Poster 3

Accelerated Oxygen-Dependent Stability: A Case Study with Chlorpromazine

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Purpose

Oxidation is a common degradation pathway for pharmaceutical drug products and can often limit shelf life. It has been difficult to predict the impact of oxygen level and oxygen barrier properties of packaging on long-term stability since there are currently no established protocols for modeling oxygen sensitivity under accelerated conditions. This present work proposes a new formalism for carrying out such studies using a combination of isoconversion (time to reach a specification limit) with a modified Arrhenius equation that accounts for the stability impact of temperature, humidity, and oxygen level. The proposed dependence postulates that the oxygen sensitivity is independent of the impact of temperature and relative humidity (no significant cross-term dependencies). A case study was undertaken using chlorpromazine tablets to validate the approach.

Methods

Formulated tablets of chlorpromazine (3.6 mg) were placed into canning jars with saturated salt solutions to control humidity (21- 80% RH) and sealed at four different oxygen levels: 21 (ambient), 10, 5, and 2%. Jars were placed in ovens at various elevated temperatures (60- 85°C). Degradant growth was quantified through HPLC analysis. The data were used to determine isoconversion times at each condition which in turn were fit to a modified Arrhenius equation. Long-term samples were set up at varying oxygen levels and stored at 25°C/60% RH and 40°C/75% RH for comparison to the model.

Results

Chlorpromazine's primary oxidative degradants, chlorpromazine sulfoxide and chlorpromazine N-oxide, both show growth consistent with the proposed oxygen- and moisture-modified Arrhenius equation with data consistent with there being no significant cross-terms between the oxygen level and the relative humidity and temperature dependencies. The model predictions are consistent with the observed degradant growth in long-term samples.

Conclusion

A modified Arrhenius equation, in combination with isoconversion, enables the accelerated determination of shelf life for oxidative processes.

Keywords: Oxygen Sensitivity, Accelerated Stability Modeling