Accelerated Stability Assessment Program (ASAP*prime*®): Modeling for Rapid Shelf Life Determination

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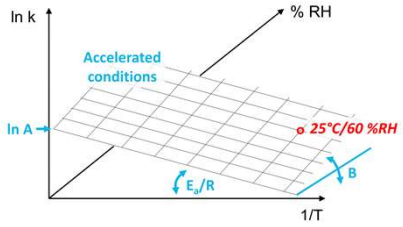
Goals

- Drug product shelf life determination can slow down new drug substance and product introductions
- Shelf life determination is historically difficult to accelerate predictably
- The ASAP*prime*® process aims to dramatically accelerate shelf life determinations

ASAP*prime*® Principles

1. Focus on time to hit specification limit (isoconversion time) rather than true rate constant
2. Use the moisture-modified Arrhenius equation:

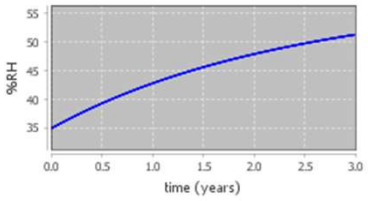
$$\ln \frac{1}{isoconversion\ time} = lnA - \frac{E_a}{RT} + B(RH)$$



A	= collision frequency
E_a	= activation energy (temperature sensitivity)
R	= gas constant
T	= temperature in K
B	= humidity sensitivity
RH	= equilibrium relative humidity (what the sample actually sees)

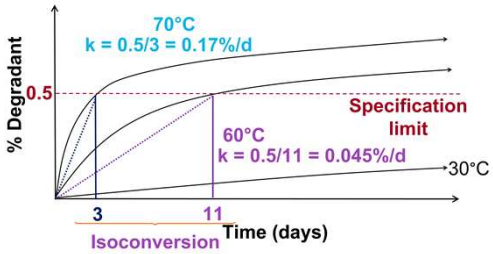
3. Calculate internal RH as a function of time inside packaging
   a) Moisture sorption isotherms of product and desiccants
   b) Moisture permeability of package
   c) Initial water activity of product
   d) Storage conditions

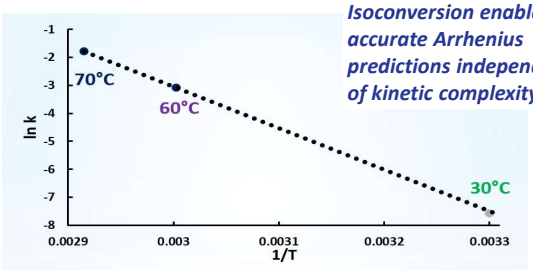
Example: Internal RH for 20 tablets in a 60-cc HDPE bottle stored at 25°C/60% RH



4. Determine probability of passing using statistics

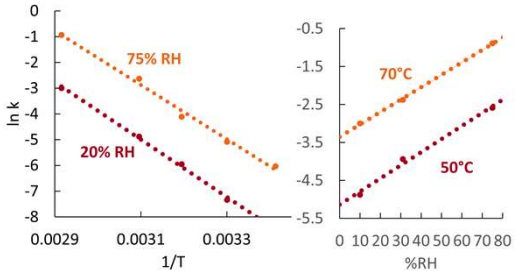
Isoconversion



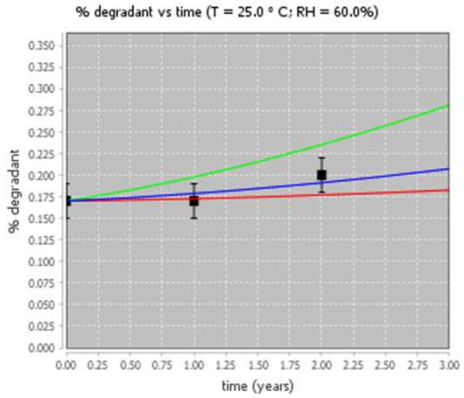


Isoconversion enables accurate Arrhenius predictions independent of kinetic complexity

Moisture-Modified Arrhenius



Example: Drug product showing independent T + RH impacts following moisture-modified Arrhenius equation (E_a = 22.2 kcal/mol; B = 0.031)



Example: Capsule drug product packaged in HDPE bottles modeled using two-week ASAP*prime*® study (50–80°C). Blue line is the mean prediction, with green and red lines representing ± 1σ. Squares are from the long-term study. Probability of passing against a specification limit of 0.3% at two years is 96%. Derived from data presented by S. Thielges at the 2015 Science of Stability Conference.

Conclusions

- ASAP*prime*® has successfully been used to determine shelf life for a wide range of products: solids, liquids, semi-solids, small molecules, some biologicals, and probiotics
- ASAP*prime*® has successfully been used to model shelf life dependent on chemical stability, appearance, dissolution, amorphous crystallization, and viscosity
- ASAP*prime*® has successfully been used in many regulatory filings globally

Example Publications

- Flavier, et al. Accelerated shelf life modeling of appearance change in drug products using ASAPprime®. *Pharm. Dev. Tech.* **2022**, 27(6), 740-8.
- Waterman, et al. Accelerated stability modeling for peptides: a case study with bacitracin; *AAPS PharmSciTech,* **2016**, 1-7
- Waterman, et al. A scientific and statistical analysis of accelerated aging for pharmaceuticals Part 1: accuracy of fitting methods; *J. Pharm. Sci.* **2014**, 103, 3000-3006

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