Applications of Predictive Stability in Early Development

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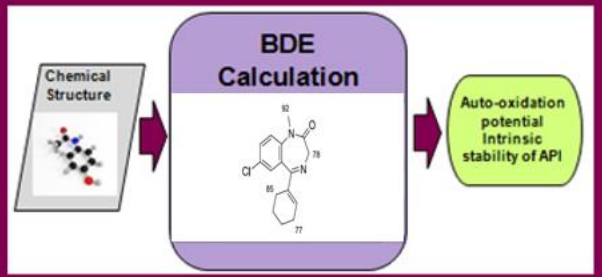
Overview

- Predictive stability tools
  - BDE tool
  - Zeneth
  - ASAP
  - Packaging predictions
- Phase I development case studies
  - IV solution
  - Tablet
  - Capsule
- Conclusions

Predictive Stability Tools

Bond Dissociation Energy (BDE) Tool

Predicts risk of autoxidation

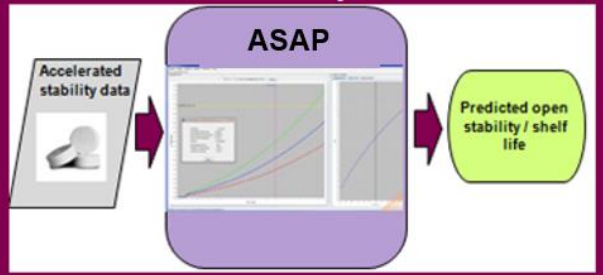


Zeneth

Predicts potential degradants and excipient interactions

ASAP Studies

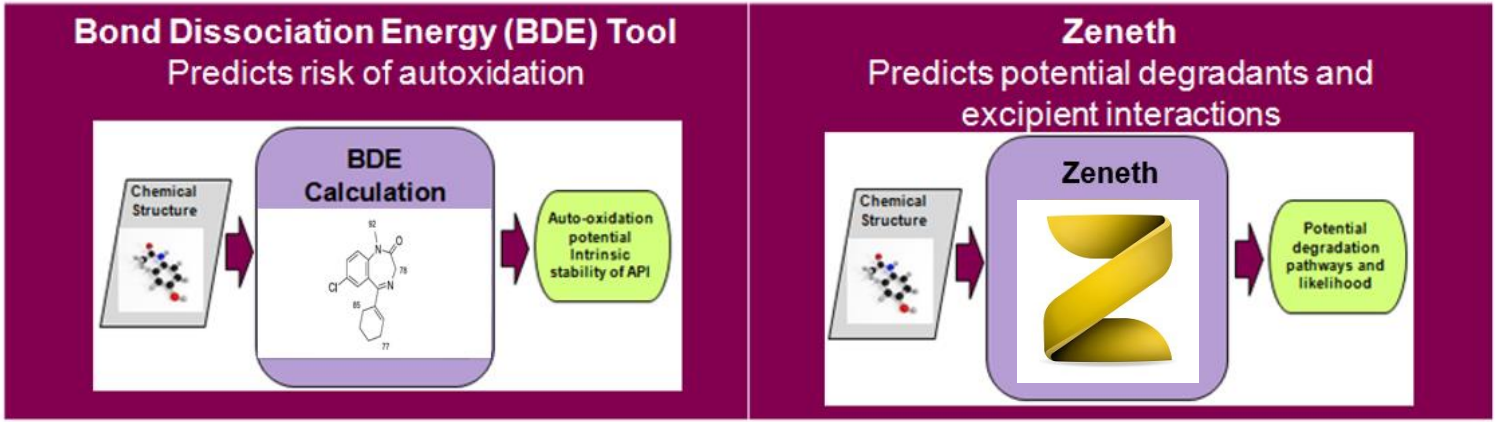
Predict shelf life from stressed chemical stability studies



Packaging Predictions

Predicts product water content on storage and in use stability

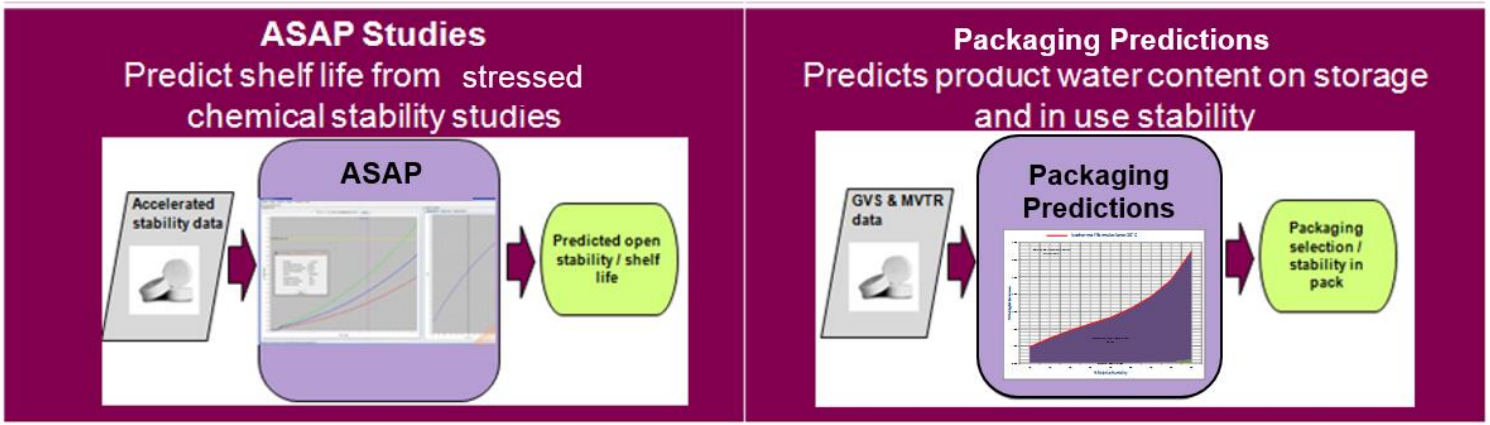
Predictive Stability Tools



- Determine risk of autoxidation
- Performed early in development
- Used to compare lead compounds
- If autoxidation risk identified, followed up with EPR spectroscopy analysis to monitor for radical formation

- Determine potential degradants
- Performed early in development before forced degradation studies and method development
- Used to identify possible excipient incompatibilities to support formulation development

Predictive Stability Tools

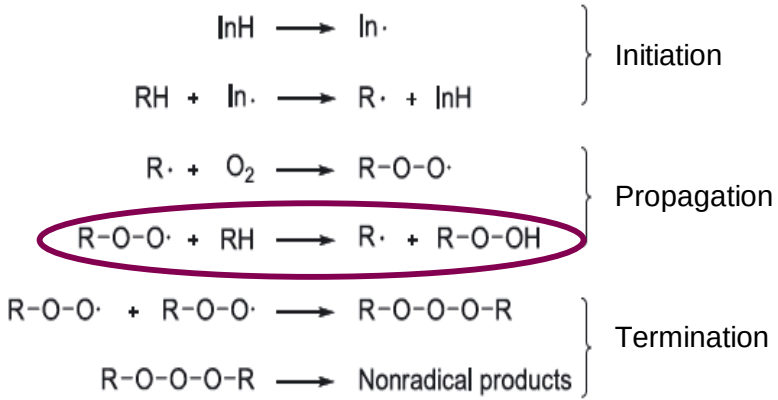


- Used throughout development to predict drug substance or product stability

- Used to support pack selection
- Determine the need for desiccant
- Set water content specifications
- Used to support pack changes during development
- Used to support pack changes post approval

Bond Dissociation Energy Tool

The BDE values can be accurately calculated for hydrogen atoms in a molecule using relatively fast DFT methods[1]. The risk of autoxidation can then be estimated.

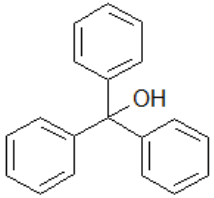


BDE < 87 kcal/mol = risk for autoxidation

In principle, the chain reaction can be fast as long as the breaking CH-bond is weaker than the OH bond (87 kcal/mol) that is formed in the hydrogen transfer.

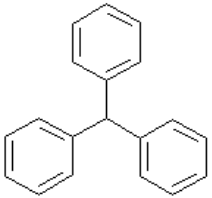
[1]T. Andersson, A. Broo, E. Evertsson, *J. Pharm. Sci.* 103, (2014), 1949-1955

Bond Dissociation Energy Tool



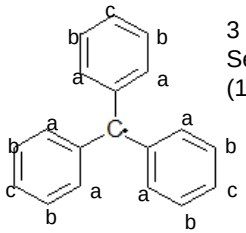
Triphenylmethanol

BDE = 96 kcal/mol



Triphenylmethane

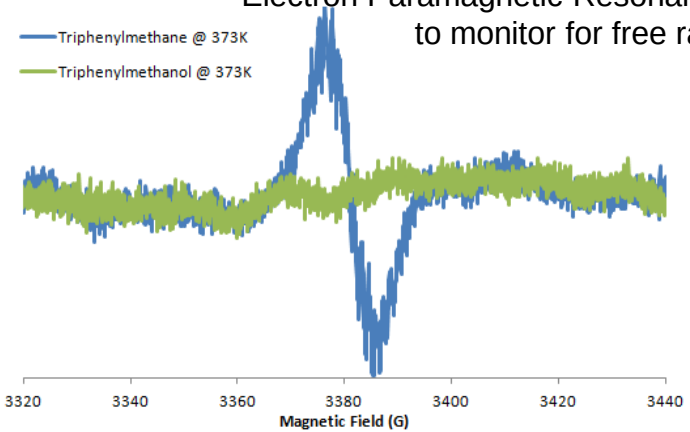
BDE = 72 kcal/mol

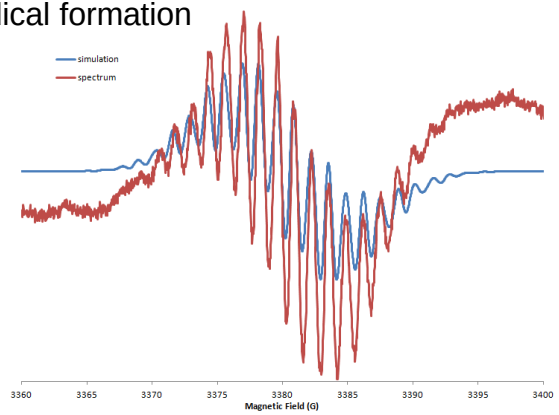


Triphenylmethane radical

3 types of non-equivalent protons
Septet of septet of quartets
(196 lines!)

Electron Paramagnetic Resonance spectroscopy performed to monitor for free radical formation





Simulation based on coupling constants from [2] P. Brovetto, G. Bussetti, Rendiconti del Seminario della Facoltà di scienze dell'Università di Cagliari, 39 (3-4) p.387

Zeneth

Zeneth is designed to predict potential degradants of a compound from the chemical structure.

- 446 known and validated transformations (version 7.0, 2016 knowledge base)
- Data from published sources and data donated by a consortium of member organisations
- Drug Substance and Drug Product stability

Benefits of Zeneth[3]:

- Provides degradation information when no experimental data is available
- Data generated can be used to support regulatory submissions
- Assist in the selection of excipients, highlighting potentially problematic ones
- Helps in assignment of structure to forced degradation work
- Prevents the overlooking of possible pathways through unbiased application of transformations
- Presence or absence of conditions (light, water, oxygen, radical initiators, peroxides, metal, temperature, pH)
- Relative likelihood of competing reactions

[3] http://www.lhasalimited.org/products/zeneth.htm

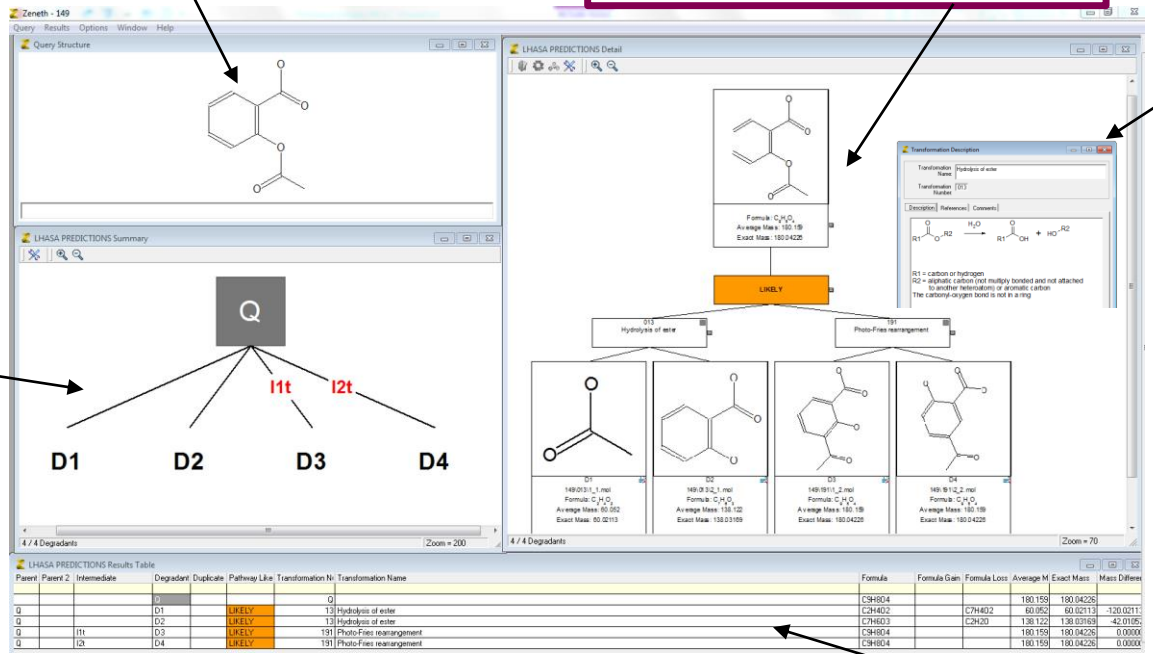
Zeneth

Example query compound

Zeneth predictions displayed in a tree layout. Zoom out for high level view & zoom in for compound specific detail

Transformation description and references to supporting literature

Simplified tree view of results



Zeneth also includes a list of common excipients and is able to predict whether they are likely to interact with the query compound

Table to show all degradants generated. Can be filtered upon molecular formula or molecular mass

ASAP Studies

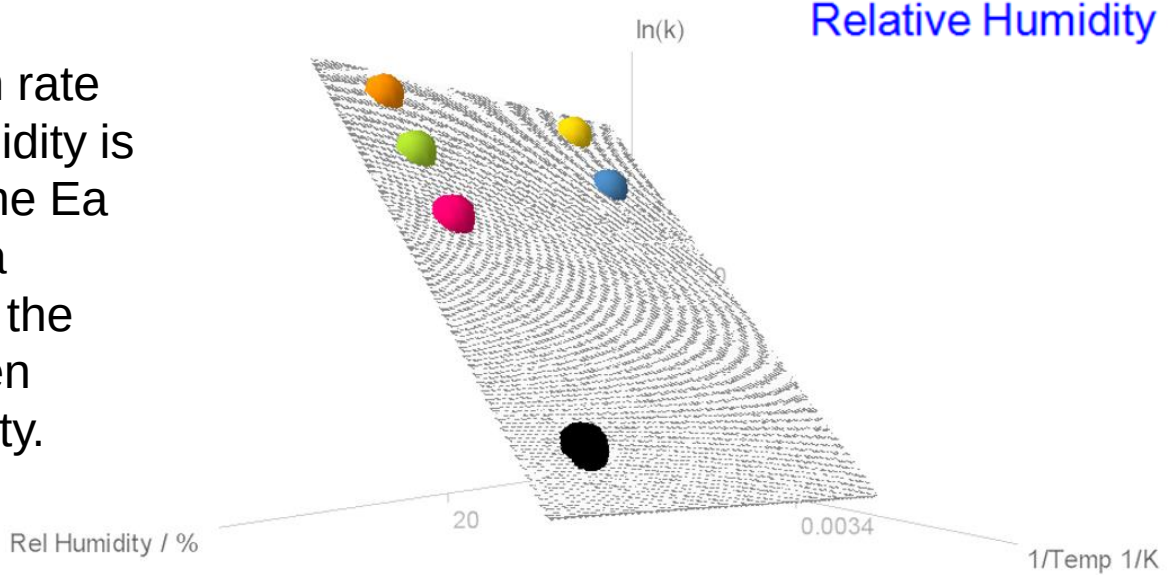
Based on the Arrhenius equation modified for solid state degradation

Sensitivity to moisture

$$\ln(k) = \ln(A) - Ea/RT + (B \times RH)$$

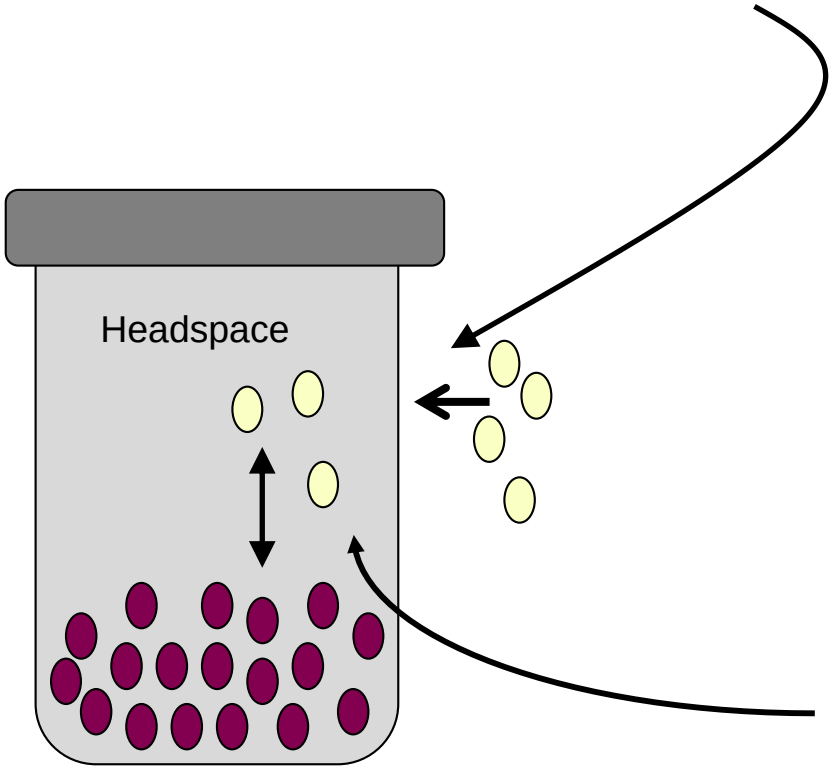
Relative Humidity (%)

If the change in reaction rate with temperature & humidity is measured, can determine Ea and ln (A) and B and via extrapolation determine the reaction rate at any given temperature and humidity.



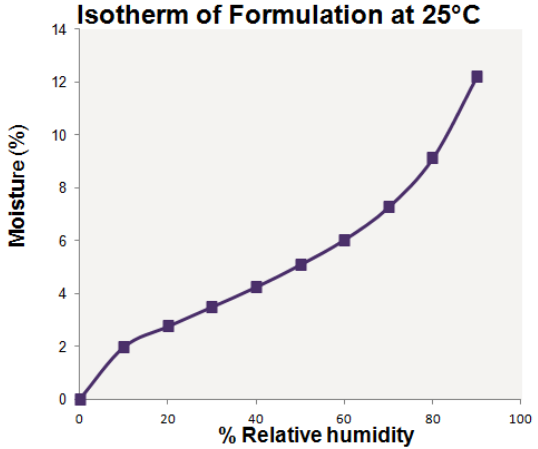
K. Waterman and S.Colgan, *Regulatory Rapporteur*, 5 (2008) 9-14.
K.Waterman et al, *Pharm. Res.*, 24 (2007) 780-790.

Packaging Predictions



Depends on permeation of the barrier

Difference in partial pressure of water between ambient environment and headspace



Equilibrium between headspace and tablets is defined by the Gravimetric Vapour Sorption isotherm of the tablets

Phase I formulation development - IV solution

Applications of predictive stability tools

1. Drug substance – BDE and Zeneth predictions
2. Drug substance - ASAP study
3. Drug product – Zeneth predictions, excipient incompatibilities
4. Drug product prototype screening – ASAP
5. Drug product shelf life prediction – ASAP
6. Regulatory Applications

Phase I formulation development - IV solution

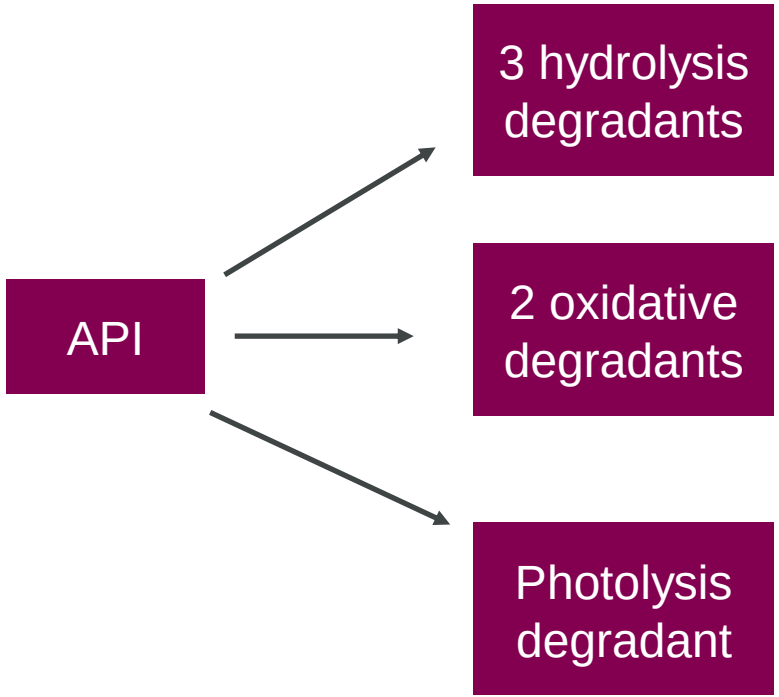
1. Drug substance – BDE and Zeneth predictions

Zeneth Conditions

- 20°C, pH 1, 4, 7, 10 and 14 in presence of water, peroxides, radical initiators, metals, oxygen and light
- 50°C, pH 1, 7 and 14 in presence of water, peroxides, radical initiators, metals, oxygen and light
- A second screen in the presence of formaldehyde was performed
- Only degradants deemed likely or highly likely were included
- To simplify the screen secondary degradants were only investigated when deemed very likely
- Similarly degradants were not allowed to react with themselves

Phase I formulation development - IV solution

1. Drug substance – BDE and Zeneth predictions



Lowest BDE = 84 kcal/mol

In line with one of Zeneth oxidation predictions

Phase I formulation development - IV solution

2. Drug substance ASAP study

Temperature (°C)	Humidity (% RH)	Storage Time (weeks)
Initial	Initial	0 (3 repeats), X
50	75	3, Sx2
60	11	3, Sx2
60	75	3 (5 repeats), Sx2
70	11	3, Sx2, C, X
70	75	3, Sx2, C, X
80	30	3, S, C, X

Impurities analysis by LC at all time points
S = spare samples, pulled after 8 and 12 weeks
X = XRPD sample, C = sample for chiral testing

No degradation was observed

Phase I formulation development - IV solution

3. Drug product – Zeneth predictions, excipient incompatibilities

No interactions were predicted by Zeneth between the API and any of the excipients or known excipient impurities.

Zeneth did not predict a peroxide mediated degradation mechanism for the API.

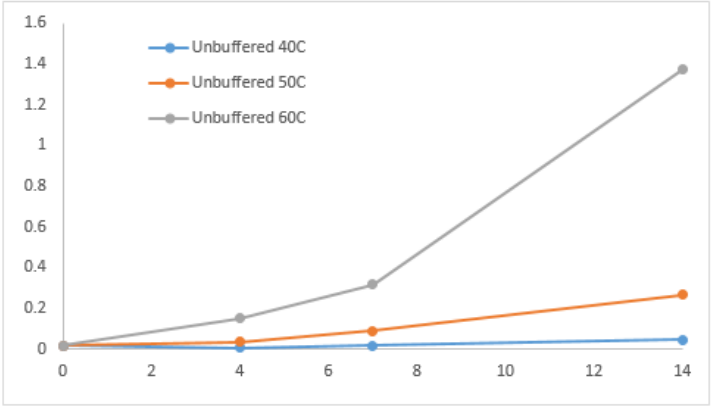
Based on these predictions there was a low risk of an API:excipient interaction in this formulation.

However API degradation is known to be pH dependant.

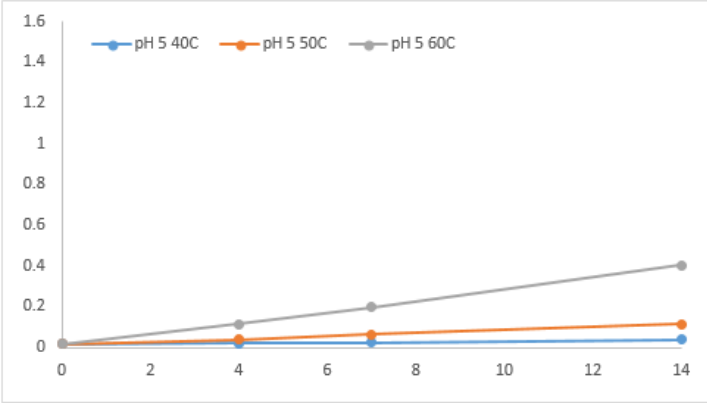
Phase I formulation development - IV solution

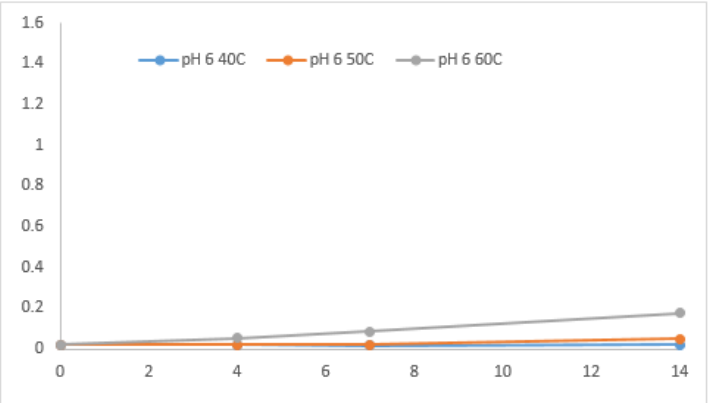
4. Drug product prototype screening – ASAP

Three formulations screened; unbuffered, pH 5 and pH 6
One main hydrolysis degradant observed (previously predicted by Zeneth)



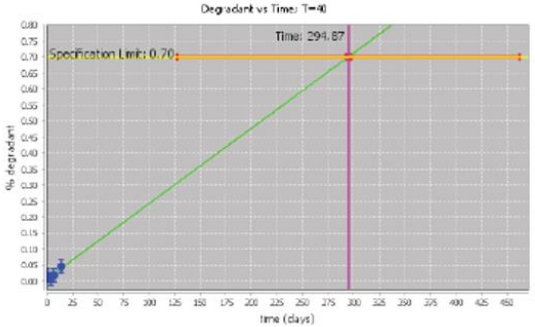
Unbuffered solution gave most degradation followed by pH 5 and then pH 6 the least degradation

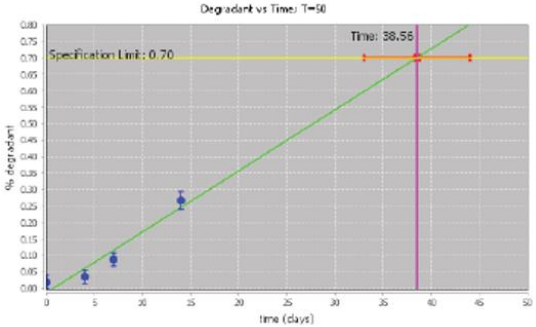




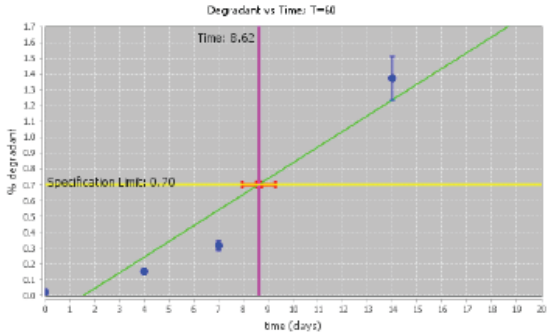
Phase I formulation development - IV solution

4. Drug product prototype screening – ASAP





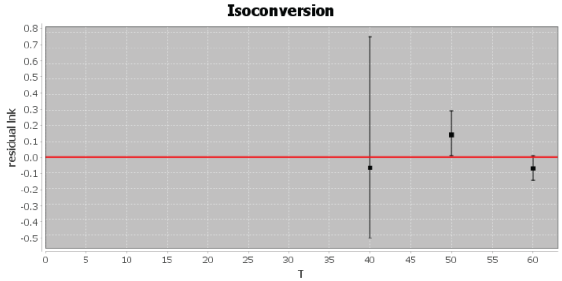
Unbuffered solution results
Assuming linear fit to the degradation kinetics



Arrhenius Data

lnA	52.9	±	8.8	
E_a	36.6	±	5.8	kcal/mol
B	-	±	-	
R^2	1.00			
Q^2	0.93			

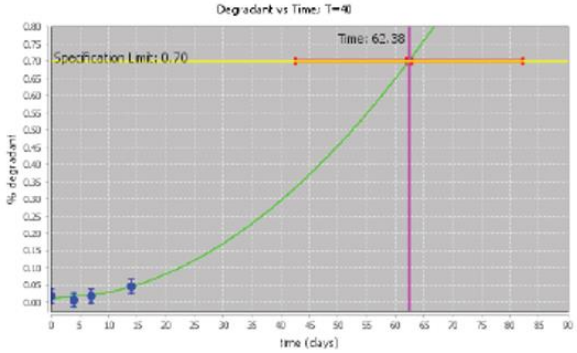
Residual Plot

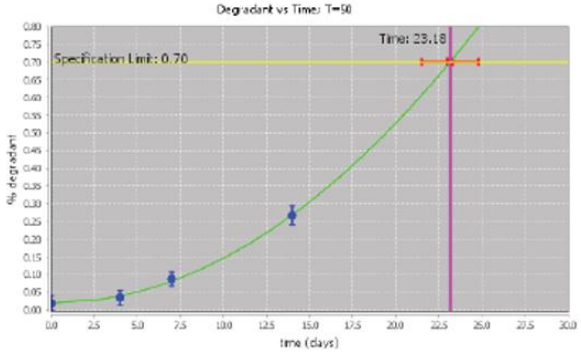


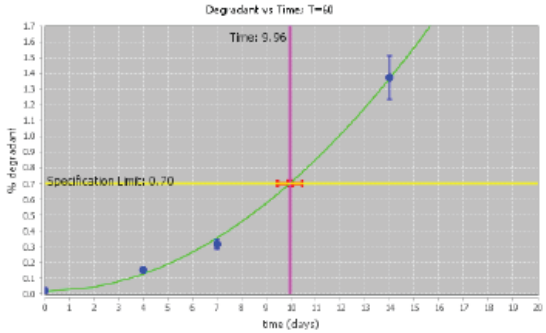
A “good” model was generated, although limited degradation at some conditions.

Phase I formulation development - IV solution

4. Drug product prototype screening – ASAP



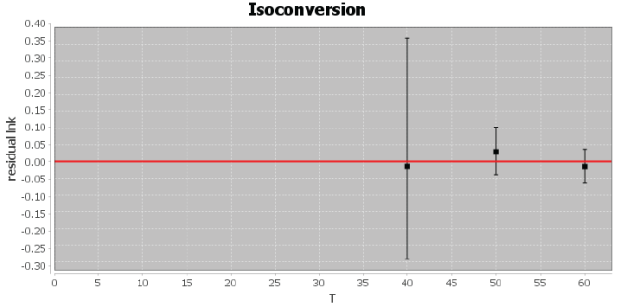




Unbuffered solution results
Assuming non-linear fit to the degradation kinetics

lnA	26.1	±	5.9	
E_a	19.0	±	3.9	kcal/mol
B	-	±	-	
R^2	1.00			
Q^2	0.99			

Residual Plot



A “good” model was generated, although limited degradation at some conditions.

Phase I formulation development - IV solution

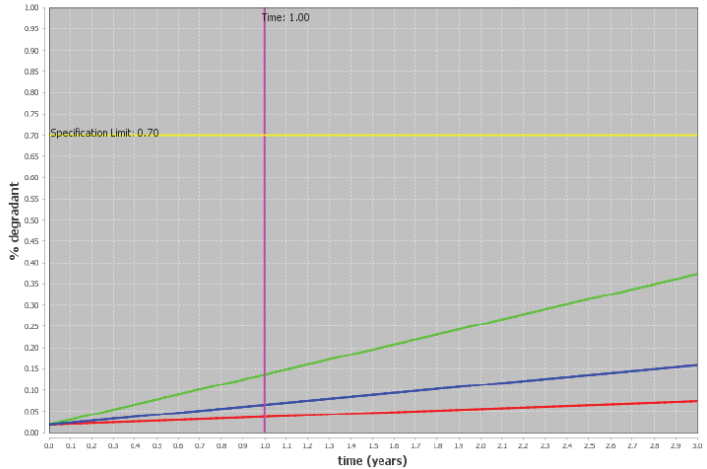
4. Drug product prototype screening – ASAP

Predictions at 25°C/60% RH

Linear fit

Spec Limit	0.70	
Median Shelf-Life	> 3.00	years
Probability of Passing	99.81	%

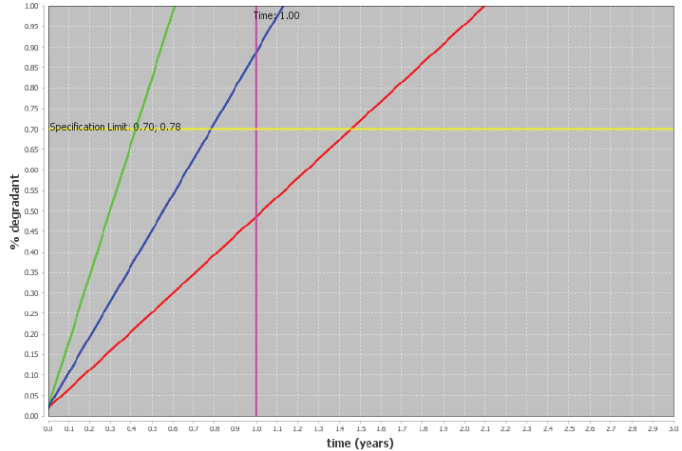
Degradant/Time Plot



Non-linear fit

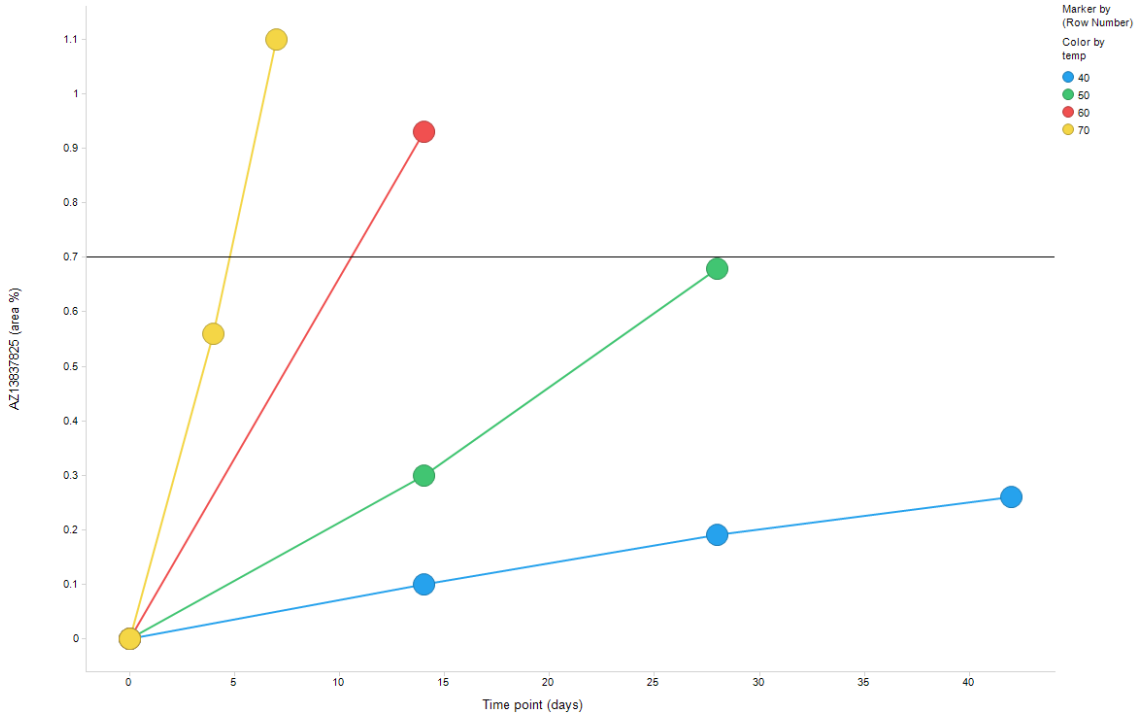
Spec Limit	0.70	
Median Shelf-Life	0.78	years
Probability of Passing	34.80	%

Degradant/Time Plot



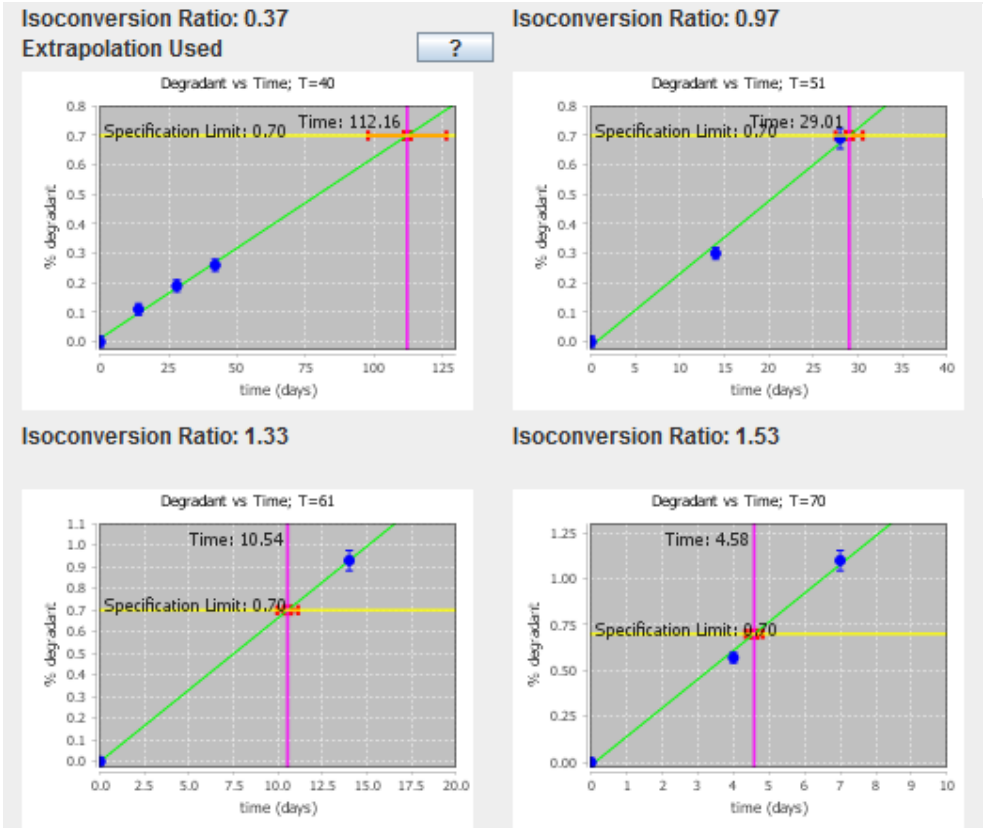
Phase I formulation development - IV solution

5. Drug product (pH 5 buffer) shelf life prediction – ASAP



Phase I formulation development - IV solution

5. Drug product (pH 5 buffer) shelf life prediction – ASAP

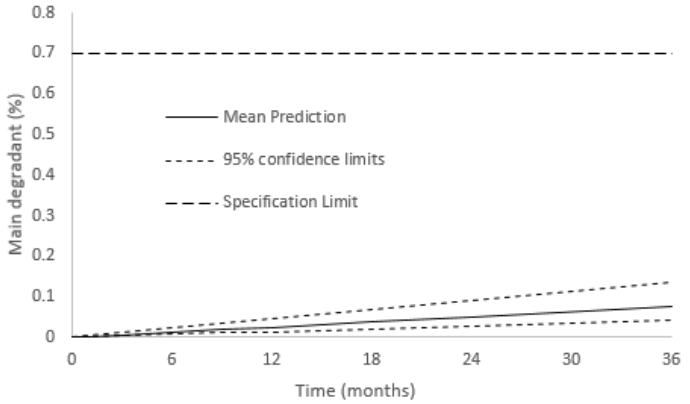


Arrhenius Data

lnA	31.3	±	1.4	
E_a	22.6	±	0.9	kcal/mol
B	-	±	-	
R^2	1.00			
Q^2	0.98			

"Good" model

3 year shelf life prediction at 5°C



Phase I formulation development - IV solution

6. Regulatory Applications

- Drug substance and drug product ASAP data was presented in the Phase I regulatory submission to support a 12 month shelf life/retest period, in the absence of long term stability data
- The MHRA requested ICH compliant stability data for both the substance and product
- There were no questions from Germany on the drug substance stability section but they queried the shelf life claim for the drug product
- The submission was accepted with no questions in Holland

Phase I formulation development - tablet

Applications of predictive stability tools

1. Drug substance – BDE and Zeneth predictions – 4 main degradants predicted
2. Drug substance ASAP study – minimal degradation detected
3. Drug product – Zeneth predictions, excipient incompatibilities - no significant risk identified
4. Drug product shelf life prediction – ASAP
5. Regulatory Applications

Phase I formulation development - tablet

4. Drug product shelf life prediction – ASAP

ASAP studies for 2 formulation strengths, 5 and 50 mg

Protocol for impurities and appearance

Temperature (°C)	Humidity (%RH)	Storage Time (weeks)
Initial	Initial	0
50	75	3, 6, S
60	30	3, 6, S
60	75	3, 6, S
70	11	2, 3, 6, S
70	75	2, 3, 6, S
80	30	2, 3, 6, S

Protocol for dissolution

Temperature (°C)	Humidity (%RH)	Storage Time (weeks)
Initial	Initial	0
40	11	[4]
40	55	[4]
40	75	4

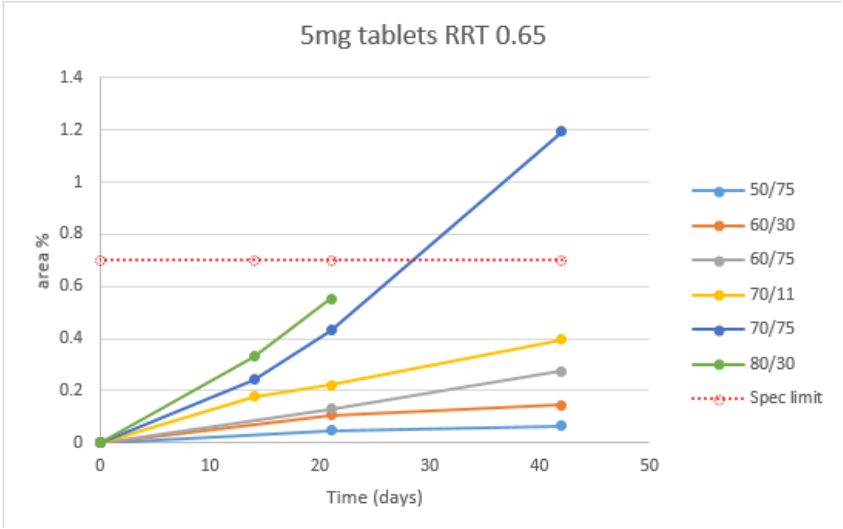
[ ] = optional

S = spare sample

Phase I formulation development - tablet

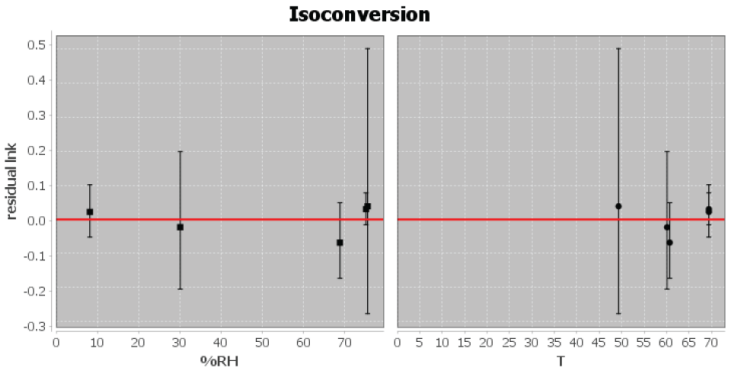
4. Drug product shelf life prediction – ASAP

No change in dissolution profile or appearance during study



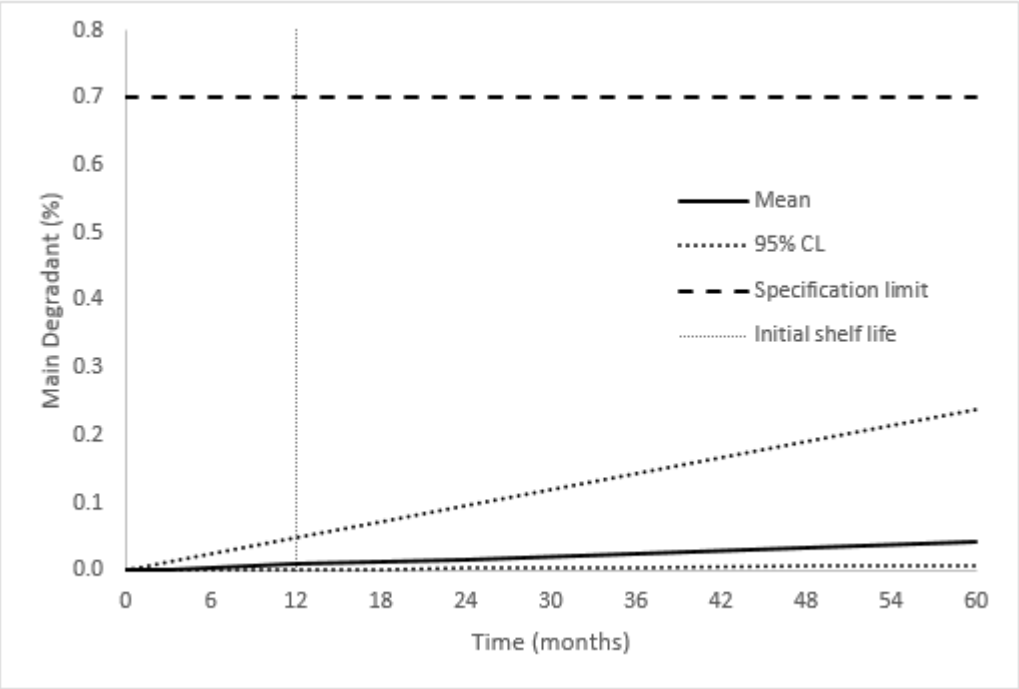
lnA	40.5	±	6.2	
E_a	30.8	±	4.2	kcal/mol
B	0.0147	±	0.0021	
R^2	1.00			
Q^2	0.98			

"Good" model



Phase I formulation development - tablet

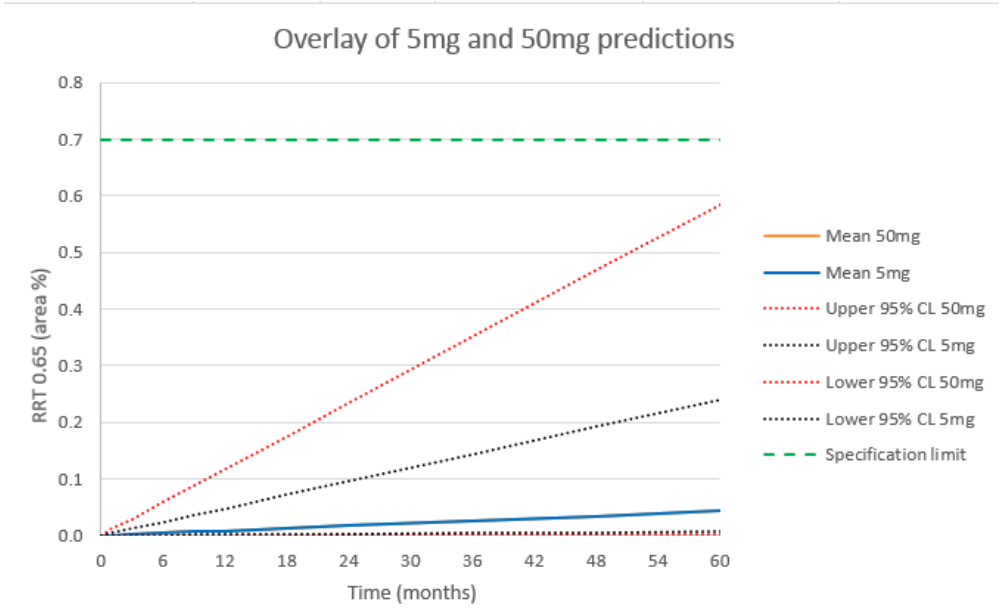
4. Drug product shelf life prediction – ASAP



Predictions at 25˚C/60% RH support an initial shelf life of 12 months but suggest the product is likely to achieve 5 years

Phase I formulation development - tablet

4. Drug product shelf life prediction – ASAP



- When comparing both strengths of tablets, it can be seen that the error for the 50mg tablets is much larger than for the 5mg
- This is because the 50mg tablets did not degrade as much as the 5mg, therefore increased extrapolation required to reach specification

Phase I formulation development - tablet

5. Regulatory Applications

- Drug substance and drug product ASAP data was presented in the Phase I regulatory submission to support a 12 month shelf life/retest period, in the absence of long term stability data
- Submitted to UK and USA
- Waiting for questions

Phase I formulation re-development - capsule

Applications of predictive stability tools

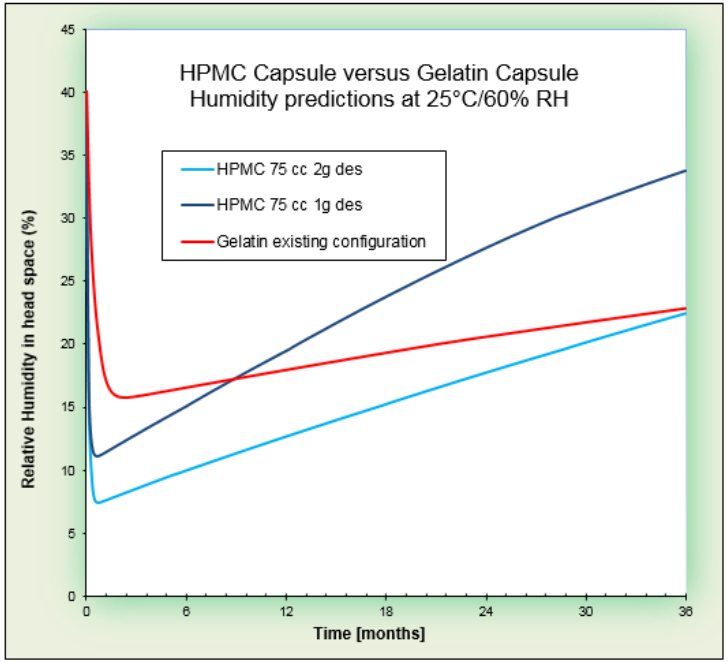
1. Packaging predictions drug product
2. Drug product shelf life prediction – ASAP
3. Regulatory Applications

Phase I formulation re-development - capsule

1. Packaging predictions

- Reformulation from Gelatin capsules to HPMC capsules

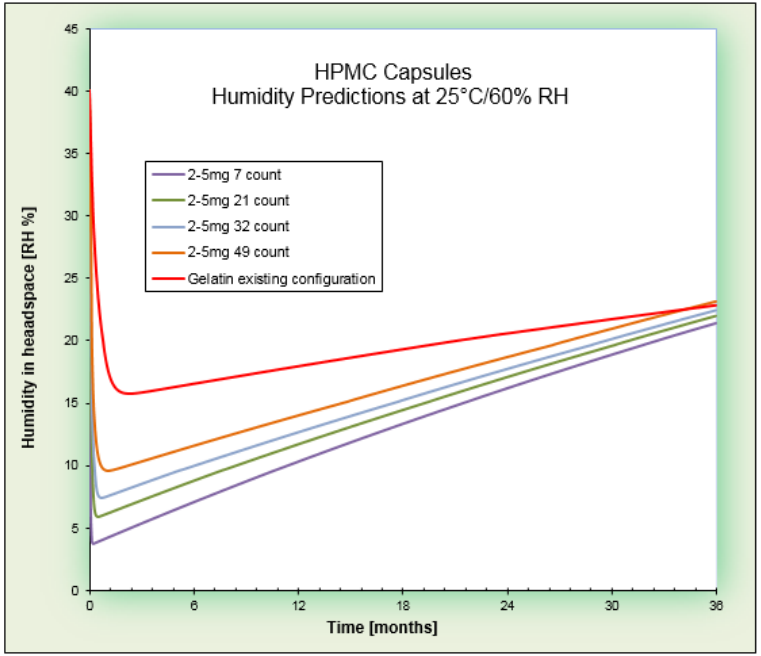
- Performed packaging predictions to determine humidity in bottle for existing gelatin formulation and to predict humidity for the HPMC capsules in a new bottle and decide on the level of desiccant required



Phase I formulation re-development - capsule

1. Packaging predictions

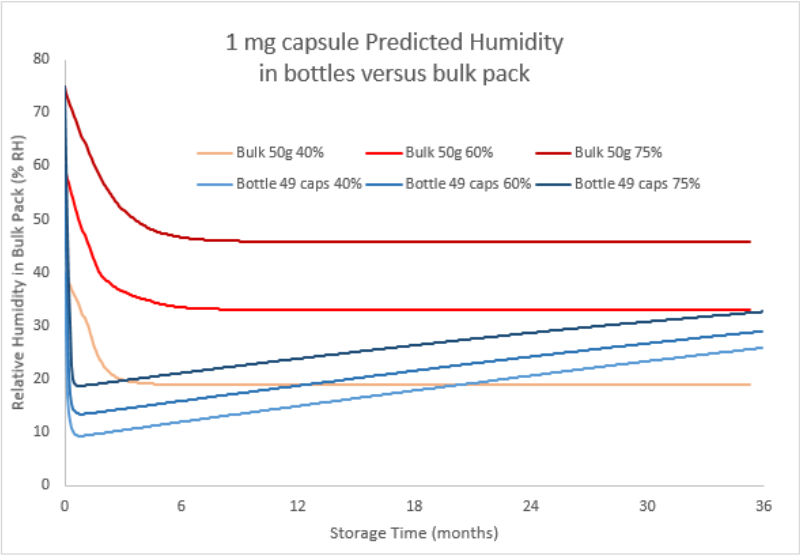
- Reformulation from Gelatin capsules to HPMC capsules
- Performed packaging predictions to determine humidity in bottle for existing gelatin formulation and to predict humidity for the HPMC capsules in a new bottle and decide on the level of desiccant required
- Also predicted the impact of changing the capsule count

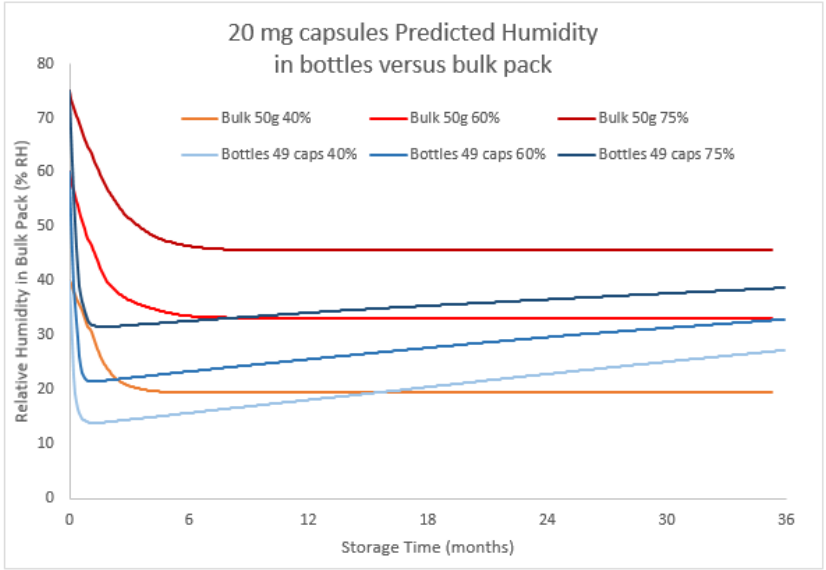


Phase I formulation re-development - capsule

1. Packaging predictions

Packaging predictions to compare the bottle and bulk packs were also performed, bottles containing 49 tablets and the bulk pack with 50 g desiccant.





When packing at 60 or 75% RH the bulk pack is less protective than the bottle.

At 40% the packs are more equivalent over the 3 year period.

Phase I formulation re-development - capsule

2. Drug product shelf life prediction – ASAP

- Two formulation strengths, 1 mg and 20 mg

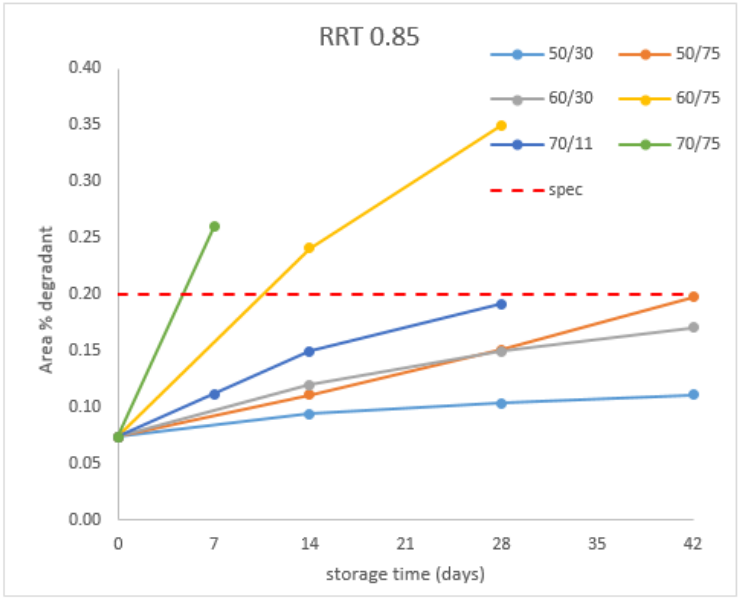
Temperature (°C)	Humidity (% RH)	Storage Time (weeks)
Initial	Initial	0 (3 repeats), X
50	30	2, 4, S
50	75	2, 4, S
60	30	2, 4 (5 repeats), S
60	75	2, 4, S
70	11	1, 2, S, C, X
70	75	1, 2, S, C, X

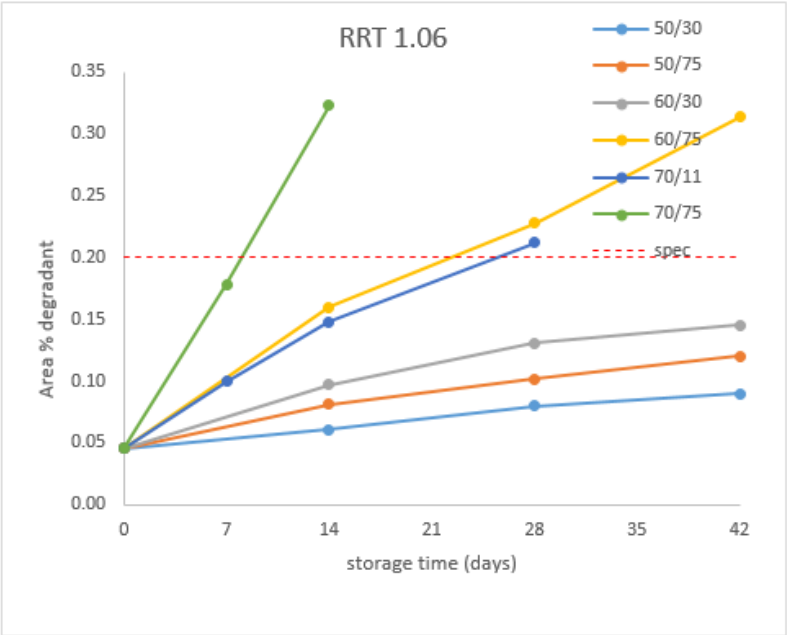
Impurities analysis by LC at all time points (2 capsules per analysis)
S = spare sample, X = XRPD sample, C = chiral sample

Phase I formulation re-development - capsule

2. Drug product shelf life prediction – ASAP

Main degradants identified as RRT 0.85 and RRT 1.06, both with an initial specification limit of < 0.2%

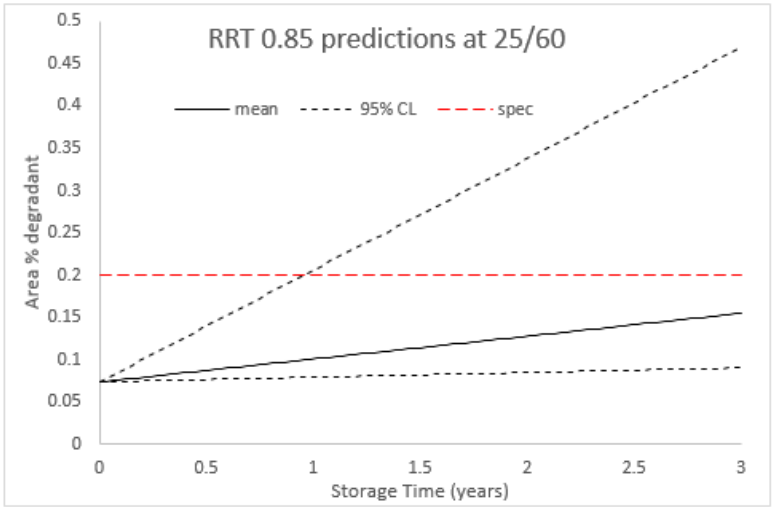




Phase I formulation re-development - capsule

2. Drug product shelf life prediction – ASAP

RRT 0.85 – 3 year shelf life based on mean prediction. The upper 95% confidence limit of the predictions just falls short of 1 year shelf life at 25/60 open.



A “good” model was generated for RRT 0.85, with R^2 and Q^2 terms > 0.9 and no evidence of outliers (all residuals crossing the line).

In total, ran 8 ASAP models across two formulation strengths, but RRT 0.85 was determine to be the shelf life limiting attribute.

Based on the ASAP study the specification limit for this impurity was increased to 0.7%. Higher humidity potentially in bulk pack no longer an issue.

Phase I formulation re-development - capsule

3. Regulatory Applications

- HPMC capsule ASAP data was presented in the IND, alongside 1 months long term stability data
- Submitted to USA
- Accepted without questions
- ASAP data was used to support an internal 12 month shelf life for the bottle pack configuration and a 6 month shelf life in the bulk pack

Conclusions

- Predictive stability tools can be used to support development
- Zeneth and BDE tools can aid understanding of potential degradation mechanisms across both substance and product
- ASAP and packaging predictions are powerful tools to predict chemical degradation, water content and pack humidity and can influence pack selection, pack configuration, storage conditions, shelf life/retest period claims, specification setting and control strategy
- Regulatory acceptance of predicted stability data is growing

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