ASAP: Accelerated Stability Assessment Program

Improved Protocol and Data Analysis for Accelerated Shelf-Life Estimation of Solid Dosage Forms

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A more rapid and accurate accelerated aging protocol is used to determine the shelf-life of drugs in solid dosage forms based on different drug development phases, from excipient compatibility through late development. Reliable estimates for temperature and relative humidity effects on chemical stability are provided using the combination of an isoconversion paradigm and a humidity-corrected Arrhenius equation. Imprecision is incorporated into a Monte-Carlo simulation to propagate the variation inherent in the experiment. In early development phases, greater imprecision in predictions is tolerated to allow faster screening with reduced sampling. As programs progress, early development data are used to design appropriate test conditions for late stage stability programs. Parameters generated from the protocol also allow package selection without explicit screening. The Accelerated Stability Assessment Program, ASAP, is being used to define the critical degradation products for developing analytical methods, to select the appropriate packaging configuration, and to understand the stability impact of changes in the active pharmaceutical ingredient (API) or drug product manufacturing processes and ingredients.

In solution, chemical kinetics is characterized by a transformation from starting material to product following a reaction order. In the solid state, the situation is complicated by the multiplicity of molecular states. For example, molecules of an API in

a formulation can exist in crystalline bulk, at the surface of the crystal, at defect sites as well as in amorphous states (either high energy or dissolved in the surrounding material). Each of these states often shows distinctly different reaction rates. Typically, the bulk crystalline API will react most slowly due to the lattice energy that must be overcome to cause reaction. The result of this heterogeneous kinetic situation is that the rate of API conversion to a degradation product will be a superposition of separate rates. This ultimately means that defining a rate constant for conversion of API to degradant in a classical sense can be futile.

The situation becomes still more complicated when temperature changes are evoked. The Arrhenius equation describes the effect of temperature on reaction rates in solution and gas phase:

$$\ln k = \ln A - E_a/(RT) \quad (1)$$

where k is the rate constant, A is an intercept related to the collision frequency, E_a is the activation energy for the chemical conversion, R is the gas constant and T is absolute temperature. As stated above, in the solid state, it may be difficult to impossible to determine the rate constant(s) describing the overall chemical conversion. Moreover, at different temperatures, the relative contribution of API in each of its different physical forms can be different. The result has generally been that many solid-state stability studies on drug products have been considered non-Arrhenius.

The situation can be operationally remedied with the introduction of an "isoconversion paradigm." In the isoconversion paradigm, a rate constant is defined as the reciprocal of the time needed to reach the specification limits of a degradant. This results in a rate constant that has potential contributions from different physical forms of

the API; however, this proportion is kept constant across any accelerated storage conditions. By employing this isoconversion paradigm (at a constant relative humidity), the vast majority of API degradation processes appear to be Arrhenius. Exceptions occur when there is a phase transition such as a melt, glass transition or deliquescence. With these exceptions in mind, the isoconversion paradigm allows the general use of relatively high temperatures (to 80°C) to accurately determine ambient shelf-life by Arrhenius extrapolation.

To handle the range of relative humidities a drug product could be exposed to, we have found that chemical degradation universally follows a modified Arrhenius equation:

$$\ln k = \ln A - E_a/RT + B(ERH) \qquad (2)$$

where B is a fitting constant indicative of the moisture sensitivity of a particular system and ERH is the equilibrium relative humidity. The equation shows that relative humidity effects on API degradation are exponential. The moisture sensitivity of reactions does not indicate hydrolytic processes are involved. In fact, hydrolytic processes do not have significantly different B terms than other chemical mechanisms. The range of observed values for B is between 0 and 0.09. This exponential dependence can result in enormous differences in shelf-life depending on the relative humidity for storage or on the presence of desiccants. That this equation appears to be universal suggests that the dominant role of ERH on reaction rates is to affect mobility: ERH modifies the collision frequency but not the activation energy.

With the modified Arrhenius equation and the isoconversion paradigm, it is possible to define a design of experiment (DOE) protocol for stability. Using a five-point protocol varying temperature and ERH simultaneously, data can be generated that

provide statistically meaningful fitting of the parameters in the equation. It should be noted that the times at each stability condition have to be adjusted to be consistent with the isoconversion paradigm. This means that average parameters are used in early studies, while the times are adjusted as data are available. It has generally be found that a two-week stability protocol provides reasonable data for accurately and precisely (propagating errors through a Monte-Carlo simulation procedure) projecting multiyear drug stability. A screening protocol for drug product is shown in Table 1.

Temperature (°C)	**Equilibrium Relative Humidity (%)**	**Number of Days at Storage Condition**
50	75	14
60	40	14
70	5	14
70	75	1
80	40	2

Table 1 General screening protocol for drug stability in drug products. Samples are stored at each condition exposed to the relative humidity of the environment (open bottle). Typically, an additional sample is stored at 5°C to use as the initial control sample. For the best statistics in the experiment, all samples (including the control) should be analyzed as a single batch (i.e., samples removed from the stability chambers early should be held at 5°C until all samples are ready to be analyzed).

Once the moisture sensitivity of drug stability is explicitly known for a system, stability in a package configuration becomes a matter of calculating the ERH inside a package as a function of time. This calculation can be accomplished using the initial relative humidity inside the package, the external relative humidity, the moisture adsorption isotherm of all internal components (including for example, any desiccants)

and the moisture vapor transmission rate (MVTR) of the packaging. Using this model, we have successfully predicted the effect of such factors as the number of tablets in a bottle on the shelf-life of drug products. With the exponential dependence of stability with respect to relative humidity, one can sometimes observe what appears to be a threshold behavior: more rapid reaction as the relative humidity in a package increases. With this model validated, it is now possible to eliminate package screening since the results are accurately predicted from the science.