



Strategies and Tactics in the Selection of Drug Form in Exploratory Development

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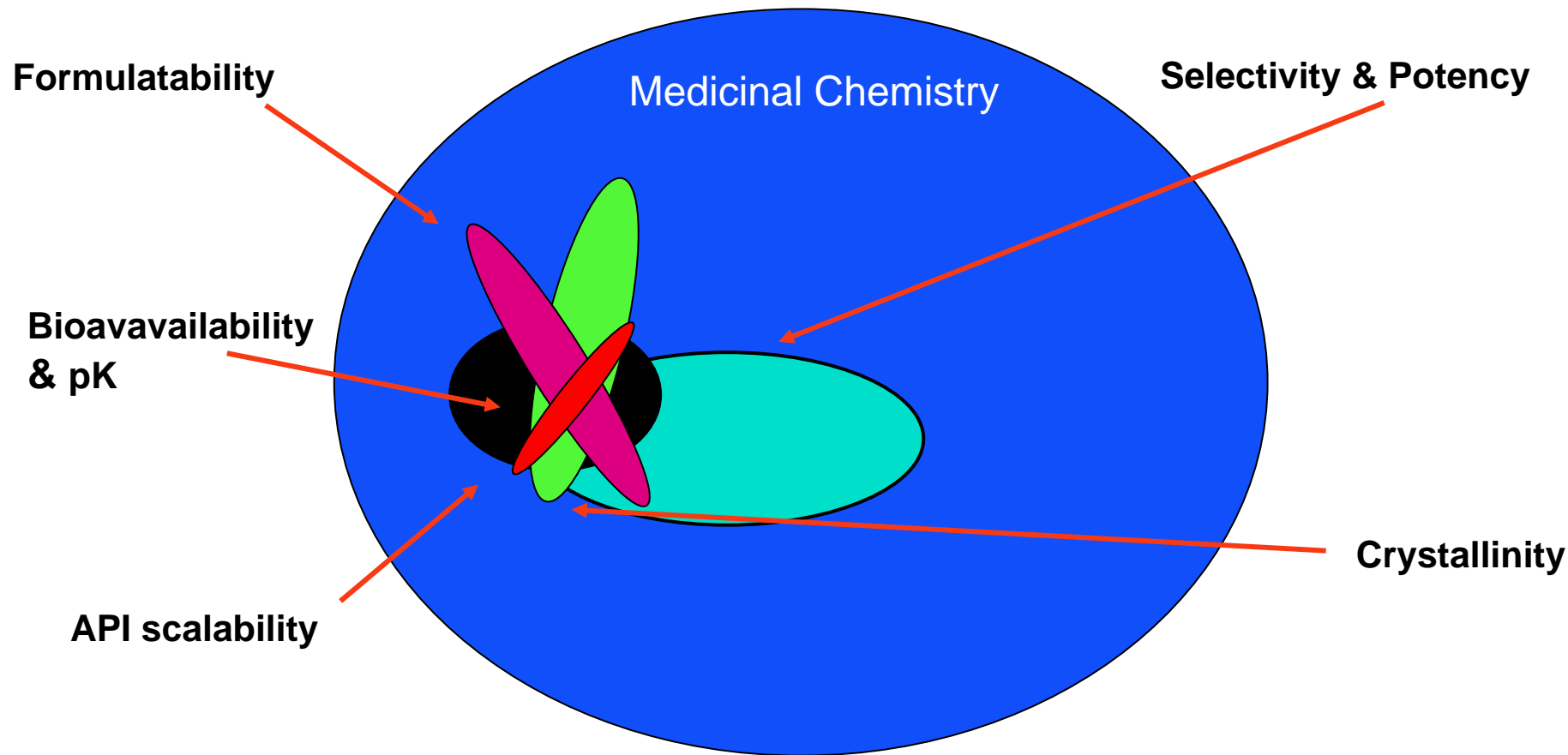


Overview

- ◆ **Drug Discovery / Development Interface**
 - Eliminate surprises that delay programs
 - ↑↑↑ Knowledge to select the best candidate
 - Educate and Train Discovery Chemists
- ◆ **Characterization of Leads**
 - Properties of the leads end up in the drug candidate
 - Knowledge = Power
- ◆ **Case Studies**
 - Life in the real world
 - Tactics to rapidly overcome challenges
- ◆ **Outsourcing**
 - It is a Global World
 - Capacity and Capability



Selection of Drug Form: Multi Dimensional Challenge





Identification of the Lead Candidate!

Medicinal Chemistry Tendencies

◆ Focus on compounds with:

- Highest binding and potency

- Ignore other attributes

- Rule of Five

Solubility and Permeability

High throughput methods

Solubility can vary by 10^6

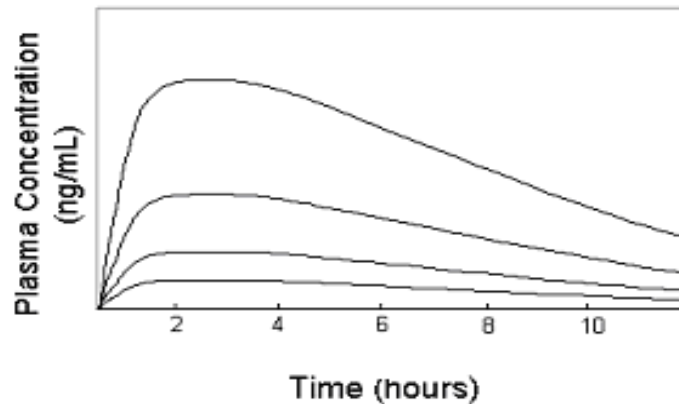
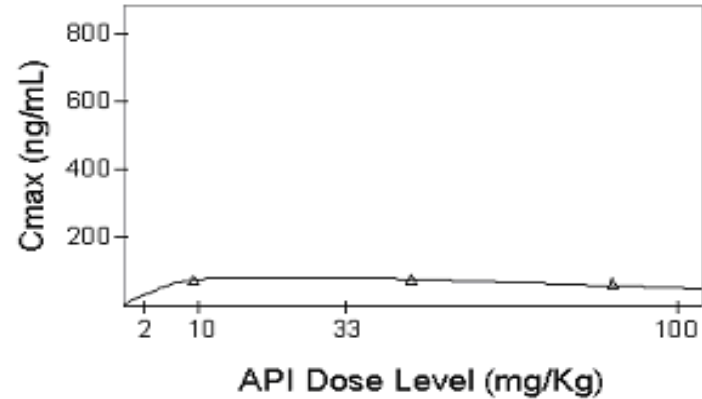
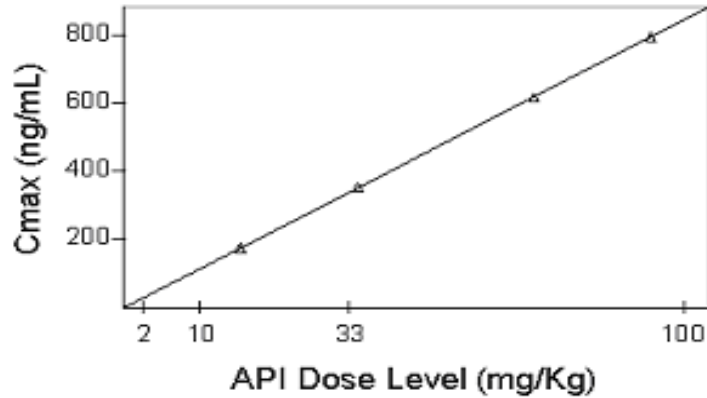
Permeability can vary by 50X

- Candidate solid state form

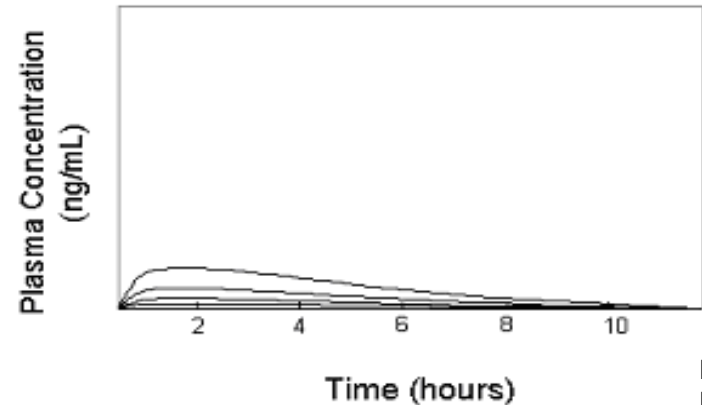
Amorphous or Crystalline



Solubility and Response



Increasing API dose and linear dose response



Increasing API dose and solubility limited absorption



Exploratory Development Form

Amorphous

- + Higher solubility**
- Lower chemical and physical stability**
- Must control form during development**

Crystalline

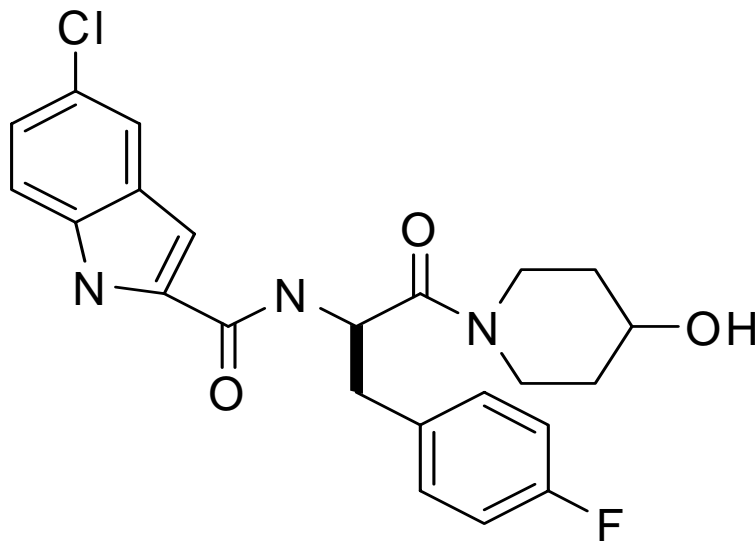
- Lower solubility**
- + Higher chemical and physical stability**
- + Better for development**

It is critical to understand the properties of the API form during selection, to select the best drug candidate



Example: Amorphous vs Crystalline

- Amorphous
 - Bioavailability 65% C_{\max} 1.7ug/mL
- Crystalline
 - Bioavailability 8% C_{\max} 0.3ug/mL





Modern Chemists' Talents

- ◆ **Structure Determination of Strychnine**
 - **Solved by Woodward**
 - **Chemical degradation**
 - **Melting point of crystalline degradants**
- ◆ **Today's chemists**
 - **New technology has changed synthetic chemists**
 - **High resolution NMR**
 - **High resolution mass spectrometry**
 - **Crystallization is becoming a lost art**
 - **Key in industrial process chemistry**
 - **Manufacturing**

J. Am. Chem. Soc. 1948, 70, 2107-2115.

Tetrahedron 1963, 19, 247-288.



Education: A Practical Reality

“Hands on” crystallization course

- ◆ **Concepts and Theory of crystallization**
 - **Nucleation**
 - **Supersaturation**
 - **Crystal packing**
 - **Powder x-ray diffractions (PXRD)**
- ◆ **Fundamental crystallization techniques**
 - **Systematic approach to crystallization**
- ◆ **Eliminates development surprise**
- ◆ **Immediate Return On Investment**



Solid-State Properties: Analysis / Decision Processes

Stage 1

- ◆ Birefringence
- ◆ PXRD
- ◆ Purity assessment
- ◆ Stoichiometry
- ◆ Thermal analysis
- ◆ Kinetic hygroscopicity
- ◆ Bioavailability

Stage 2

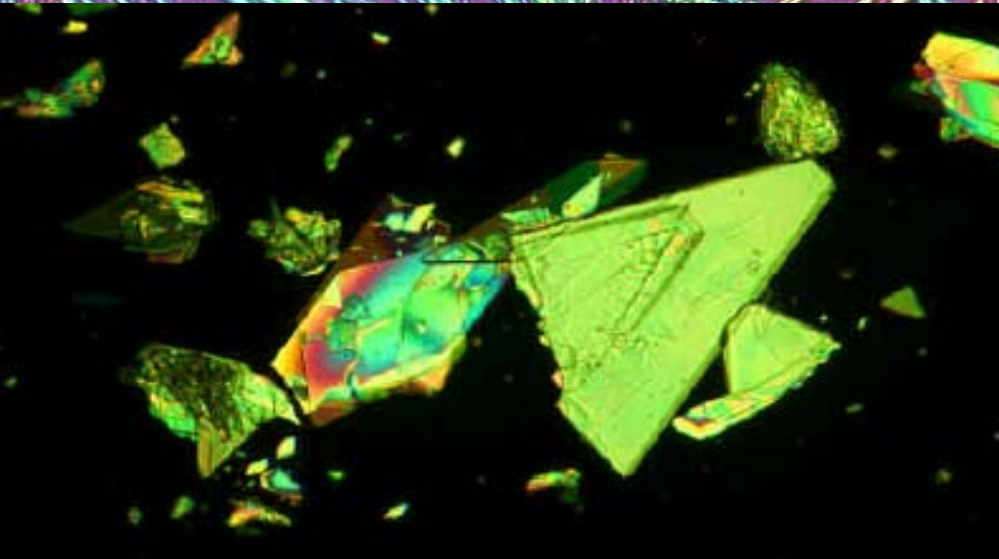
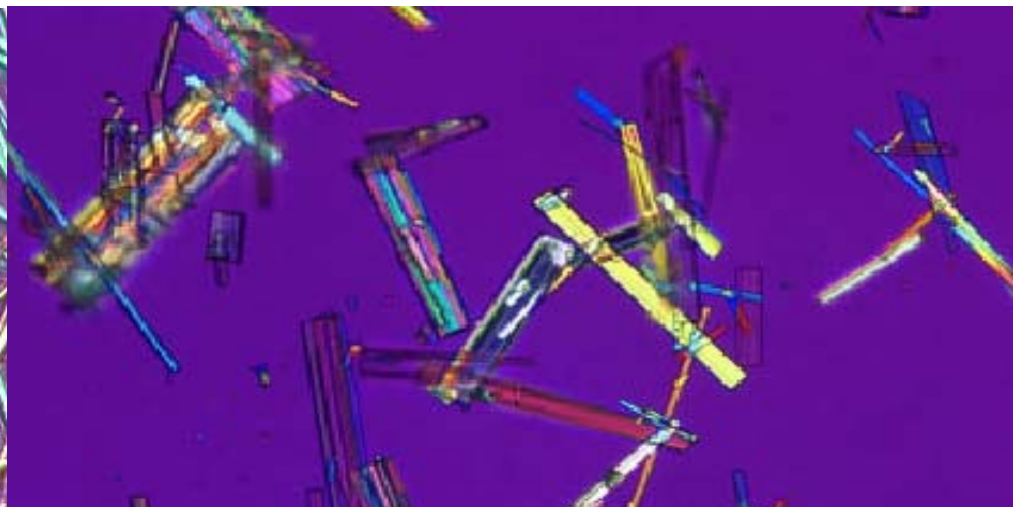
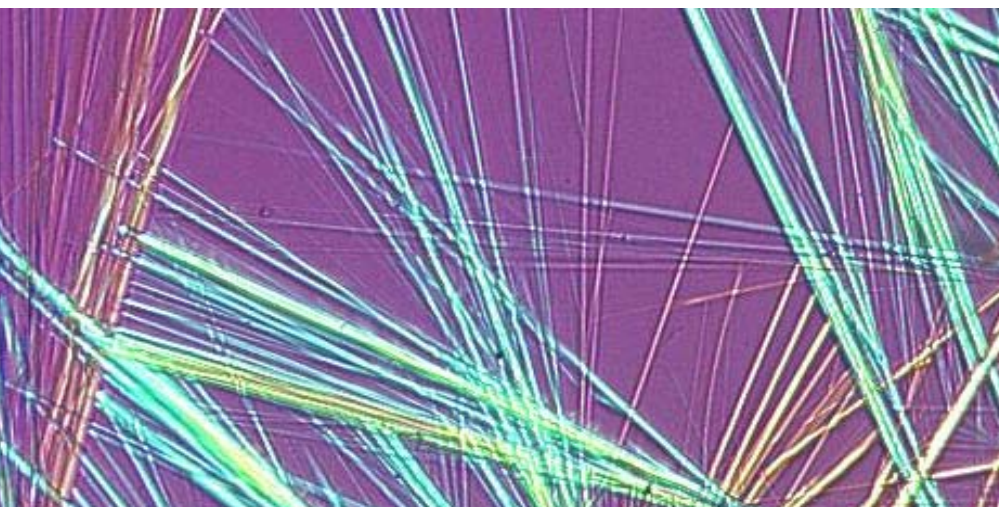
- ◆ Hydrate screening
- ◆ Determine low-energy form
- ◆ API accelerated stability

Stage 3

- ◆ Polymorph screening
- ◆ DP stability projections



Case Studies



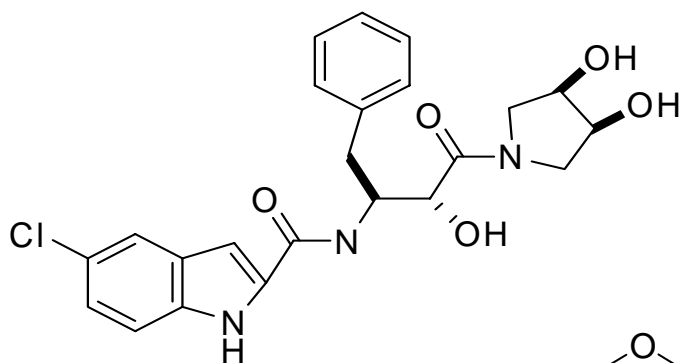


Meeting the Challenges in Exploratory Development

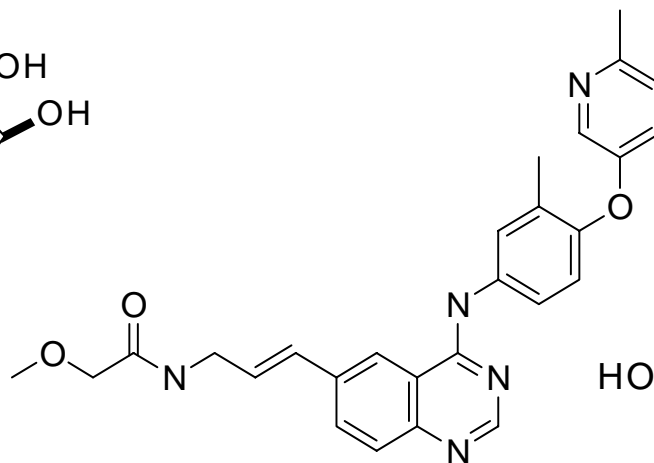
Case Studies

- ◆ Meant to demonstrate
 - Complexity
 - Uncertainty in discovering a viable solution
- ◆ Challenges presented
 - Amorphous to crystalline
 - Overcoming solubility limited absorption
 - API stability
 - Drug Product stability
 - Hydrates
 - A candidate with multiple issues - “a complex salt”

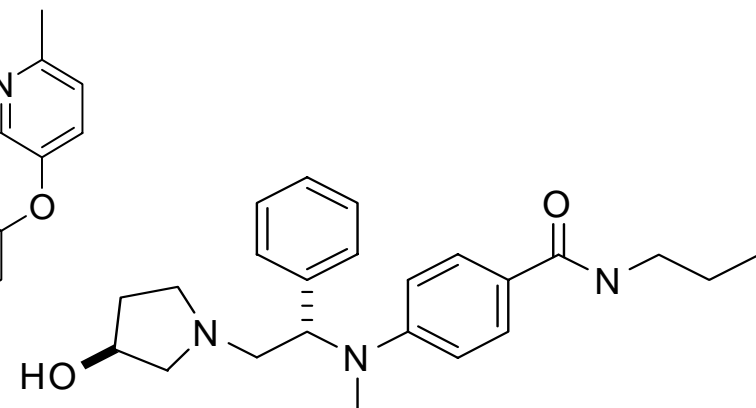
- ◆ Ionization increases crystallinity and solubility options



1



2



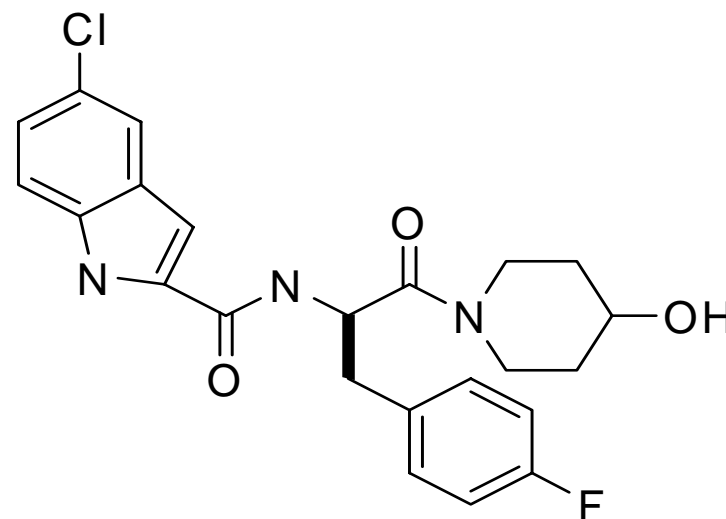
3



Crystallization of Amorphous Candidates

Non-ionizable compounds represent the highest risk level

- ◆ **Solubility screening**
- ◆ **Various crystallization techniques**
 - **Slow evaporation**
 - **Antisolvent addition**
 - **Vapor phase diffusion**
- ◆ **Hydrates and solvates**
 - **Require water / solvent**
 - **May lead to crystalline anhydrous form**
- ◆ **If initial attempts fail, then purify to $\geq 99.9\%$**

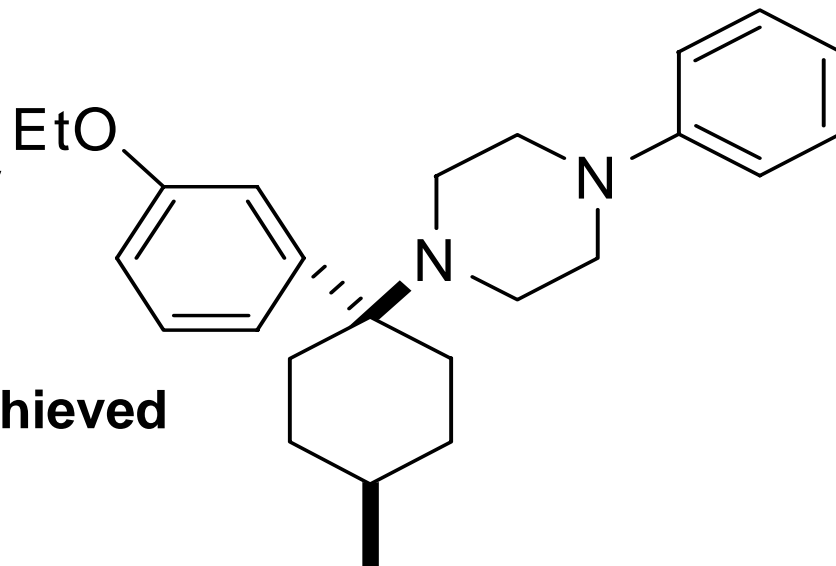


- ◆ Fumerate salt

- Excellent chemical yields
- Highly crystalline
- 50ug/mL aqueous solubility

- ◆ Result

- Target organ toxicity not achieved
 - 5,000mg/Kg





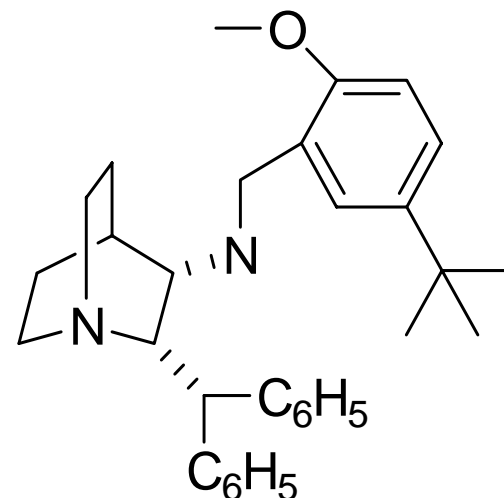
Overcoming Solubility Limited Absorption

- ◆ **Lowest risk**
 - **Compound is ionizable**
- ◆ **Possibility of mono- and di- salts**
 - **Evaluate various**
 - **Crystallization techniques**
 - **Counterions**
 - **Free base as development form**
- ◆ **In this case, a solution was discovered**
 - **Dimesylate**
 - **31mg/mL solubility**
 - **Target organ toxicity achieved @ 85mg/Kg**



API Stability

- ◆ **Crystalline benzoate salt unstable @ 5°C**
 - Crystallinity does not guarantee success
 - Oxidative degradation pathway
- ◆ **Attempts fail to increase stability**
 - Extensive time effort
 - Need to complete Stages 1 & 2
 - Automation of limited value
 - Leads require scale up and characterization
 - Stability program
 - Accelerated 70°C / 75%RH for 3 weeks
 - Trade off - highly aggressive stressing vs time
 - Citrate discovered
 - <0.10% degradation @ 70°C / 75% RH for 3 weeks





API Stability: Characterization is Critical

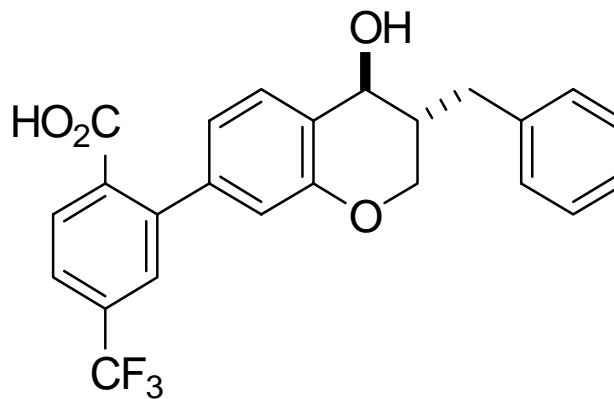
Remember Stage 1 Characterization

◆ Chemical and Form Purity

- Chemical purity
 - Ability to discover a crystalline form
 - Physical properties
- Physical Form purity
 - Chemical Stability

◆ Degradation

- Occurs more rapidly @ 40°C / 75%RH vs ambient
- Levels off at 2-3%
- Intrinsic property?
 - Induced by impurities?
 - Degradation on crystal surface?
 - Due to crystal defects?
- Root cause?

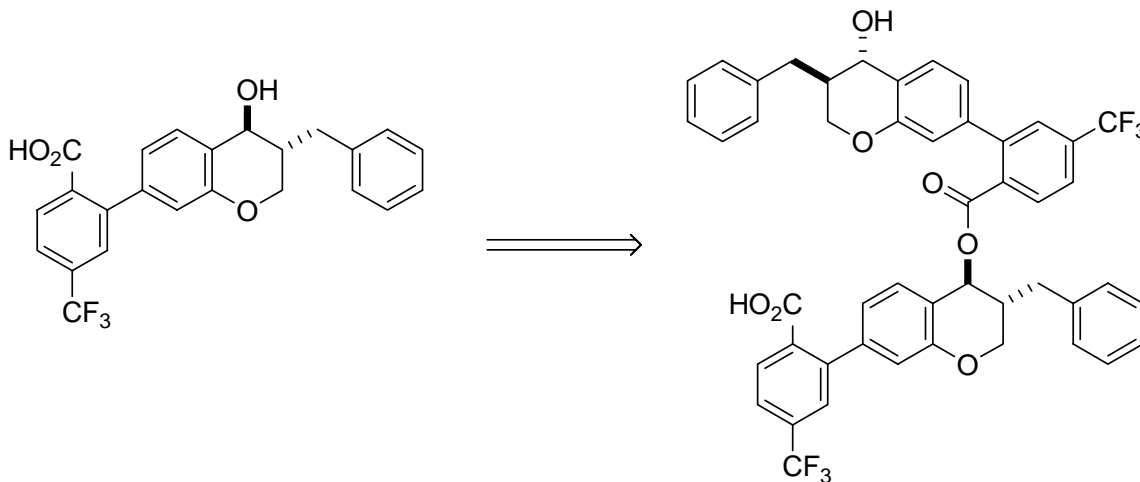




API Stability: A Case of Physical Form Purity

Root cause

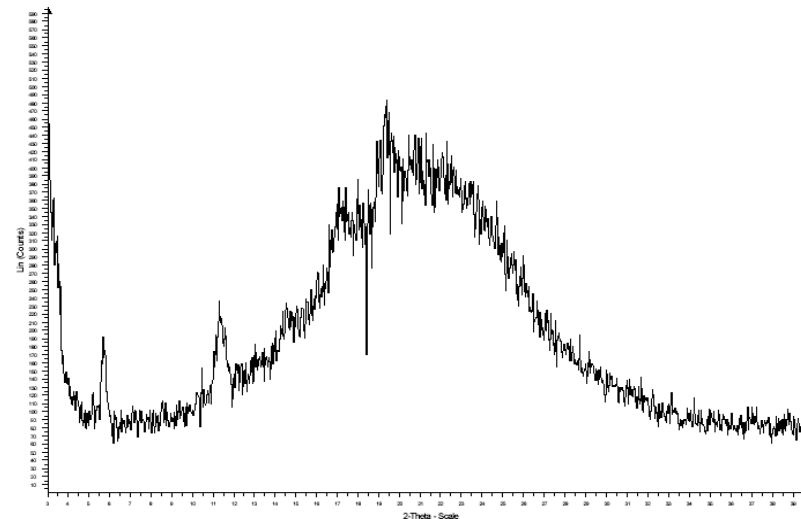
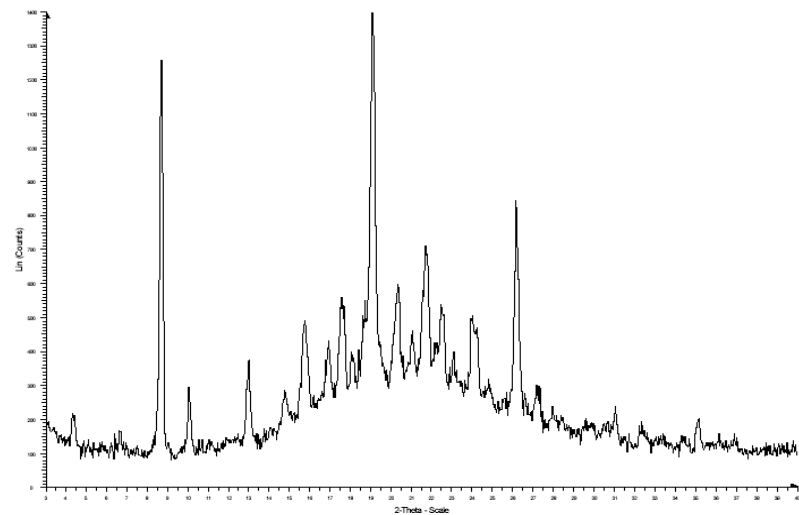
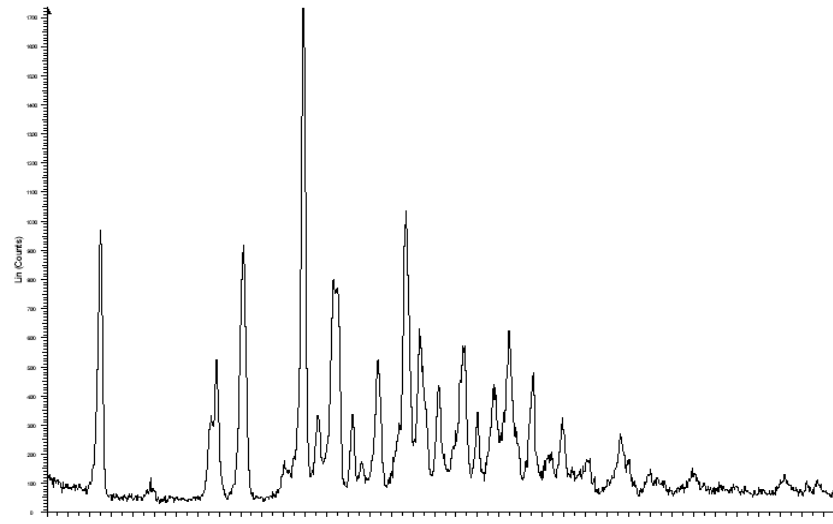
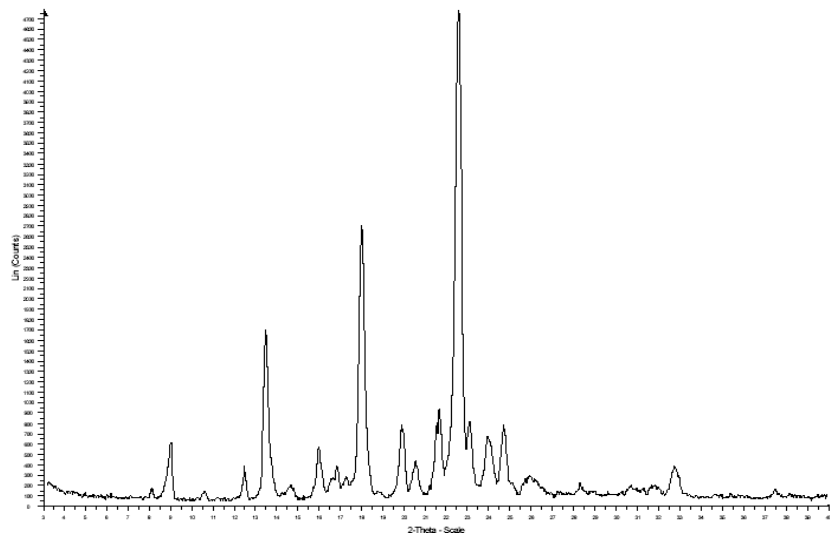
- Identification of impurity is key
 - Esterification
- Amorphous content is identified
 - Rate is much faster with amorphous material
- Fully crystalline material has acceptable stability





Levels of Crystallinity

Chemical Analysis Introduction to X-ray Powder
Diffraction. John Wiley & Sons Inc. 1996.
J. Am. Chem. Soc. 1994, 116, 5766-5773.





Discovering Hydrates

Not Straightforward

- ◆ **Moisture balance provides kinetic analysis**
 - **Hygroscopicity measurement**
- ◆ **Three conversions useful for anhydrous to hydrate**
 - **Accelerated stability**
 - **70°C / 75%RH**
 - **Thermodynamic solubility determination in water**
 - **Water activity studies**
 - **Provides anhydrous/hydrate phase boundary**

Thermochimica Acta 1995, 248, 61-79.

Journal of Pharmaceutics. 1996, 139, 33-43.

International Journal of Pharmaceutics 1996, 135, 151-160.

International Journal of Pharmaceutics 2002, 247, 1-10.



Impact of New API Hydrate Form

◆ Benzoate salt

- **Stable to kinetic moisture balance**

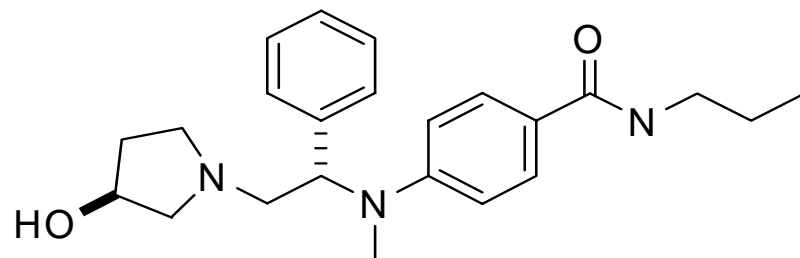
- Non-hygroscopic

- **Aqueous solubility study**

- Initially 150mg/mL solubility
- Monohydrate discovered

Precipitate observed after 2 weeks

- Hydrate aqueous solubility drops precipitously - 7mg/mL





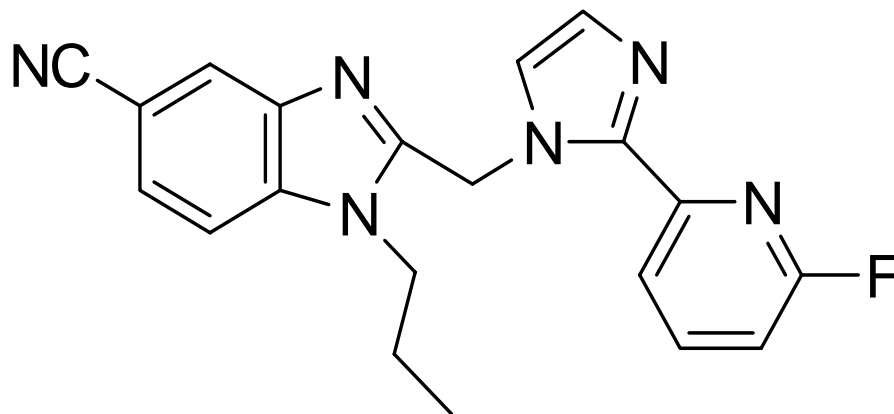
Water Activity Study

Mole Fraction of water in IPA	Water Activity	Isolated Solid
0.03	0.1	Anhydrous & Hydrate
0.11	0.3	Anhydrous & Hydrate
0.20	0.5	Hydrate
0.33	0.7	Hydrate
0.45	0.8	Hydrate
0.90	0.9	Hydrate



Hydrate Example

- ◆ Hydrate initially identified in water activity studies
- ◆ Accelerated stability
 - 12 weeks @ 40°C / 75%RH
 - Hydrate PXRD diffraction peaks beginning to emerge





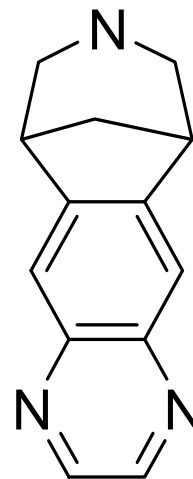
Drug Product Stability

- ◆ **Mixtures are less stable than pure materials**
- ◆ **Formulation process induces stress**
 - **Milling**
 - Creation of amorphous phase
 - Crystal defects
 - **Wet granulation**
 - API dissolution
 - **Compaction forces**
 - High stresses



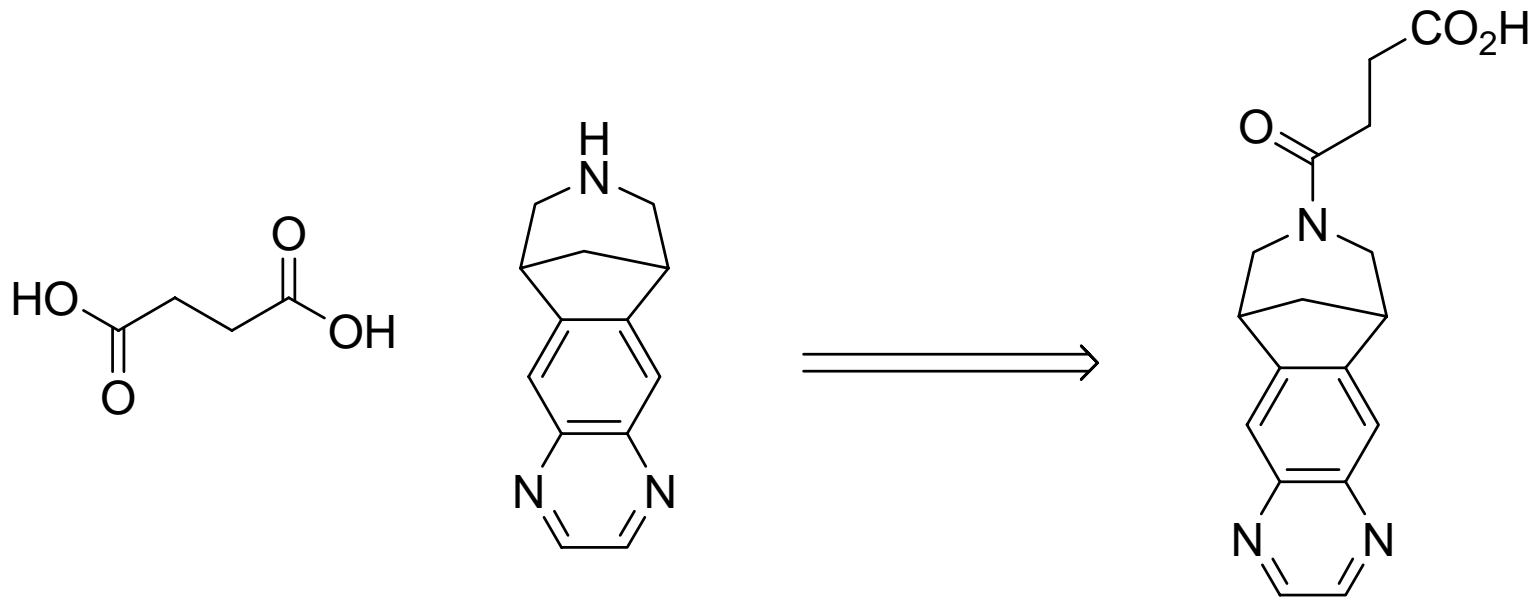
Drug Product Stability

- ◆ **Succinate salt**
 - Crystalline form discovered
 - Increases purity from 95 to $\geq 99\%$
- ◆ **API chemically and physically stable**
 - Accelerated 70 / 75°C 3 weeks
 - No impurity growth $\geq 0.1\%$
- ◆ **New impurity detected in drug product**
 - **Structure identified**
 - Reaction with counterion and free base
 - **Alternative formulations did not prevent formation**





Drug Product Stability





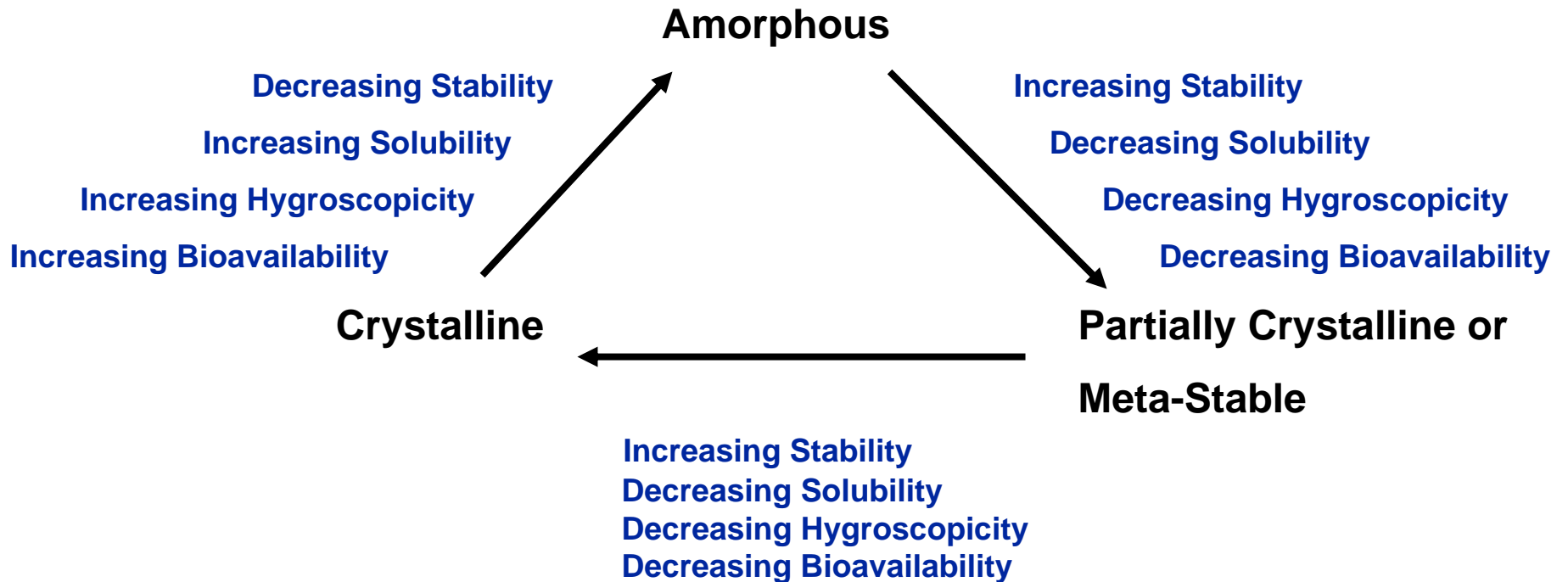
Drug Product Stability

- ◆ **Alternative salts hygroscopic**
 - **At times deliquescent**
- ◆ **Citrate and L- tartrate discovered**
 - **Citrate is a channel hydrate**
 - **0 – 3.3% weight gain depending on relative humidity**
 - **Tartrate had 3 forms**
 - **2 anhydrous forms and a hydrate**
 - **Phase boundary for hydrate was $\geq 85\%RH$**
 - **Both salts have propensity for hydration**
 - **Tartrate has better stability in drug product**
 - **High research commitment due to complexity**



Multiple Candidate Issues

- ◆ **Balancing solid state properties**
 - **Changing a property impacts others**

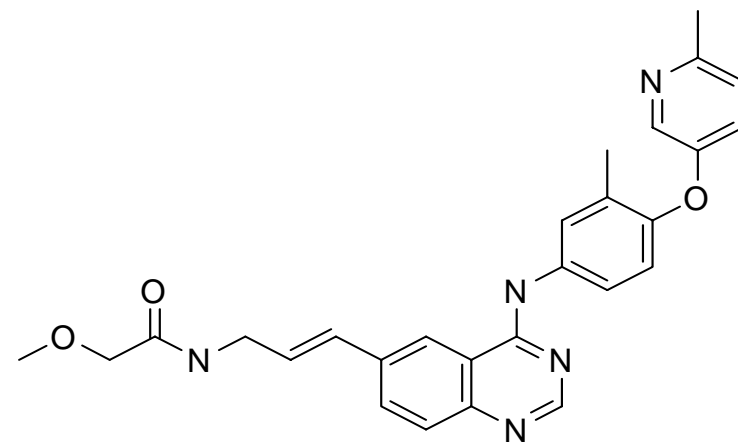




Multiple Candidate Issues

Crystalline Mesylate Salt

- ◆ Hygroscopic to the point of deliquescence
- ◆ Poor physical/chemical stability
- ◆ Good bioavailability
 - High dose level required
- ◆ pK_a's 4.6 & 5.1
- ◆ Only strong acids will make salts
 - HCl





Continuum from Salt to Co-crystal

◆ Drug Form Finalists

- **HCl, Di-maleate, Di-malonate, Sesqui-succinate**
 - Fully ionized salt – HCl
 - Hydrogen bonded complex – sesqui-succinate
- **Optimum balance of properties**
 - Necessitates predetermined requirements
 - Bioavailability, stability, hygroscopicity
 - Sesqui-succinate



Co-crystals

- ◆ **New solid state form approach**
- ◆ **Potential to enhance solubility**
 - **Even non- ionizable compounds**
- ◆ **Unpredictable outcomes**
 - **Research phase space is immense**
- ◆ **Not a preferred option**
 - **Grinding is a method of synthesis**
 - **Drug product formulation**
 - **Processes include grinding**

Chemistry of Materials 1989, 1, 10-12.
Chem. Comm. 1996, 987-988.
Crystal Growth and Design 2003, 3, 909-919.
J. Am. Chem. Soc. 2004, 126, 13335-13342.
Comm. 2004, 890-891.

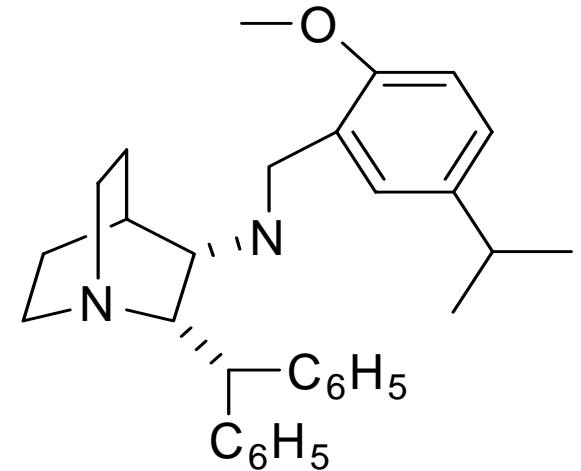
◆ Augmented Challenge

• Solubility

- Identify most soluble form
 - Physiological acceptable range
 - Various temperatures
- Understand impact of buffers / additives

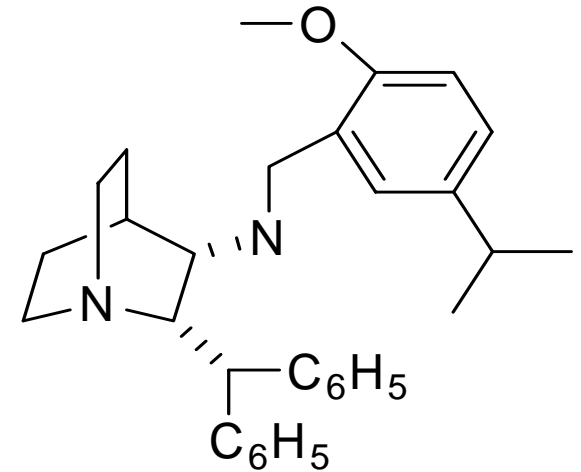
• Stability

- Ability of human eye to detect very low levels
 - Particulates, haze, color
 - Degradation of API
 - Insoluble impurities
 - New impurities
 - Change in crystallization
 - New synthetic route



API

- **Dihydrochloride dihydrate**
 - Solubility 75mg/mL pH 2.2
 - Buffered solubility >27mg/mL pH 4.3
- **Value of understanding additives / buffers**
 - Citrate monohydrate
Solubility 4.3mg/mL pH 3.56
 - Citric acid would have dramatically lowered API concentration





Unpredictable science

- **Modeling of pharmaceuticals is futuristic**
 - Emerging science
- **Purity is often overlooked**
 - Precluding nucleation of new forms
- **Screening techniques often employed**
 - Evaporation of API solution to dryness
 - Antisolvent addition to API solution
 - Cooling API solution to induce crystallization
 - Reslurrying solid API in solvents



Polymorphism

- **Lowest energy form – development choice**
 - Greatest physical stability
 - Slowest to nucleate
 - Ostwald's Rules – At times the hardest to find
 - Highest crystal density
 - Not necessarily the highest melting point
 - Lowest solubility
 - Lowest bioavailability
- ***Highest risk; not finding the low energy form***

Acta Pharm. Technol. 1982, 28, 1-20.

Pharmaceutical Research 1995; 12, 945-954.

Crystallization Technology Handbook. Marcel Dekker Inc. 2001.

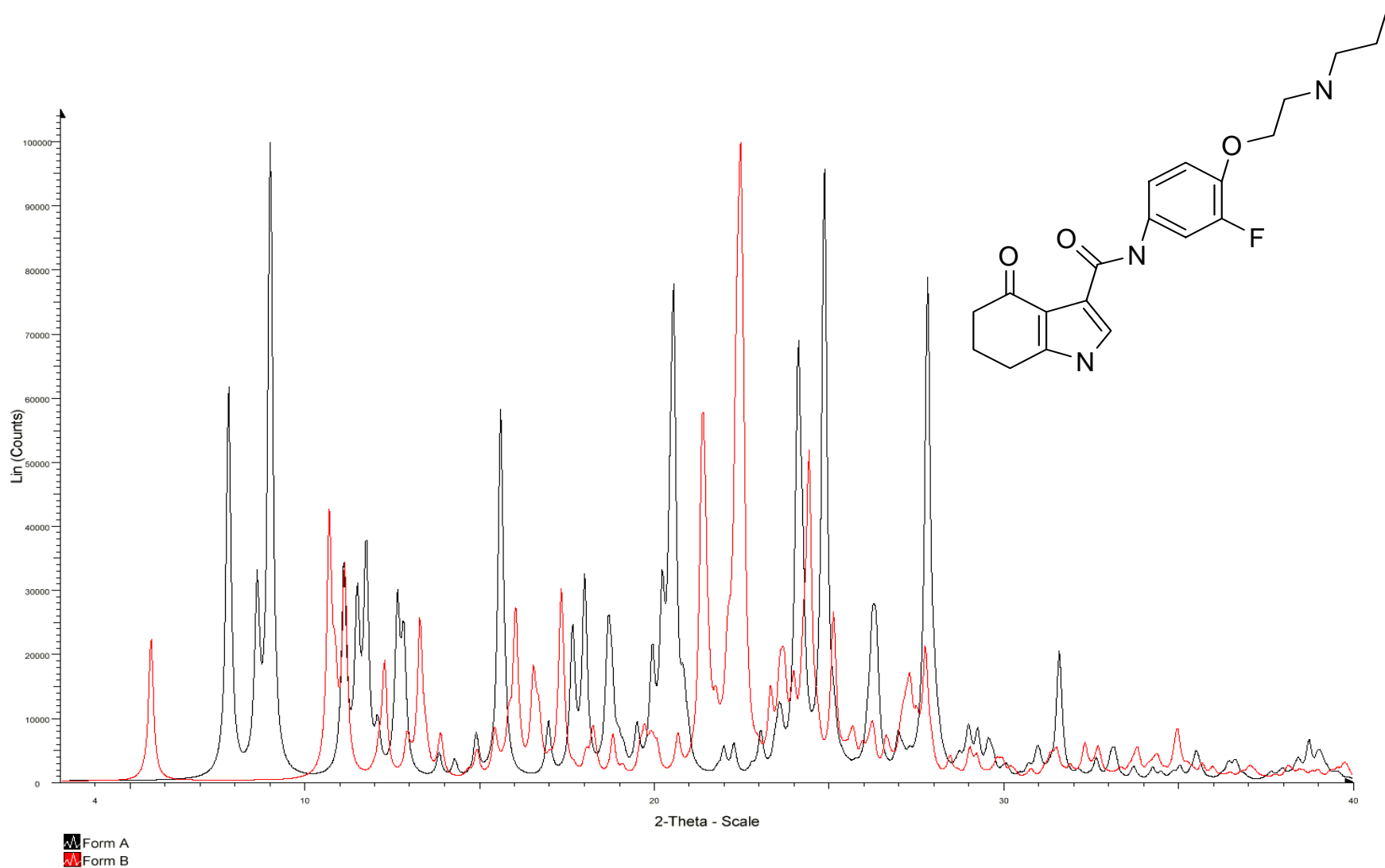
Organic Process Research and Development 2000, 4, 384-90

Acc. Chem. Res. 1995, 28, 193-200.

Angew. Chem. Int. Ed. 1999, 38, 3440-3461.



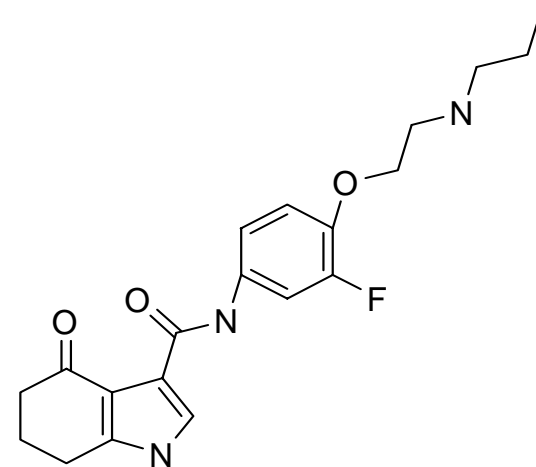
Polymorphism





Polymorphism

Characterization Data:
Forms A and B of Anhydrous Mesylate Salt



	Form A	Form B
Melting Point	206°C	203°C
Heat of Fusion (joules/g)	103.6	114.7
Single Crystal Density (g/cm³)	1.338	1.372



Business Models

- ◆ **No one path**
 - **Large companies**
 - Internal capability
 - Capacity / Portfolio needs flux
 - **Small companies**
 - Often no formulation / materials science expertise
- ◆ **Outsourcing**
 - **Augments changing capacity needs**
 - **High level of capacity**
 - **Capability varies**
 - **Identification of best partner is key**
 - **Active management of programs is critical**
 - **Efficiency = $\frac{\text{Speed X Quality}}{\text{Cost}}$**



Key Themes

- ◆ **Understand drug form to select best candidate**
 - **Inherent candidate risk**
 - Amorphous and Ionization
- ◆ **Characterization is critical**
 - **Candidate selection**
 - **API lots**
 - **To solve development issues**
- ◆ **Case studies**
 - **Underscore ambiguity and complexity**
- ◆ **Outsourcing**
 - **Useful resource for companies of any size**