Investigation of Solid-state Stability of a Co-crystal API in Formulation Development by XRPD and ss-NMR Spectroscopy

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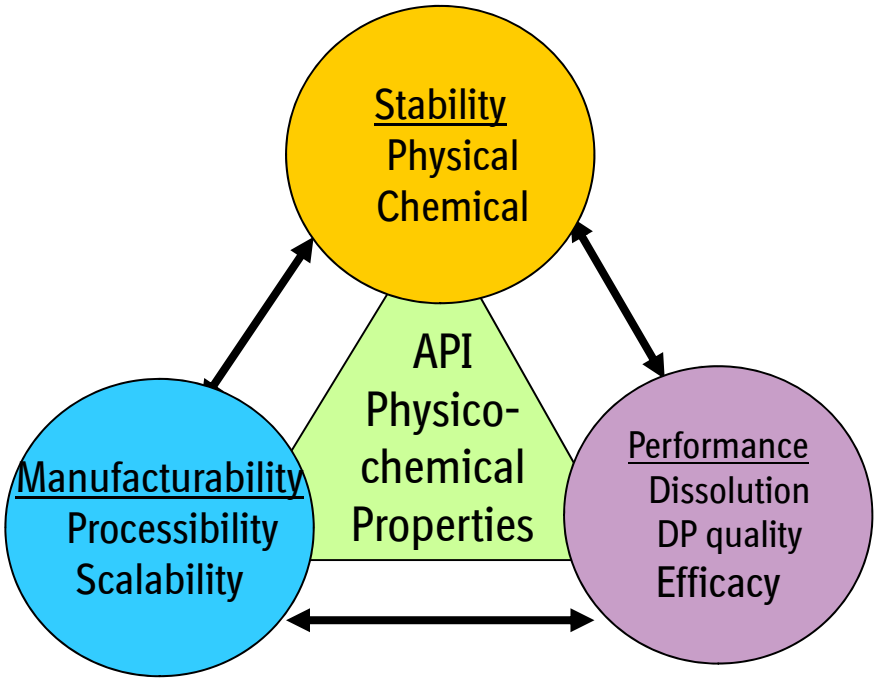
Outline

- Introduction
  - Multi-component API
  - Solubility behavior
- Formulation development of a cocrystal API
  - Cocrystal API – physicochemical properties
  - Initial formulation development
  - Stability investigation
  - New formulation effort
- Summary

Enhancing Drug Product Developability

- In recent years, majority of drug candidates have poor solubility and slow dissolution – BCS class II or IV
- Solubility and dissolution limited exposure imposes significant challenge in achieving clinical efficacy – undesired physicochemical properties
- Pressing needs to improve the efficiency of drug delivery, time and speed
- Most cost-effective and time-saving approach is to modify the API physicochemical properties – salt/cocrystal



Co-crystallization

$mD + nX \rightleftharpoons mD^{a+} \cdot nX^{b-}$

m, n = 0; *a, b* = 0, fraction or integers (neutral or weak acid/base)

A salt or a cocrystal contains two or more components

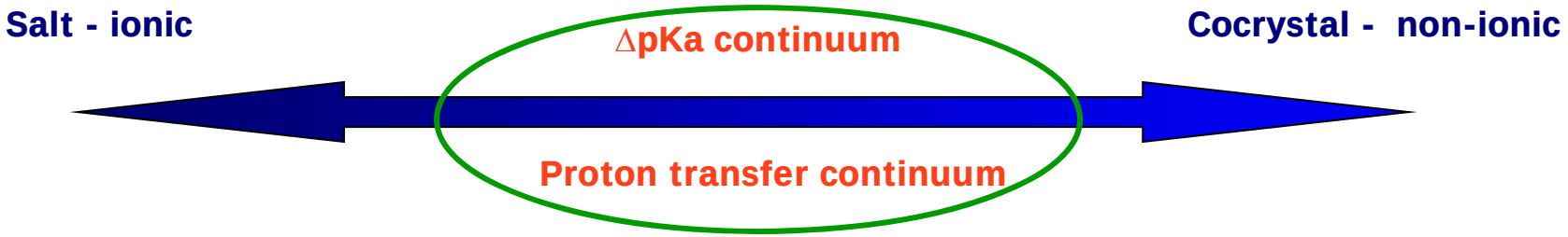
Association by <u>intermolecular</u> interactions

Salt - ions Stronger, direct

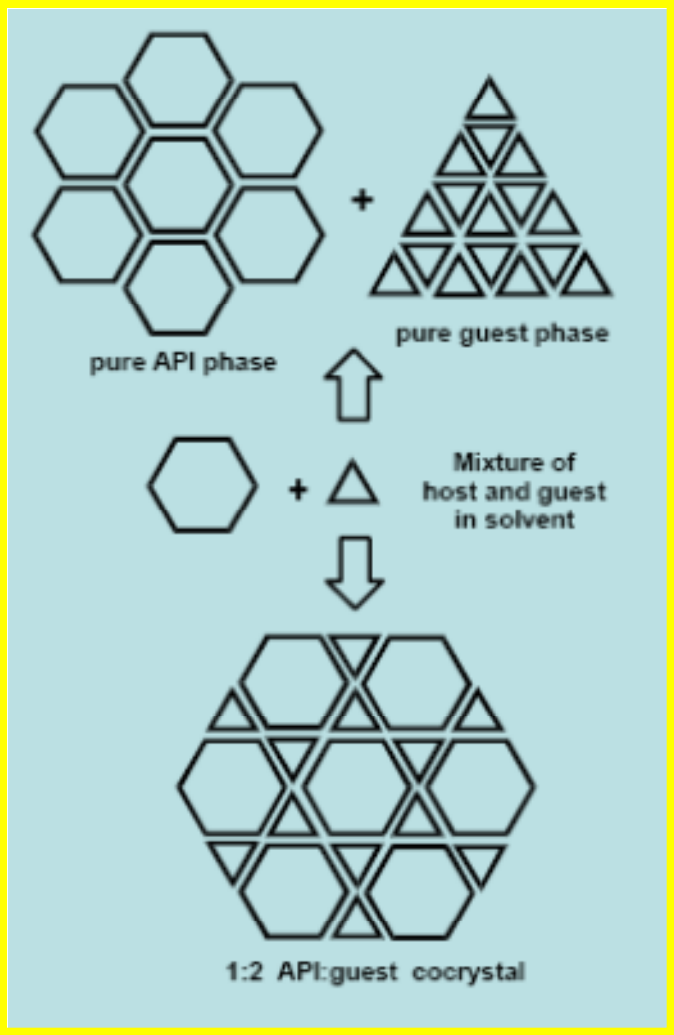
Cocrystals - hydrogen bonding, or VdW interaction

Mixed – ionic and hydrogen bonding or partial proton transfer

} Weaker Multiple



Advantage of Multi-component API



C. Aakeroy, KSU, 2009

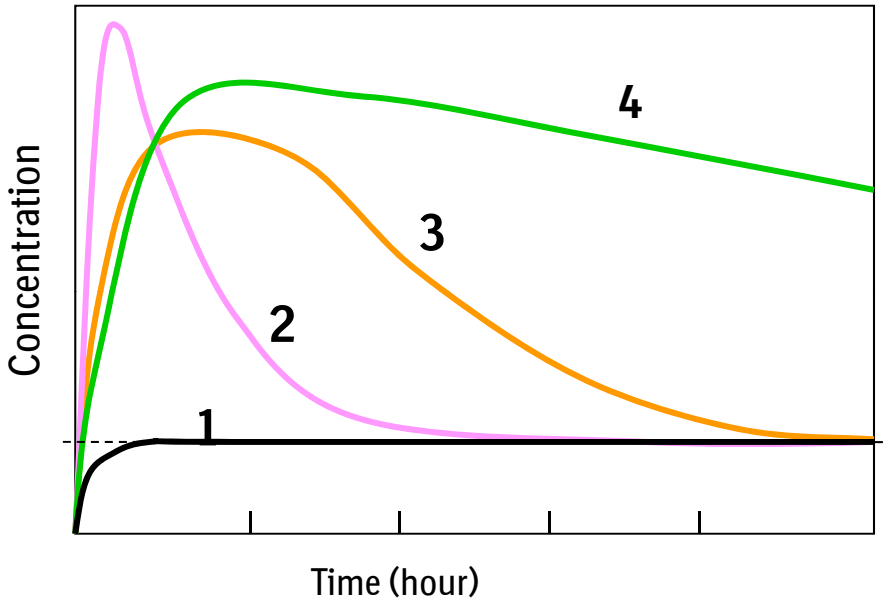
Discovery safe and effective crystalline API without making/breaking covalent bonds.....

Multi-component APIs allow tuning the properties of drug substances to optimize developability of NCEs

- **Soluble guest molecule**
- **Modify intermolecular interactions and packing**

Limitations = Considerations

Solubility Behavior of Multi-component API



- 1 is the free form
- Salts or cocrystals, 2 ,3, 4, can provide higher dissolution
- Precipitation rate varies depending on many factors and may be controlled by selection of API or excipients

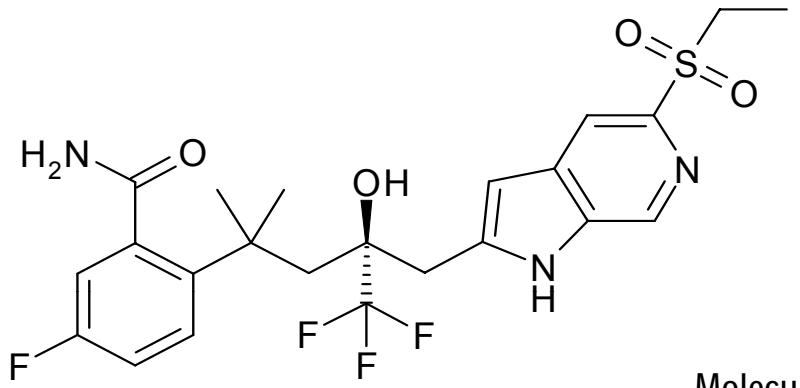
Factors:

- pH
- Particle size
- Additives –surfactant, polymer
- Impurity
- Solvent composition
- Concentration
- Temperature
- Phase transformation
- Fluid dynamics –stirring
- Apparatus

Kinetic solubility ⟷ Equilibrium solubility

complementary

Formulation Development of Cocrystal API



Molecular Weight = 515.53
Molecular Formula = $C_{23}H_{25}F_4N_3O_4S$

- Compound X is a weak base with a pKa of ~3.9 initially by titration, possible for salts
- Projected high dose - 400 mg QD and low intrinsic solubility – S_0 ~4 μg/mL, predicted a solubility limited absorption

Solid Form Selection

- Six crystalline 'salts' of compound X were isolated at the candidate nomination stage, only two were scalable, Salt 2 and Salt 3
- **Phosphate salt** showed the most favorable physicochemical profile
  - Salt 2 is high melting, non-hygroscopic
  - Apparent solubility increased 50 fold compare to the FB
  - Bioavailability in rat showed a 4-fold improvement with suspension dosing
  - Dose was reduced by 10 fold
  - Physical and chemical stabilities were acceptable
- The pKa of the parent compound was found to be 1.8
- The single crystal structure of the phosphate salt revealed no proton transfer between the acid and the parent compound, thus, it is classified as a cocrystal

Comparison of Free Form and Cocrystal

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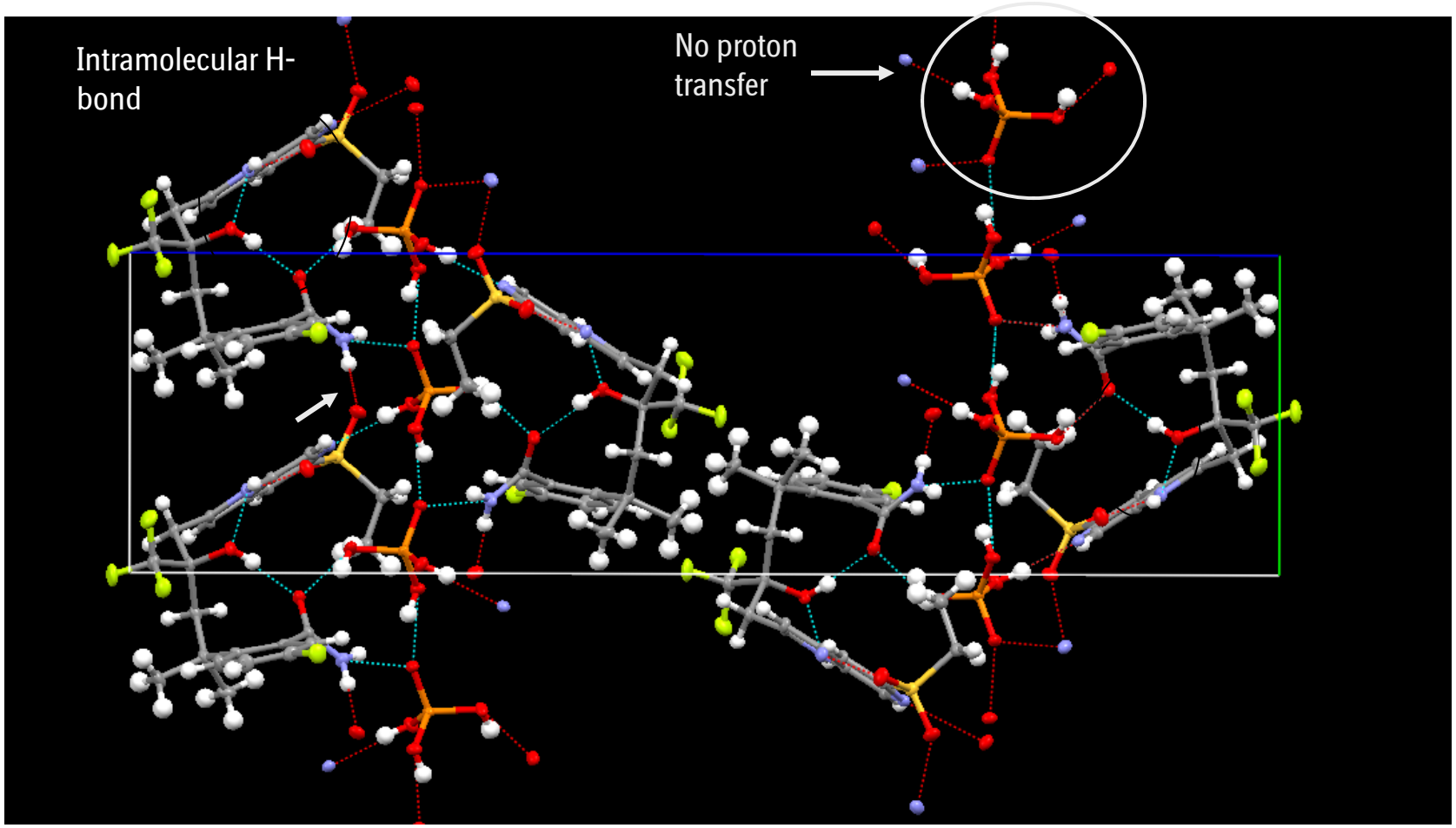
Parameter	BS	PH
Aqueous Solubility (µg/mL)	(24 hr) $pH_{2.0}$ 7.2 $pH_{4.5}$ 4.4 $pH_{6.8}$ 4.1	(2, 24 hours) $pH_{2.0}$ **82, 22** $pH_{4.5}$ **130, 12** $pH_{6.8}$ **85, 10**
Projected Human Dose (Allometry)	980 - 1300 mg/day	155 - 390 mg / day (Phosphate)
Dose Number	1000 – 1300, BCS II	150 - 380 (using S_0) BCS II 8- 20 (using S_{2hr})
Crystallinity	Crystalline	Crystalline
Thermal Behaviour	Melting Point (onset) = 226°C Heat of Fusion = 100 J/g Loss on Heating = 0.7%	Melting Point (onset) = 203°C Heat of Fusion = 92 J/g Loss on Heating = 0.4%
Early Polymorph Screen	Moderate Tendency	No Indication to date
Hygroscopicity, 80% RH	+ 0.2 %	+ 0.8 %
Bioavailability	Mouse (Suspension) = 41% Rat (Suspension) = 10% Dog (Suspension) = 5% Cyno (Suspension) = 4%	Rat (Suspension) = 36 - 42%

Cocrystal API of drug and PH enabled the candidate nomination

Crystal Structure of the Cocrystal



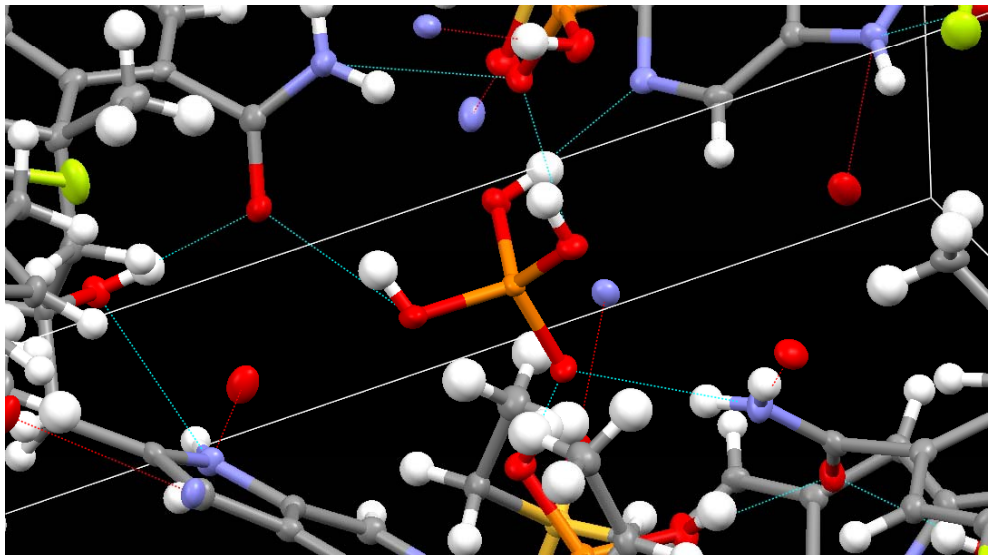
Space group: $P2_12_12_1$
Cell dimention:8.33, 9.35, 33.52

R1 = 0.0343

Data by H. Nar

Crystal Structure of the Cocrystal

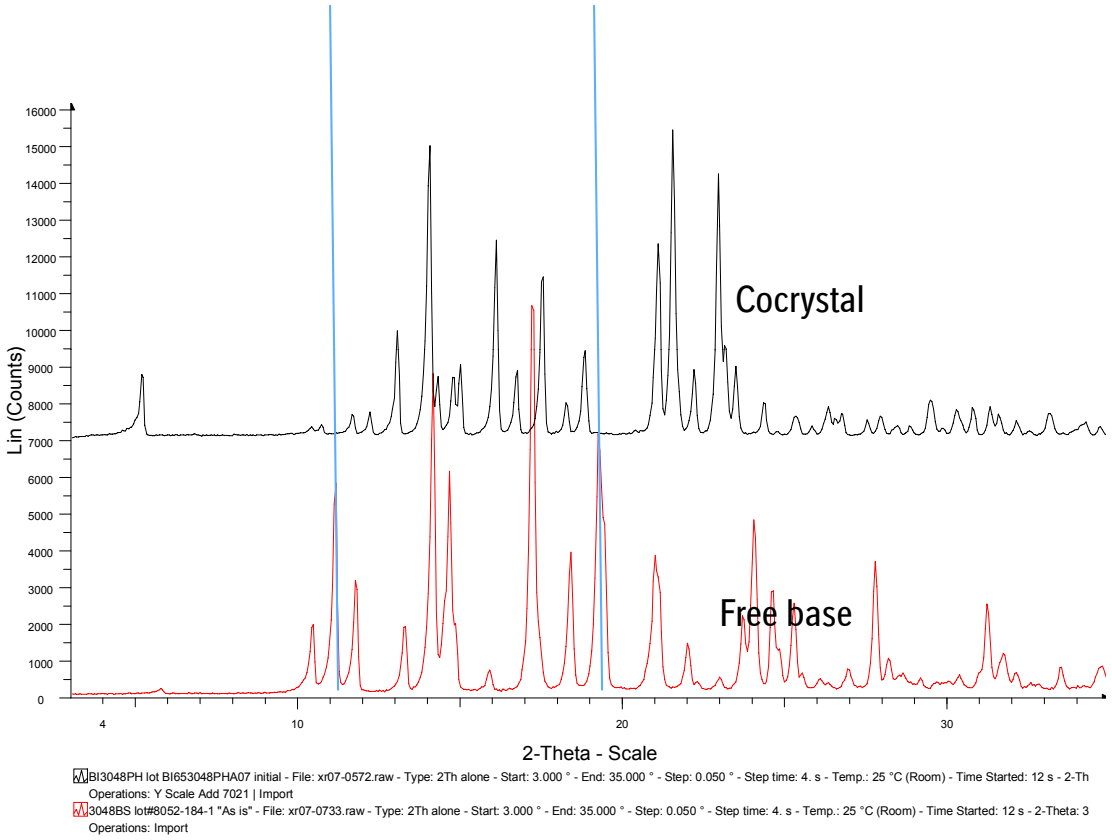
- The drug molecule has 4 H-bond donors and 4 H-bond acceptors
- Phosphoric acid contains 3 H-bond donors and 4 H-bond acceptors

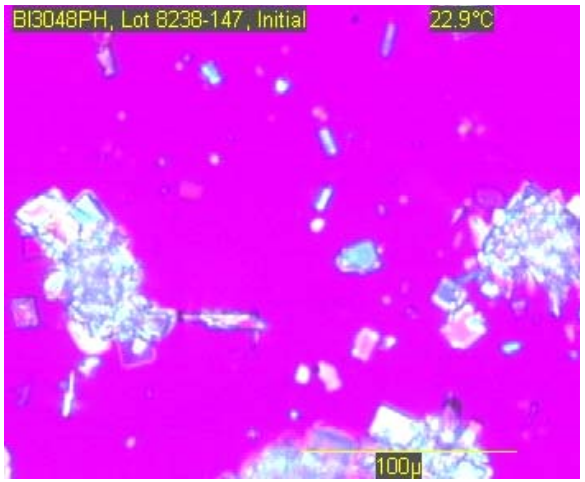


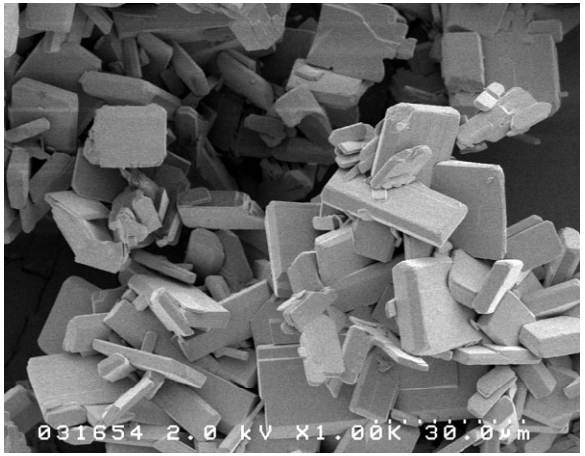
Cocrystal structure

- No proton transfer from the acid to the drug molecule
- The acid forms a chain along the c axis
- 2 intra-molecular H-bonds; 9 inter-molecular H-bonds

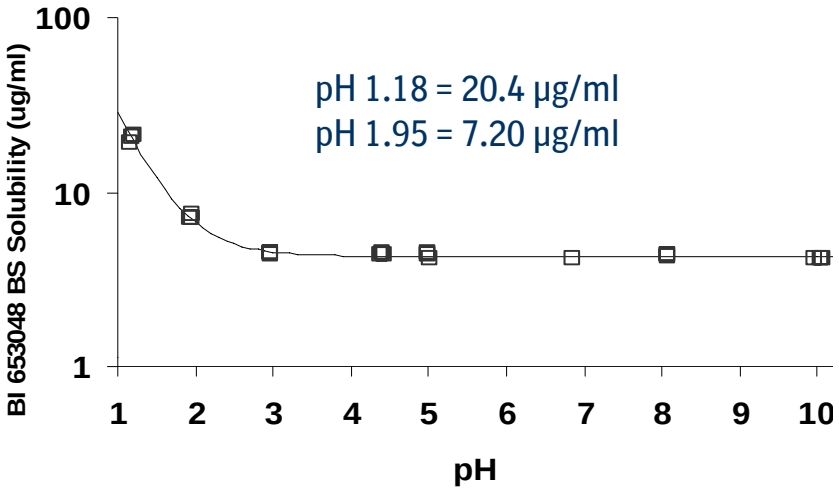
Crystallinity and Morphology



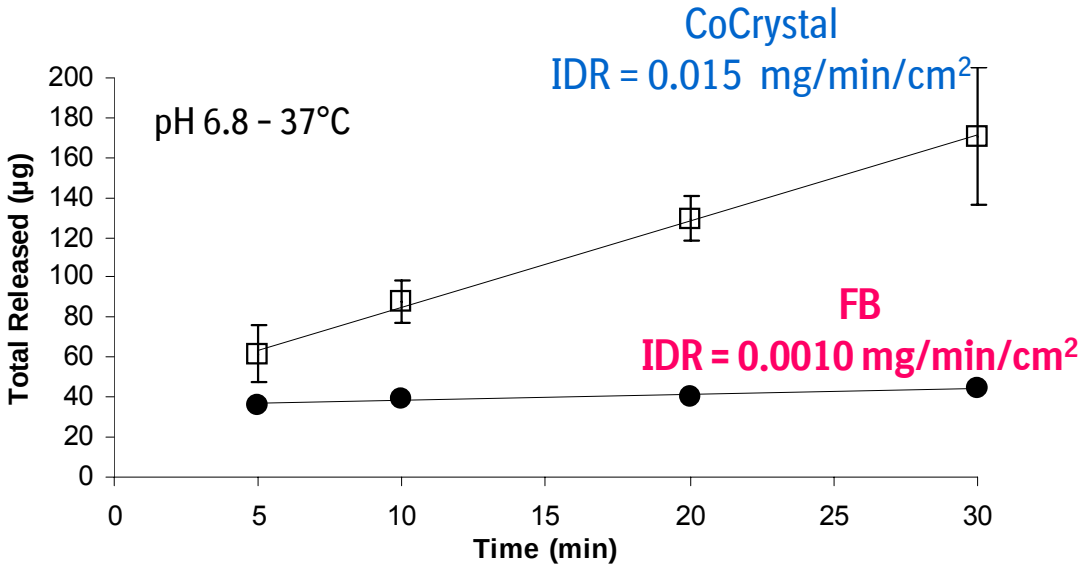




Solubility and Dissolution



Free base -
Low solubility

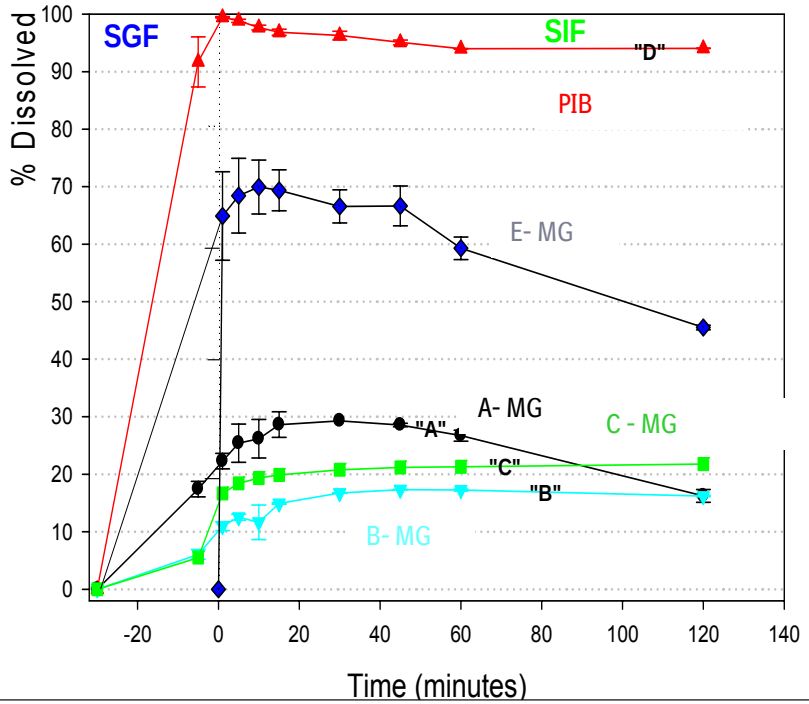


Phosphate is 15x faster than BS but relatively low, therefore may be still dissolution limited

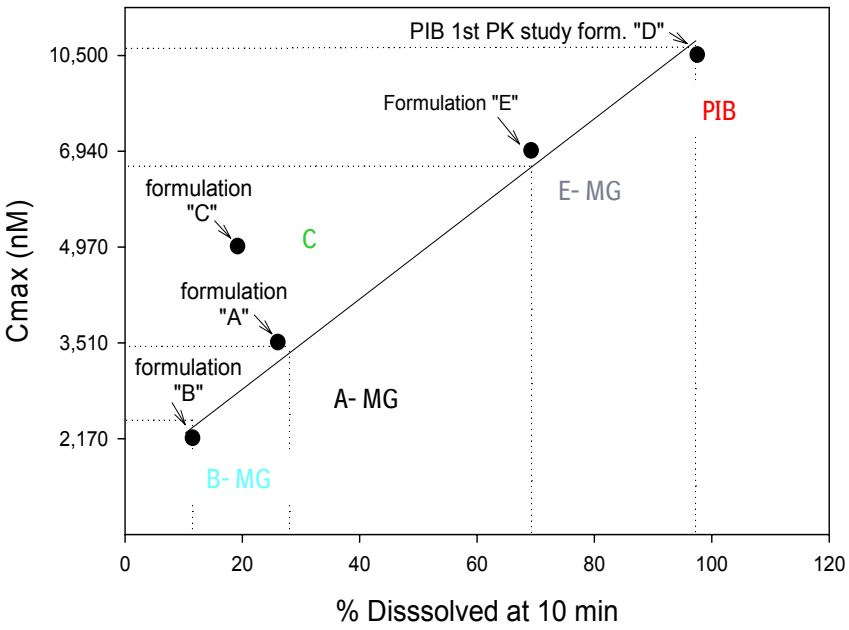
In-Vitro and *In-Vivo* Correlation

Dissolution of capsules filled with melt granules

(two-step dissolution, 100 mL SGF for 30 min. and 400 mL SIF for 60 min. paddle 50 rpm and then 250 rpm for 60 min at T=90 n



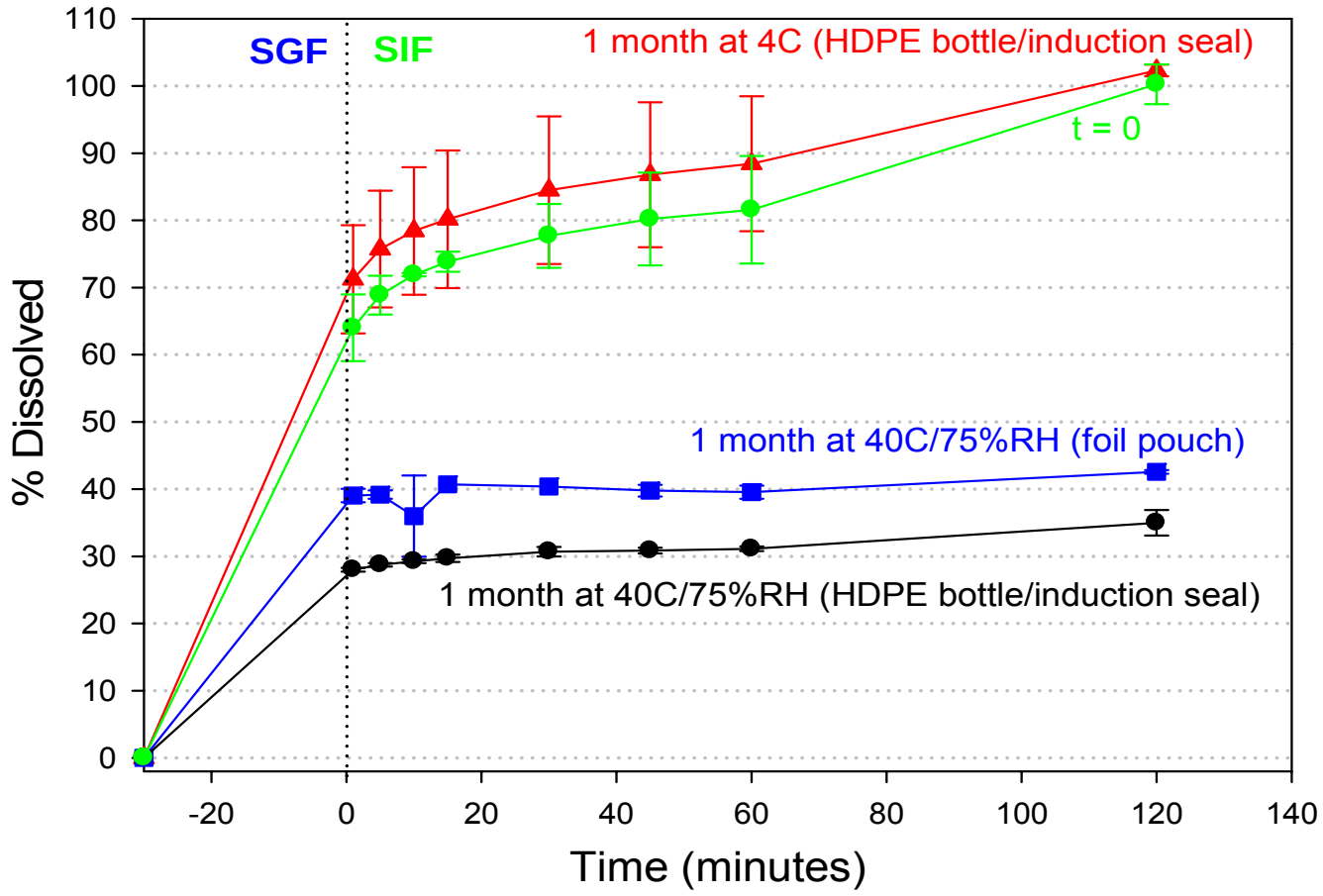
In vitro and in vivo correlation



Formulations “A”, “B”, “D” and “E” provide a good *in-vitro* and *in-vivo* correlation with Cmax and AUC

Formulation E is selected for capsule formulation

Dissolution Profile of Stability Samples (Capsules)



capsules, 1 M at 4C, HDPE bottle, XP8954
capsules, 1 M at 40C/75%RH, foil pouch, XI
capsules, 1 M at 40C/75%RH, HDPE bottle,
capsules, t=0, 8954-188 (n=2)

Capsule filled with melt granules

Cocrystal as DS is stable up to 40°C

Cocrystal in capsules is stable at 4°C

Cocrystal in capsules is not stable

Capsule Stability – Mapping Solid Form Conversion

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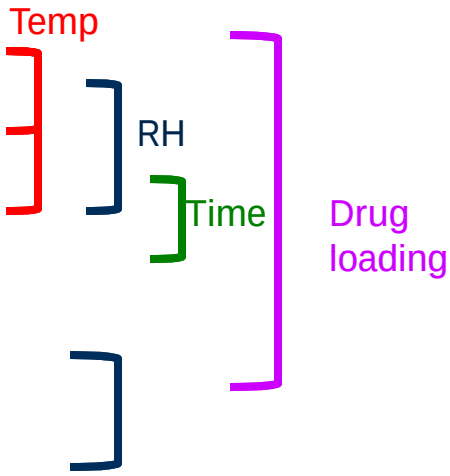
25 mg Capsules

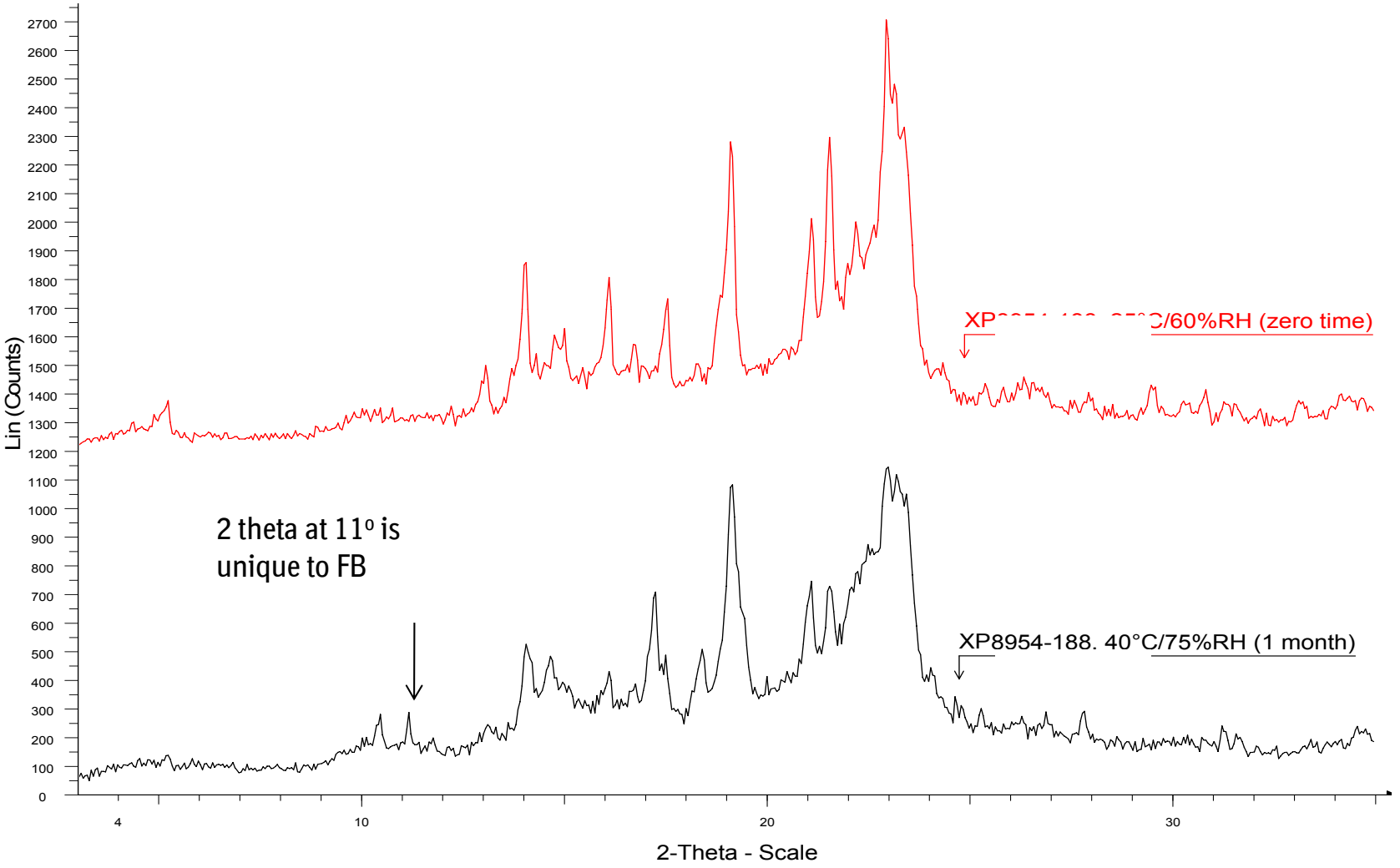
75 mg Capsules

Storage condition	API phase
2 M @ 25°C/60% RH	CC + FB
2 M @ 40°C/60% RH	FB
2 M @ 4°C	CC
4 M @ 4°C	CC + New
4 M @ -20°C	CC
2 M @ 25°C/60% RH	CC + New
2 M @ 4°C	CC



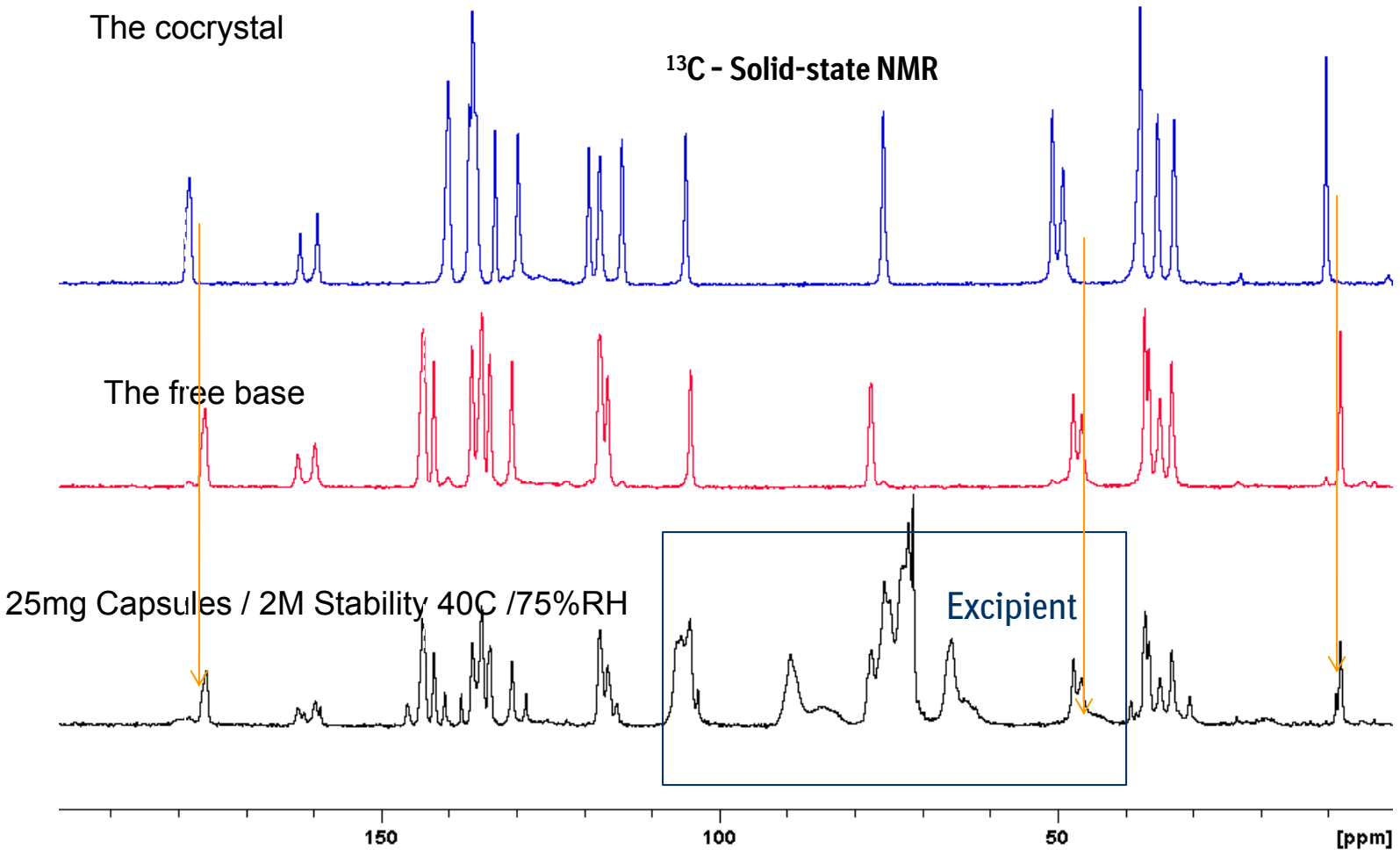
- Three solid phases of the drug in capsules – CC, FB and an unknown (New)
- Temperature, relative humidity and time affected the rate of conversion
- 25 mg capsules showed faster rate of conversion, which were filled with same melt granules as 75mg but had larger head-space (moisture)

XRPD Patterns of Granules in Capsules



It appears that cocrystal is converted to free base after storing 1month at 40°C/75%RH.

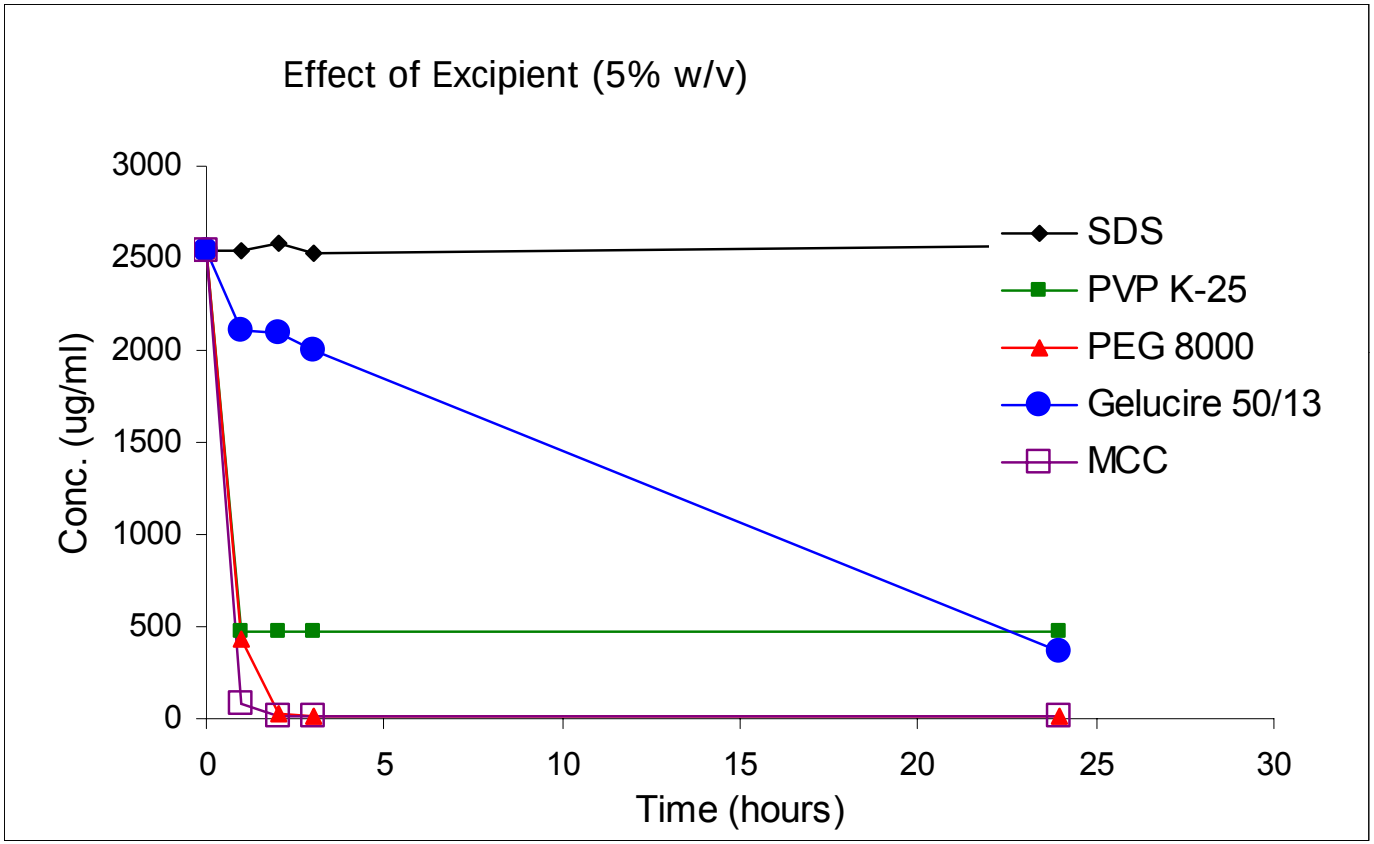
Phase Conversion in Formulation by ^{13}C ss-NMR



- Dissolution due to conversion from cocrystal to freebase

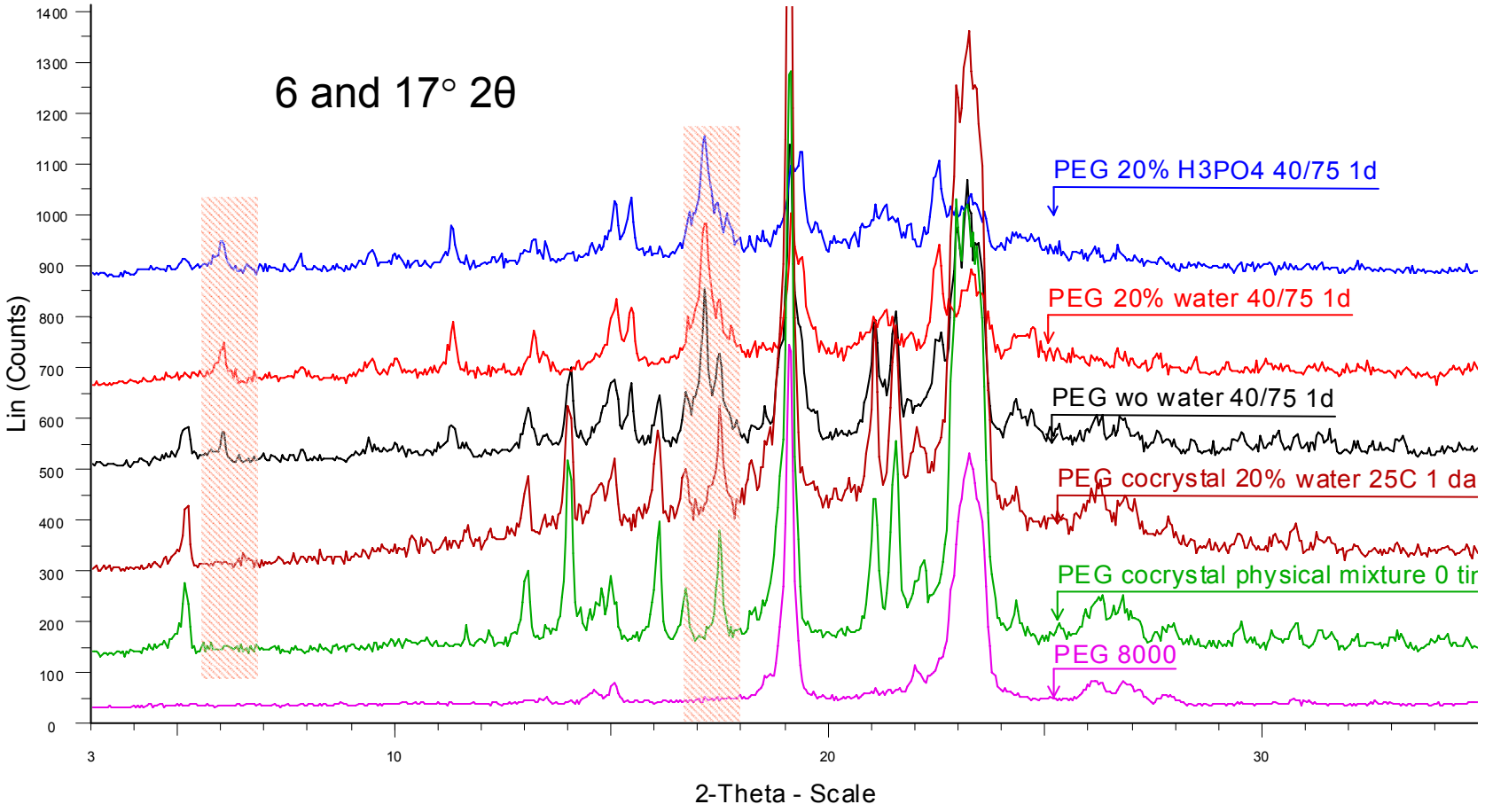
In some samples, a new phase was detected

Excipients - Maintaining Supersaturation



- PEG 8000 (used in capsule formulation) and MCC cannot maintain supersaturation
- SDS is most effective in maintaining supersaturation
- The precipitate from PEG 8000 is the phase identified in ss-NMR in capsules

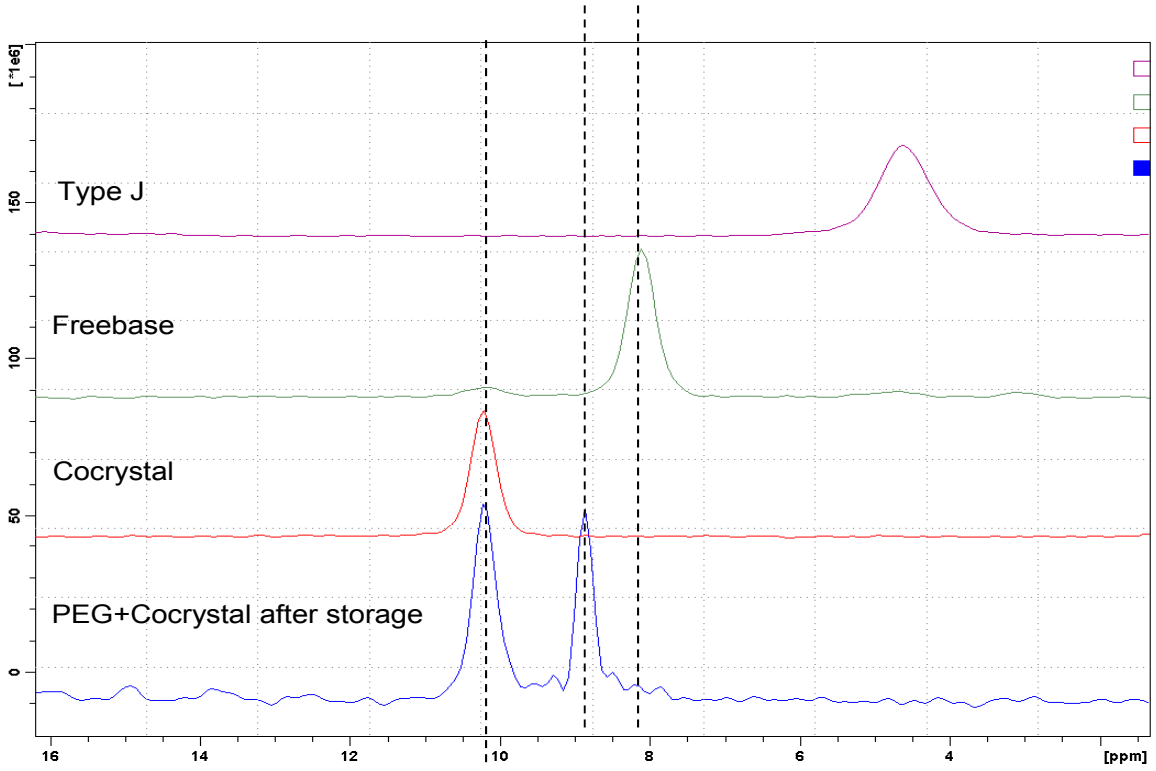
XRPD - Cocrystal and PEG 8000



New phase was confirmed by ^{13}C SS-NMR

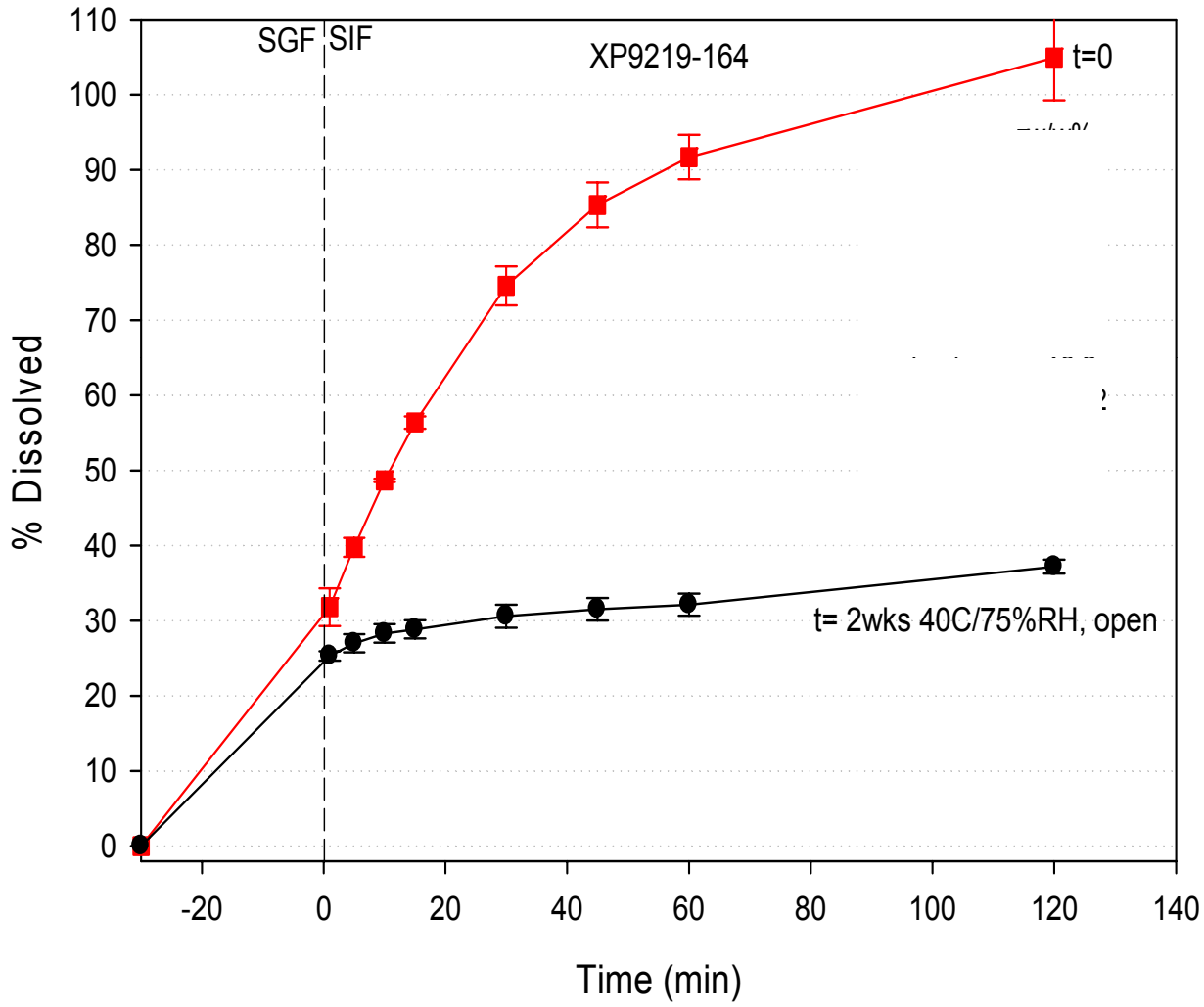
Excipients containing PEG chain also facilitated the conversion

^{13}C ss-NMR - Cocrystal and PEG 8000



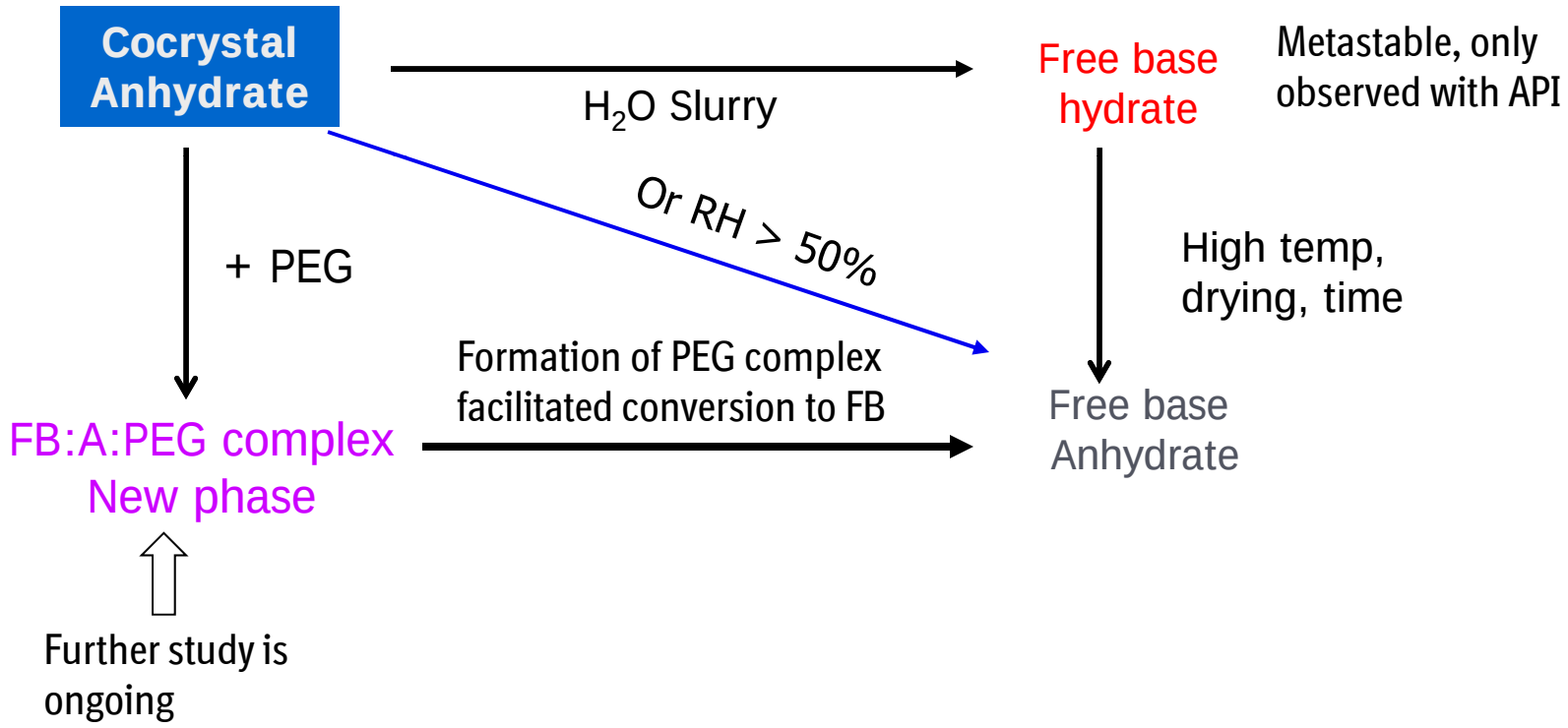
^{13}C SS-NMR spectrum of the mixture of PEG 8000 and CC after storage at 40°C/75% RH for one day

Dissolution of Wet Granulation



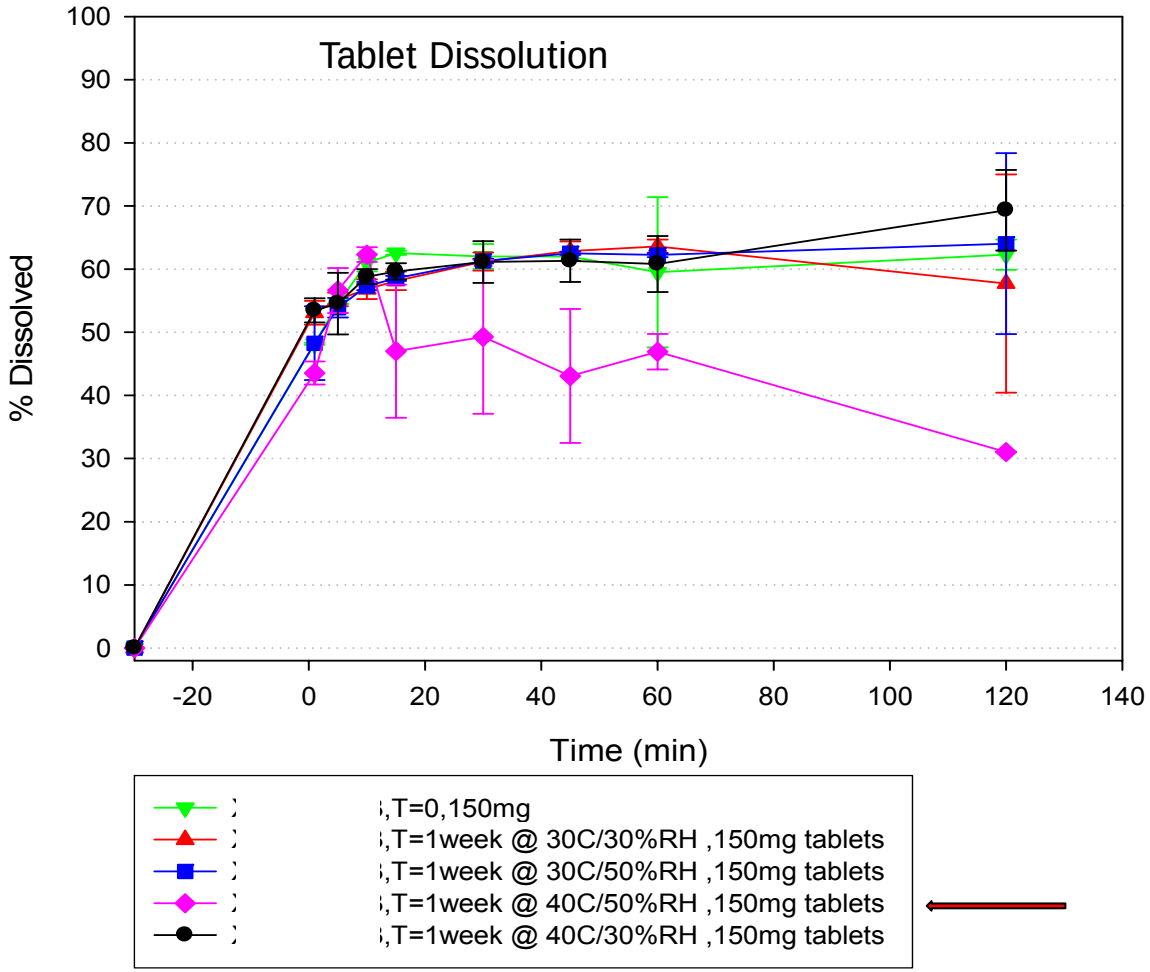
Wet granulation with PEG 8000 shows a significant drop on dissolution at 40°C/75%RH for 2 wks, open

Solid Form Conversion – Map and Kinetics



Storage Condition – Moisture Effect

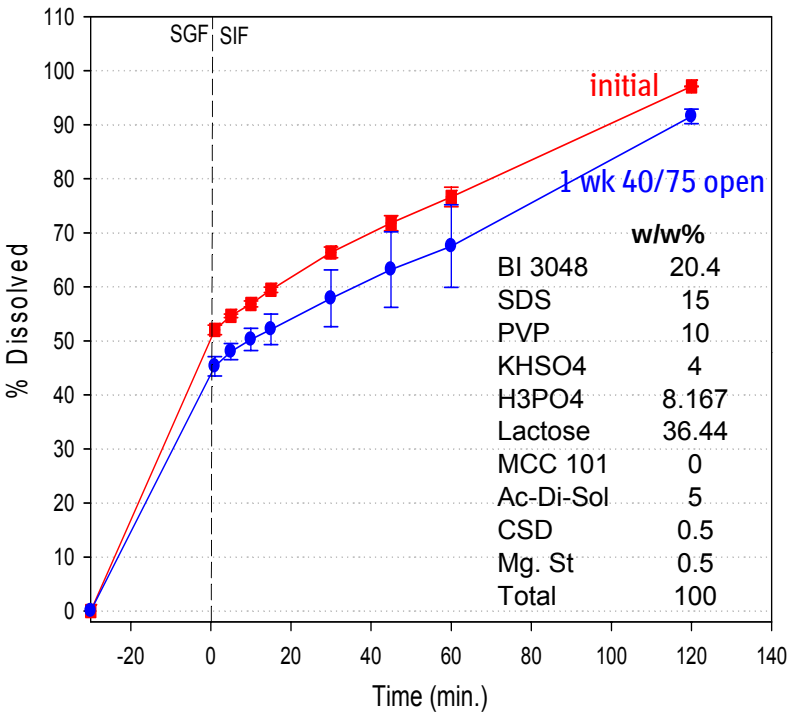
Four tablet formulations were developed, using a combination of solubilizer and precipitation inhibitor.

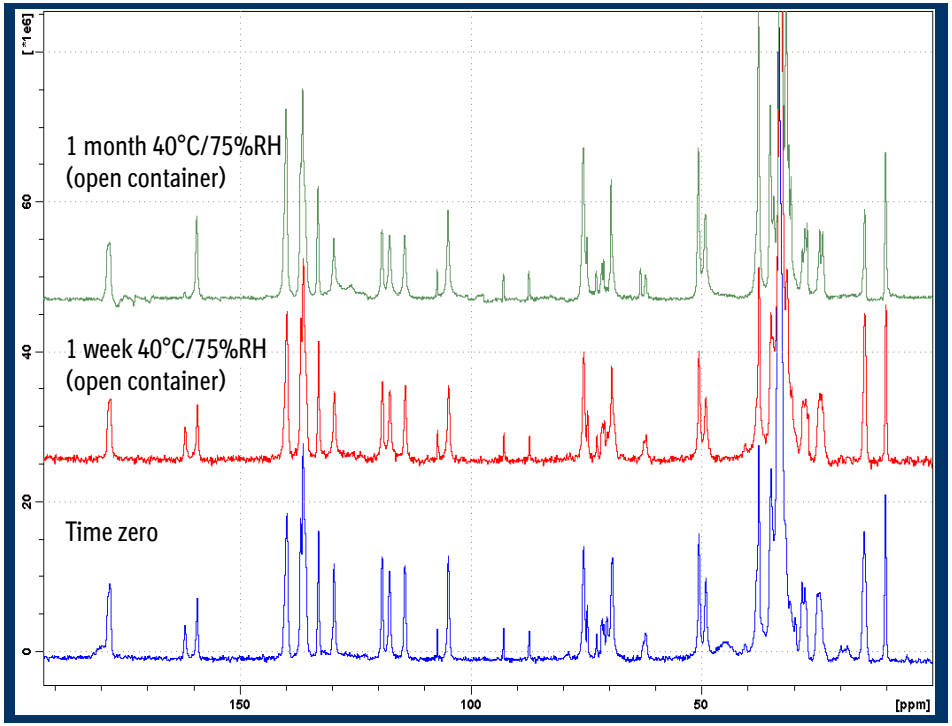


- Decrease in dissolution rate @ 50% RH (40°C)
- No change @ 30% RH (40°C)

Moisture induced phase transition – minimizing moisture exposure by packaging with desiccant

Tablet Stability - Confirmation





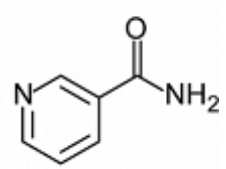
After stored at 40°C/75%RH for1 month in open container, the wet granulation using a H3PO4 solution as a granulation agent is still a co-crystal which is confirmed by SSNMR

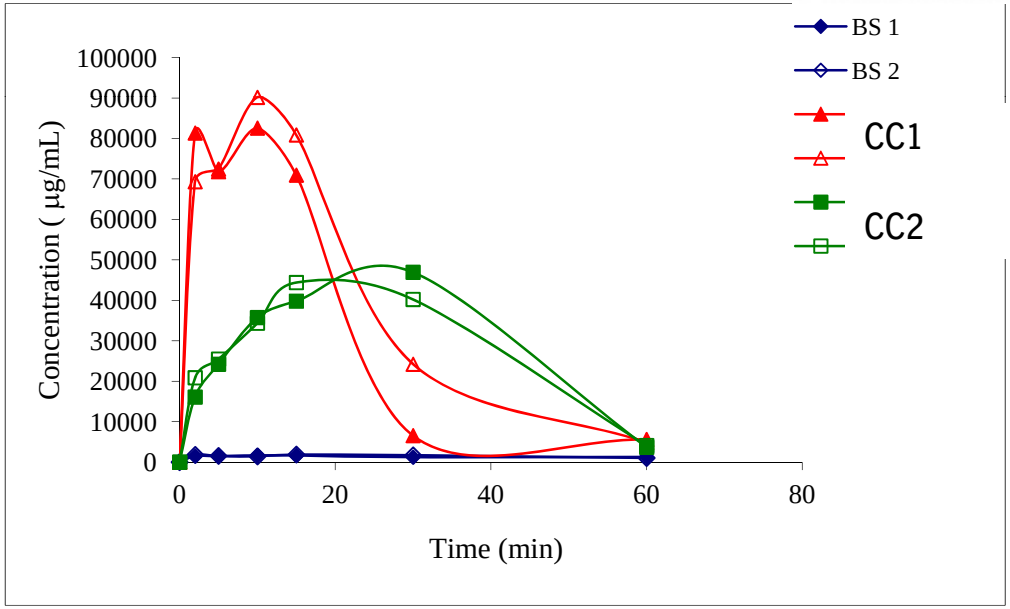
Cocrystal options

Boehringer Ingelheim

Melting temp (C)	
Free base :	224
PH CC1:	203
NCTA CC2 :	191

Nicotinaminde





Formation of cocrystals can modify physicochemical properties of the API which may offer alternative delivery profile

Summary - Cocrystal API

- The cocrystal of API improved dissolution rate significantly and enabled candidate nomination
- The cocrystal API showed excellent solid-state stability as API
- In an early formulation, a significant drop in dissolution was observed and attributed to the API phase conversion to the free base identified by XRPD and ss-NMR
- The conversion were induced by excipients – PEG, and a combination of high humidity and high temperature
- Judicious selection of excipients and storage conditions prevented phase conversion and a stable tablet formulation was developed
- A combination of XRD and solid-state NMR techniques provided solid-state characterization in formulation

Acknowledgments

Cocrystal selection and preparation

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Formulation development

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Crystal structure

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