Modeling of Long-Term Color Change Using ASAP*prime*®

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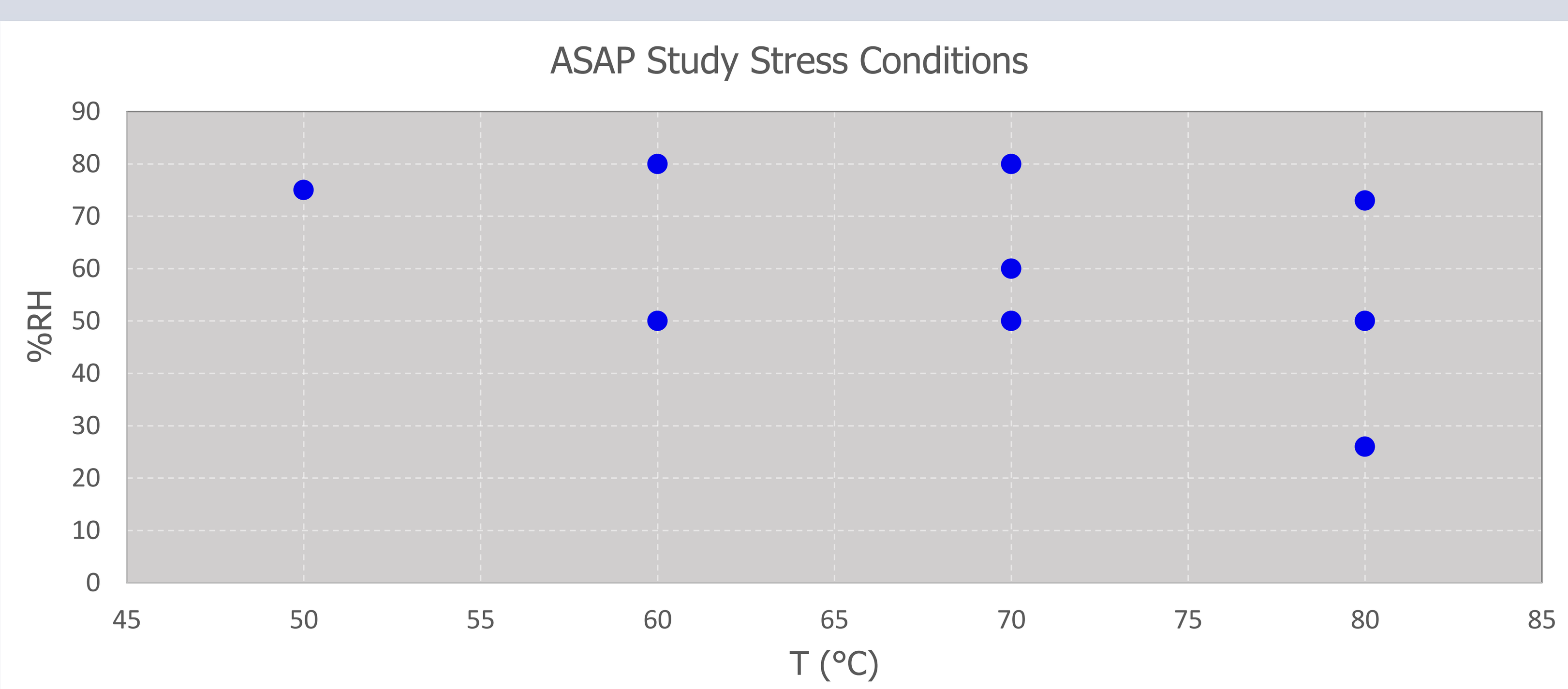
INTRODUCTION

- Visual appearance is one of the quality attributes for pharmaceuticals. A change in color during storage may result in product failure.
- Traditional long term stability studies are expensive and time consuming, but accelerated studies can provide faster feedback.
- The Accelerated Stability Assessment Program (ASAP) approach is commonly used to assess chemical stability of drug substances and drug products, but can also be used to predict shelf-life based on physical stability parameters, such as dissolution or color.
- Indigo carmine tablets were used in a case study to predict the color-limited shelf life, with color change modeled using the moisture-modified Arrhenius equation.

FORMULATION & STUDY DESIGN

- Indigo carmine tablets were prepared by wet granulation and stressed at high temperature and relative humidity conditions.
- Indigo carmine is a common dye used in pharmaceuticals and has a known incompatibility with lactose.

Component	Unit Quantity (mg/tablet)
Indigo Carmine	2.4
Microcrystalline Cellulose	74.9
Alpha-D-Lactose	92.9
Starch	27.6
Magnesium Stearate	2.3
Total	**200**



METHODS

Stress

- For the ASAP study, three tablets were sealed in Ball® jars with saturated salt solutions to control relative humidity.
- For the long-term study, tablets were stored in heat induction sealed HDPE bottles in humidity- and temperature-controlled chambers.

Colorimetry

- Tablet color is measured with a HunterLab ColorQuest XE colorimeter, which quantifies color using the CIELAB colorimetric standard in terms of L* (dark vs. light), a* (green vs. red), and b* (blue vs. yellow).

Tablets stressed at 80°C/73% RH/ 1 day, representing ΔE^*=9.3 (top), vs. control tablet (bottom).

- Total color change is calculated at each stress condition and compared to control tablets using the CIE76 formula.

$$\Delta E^* = \sqrt{(L^* - L_0^*)^2 + (a^* - a_0^*)^2 + (b^* - b_0^*)^2}$$

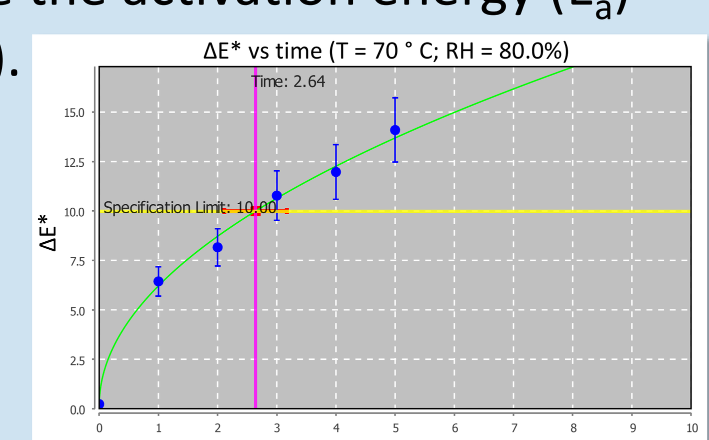
- ΔE^*=10 was chosen as the specification limit due to noticeable color change.

Model

- ASAP*prime*® determines the isoconversion time at each condition and fits the data to the moisture-modified Arrhenius equation to determine the activation energy (E_a) and moisture sensitivity term (B).

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

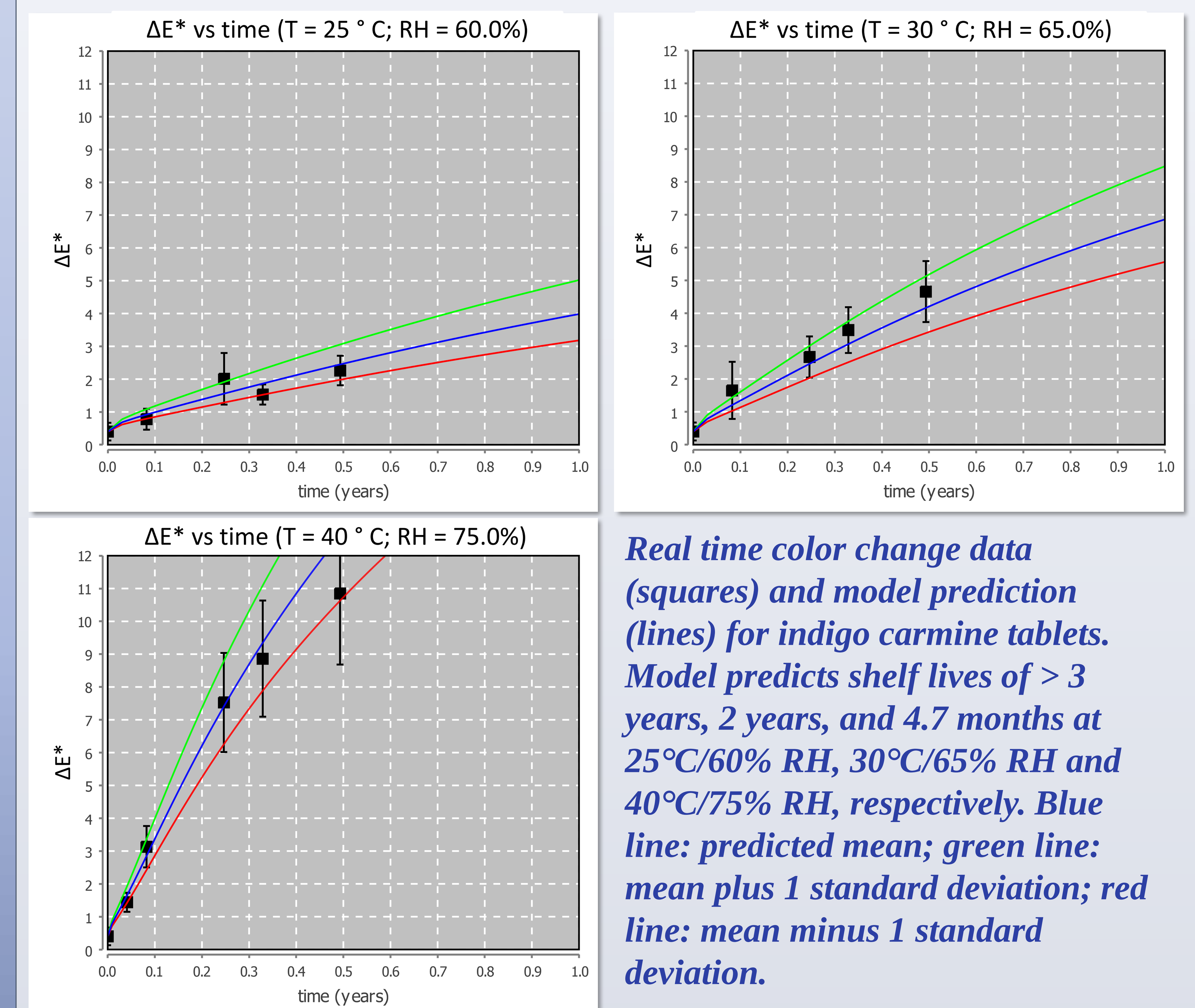
- The fitted model is then used to predict shelf-life at long-term storage conditions in packaging.



Example data from 70°C/80%RH stress condition.

RESULTS

ln(A)	E_a (kcal/mol)	B	R^2	Q^2
29.7 ± 2.9	23.5 ± 2.0	0.079 ± 0.005	0.98	0.93



Real time color change data (squares) and model prediction (lines) for indigo carmine tablets. Model predicts shelf lives of > 3 years, 2 years, and 4.7 months at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH, respectively. Blue line: predicted mean; green line: mean plus 1 standard deviation; red line: mean minus 1 standard deviation.

CONCLUSION

- The ASAP study generated a model with a high degree of confidence for the prediction of color loss in indigo carmine tablets.
- The predictive model is corroborated by real time data.
- Color change can be quantified in the CIE L*a*b* color space and modeled to accurately predict shelf-life in packaging.

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ACKNOWLEDGEMENTS

The authors would like to acknowledge Jennifer Chu and Lili Chen at FreeThink Technologies, Inc. for their contributions to this project.