课程四：药物共晶-药物晶型开发的新热点

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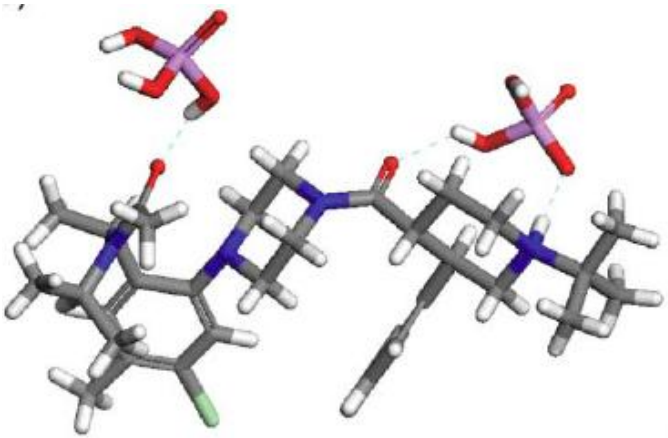
提纲

- 药物共晶简介
  - 为何要开发药物共晶？
  - 共晶发展历史
  - 共晶的定义和表征
- 形成共晶的方法
- 药物共晶的案例分析
- 共晶筛选和工艺放大的策略：三元相图的应用

药物共晶简介

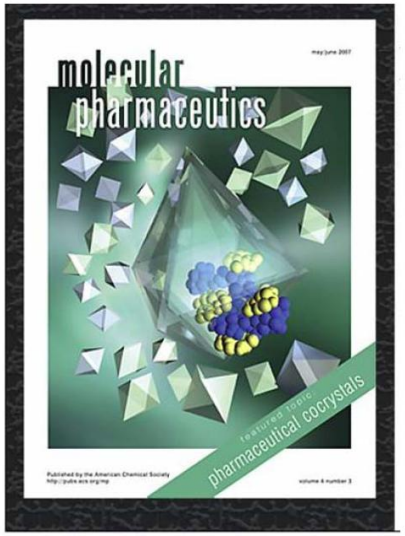


为何要开发药物共晶？

- Co-crystals can enhance physicochemical properties of NCEs
  - an alternate crystal engineering opportunity to salts, polymorphs, amorphous material etc.
    - No crystalline salt or free form
    - Crystalline salt or free form doesn't show suitable properties for development
  - Hygroscopicity, solubility, dissolution, bioavailability
  - Controlled delivery (pH-dependent solubility)
- IP protection
- To predict/avoid unexpected drug-excipient interaction in formulation

共晶发展历史

- Non-pharmaceutical co-crystals: 1890's
  - Photographic films
- Pharmaceutical co-crystals relatively novel, but many case studies have been published in past years
- Academic interest has been driving industrial interest
  - University of Michigan, Professor Nair Rodriguez
  - University of South Florida, Professor Michael J. Zaworotko
  - University of Cambridge, Professor William Jones
- Cocrystal is becoming a must-study area in top pharmas now
- 共晶给仿制药公司提供了挑战新药公司对于药物晶型专利的保护的新机会



2007年6月4日

2007年6月18日

共晶定义

- +20 articles dealing with the definition of co-crystals
- Disagreement among researchers

Physical state of guest / Forces holding components together	Liquid at RT	Solid at RT
Ionic	Salt	Salt
Hydrogen, Wan der Walls etc.	Solvate or co-crystal	Co-crystal

共晶定义

- Cocrystals are crystals that contain two or more different molecular components
- Components are solids at room temperature
- Often rely on hydrogen-bond assemblies between neutral molecules of the API and other components
- are a homogeneous crystalline phase with well-defined stoichoimetries AB, AB2, etc

共晶 vs. 盐类

- How to differentiate between co-crystals and salts?
  - It is all about the location of the hydrogen
- Frequently used methods:
  - pKa value differences – Is the acid sufficiently strong to ionize the base?:
    - ΔpKa (base-acid)< 0 → Co-crystal
    - ΔpKa (base-acid) > 3 → Salt
  - C-O bond distances in acid co-crystals - A carboxyl anion has two similar C-O values; A neutral carboxyl group has two distinctively different C-O values
    - Δ C-O< 0.03 Å → Co-crystals
    - Δ C-O> 0.08 Å → Salts

Source: Childs et al., *Mol. Pharm.* 2007.; Aakeroy et al. *Cryst. Growth Des.* 2006

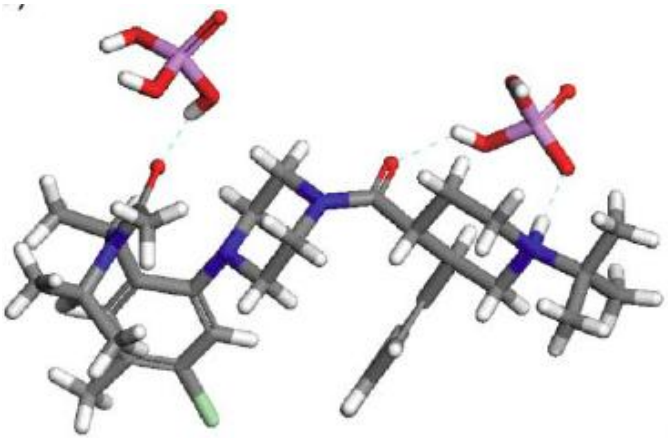
共晶的表征和定义

- How to differentiate between co-crystals and salts?
  - IR spectra
  - ssNMR
  - Single crystal X-ray diffraction

- If it works – why is the definition important?
  - Scientific communication
  - Regulatory approvals
  - Intellectual property

Source: Childs et al., *Mol. Pharm.* 2007.; Aakeroy et al. *Cryst. Growth Des.* 2006; Cooke et al., Am. Pharm. Rev., 2007

怎样形成药物共晶?

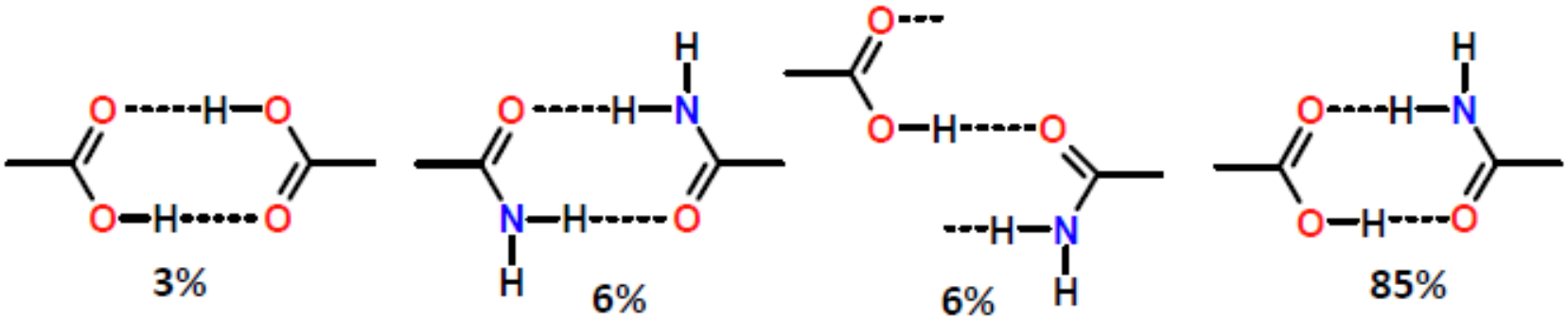


共晶形成体的选择

- Non pharmaceutical co-crystals
  - Only requirement: hydrogen bond donor and acceptor present
- Pharmaceutical co-crystals
  - Pharmaceutically acceptable formers:
    - GRAS list, Food additives
    - Like salts: company culture -> pharmaceutically acceptable salt formers
- Understanding success factors
  - Predicting hydrogen bond formation
    - Using the CSD: Cabamazepine (MaMahon et al, 2004)
  - Predicting resulting physicochemical properties
    - Pharmaceutical co-crystal structure-property relationship

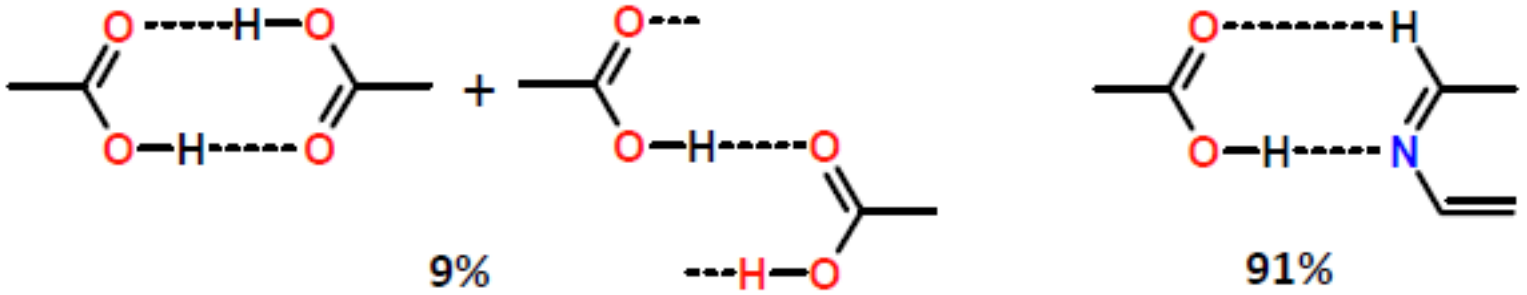
形成氢键的选择性数据库分析

Carboxylic acid and primary amide



CSD Version 5.29, January 2008 update

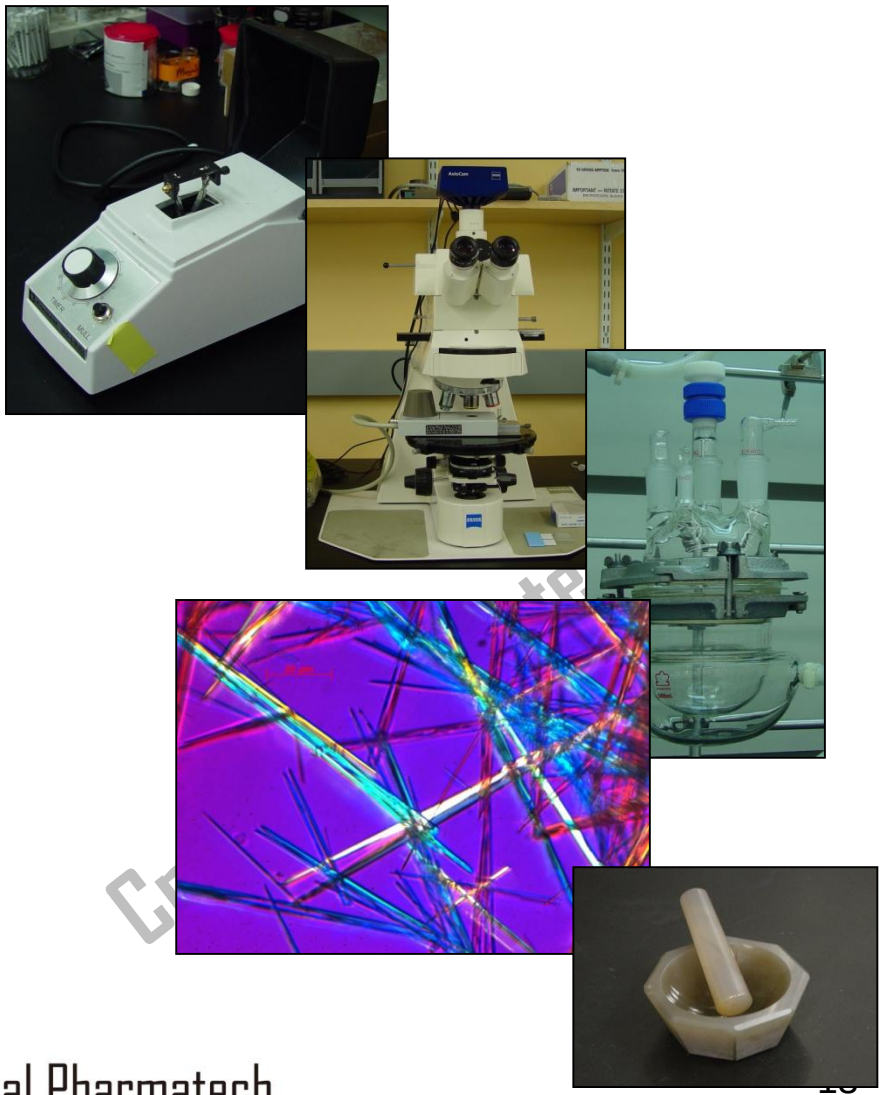
Carboxylic acid and pyridine



T. Steiner, Acta Crystallogr., ***2001****, B57, 103*

形成共晶的各种方法

- Solvent crystallization
- Slurry conversion
- Grinding of solids
  - Solvent-drop grinding
- Blending of powders
- Heating solids
- Melt crystallization
- Sublimation

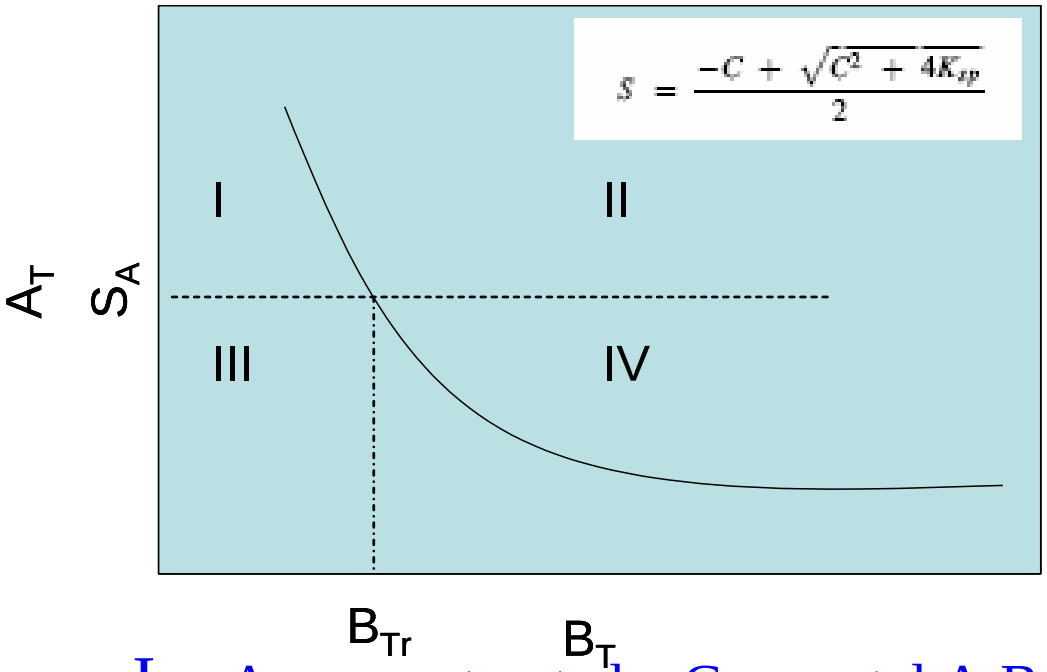


共晶的应用

- Co-crystals can be used to design crystals with desirable pharmaceutical properties – for example
  - Polymorphism: Piracetam, Gentisic Acid, and P-Hydroxybenzoic acid pharmaceutical co-crystals
  - Chemical stability: Carbamazepine co-crystals
  - Melting points: Ibuprofen, flurbiprofen, aspirin co-crystals
  - Solubility and dissolution: Fluoxetine Hydrochloride and itraconazole co-crystals
  - Pharmacokinetic properties: Co-crystals of a sodium channel blocker and AMG 517 sorbic acid

Source: Bailey Walsh et al., Chem Commun , 2003; Remenar et al., J Am Chem Soc, 2003; Wishweshwar et al, Chem. Comm., 2005; Rodriguez-Hornedo et al., Enc. Pharm., Tech., 2007; Childs et al., J Am Chem Soc, 2004.

共晶相图



Assumptions:

- $S_A < S_B$
- $S_A < S_{A:B}$ in stoichiometric solutions
- No complexation or ionization of co-crystal components in solution
- The solubility of A is independent of concentration of B in solution
- B_{TR}: $S_A = S_{A:B}$

I. A supersaturated – Co-crystal A:B undersaturated

II. A and co-crystal A : B supersaturated

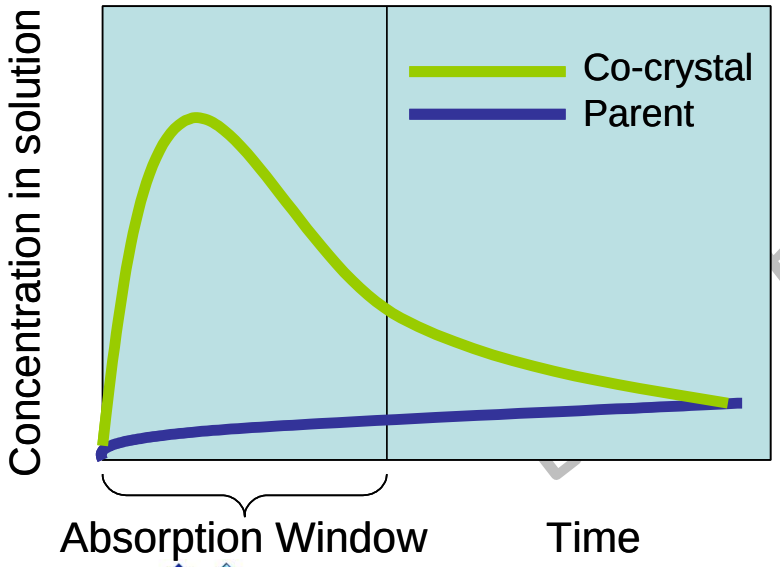
III. A and co-crystal A : B undersaturated

IV. Co-crystal A:B supersaturated – A undersaturated

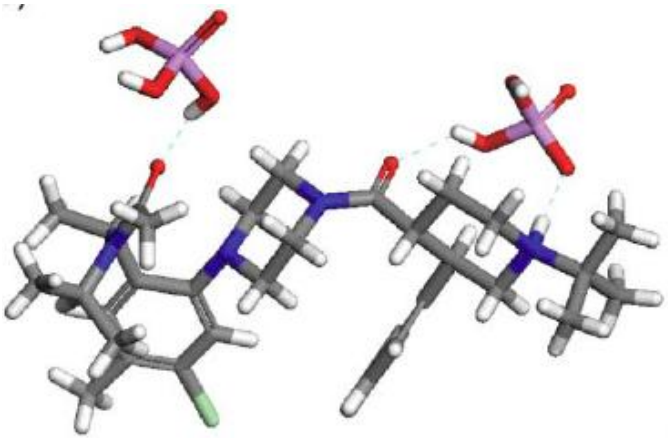
Adapted from: Rodriguez-Hornedo et al., Encyclopedia of Pharmaceutical Technology, 2007

共晶相图

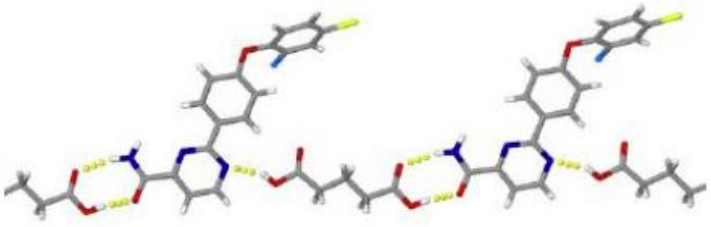
- Phase diagram consequence
  - Many co-crystals, with enhanced solubility over parent drug, will disproportionate in aqueous media
  - These co-crystals will rely on supersaturation for exposure enhancement
  - Dissolution rather than solubility is the relevant parameter

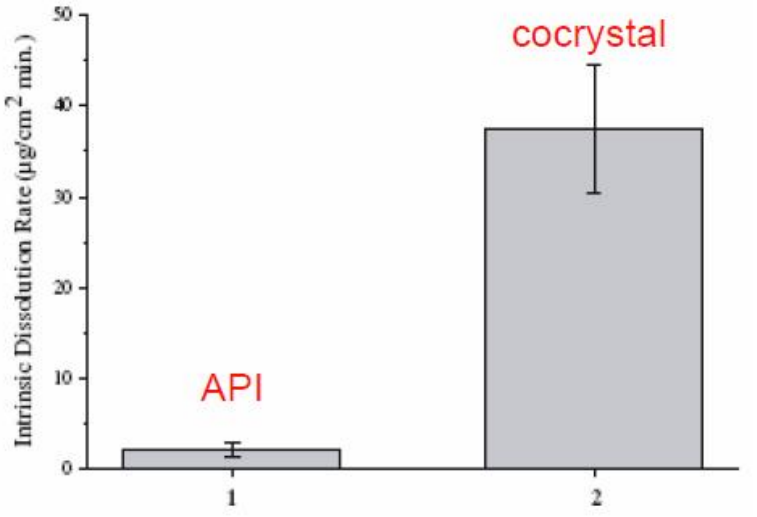


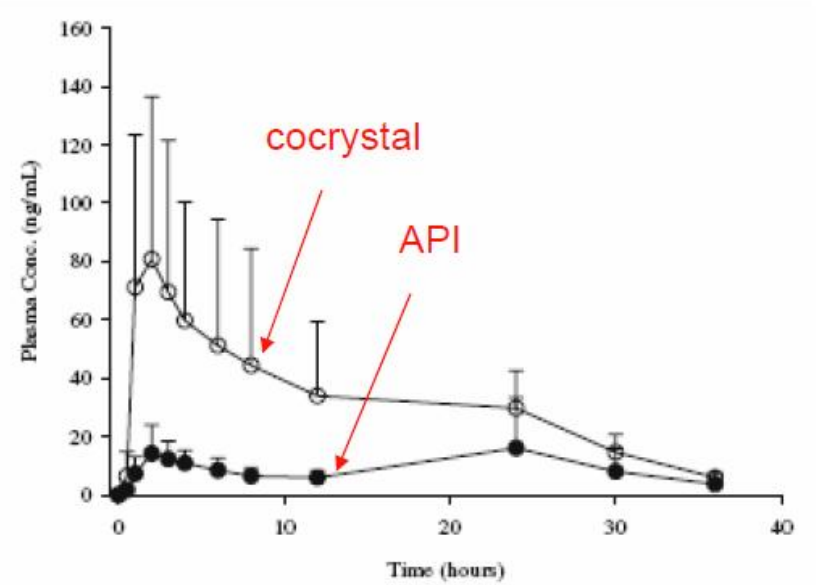
药物共晶多种案例分析



药物共晶案例1：
共晶提高溶出速率和生物利用度





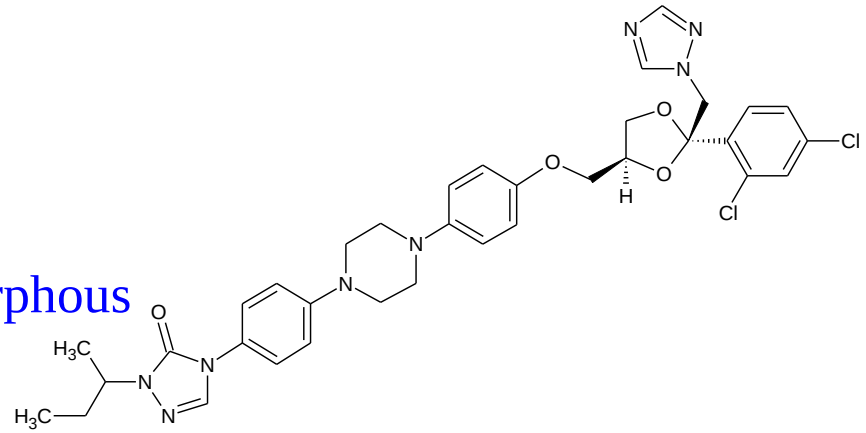


API: 2-[4-(4-chloro-2-fluorophenoxy)phenyl] pyrimidine-4-carboxamide

McNamara D,, Childs, S, et al., Pharm. Res., 2006

药物共晶案例2:
Co-crystals of Itraconazole (Sporanox)

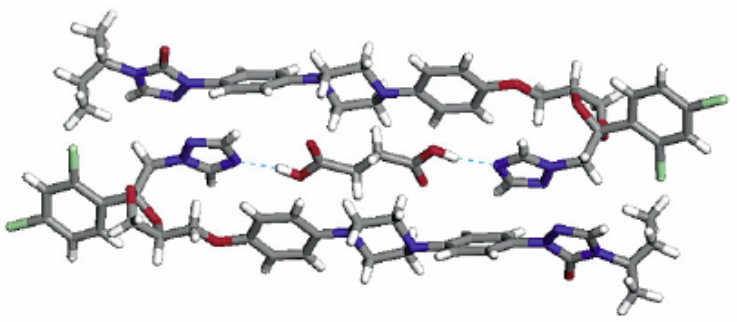
- Itraconazole
  - Fungal infections
  - Water insoluble
  - PO formulation: spray-dried amorphous material on sucrose



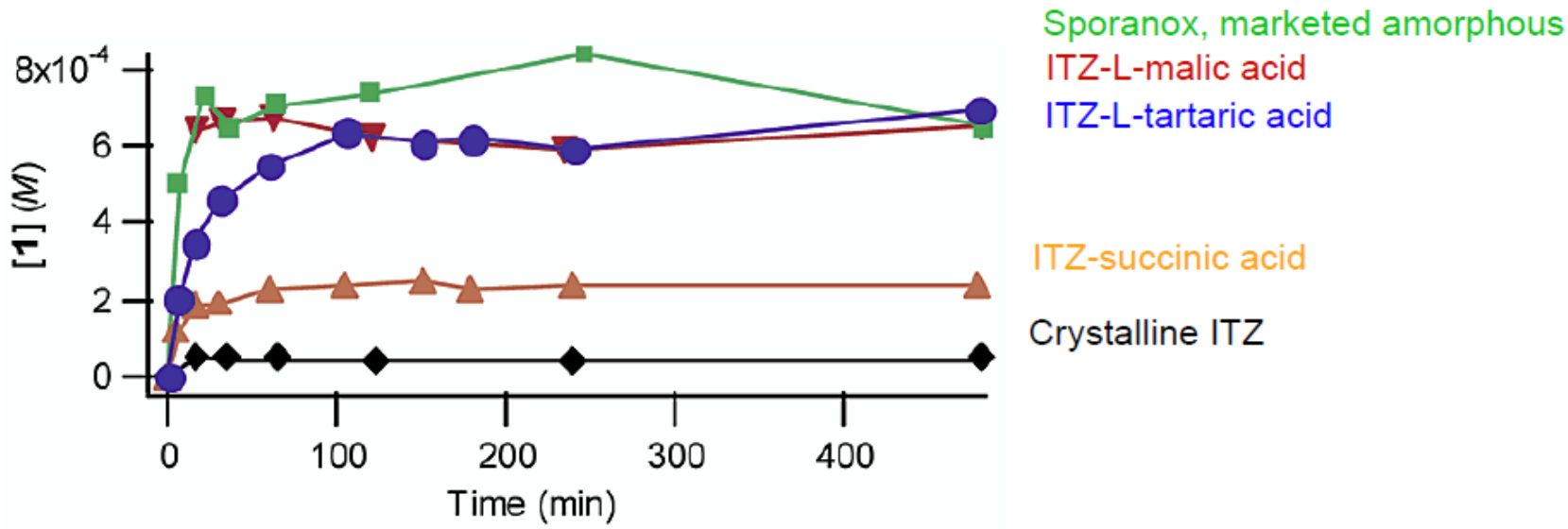
- Co-crystals with several organic dicarboxylic acids (e.g. fumaric acid and succinic acid) was reported.
- Significantly better dissolution profiles than crystalline Itrconazole:
  - Co-crystals achieved 4 to 20-fold higher concentrations than the crystalline form of itraconazole
  - Dissolution profiles were similar to the marketed amorphous form

Source: Remenar et al., J Am Chem Soc, 2003

共晶 vs. 无定形溶出速率



Itraconazole-succinic acid cocrystal



共晶的溶出速率可以达到和无定形一样

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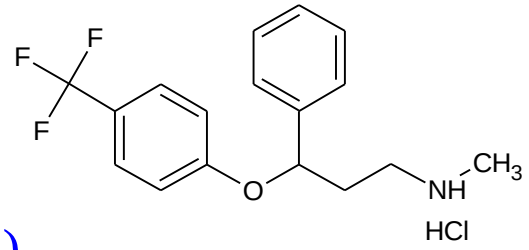
药物共晶案例3:
Fluoxetine Hydrochloride (Prozac)

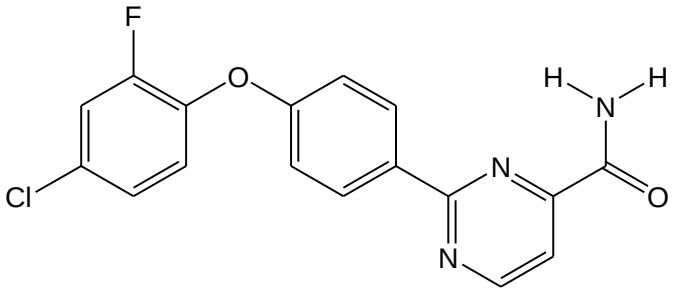


- Antidepressant
- Co-crystals studied:
  - 1:1 co-crystal with benzoic acid (BAC)
  - 2:1 co-crystals with succinic acid (SAC) and fumaric acid (FAC)
  - Chloride mediated carboxylic acid synthon
- Distinctly different dissolution profiles:
  - BAC<Fluoxetin HCl<FAC<SAC
- Co-crystal with most favorable dissolution profile (SAC) reverted back to fluoxetine hydrochloride
  - Other co-crystals remained the same phase

Source: Childs et al., JACS, 2004.

药物共晶案例4: A Sodium Channel Blocker

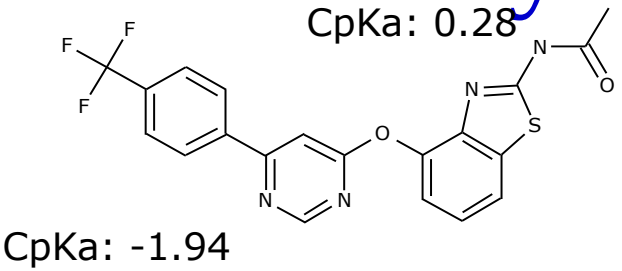
- A glutaric acid co-crystal of a sodium channel blocker had an 18-fold increase in the dissolution rate over the parent compound
  - After a 24-hour exposure to dissolution media, the material reverted back to the parent drug.



- Dog PK studies resulted in a 3-fold increase in exposure of the co-crystal over the parent compound.

Source: McNamara et al., Pharm Res, 2006

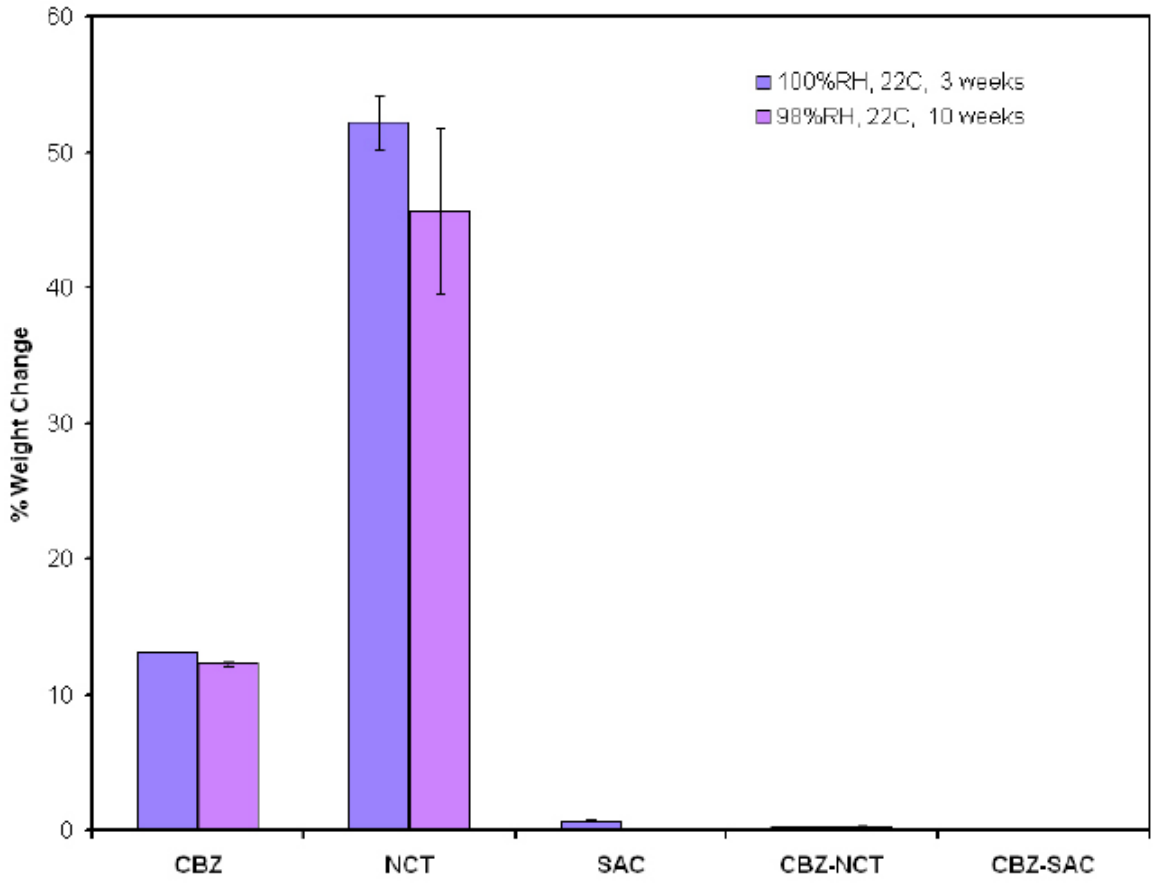
药物共晶案例5:
AMG 517 Sorbic Acid Co-crystal



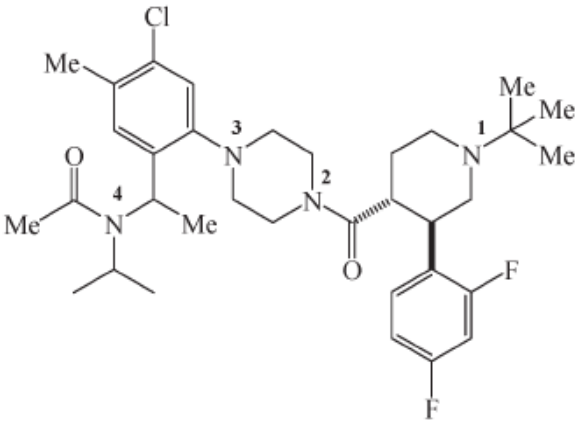
- Insoluble in aqueous media
- Salt formation not feasible
- Solubility limited absorption observed in preclinical PK studies using the free-base
- The sorbic acid co-crystal was discovered serendipitously in a preclinical formulation
  - Solubility:
    - Preclinical formulation: $S_{co\text{-}crystal} < S_{freebase}$
    - FaSIF: X 100 increase solubility in FaSIF at 1 hour; Disproportionation observed at 2 hour
  - Rat PK:
    - Mean Cmax and AUC0-inf increased by 8 and 9-fold at comparable doses of 500 mg/kg sorbic acid co-crystal and free base

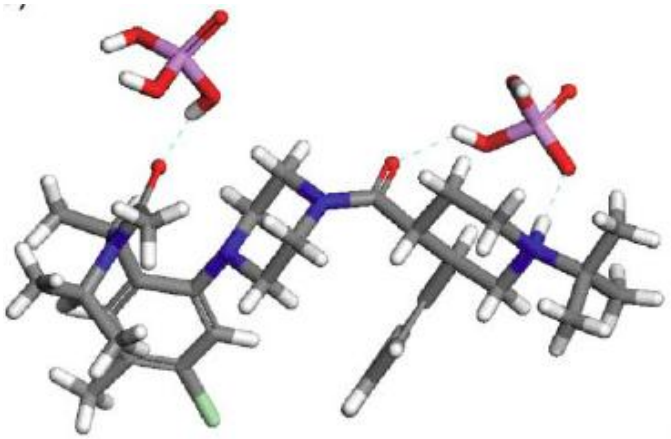
Literature source: Bak et al., J. Pharm. Sci., 2008; Doherthy et al., *J. Med. Chem.,* 2007

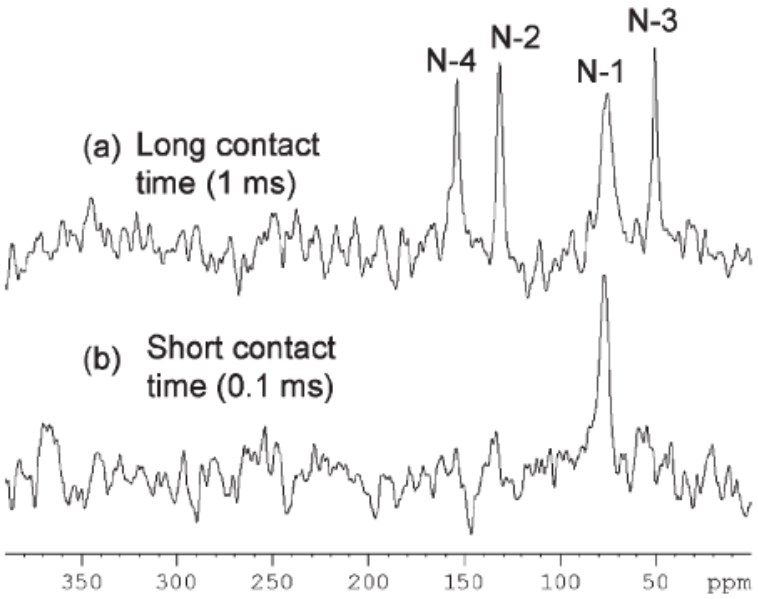
药物共晶案例6：
共晶降低药物的引湿性



药物共晶案例7：
Monophosphate salt with Phosphoric Acid



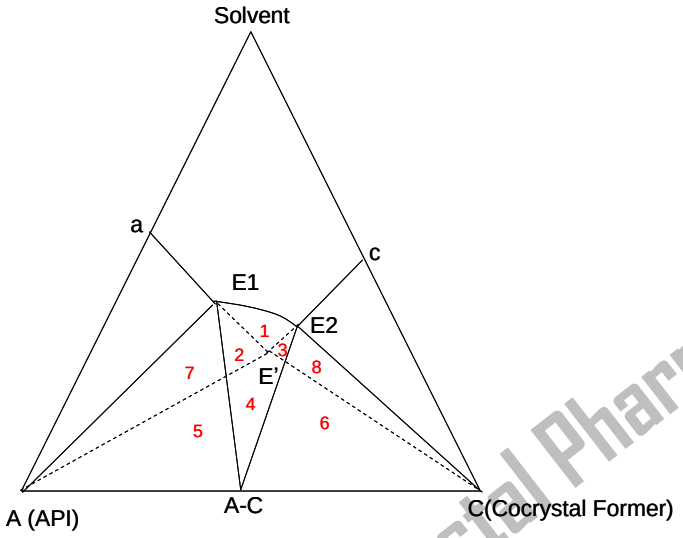


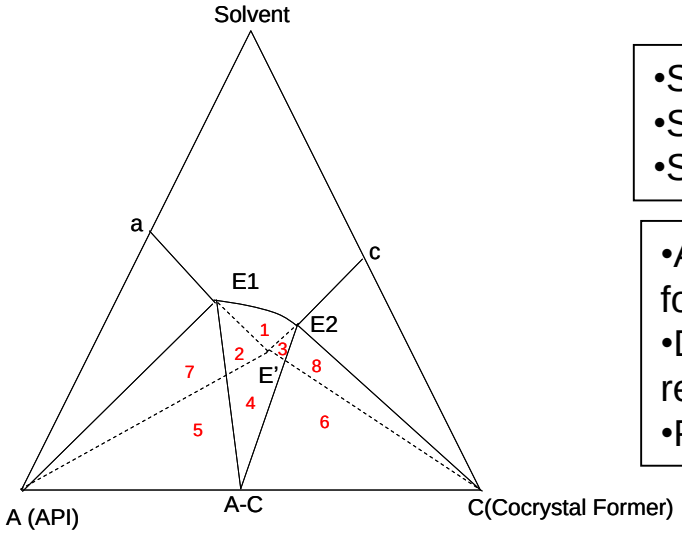


Chen, et al, Chem. Commun., 2007, 419

Merck:
The formation of this cocrystal enabled us to develop a stable crystalline and bioavailable solid form for pharmaceutical development where otherwise only unstable amorphous free form or salts could have been used. “

如何进行共晶筛选和共晶放大工艺：三元相图的应用



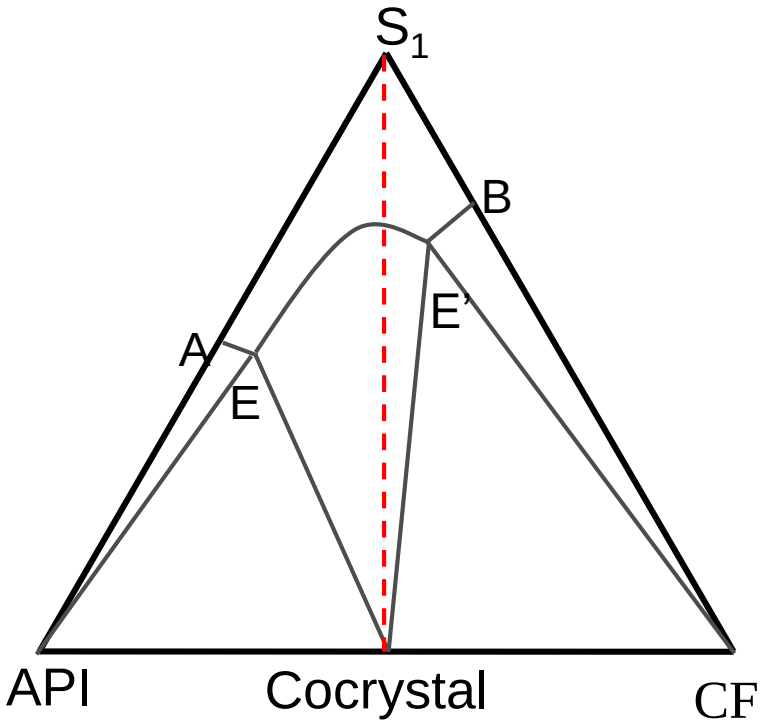


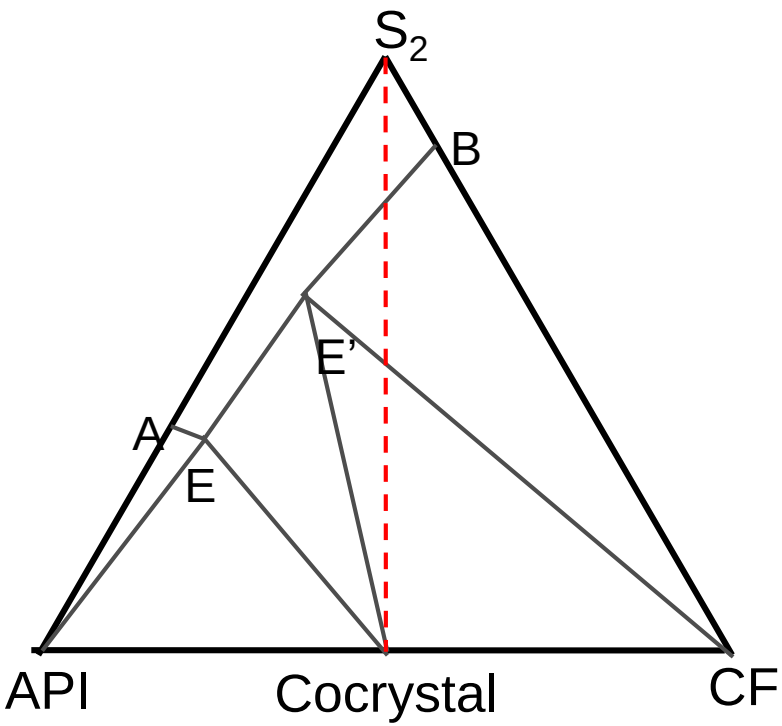
- Solution based
- Slurry based
- Solid based

- All about generating suitable supersaturation for co-crystal.
- Different levels of supersaturation could result in different co-crystals.
- Powerful tool: Ternary phase diagram

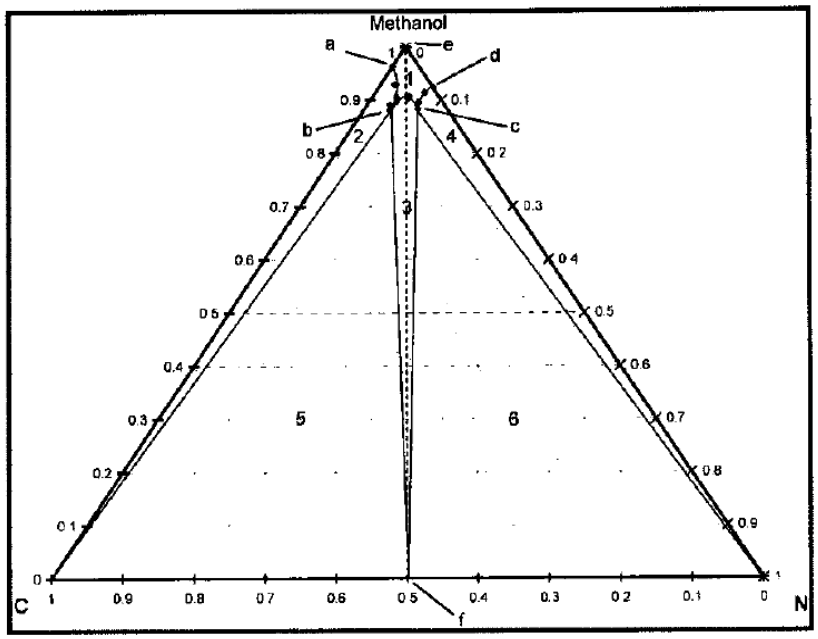
Zone	API	Cocrystal Former (CF)	Cocrystal	Kinetic Solid Phase	Equilibrium Solid Phase	To isoalate pure cocrystal without templates	To isolate pure cocrystal with templates	To screen cocrystal with templates
1	un-saturated	un-saturated	supersaturated	cocrystal	cocrystal	■		
2	supersaturated	un-saturated	supersaturated	cocrystal+API	cocrystal		■	
3	un-saturated	supersaturated	supersaturated	cocrystal+CF	cocrystal		■	
4	un-saturated	un-saturated	supersaturated	cocrystal+API+CF	cocrystal		■	
5	supersaturated	supersaturated	supersaturated	cocrystal+API+CF	cocrystal+API			■
6	supersaturated	supersaturated	supersaturated	cocrystal+AP+CF	cocrystal+CF			■
7	supersaturated	un-saturated	supersaturated	cocrystal+API	cocrystal+API			■
8	un-saturated	supersaturated	supersaturated	cocrystal+CF	cocrystal+CF			■

案例分析：共晶体系的三元相图





案例分析：Co-Crystal of Trans-Cinnamic Acid and Nicotinamide*



- Slurrying 1:1 mixture of C and N in methanol resulted in pure co-crystal

*R., A. Chiarella, et al, CG&D, 2007, 7 (1223)

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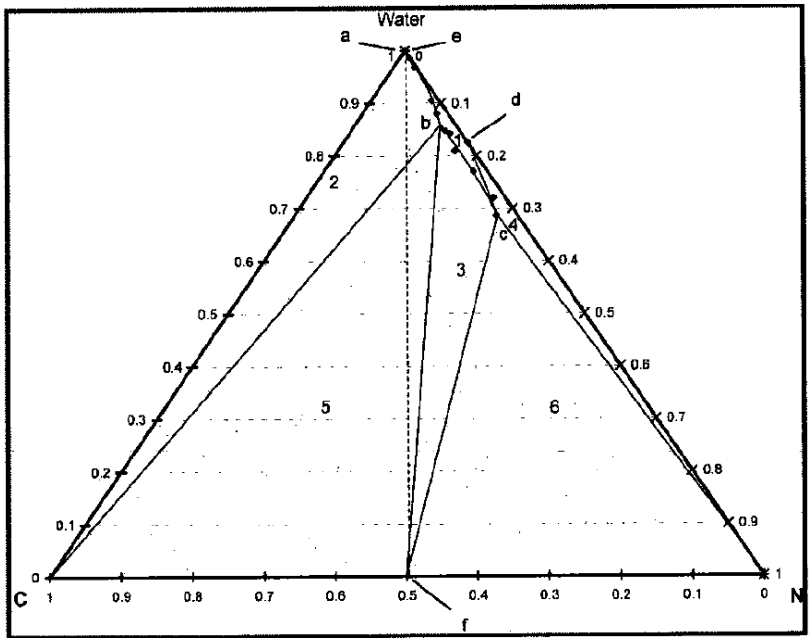
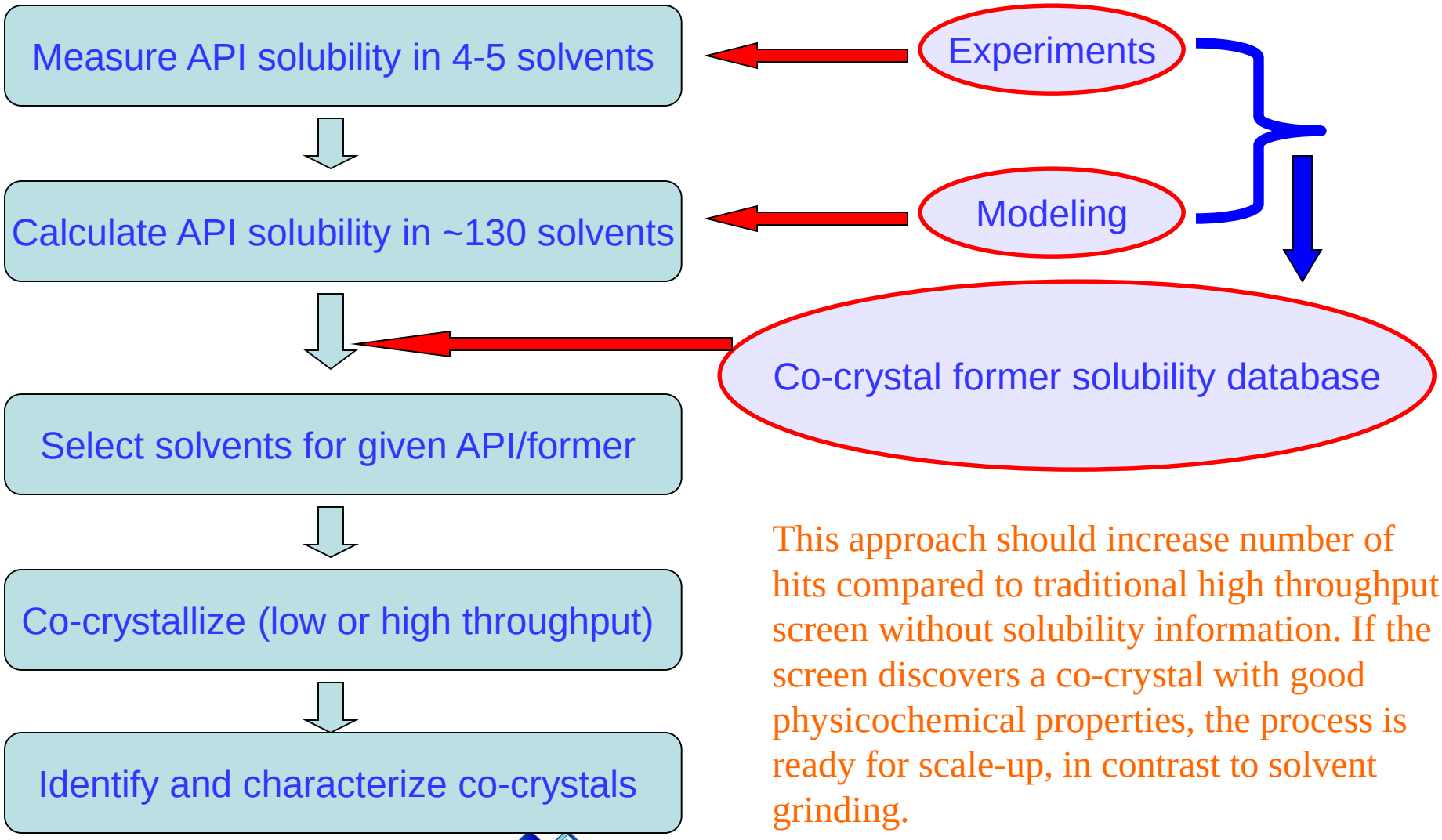
案例分析：Co-Crystal of Trans-Cinnamic Acid and Nicotinamide*



- Slurrying 1:1 mixture of C and N in water resulted in pure C

*R., A. Chiarella, et al, CG&D, 2007, 7 (1223)

晶云：优化的共晶筛选实验设计



This approach should increase number of hits compared to traditional high throughput screen without solubility information. If the screen discovers a co-crystal with good physicochemical properties, the process is ready for scale-up, in contrast to solvent grinding.

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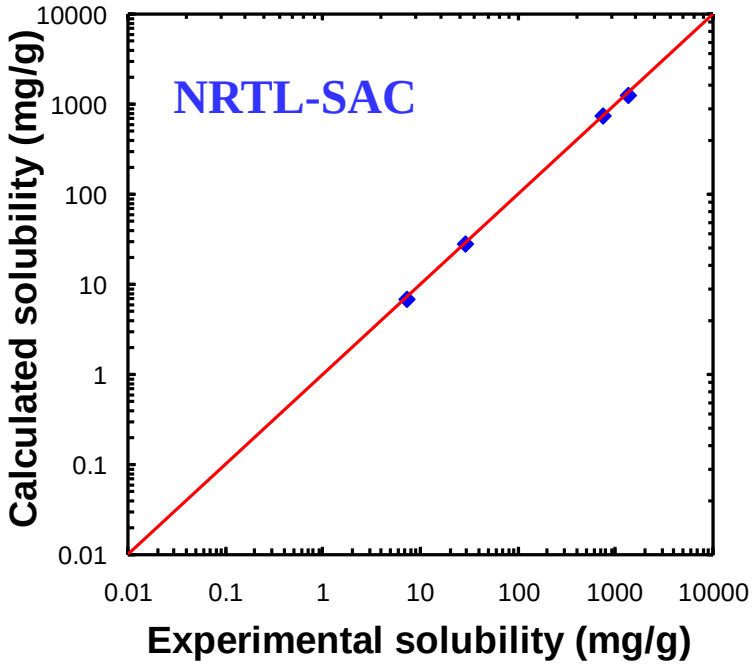
溶解度：实验测量和模型计算

Solvent	Solubility (exp) (mg/g)	Solubility (calculated) (mg/g)
H2O	1330	1279
MeCN	28.1	28.11
IPAc	7.016	7.016
MeOH	720.	742.4



Solubility of co-crystal formers in 4-5 solvents was measured. Solubility in other solvents was then calculated from NRTL-SAC model with ASPEN software. Values given are for L-Tartaric Acid.

总结

- 利用共晶来改善药物分子的理化性质是一种新的有效途径，共晶筛选正逐渐成为大制药公司晶型研究中的一个必要课题
- 通过共晶筛选，得到新的药物晶型，是仿制药公司规避创新药公司晶型专利的一种有力手段
- 共晶的筛选策略不同于盐类晶型的筛选，需要充分理解共晶形成的热力学和动力学，合理设计实验
- 三相图是指导共晶筛选和工艺放大的很好的工具

谢谢大家！