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Effect of Oxygen Level and Temperature on Stability of Lipids

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PURPOSE

In the presence of oxygen, lipids undergo autoxidation to form oxidative degradation products. Lipids are common excipients used to deliver active pharmaceutical ingredients (APIs), so the ability to devise a predictive model of lipid oxidation based on short term data would aid in drug formulation. A predictive model of lipid stability was developed based on the growth of primary and secondary oxidation products in a model lipid, sesame oil, under a variety of accelerated stress conditions. An Accelerated Stability Assessment Program (ASAP) study was carried out in which samples were stressed at different times, temperatures, and oxygen levels and the resultant data set used to predict when the product would reach the specification limit.

OBJECTIVE

To demonstrate that growth of primary and secondary oxidative degradant products in oils can be modeled using the Arrhenius equation and ASAP*prime*®.

METHODS

- Samples of sesame oil (NF grade) were degassed and prepared at a variety of oxygen levels: 0%, 2%, 4%, 10%, and ~21% (ambient).
- Samples were stored in Ball® jars of sufficient volume such that oxygen was in excess, and placed in 50° C, 60° C, 70° C, and 80° C ovens for stressing up to 21 days.
- The growth of primary and secondary oxidation products over time was quantified with peroxide value (PV) and anisidine value (AV) tests, respectively, using methods described in USP 41 <401> (titration for PV and spectroscopic measurements for AV).
- The PV, AV, and calculated total oxidation values (TOTOX) were modeled using the ASAP*prime*® software program. The specification limits used to determine the shelf-life for modeling were 10 milliequivalent oxygen atoms (meq)/kg oil for PV, 15 meq/kg for AV, and 35 meq/kg for TOTOX.
- Using experimentally derived data on the time to failure (time to hit the specification limit) at each stress condition, a model was built to predict the time to failure under ambient conditions.
- The oxygen level in the oil was measured optically with a FireStingO_2 meter with a sensor dot and used to calculate the oxygen solubility in the oil.

RESULTS

Oxidation was quantified for all stressed samples (**Figure 1**). Changes in PV and TOTOX over time for a given stress condition were modeled using ASAP*prime*® with a default fit (linear or bilinear). Changes in AV over time were modeled with an Avromi-Erofeyev fit (a kinetic fit with lag), which is characteristic of secondary degradation. From these data, the time to failure (i.e. time needed to hit the specification limit) for PV, AV, and TOTOX was derived for each stress condition. The failure times at **ambient oxygen levels** and varied temperatures were well modeled by the Arrhenius equation (**Eq. 1**). An example of the resultant model predictions for time to failure under ambient conditions is given in **Figure 2**.

$$lnk = lnA - \frac{E_a}{RT} \qquad \text{Equation 1}$$

The times to failure for PV, AV, and TOTOX at **all oxygen levels** and temperatures were well modeled using a modified Arrhenius equation assuming a log dependence on the oxygen concentration (**Eq. 2**). No cross-term involving both temperature and oxygen was needed.

$$lnk = lnA - \frac{E_a}{RT} + Cln\frac{\%O_2}{21} \qquad \text{Equation 2}$$

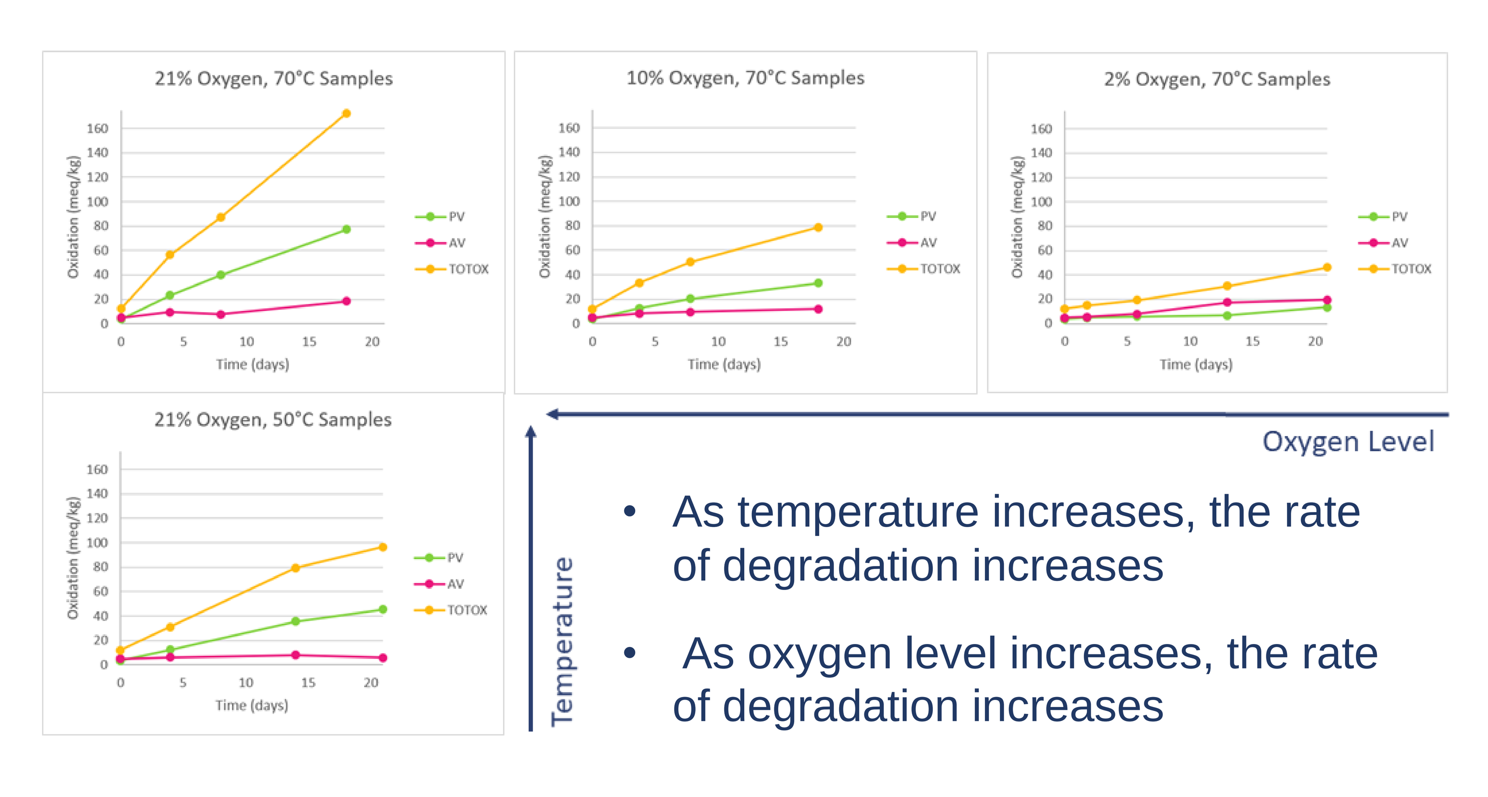

Figure 1. The changes in PV, AV, and TOTOX over time for selected stress conditions.

The PV and TOTOX values showed a low temperature dependence (E_a ~ 7 kcal/mole) and strong oxygen level dependence. The AV values had a higher E_a (~17 kcal/mole) and weak oxygen level dependence. TOTOX, which combines PV and AV, more strongly reflects the generation of PV. Parameters for fits to the entire data set are shown in **Table 1**.

The room temperature oxygen solubility measured from a starting condition where the oil was saturated with oxygen was 43.1 µg/gm. The oxygen solubility measured from a starting condition where the oil is purged with nitrogen was 45.1 µg/gm. The average value of 44.1 µg/gm compared well with literature values. The oxygen solubility is needed to quantify the amount of oxygen present for comparison to real-time results.

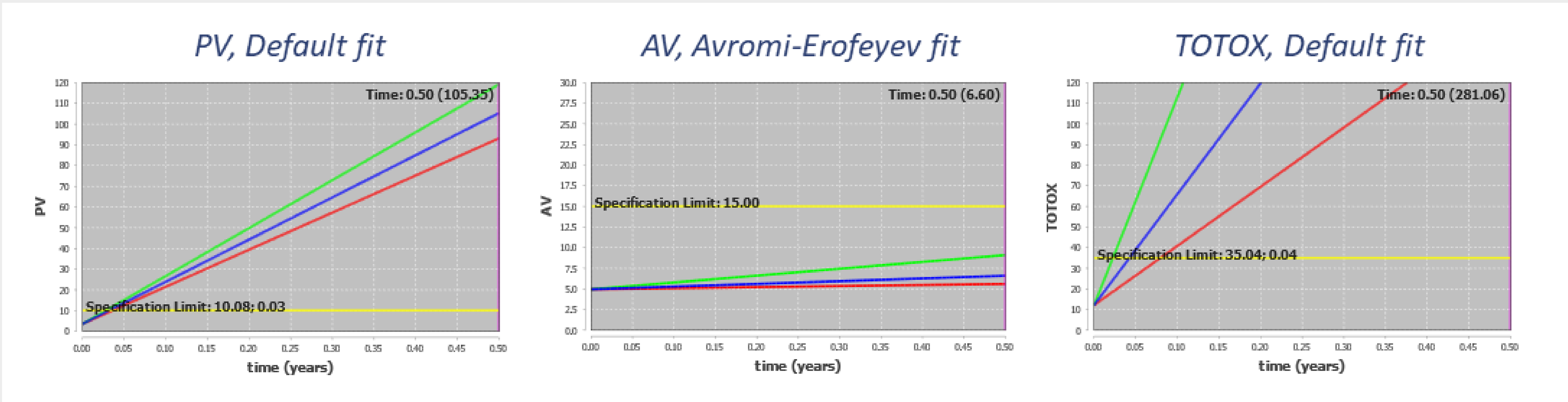

Figure 2. Example model predictions for the growth of oxidative degradants in sesame oil at ambient (21%) oxygen and 25°C. Blue: predicted mean; Green: mean plus 1 standard deviation; Red: mean minus 1 standard deviation.

Table 1. Parameters from a modified Arrhenius equation fit to accelerated oxidation data for sesame oil through ASAP*prime*® software.

	Spec Limit (meq/kg)	lnA	E_a (kcal/mol)	C	R^2	Q^2
PV	10	12.0 ± 2.2	7.0 ± 1.5	0.97 ± 0.08	0.961	0.906
AV	15	24.1 ± 4.2	16.8 ± 2.9	0.13 ± 0.06	0.928	0.800
TOTOX	35	12.4 ± 3.0	6.8 ± 2.0	0.98 ± 0.07	0.978	0.932

CONCLUSION

- Data from samples stressed for three weeks under accelerated conditions were used to develop a predictive model using ASAP*prime*® to quantify the temperature and oxygen level dependence of the growth of oxidative degradation products in sesame oil.
- A modified Arrhenius equation assuming a log dependence on the oxygen level was found to be a functional form that fit the entire data set well.
- The ability to create a predictive model of lipid oxidation can inform shelf-life assessment and packaging selection for lipid-based drug products.

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