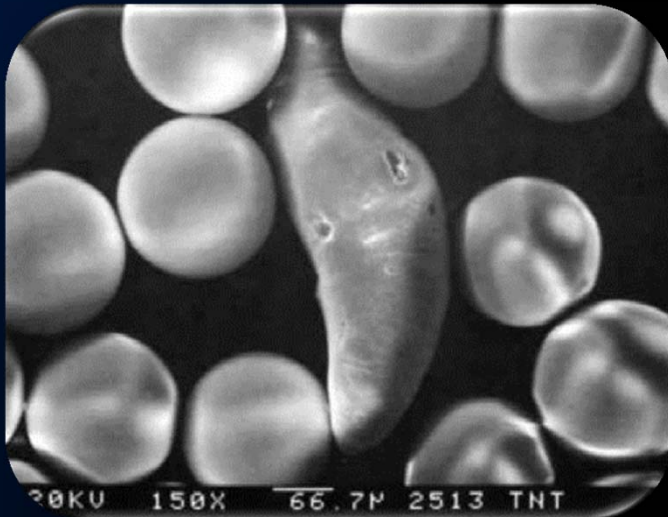
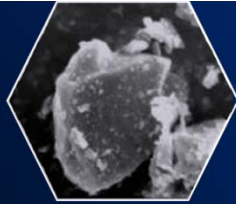




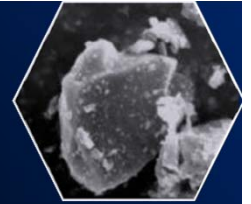
# The Right Specification



# What is Particle Size?



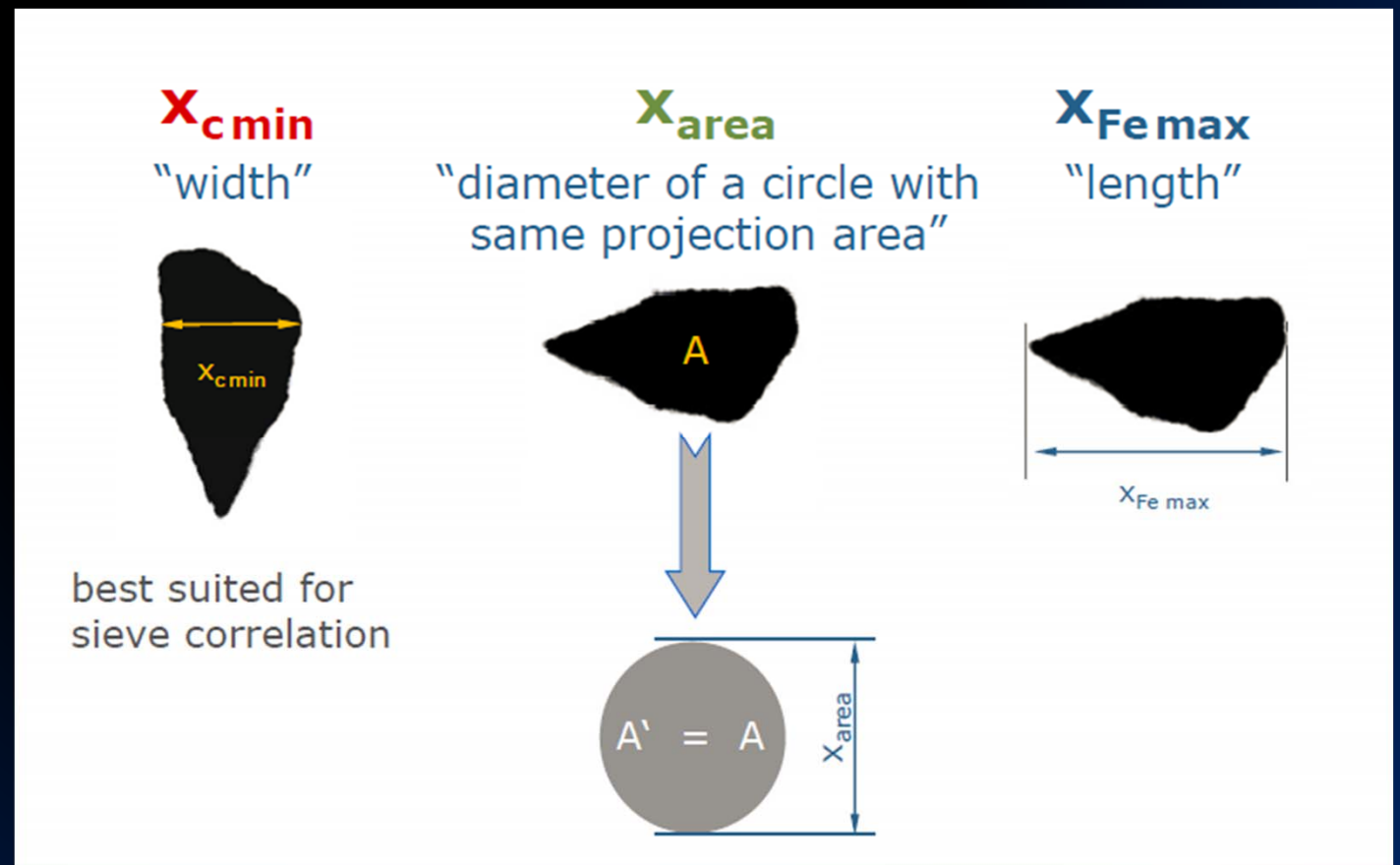
# What is Particle Size?



Measurement

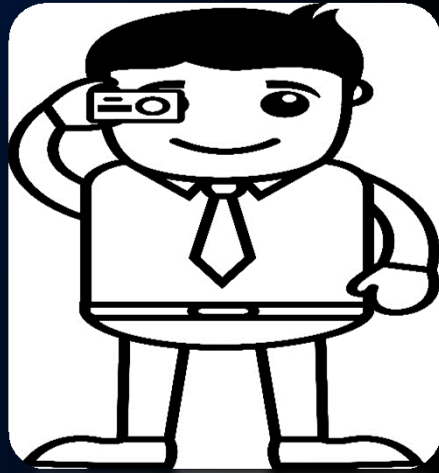
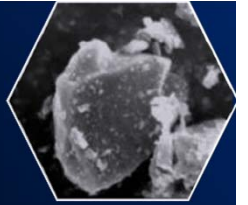
Habit

Properties





# Considerations



Take a Picture



Know your  
Customer



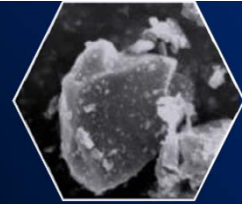
Understand the  
Application



Measurement  
Technique

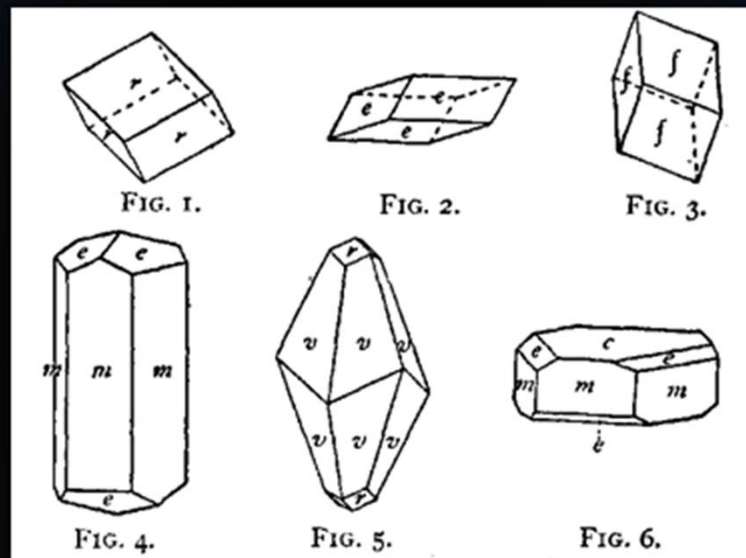


# Setting Specifications



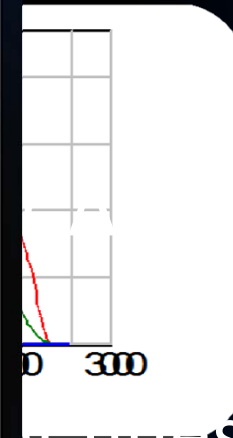
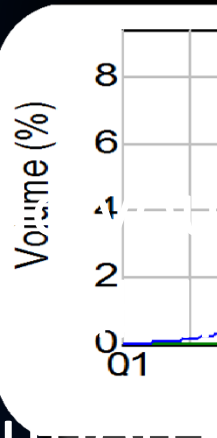
Habit – what shape do you want?

## Crystal Habit



Size –  
formul

Distribution  
larger particle



control,

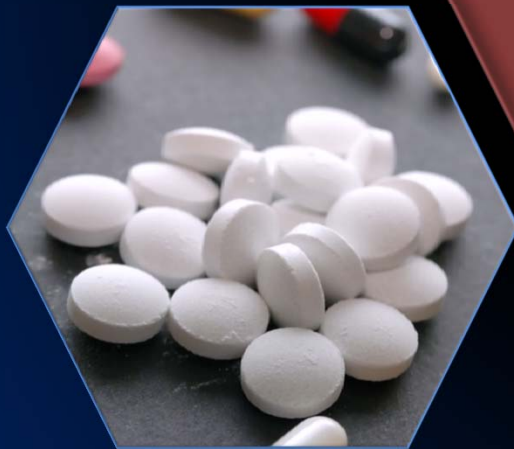
mines or

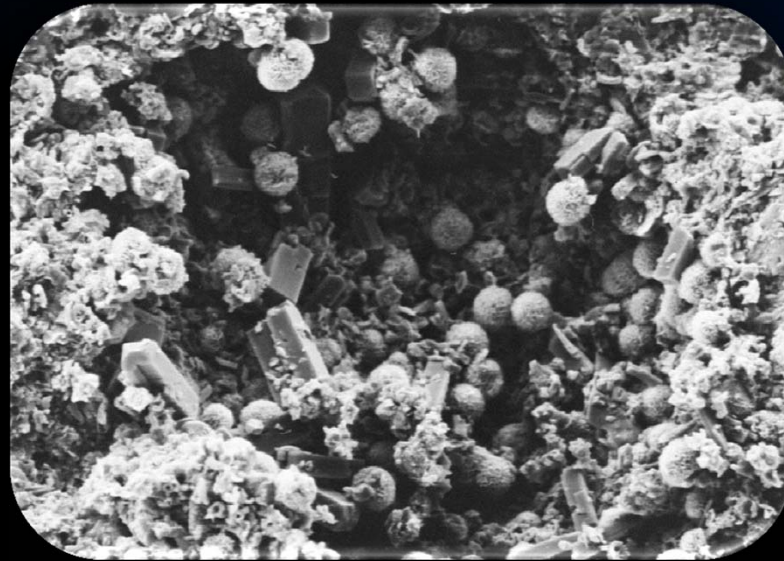
# Setting Specifications

**Make sure you choose two aspects to set for your specifications (i.e. habit and mean size, mean size and distribution, etc.)**



# Particle Effects on Performance





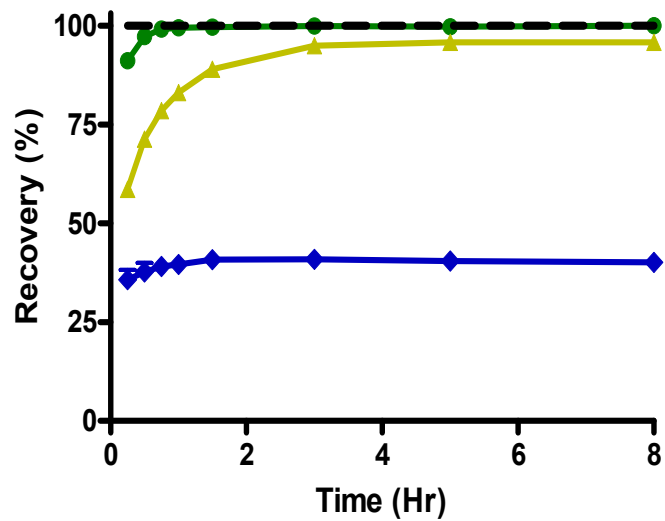
CASE STUDY #1

# PARTICLE AGGLOMERATION

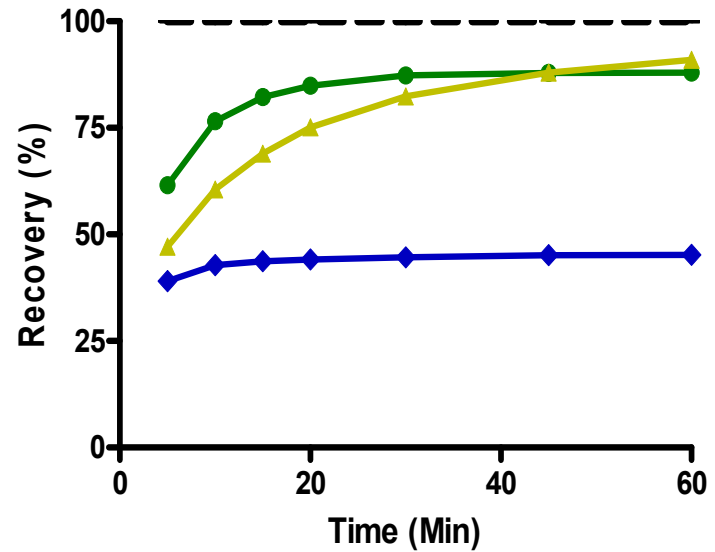
# Understanding Dissolution Variability



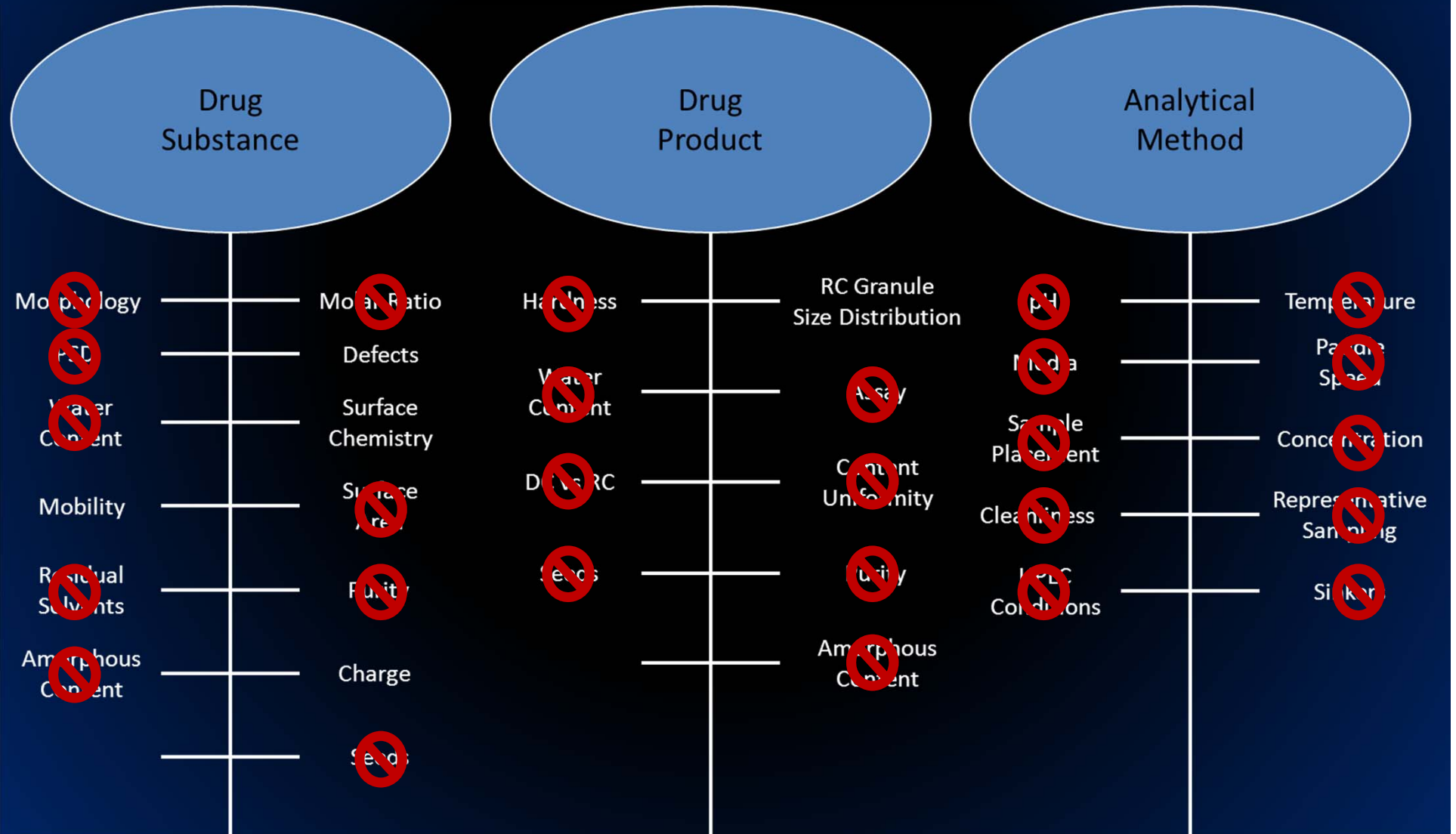
**Kinetic Solubility of API  
(0.75mg/ml) in 1%SLS (50rpm)**



**IR DC Tablet Dissolution in 1%SLS (50rpm)**

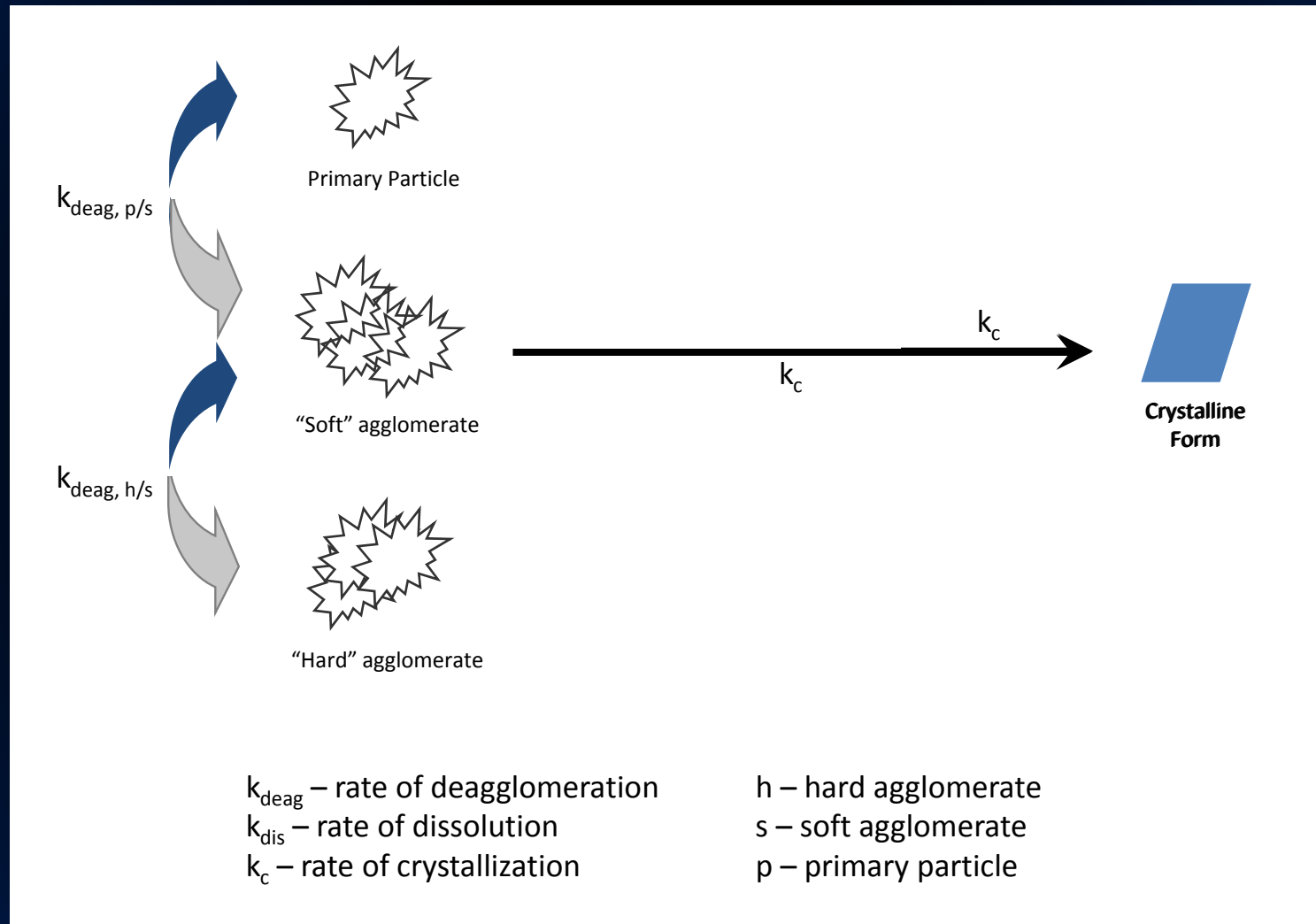


# Root Cause Analysis





# Conceptual Model for Co-Crystal Dissolution



\* Solution phase phenomena, as usual, but not specifically depicted here (proton equilibration of co-former, association phenomena, partitioning into micelle phases, if appropriate)

# Conceptual Model Raises Key Questions



## Observations

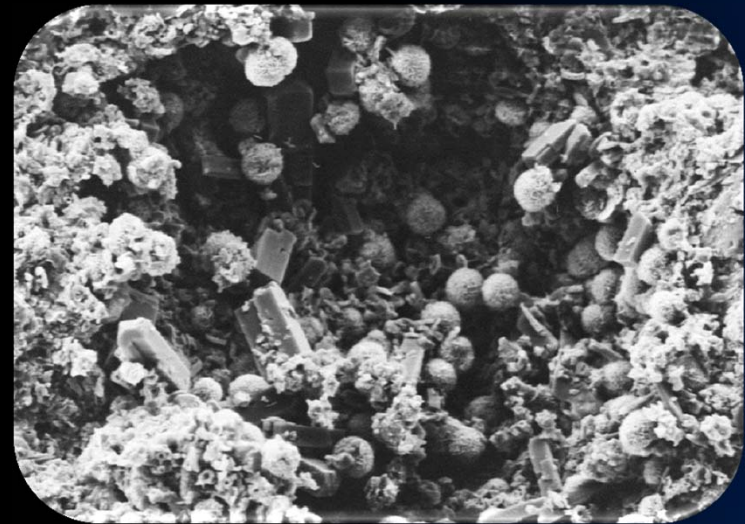
- Variable dissolution
- Variable agglomeration
- Variable crystalline content (post dissolution)

## Hypothesis

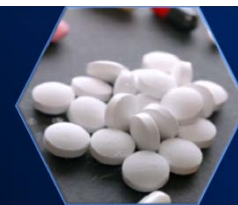
- Variability due to difference in agglomeration

## Experimental Plan

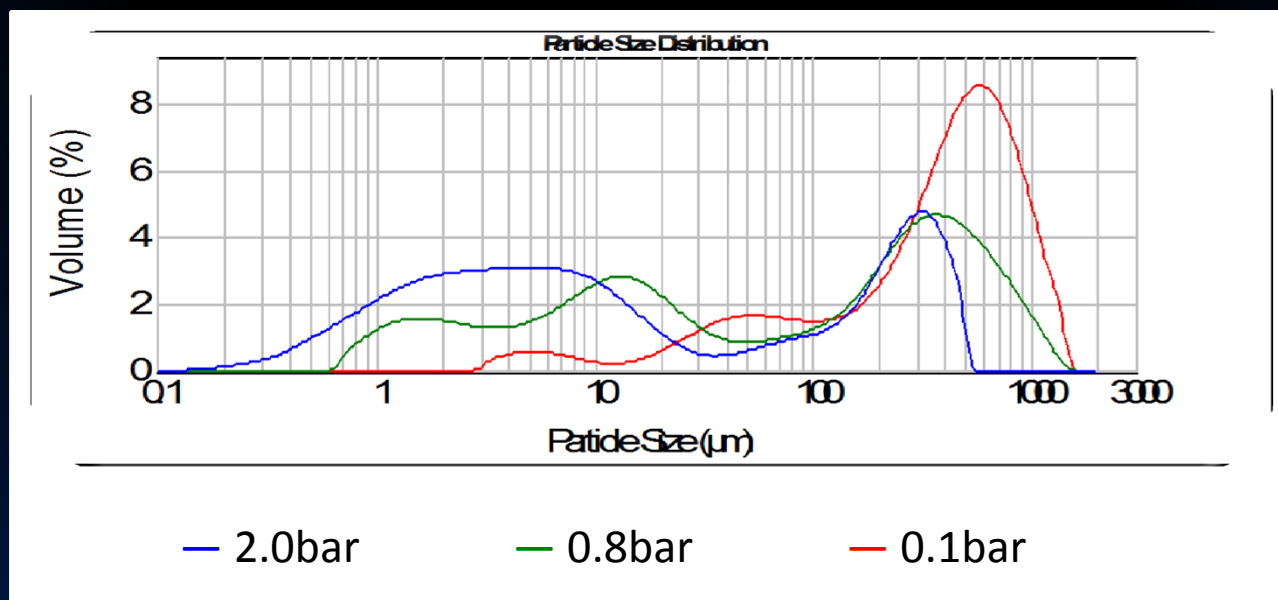
- Develop solid-state agglomeration method
- Determine total mass balance of agglomerate dissolution



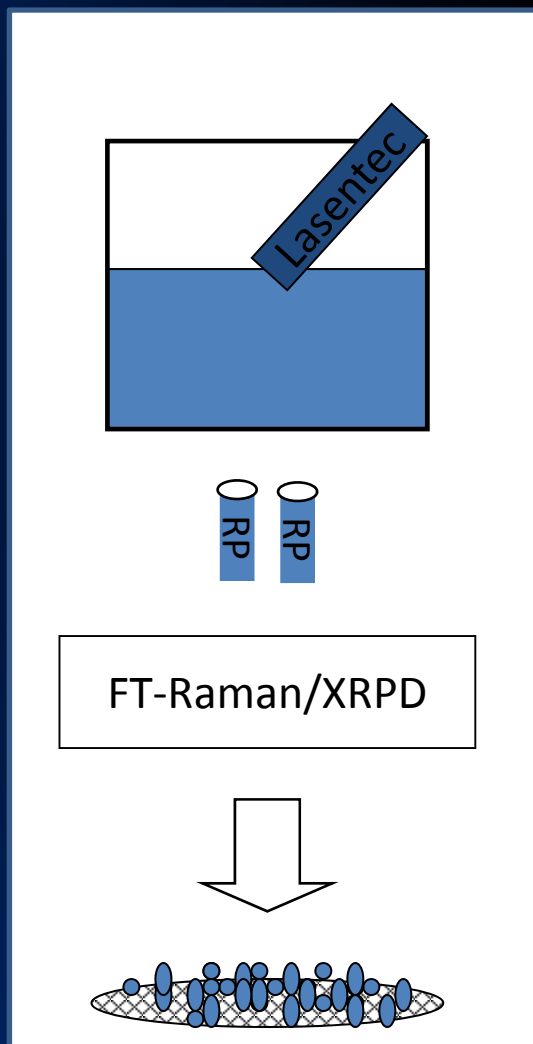
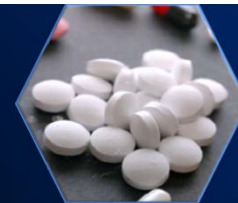
# Pressure Titrations Used as a Predictive Measure of Hard Agglomerates



- The largest mode at 2.0bar is a measure of hard agglomerates
- The  $\Delta V\%$  with pressure relates to the strength of agglomeration
- Changes in manufacturing process showed different behavior



# Mass Balance Experiment was Used to Understand Agglomeration Effect

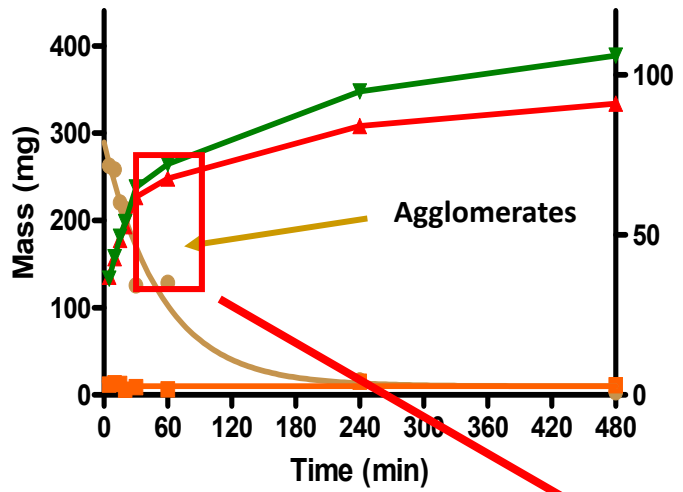


- Kinetics determined using 8 dissolution vessels
  - One per time point
  - Solids analyzed for form
  - Liquid analyzed for solutes
- FBRM used to measure cord length continuously for 8hr

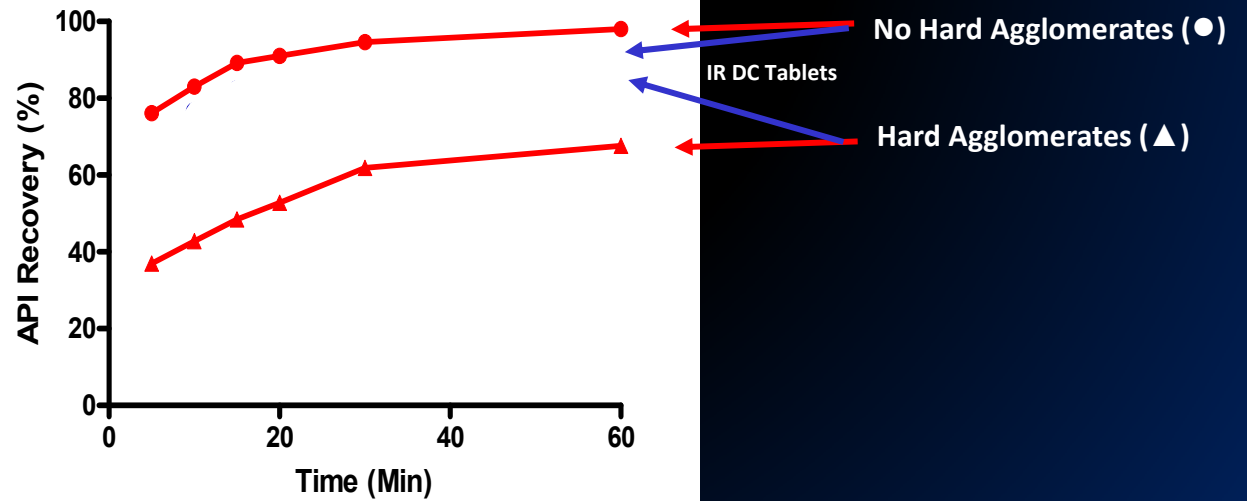
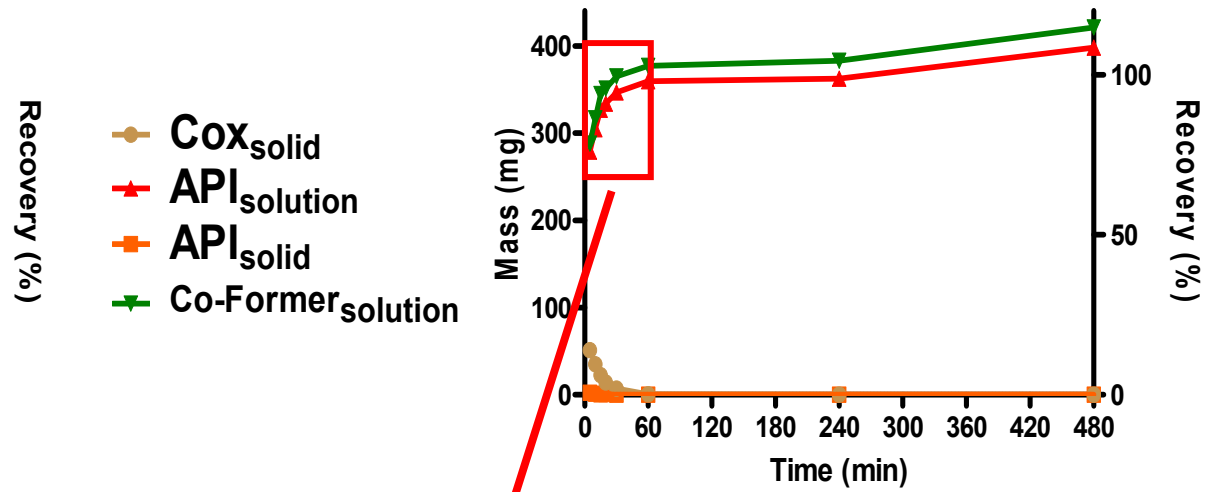




Hard Agglomerates



No Hard Agglomerates



# Conclusions

- API process changed to be an anti-solvent addition
- API drying process slowed to ensure agglomeration did not occur
- No PS specification was necessary

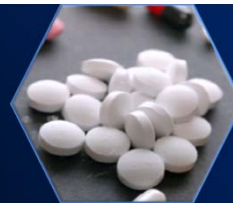




CASE STUDY #2

# SOLVENT MEDIATED PARTICLE ENGINEERING

# What's Wrong with Needles?



*"I've got high yield, low impurities, and can easily scale up filtering"*

- Anonymous Process Chemist

*"The particle size might be what I asked for, but it won't flow"*

- Anonymous Formulator



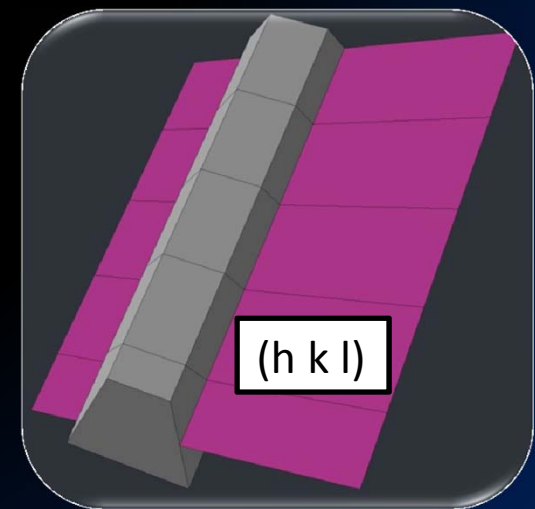
# The Problem with Needles



Long acicular particles don't flow even though they filtered



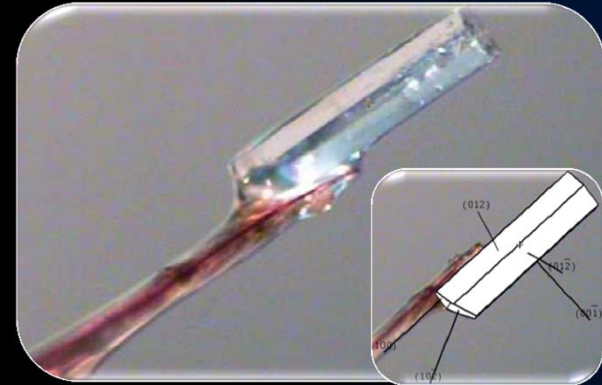
Slip-plane analysis predicted that milling wouldn't work



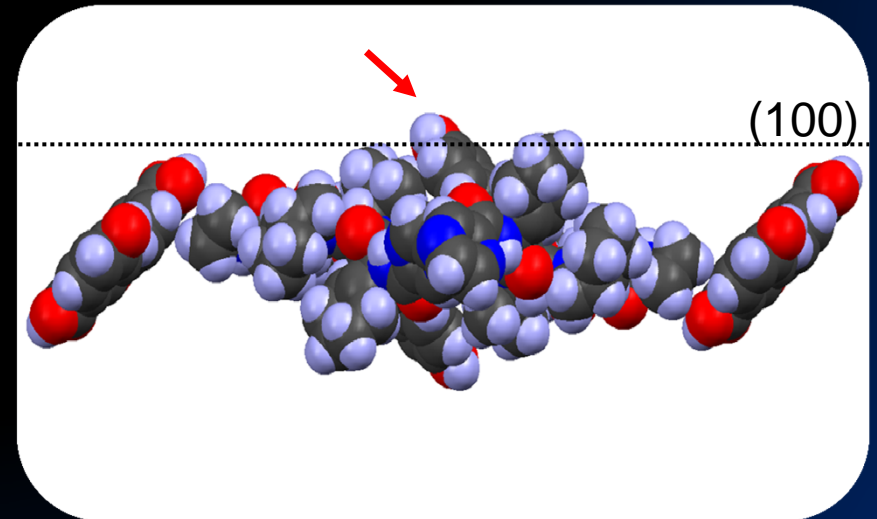
# The Solution was in the Crystal



Face-Indexing gave us a clue



Fast growing face had a free OH group on the surface



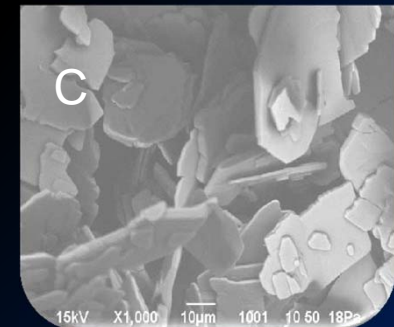
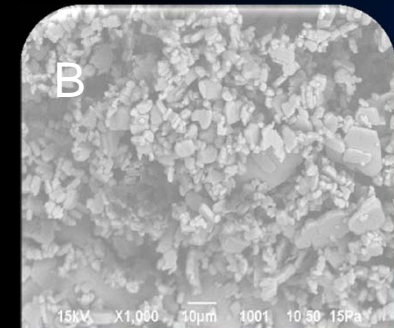
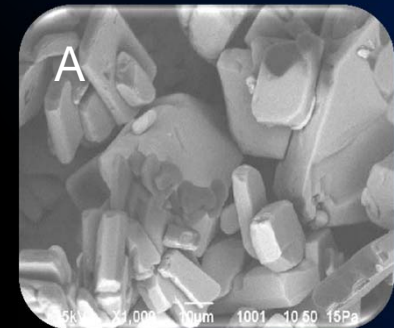
# The Solution was the Solution

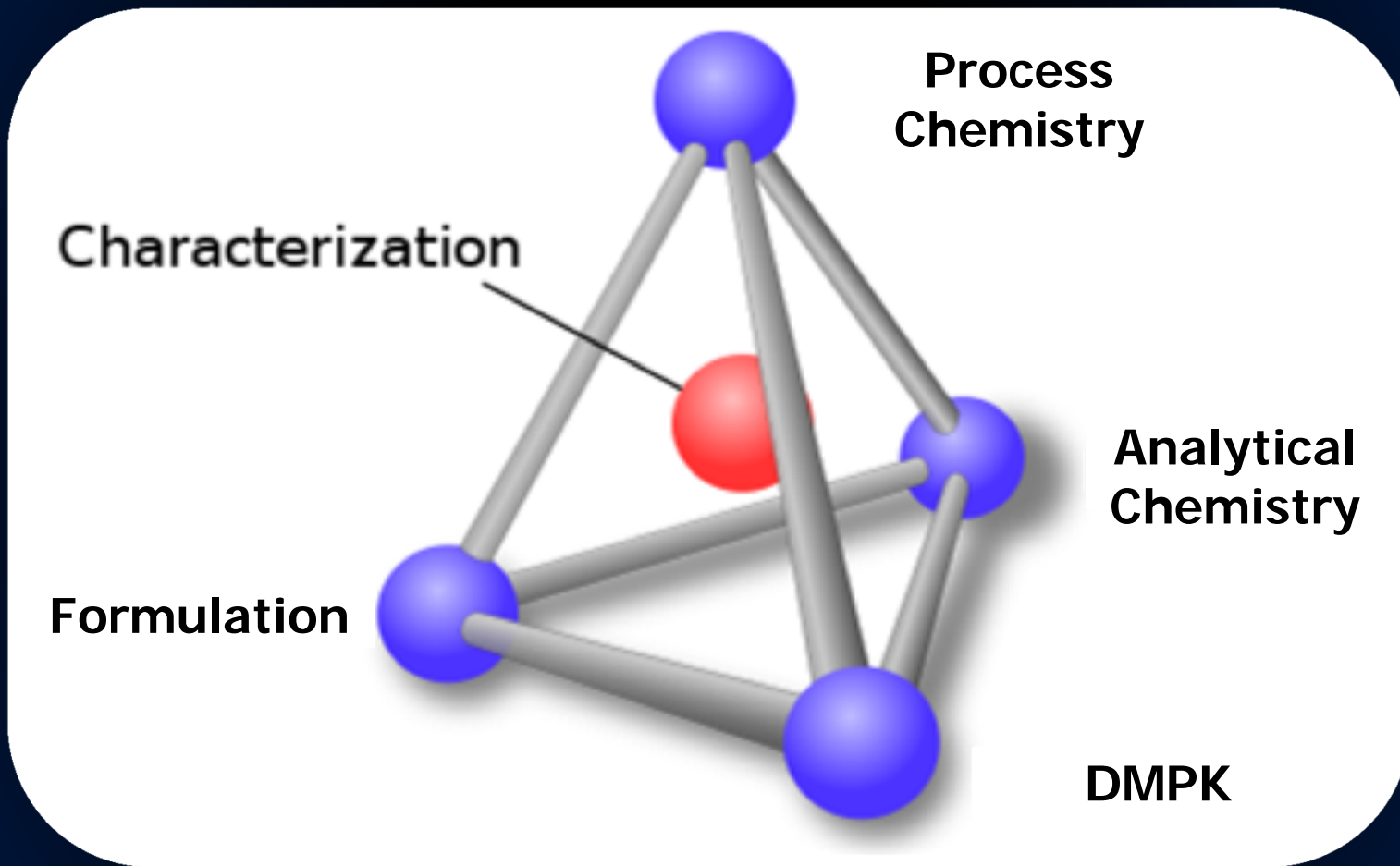
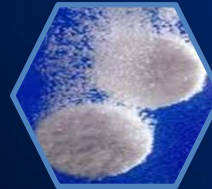


Experimented with crystallization solvents (i.e. protic vs aprotic)

By inhibiting growth on the fast face the particles shape changed

Particles flowed well and was moved forward







# Acknowledgements

## Materials Discovery

- Pat Connelly
- Steve Johnston
- Majed Fawaz
- Sneha Arekar
- Brian Luisi
- Adam O'Neil
- Mariusz Krawiec
- Ales Medek
- Praveen Mudunuri
- Brian Quinn
- Bin Song
- Hong-Ren Wang

## Analytical Development

- Yola Pesha
- Meghan Johnston
- Andrew Lange
- Jamie Ellis
- Drew Kuzmission
- Nicole Lahousse
- Meng-Chieh Lin
- Justin Pritchard
- Rajesh Penumatcha
- John Pietryka
- Sandi Porte-Walcott
- Alex Scangas
- Joe Snodgrass

## Chemical Development

- Dan Belmont
- Steffi Roeper
- Ben Littler
- Todd Blythe
- Tim Curran
- Cris Harrison
- Billie Kline
- Adam Looker
- David Miller
- Bobbianna Neubert-Langille
- Bill Nugent
- Brian Phenix
- Jerry Tanoury
- Mike Waldo
- David Wilcox

## Formulation Development

- Eleni Dokou
- Getz Knezic
- Rahela Gasparac
- Irina Kadiyala
- Tapan Sanghvi
- Steve Wahn
- Nick Cardoso
- Jeff Katstra

## Research

- Nigel Ewing
- Eric Block
- Frank Holland
- Dave Deininger
- Jim Empfield
- Greg May
- David Messersmith
- Nathan Waal
- Peter Connolly
- Marc Jacobs
- Ernst terHaar
- Rene Rijnbrand
- Mark Namchuk
- Youssef Bennani
- Mark Murko

## Collaborators

- Rolf Hilfiker, Markus von Raumer (Solvias)
- Chris Frampton, Alan Chorlton, Craig Grant (Pharmorphix)
- Simon Bates, Steve Byrn (SSCI)
- Don DePietro (TA Instruments)
- Allan Myerson, James Evans (MIT)
- Paul Dawson (Malvern)
- Ken Baker (Ken Baker Associates)
- Orn Almarsson (Alkermes)
- Elizabeth Vadas (InSciTech)
- Robb Westby (JEOL)
- Roger Davey (Univ of Manchester)
- Sally Price (Univ College London)
- George Zografi (Univ of Wisc-Madison)

# Tools to Tackle Particle Characterization

	LA-960	LA-350	CAMSIZER P4	CAMSIZER X2
Technology	Laser Diffraction	Laser Diffraction	Dynamic Image Analysis	Dynamic Image Analysis
Measurement Output	Particle Size	Particle Size	Particle Size and Shape	Particle Size and Shape
Measurement Range	0.01 $\mu\text{m}$ to 5000 $\mu\text{m}$	0.1 $\mu\text{m}$ to 1000 $\mu\text{m}$	20 $\mu\text{m}$ to 30 mm	0.8 $\mu\text{m}$ to 8 mm
Typical Sample Amount*	10 mg to 5 g	10 mg to 5 g	25g to 2.5 kg	< 20 mg to 100 g
External Dimensions	705 x 565 x 500 mm	297 x 429 x 376 mm	650 x 850 x 350 mm	850 x 580 x 570 mm
Light Source/ Resolution	605 nm Laser Diode 405 nm LED	605 nm Laser Diode	60 images/s 1.3MP Dual Cameras	>300 images/s, 4.2 MP Dual Cameras



# **HORIBA**

Scientific



[www.horiba.com/particle](http://www.horiba.com/particle)  
[labinfo@horiba.com](mailto:labinfo@horiba.com)  
1-800-446-7422