

# Strategies to Expand Solid-state Landscapes of Drugs to Enable Successful Tablet Formulation Development

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# Outline

## 1. Introduction

- Why expanding solid state landscape?

## 2. Strategies to prepare new solid forms

- a. Capturing metastable forms
- b. Salt formation of poorly ionizable drugs
- c. Conjugate acid base (CAB) cocrystal

## 3. Conclusions

# Challenges in Tablet Development

A main challenge in solid dosage form development is deficient API properties.



manufacturing processes

Each solid form exhibits different physico-chemical and mechanical properties



# Strategies for Solving API Related Problems

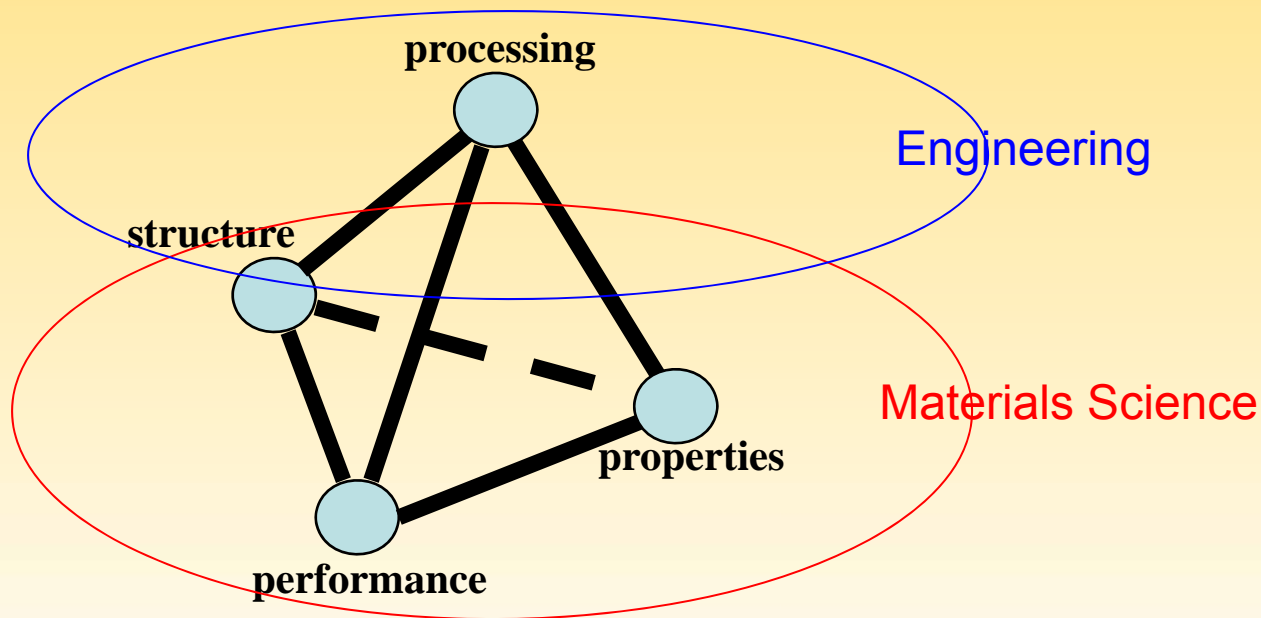
API Crystal  
engineering



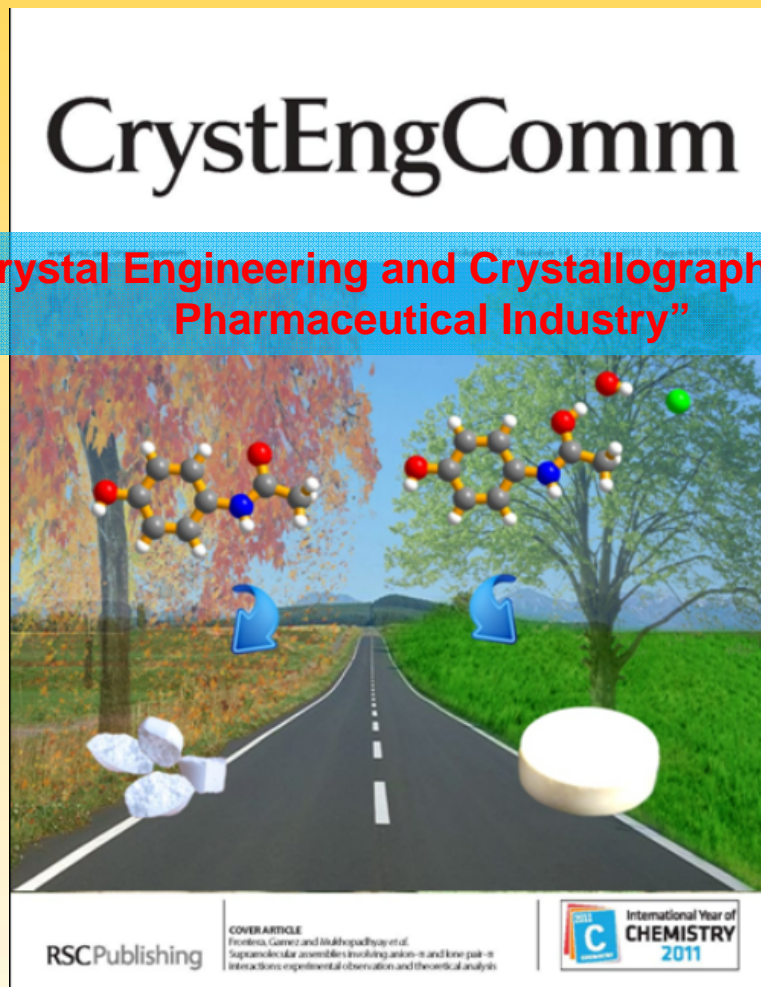
Particle  
engineering



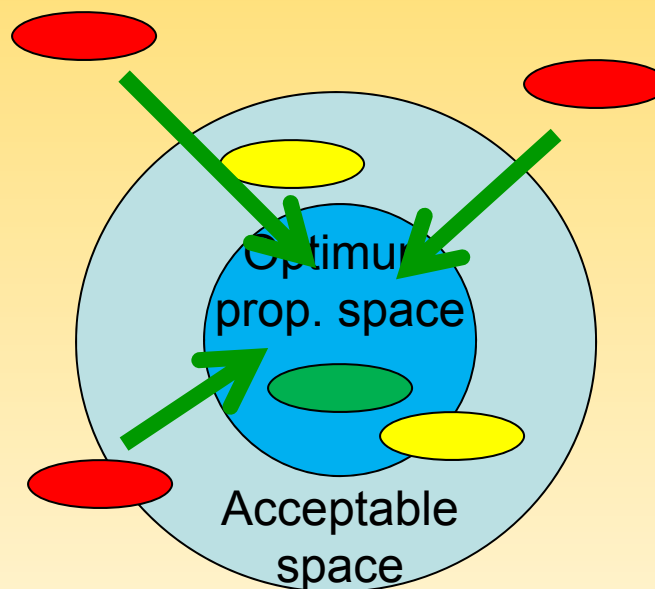
Process  
engineering



# Why Pharmaceutical Crystal Engineering?



Ideally, design crystals with optimum properties



Unacceptable prop. space

One practical engineering approach is to isolate as many solid forms as possible!

# Making a Difference by Crystal Engineering

## Common types of solid forms

1. Polymorphs
2. Salts
3. Cocrystals

## Pharmaceutical properties

1. Stability
2. Solubility
3. Tableability
4. Flowability
5. Purity
6. Melting point
7. Stickiness

# 1. Harvesting Metastable Forms

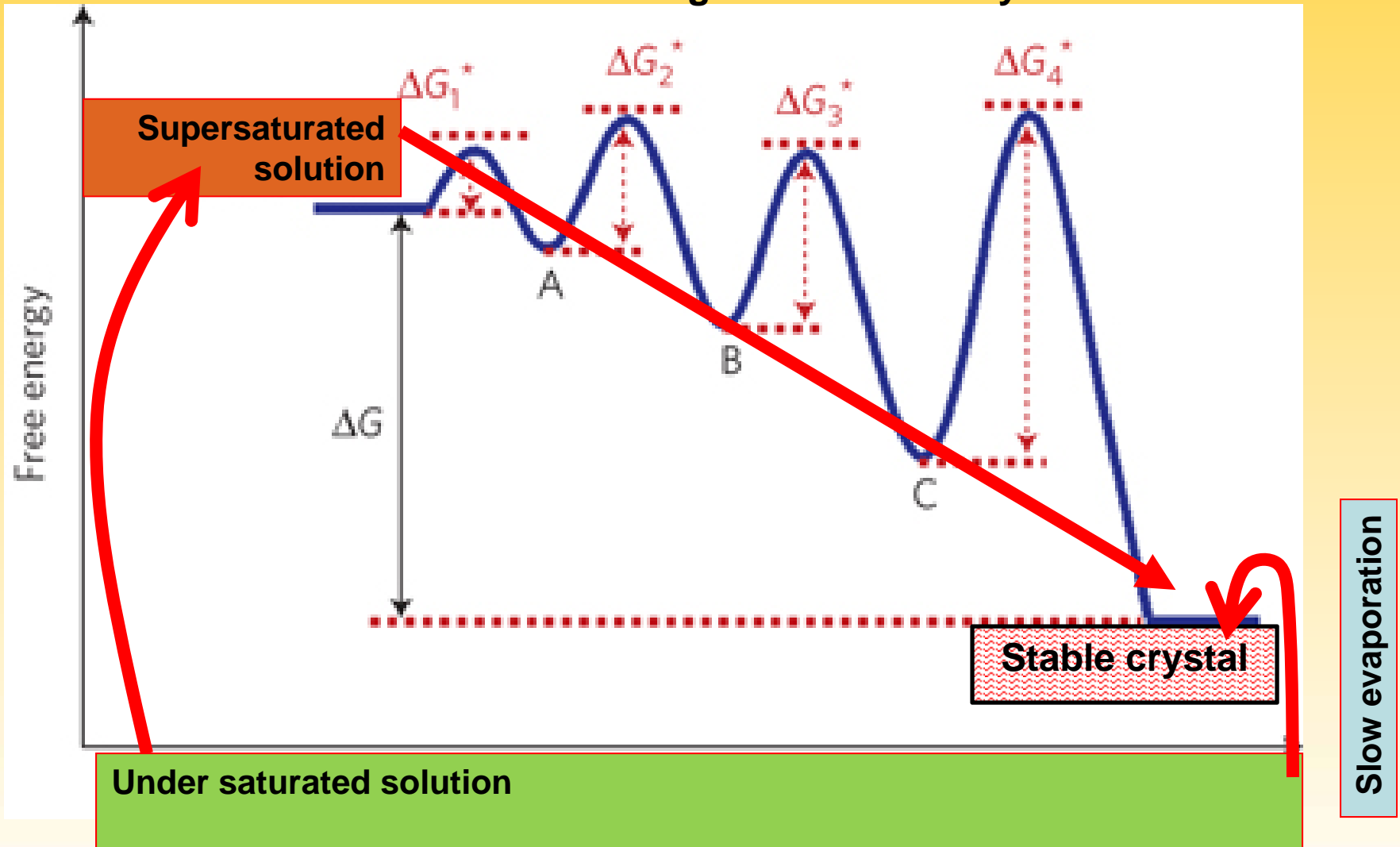
- Metastable crystal forms are often obtained during screening
- A large quantity is required to study bulk physical properties
- Synthesis of a large quantity of pure metastable solid forms is challenging



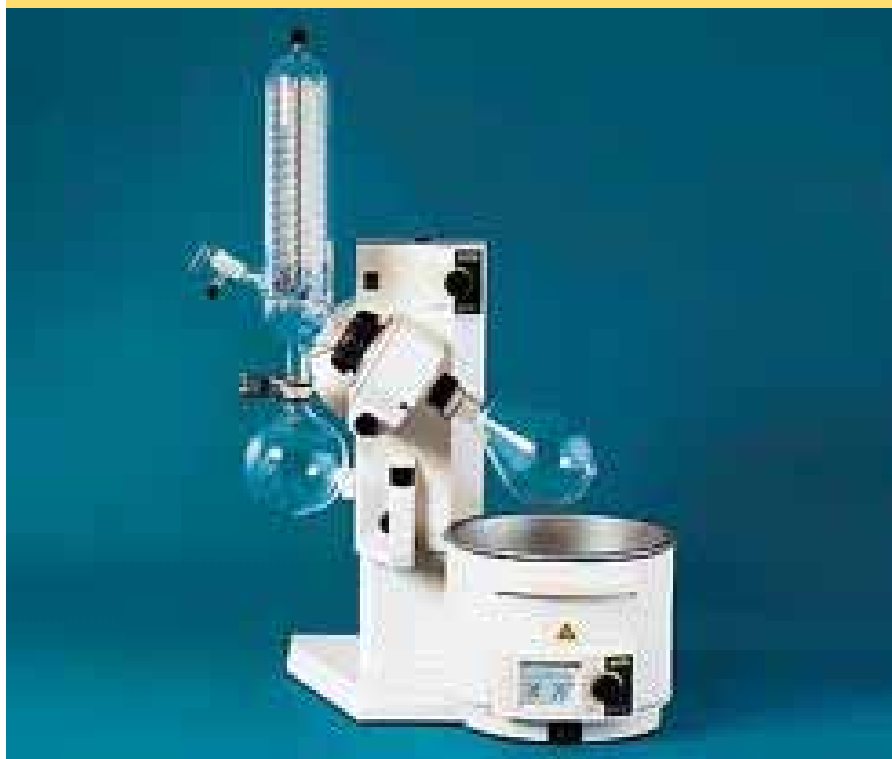


# Kinetics vs. Thermodynamics

Oswald's rule of stage for solution crystallization



# Fast Solvent Removal

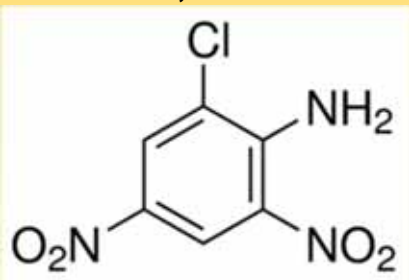


1. Analogous to precipitation
2. But under more controlled crystallization environment (temperature & solvent)
3. Suitable for isolating metastable polymorphs & cocrystals
4. Suitable for compounds sensitive to moisture or oxygen (under vacuum)
5. Batch size (5 g or larger)

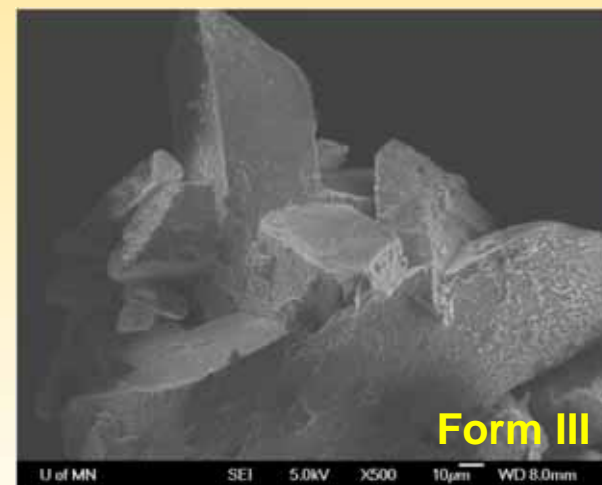
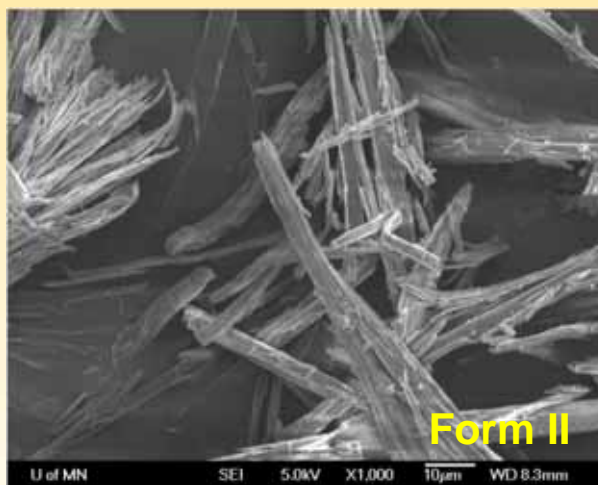
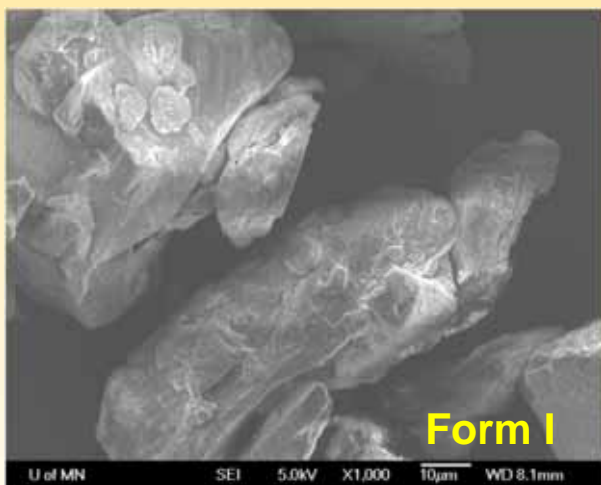
# CDNA polymorphs

Concomitant polymorphs when crystallizing from a solution by evaporation.

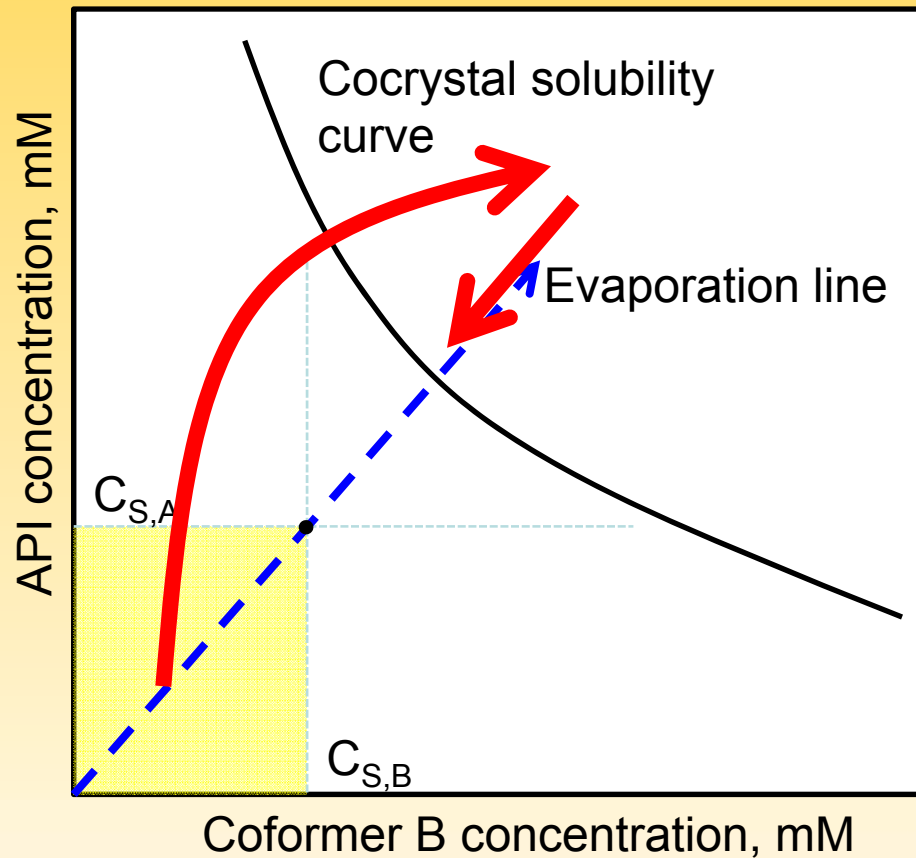
6-Chloro-2,4-dinitroaniline



Solvent	Pressure (mbar)	Temp. (°C)	rpm	Form obtained
Acetone	430	50	130	I
Dichloromethane	900	50	130	II
Ethyl Acetate	300	50	130	III



# Preparing Metastable Cocrystals



Slow removal favors thermodynamic form:  
**Coformers A & B**

Fast removal favors metastable form:  
**Cocrystal**

Outcome is affected by  
temperature and solvent

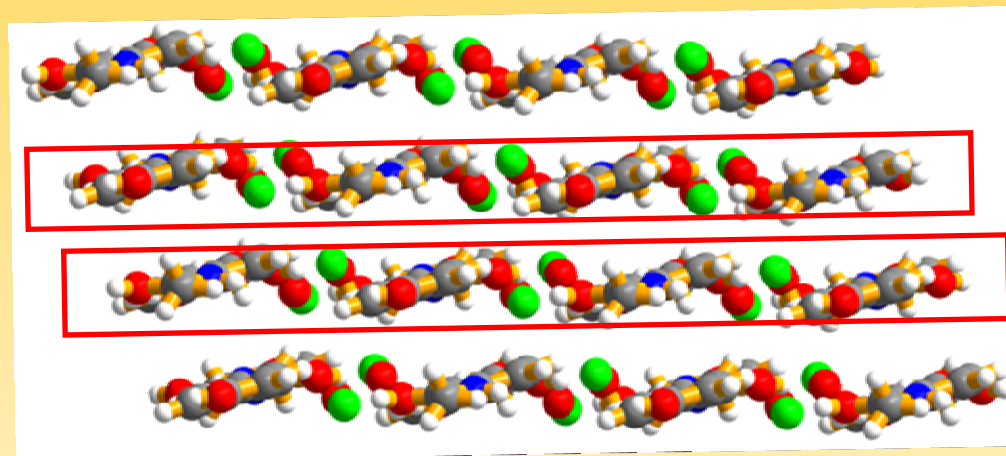
e.g., Ibuprofen – nicotinamide

## 2. Preparing Salts of Drugs

- Many drugs only contain weakly ionizable functional groups, e.g., amides, urea
- 30% APIs are considered “**non-ionizable**”
- Salt formation of these drugs has been difficult even with strong acids, e.g., HCl ( $pK_a = -6$ )
- Many readily **ionizable** drugs form hydrated salt (e.g., caffeine)

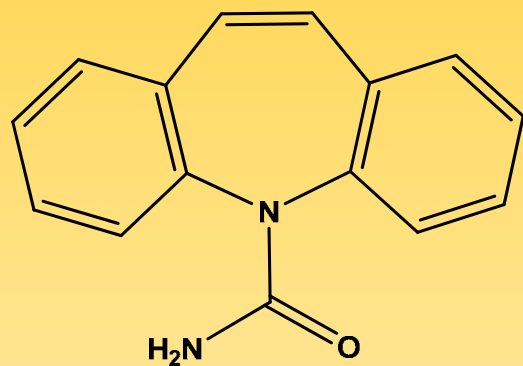
# Acetaminophen HCl (monohydrate)

previously thought non-ionizable



Crystallized from concentrated  
HCl(aq.) (HCl  $pK_a = -6$ )

# Carbamazepine



Carbamazepine (CBZ)

59 unique structures in CSD (2012)

**Why?**

HCl (pKa = -6)

CBZ (pKa = 7)

$\Delta$ pKa = 13 (> 3)

**No HCl salt formation even with concentrated hydrochloric acid.**

CBZ dihydrate was obtained

# Carbamazepine HCl

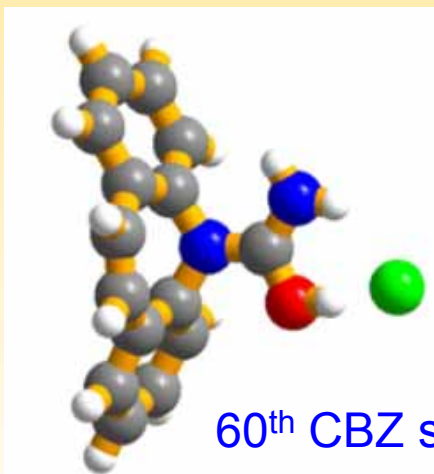
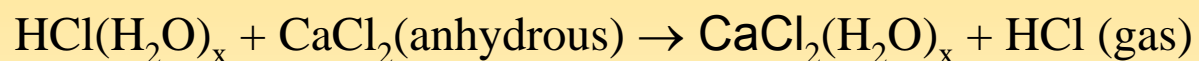
Eliminate dihydrate by avoiding water

1. HCl organic solutions

2. *in situ* HCl generation



3. Generation and purging HCl gas

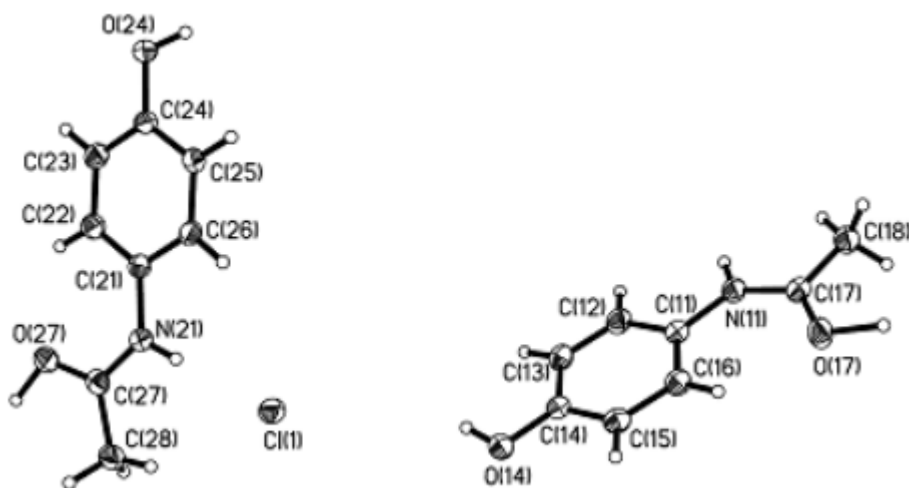


60<sup>th</sup> CBZ structure

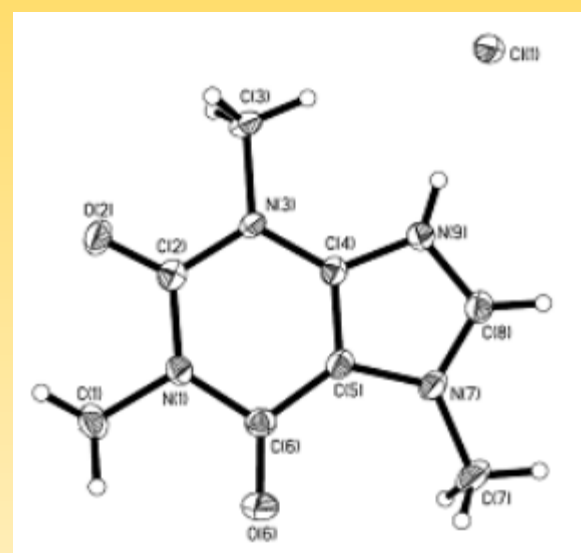




# Anhydrous HCl Salts



Acetaminophen HCl hemi salt



Caffeine HCl salt

# 3. CAB cocrystals

- ❖ Conjugate acid & base (CAB) are compounds that differ by one proton



- ❖ Exceptional strength of CAB H-bonds

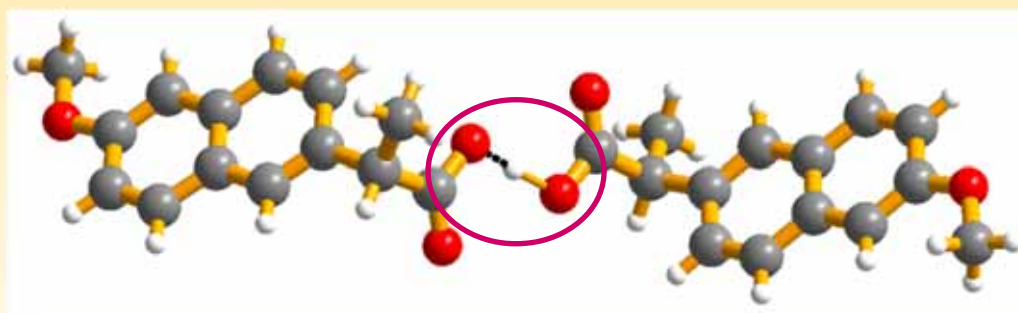
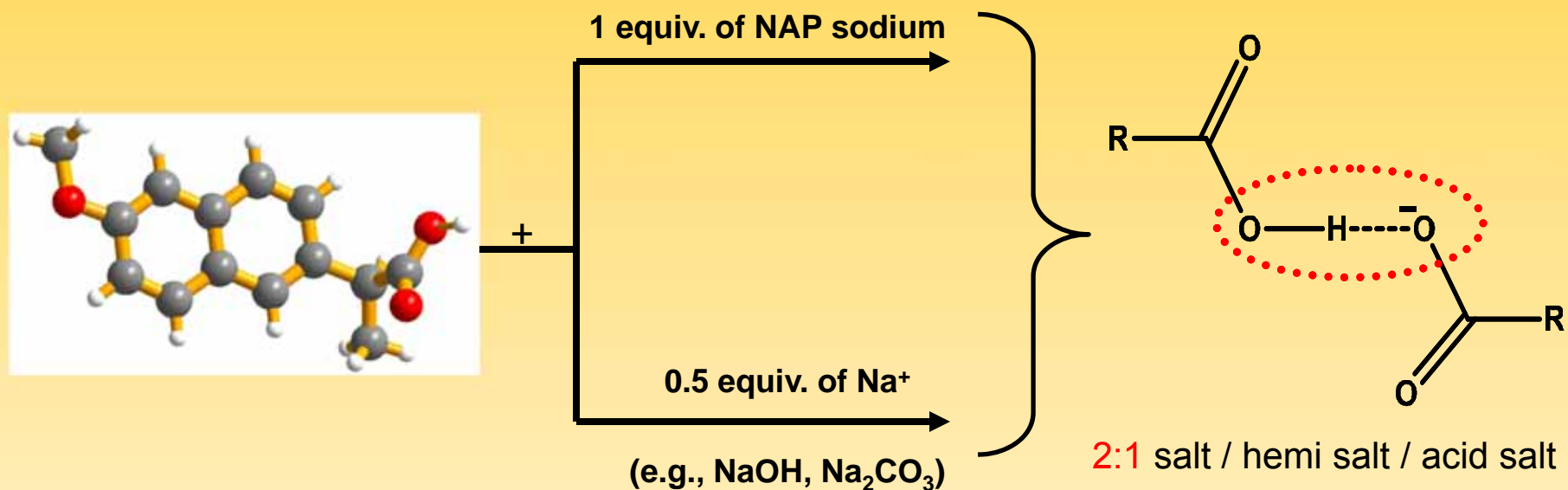
$[\text{N}\cdots\text{H}\cdots\text{N}]^+$ ,  $[\text{O}\cdots\text{H}\cdots\text{O}]^-$ ,  $[\text{N}\cdots\text{H}\cdots\text{N}]^-$ ,  $[\text{F}\cdots\text{H}\cdots\text{F}]$  strongest H-bond known so far

- 1) Short A...D bond distance (2.2 – 2.5 Å)
- 2) Nearly linear bond angle (175-180 deg)

J. Emsley, *Chem Soc. Rev.*, **1980**, 9, 91-124  
F. Hibbert et al, *Adv. Phys. Org. Chem.*, **1991**, pp. 255-379

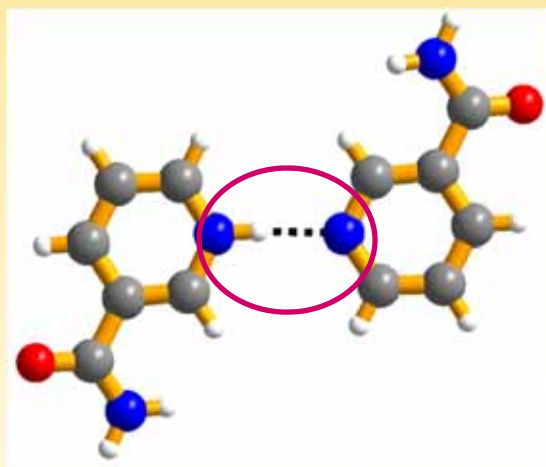
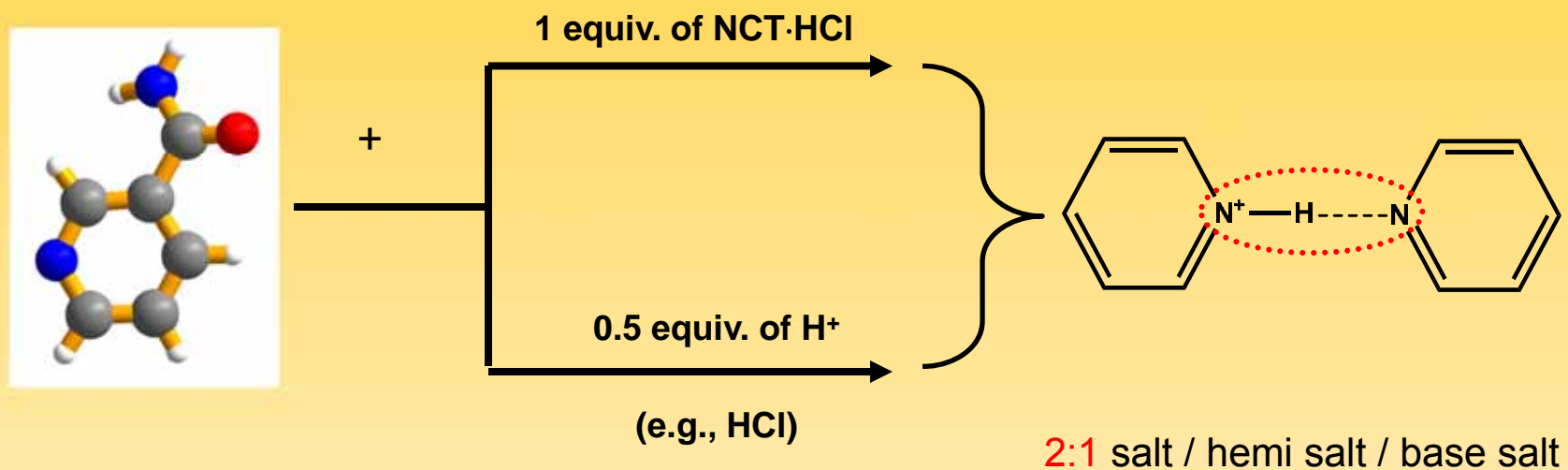


# Synthesis of Naproxen (NAP) CAB Cocrystal



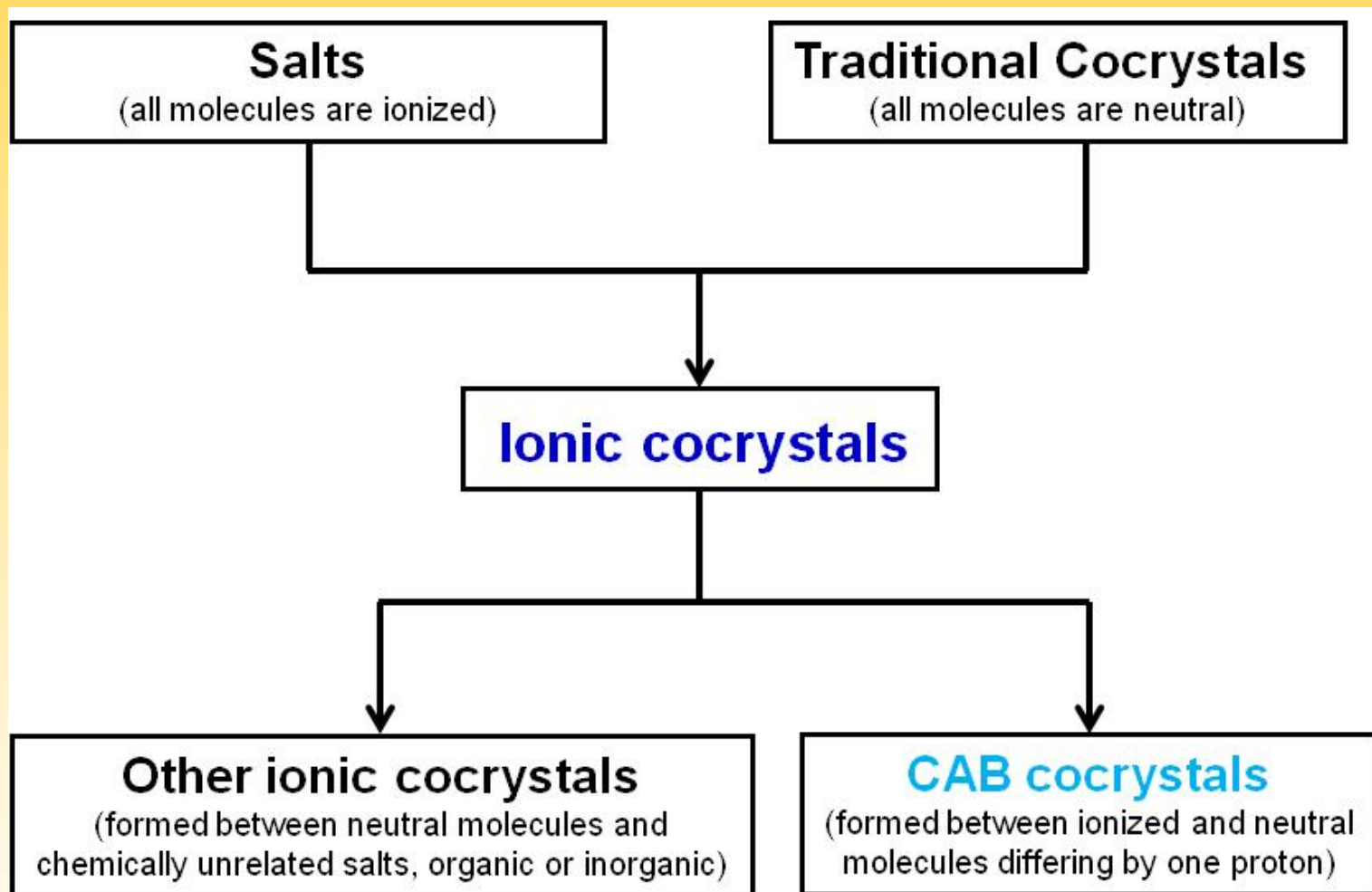
CAB Interaction (O...O distance of 2.47 Å).

# Synthesis of Nicotinamide (NCT) CAB Cocrystal



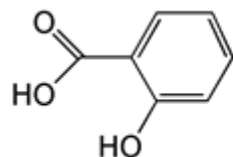
CAB Interaction (N...N distance of 2.77 Å).

# Relationship of CAB cocrystal to other crystal types

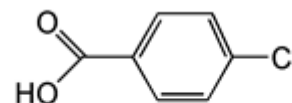


# Pseudo-CAB cococrystals

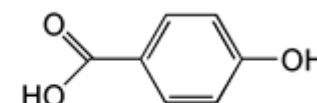
Cocrystals formed between chemically distinct acids or bases through CAB H-bond synthons.



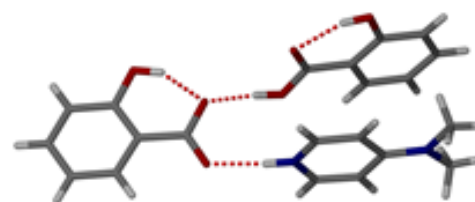
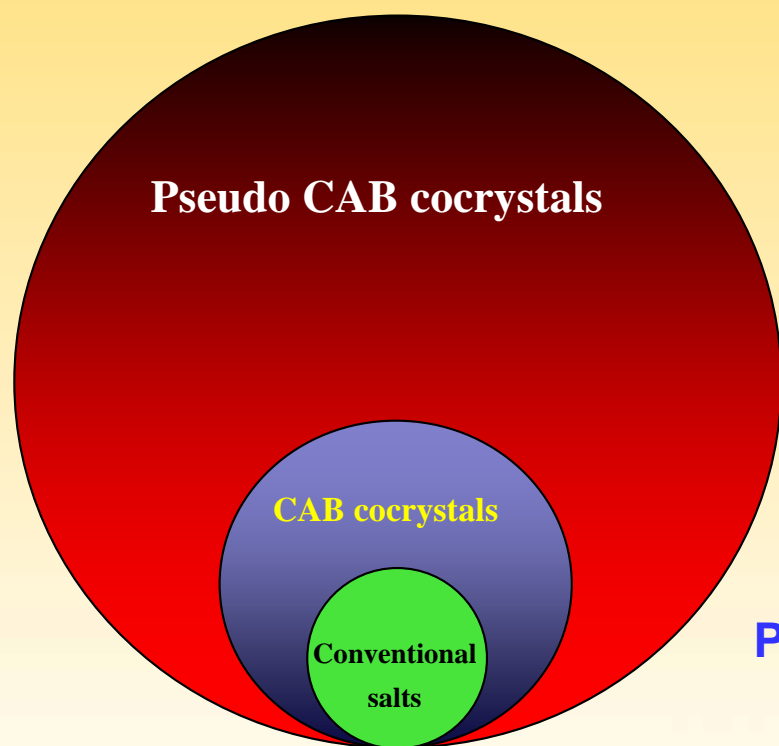
Salicylic acid, Sach



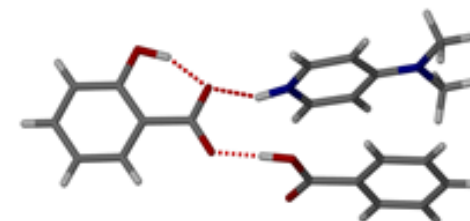
4-chlorobenzoic acid, ClBzH



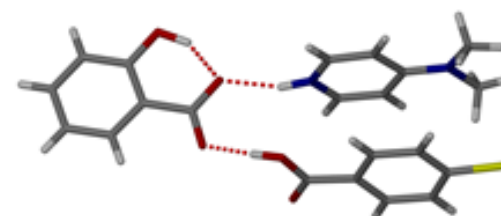
4-hydroxybenzoic acid, OHBzH



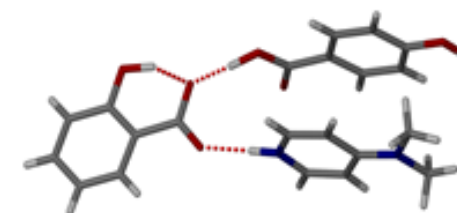
CAB<sup>2</sup>



Pseudo CAB<sup>3</sup>



Pseudo CAB<sup>4</sup>

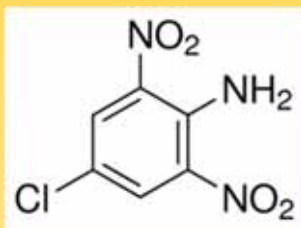


Pseudo CAB<sup>5</sup>

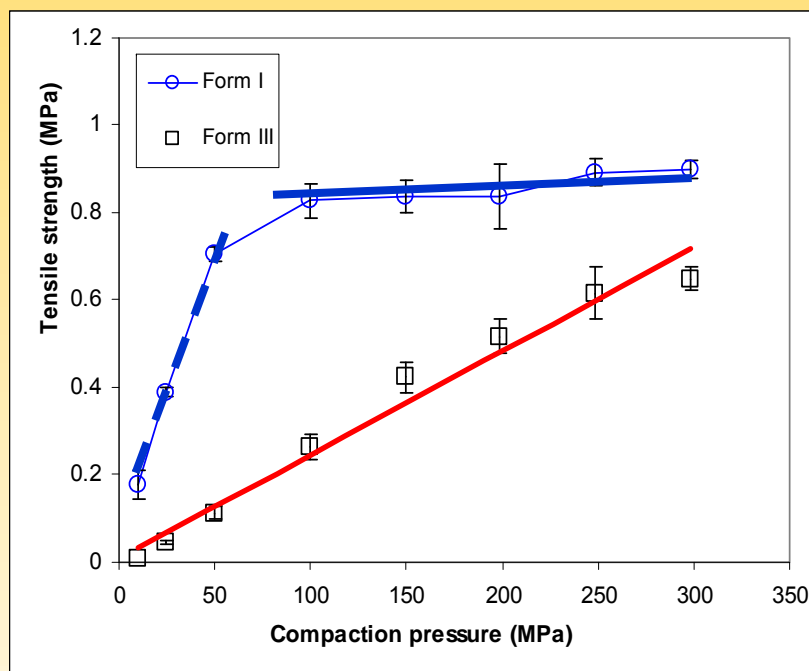
# Pharmaceutical Advantages of Expanded Solid-state Landscape

1. Tabletability
2. Stability
3. Solubility
4. Taste
5. Hygroscopicity

# Tabletability Enhancement by Polymorph



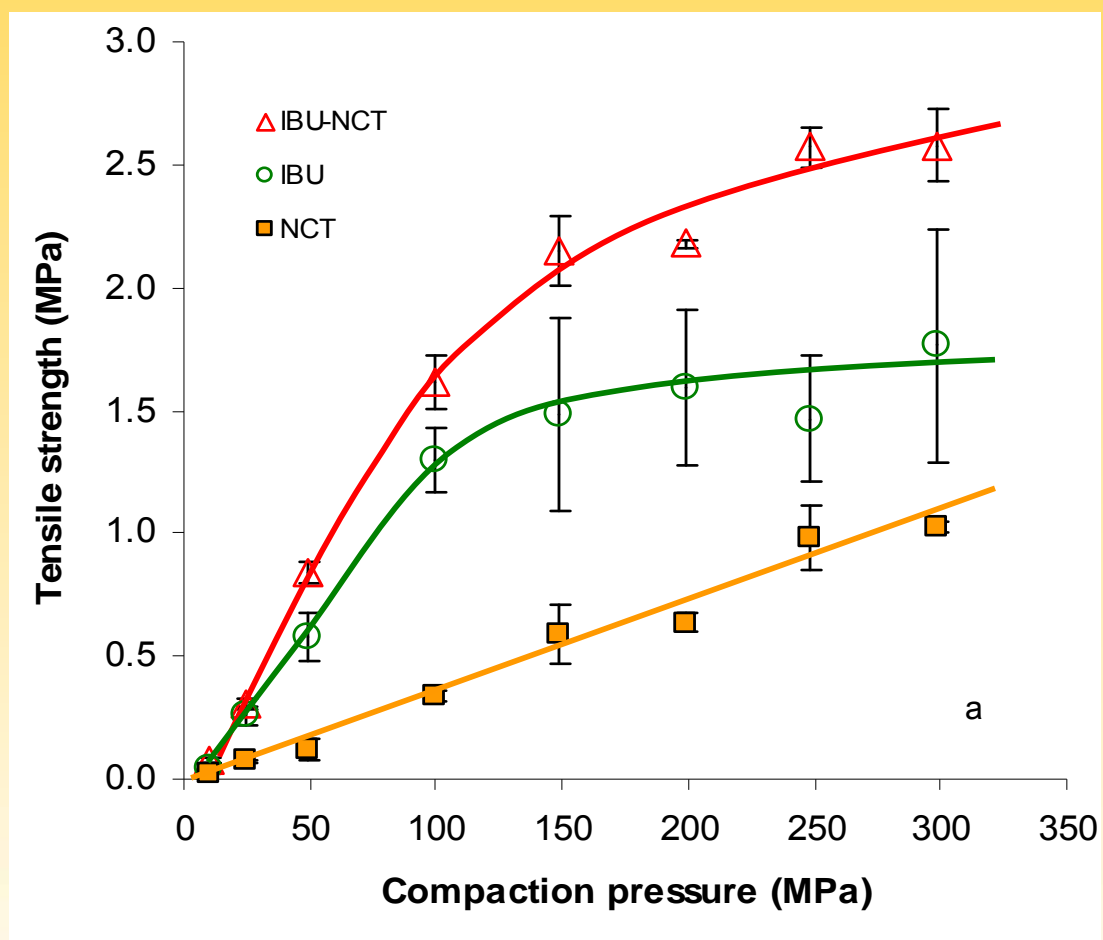
6-chloro-2,4-dinitroaniline



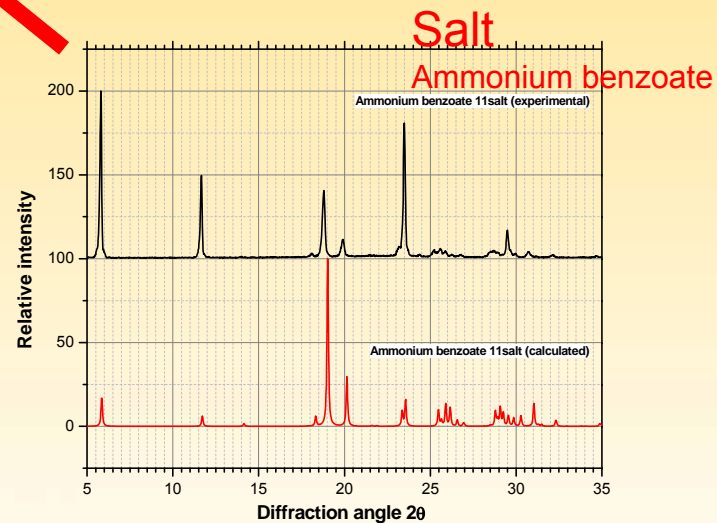
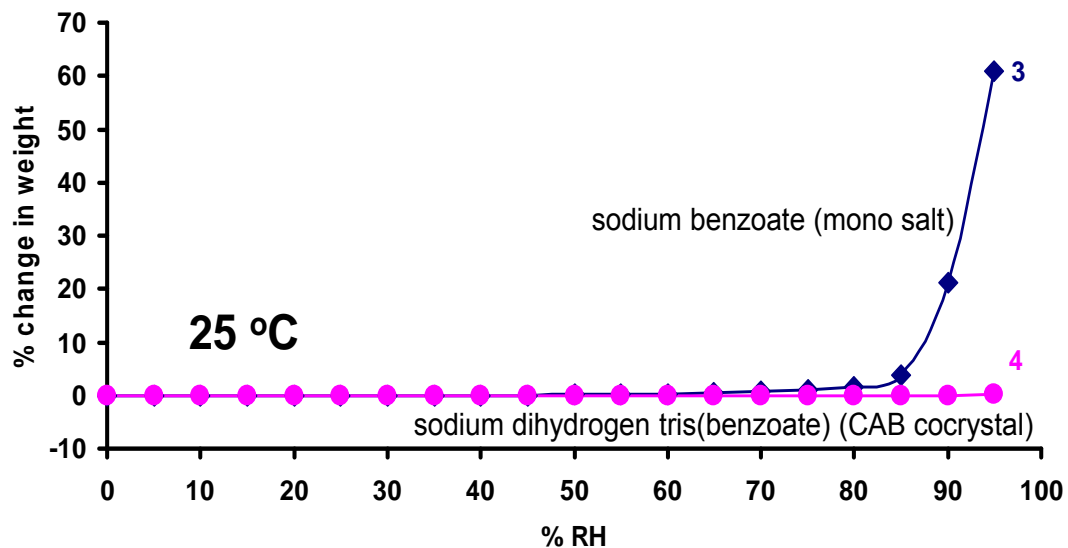
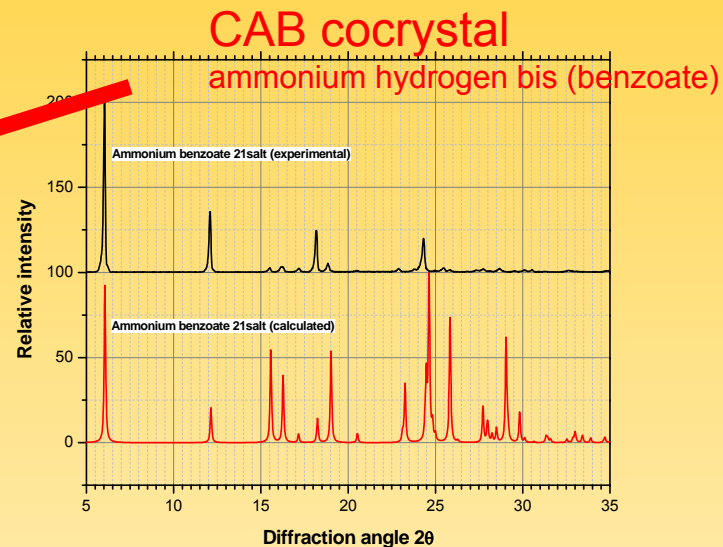
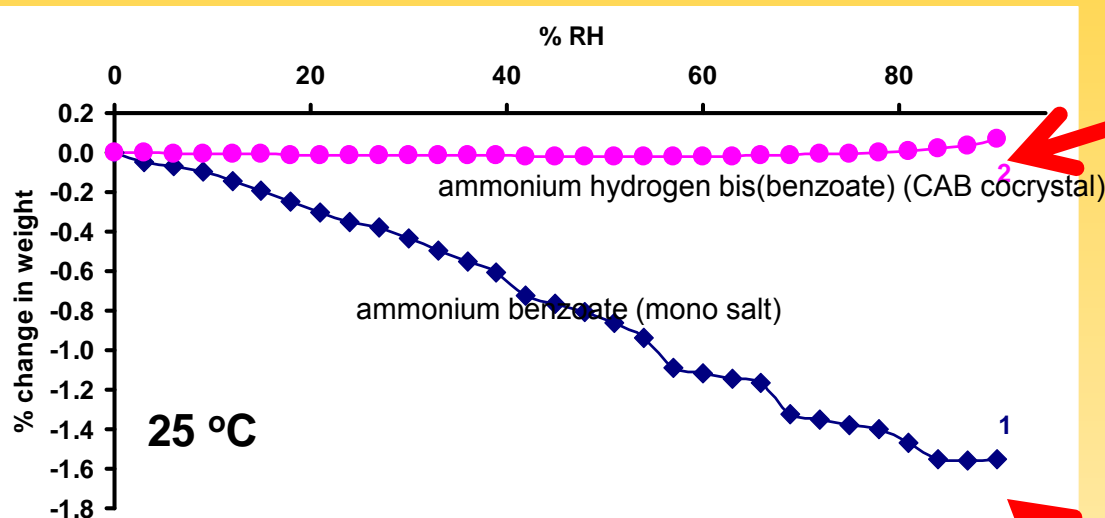


# Unstable Cocystal: Ibuprofen – nicotinamide

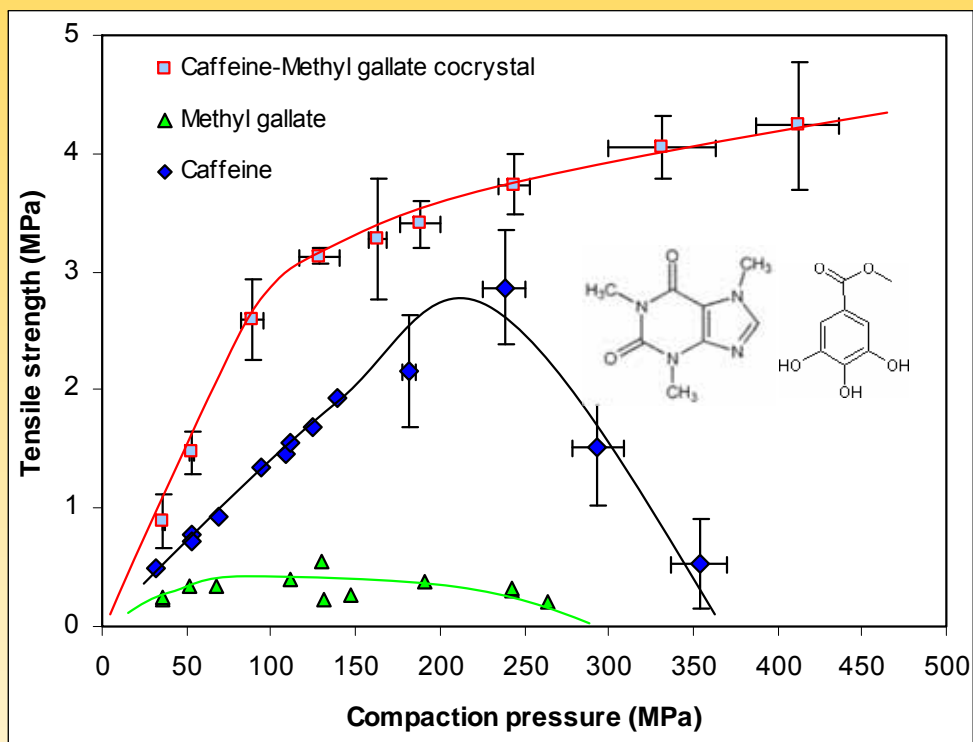
Bulk cocystal could be prepared using the fast solvent evaporation process.



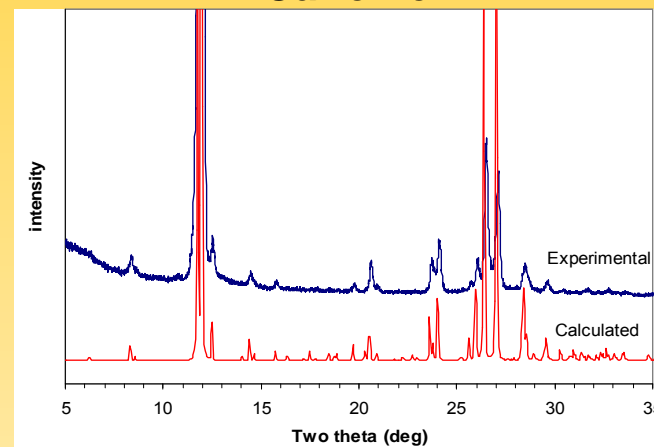
# Stability enhancement by CAB cocrystals



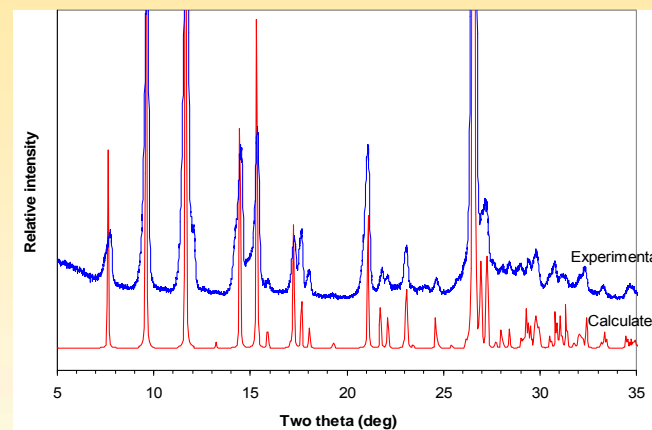
# Tabletability Enhancement by cocrystallization



Caffeine II

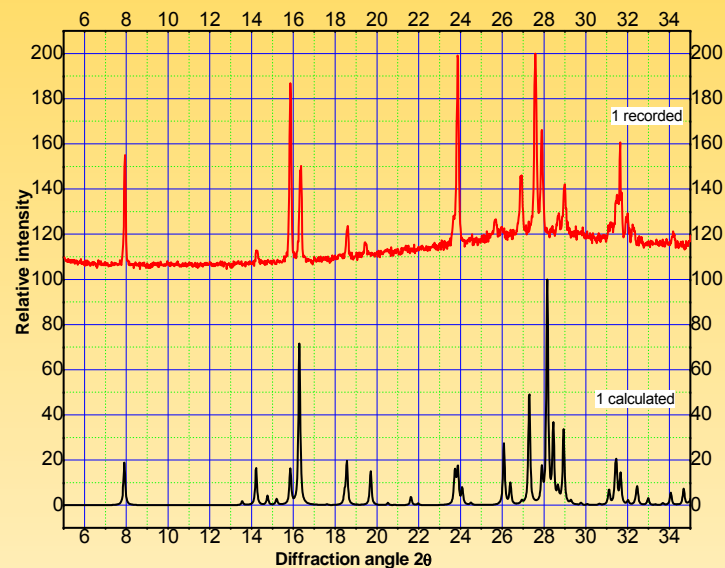
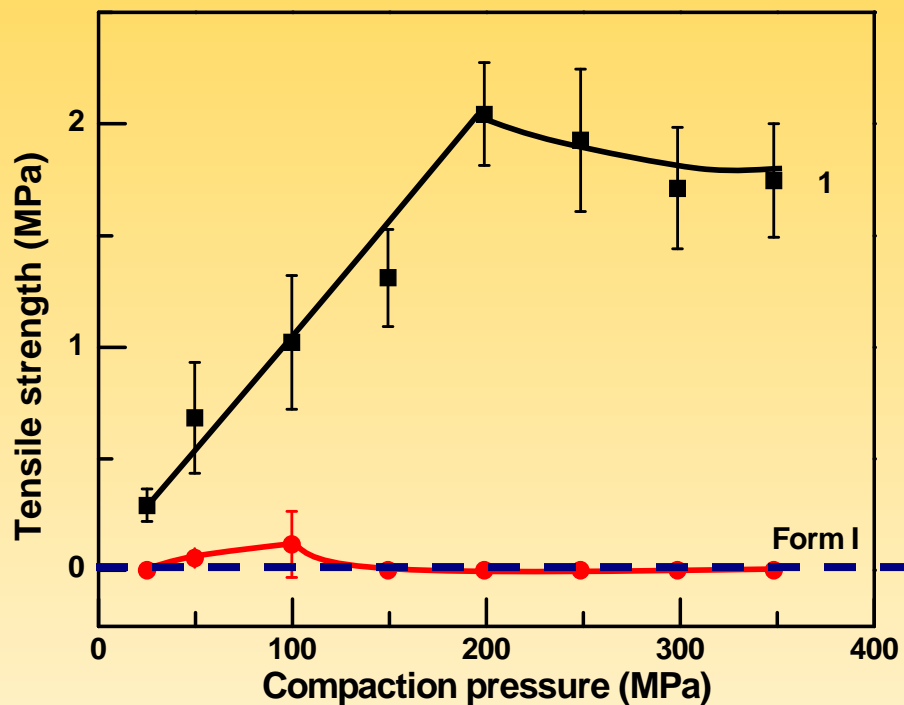


Methyl gallate-Caffeine cocrystal



Tabletability of the cocrystal is significantly better than both methyl gallate and caffeine.

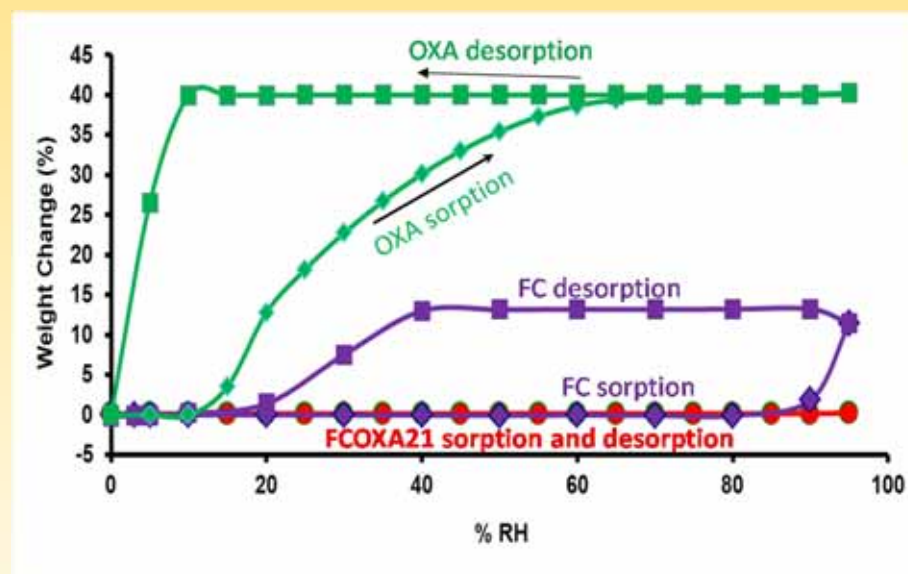
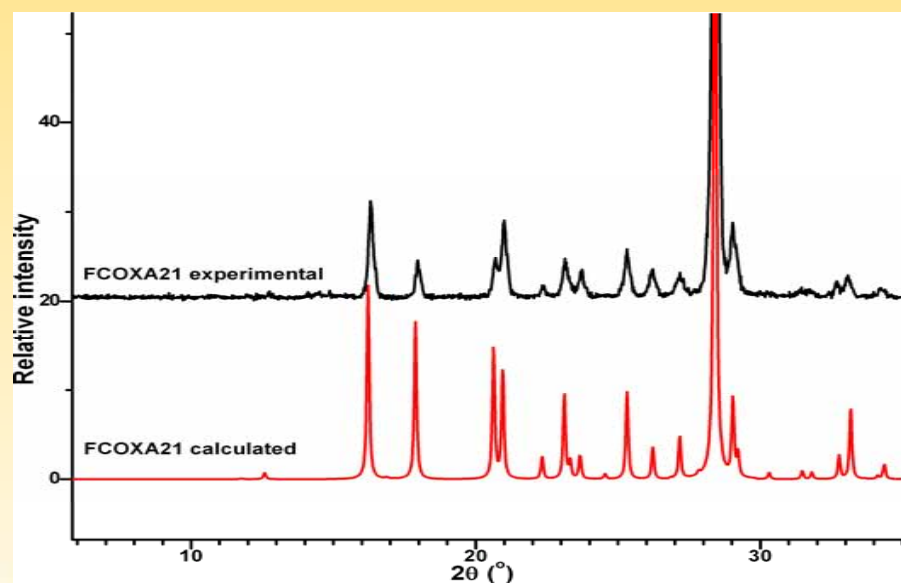
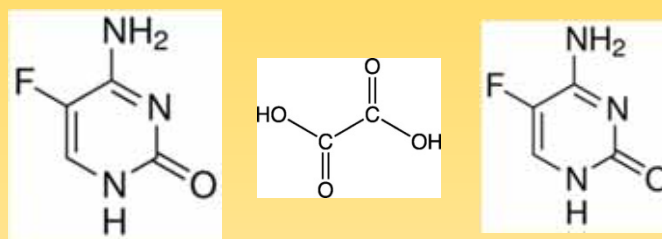
# Tabletability Enhancement by Salt formation



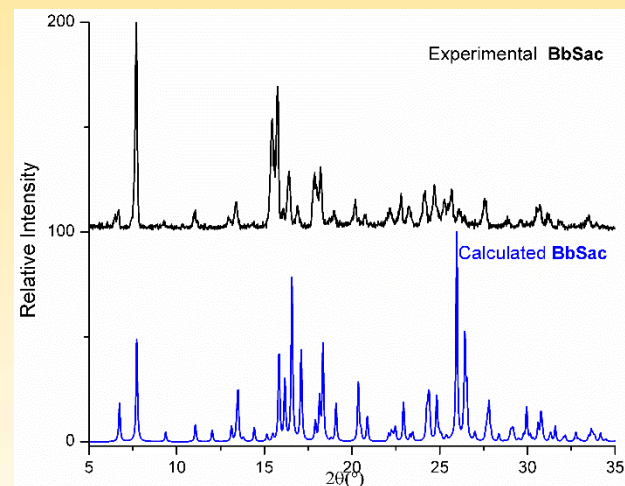
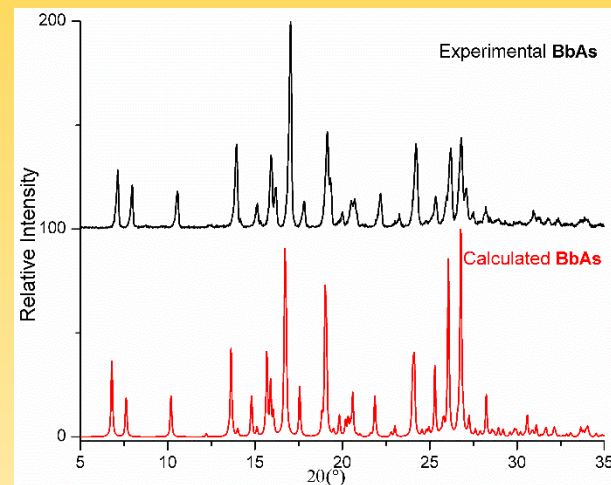
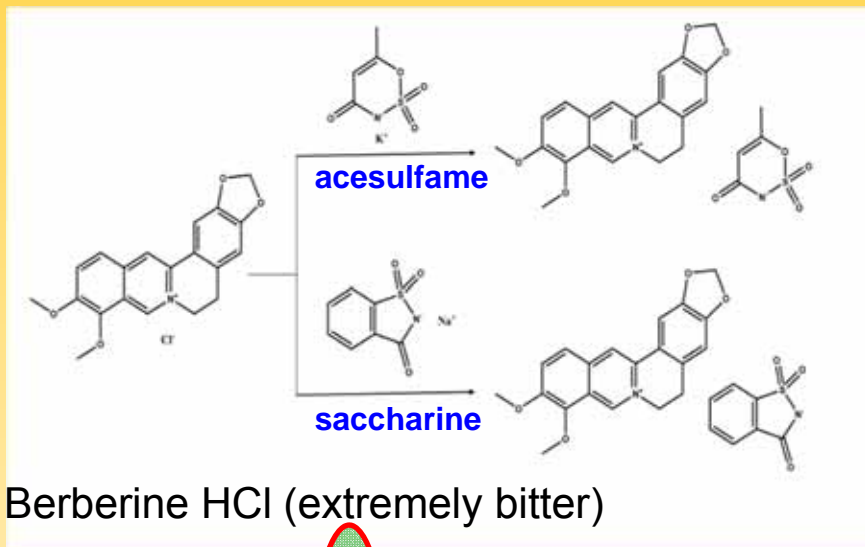
**Acetaminophen HCl (monohydrate)**

Crystallized from concentrated HCl(aq.)

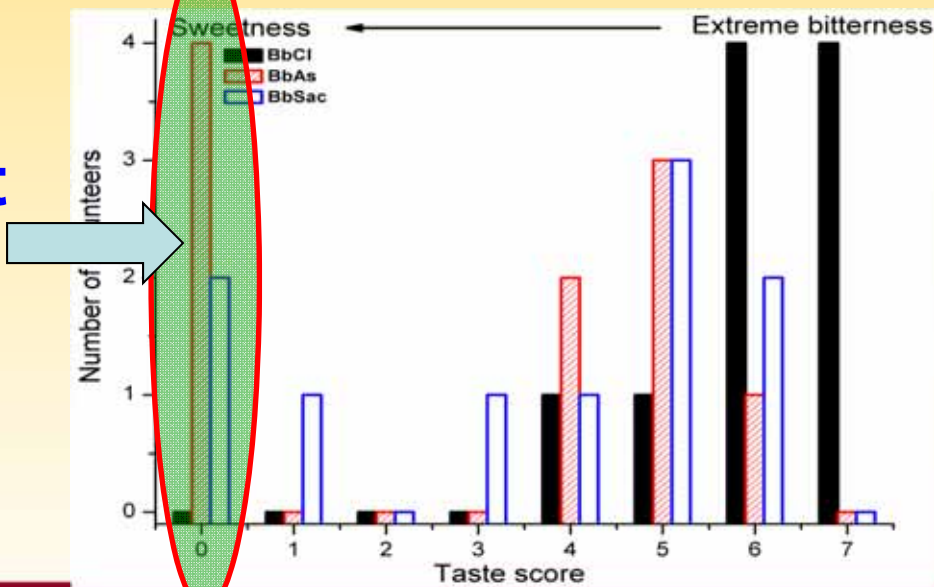
# Improved Tableability & Hygroscopicity by Salt Formation



# Enhanced Taste Profile by Salt Formation



Sweet Salts



# Conclusions

1. Fast solvent removal is a promising technique for preparing bulk quantities of metastable solid forms
2. Salts can be prepared for poorly ionizable drugs with judicious selection of experimental conditions
3. Charge assisted H-bonding is useful for designing CAB cocrystal
4. Various pharmaceutical properties can be improved by using a suitable crystal form of a drug
5. PXRD plays a critical role in all these investigations

# Acknowledgements

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