research center pharmaceutical engineering

Science of Stability 2017
3rd -5th October 2017, Dublin

We make tomorrow's drugs possible.

Drug–excipient interactions in the solid state:
The role of different stress factors

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K1 Competence Center - Initiated by the Federal Ministry of Transport, Innovation and Technology (BMVIT) and the Federal Ministry of Science, Research and Economy (BMWFW).
Funded by the Austrian Research Promotion Agency (FFG), Land Steiermark and the Styrian Business Promotion Agency (SFG).

Background and Introduction

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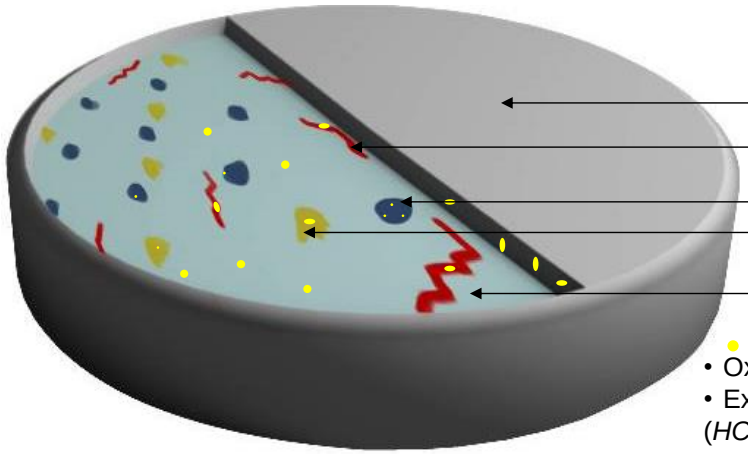
Conventional approaches and relevance

Forced degradation in solution

Relationship ??

Link ??

Drug-degradation/ excipient interaction in powders (T, %RH)



Final product (formulation, packaging)

Can we predict drug degradation chemistry?

- Knowledge based expert systems:

  Zeneth, Delphi, CAMEO, Reactionpredictor

- Databases (algorithms, statistics)

ACD Labs, Marvin (ChemAxon)..

DRUG DEGRADATION DATABASE

- Ab initio (quantum chemistry)

Fukui functions, BDE, Charges (HSAB), NMR shifts…

Latest News
Web Date: March 4, 2015

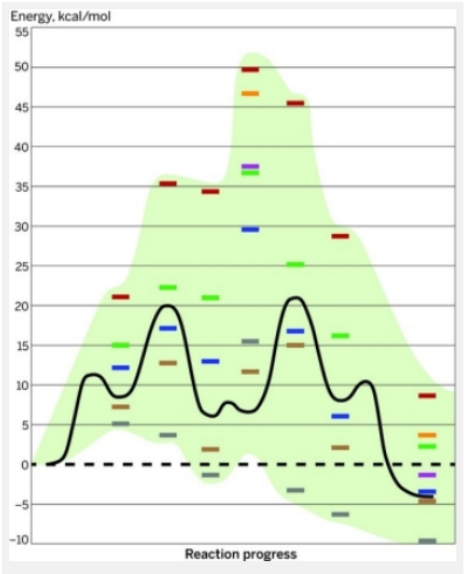
c&en CHEMICAL & ENGINEERING NEWS

Computational Models Of Multistep Reaction Are Called So Flawed They Are 'Not Even Wrong'

Reaction Chemistry: Study reveals mechanism theoretical work didn't predict

*By **Stuart A. Borman***

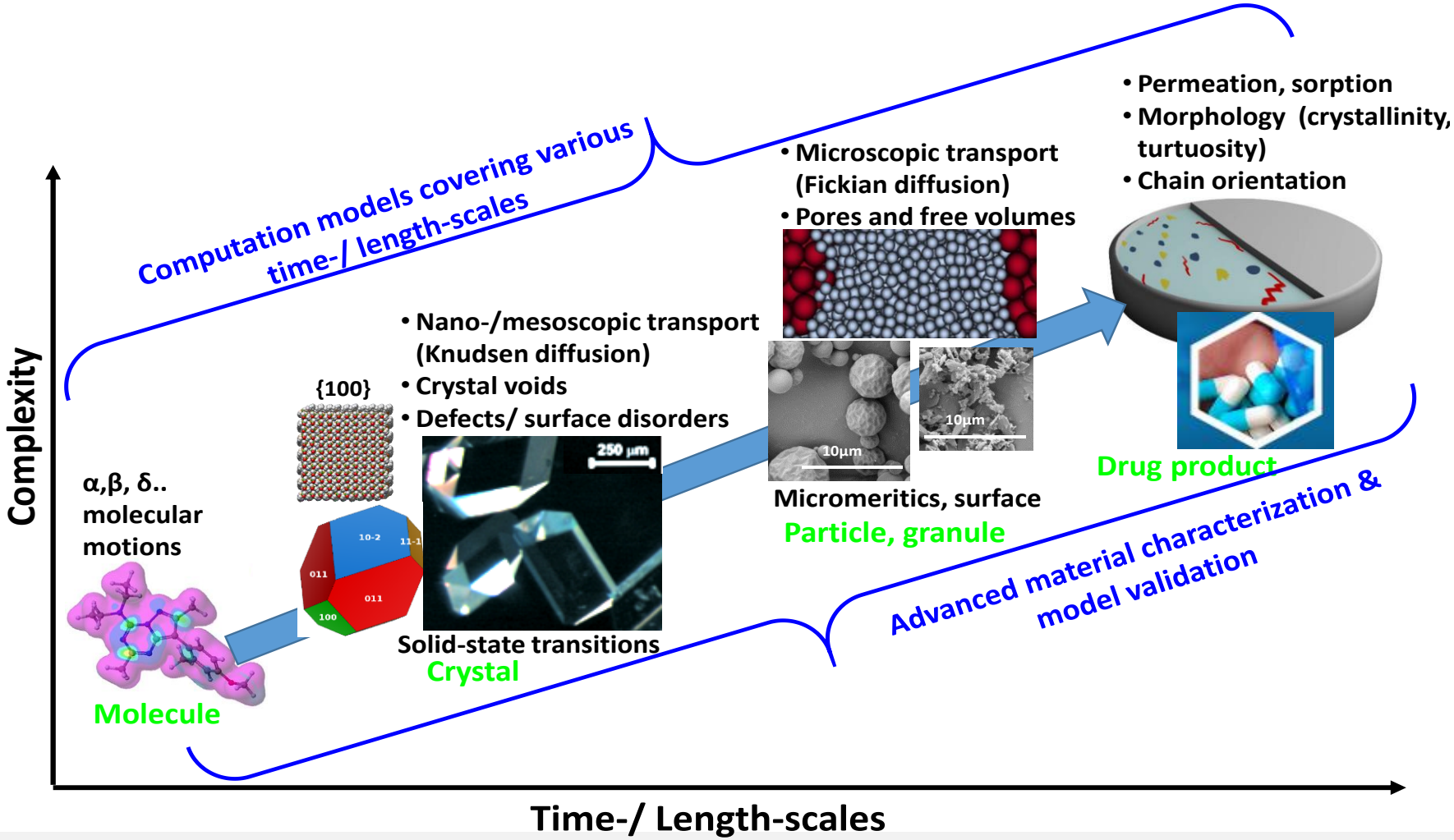
[+]Enlarge



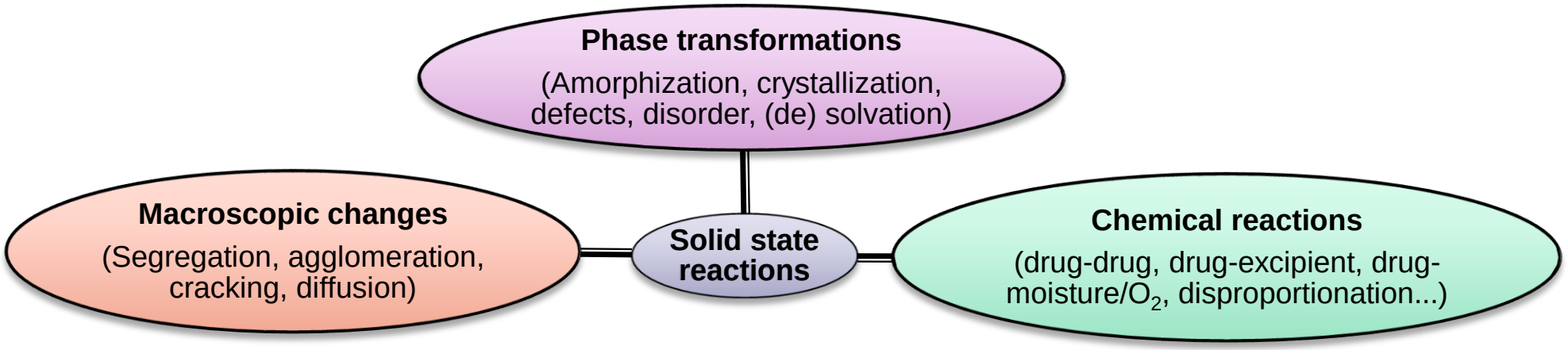
Chemists often use computational methods to predict reaction pathways and energies, but some researchers question their usefulness because the models sometimes produce highly variable, head-scratching results. Now, a detailed case study of a multistep organic reaction attacks the utility of computer modeling of that reaction in an unusually blunt way.

The authors conclude that the reaction mechanism is a simple one that undergraduates could guess and that a complex mechanism predicted by years of computational studies is "not even wrong"—so flawed and off-base that calling it incorrect is too kind.

Solid-state degradation: somewhere within microstructural hierarchy



Solid-state degradation: competing with physical transitions



Induction & growth (challenging theoretically / experimentally)

SbD approach: From Trial and Error to QbD

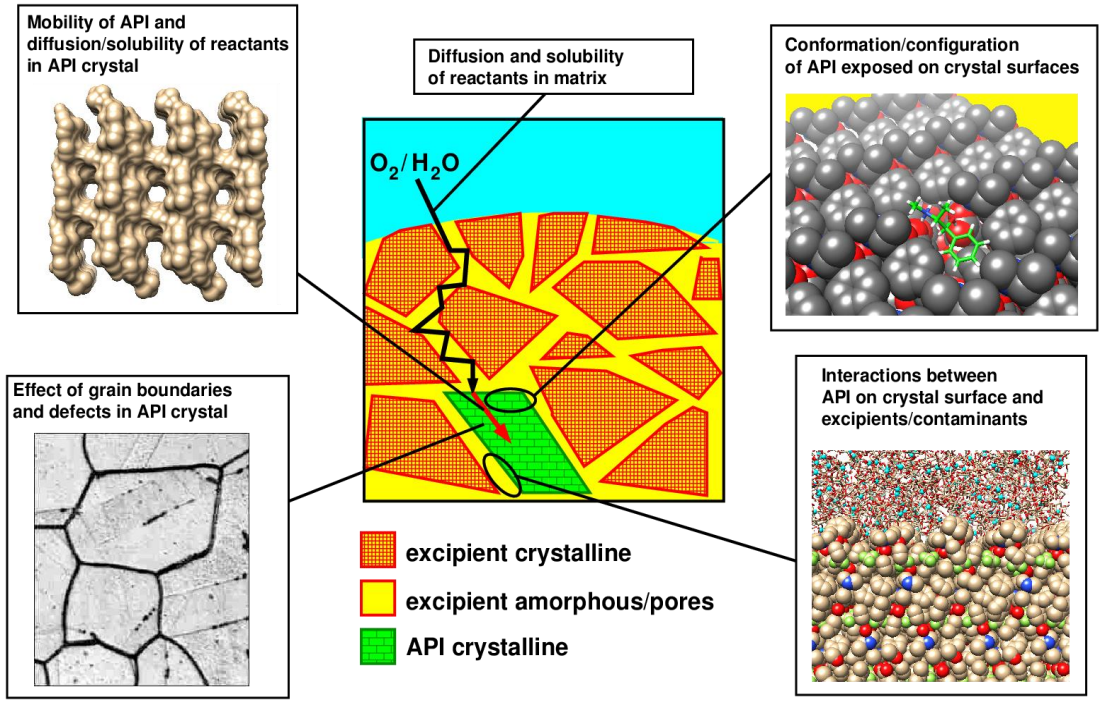
Use theoretical models/ simulation & experimentals to understand relevant factors

For a given API, can we flag/identify from first principles (*in-silico*)

likely chemical instability in given solid formulations?

Structure of the Project

- API crystal, reactions with excipients (solid-solid)
- API crystal, reactions with impurities/H_2O (solid-gas/ vapour)
- Impact of disorder/ amorphous content in API crystals
- Reactants diffusion through excipient and API crystals (pores)



API crystal, reactions with excipients

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API crystal, reactions with excipients (solid-solid)

- Particulate properties (size, shape, surface areas)
- Moisture/ humidity
- Temperature

Reaction takes place on crystal surface (via surface detachment)

Molecular loosening at reaction site

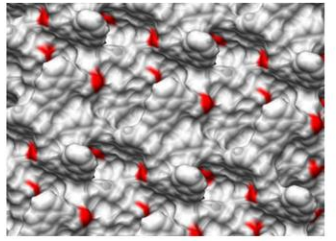
Bond breakage/formation

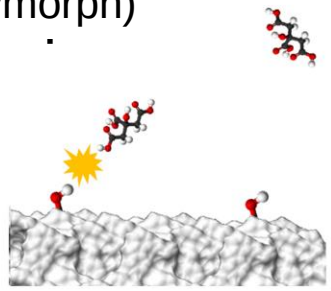
Amorphous and/or crystalline solid solution of reactant & product

Spinodal (product) phase separation (nucleation, growth)

Paul & Curtin, Acc Chem Res 1973

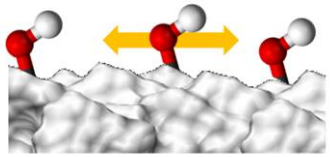
Crystal surface structure (API chemistry, polymorph)

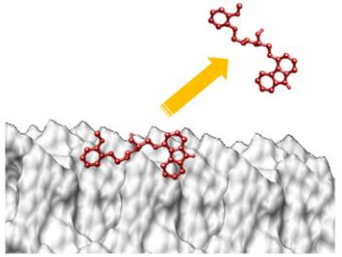




ERSA: The exposed reactive surface area

nCE: The number of close encounters between API & CA reactive parts





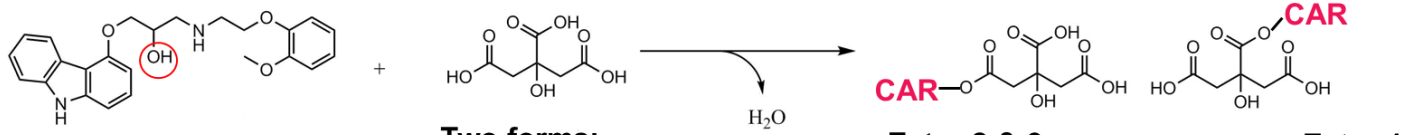
RMSF: Relaxation & vibrational amplitude of surface molecules

E_{bind}: Binding energies of surface molecules

API crystal, reactions with excipients (solid-solid)

Solid-state esterification of APIs with citric acid (CA)

Carvedilol (CAR)

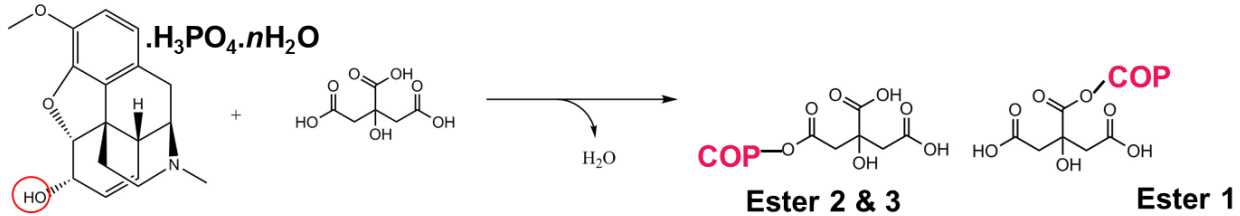


Two anhyd. forms:
form II, form III (stable form)

Two forms:
Anhydrous (CA-A),
Monohydrate (CA-M)

Larsen et al. J Pharm Biomed Anal (2009)

Codeine phosphate (COP)



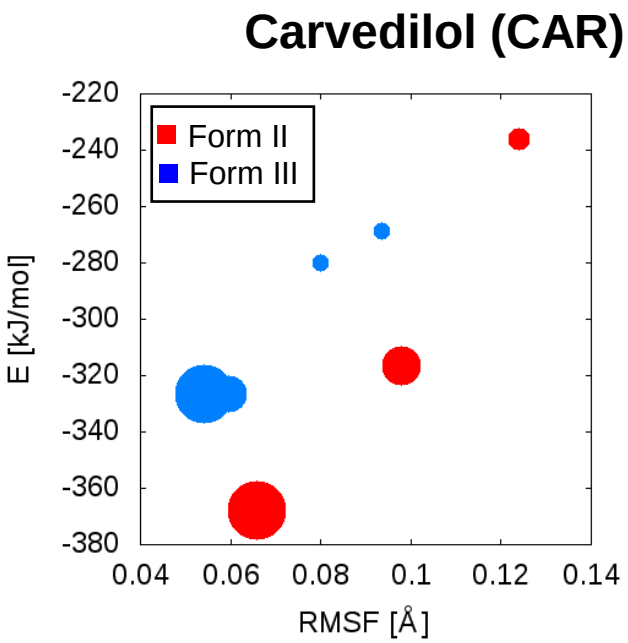
Two hydrates:
Hemi-hydrate (HH, *n=0.5*) and sesqui-hydrate (SH, *n=1.5*)

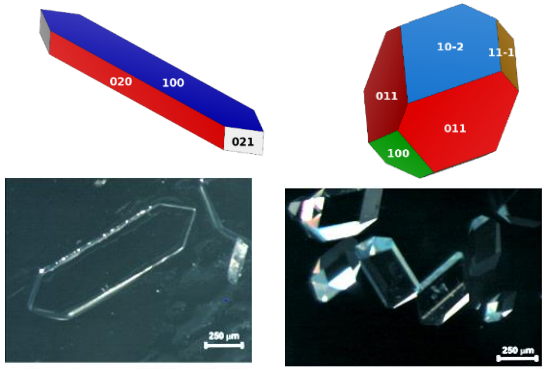
Silver and Sundholm. J Pharm Sci (1987)

Different surface structures:
- 2 APIs
- 2 polymorphs/API
- **2 different CSDs**

Influence of moisture:
- 50°C/4%RH
- 40°C/50%RH
- 70°C/100%RH
- In solution

API crystal, reactions with excipients (solid-solid): Modeling



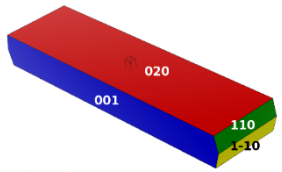


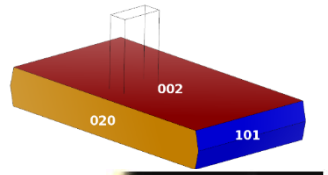
Descriptors	Form II	Form III
ERSA (%/habit)	1.3	5.0
nCE	0.0728	0.1642

- Surface stability (RMSF, Ebind) says form II is more reactive
- Surface structure (ERSA, nCE) says form III is more reactive

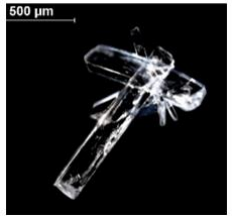
API crystal, reactions with excipients (solid-solid): Modeling

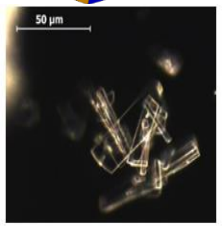
Codeine phosphate (COP)





Descriptors	Hemi-hydrate (HH)		Sesqui-hydrate (SH)	
ERSA (%/habit)	4.95		2.35	
E_{bind} (kJ/Mol)	-690 {0-20}		-790 {002}	



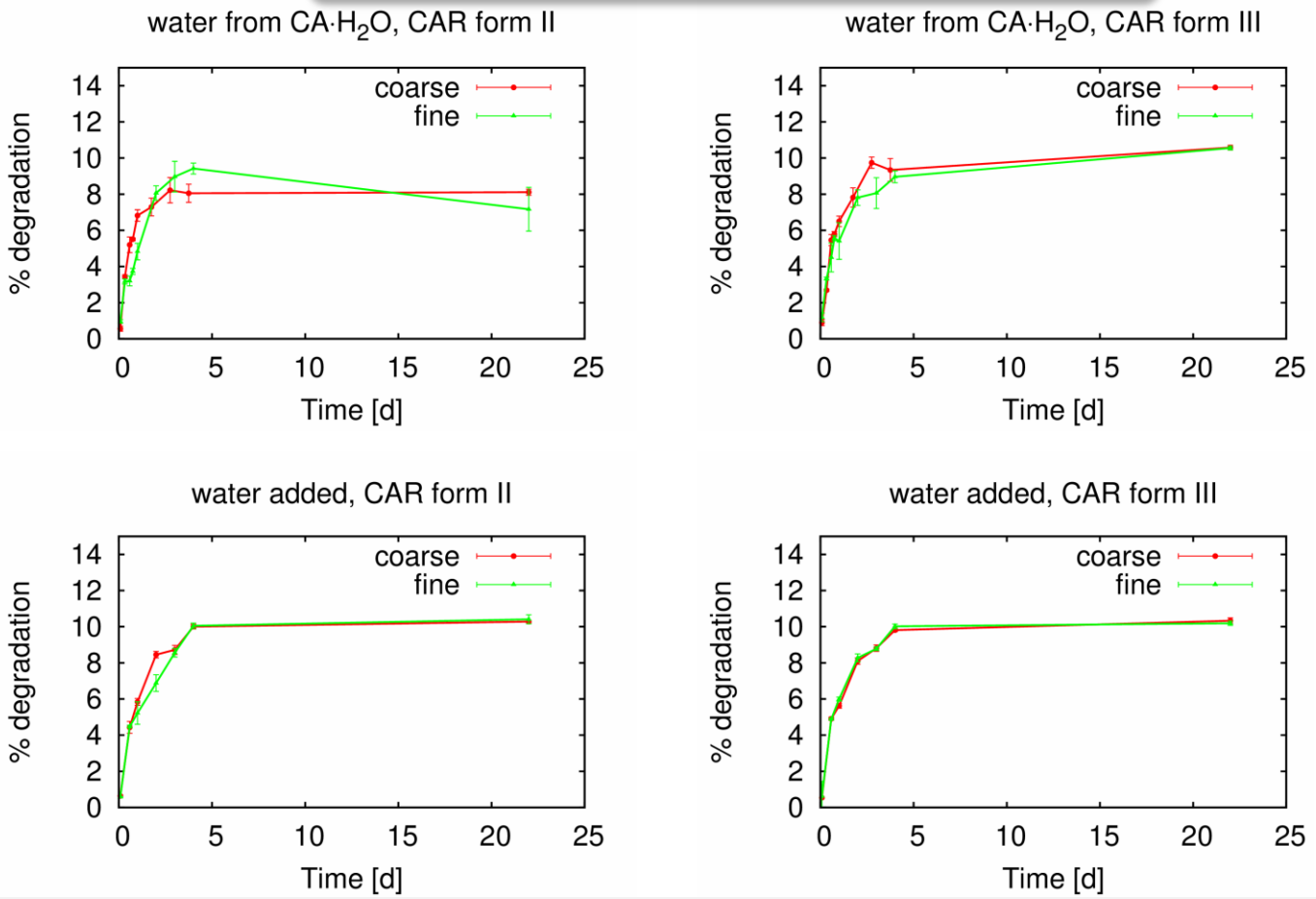


- Descriptors on both mobility and structure of crystal surface imply HH to be more reactive than SH

API crystal, reactions with excipients (solid-solid): Experimental

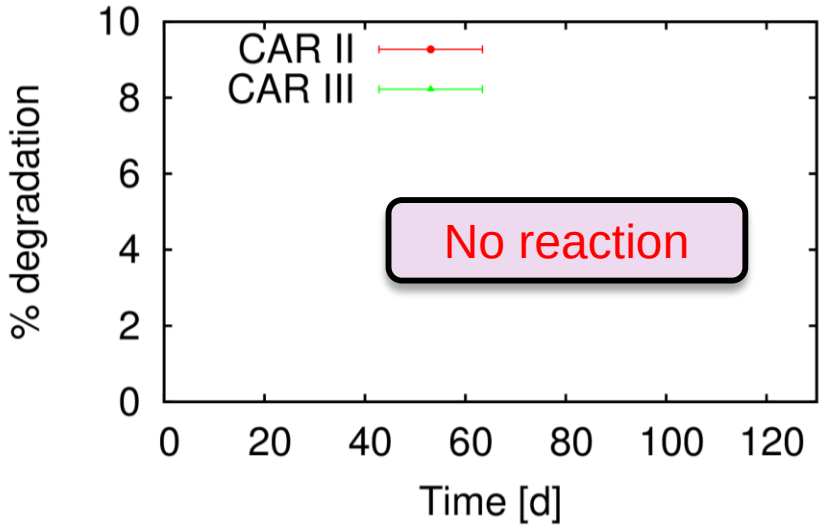
- Citric acid deliquescence causes fast reaction
- Same effect with anhydrous CA plus explicitly added water and water from CA.H_2O
- Crystal form and size of the CAR have no impact on solid-state esterification

70°C sealed pans (estimated %RH ≈ 100)

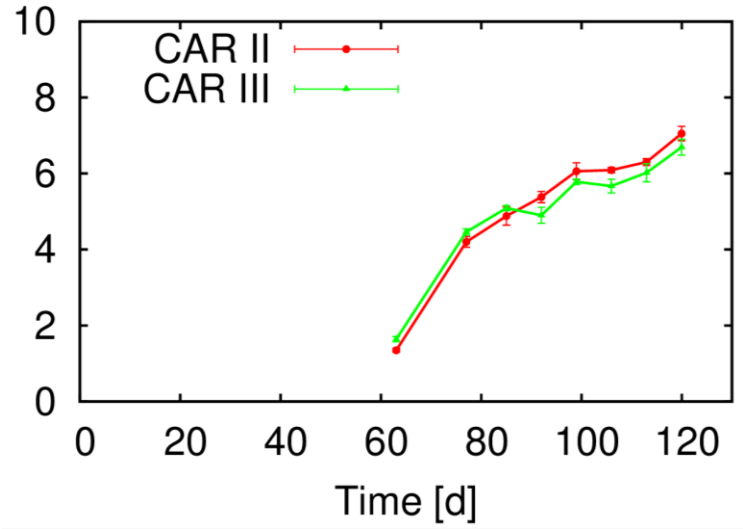


API crystal, reactions with excipients (solid-solid): Experimental

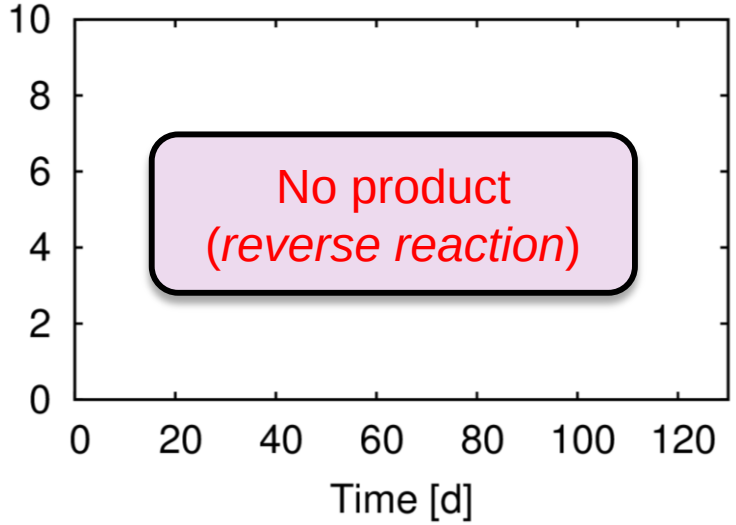
50°C/4%RH, CAR:CA=1:10



40°C/50%RH, CAR:CA=1:10

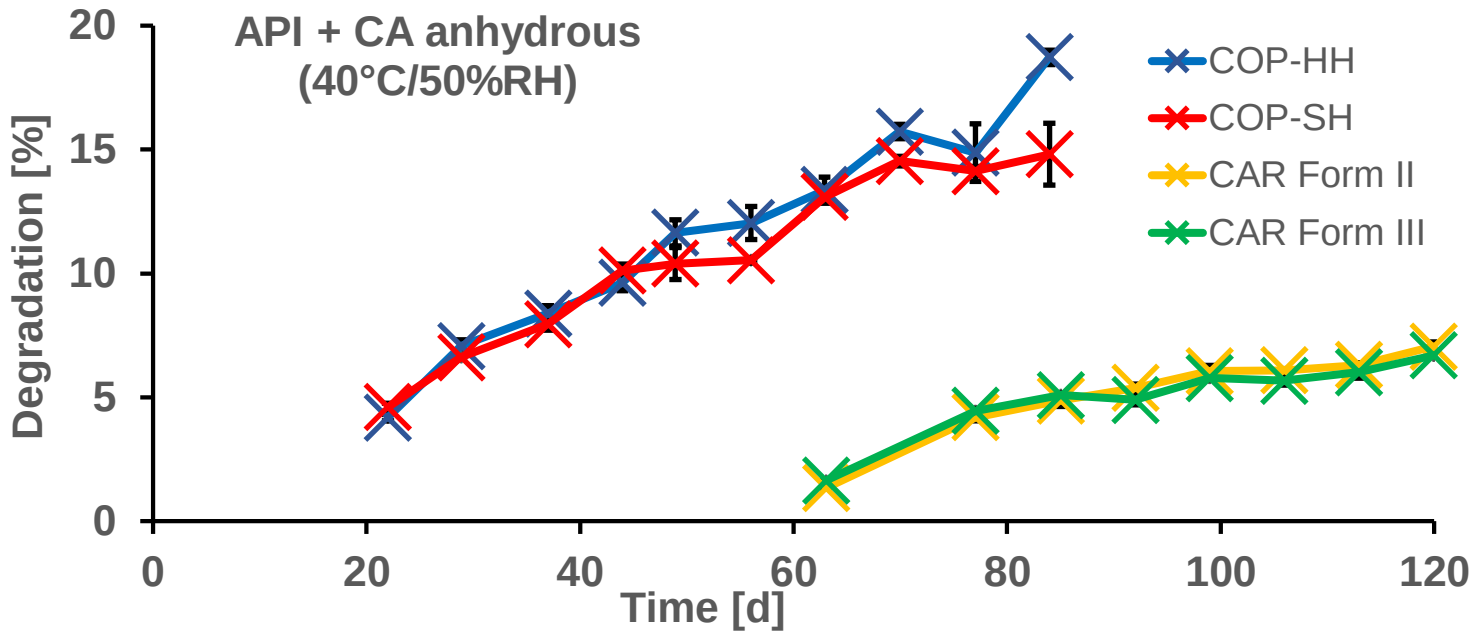


Aq. Sol. (15.7 g.mL^{-1}), CAR:CA=1:10



- Humidity has a profound impact on CAR degradation
- Crystal form of the CAR has no impact on solid-state esterification

API crystal, reactions with excipients (solid-solid): Experimental



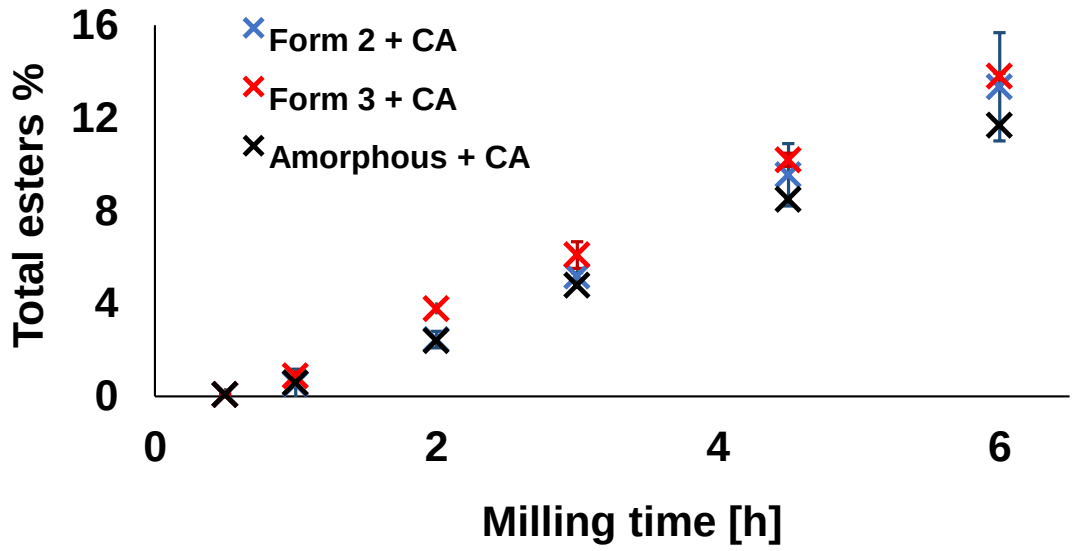
- COP reacts with CA faster than CAR
- For solid CA and solid CAR/COP, the degradation kinetics are independent of the API's crystal forms

Co-processing reactive drug-excipient: A case of co-milling

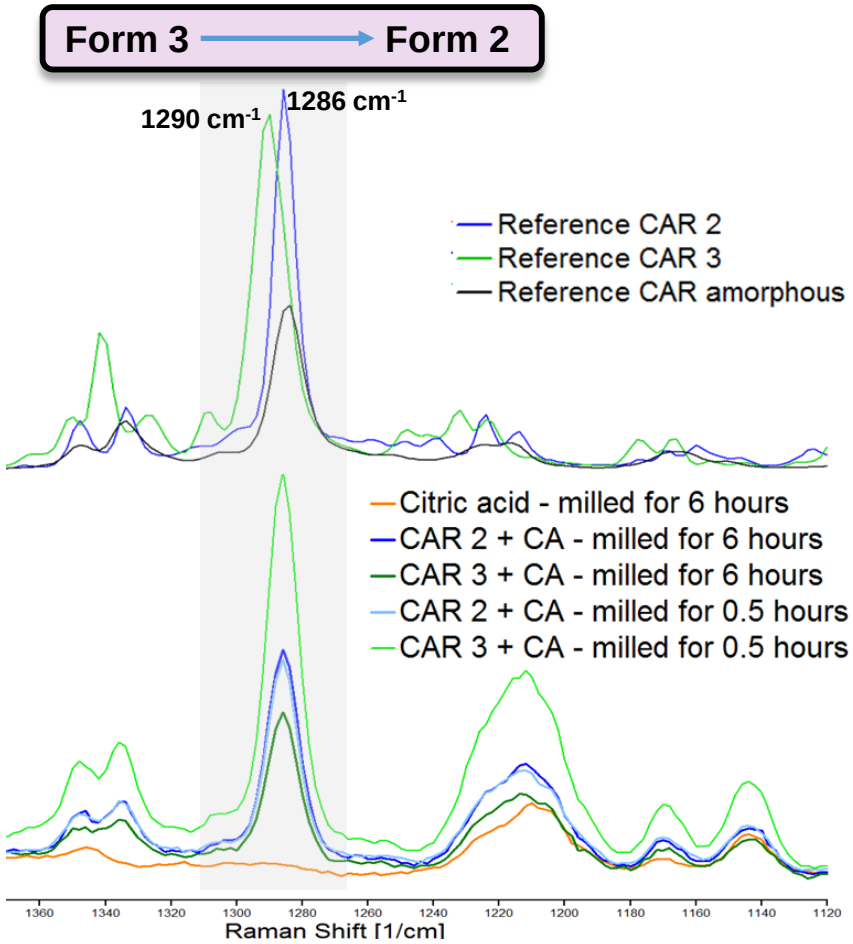
Ball milling

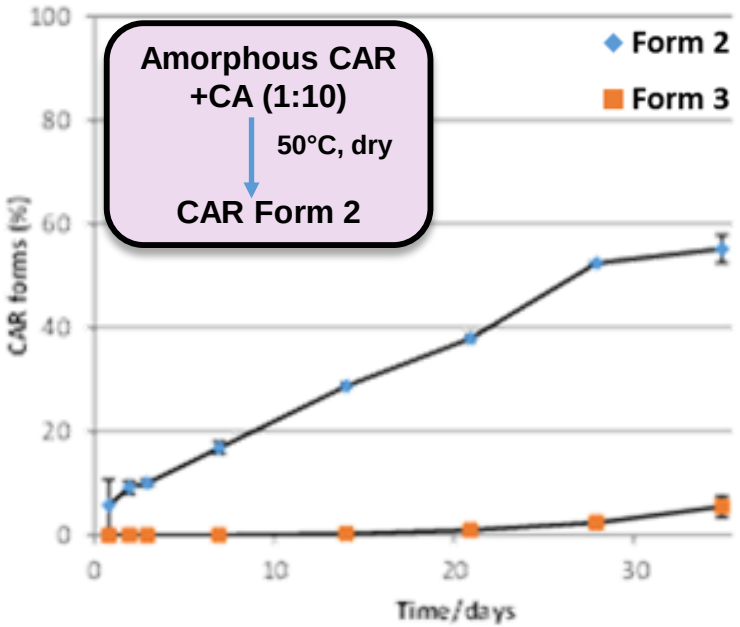
- 25 Hz (Powder temp. up to 60°C)
- Ambient RH (~50%)
- Water content at end of milling (≤0.9%)
- No particle size reduction after milling for 0.5h+
- Different starting solid form of CAR:
  Form 2, form 3 & amorphous

Mechano-activated esterification of CAR + CA anhydrous (1:10)



Co-processing reactive drug-excipient: A case of co-milling

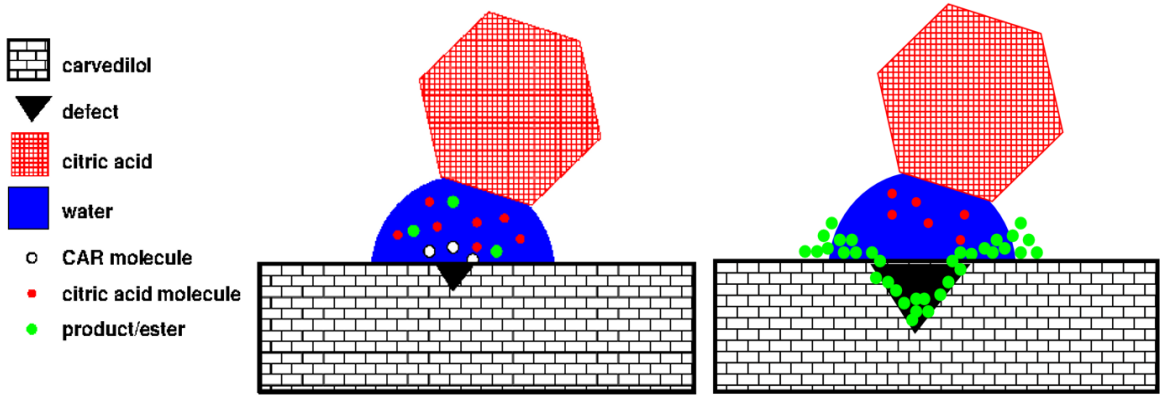


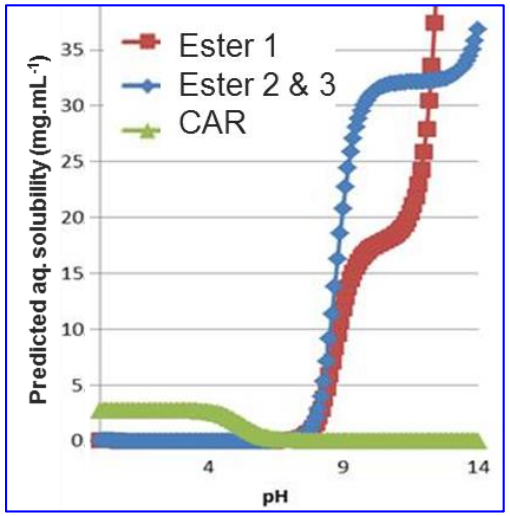


- Form 3, a stable monotrope of form 2, gets amorphicized during milling and transiently crystallizes to form 2 (Tg: 40°C)
- Possible mechano-activated competition between transient de-amorphization and chemical reaction, irrespective of starting solid forms

What did we learn so far on solid-state esterification?

- The reaction seems to rather happen **in solution** (*water layers/ droplets adsorbed on surfaces*)
- The role of water as **a plasticizer** is instrumental, while the (**microscopic) crystal surface structure** seems less imp
- The formed esters precipitate in the localized water on defect surface and gradually conceal the site (plateau)





- Mechano-activated (milling-induced) crystal disordering accompanies faster esterification

API crystal, reactions with reactive impurities /H_2O

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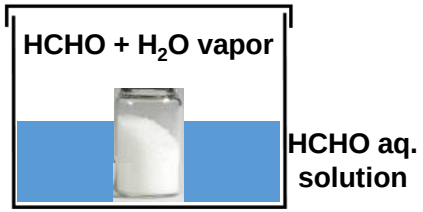
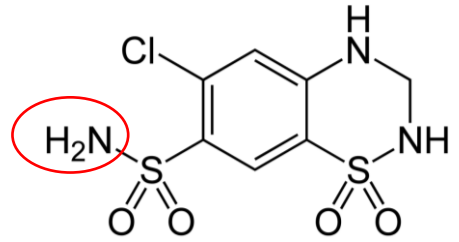
API crystal reactions with reactive impurities of excipients

Drug crystal + HCHO reaction

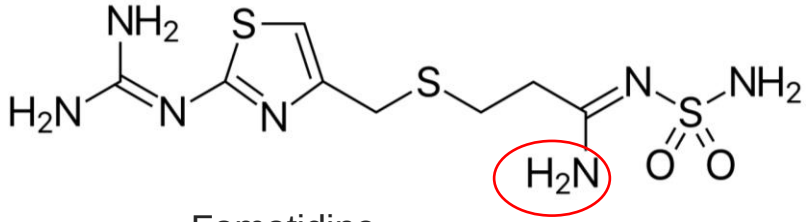
Compound	Temp	Time (d)	% Degradation	Rank
Famotidine	RT	1	54	3
Hydrochlorothiazide	RT	1	24	3
Compound 1 (C1)	RT	1	24	3
Compound 2 (C2)	50°C	1	18	2
Compound 3 (C3)	50°C	1	5	1
Compound 4 (C4)	50°C	1	0.3	1

Data from Greg Sluggett (Pfizer)





Hydrochlorothiazide

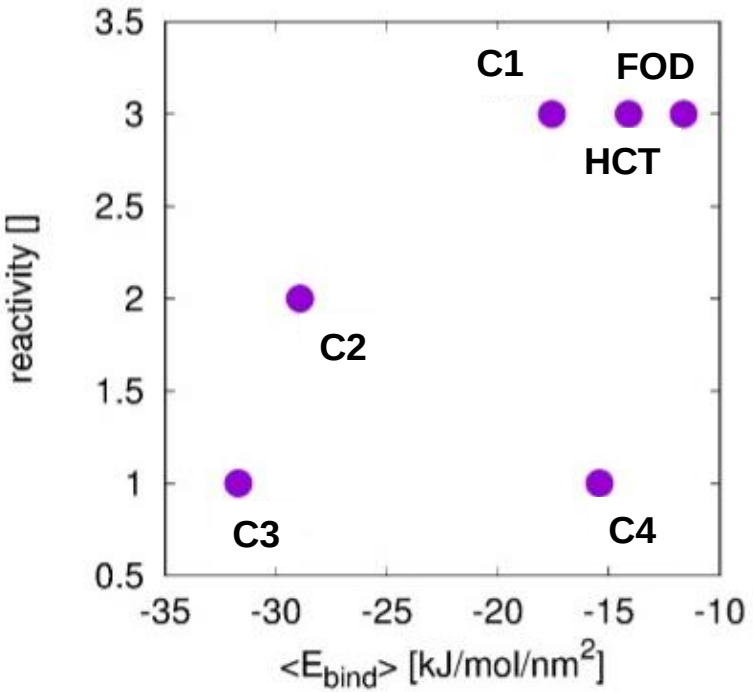


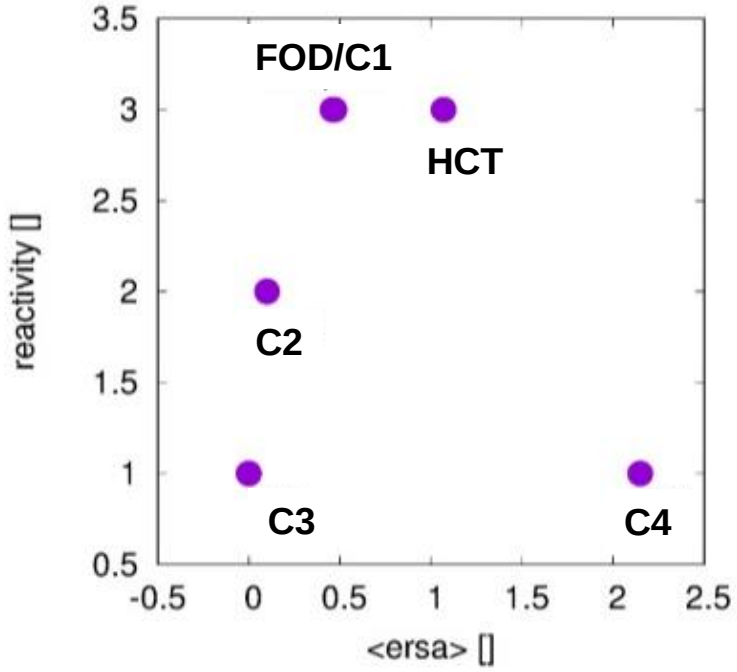
Famotidine

API crystal reactions with reactive impurities of excipients

Drug crystal + HCHO reaction

Famotidine	**: FOD**
Hydrochlorothiazide	**: HCT**
Compound 1	**: C1**
Compound 2	**: C2**
Compound 3	**: C3**
Compound 4	**: C4**





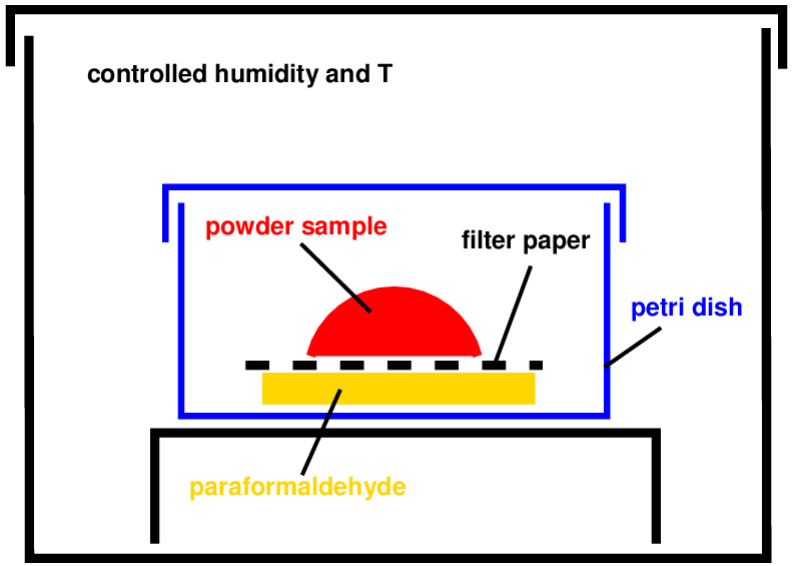
- Chemistry is not well established, and modelling based on static structures

API crystal reactions with reactive impurities of excipients

Drug crystal + HCHO reaction

For the HCHO test set are relative reactivities due to

- variations in exposed reactive groups (ERSA)?
- Variations in surfaces stabilities (E_{bind})?
- Different intrinsic reactivities?
- Salt vs free base?

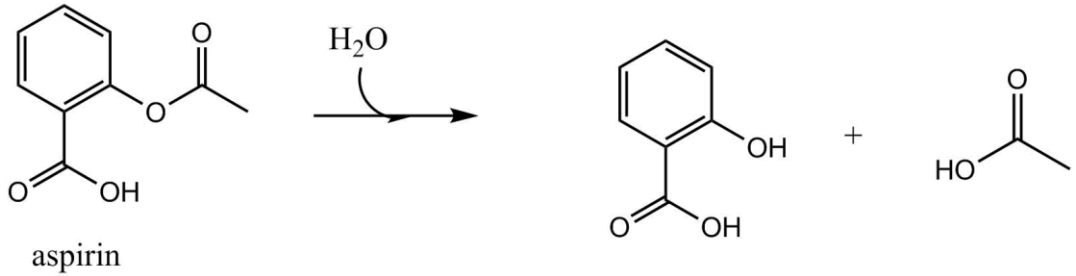


Controlled experiments:

- Solid and solution (quantitative)
- Milder and identical conditions (RT)
- Controlled water content

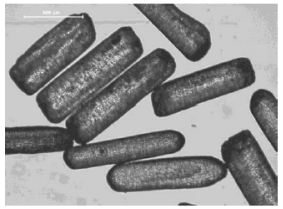
API crystal reactions with H2O: Role of crystal habit/surface

To what extent can an API crystal anisotropy and surface roughness contribute solid-state reactivity?



Aspirin hydrolysis

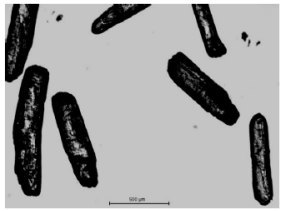
Supersaturation tuning via thermal gradient



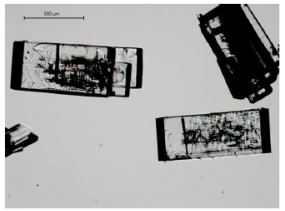
constant temperature

vs.

temperature cycling



Needle

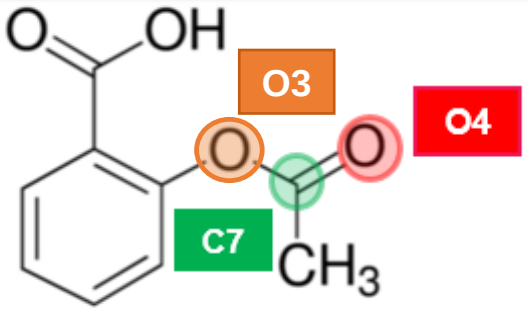


Plate

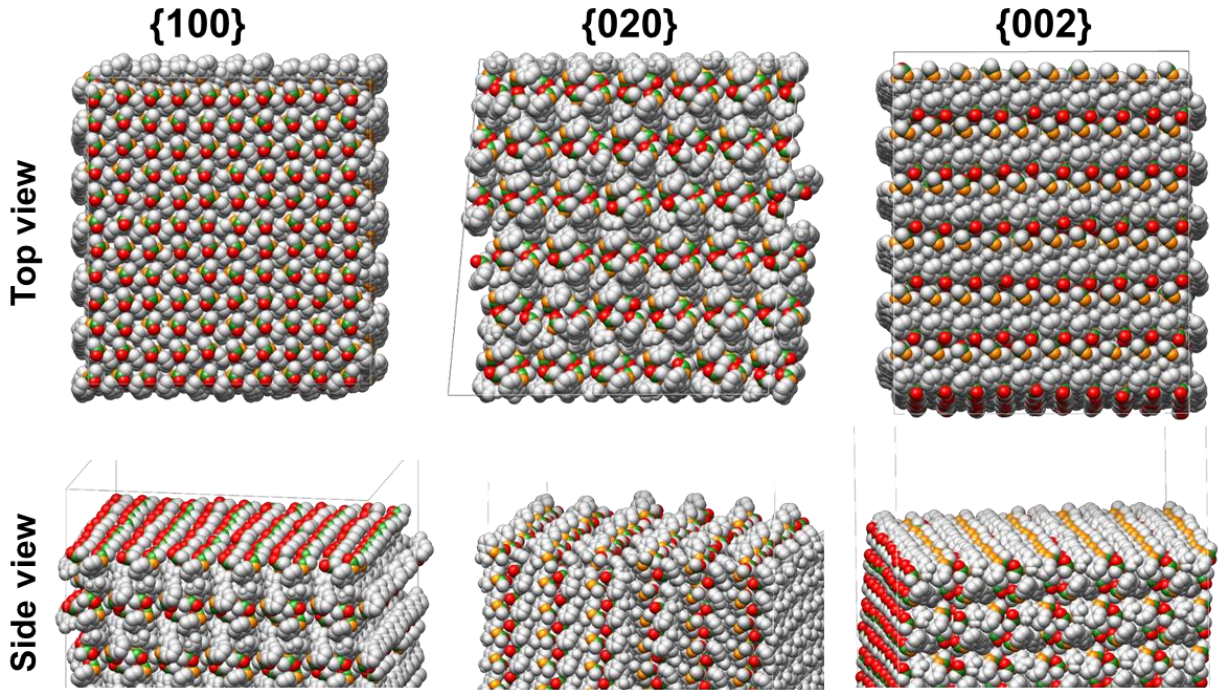
Controlled size & habit (surface roughness?)

API crystal reactions with H_2O: Role of crystal habit/surface

Varying crystal habits → different rate/extent of hydrolysis i.e. f(ERSA)
Plates: Most prominent face: {100}
Needles: Smallest face: {020}



Face	O4/%	C7/%	O3/%	dhkl-rank
100	29.39	5.66	0.10	1
020	10.82	1.34	3.47	18
002	3.03	0.02	4.83	4



- But, hydrolysis can happen in solution rather……

Conclusion and outlook

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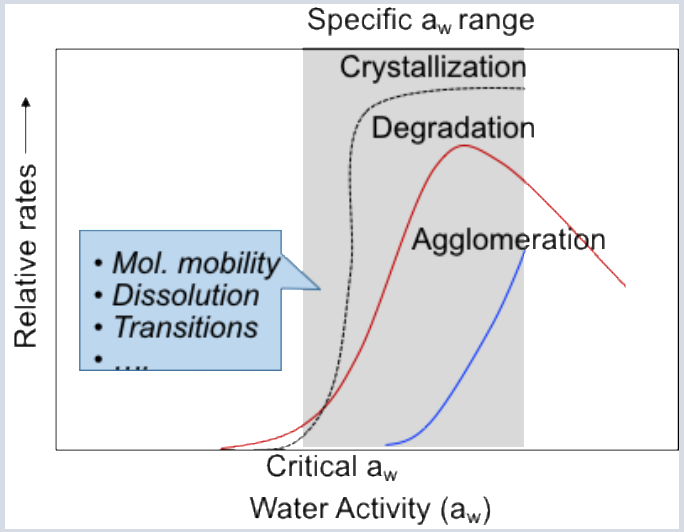
Funded by the Austrian Research Promotion Agency (FFG), Land Steiermark and the Styrian Business Promotion Agency (SFG).

Physical-chemical ASAP !



- **Crystallization**
(Avrami, Kissinger…)
- **Structural Relaxation**
(AG, VFT, KWW…)
- **Degradation**
(Arrhenius, Avrami, Prout-Tompkin..)

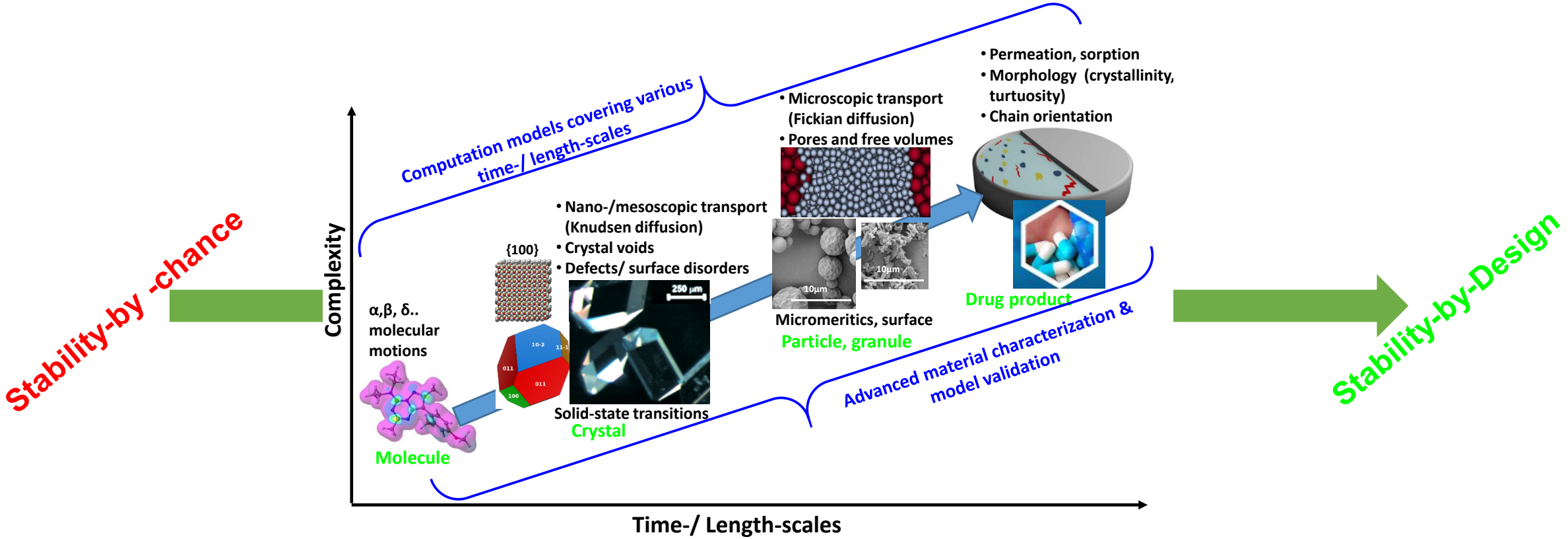
(Tg plasticization, hydrate van´t Hoff points, Nagi´s coupling)

Reliable analytical methods to quantify spatio-temporally solid-states and transitions (eg. non-amorphous disorder)

- **Moisture** diffusion & **microstructures**, high resolution porosimetries
- Speciation of free, bound, active states of water molecules

Descriptors from first principles
- Mobility, □ G, mechanical properties
- Amorphization tendency and the life of amorphous states

Finally…



The rational combination of experimental & theoretical approaches requires a sound knowledge of the strengths and limitations of the used methods and algorithms

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