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

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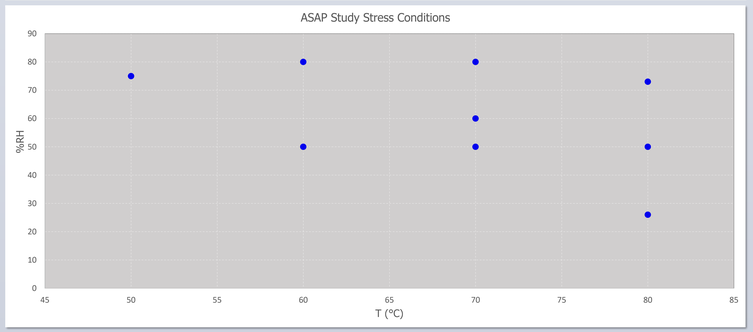
INTRODUCTION

- The Accelerated Stability Assessment Program (ASAP) approach is commonly used to assess the chemical and physical stability of drug substances and drug products.
- To demonstrate the applicability of ASAP to color change as a quality attribute, tablets formulated with indigo carmine dye were stressed at elevated temperature and equilibrium relative humidity (RH) conditions and color change was measured using the CIELAB colorimetric standard.
- The data were used to build a model employing the moisture-modified Arrhenius equation and the ASAP*prime*® software, which was shown to accurately predict color change in comparison with real time data generated over 9 months.

FORMULATION & STUDY DESIGN

- Indigo carmine tablets were prepared by wet granulation and pressed into 200 mg tablets.
- Tablets were stressed at conditions ranging from 50°C to 80°C and 20% to 80% RH for up to one month.
- Upon stressing, indigo carmine is reduced by lactose and tablets change color from blue to yellow.

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, five tablets were stored in 40 cc heat induction sealed HDPE bottles in humidity- and temperature-controlled chambers.

Colorimetry

- Tablet color was 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 was calculated at each stress condition and compared to control tablets using the CIE76 formula.

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

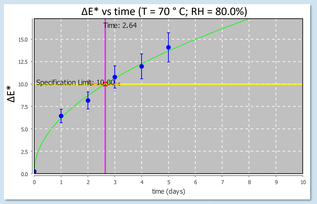
- ΔE^*=10 was chosen as the specification limit due to noticeable color change.

Model

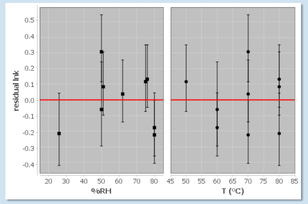
- The isoconversion times at each condition were determined using a diffusion fit. The data were fit to the moisture-modified Arrhenius equation to determine the activation energy (E_a) and moisture sensitivity term (B).

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

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



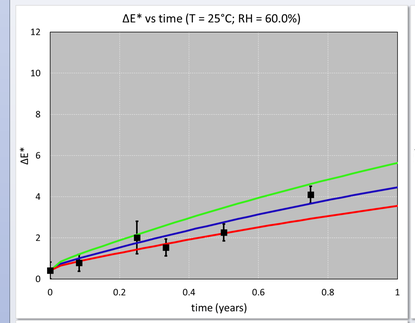
Example data from 70°C/80%RH stress condition.

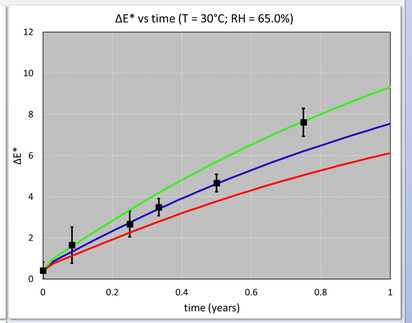


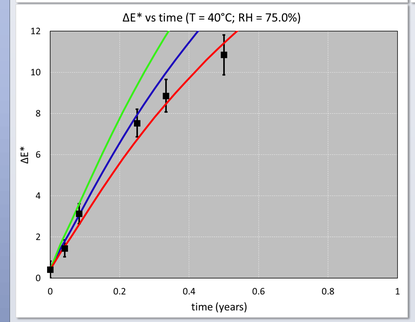
Residuals plot of data fit to the model.

RESULTS

ln(A)	E_a (kcal/mol)	B	R^2	Q^2
29 ± 4.2	23 ± 3.0	0.080 ± 0.008	0.97	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 over nine months.
- Color change can be quantified in the CIE L*a*b* color space and modeled to accurately predict shelf-life in packaging.

REFERENCES

Waterman KC, Adami RC. Accelerated aging: prediction of chemical stability of pharmaceuticals. Int J Pharm. 2005;293:101-25.

Kesselhelm AS, Bykov K, Avorn J, Tong A, Doherty M, Choudhry NK. Burden of Changes in Pill Appearance for Patients Receiving Generic Cardiovascular Medications After Myocardial Infarction. Ann Intern Med. 2014;161:96–103.

Berberich J, Dee K-H, Hayauchi Y, Pörtner C. A new method to determine discoloration kinetics of uncoated white tablets occurring during stability testing—an application of instrumental color measurement in the development pharmaceutics. Int J Pharm. 2002;234:55–66.

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