Degradation of Pharmaceutical Solids Accelerated by Changes in Both Relative Humidity and Temperature and Combined Storage Temperature and Storage Relative Humidity (T×h) Design Space for Solid Products

By William R. Porter  Jun 19, 2013 8:11 am PDT

Achieving stability by design for solid products requires, as one component, the exploration and establishment of boundaries for a storage temperature × relative humidity design space within which the kinetics of degradation of a solid drug or drug product can be predicted using an extended Arrhenius model for the dependence of reaction rates or, equivalently, shelf life on a combined function of both relative humidity and reciprocal absolute temperature. Practical considerations for the design of combined thermal and relative humidity stress degradation experiments and a detailed explanation of proper data analysis methods are defined and illustrated.

Key points include the following:

- Achieving stability of both the drug substance and drug products is a key quality goal. Although thermal stress degradation experiments are a key tool for product development teams to achieve this goal for liquid products and drug substances in solution, the role of relative humidity and its interaction with thermal stress must be studied to understand and predict the degradation kinetics of solid drug substances and solid drug products, such as tablets or capsule dosage forms.
- A combined storage temperature and relative humidity design space can be constructed based on the realization that the drug substance retest date or drug product shelf life is dependent on a function of both the storage temperature and storage relative humidity. These effects can be measured experimentally under different conditions of thermal and relative humidity-induced stress. The existence of a combined storage temperature and relative humidity design space is implicit in current stability guidelines.
- Thermal and relative humidity conditions that result in a physical change of state, such as melting or hydration/dehydration, bound the combined storage temperature and storage relative humidity design space. The kinetics of degradation can be predicted successfully for any combination of relative humidity and temperature values within the boundaries of this design space using an extended Arrhenius model for the combined effect of absolute temperature and relative humidity on chemical kinetics.
- The concept of mean kinetic temperature and the related concept of mean kinetic relative humidity are special cases of a more general concept that a set of temperature and relative humidity pairs of points exist such that the extent of degradation is the same for every combination of temperature and relative humidity values that lie on this line segment in the
temperature × relative humidity design space.

- Determining time-to-failure (shelf-life) under accelerated conditions is all that is necessary to project time-to-failure under other conditions independent of mechanism or kinetic rate constant evaluation. The actual rate of degradation obtained using any particular kinetic model is not required. Straightforward application of an expanded Arrhenius model that includes both the effects of reciprocal absolute temperature and relative humidity under isoconversional conditions leads to efficient designs for stress degradation experiments that combine the effects of both factors.

- Once a set of temperature and relative humidity stress degradation experimental conditions have been defined that are predictive of degradation under less stressful (normal storage) conditions, experiments using these defined stress conditions can be used routinely to test future batches to predict their stability properties or to verify that process changes do not adversely affect stability properties of the product.

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