Influence of Physical Form Changes on Impurity Formation

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Phase Transformations

- Polymorphic form transformation
- Hydration or Dehydration (more generally desolvation)
- Amorphous Form to Crystalline and vice versa
- Salt to Free Form

- These can result in change of mechanism of decomposition during storage

Solid Form Energy Landscape

$$\Delta G_2 - \Delta G_1 = RT \ln \frac{X_1}{X_2}$$

Hoffman JD. 1958. Thermodynamic driving force in nucleation and growth processes. J Chem Phys 29: 1192–1193.

	Solubility Ratio
• Amorphous versus Crystalline[1]	12 to 1652
• Salt versus Free form	
• Anhydrate versus Hydrate[2]	4.09
• Polymorph versus Polymorph[2]	1.76

Cocrystals Can be greater or lower solubility

1. Hancock, Bruno C.; Parks, Michael. Pharm. Res. **2000**, 17(4), 397.
2. Pudipeddi, M., Serajuddin *J. PHARM. SCI*. **2005**, 94(5) 929-939.

Solid-State Reaction

- When the liquid reaction does not occur or is much slower.
- When a pronounced difference is observed in the reactivity of closely related molecules.
- If different products are formed than in the liquid state.
- If different crystalline forms have different reactivity or products.
- If it occurs at a temperature below the eutectic point of the starting material and products.

Morawetz, H. Reactivity of organic crystals. Science (1966), 152(3723), 705-11.

Solid-State Reaction Pathway

1. Loosening of the molecules at the reaction site
2. Molecular Change
3. Solid-Solution Formation
4. Separation of Product Phase

Paul, Iain C.; Curtin, David Y. Thermally induced organic reactions in the solid state. Accounts of Chemical Research (1973), 6(7), 217-25.

1. Different Reactivity of Polymorphic Forms

-Photochemical reactions
-Reaction resulting from desolvation/dehydration

Topochemical Postulate

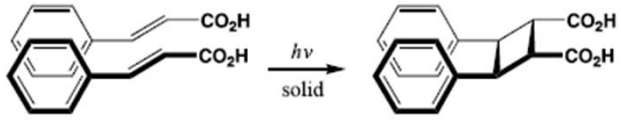


Fig. 1 Solid-state photodimerization of β-cinnamic acid.

Schmidt, G.M.J. Photodimerization in the solid state. Pure Appl. Chem. 1971, 27, 647–678.

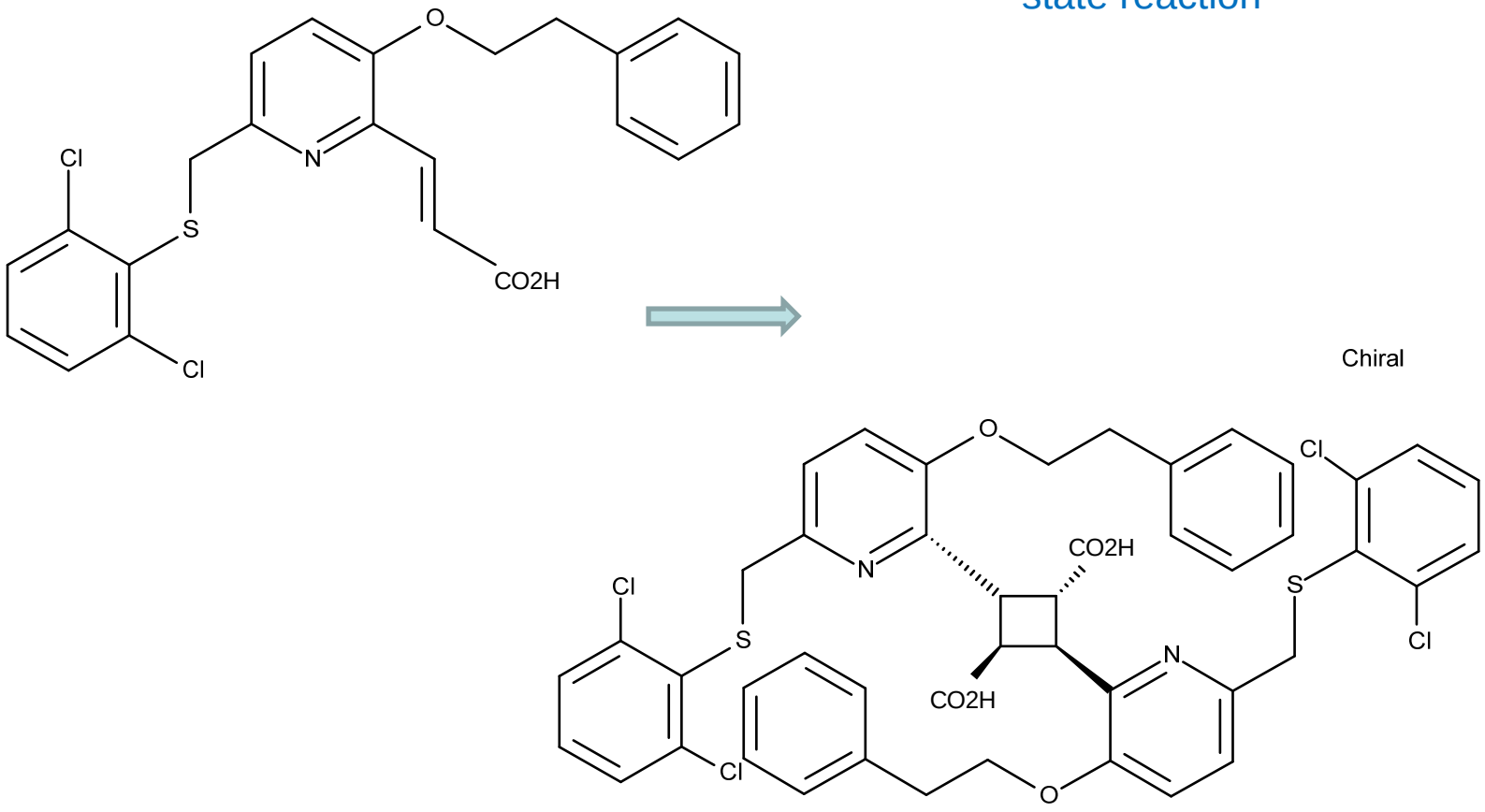
1. Used to predict a photoinduced [2 + 2] cycloaddition reaction in the solid state
2. Molecular arrangement in crystal determines whether or not reaction will take place and the molecular structure of the product
3. Involves nearest-neighbor molecules
4. occurs with minimum atomic and molecular movement for the [2 + 2] photoreaction,
5. Double bonds of the reactants should, as determined by Schmidt, be separated by <4.2 A and aligned in parallel.

Schmidt's work in many ways marked the beginning of "Crystal Engineering"

Kearsley, S.K. The Prediction of Chemical Reactivity within Organic Crystals Using Geometric Criteria. In Organic Solid State Chemistry; Desiraju, G.R., Ed.; Elsevier: New York, 1987; 69–115.

Photodimerization of Leukotriene B Antagonist

A pharma example of a true solid state reaction



Orford, Colin; Webb, Michael L.; Cattanach, Kaye H.; Cottee, Frank H.; Escott, Richard E.; Pitfield, Ian D.; Richards, Jeffrey J. **An analytical and structural study of the photostability of some leukotriene B4 antagonists. Special Publication - Royal Society of Chemistry (1998), 225(Drugs: Photochemistry and Photostability), 182-193.**

A true Solid-State Reaction

- HPLC peak area
- (4 hrs exposure to Xenon light)
- Form I 100% to almost exclusively to dimer
- Form II 4% to polymeric products

Orford, Colin; Webb, Michael L.; Cattanach, Kaye H.; Cottee, Frank H.; Escott, Richard E.; Pitfield, Ian D.; Richards, Jeffrey J. **An analytical and structural study of the photostability of some leukotriene B4 antagonists. Special Publication - Royal Society of Chemistry (1998), 225(Drugs: Photochemistry and Photostability), 182-193.**

Lattice afford Orientation and Distance

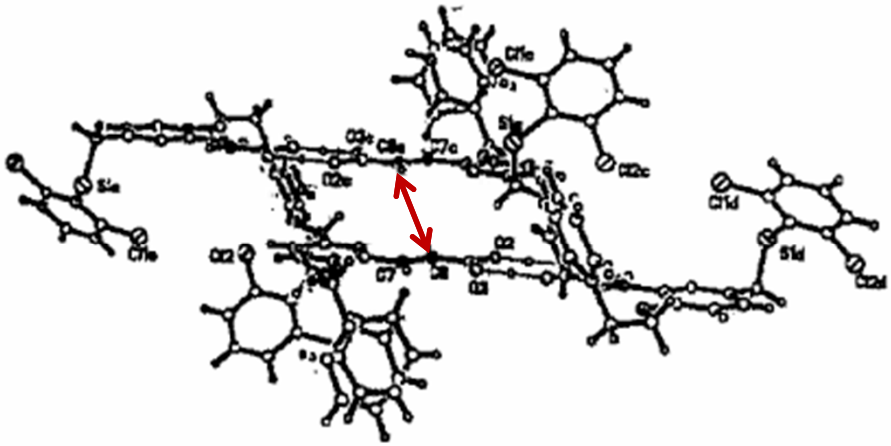


Figure 9 *Crystal structure of (2) form I.*

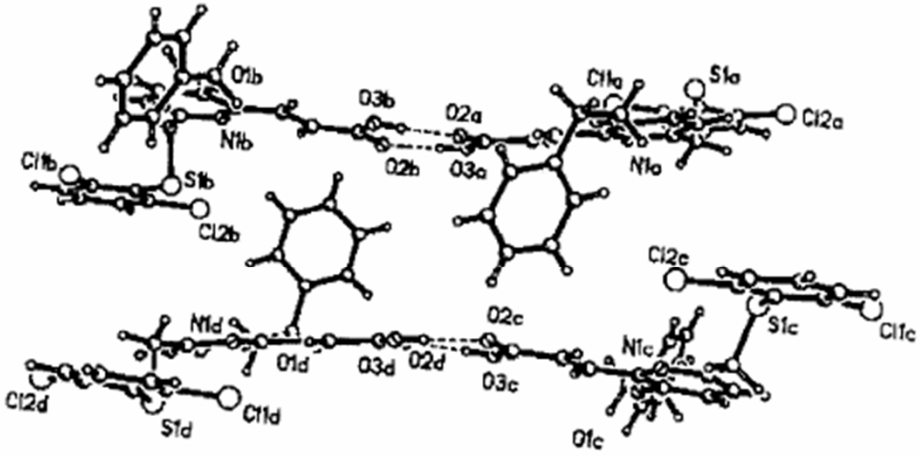
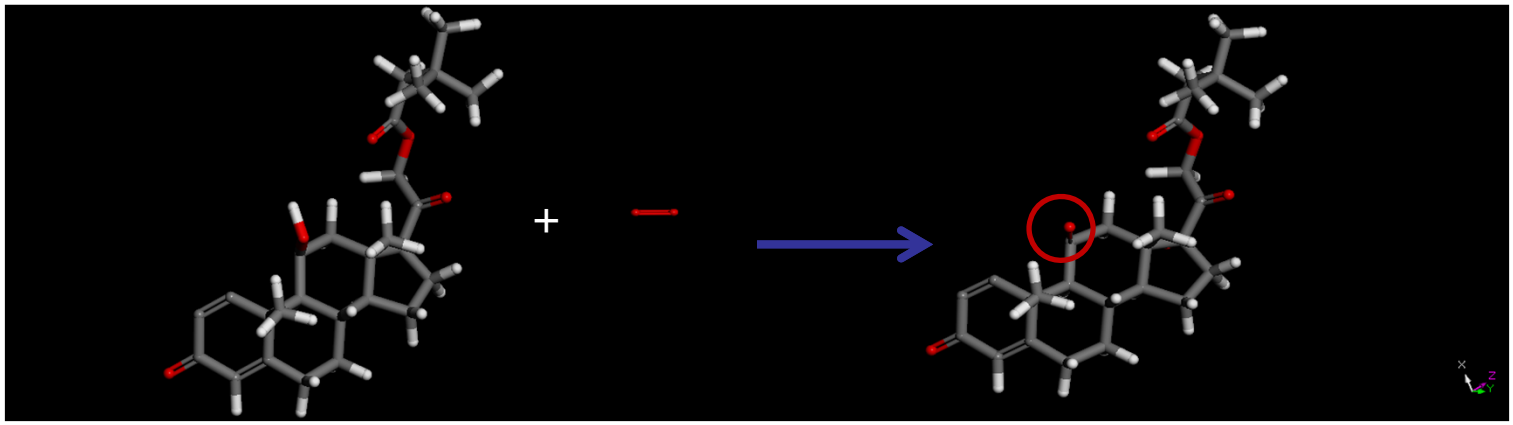


Figure 10 *Crystal structure of (2) form II.*

2. Reaction involving dehydration/desolvation

Oxidation of Perdnisolone-*tert*-butylacetate

A second pharma example of a true solid state reaction

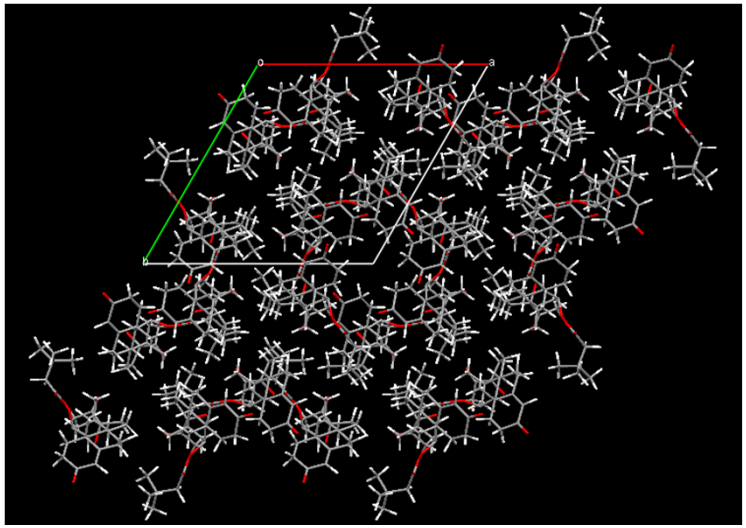


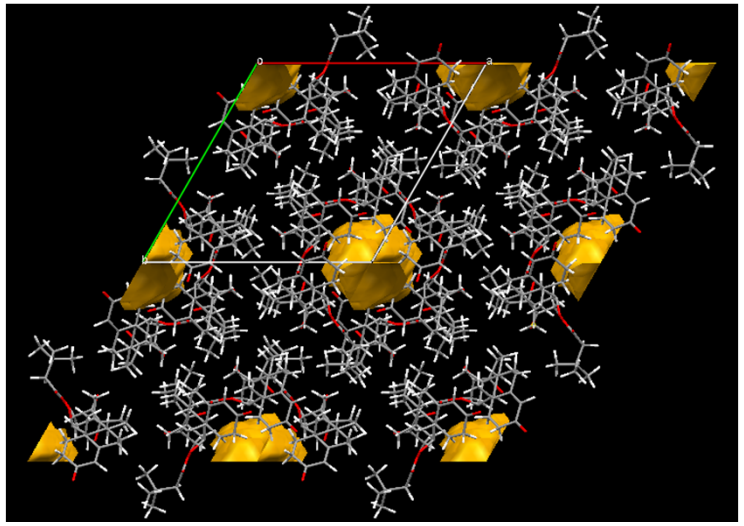
5 crystal forms of 3 general structure types:

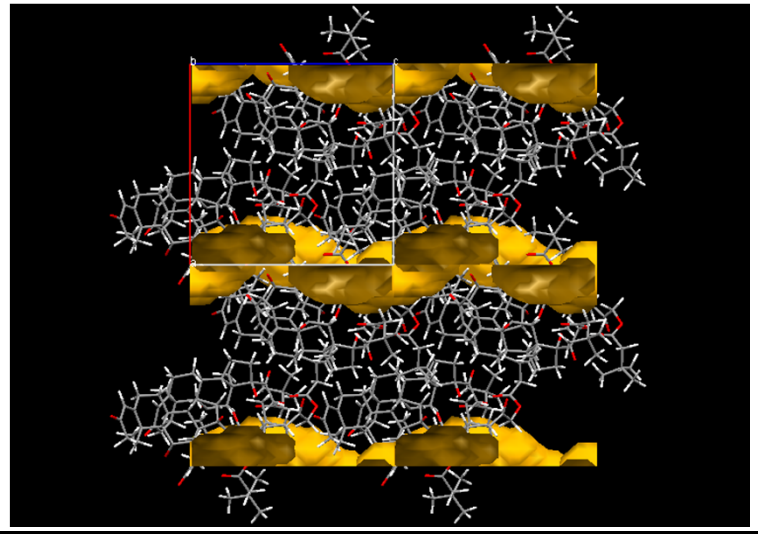
Type A non-stoichiometric solvate and reactive
Type B stoichiometric solvates and non reactive
Type C non-solvated and non reactive

Byrn, Stephen R.; Sutton, Paul A.; Tobias, Brian; Frye, James; Main, Peter. **Crystal structure, solid-state NMR spectra, and oxygen reactivity of five crystal forms of prednisolone tert-butylacetate. Journal of the American Chemical Society (1988), 110(5), 1609-14.**

Prednisolone 21-tert-butylacetate







A second pharma example of a true solid state reaction

Rarely are Reactions Truly Solid-State

Morawetz, H. Reactivity of organic crystals. Science (1966), 152(3723), 705-11.

- Usually initiates within amorphous component, at defect sites, or within eutectics formed between components

- Increased water content and/or temperature increases the rate

  Carstensen, J.T. Solid Pharmaceutics: Mechanical Properties and Rate Phenomena; Academic Press: New York, 1980.

- Disregarding pH effects, less soluble almost always affords better chemical stability higher solubility reduces deliquesence humidity

Their reaction mechanisms are usually more complex!

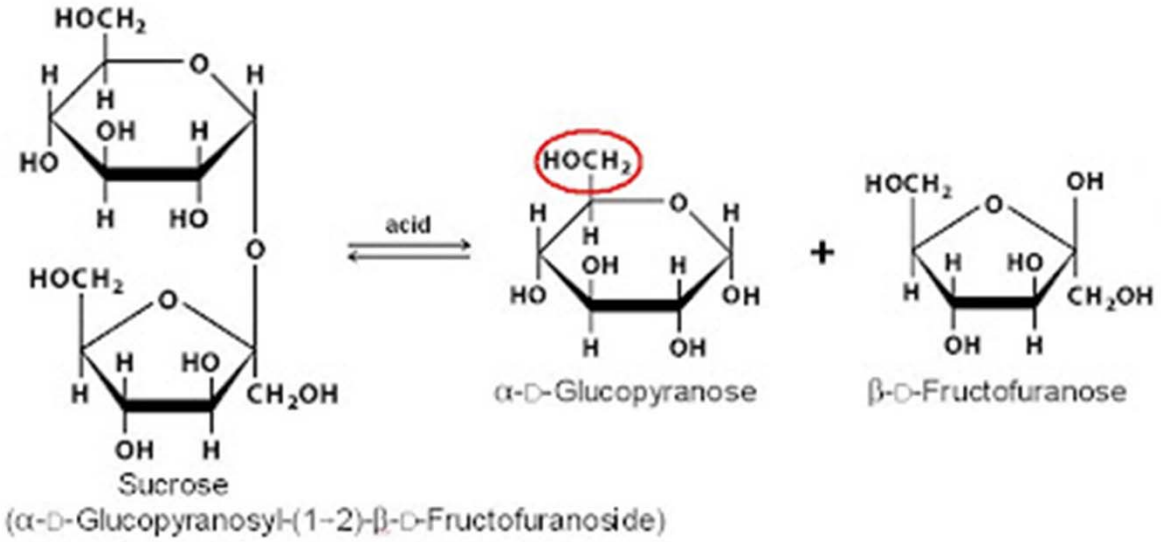
Reactions involving Liquifaction

- Occuring at a temperature above its eutectic point (of two materials in contact)
- Occuring at a humidity above its deliquesence point

Reactions that do not meet the criteria of a true solid state reaction as described by Morawetz –

Morawetz, H. Reactivity of organic crystals. Science (1966), 152(3723), 705-11.

Sucrose Hydrolysis and Deliquesence Lowering



Adnan K. Salameh and Lynne S. Taylor Role of Deliquescence Lowering in Enhancing Chemical Reactivity in Physical Mixtures *J. Phys. Chem. B* 2006, 110, 10190-10196.

Deliquescence Lowering

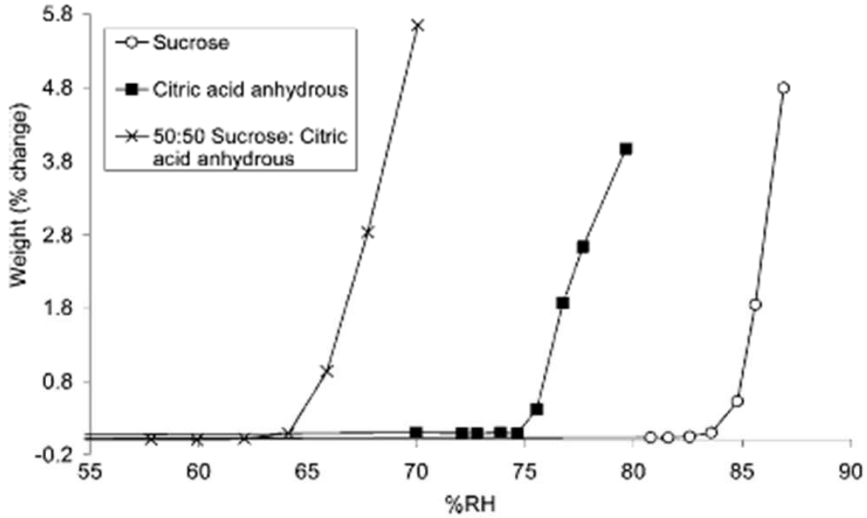


Figure 1. Moisture sorption data of sucrose and citric acid anhydrous, and a 50:50% w/w physical mixture at 25 °C.

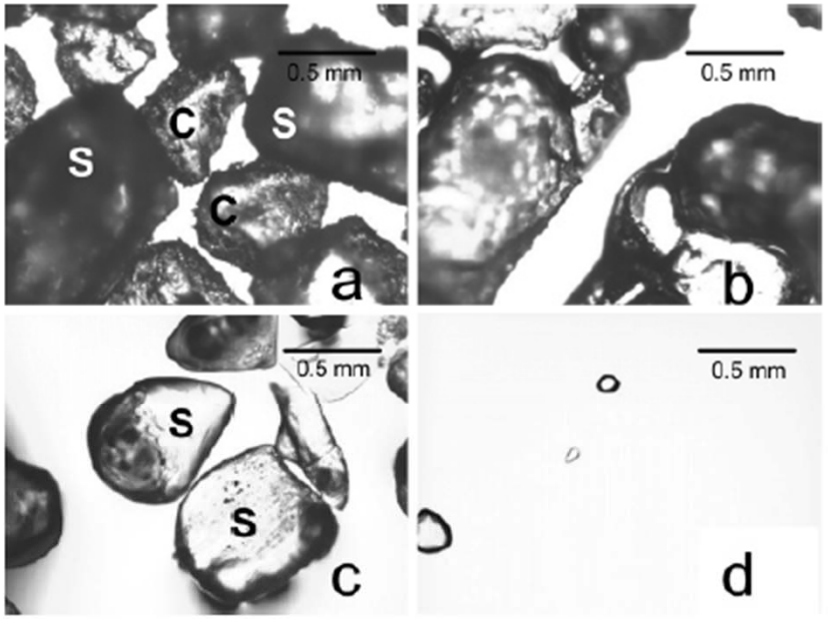


Figure 4. Visualization of deliquescence in mixtures of sucrose and citric acid anhydrous. (a) Sucrose crystals (crystals annotated with "S") and citric acid crystals (crystals annotated with "C") stored at 72% RH, 25 °C. Time = 0 min. (b) After 2 h. (c) After 6 h. (d) After 16 h, with complete dissolution of sucrose and citric acid crystals after 17 h.

Often Multiple E_{act} Due to Changing Mechanism

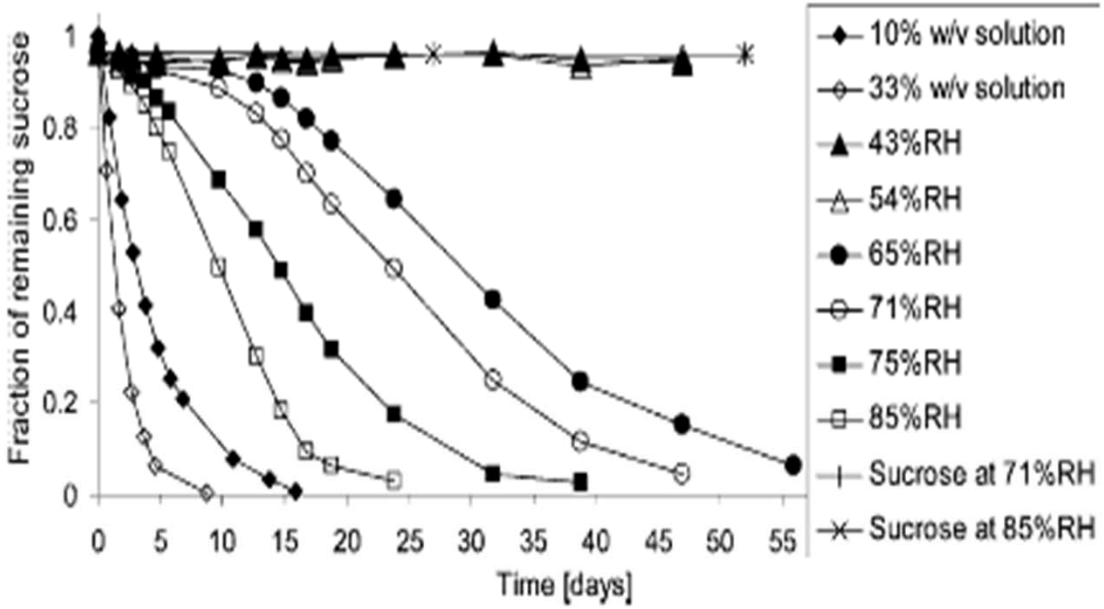


Figure 3. Sucrose inversion kinetic profiles in solutions and physical mixtures of sucrose and citric acid anhydrous stored at various relative humidities at 22 °C.

The ones above the deliquesence point for the mixture have a much reduced lag time due to deliquesced moisture, whereas the ones at lower humidity have a typical lag phase until sufficient degradant build up for the “solution” dominated decomposition to occur.

3. Reactions Involving Amorphous form vs Crystalline Form

Problem with In-license Compound

Hydrolysis of an Amide requiring storage at 5^0C (unacceptable)

Company had gone to multiple (reputable) out sourcing companies to attempt to crystallize, conduct salt screening and cocrystal screening over a 2 year period

They were unsuccessful at crystallizing it; but selected an amorphous salt due to its improved flow properties compared to the amorphous free base form

Water's role in Amorphous solids

1. Can play a role as a direct reactant (hydrolytic reactions).
2. Can play a role as a product and through its production have an inhibitory effect on the extent of reaction through its activity (unless the reaction is irreversible).
3. Water dissolved in amorphous matrix can simply act as a medium (solvent) to influence local polarity without directly participating in the reaction.
4. Can act as a plasticizer influencing mobility/diffusivity.

   Increasing water content by a few percent can increase the rate of diffusion limited reactions by several orders of magnitude through its plasticizing effects.

Reactions in amorphous solids are usually diffusion controlled

$$k = 4d^{*}DrNa$$

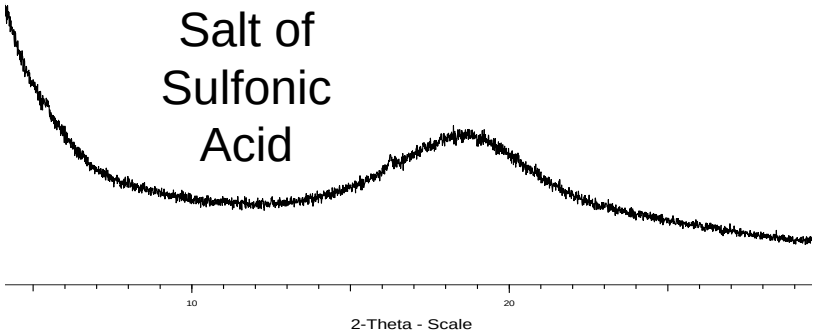
d* is the collision diameter, D is the diffusion coefficient, N is avagadro's number

Shalaev, E.Y. and Zografi, G. How does Residual Water Affect the Solid-State Degradation of Drugs in the Amorphous State? (1996), 85 (11), 1137-1141.

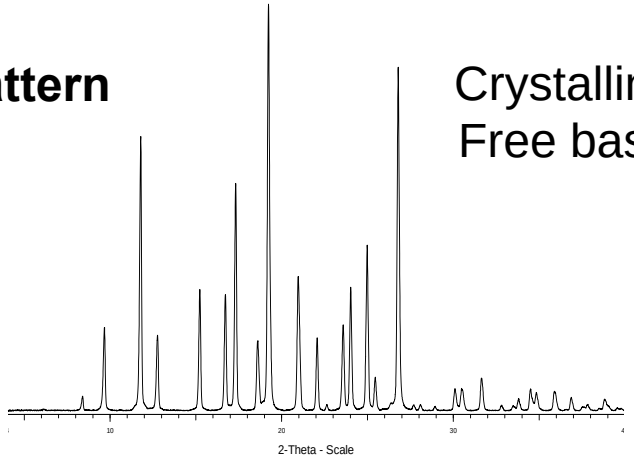
Comparison of Forms

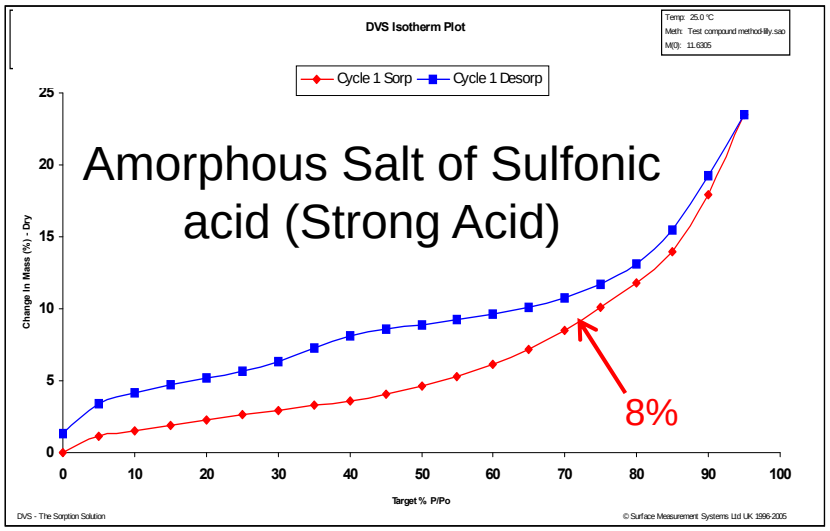
XRPD pattern

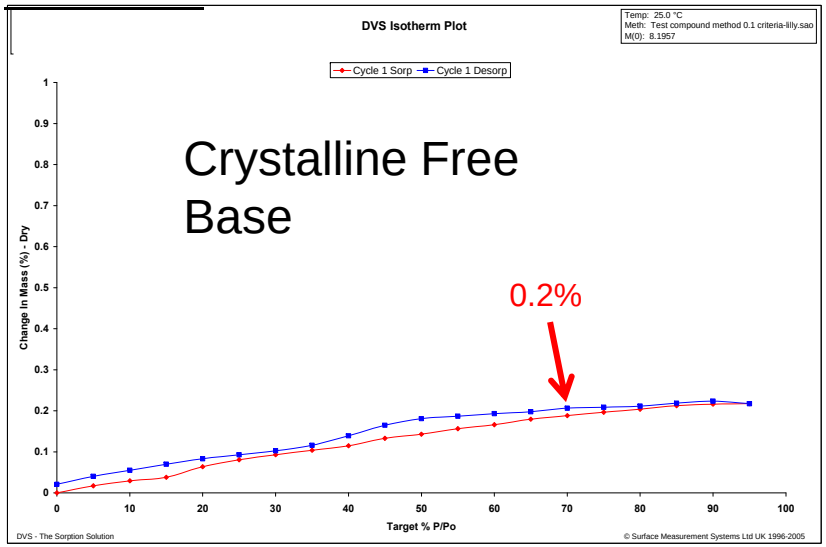
Amorphous Salt of Sulfonic Acid



Crystalline Free base







Solid-State Stability

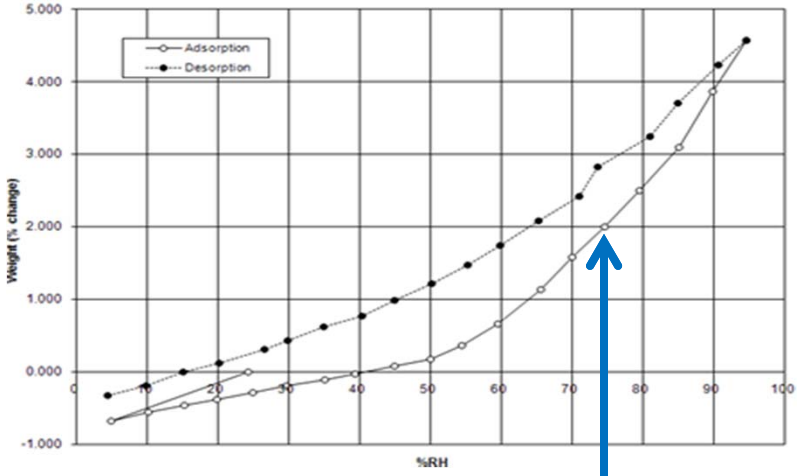
Amorphous Napadisylate

Condition	API 7 days %remaining	API 14 days %remaining
Light	98.3	96.8
40°C	99.0	99.3
50°C	98.9	97.8
70°C	96.8	96.8
40°C/75%	36.8	44.0
50°C/75%	50.7	46.2

Crystalline Free base

Condition	API 7 days %remaining	API 14 days %remaining
Light	100.3	100.3
40°C	99.9	100.7
50°C	100.0	100.4
70°C	100.0	99.9
40°C/75%	99.9	99.5
50°C/75%	100.3	98.2

Double trouble, Amorphous salt was more hygroscopic and acidic



The amorphous free base only takes up 2.5% moisture at 75% R.H,

while their amorphous salt takes up 8.5%

Table 4. Solution Results at Various pH Values

Exposure Condition	Hours	Days	Assay (% Initial)	Impurities (%)	Sample ID
0.1N HCl/ACN 70C	0.1	0.0	103.1	1.4	100940_1
	22.8	1.0	56.9	44.0	100940_9
	46.8	2.0	31.1	68.5	100940_17
	70.9	3.0	15.2	84.5	100940_25
	94.9	4.0	8.6	91.3	100940_33
	118.9	5.0	< 5.0	-	100940_41
H2O/ACN 70C	0.1	0.0	101.8	0.4	100940_4
	22.8	1.0	92.7	7.5	100940_12
	46.8	2.0	90.6	10.0	100940_20
	70.9	3.0	88.0	14.5	100940_28
	94.9	4.0	89.1	13.6	100940_36
	118.9	5.0	83.4	18.6	100940_44

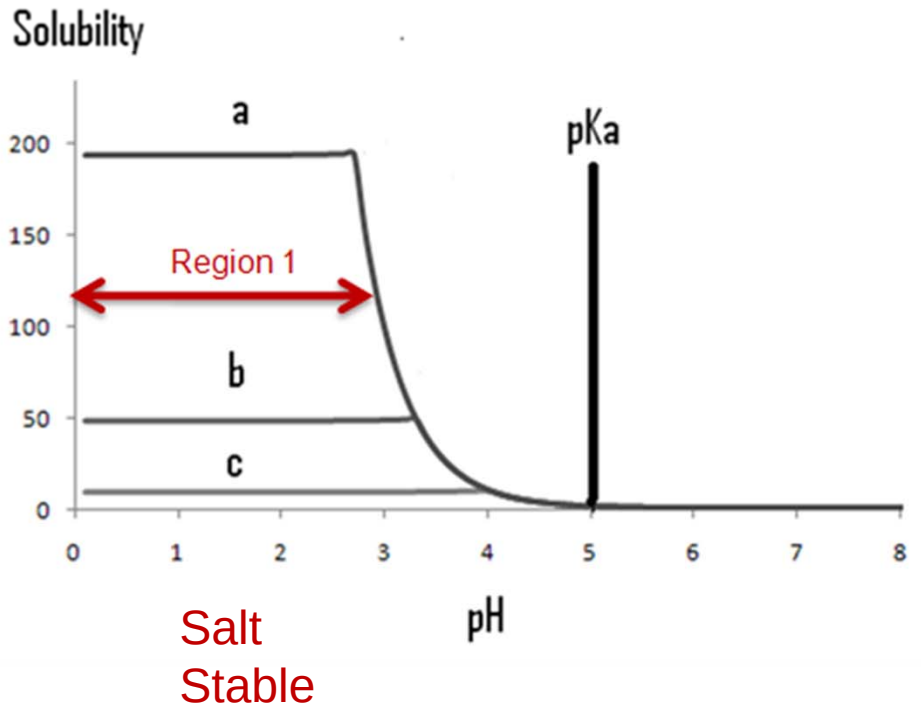
Very unstable in Acidic Conditions

They solved a minor powder flow issue and created a major stability issue (more soluble salt and acidic environment)

– fortunately crystalline free base readily solved the problem – stable for years at RT

4. Dissociation of Salts
“disproportionation”

Solubility Profile of a Salt of a Weak Base as a Function of pH

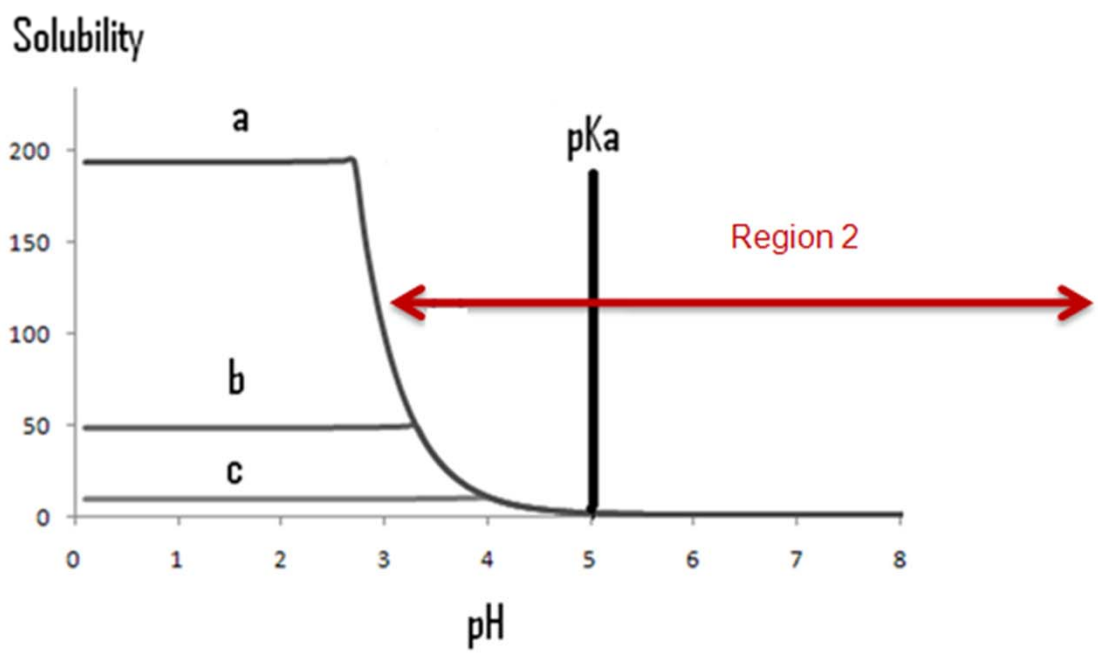


When pH< pHmax,
The solubility can be described as

$$S = \sqrt{Ksp \cdot \left(\frac{H^+ + K_{ac}}{K_{ac}}\right) \cdot \left(\frac{H^+ + K_a}{H^+}\right)}$$

Figure 2. Solubility diagram of salts of a weak base having an intrinsic solubility of 1 mg/mL, and p*K*a of 5.0 with salt forms a (hydrochloride), b (sulfate) and c (tosylate), having solubility's of 200, 50 and 10 mg/mL, respectively.

Solubility Profile of a Salt of a Weak Base as a Function of pH



when pH > pHmax

the free base solubility is limiting,

$$S = S_0 \cdot \left(\frac{H^+ + K_a}{K_a} \right)$$

Figure 2. Solubility diagram of salts of a weak base having an intrinsic solubility of 1 mg/mL, and p*K*a of 5.0 with salt forms a (hydrochloride), b (sulfate) and c (tosylate), having solubility's of 200, 50 and 10 mg/mL, respectively.

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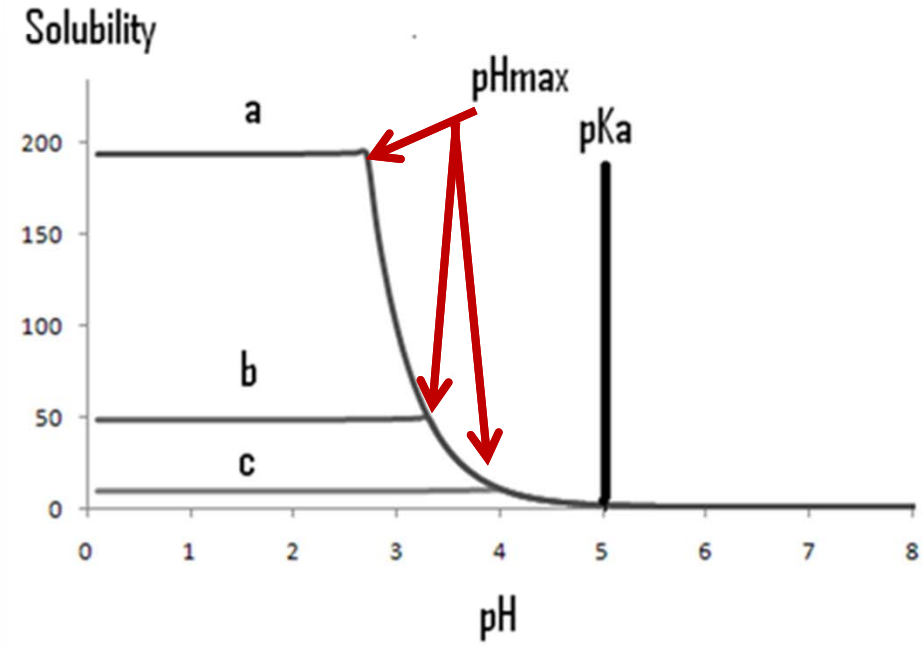


At pHmax, the two solubility curves intersect :

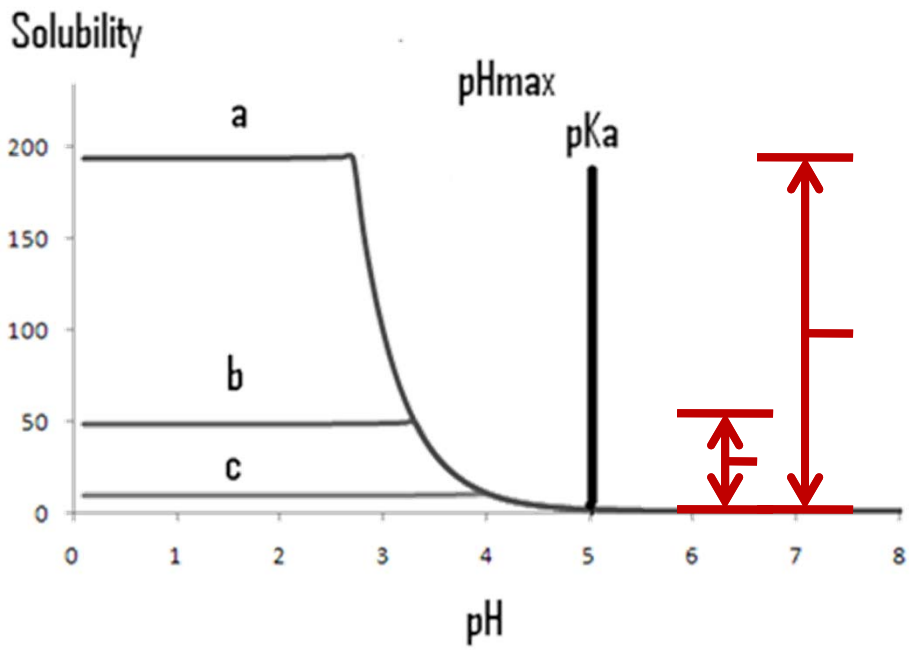
$$S_0 \cdot \left(\frac{H^+_{max} + K_a}{K_a} \right) = \sqrt{Ksp \cdot \left(\frac{H^+_{max} + K_{ac}}{K_{ac}} \right) \cdot \left(\frac{H^+_{max} + K_a}{H^+_{max}} \right)}$$

$$H^+_{max} >> K_a \ and \ K_{ac} >> H^+_{max}$$

$$pH = pK_a + \log\left(S_0 / Ksp^{0.5} \right)$$

Figure 2. Solubility diagram of salts of a weak base having an intrinsic solubility of 1 mg/mL, and p*K*a of 5.0 with salt forms a (hydrochloride), b (sulfate) and c (tosylate), having solubility's of 200, 50 and 10 mg/mL, respectively.

Solubility Profile of a Salt of a Weak Base as a Function of pH

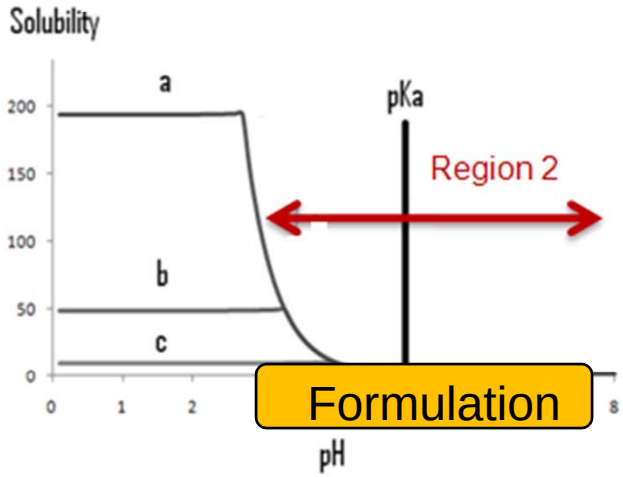


$$\Delta G \approx -RT\ln(S_{salt}/S_{freebase})$$

Figure 2. Solubility diagram of salts of a weak base having an intrinsic solubility of 1 mg/mL, and p*K*a of 5.0 with salt forms a (hydrochloride), b (sulfate) and c (tosylate), having solubility's of 200, 50 and 10 mg/mL, respectively.

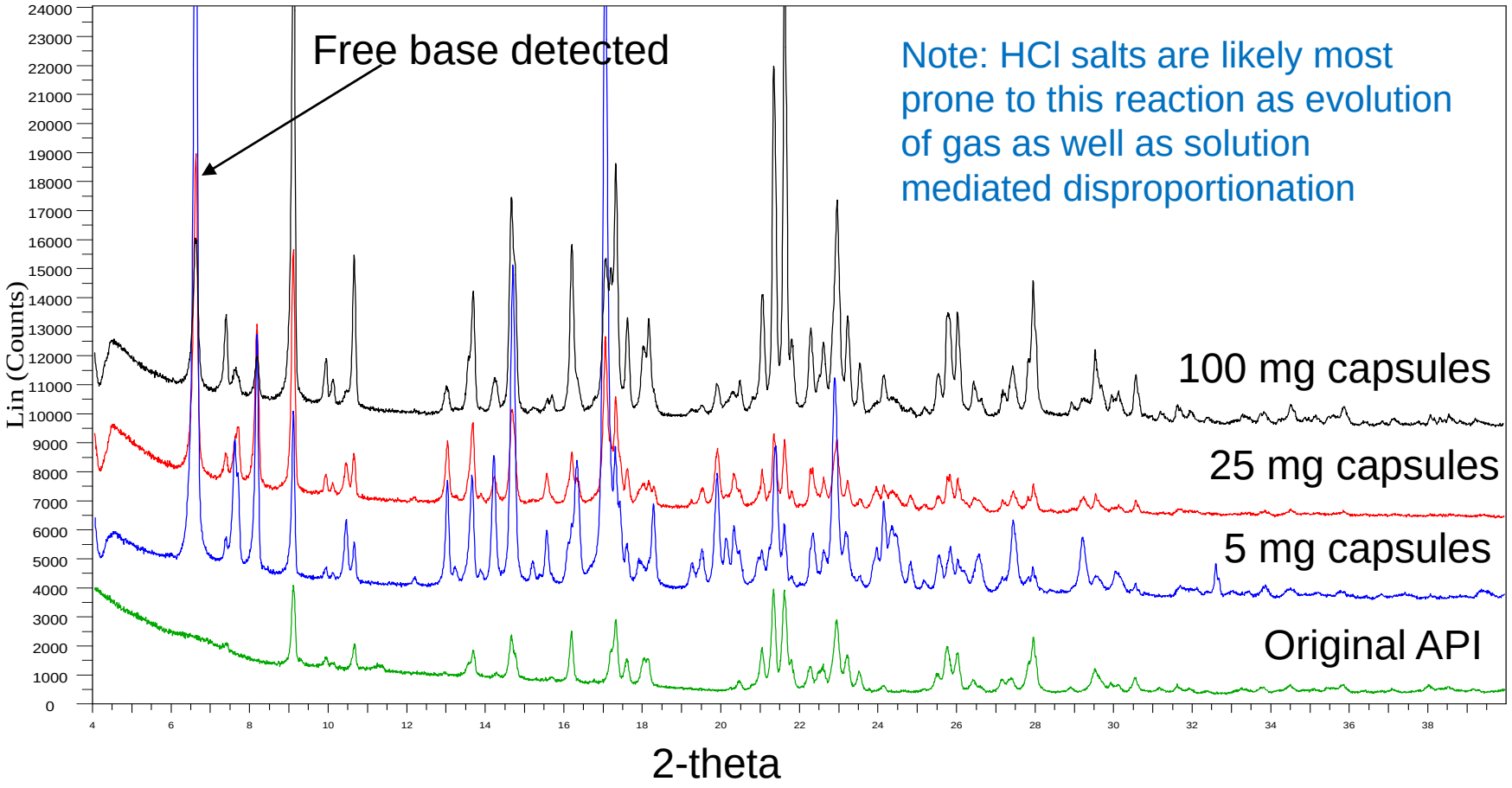
pH Micro-environment of Excipients

Sodium Croscarmellose	5-7
Lactose	6.1
Mannitol	4.7
Microcrystalline Cellulose	4.7
PVP	3.7
Crosspovidone	4.9
Colloidal SiO2	5.2
Magnesium Stearate	7.1
Maize Starch	6.3
Hydrogenated castor oil	7.5
Dibasic Calcium Phosphate Anhydrous USP (A-Tab granules)	2.21
Dibasic Calcium Phosphate Anhydrous (Sigma Chemicals)	3.59
Microcrystalline cellulose NF (Avicel PH102)	4.03
Microcrystalline cellulose JP (Avicel PH101)	4.07
Microcrystalline cellulose NF (Avicel PH105)	4.14
Lactose monohydrate NF (Fast Flo 316, spray-dried)	4.24
Sodium starch glycolate NF (Explotab)	4.77
Calcium carbonate USP (Vicron 75-17-FG)	6.58
Carbonate carbonate USP (Calcipure GCC300)	7.20
Magnesium stearate NF	7.45
Calcium carbonate USP (Precarb 150)	7.69
Calcium carbonate USP (Vicality Medium PCC)	8.07

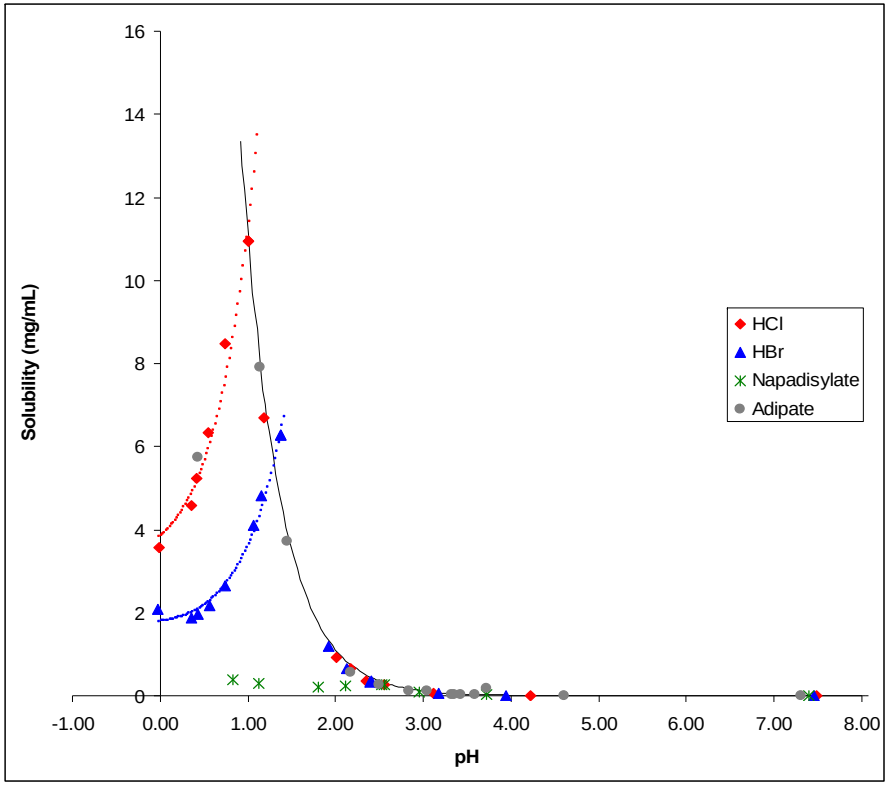


Govindarajam R., Zinchuk A., Hancock B., Shalaev E, and Suryanarayanan R. 2006.
Ionization States in the Microenvironment of Solid Dosage Forms: Effect of Formulation Variables and Processing.
Pharm. Res. 23(10):2454-2468.

XRPD of Capsule content – HCl salt form shows disproportionation



Solubility, is more better?



Salt	pHmax	*K*sp [M]2	Solubility
HCl	0.98	2.8 x 10 -3	22.2
HBr	1.30	0.77 x 10 -3	11.7
Napadisylate	2.51	0.0031 x 10-3	0.74
Adipic acid CC	NA	NA	NA
Free Base	NA	NA	0.0017

Using Prototype Formulations

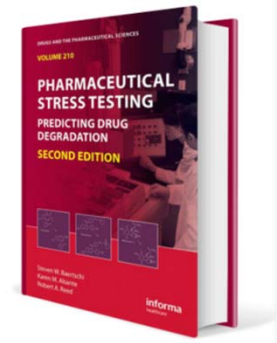
Rate of Disproportionation in solid state:

HCl >HBr and Adipic acid CC >>> Napadisylate

Experimental Physical Stability Screen

- Use Prototypical Formulations:
  - Wet Granulation Formulation (Formulation 1)
  - Roller compaction/Direct Compression (Formulation 2)
  - Capsule Formulation (Formulation 3)

Typically 20% by weight API



BUY 2ND EDITION NOW

	Formulation #1		Formulation #2		Formulation #3	
Ingredients	**mg/cap**	**% w/w**	**mg/cap**	**%w/w**	**mg/cap**	**%w/w**
Lactose Spray Dried	51	42.5	--	--	--	--
MCCell PH102	51.1	42.5	51.8	43.125	--	--
Povidone K29/32	6	5	--	--	--	--
Croscarmellose Sodium	9.1	7.5	--	--	--	--
Sodium Lauryl Sulfate	1.5	1.25	--	--	--	--
Mag Stearate	1.5	1.25	1.5	1.25	--	--
Mannitol	--	--	51.8	43.125	--	--
Hydroxypropylcellulose	--	--	6	5	--	--
Low-Substitution HPC	--	--	9.1	7.5	--	--
Lycatab C	--	--	--	--	105	87.5
Starch Silicone 5% PB	--	--	--	--	15	12.5
Final Blend	**120**	**100**	**120**	**100**	**120**	**100**

Physical Form Changes on Impurity Formation

Very few reactions are true solid-state reactions.

Moisture generally increases the rate of reaction.

Increased solubility generally results in increased instability, whether it is physical instability or chemical instability.

Products of reactions often result in reduction of the temperature of melting of a compound, can act as cosolvent where liquefaction (or deliquesence lowering) can result in liquid-state kinetics of accelerating as decomposition progresses.

Phase transformations during stability testing will result in different mechanisms for decomposition, potentially resulting in different products.

Acknowledgements

- Bob Wenslow and Crystal Pharmatech
- Steve Baertschi and the Organizing Committee
- Jeremy Merritt
- Tim Woods
- Jeff Peterson

Delivering the impact of solid state properties in pharmaceutical development.

Crystal Pharmatech

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