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Accelerated Stability Assessment Program

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3rd October 2017
Science of Stability conference

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Introduction to ASAP principles

- Accelerated Stability Assessment Program

- Accelerated stress study (~ 1 month) :
  - *Solid dosage form*: evaluating impact of temperature and humidity on API stability on chemical degradation
  - *Liquid dosage form*: evaluating impact of temperature on API stability on chemical degradation

- Based on Arrhenius equation

- Statistical prediction of shelf life

ICH vs. ASAP

Methodology in Small Molecules

ICH	ASAP
Long-term: 25°C/60%RH, 30°C/75%RH **Accelerated conditions:** 40°C/75%RH, 50°C Primary container Minimum 6 months	**Broader range of conditions:** (40°C to 80°C, 10 to 75%RH) Open dish studies 1month
In development time frame •Little or no degradation after 1M and/or 2M •Uncertain relationship to long-term stability performance •Extrapolation of 1M and/or 2M data to estimate shelf life is prone to error	•**Isoconversion** : no kinetic assumption •**Arrhenius equation (humidity corrected for solid)** •**Statistical approach** •Confidence in shelf-life projections
ICH allows 2 or 4 fold extrapolation (No kinetic consideration)	**Kinetic understanding of the degradation**

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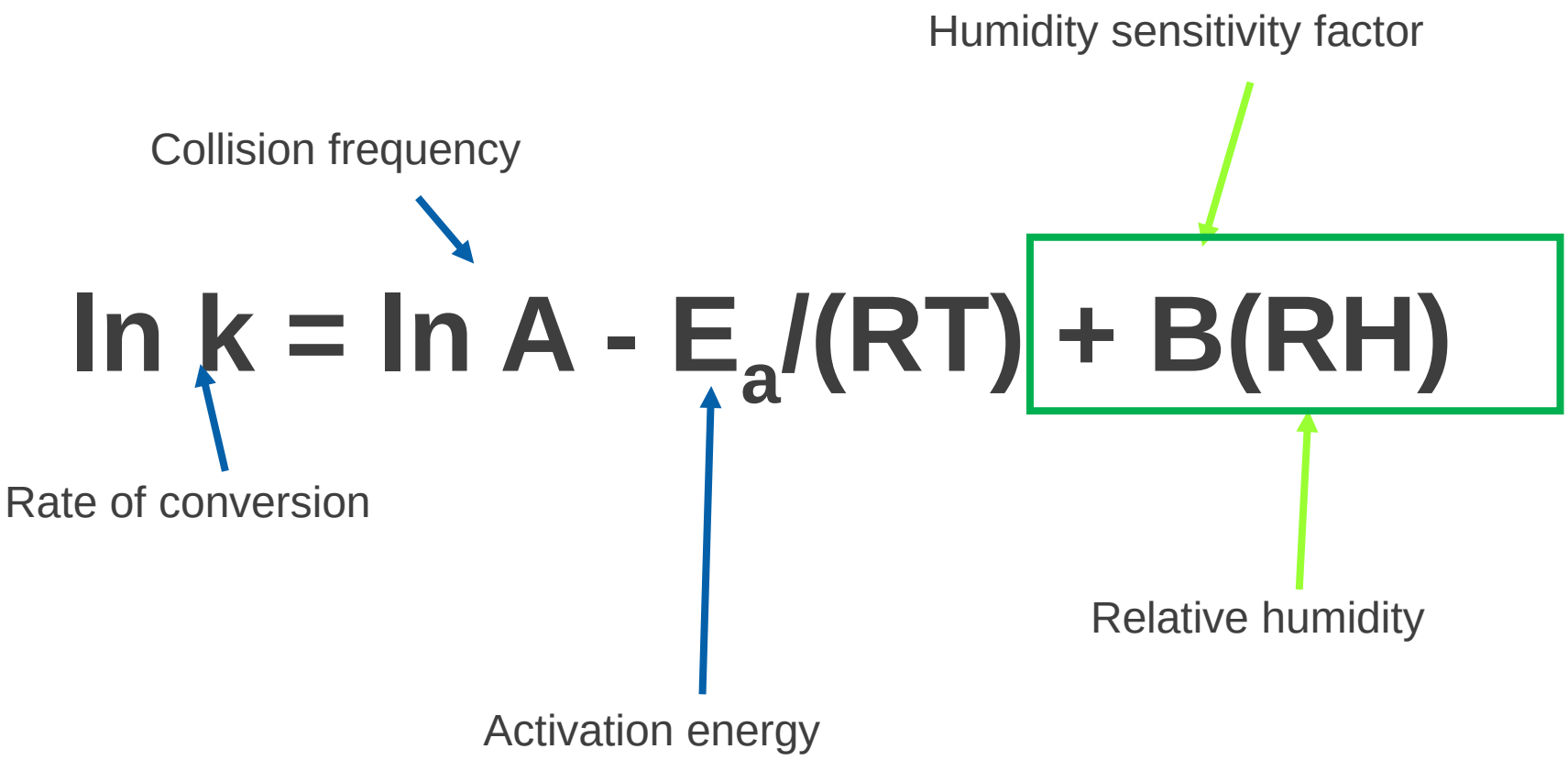
Humidity Corrected Arrhenius Equation



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Isoconversion paradigm

Classic use of Arrhenius equation is limited to linear kinetic

A significant proportion of degradation reaction are not linear!

What to do?

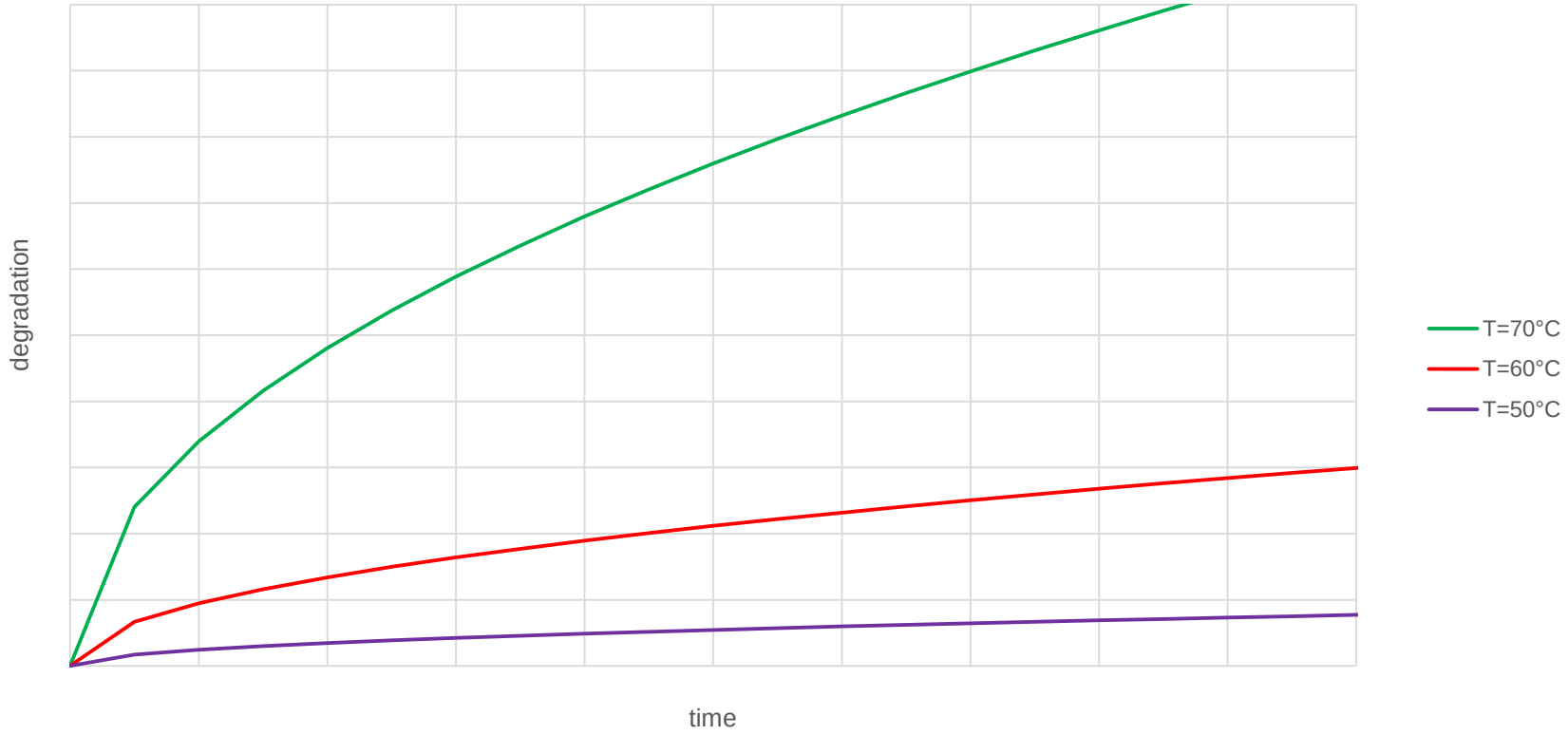
Use a kinetic free model or isoconversion:

The time required for a particular product to fail to meet specifications is independent of the reaction pathway, as long as that pathway is not changed during storage.

Time to failure at each condition!

Isoconversion paradigm

Diffusion degradation



$$[deg] = kt^{1/2}$$

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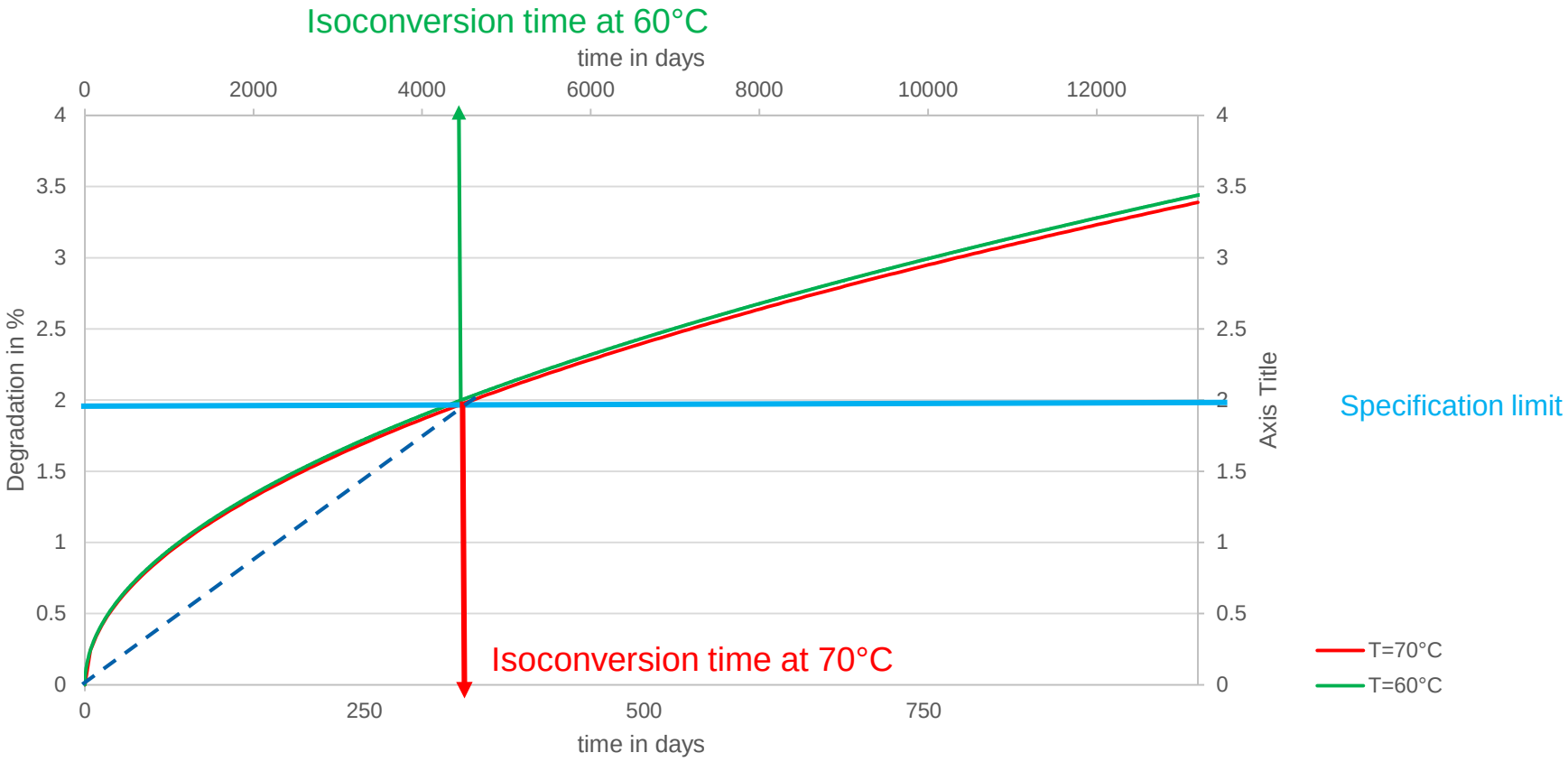
Isoconversion paradigm

Identical pathway to failure



Advantage: almost all kinetic might be modeled

Disadvantage: lose information/increase error since only 1 time point is used per condition

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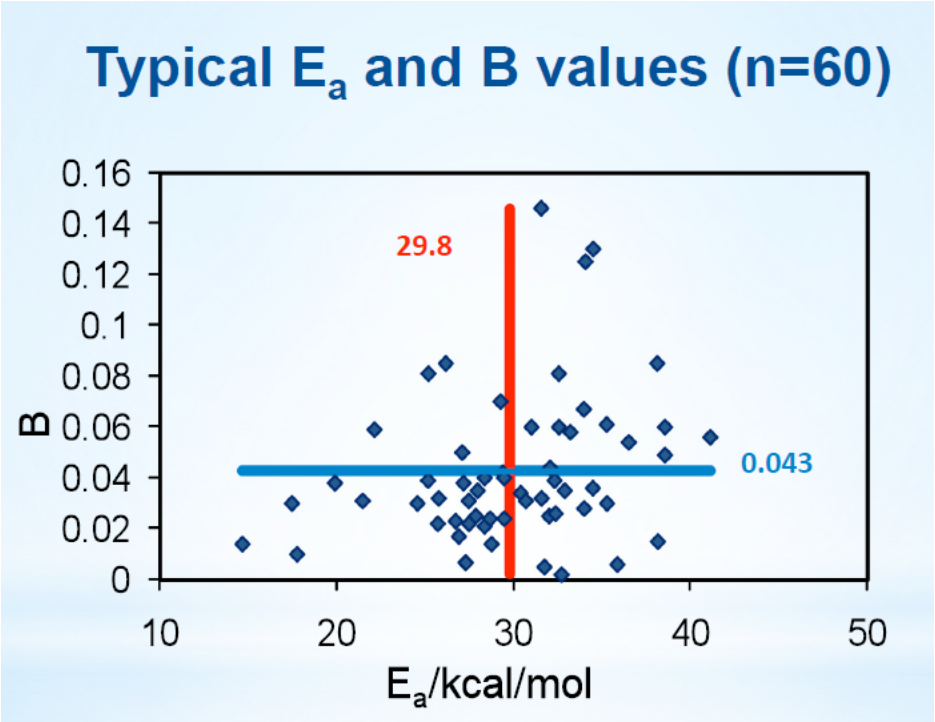
Activation energy Ea

Temperature effects



Ea range:

- 13 kcal/mol low activation energy
- 25 kcal/mol medium activation energy
- 30 kcal/mol average activation energy
- 40 kcal/mol high activation energy

Extrapolation per 10°C:

- X 2.0
- X 3.8
- X 4.9
- X 8.3

Graph taken from K. Waterman's presentation

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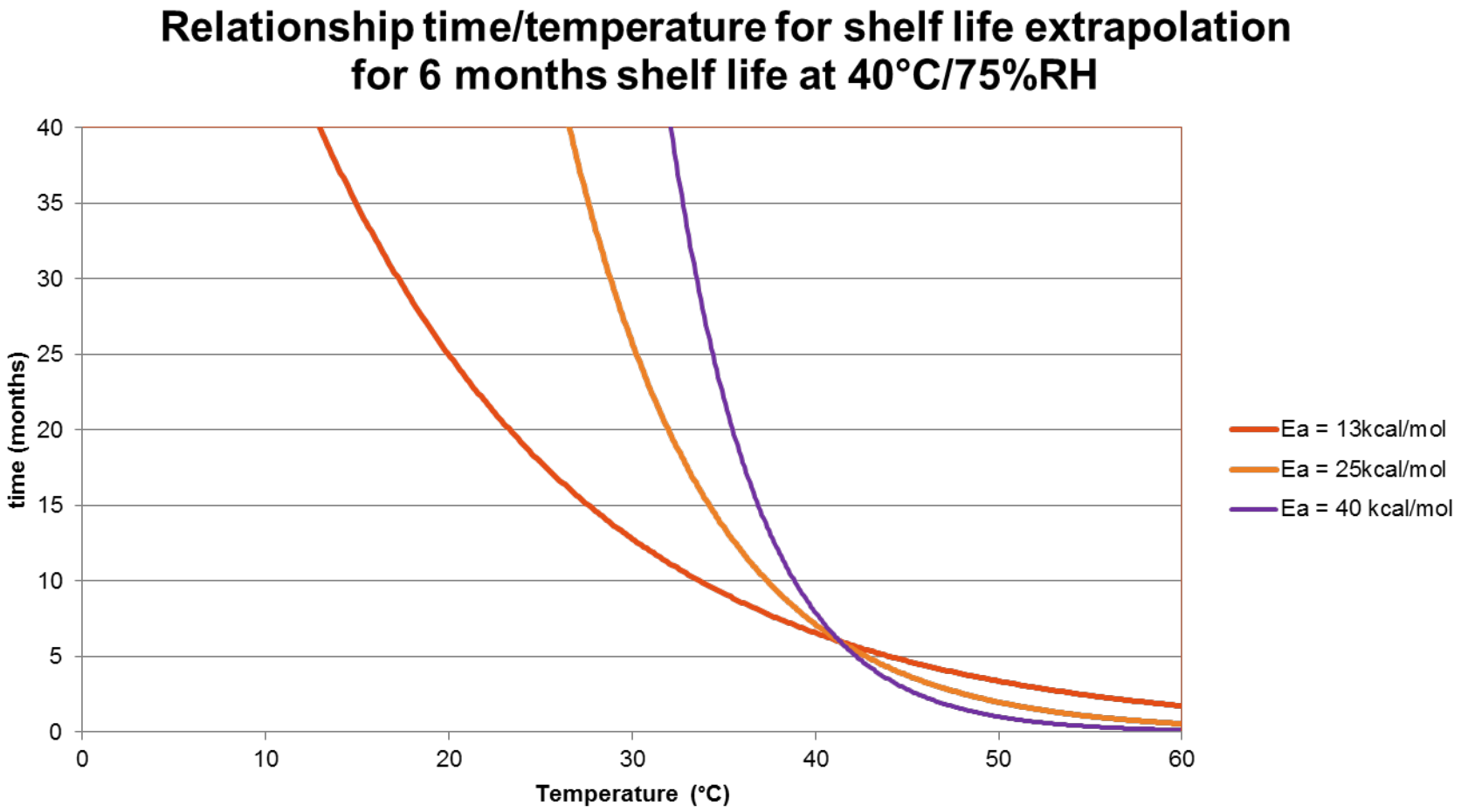
Activation energy Ea

Extrapolation issue 1



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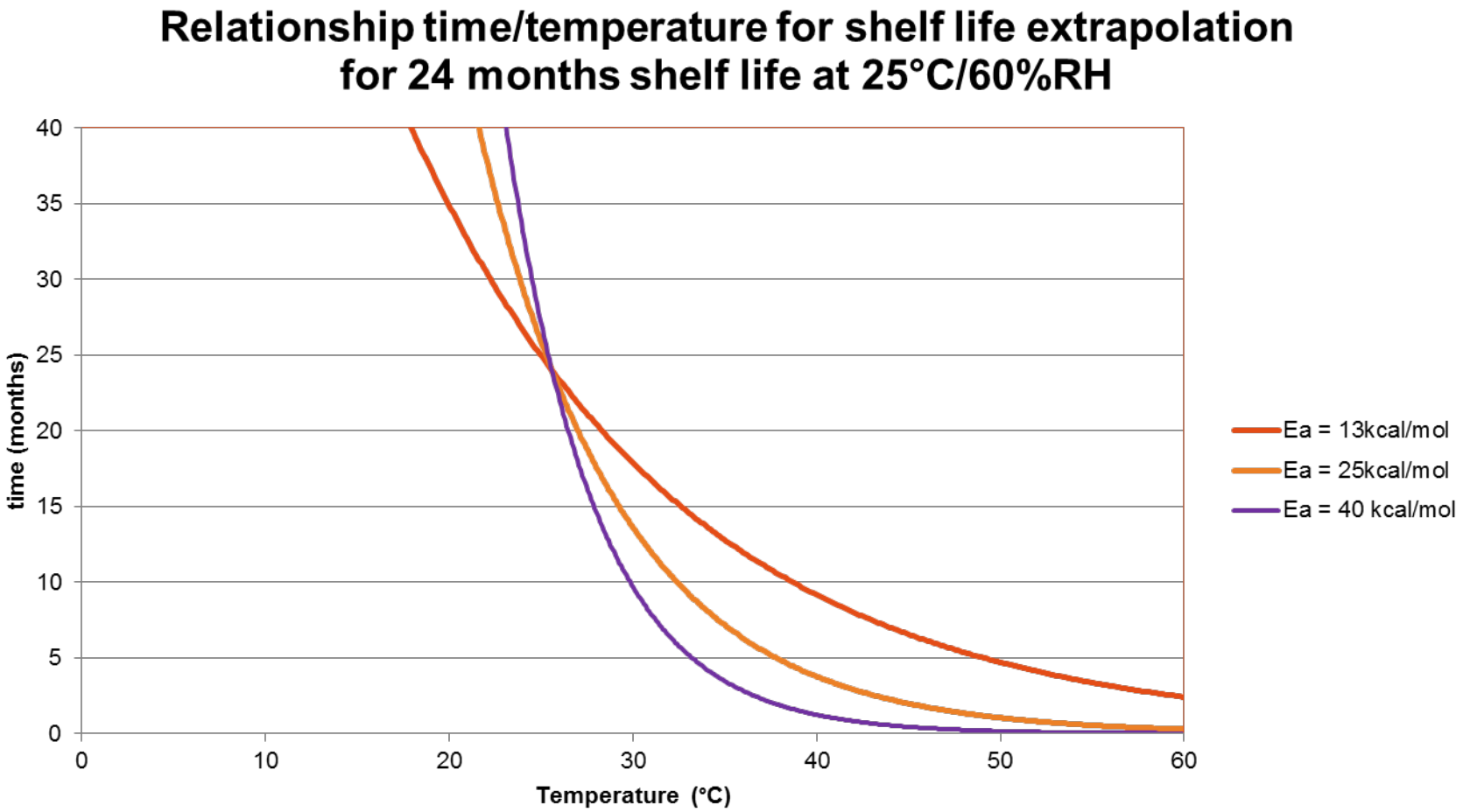
Activation energy Ea

Extrapolation issue 2



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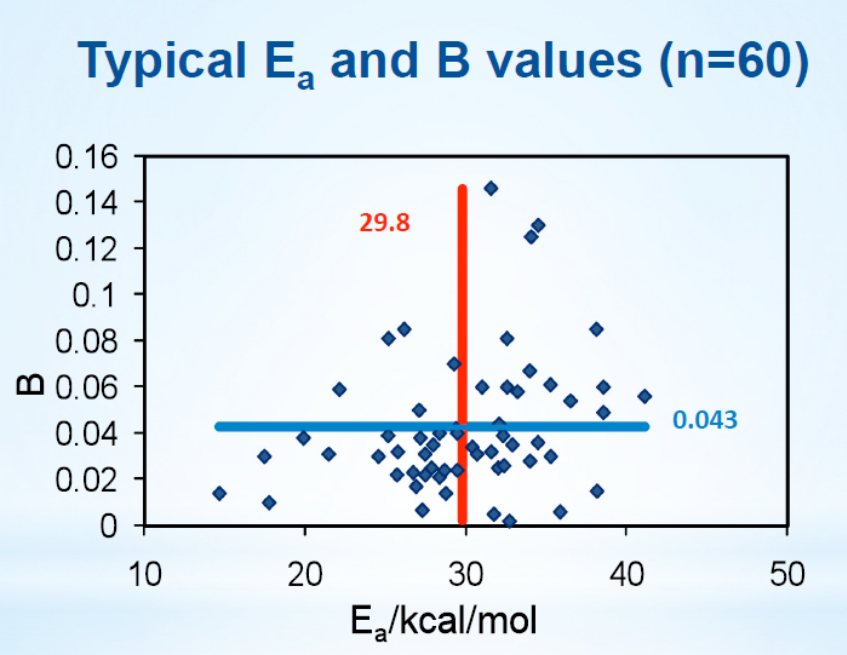
Humidity impact B factor



For solid forms (tablet, capsule, powder…) the humidity can be a very critical parameter to understand and control!

B factor range:

- B = 0.00 (not humidity sensitive)
- B = 0.04 (average humidity sensitive)
- B = 0.1 (highly humidity sensitive)

Humidity intake which double rate

- No changes
- 18%RH
- 7%RH

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Humidity impact on storage

Impact of B on Shelf life

For open dish or poor packaging, impact of chamber requirement of ± 5°C on shelf life of drug product

B	25°C/55%RH Open dish	25°C/60%RH Open dish	25°C/65%RH Open dish	25°C/75%RH Open dish
0 Not humidity sensitive	5.0	5.0	5.0	5.0
0.04 Average humidity sensitive	6.1	5.0	4.1	2.7
0.1 Highly humidity sensitive	8.3	5.0	3.0	1.5

Better select the right packaging early enough!

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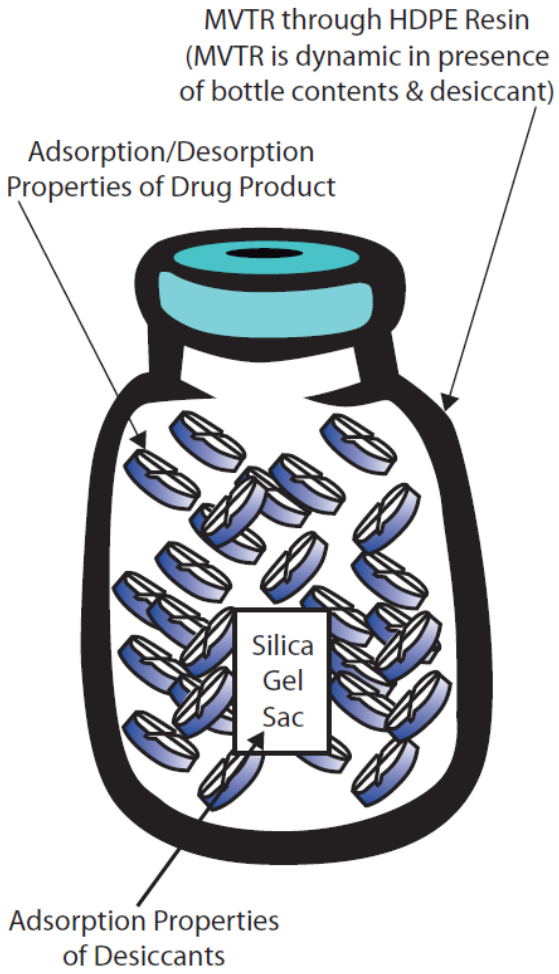
Input required for packaging simulation

MVTR



For packaging:

- Configuration (size)
- MVTR Moisture Vapor Transmission Rate
  - The rate at which water vapor passes through a specific area of barrier material. As MVTR is reduced, dry torage time is increased and desiccant loading is reduced.
  - MVTR is measured in grams of water per unit per 24 hours (g / bottle or cavity / day)

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Absorption capacity of the drug product

GAB (Guggenheim, Anderson and de Boer)

- The sorption isotherms can be approximated by the GAB

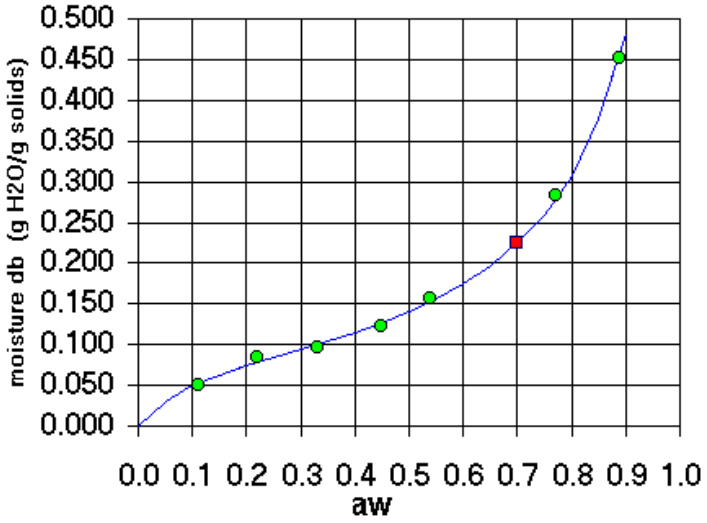
$$w = \frac{w_m C K a_w}{(1 - K a_w)(1 - K a_w + C K a_w)} \qquad (1)$$

where:

w – moisture content (d.b.)

a_w – water activity

w_m, K, C – three free sorption parameters characterising the sorption properties of the material



- Number of tablet and weight
- Initial water activity

Czech J. Food Sci. Vol. 28, 2010, No. 5: 345–354

E.O. Timmermann / Colloids and Surfaces A: Physicochem. Eng. Aspects 220 (2003) 235/260

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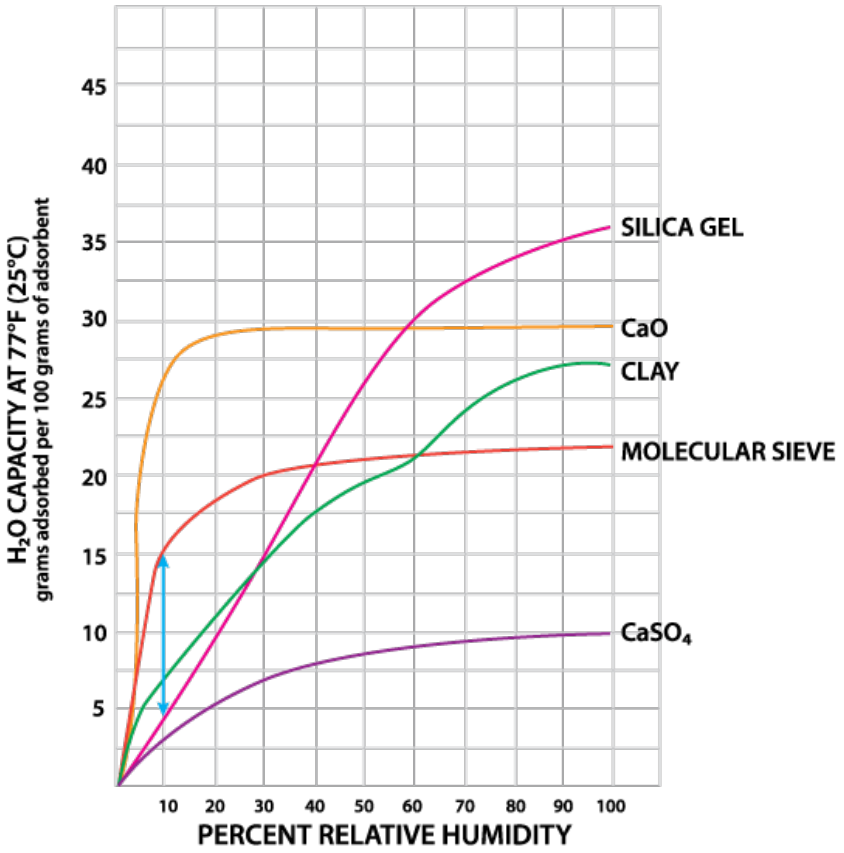
Desiccant

Addition of desiccant might be required:

- Select the type
- Quantity



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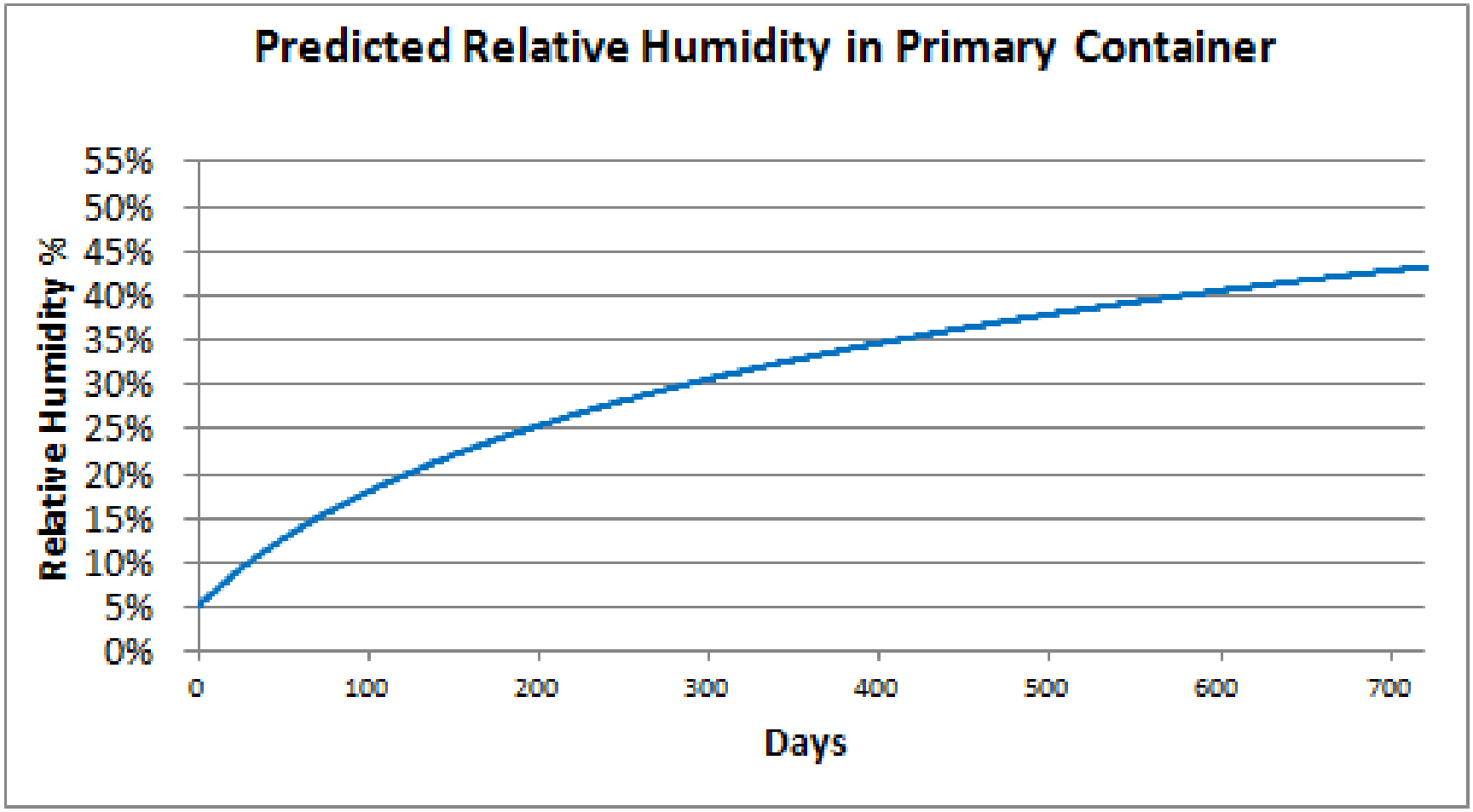
Desiccant



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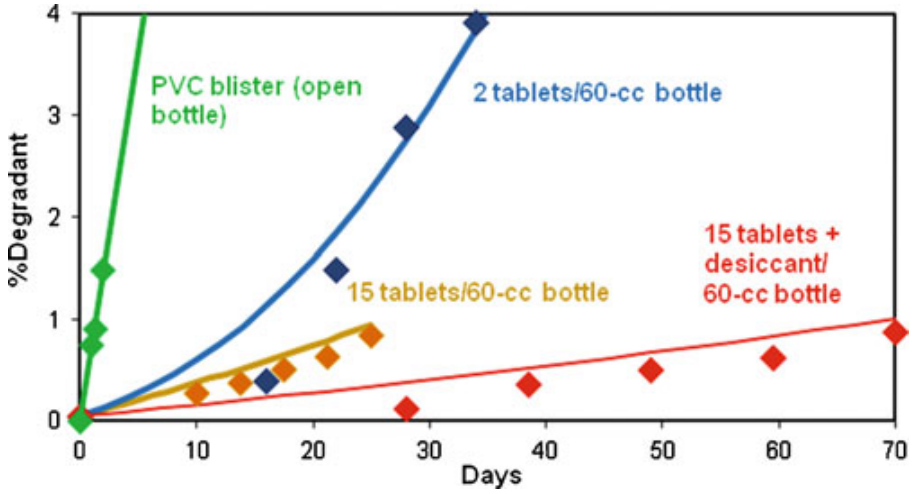
Packaging prediction

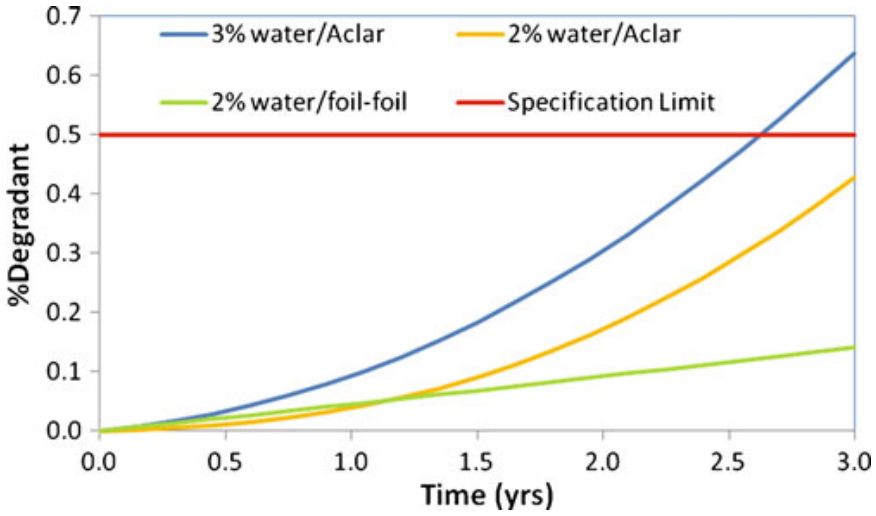


Initial water optimization:

- Evaluate impact of initial DP water content on degradation or other parameters
- Optimize drying process

Packaging set up optimization:

- Select right packaging
- Optimize desiccant amount required
- Avoid starting stability on multiple configuration



K. Waterman, AAPS PharmSciTech, Vol. 12, No. 3, September 2011

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ASAP Protocol for solid

- General condition if no more information available
- Protocol can be applied to DS and DP

Conditions		Time points
T (°C)	%RH	days
50	75	3-7-**14**
60	50	3-7-**14**
70	11	3-7-**14**
70	75	1-**3**-7-14
80	50	1-**3**-7-14

- Protocol needs to be adapted based upon stability of the DS or DP

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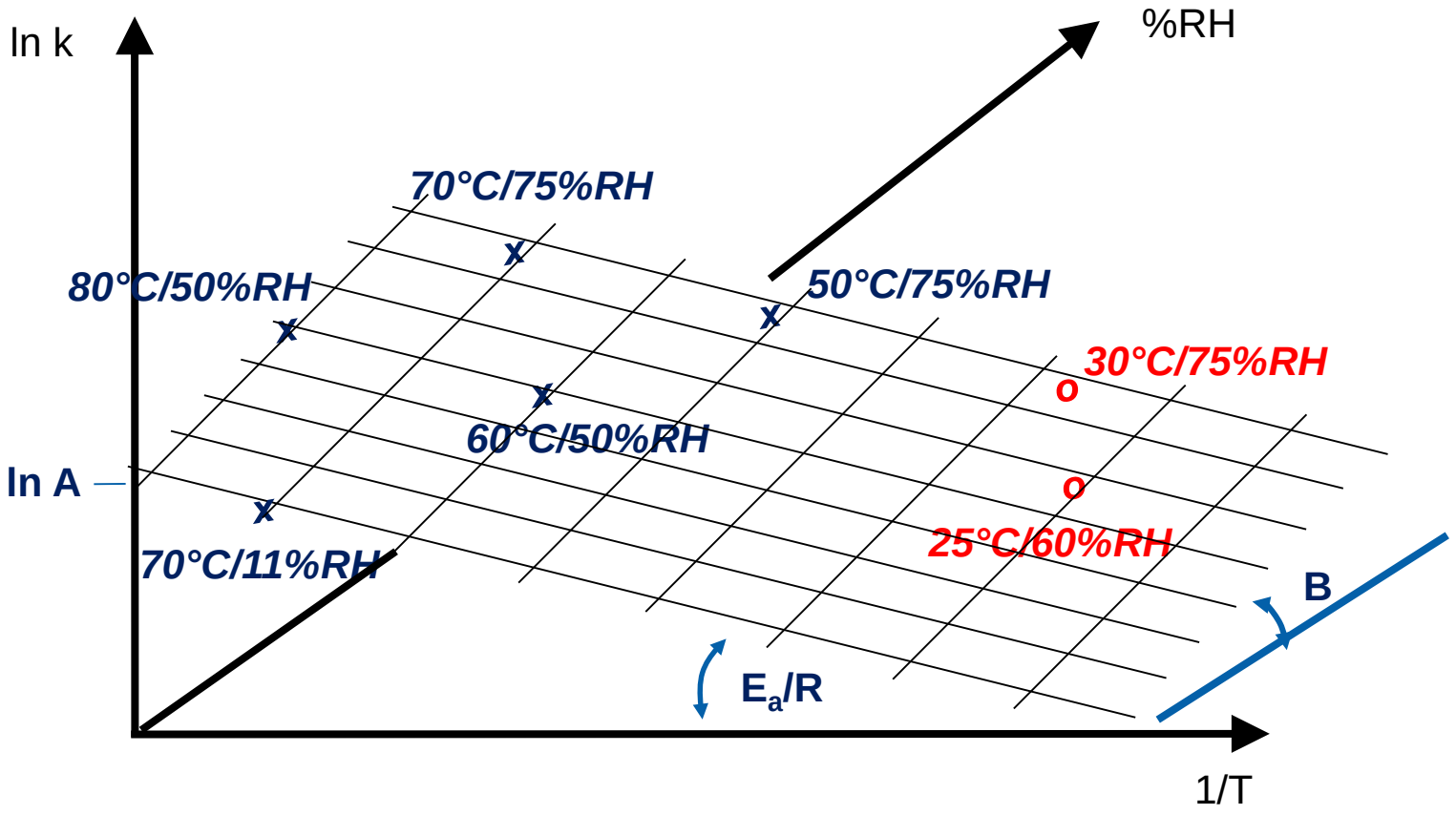
ASAP Design of Experiment:

Determining the Plane for solid

$$\ln k = \ln A - E_a/RT + B(\%RH)$$



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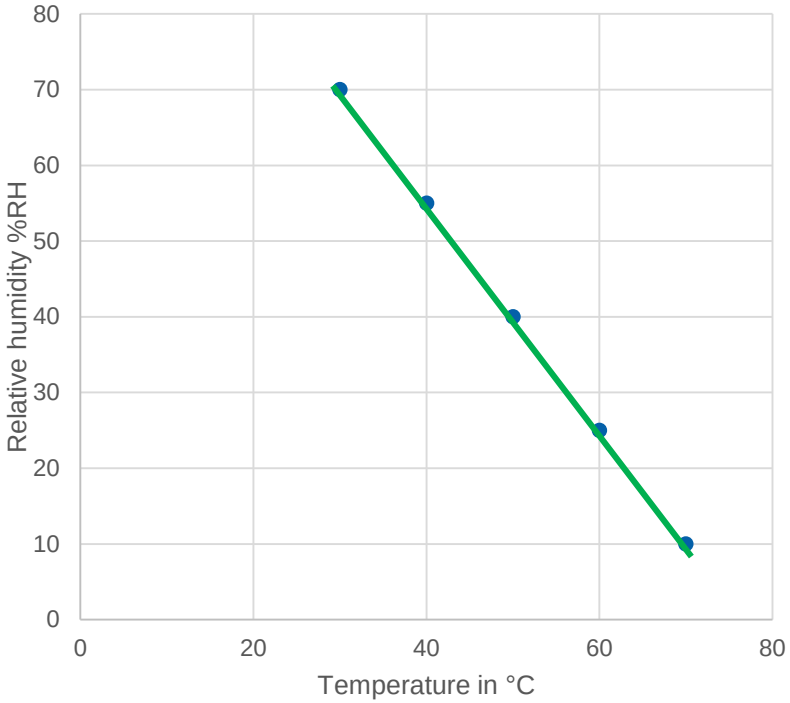
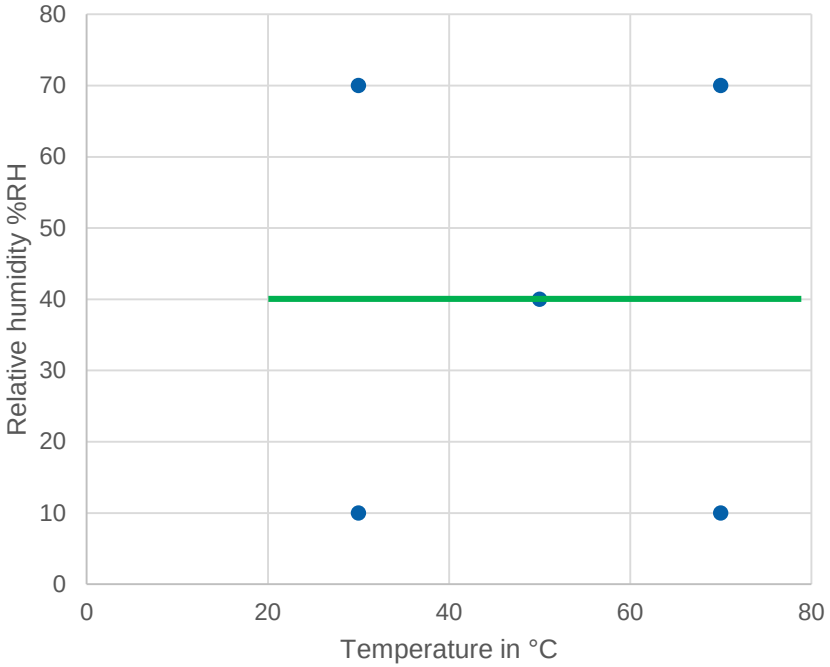
Protocol Design

Considerations

- 3 conditions to solve the Arrhenius equation (for solid)
- extra conditions (degree of freedom)
- => 5 conditions or more





http://www.statisticshowto.com/what-is-the-pearson-correlation-coefficient

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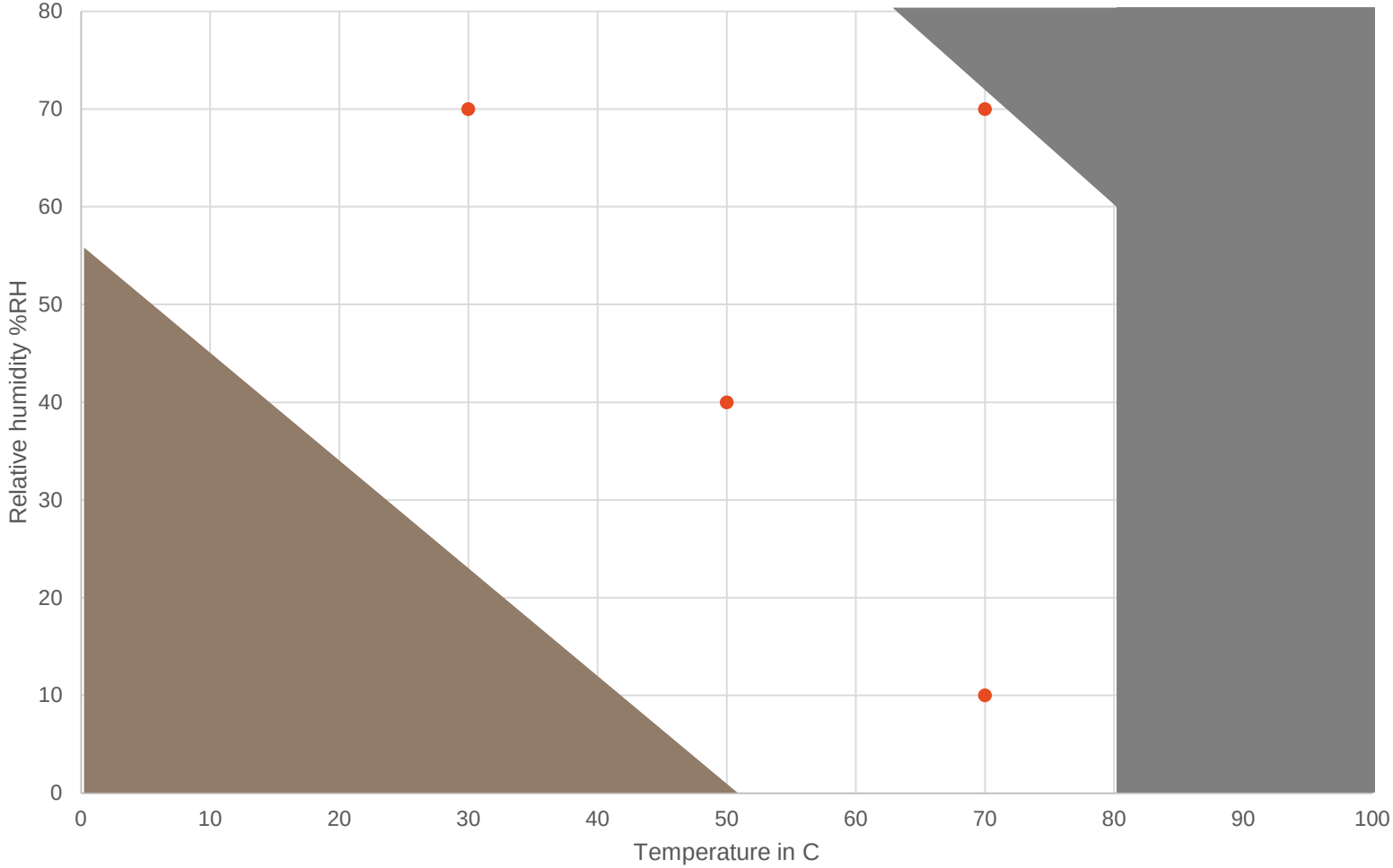
Protocol Design

Sample and time constrain



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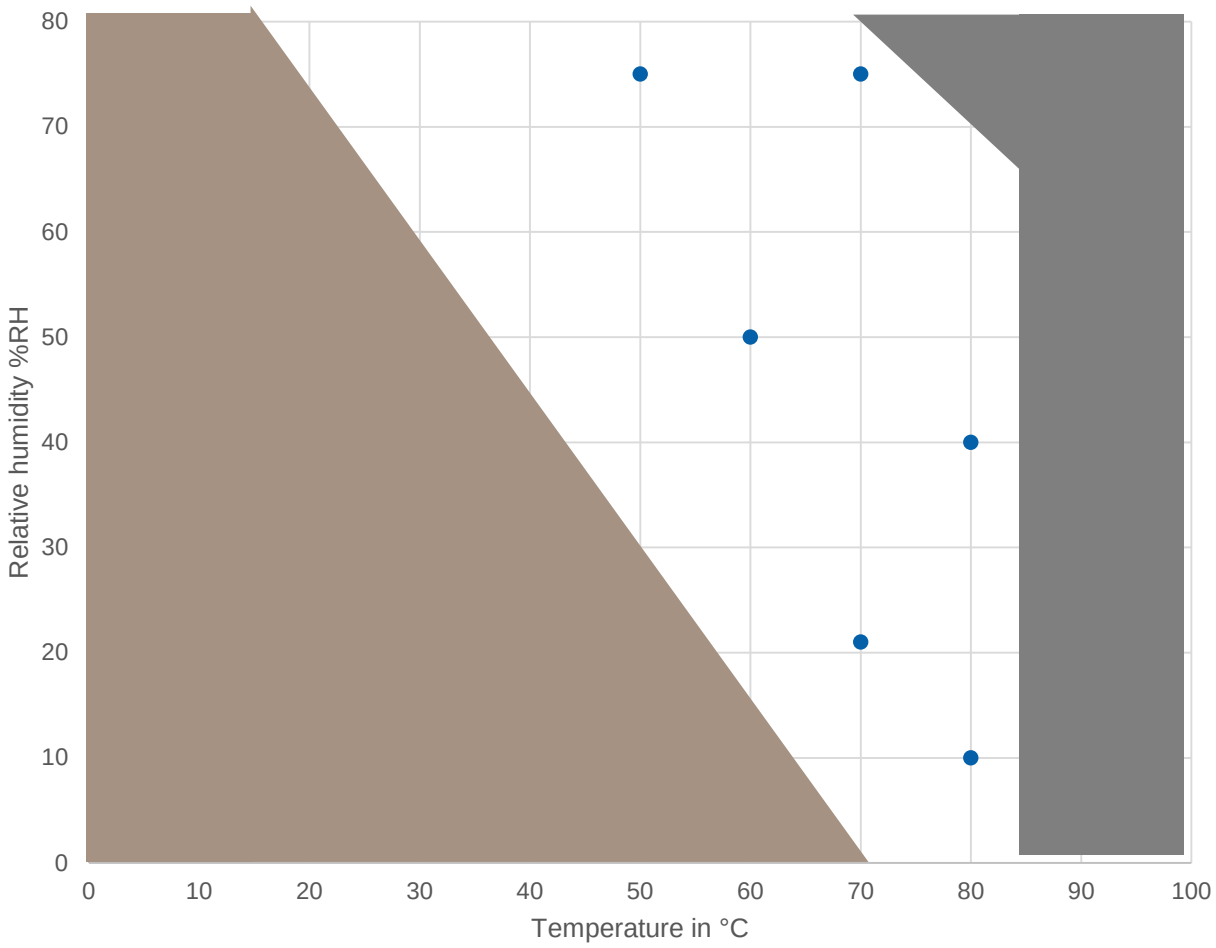
Protocol Design

Sample and time constrain



Temperature (°C)	%RH	Time (days)
50	75	Up to 21
60	50	
70	75	Up to 7
80	10	
70	21	
80	40	Up to 14

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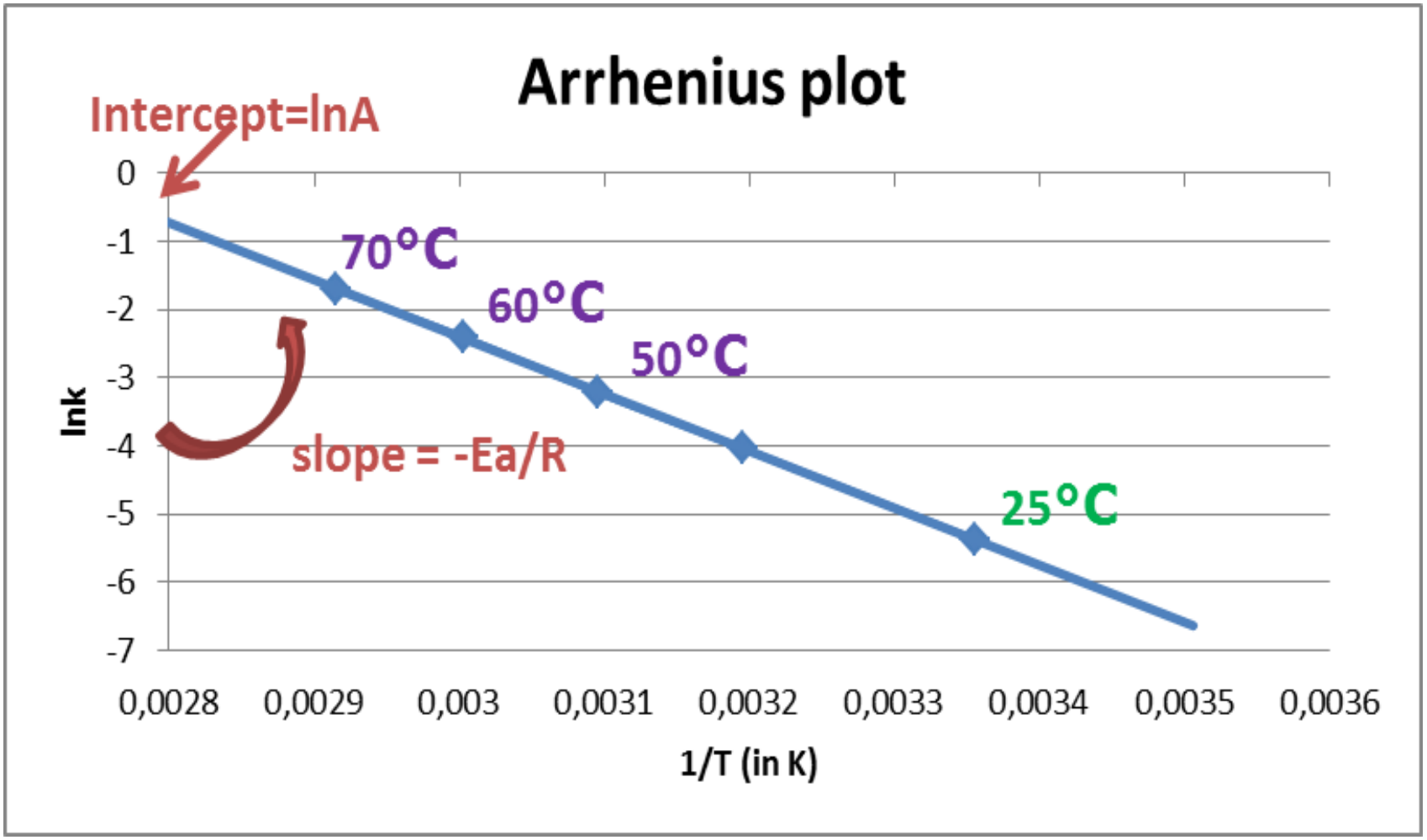
ASAP protocol for liquid formulation

Conditions	Time points
T (°C)	days
5	14
30	(7-14)
40	7-14
50	7-14
60	7-14
70	(7-14)

- Protocol needs to be **adapted** based upon available stability information

ASAP Design of Experiment :

Determining the line for liquid



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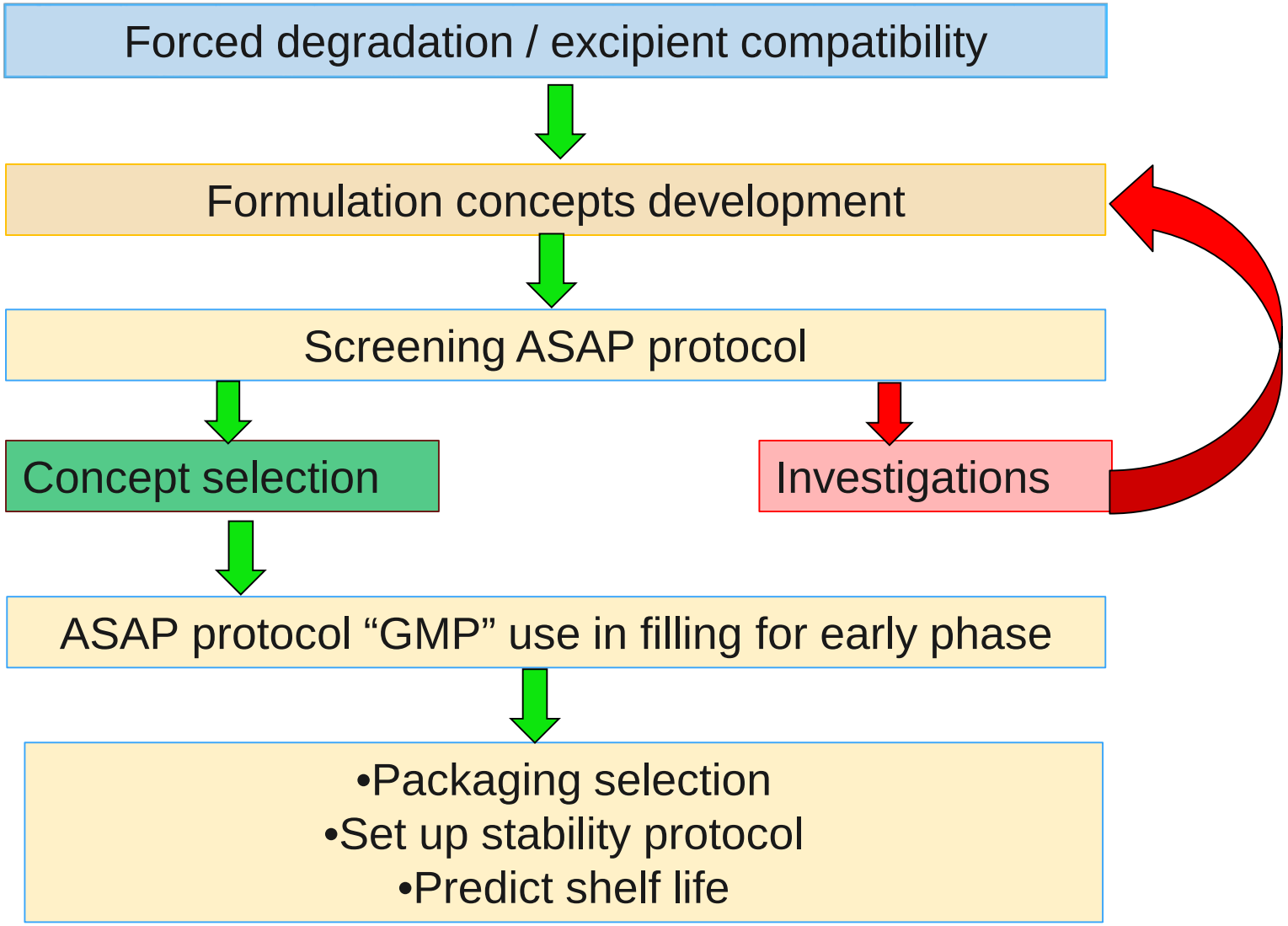
Potential Applications of ASAP

- NME selection screening
- **Establish stability profiles based on temperature and humidity for variants to support variant selection, shelf-life projections and packaging selection for Drug Substance and Drug Products during clinical phase and provide scientifically based support for filings**
- Support filing of DS and intermediates
- **Packaging prediction to minimize number of packages studied on Registration Stability**
- Evaluation of process robustness
- Post filling/commercial changes (packaging, supplier….)
- *Support in use periods*
- *Support change in packaging configurations (bottle size, unit counts)*

DP development flow



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Resources comparison

3 strengths

ICH	ASAP
Long-term: 5%C, 25°C/60%RH, **Accelerated conditions:** 40°C/75%RH, **4 packaging** **6 months**	**Broader range of conditions:** (40°C to 80°C, 10 to 75%RH) Open dish studies 1 month
• 120 samples for assay purity • 120 samples for water • Over 4 time points • FTE: 16 weeks (full time FTE)	•80 samples for assay purity but done in 1 time point •3 DVS for water simulation •FTE: 3 weeks (full time FTE)
Disso information in addition	**Can be compensated by humidity screen**

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Equipment required to start

- 5 Ovens with temperature range of 40°C to 80°C (± 2°C)
- 40 desiccators
- Loggers for GMP
- Humidity fixed using saturated salt solution
- Software for data interpretation

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Relative humidity using saturated salt solution

From L. Greenspan, *J. Res. Nat. Bur. Standards*, **81A,** 89 (1977)

Equilibrium relative humidity of some saturated salt solutions 25□C			
Salt	**R.H. %**	**Salt**	**R.H. %**
Cesium flouride	3.39 □ 0.94	Sodium bromide	57.57 □ 0.40
Lithium bromide	6.37 □ 0.52	Cobald chloride	64.92 □ 3.50
Zinc bromide	7.75 □ 0.39	Potassium iodide	68.86 □ 0.24
Potassium hydroxide	8.23 □ 0.72	Strontium chloride	70.85 □ 0.04
Sodium hydroxide	8.24 □ 2.1	Sodium nitrate	74.25 □ 0.32
Lithium chloride	11.30 □ 0.27	Sodium chloride	75.29 □ 0.12
Calcium bromide	16.50 □ 0.20	Ammonium chloride	78.57 □ 0.40
Lithium iodide	17.56 □ 0.13	Potassium bromide	80.89 □ 0.21
Potassium acetate	22.51 □ 0.32	Ammonium sulphate	80.99 □ 0.28
Potassium flouride	30.85 □ 1.3	Potassium chloride	85.06 □ 0.38
Magnesium chloride	32.78 □ 0.16	Strontium nitrate	85.06 □ 0.38
Sodium iodide	38.17 □ 0.50	Potassium nitrate	93.58 □ 0.55
Potassium carbonate	43.16 □ 0.39	Potassium sulphate	97.30 □ 045
Magnesium nitrate	52.89 □ 0.22	Potassium chromate	97.88 □ 0.49

JOURNAL OF RESEARCH of the National Bureau of Standards - A. Phys ics and Chemistry
Vol. 81 A, No.1 , January- February 1977

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Use in filing and post commercial

ASAP is not just a development/screening tool it can be successfully used in filling to support shelf life

- For phase I shelf life application only ASAP data
- For phase IIa shelf life application with 1 or 3 months ICH
- As supportive tool for scientific justification of specification in late phase
- Changes post approval: packaging changes, supplier changes

Question ?

Degradant levels at 14 days (0.50% specification limit):

Formulation	50°C	60°C	70°C
1	0.04	0.09	0.18
2	0.07	0.28	0.90

?

ASAP, Training exercise from Freethink

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Question ?

Degradant levels at 14 days (0.50% specification limit):

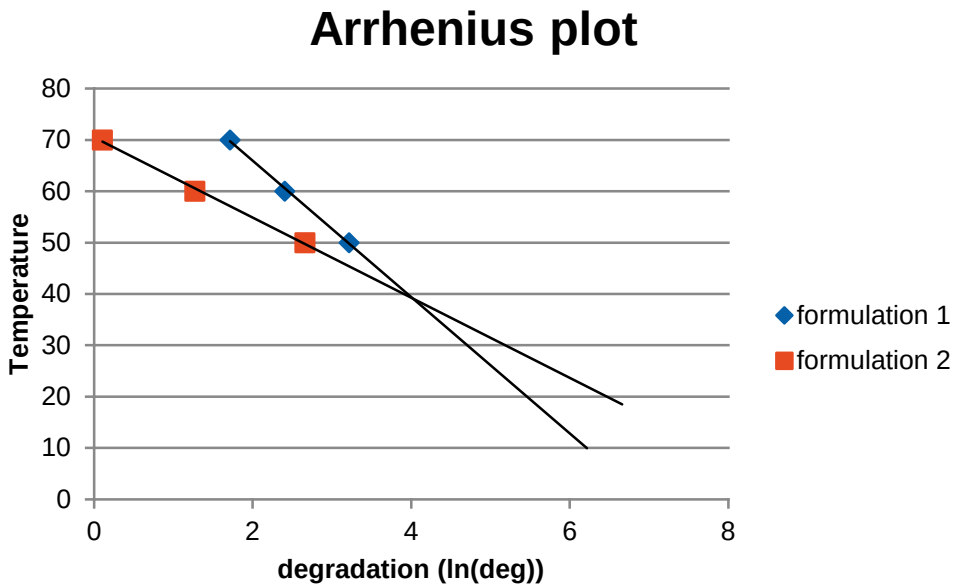
Formulation	50°C	60°C	70°C
1	0.04	0.09	0.18
2	0.07	0.28	0.90

Formulation	3 years	lnA	Ea
1	60 %	20.0	16.6
2	92 %	38.6	28.1

ASAP, Training exercise from Freethink

Answer

- Do not use a single temperature to select concept
- Design your space every time to induce failure
- With enough time point to well define isoconversion
- ASAP failure only brings knowledge about your compound



You need to make your product fail if you want to understand when and how it will fail!

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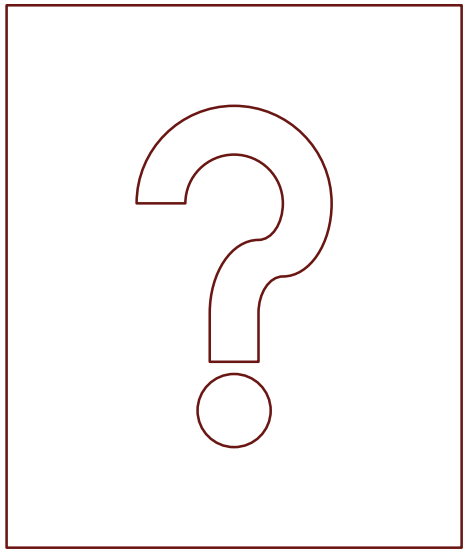
Conclusion

- Shorten Drug Product development
- Improve scientific understanding
- **Gain time by increasing product knowledge!**

Thank you!



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