

Use of ASAP for Accelerated Stability Determinations of Viscosity Degradation in Pharmaceutical Polymers

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Introduction

Molecular weight changes for water-soluble polymers during long-term storage can result in stability failures with respect to dissolution (tablets) or settling (liquids).

• **Hypothesis:** The Accelerated Stability Assessment Program (ASAP) approach to shelf-life modeling using a humidity corrected Arrhenius equation in conjunction with a time-to-fail (isoconversion time) kinetic calculation provides a rapid and accurate methodology for modeling molecular weight changes over long-term storage

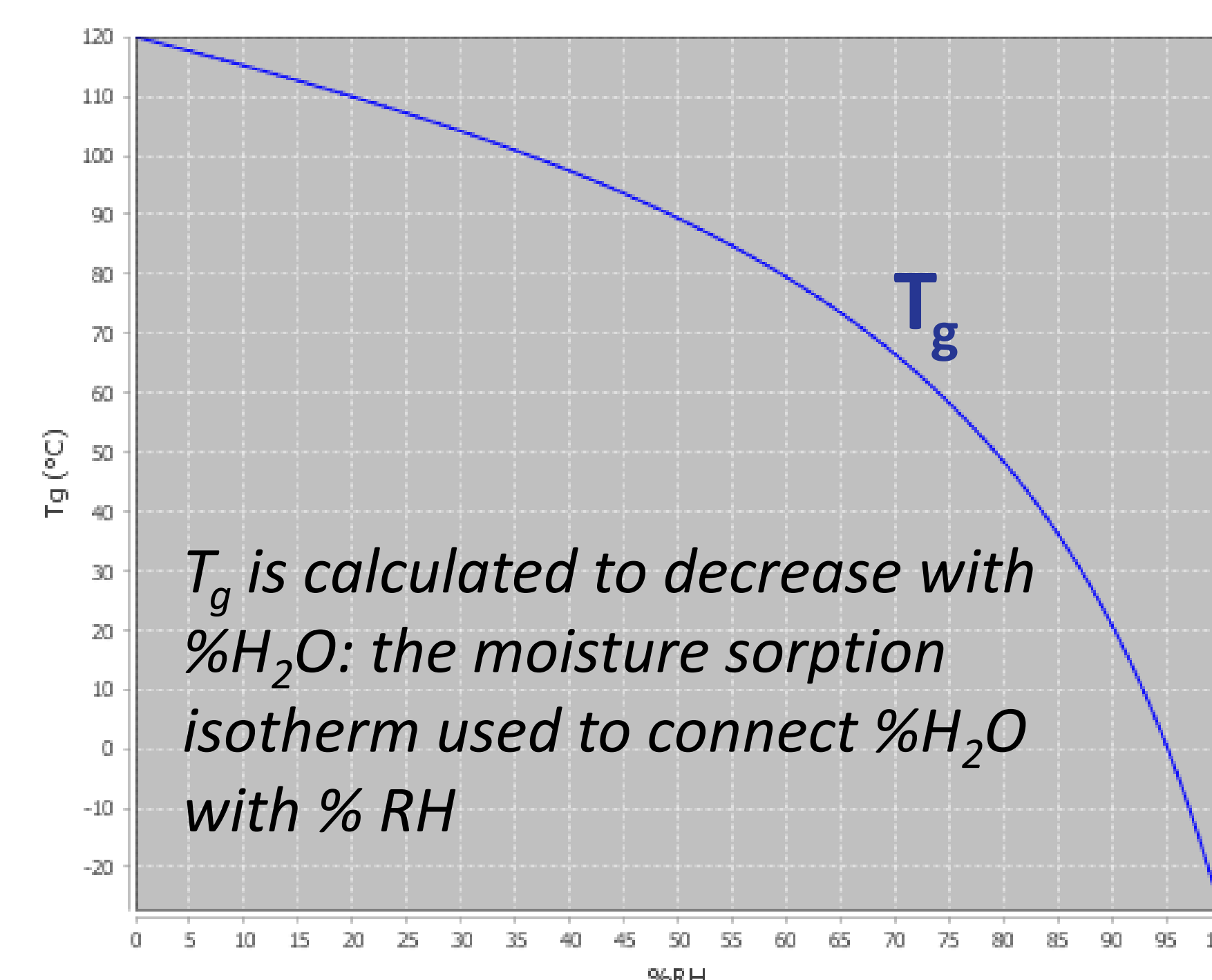
$$\ln(k) = \ln A - \frac{E_a}{RT} + B(RH)$$

- $k = 1/t_{iso}$ (isoconversion time)
- A = intercept (collision frequency)
- E_a = activation energy (temperature sensitivity)
- B = humidity sensitivity term

Study Design and Materials

Oven	T (°C)	%RH	Days (repeats)
Control	5	0	0 (6)
Oven 1	50	42 (Potassium Carbonate)	11 (3); 15 (3); 21 (3)
Oven 2	60	2 (Cesium Fluoride)	10 (3); 15 (3); 21 (3)
Oven 2	60	50 (Sodium Bromide)	2 (3); 7 (3); 21 (3)
Oven 3	70	11 (Lithium Chloride)	2 (3); 6 (3); 19 (3)
Oven 3	70	28 (Magnesium Chloride)	1 (3); 4 (3); 12 (3)
Oven 4	80	3 (Cesium Fluoride)	1 (3); 3 (3); 8 (3)
Oven 4	80	26 (Magnesium Chloride)	1 (3); 2 (3); 4 (3)

- Hydroxypropyl cellulose (HPC) (Klucel™ HF) was selected as the polymer for this project
- A specification limit of 90% of initial viscosity was assigned
- The study design excluded T and RH stress conditions above the polymer's glass transition temperature (T_g) where discontinuous behavior could occur



Sample and Solution Preparation Method

- 550 mg of HPC powder were weighed into glass vials and sealed in canning jars (n=3)
 - Saturated salt solutions were used to control humidity (see study design table)
- Following stressing, samples were re-equilibrated to ambient conditions for 48 hours
- Aqueous solutions (1% w/w) were prepared from the equilibrated powder samples
- Solutions were tested with an AMETEK® Brookfield DV2T viscometer at 60 rpm and 25°C using the Small Sample Adapter



Results

- The viscosity decreased for stressed polymer samples, which is consistent with the molecular weight decreasing under stress
- Normalized viscosity data used with ASAPprime® software as % potency

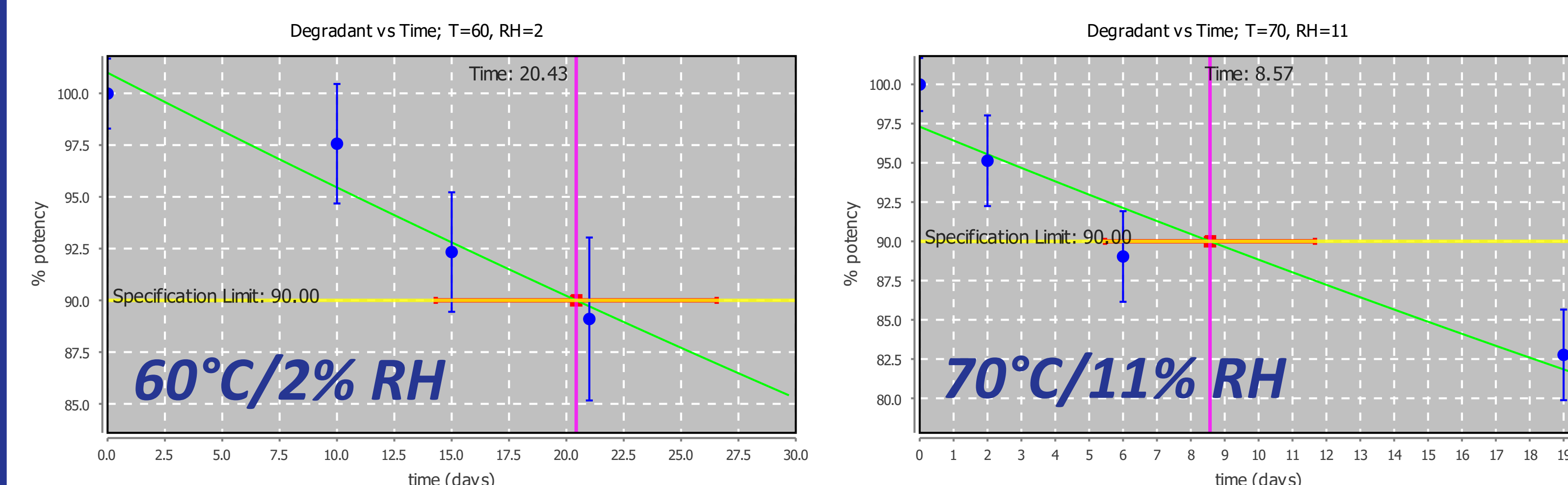
$$\text{normalized potency}(\%) = \left(\frac{\text{stressed sample viscosity}}{\text{average control viscosity for test day}} \right) * 100\%$$

- The viscosity decrease with HPC powder was found to be primarily temperature dependent (activation energy), with little humidity effect (B term)

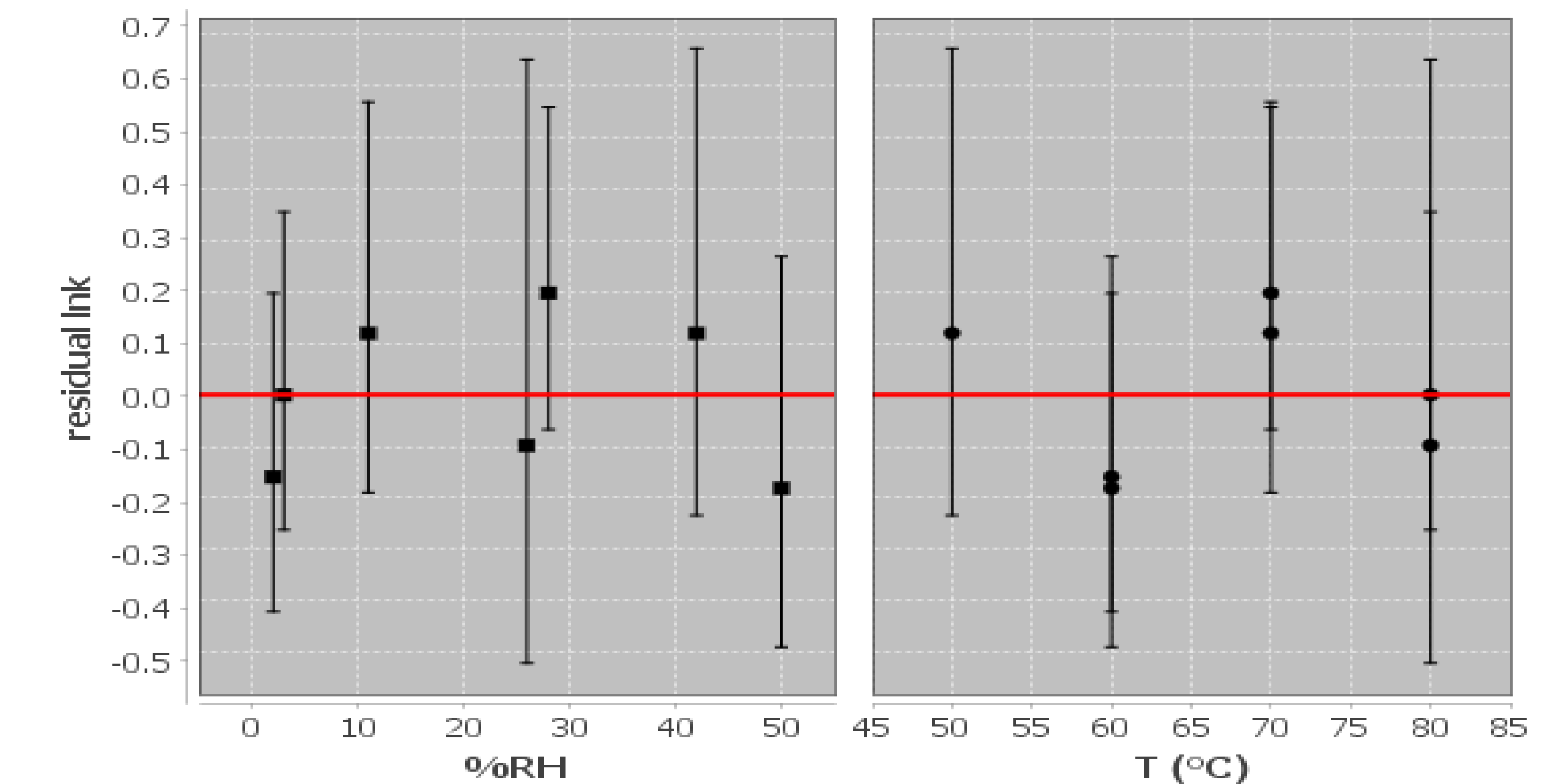
Model values generated in ASAPprime®

lnA	E_a (kcal/mol)	B	R^2	Q^2
20.9 ± 7.2	14.2 ± 4.9	-0.0038 ± 0.0117	0.96	0.84

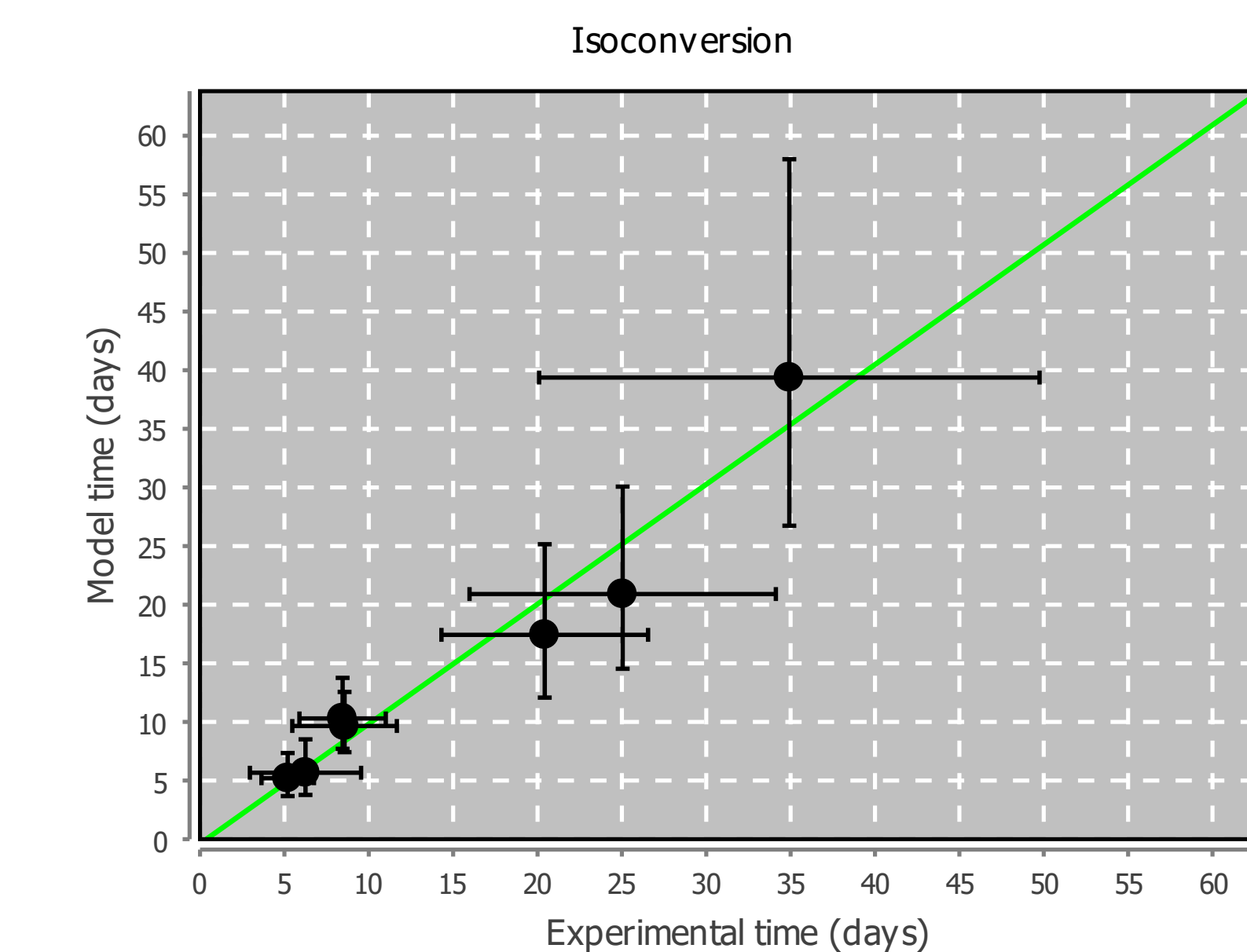
Example data for HPC viscosity decrease at two stressed conditions



Residuals plots of isoconversion times, relative to RH and temperature, showing a good fit to the model



Experimental isoconversion times vs. modeled time, in days



Conclusions

- The viscosity decrease of HPC powder under highly stressed conditions shows data consistent with the ASAP model: isoconversion times (times to hit a specification limit) follow an Arrhenius behavior and are handled effectively using ASAPprime® software

Future Work

- Validate the modeling results for Klucel™ with long-term data
- Apply this general methodology to other water-soluble polymers
- Link the behavior with tablet dissolution stability

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