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

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PURPOSE

- The Accelerated Stability Assessment Program (ASAP) approach is commonly used to assess the chemical stability of drug substances and drug products, and the utility of this approach to predict shelf-life based on physical stability attributes, such as drug product dissolution, has been shown.
- 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.
- ASAP and the ASAP*prime*® software can thus be used to make shelf-life predictions based on color change in products.

OBJECTIVE

To demonstrate the application of ASAP and the ASAP*prime*® software in predicting long-term color change of tablets in packaging.

METHODS

- A blend was prepared containing indigo carmine and standard excipients, including lactose. The blend was wet granulated and pressed into 200 mg tablets. Indigo carmine is a common blue dye used in pharmaceuticals that turns yellow upon reduction by lactose.
- For the ASAP study, three tablets were sealed in Ball® jars with saturated salt solutions to control relative humidity, and placed in temperature-controlled ovens for up to four weeks. Tablets were stressed at conditions ranging from 50°C to 80°C and 20% RH to 80% RH.
- For the long-term study, five tablets were stored in 40 cc heat induction sealed HDPE bottles in humidity- and temperature-controlled chambers for up to nine months.
- At the time of measurement, tablets were removed from the ovens or chambers and equilibrated to room temperature. 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). Total color change (ΔE*) was calculated at each stress condition 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 failure point due to noticeable color change (Figure 1).

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**

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

RESULTS

The colorimetric data were input into the ASAP*prime*® software, and the time to the failure point at each temperature and humidity condition (Figure 2) was determined. The moisture-modified Arrhenius equation was utilized to calculate the activation energy (E_a) and moisture sensitivity term (B).

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

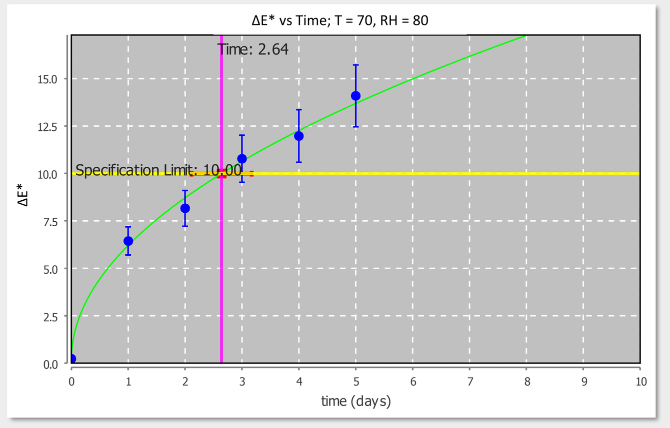

Figure 2. Example isoconversion plot from the 70°C/80% RH stress condition.

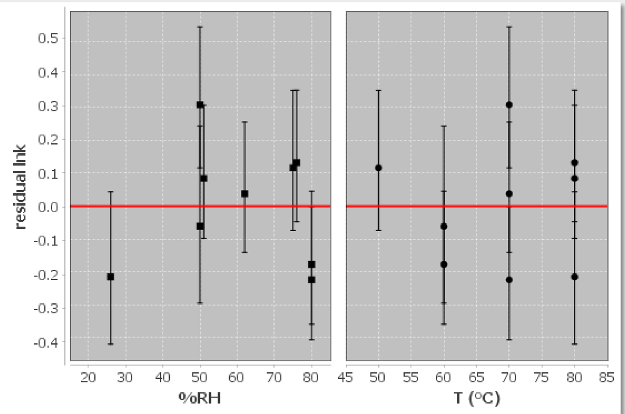

Figure 3. Residuals plot for data fit to the model.

A model was produced to predict color change over a range of temperature and humidity conditions and determine shelf life at long-term storage conditions in packaging.

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

The model parameters for tablet color change exhibited a low E_a (temperature sensitivity) of 23.5 kcal/mol, compared to an average of 27 kcal/mol for chemical degradation, and a higher than average B term (humidity dependence) of 0.079, compared to an average of 0.037. The R^2 of 0.98 and Q^2 of 0.93 indicate that the experimental data fit well to the model (Figure 3). Based on color change, the model predicts tablet 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, in 40 cc HIS HDPE bottles containing five tablets each. Real-time data over nine months closely matched the color change predicted by the model (Figure 4).

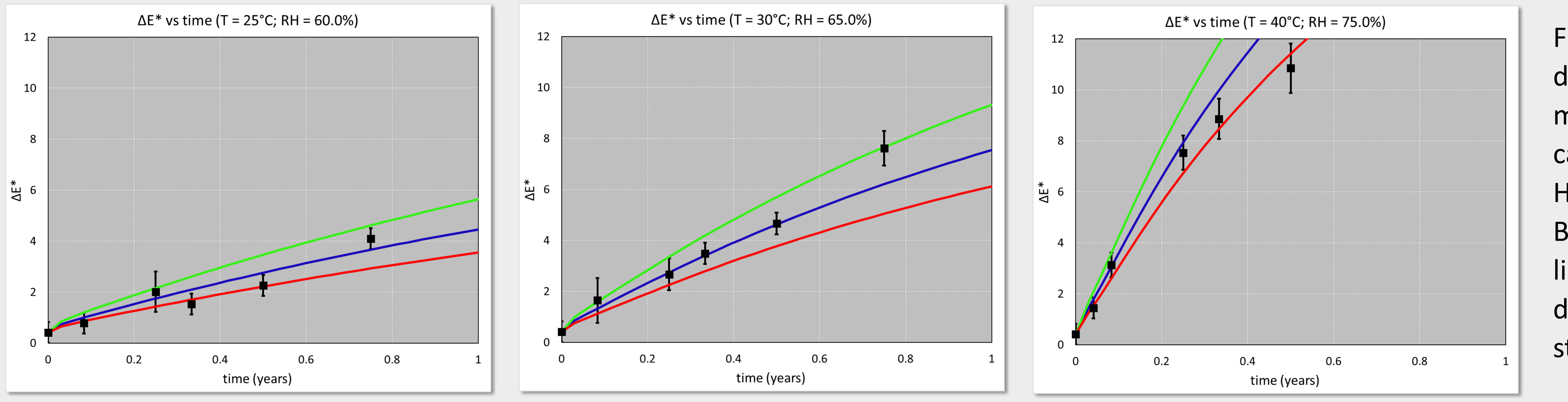

Figure 4. Real time color change data over nine months (squares) and model prediction (lines) for indigo carmine tablets packaged in 40 cc HDPE bottles (HIS, 5 tablets/bottle). Blue line: predicted mean; green line: mean plus 1 standard deviation; red line: mean minus 1 standard deviation.

CONCLUSION

An ASAP model was generated that yielded a high degree of confidence for the prediction of color change in indigo carmine tablets. The predictive model is corroborated by real time data. Color change can be quantified in the CIELAB color space and modeled to accurately predict shelf life in packaging.

ACKNOWLEDGEMENTS

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