UNDERSTANDING DEGRADATION BEHAVIOUR OF DISORDERED PHARMACEUTICAL SOLIDS

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SCIENCE OF STABILITY Philadelphia

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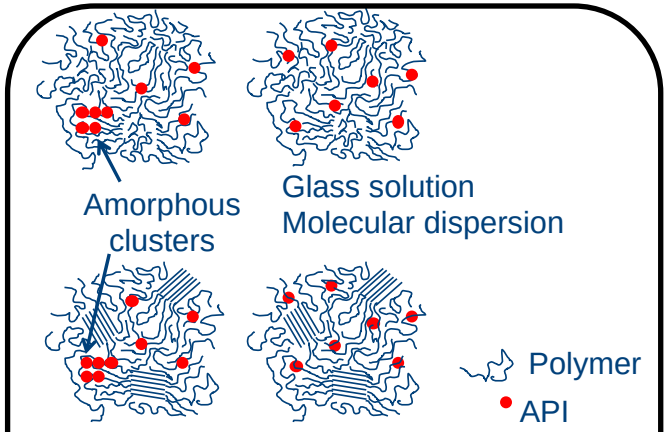
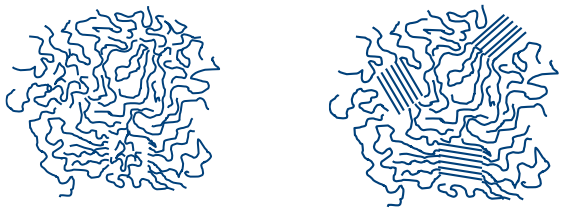
Content

Background

Disordered Pharmaceutical Solids

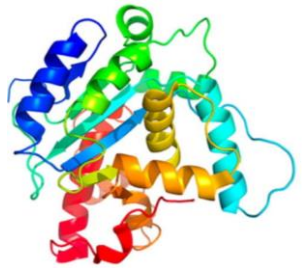




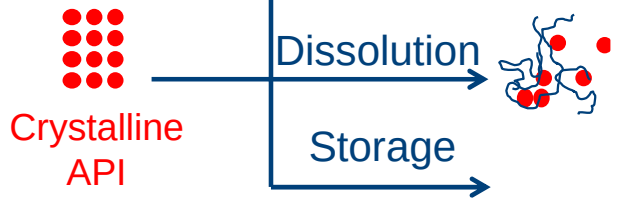
Amorphous
HPMC, PVP, Acrylates..

Semi-crystalline
PEG, PEO, EVA, Lipids...

Polymer excipients



Large molecule drugs (Protein, mABs, peptides)

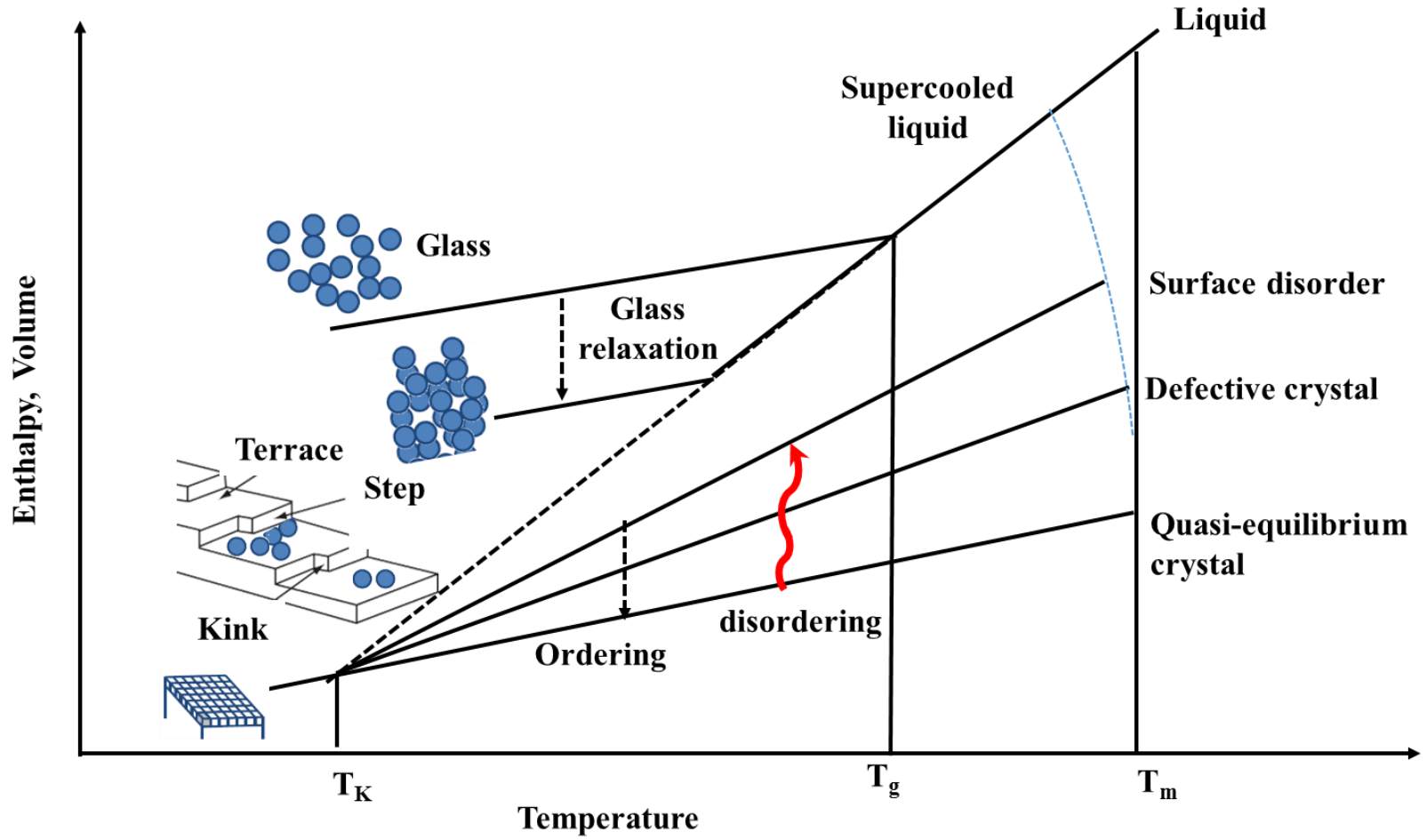


Un-intended amorphization

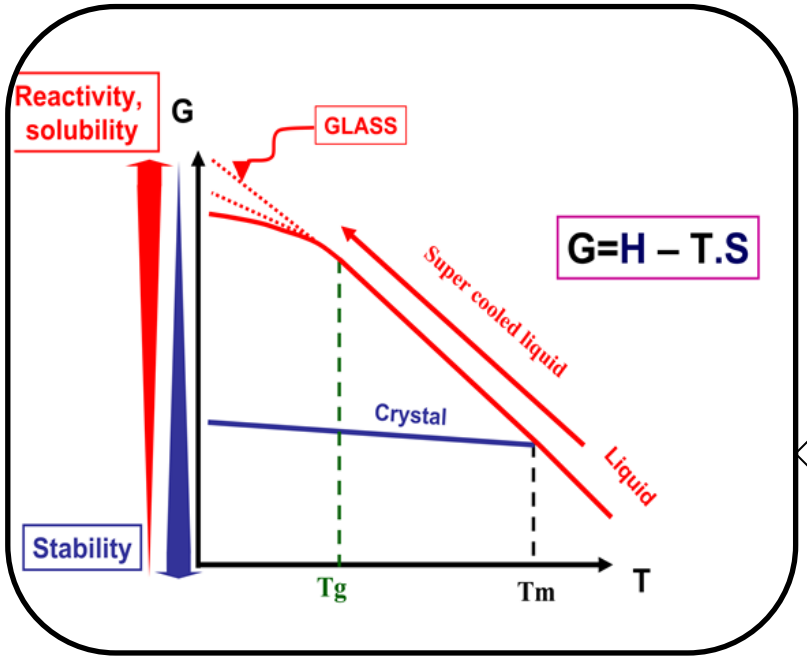
Key features:

- Higher solubility/ dissolution
- Higher physical & chemical reactivity
- Higher bulk and surface energy
- Higher hygroscopicity
- Coalescence, aggreation, poor powder flow

Energetics of disorder-order continuum

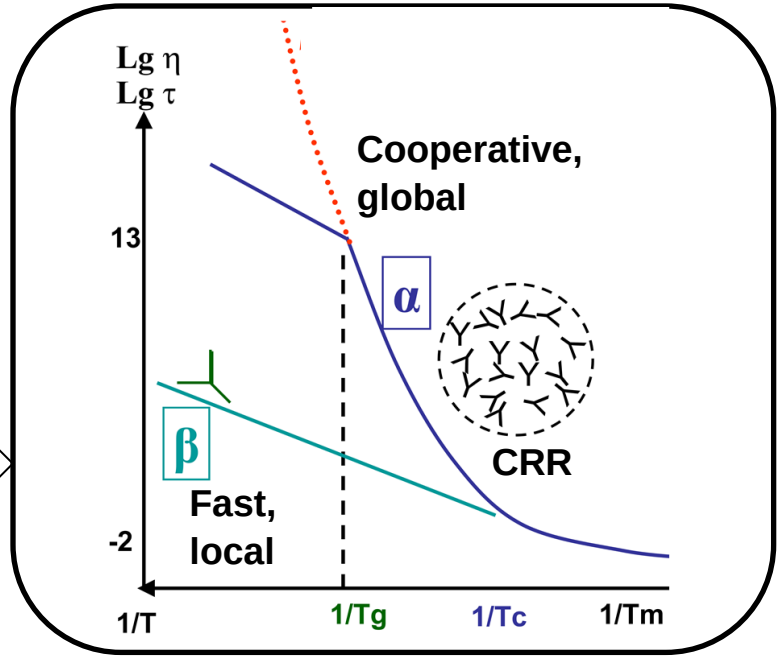


Basic physics of an disordered/ amorphous state



Energy landscape

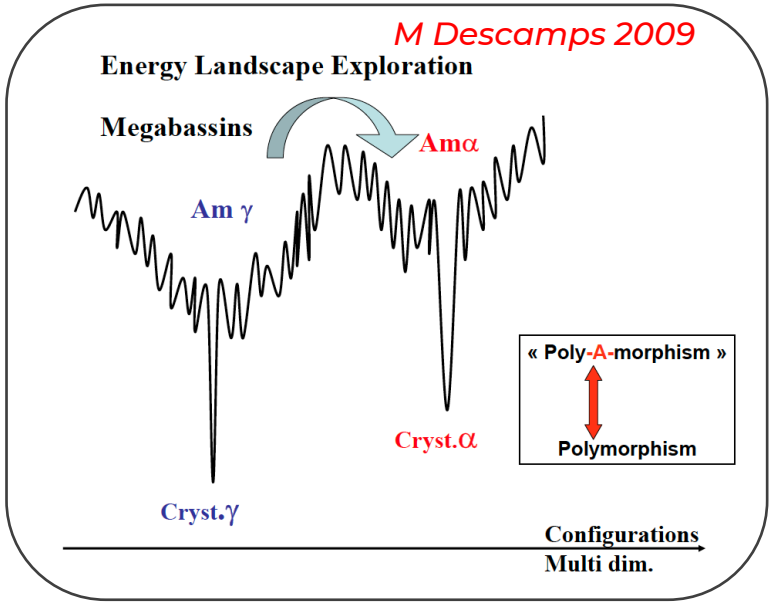
Unique local structure
(inter-atomic & inter-molecular arrangement)



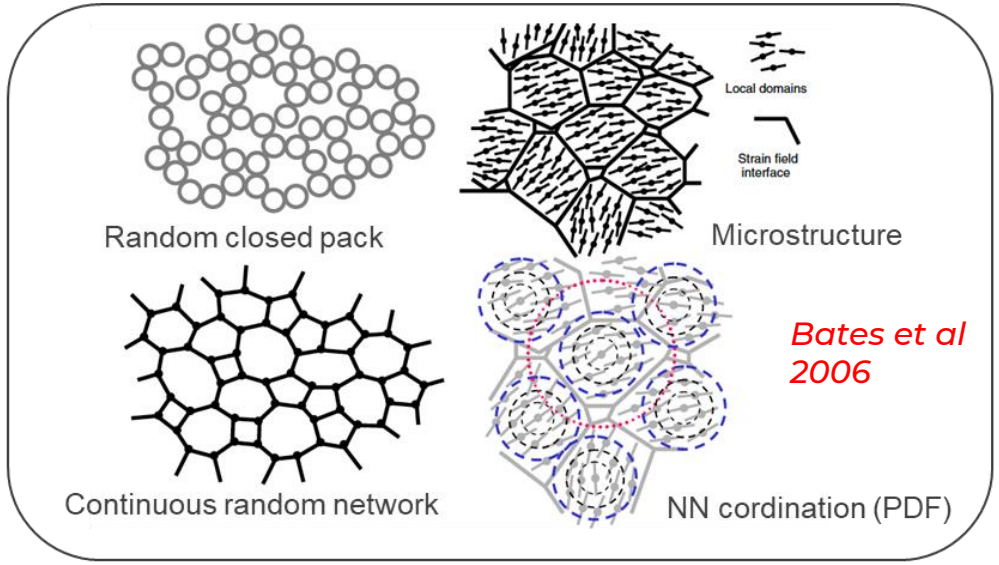
Mobility landscape

M Descamps 2009

Local Structure of Disordered Solids



Poly-amorphism



Local structures of disordered solids

Chemically identical, but physically distinct:

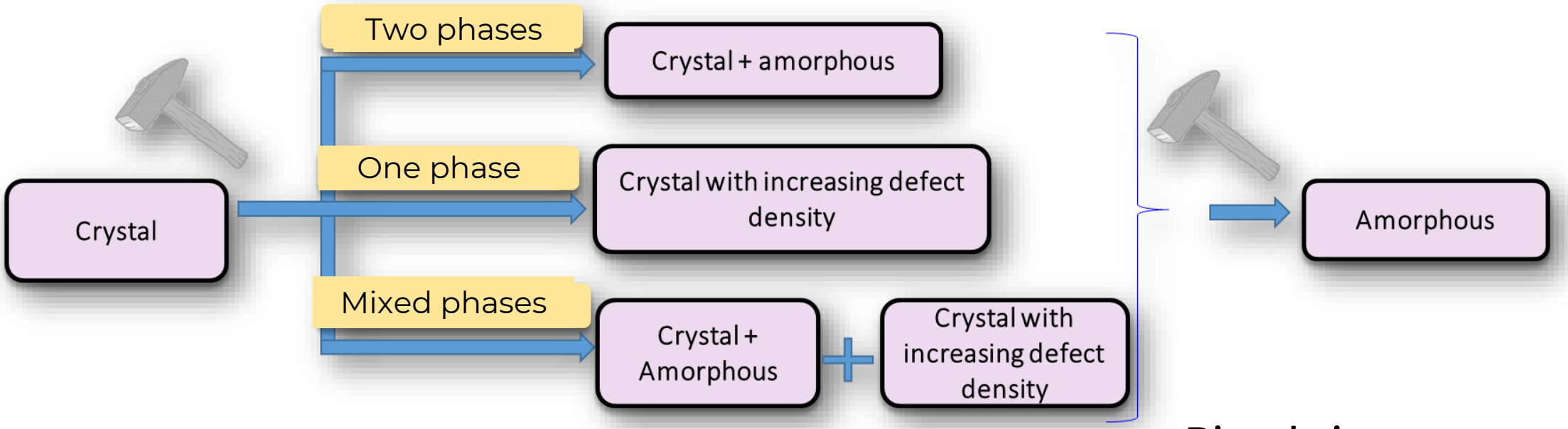
- Heterogeneity at nano-/meso-structures
- Glass temperature & poly-amorphism
- Molecular motions & interactions

"Understanding the disordered state of raw materials, intermediates and dosage forms"

Can enable prediction & control of **processing**, **performance** & **stability**

Disordered APIs and degradation

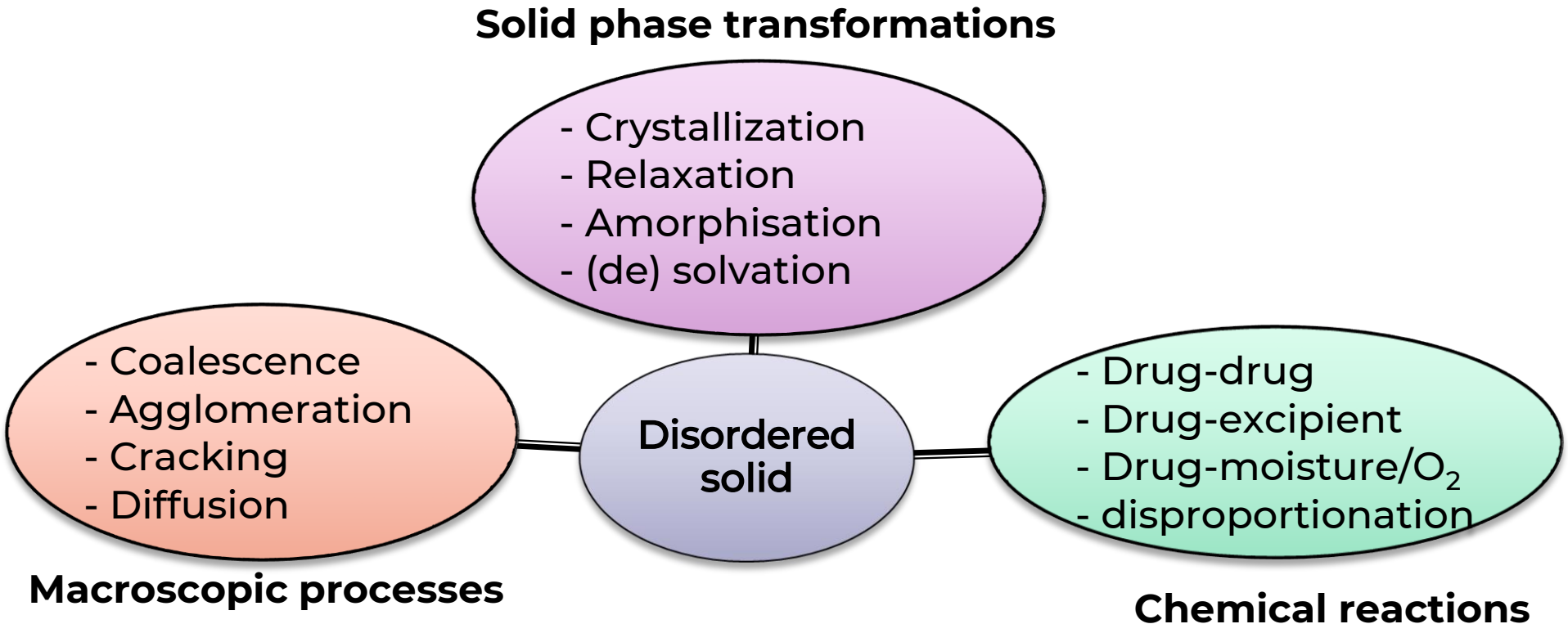
En route to solid state disordering



Disordering processes:

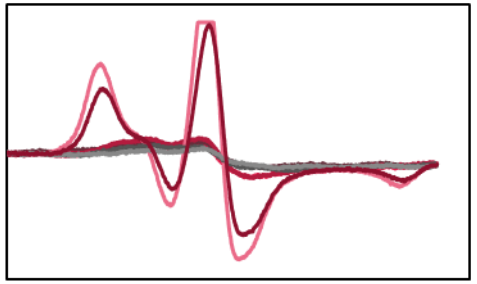
- Milling, Sieving, Blending, Granulation, Compaction
- Crystallization, Drying, Solidification

Disordered state: a common prey

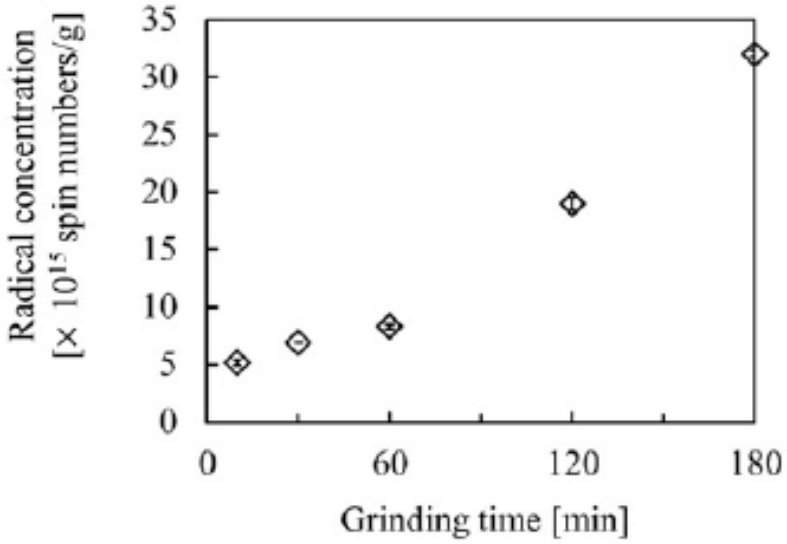


Disordered solid state: Oxidative liability

- The reaction does not explicitly require water, can be specific and auto-catalytic
- Solution and solid-state can undergo different oxidation reactions
- **Disordering can generate or enhance free radicals** (reported for sugars, amino acids, polymers, etc.), that can be reactive when subjected to accelerated storage



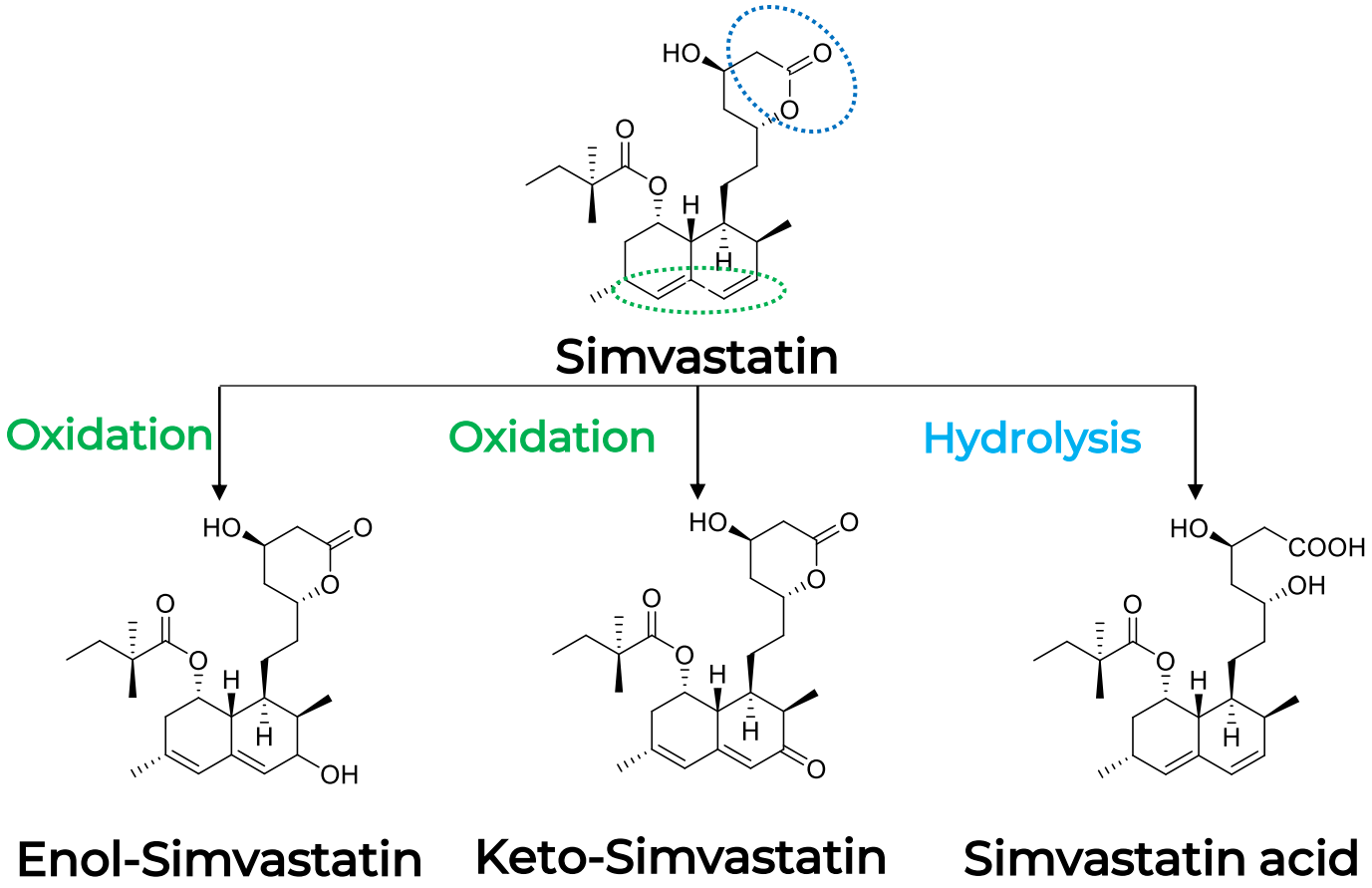
ESR of PVP



Konishi et al 2016

Case 1: Simvastatin (SIM)

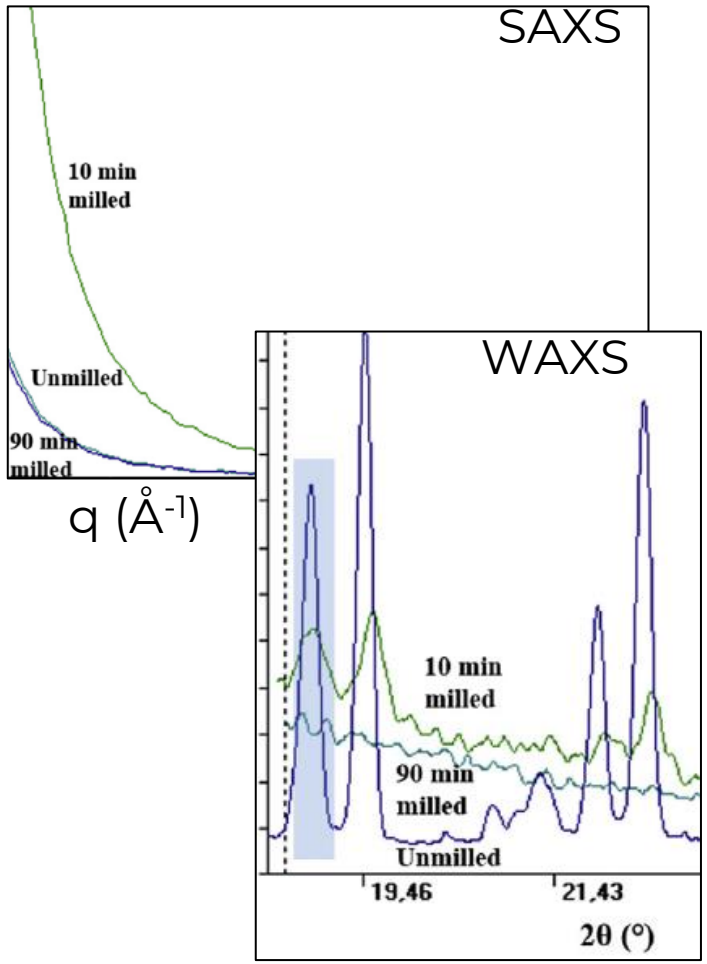
Solid-state degradation



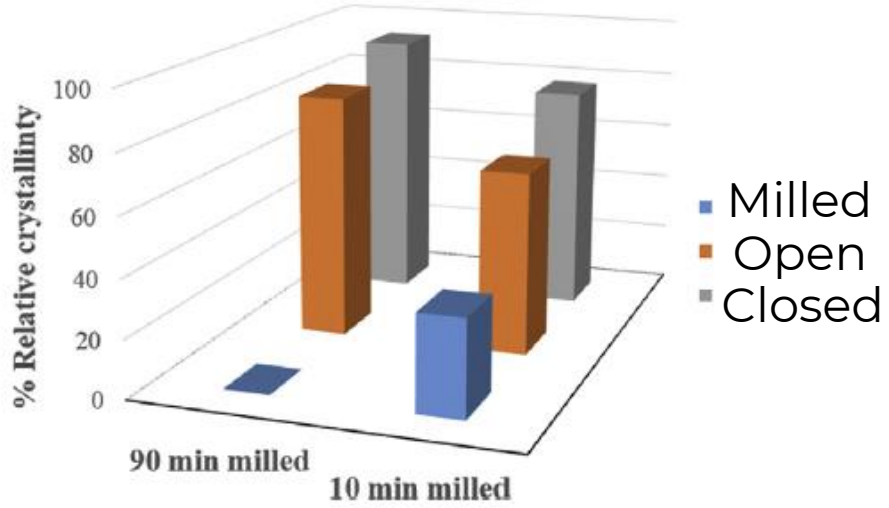
Modhave et al 2019

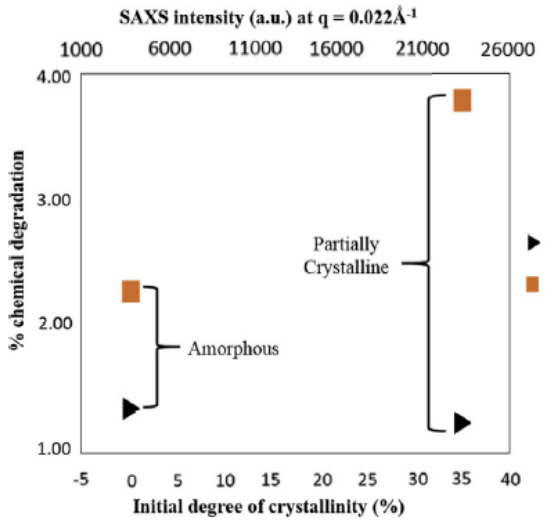
Case 1: Simvastatin (SIM)

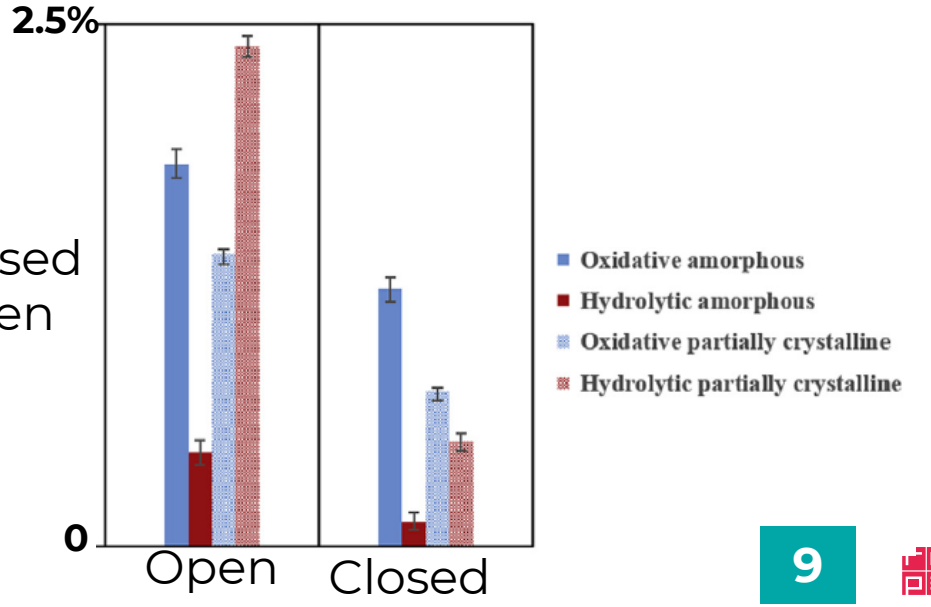
Physical & chemical reactivity following milling



40°C/75%RH, 2w
Open & closed (Tg+10)



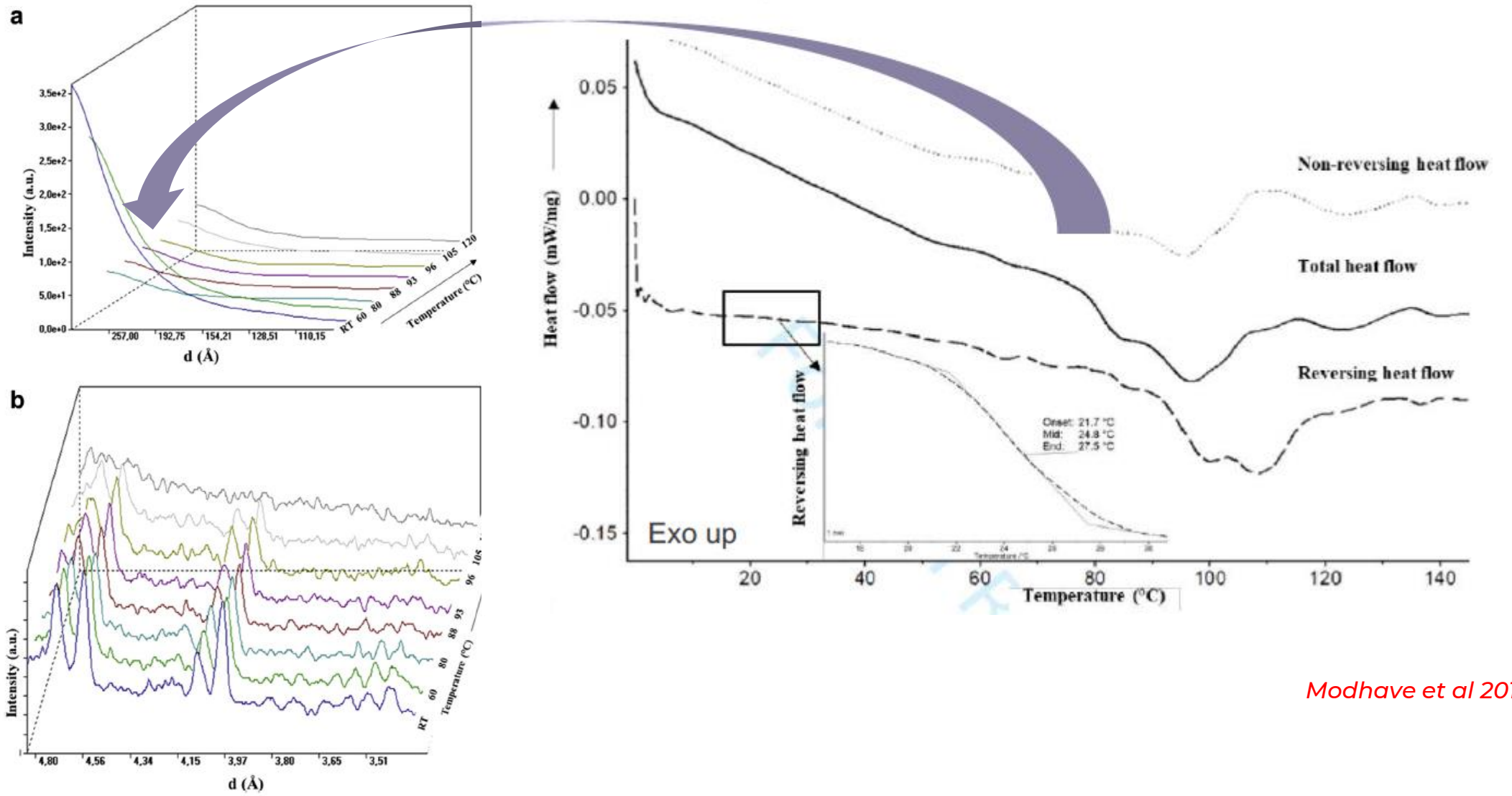




Modhave et al 2019

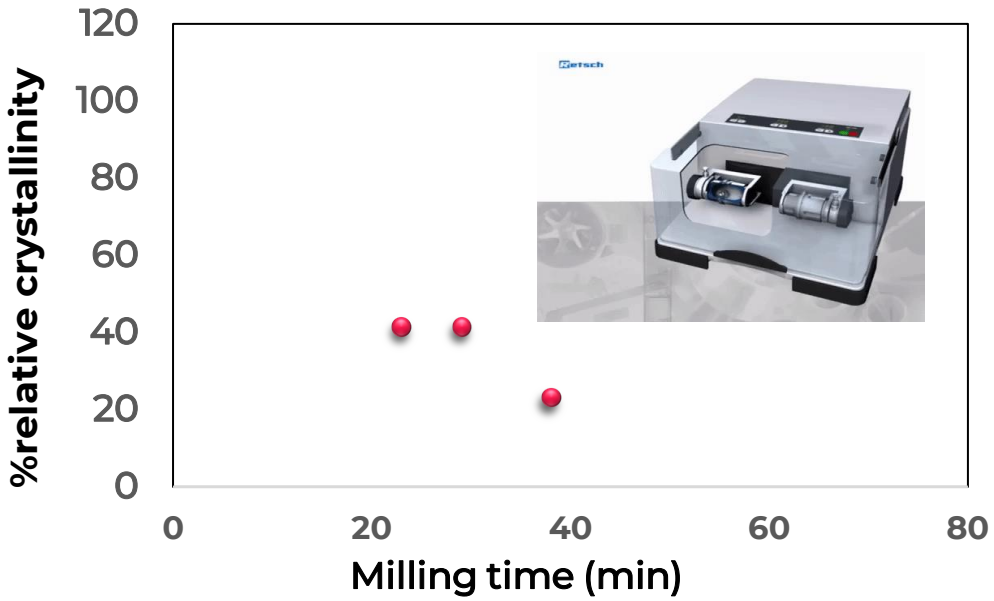
Case 1: Simvastatin (SIM)

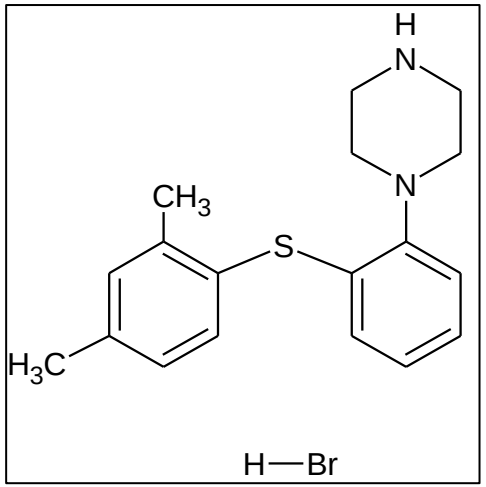
Physically rigid disordered state in the partially crystalline state



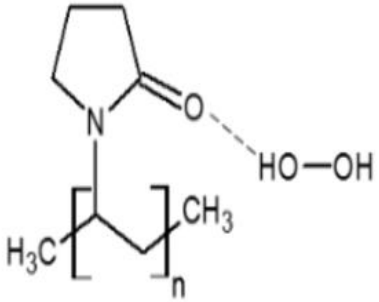
Modhave et al 2019

Case 2: Vortioxetine.HBr





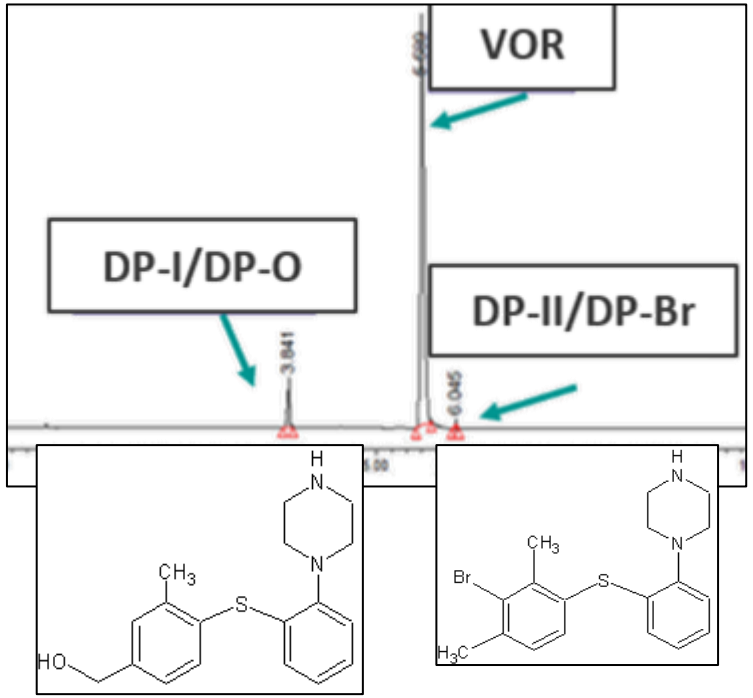
- Milling led to progressive amorphization & salt disp.



Compact with PVP-H_2O_2 complex powder

40°C/75%RH

- No marked change in crystallinity upon storage

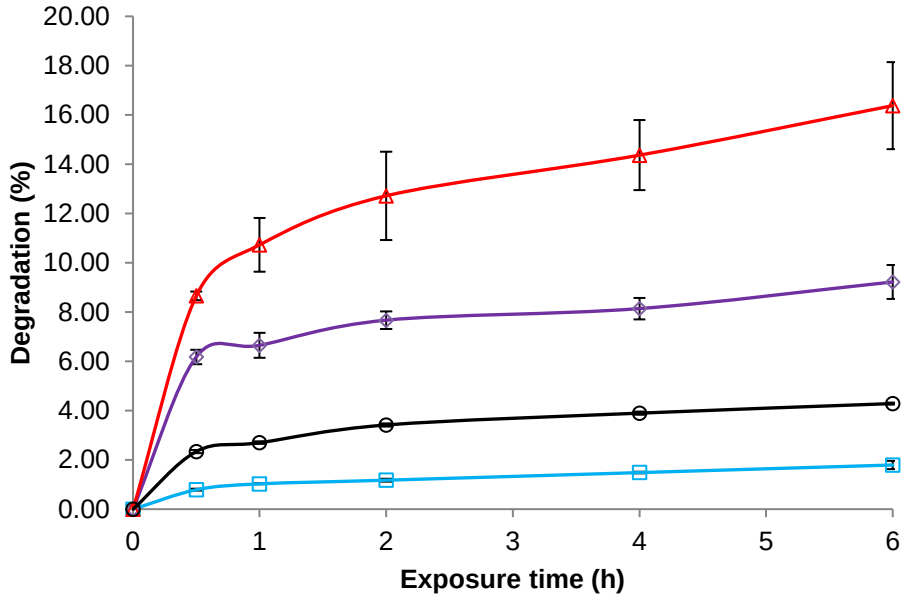


Modhave et al 2019

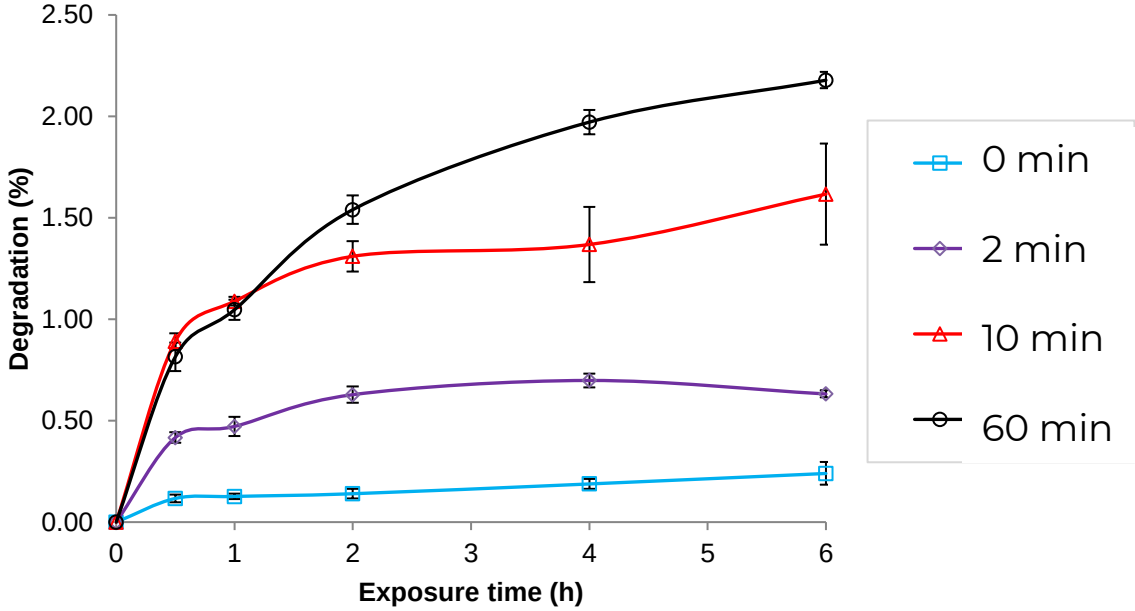
Case 2: Vortioxetine.HBr

Degradation kinetics and initial degree of disorder

Major product



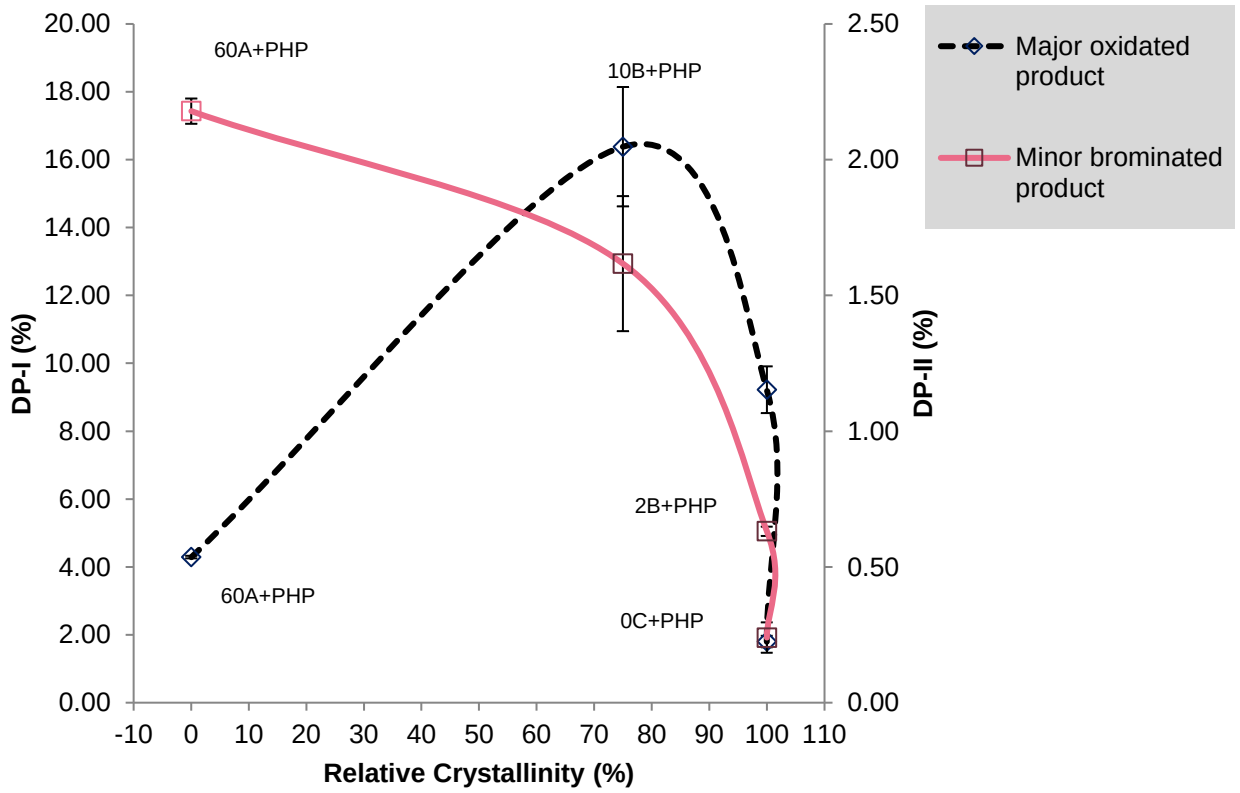
Minor product



Case 2: Vortioxetine.HBr

Degradation kinetics and initial degree of disorder

Fraction DP at final time point



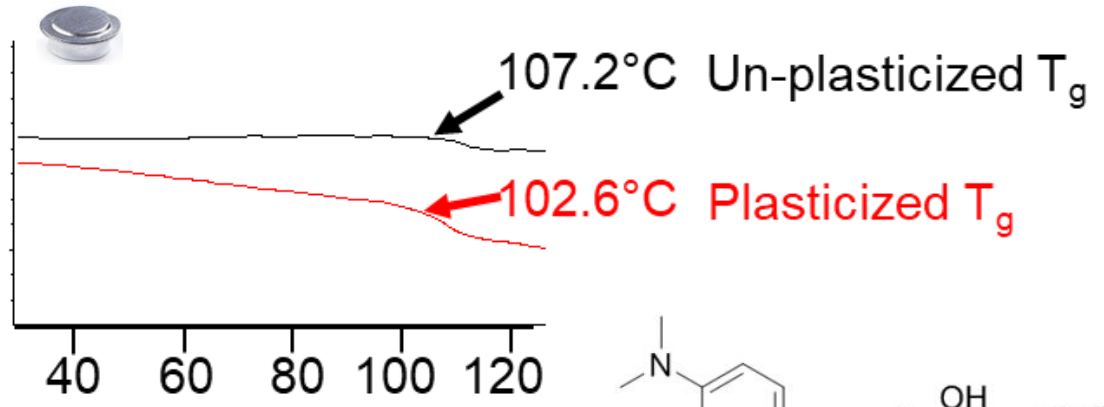
- The major oxidative product formed less in the fully amorphous sample, due to agglomeration (?)
- The minor product formation would need free HBr from disp, thus increases with increasing milling time

Case 3: Mifepristone

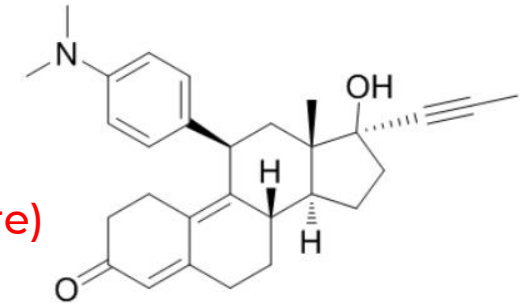
Autoxidation of a high Tg steroid

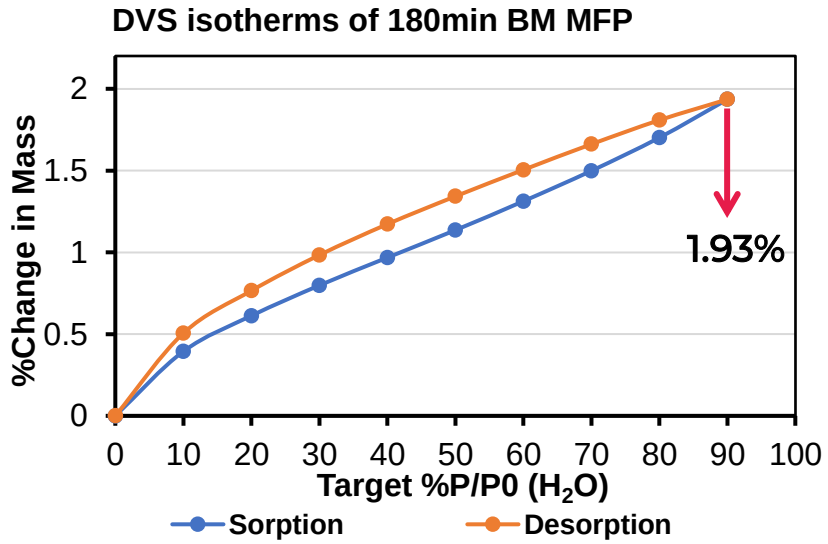
- The moisture reaches a maximum of less than 2% within 3d and remains unchanged

- The moisture plasticized-Tg is still far higher than the storage conditions used, therefore degradation happens in the GLASSY STATE OF mif



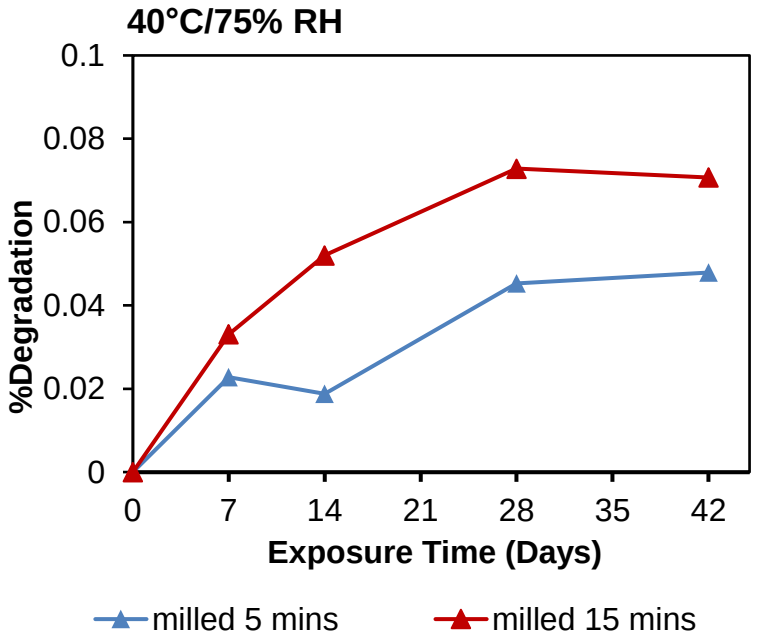
180min BM MFP-30d;
40°C/75 %RH (1.9% moisture)

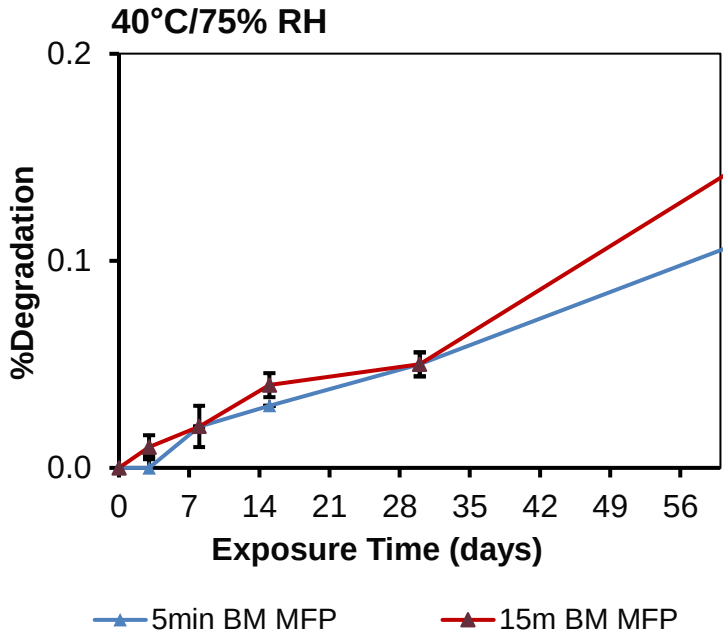


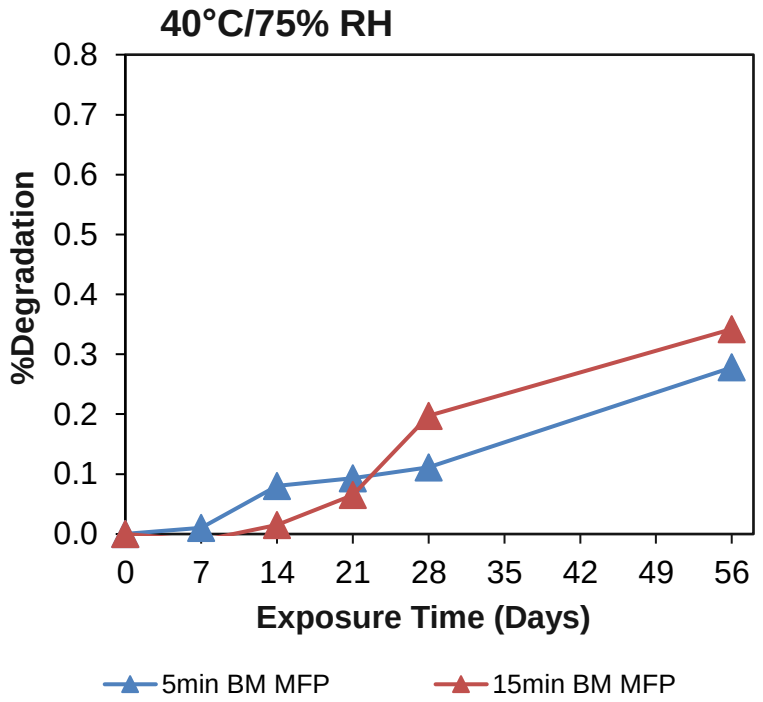


Case 3: Mifepristone

The importance of the disordered sample age, prior to the accelerated stability







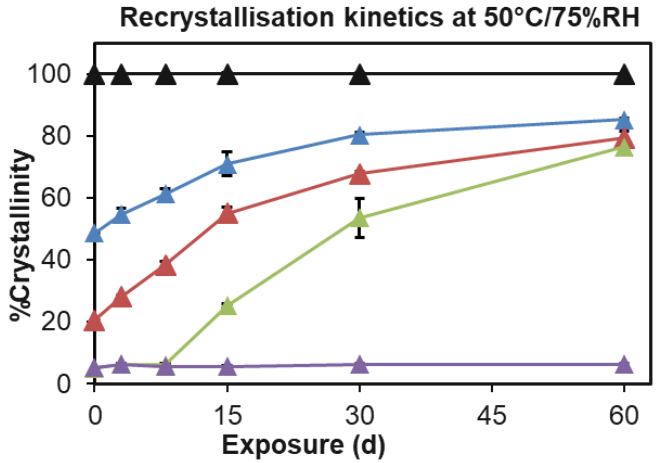
Age of sample	1-2 months	4 months	Above 6 months

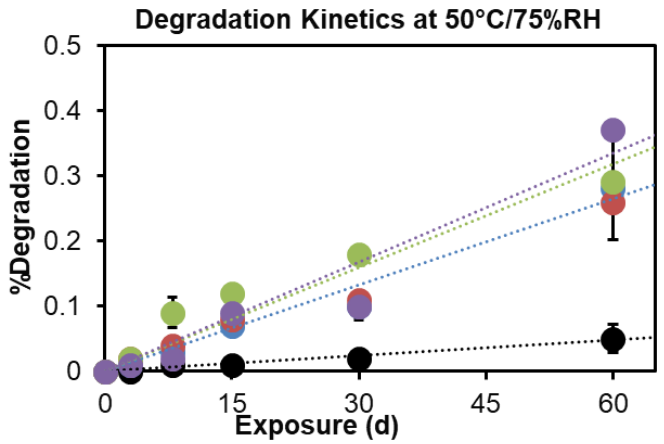
- The longer the ambient aging, the lesser the crystallization under accel. condition
- Probably due to the relaxation and change in surface energy, microstructure, etc.

Case 3: Mifepristone

Competition between sub-Tg recrystallization and autoxidation

- Degradation depends on the initial amorphous content and crystallization kinetics
- A recrystallization rate normalized degradation kinetics model under work



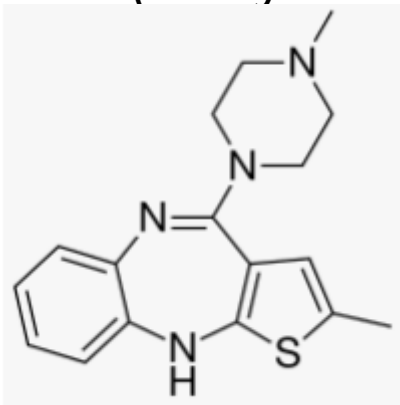


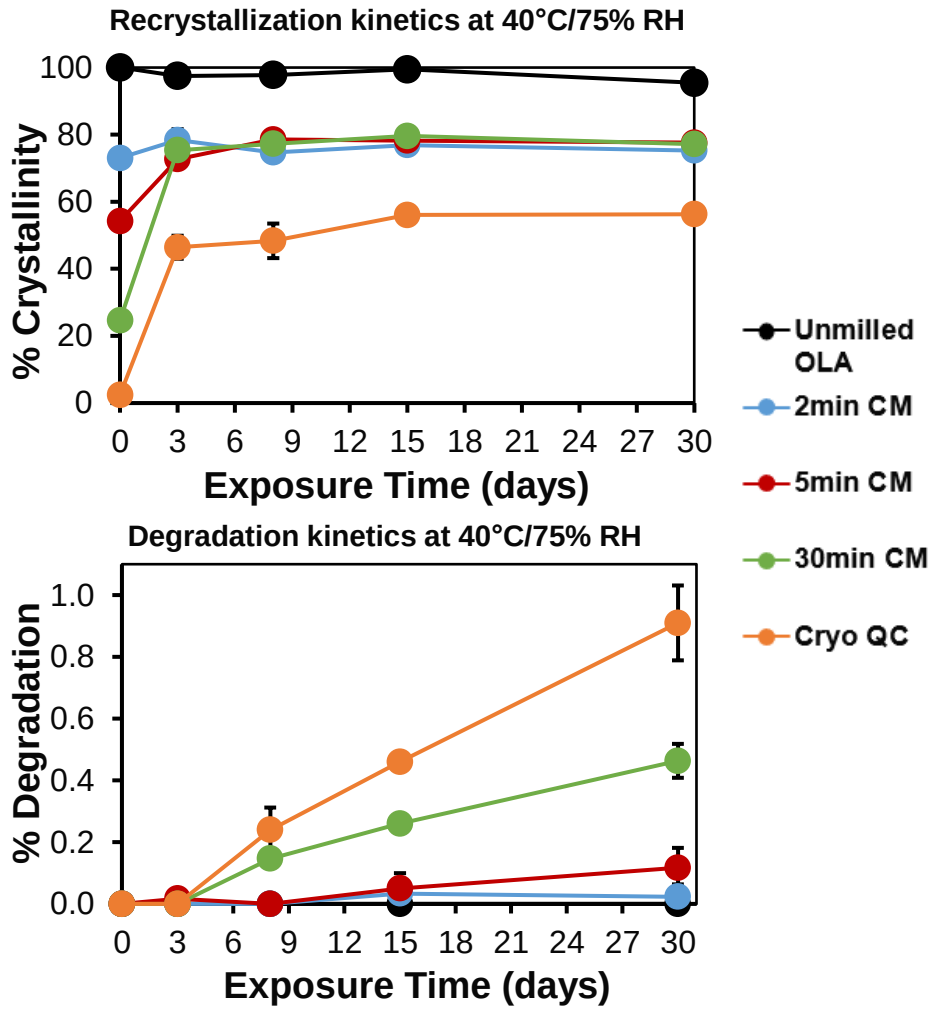
Unmilled MFP
5min BM MFP
15m BM MFP
180m BM MFP
Cryo QC MFP

Case 4: Olanzapine

Autoxidation of an intermediate Tg (60°C) disordered system

- Crystallinity reaches an equilibrium after 3d and to the same extent for intermediate disorders
- Degradation precedes crystallization and kinetics differ despite starting from similar content
- Varying degrees of plasticization is possible (study ongoing together with Janssens)

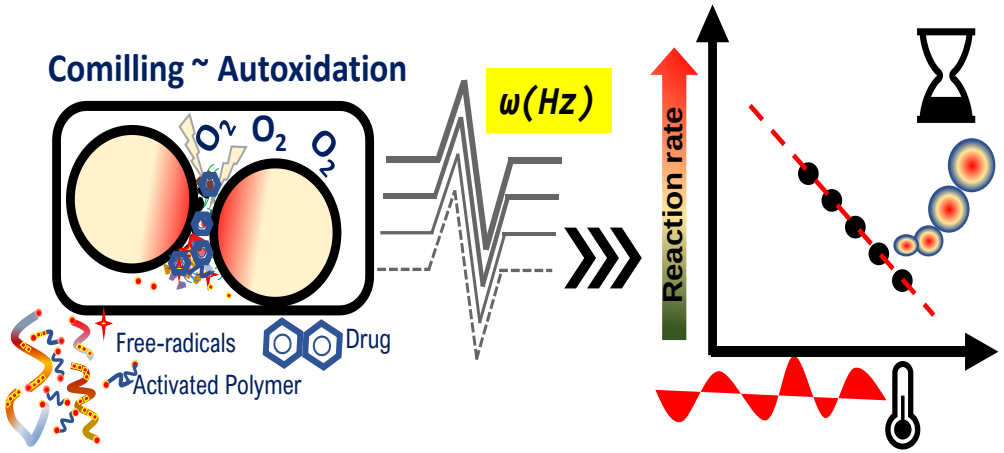




Mechano-degradation to assess the stability

Mechanoactivation–a potential tool to assess stability

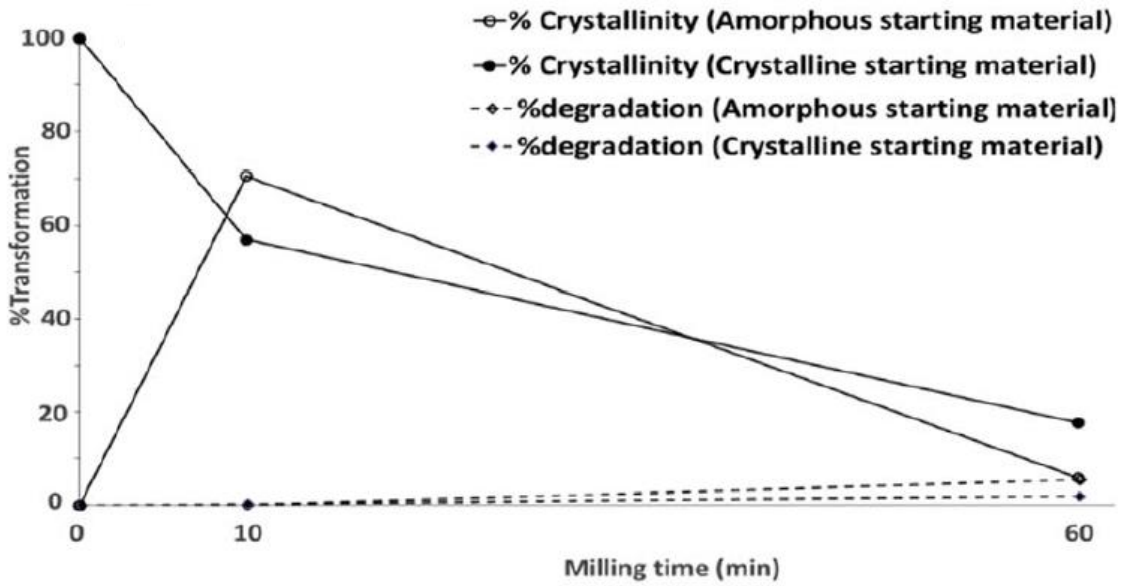
- A mature field of its own in solid-state synthesis
- Close to RT degradation reaction can be assessed
- Various parameters can be rationally optimized
- Options available for miniaturization, automation
- Possibility to co-mill drug with excipient(s) and/or with other modifiers/stressors



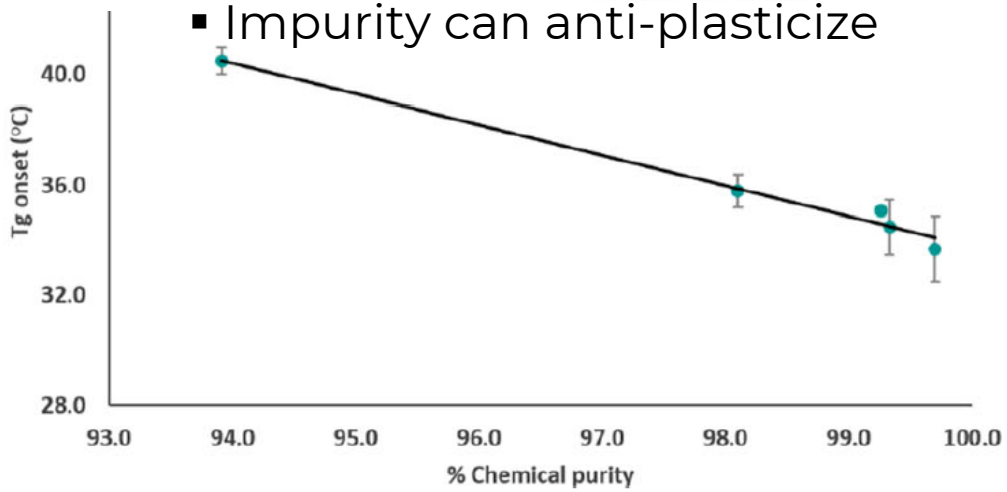
Case 1: Simvastatin

Assessing concomitant physical and chemical transition

- Solid-state transitions precede degradation



- Impurity can anti-plasticize



- Selective autoxidation

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Case 2: Variable freq milling for degradation assessment

Generated Amorphous Forms
180m BM MFP and Cryo-Quench cooled OLA

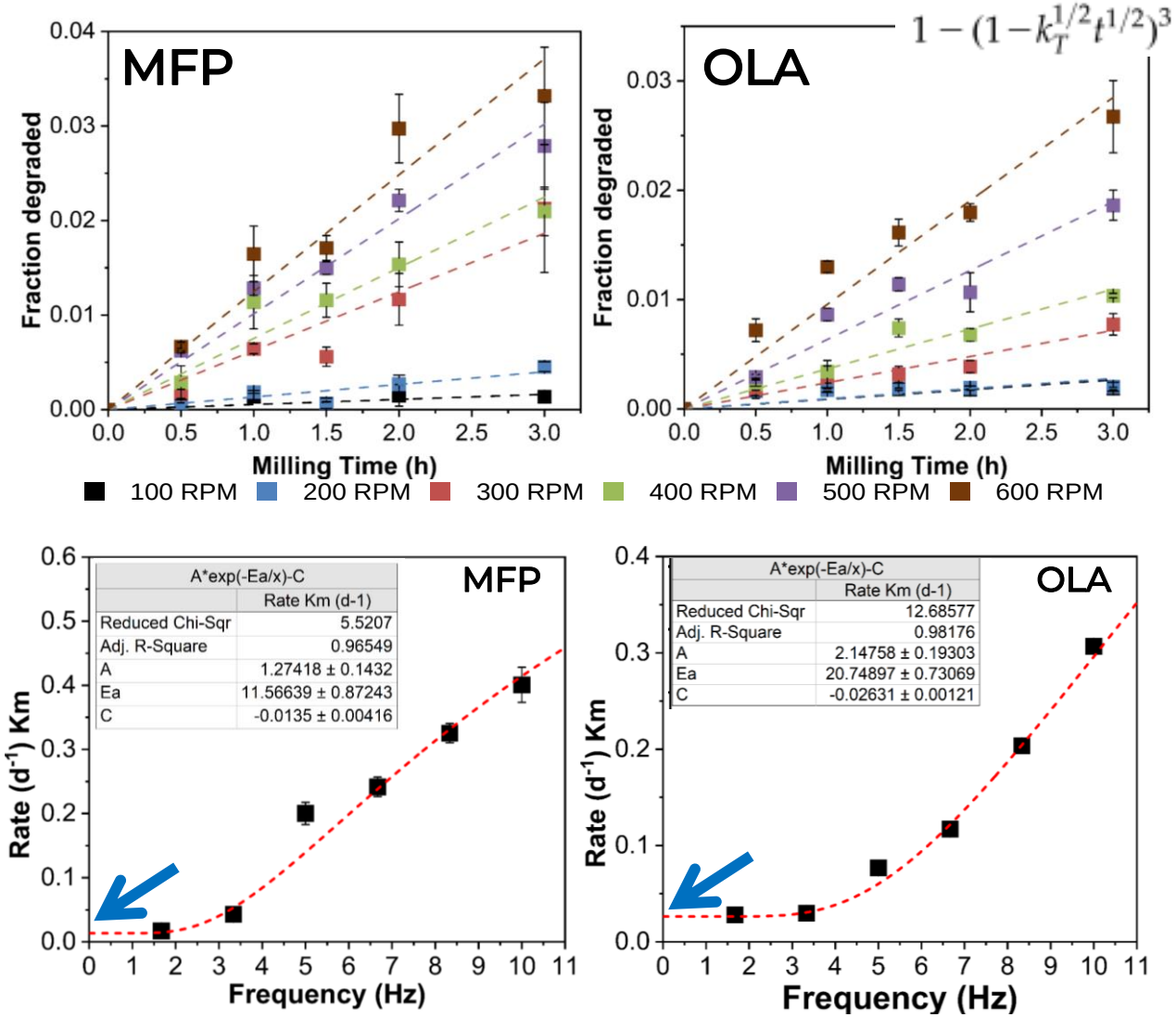
Co-mil kinetics of amo. Drugs with Copovidone Ultra S-630 (1:10)

Fitted to 3d Diffusion Model (Janders) to extract Km's

Fitting Extended Arrhenius model (Km vs Frequency)

Prediction at 0Hz?

$A*e^{(-E_a/\omega)}-C$



- Ongoing work for further optimization and generation of conventional deg. data

Drug degradation in amorphous solid dispersion

4

Amorphous solid dispersion (ASD) and autoxidation

- While the physical stability of the ASDs has been a fertile area of research, the chemical instability is largely overlooked

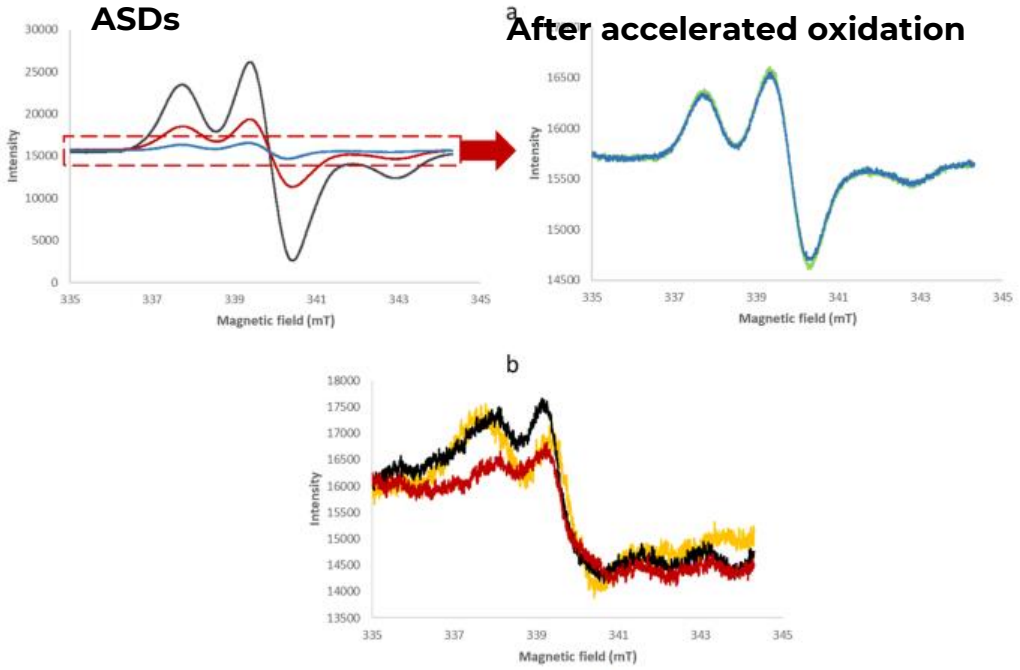
- (auto) oxidative liability can be particularly high as
  - many ASD polymer carriers can contain reactive impurities of synthetic origin (eg peroxide, free radicals), etc.
  - Reactive/oxidative species/ environment generated during stressful ASD product processing like hot melt extrusion, spray drying, mechanical milling, etc.

Nifedipine (NIF) autoxidation in NIF-PVP ASDs

condition	RT	oven			RapidOxy
	25°C/55% RH, 3 years	120 °C, 2 days	90 °C, 12 days	60 °C, 42 days	120 °C, 1 day
%DP-O (NIF-PVP K30)	1.32	2.06	2.12	2.99	19.20
%DP-O (NIF-PVP K90)	0.72	0.34	0.39	0.65	13.70
DP-O ratio (NIF-PVP K30/NIF-PVP K90)	1.83	6.00	5.51	4.62	1.40

Rapidoxy device

- ASDs prepared of NIF with PVP K30 and PVP K90 via ball milling
- Enhanced radical generation, yet no drug degradation, during ASD preparation
- C-centered radicals decreased after accelerated oxidation



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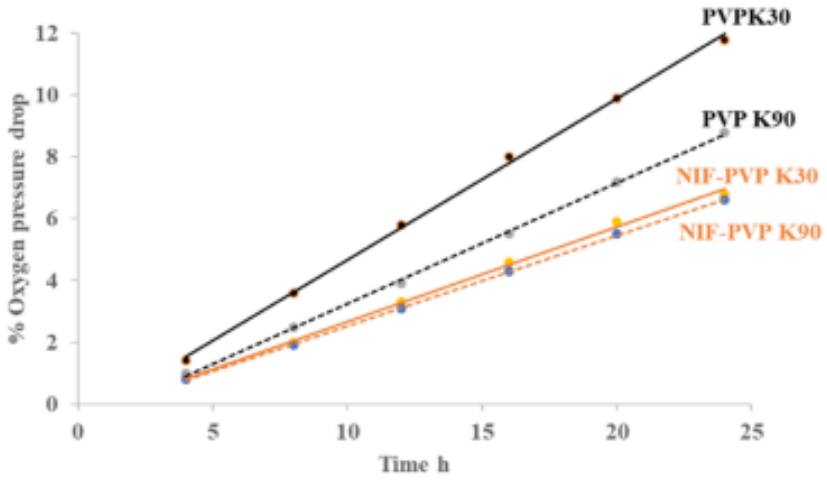
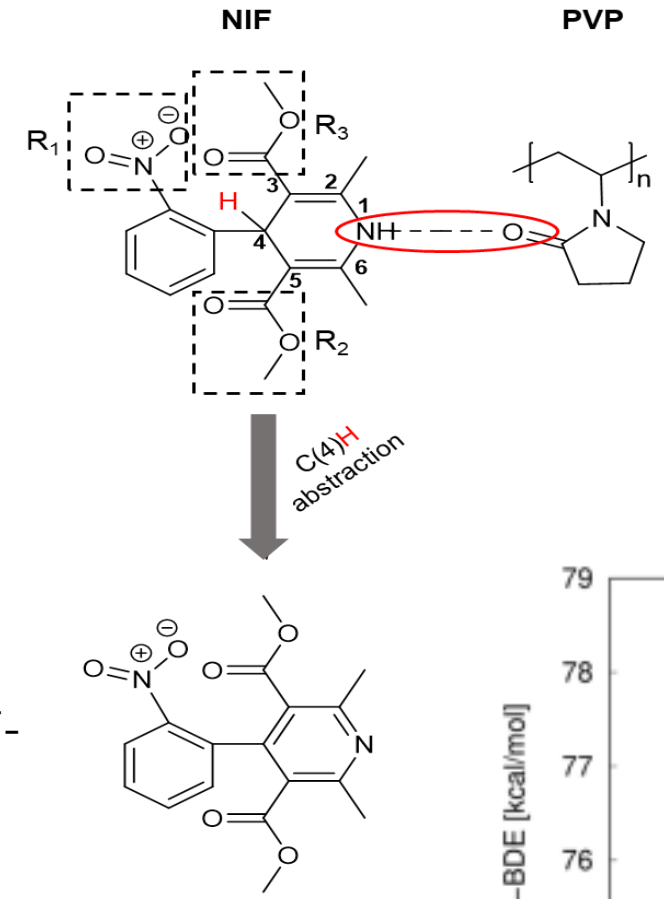
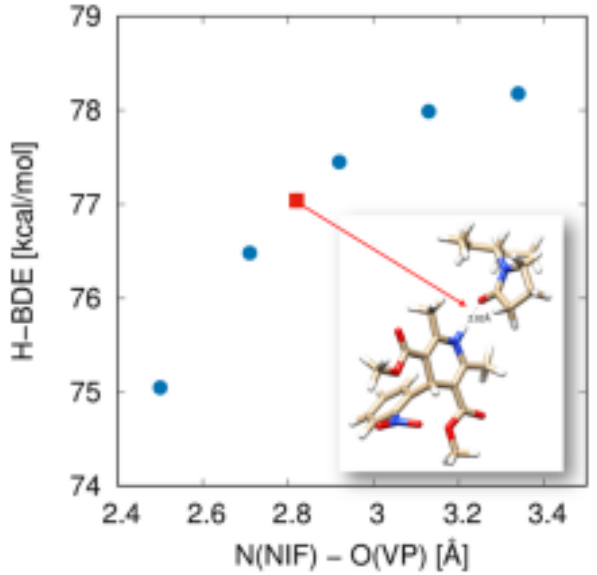
Nifedipine (NIF) autoxidation in NIF-PVP ASDs







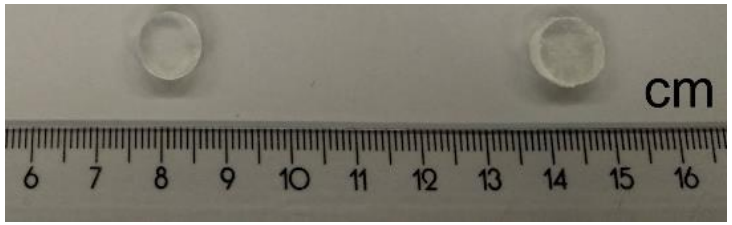
- Oxygen consumption /diffusion higher for NIF-PVP K30 ASDs
- NIF-PVP K30 with lower Tg than NIF-PVP K90

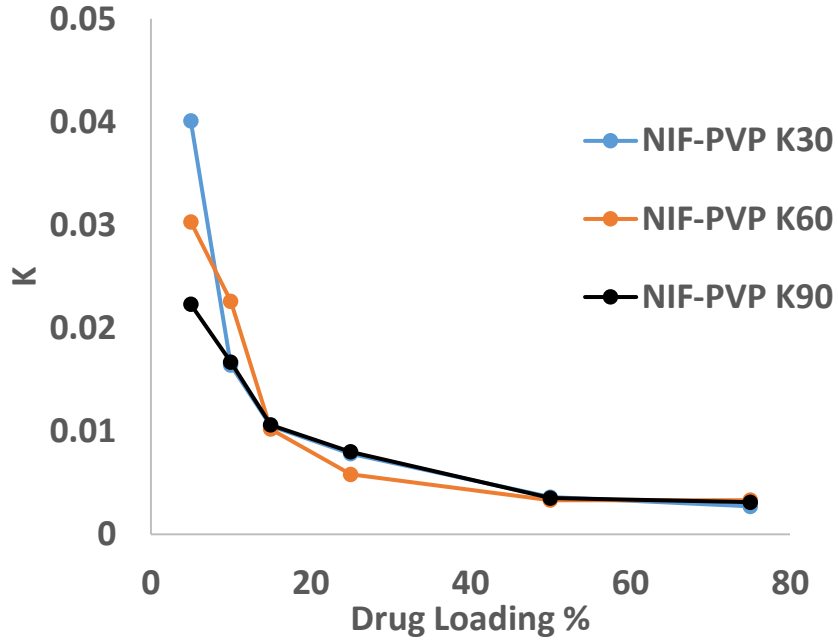
- Initial radical content in ASD, higher mobility, and oxygen diffusion, stronger H-bond interactions in K30 based system

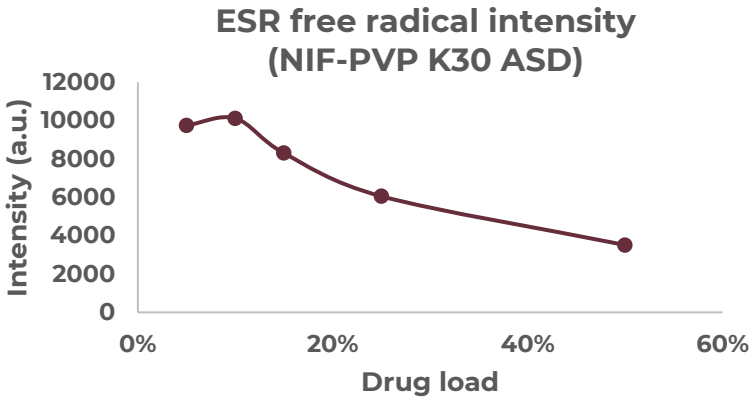
Saraf et al 2022

Drug load and degradation in NIF- PVP ASD

- ASDs were prepared as monoliths by solidifying isotropic melt, no virtually no particulate level interfaces exist (BET SSA below LoD)
- Therefore, here the effect would be dilution effect, free radical to NIF available per unit mass, and possibly other physical molecular interactions
- So, we might be dealing with fractal percolation effect (eg. interface fractal)







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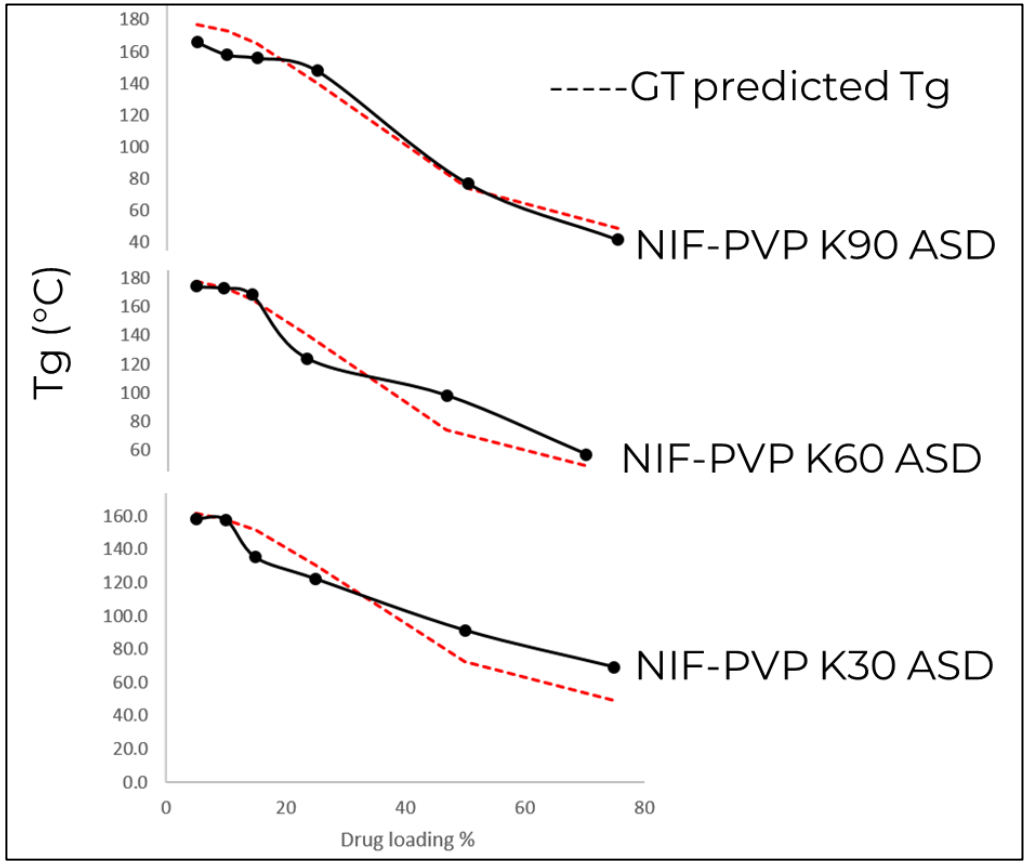
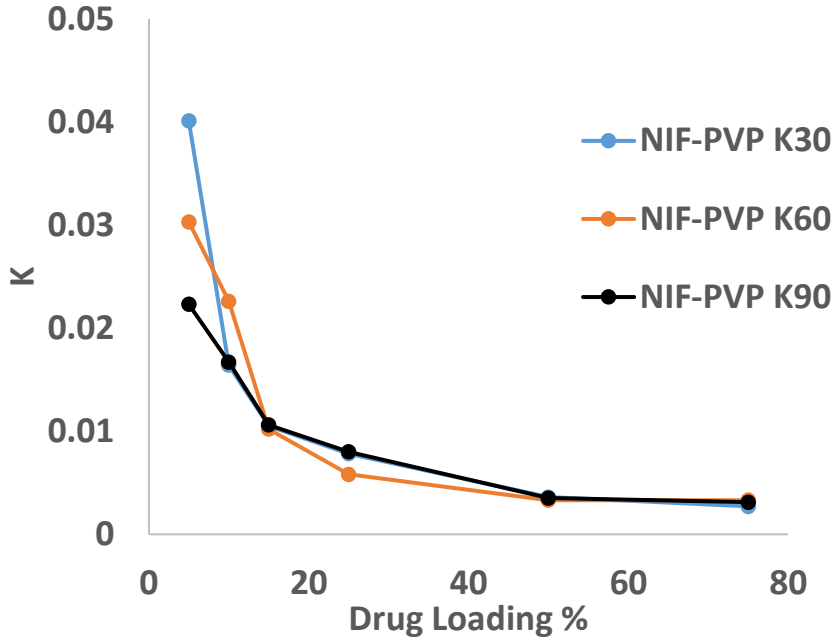
Drug load and degradation in NIF- PVP ASD

- Does molecular miscibility in ASD as a function of drug load contribute to the fractal?





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Inferences

- Disordered solid and degradation:
  - “Disordering increases degradation propensity” is not a myth, yet the relation between them may not always be proportional
  - Reverse effect: degradant´s effects on disorder stability need to be considered
  - The age of disordered solid can have a prominent impact on stability outcome

- Mechanoactivated degradation holds the potential to be further explored as an early risk assessment tool

- The chemical stability of the drug in ASD can be factored by excipient RI, and also physical interactions and drug load showed the resembling trait reported before for crystalline particle-based formulations

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Thank you!

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UNDERSTANDING DEGRADATION BEHAVIOUR OF DISORDERED PHARMACEUTICAL SOLIDS

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