

An holistic approach to profound product understanding

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Small Molecule Pharmaceutical Development | Janssen Research & Development, LLC

Art credit: Close-up of the inhibitor binding site of the colony-stimulating factor-1 receptor kinase domain.

FORCED DEGRADATION

RELEVANT DEGRADATION PATHWAYS

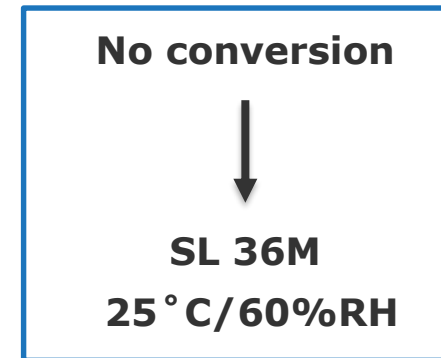
- Protonation induced elimination reaction
 - Mild acidic conditions (pH 3-6)
- Oxidation
 - H_2O_2 , metal ions and radical initiator
 - Light irradiation
- Minor degradation as solid

DRUG SUBSTANCE

RISK-BASED PREDICTIVE STABILITY ASSESSMENT

	3D	7D	14D	21D	28D	35D
T0*5						
60°C - 50%RH	-	-	-	A	A	AB
60°C - 75%RH	-	-	A	A	-	AB
70°C - 30%RH	-	-	A	-	-	AB*2
70°C - 75%RH	A	-	A	A	-	AB*2
80°C - 10%RH	-	A	-	A	-	AB
80°C - 75%RH	A	A	A*2	-	-	AB

A: Assay/Purity; B: Solid state (pXRD)

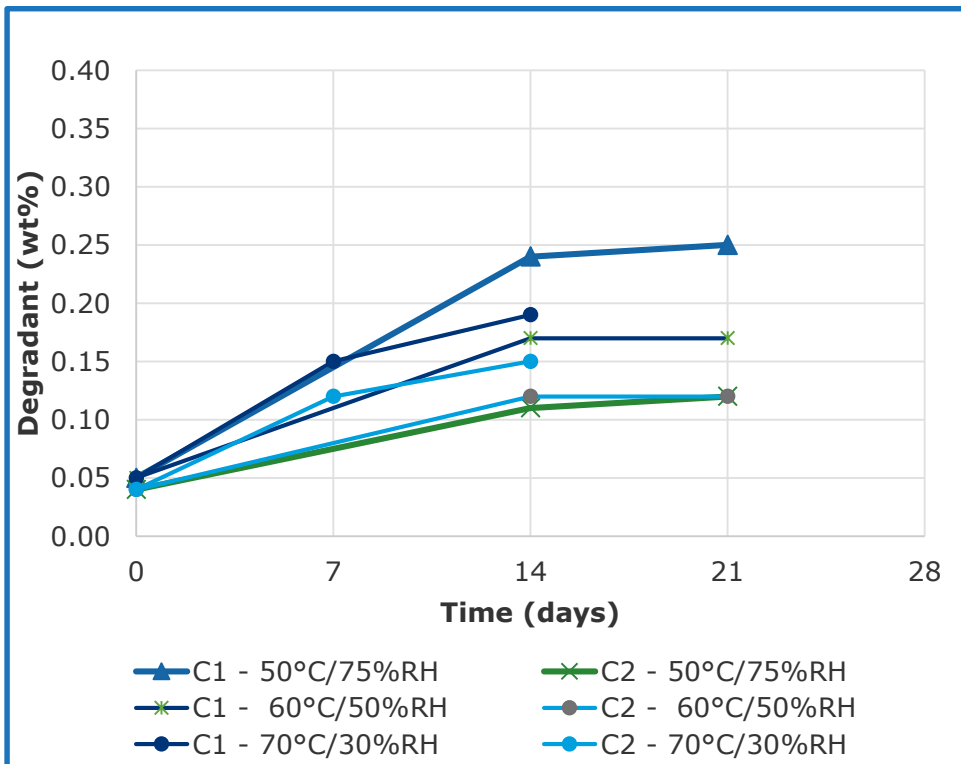


DRUG PRODUCT DEVELOPMENT

- Excipient compatibility
 - Avoid excipient with peroxide impurities
- Tablet concepts

	7D	14D	21D
50°C - 75%RH	-	A	A
60°C - 50%RH	-	A	A
70°C - 30%RH	A	A	-

DRUG PRODUCT – TABLET CONCEPT SCREENING



Main degradant: Elimination reaction
Apparent diffusion kinetics

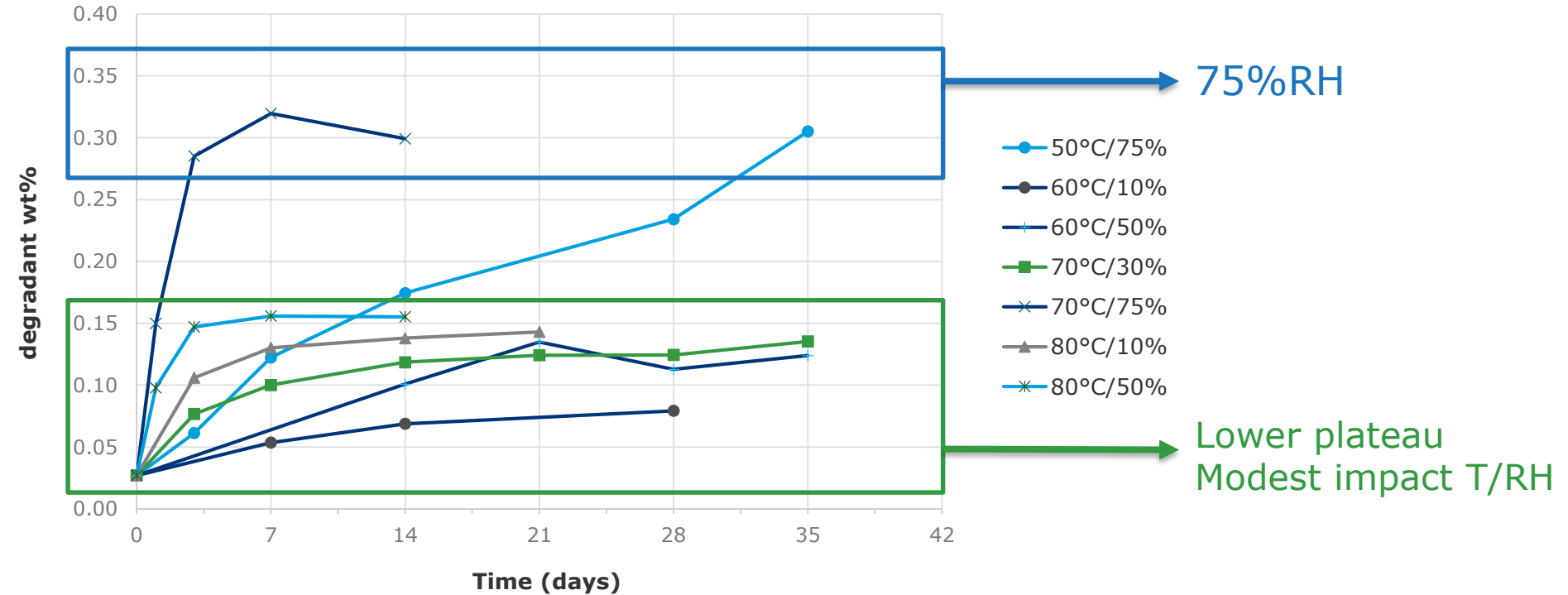
DRUG PRODUCT

RISK-BASED PREDICTIVE STABILITY ASSESSMENT

	1D	3D	7D	14D	21D	28D	35D
T0*2							
50C - 75%RH		A	A	A*2	A	A	AB
60C - 10%RH			A	A		AB	
60C - 50%RH				A	A	A	AB
70C - 30%RH		A	A	A	A	A	AB
70C - 75%RH	A	A	A*2	AB			
80C - 10%RH			A	A	A	AB	
80C - 50%RH	A	A	A	AB			

A: Assay/Purity; B: Solid state (pXRD)

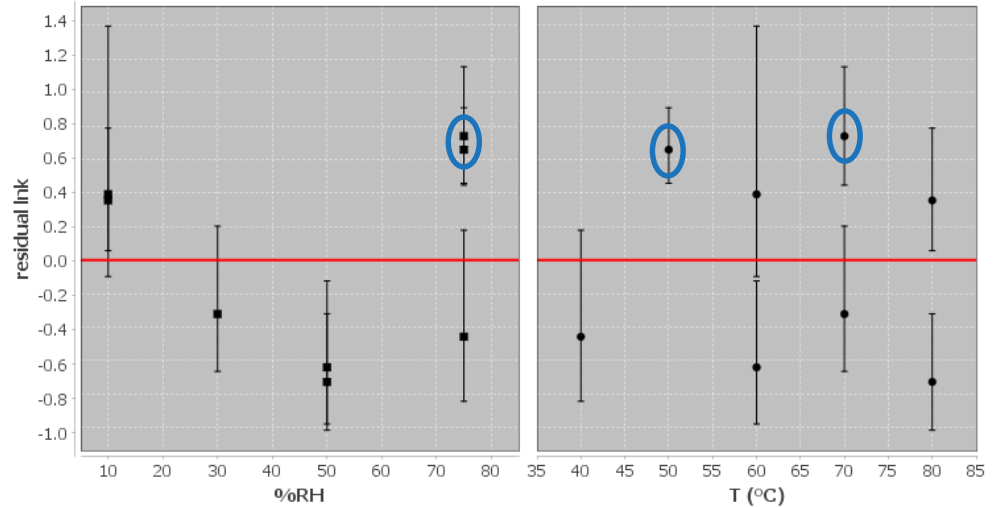
DRUG PRODUCT



DRUG PRODUCT

Model Fit: diffusion

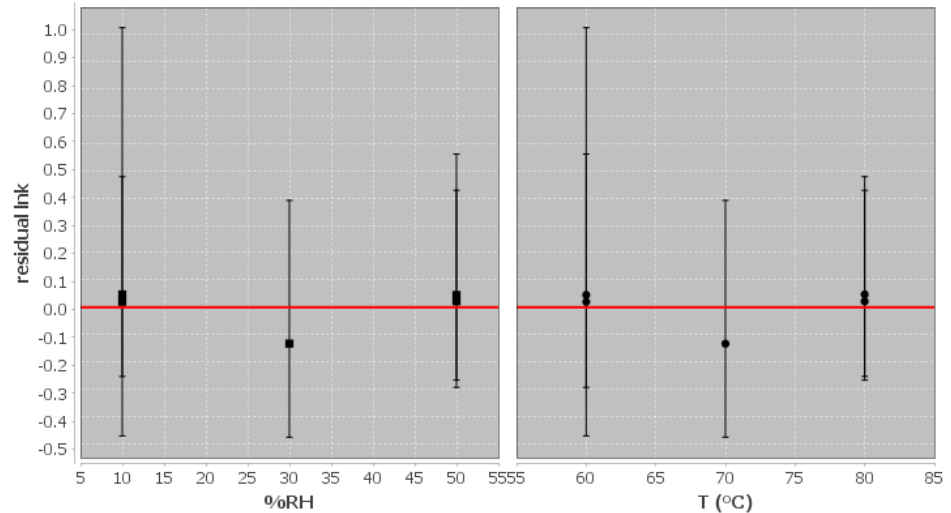
	Full data set
lnA	22.3 ± 8.9
Ea (kcal/mol)	20.3 ± 6.2
B	0.06 ± 0.02
R2	0.84
Q2	0.54



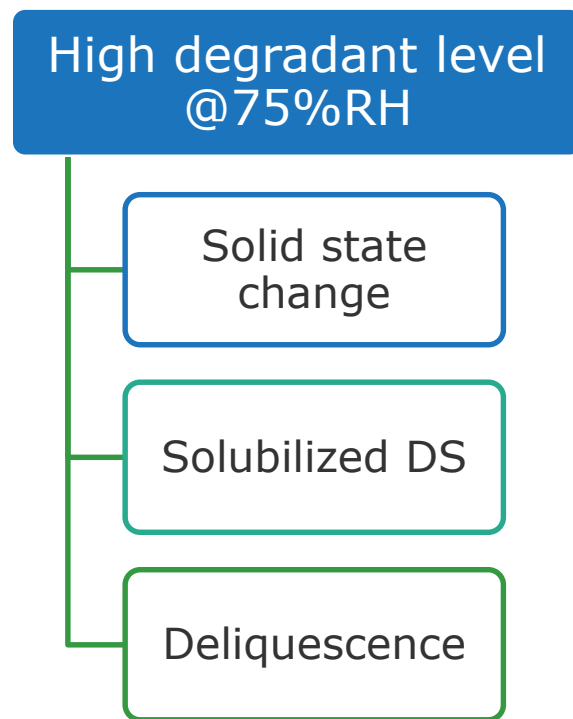
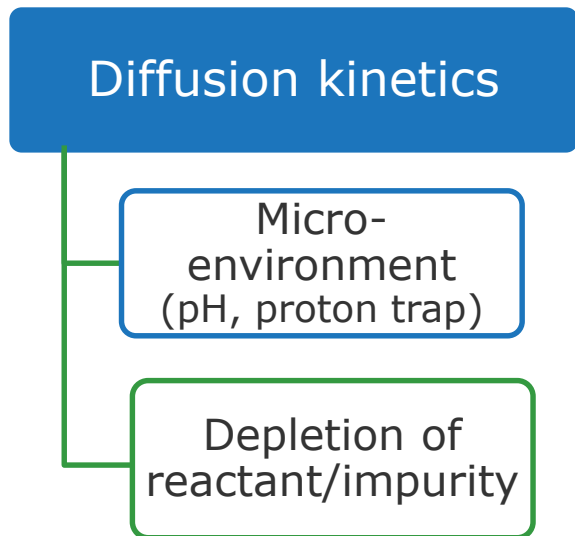
DRUG PRODUCT

Model Fit: diffusion - omitting 75%RH

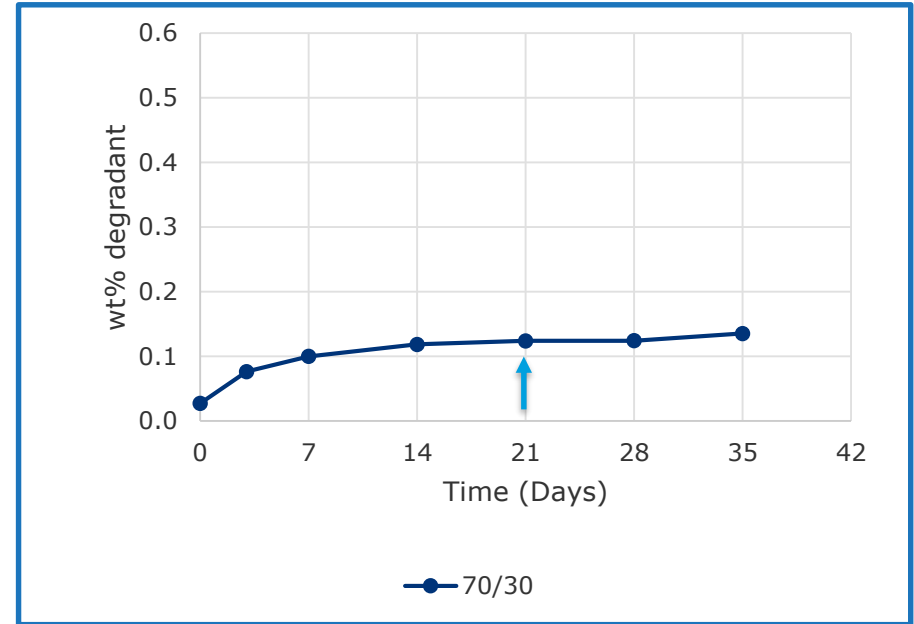
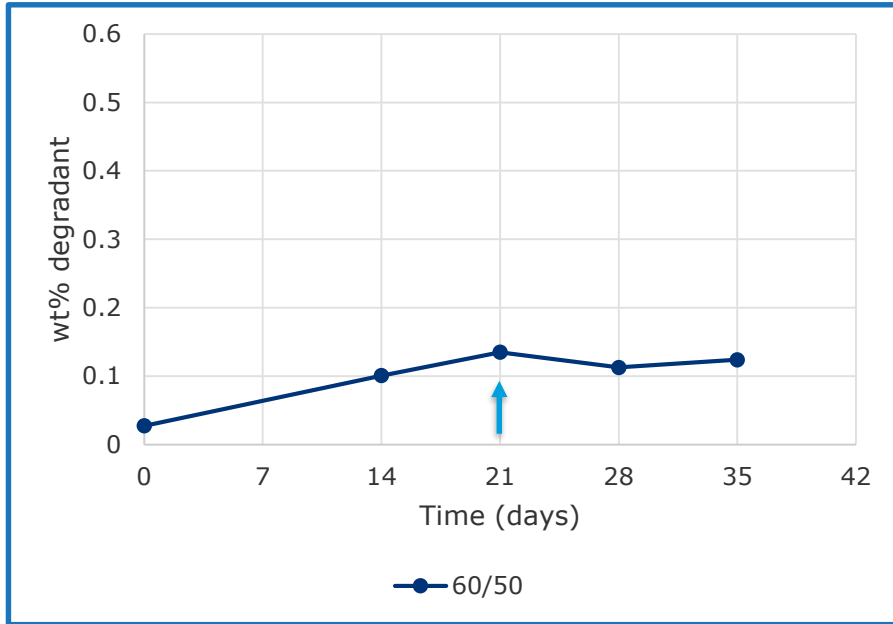
	Full data set
InA	21.8 ± 8.7
Ea (kcal/mol)	19.5 ± 6.0
B	0.03 ± 0.01
R2	0.99
Q2	0.98



ROOT CAUSE INVESTIGATION

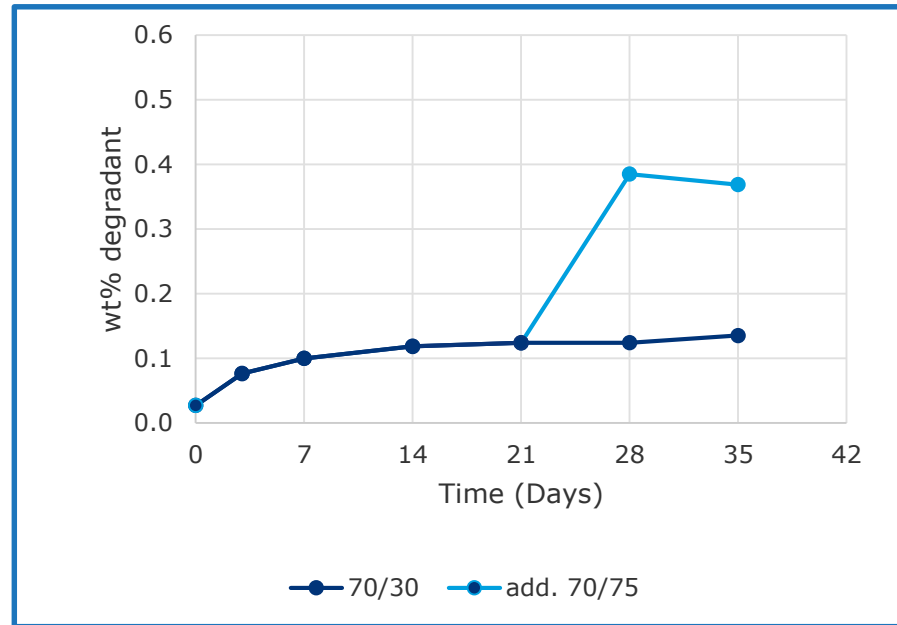
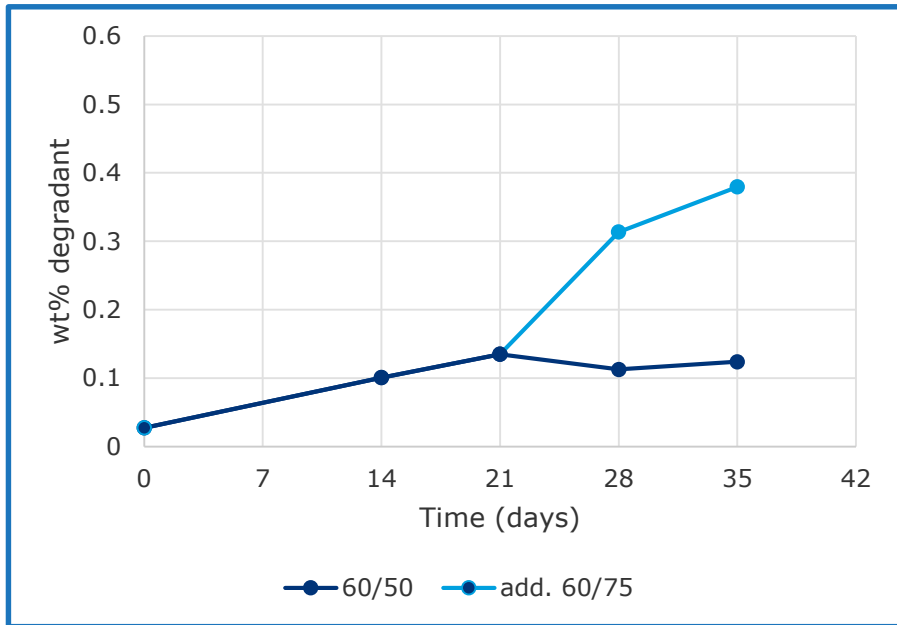


MICRO-ENVIRONMENTAL OR SURFACE EFFECT EXPOSE STRESSED TABLETS TO 75%RH



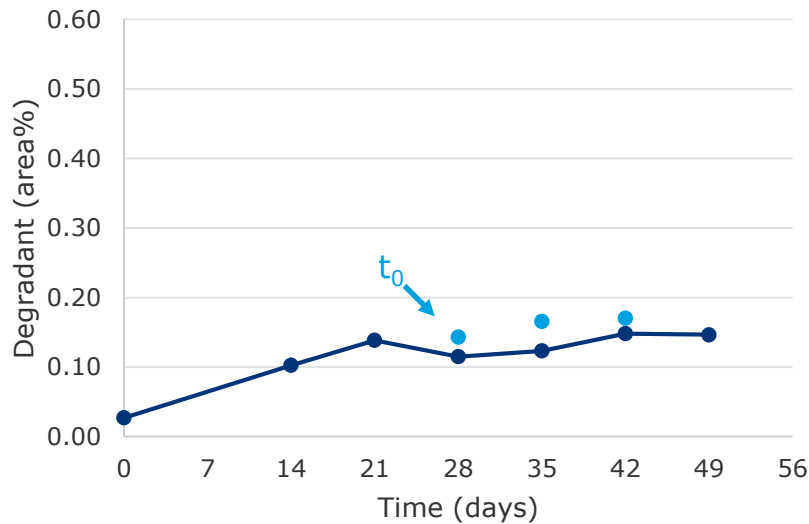
MICRO-ENVIRONMENTAL OR SURFACE EFFECT

EXPOSE STRESSED TABLETS TO 75%RH

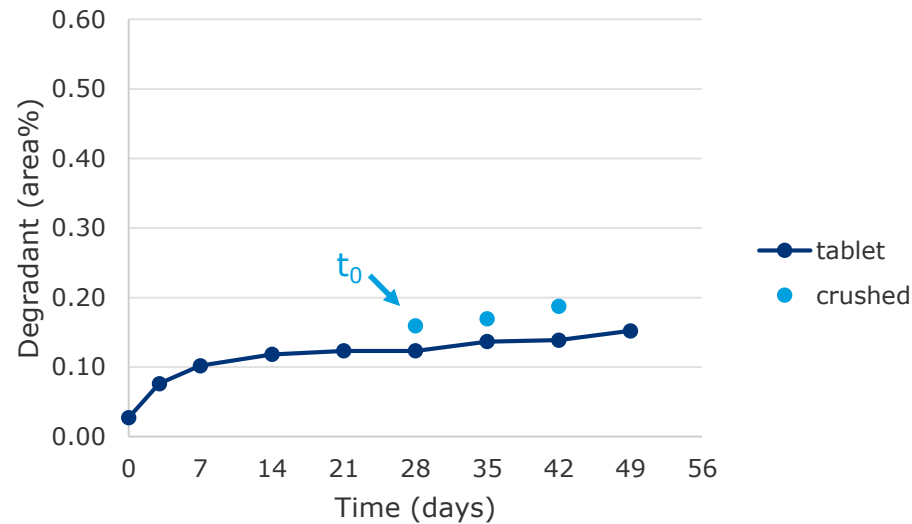


MICRO-ENVIRONMENTAL OR SURFACE EFFECT GROUND TABLETS (CONE MILL)

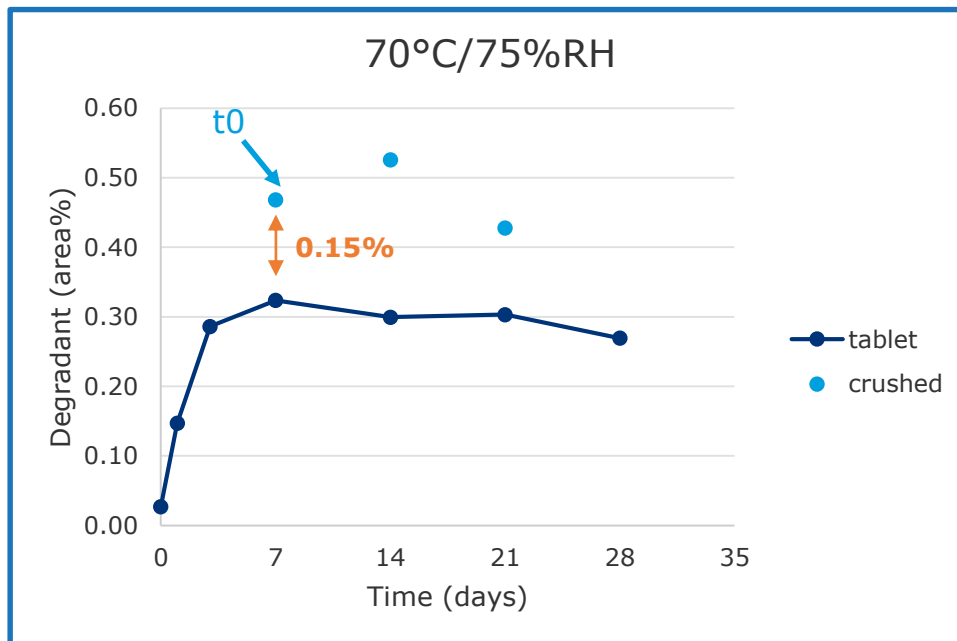
60°C/50%RH



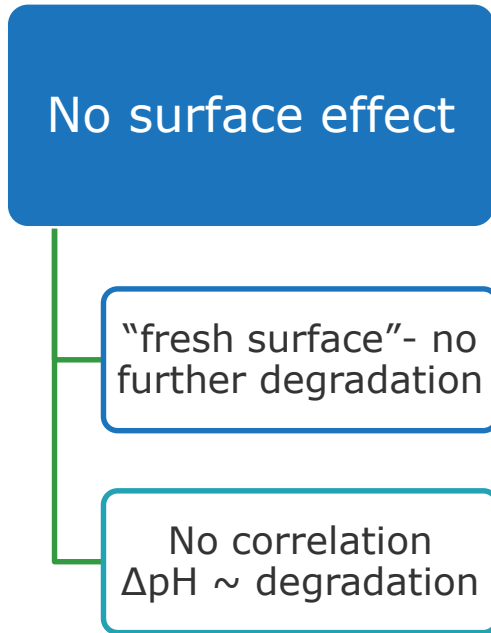
70°C/30%RH



MICRO-ENVIRONMENTAL OR SURFACE EFFECT GROUND TABLETS (CONE MILL)



MICRO-ENVIRONMENTAL OR SURFACE EFFECT







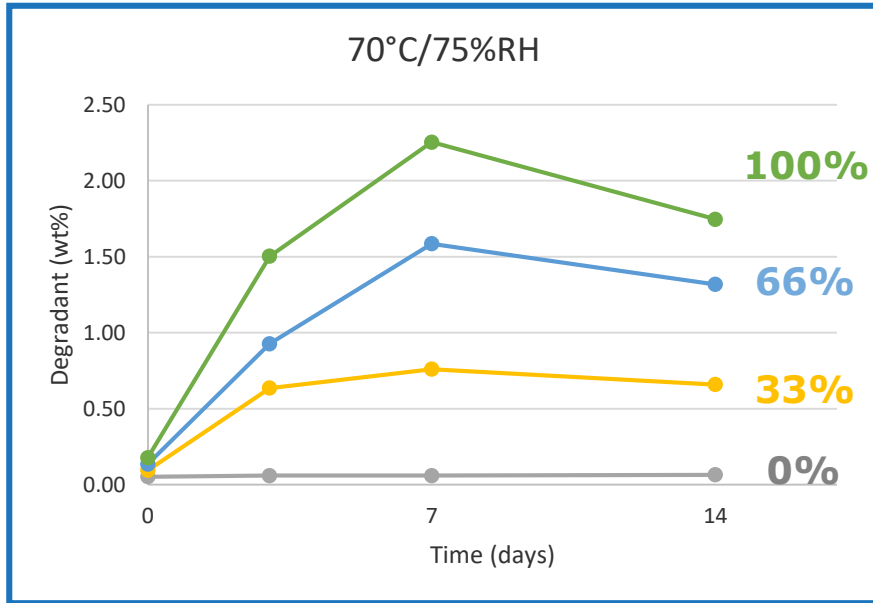
TRACES OF AMORPHOUS DS

Tablet blends

- Amorphous DS (ball milling)
- Crystalline DS
- Amorphous/Crystalline (2/1 - 1/2)

Storage conditions: 70°C/75%RH

DEPLETION OF REACTANT/IMPURITY AMORPHOUS VS CRYSTALLINE DS



—●— Cryst DS + FB

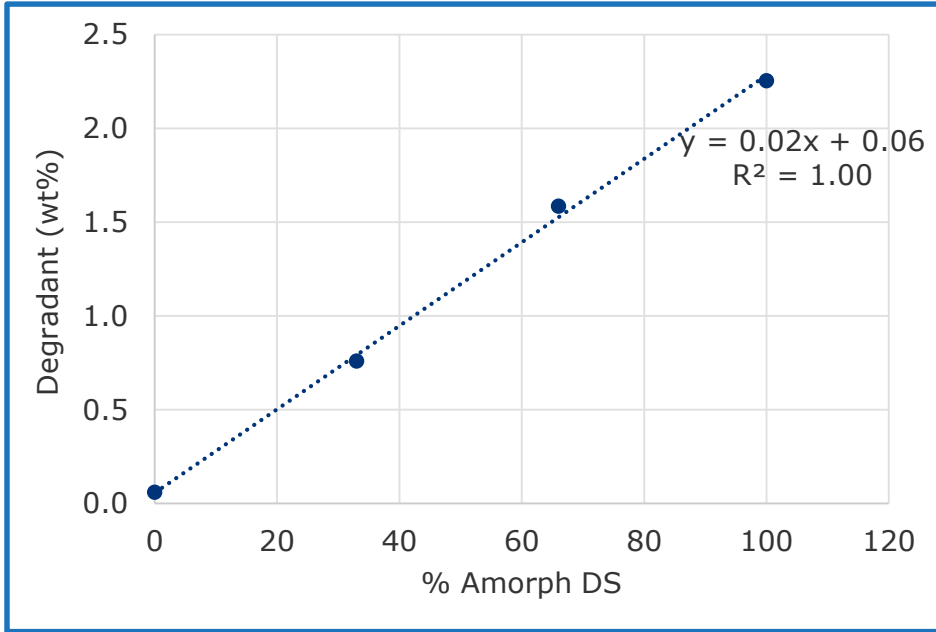
—●— Cryst/Amorph 2:1 + FB

—●— Cryst/Amorph 1:2 + FB

—●— Amorph DS + FB



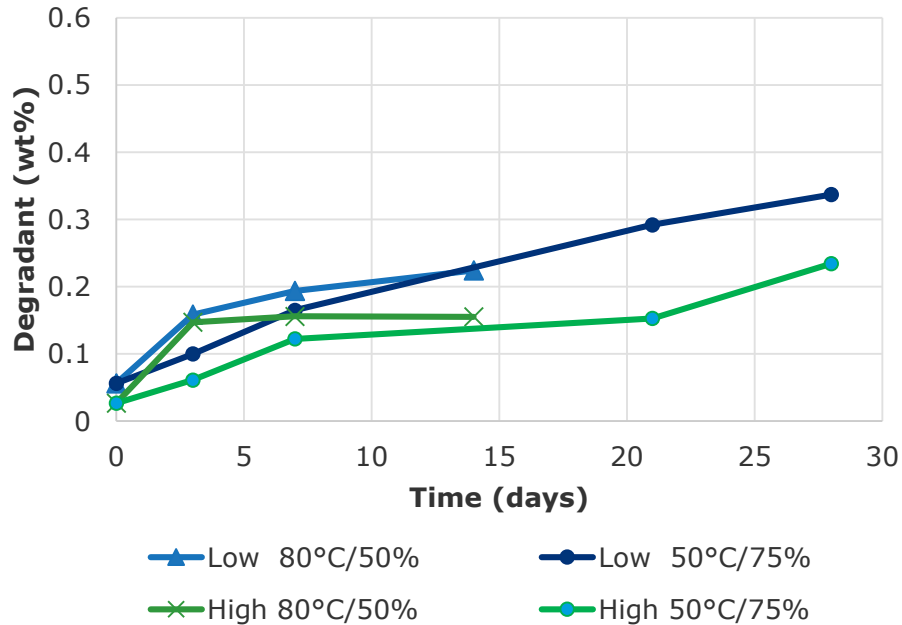
DEPLETION OF REACTANT/IMPURITY AMORPHOUS VS CRYSTALLINE DS



Blend crystalline DS \rightarrow \sim 0.06 wt%
Tablets same batch DS \rightarrow \sim 0.3 wt%
 \rightarrow \sim 10% amorphous DS
 \rightarrow Induced during compression

TABLET PROCESS INDUCES AMORPHOUS DS

TABLET VARIATIONS – 2 STRENGTHS, ≠ SHAPE



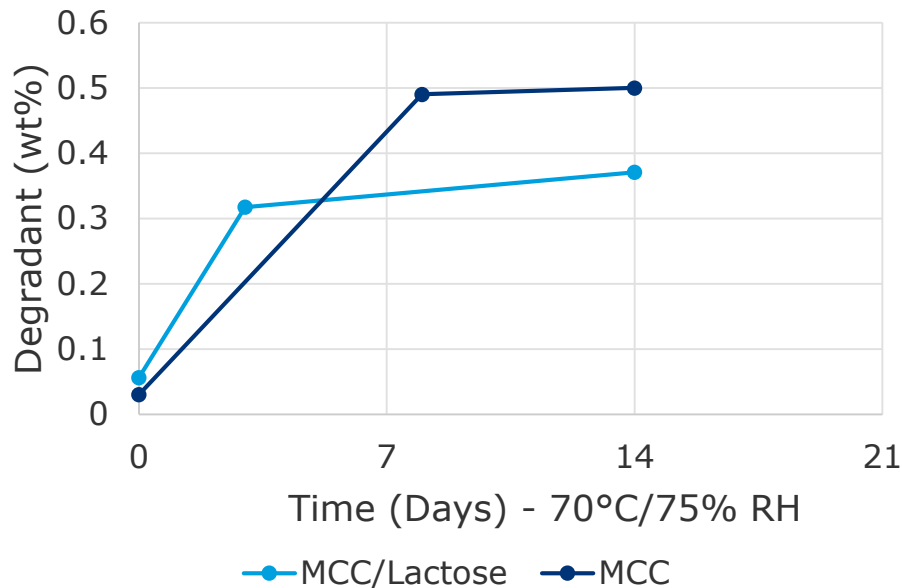
Low strength slightly higher degradant level

→ More amorphous DS induced (~5%)

→ More shear stress during compression

TABLET PROCESS INDUCES AMORPHOUS DS

TABLET VARIATIONS – FILLER 100% MCC vs MCC/LACTOSE



Higher degradant level with 100%MCC

→ More hygroscopic ($\sim 1\%$ H₂O)

→ More amorphous DS induced ($\sim 5\%$)*

* Huang et al, Mol. Pharmaceutics 2019, 16, 825-833

Challenges to quantify amorphous content



Thank you!

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Art credit: Close-up of the inhibitor binding site of the colony-stimulating factor-1 receptor kinase domain.