Rational Storage Conditions for Accelerated Testing of Stability of Solid Pharmaceuticals

To the Editor:

The F.D.A. Stability Guidelines[1] advocate the use of accelerated testing. However, aside from the test at 40 °C and 75% relative humidity (RH), the guidelines specify neither what actual tests should be run nor to what use they can be put. The guidelines also state that testing should be performed in the actual container intended for marketing. The authors greatly favor the use of accelerated tests both for liquids and solids; the following is a commentary on some present-day practices.

It would seem logical that if products are placed at high temperature stations and assayed, then the results should in some way aid in the assessment of stability. The only real quantitative way of doing this is by extrapolation. Although the extrapolated results may not be used per se for expiration period calculation, they would form what is usually denoted supportive data. Arrhenius extrapolations of solutions are usually quite accurate, precise, and unambiguous, but this is not the case for solids.

Yoshioka et al.[2–4,8] and Carstensen et al.[5–7] have reported on the profiles and phenomena to be expected in accelerated temperature and humidity testing of solid dosage forms, and the following pertinent facts apply to accelerated testing in general: (*a*) stability is often a function of both moisture content and temperature;[2–8] (*b*) if a moisture-sensitive product is placed in a nonhermetic or moisture-permeable container in a high temperature oven (which is usually of low RH), then the product may dry out at the higher temperatures; this prevents any rational extrapolation of data from the higher temperatures.

The following extrapolation techniques apply to nonbottled solid dosage forms. In the method of Yoshioka, the fraction, x, of drug decomposed after a storage time, t, a temperature, T, and a vapor pressure, P, is given by the following formula:

$$x = k'[\exp(-E_a/RT)]\, P^s\, t^n \qquad (1)$$

where E_a is the activation energy, R is the gas constant, P is water vapor pressure, and k', s, and n, are constants.[3,4] This, hence, is a four-parameter equation. It applies to moisture conditions above the critical relative humidity (CRH).

With the usual type of testing carried out in industry, there are two accelerated temperature stations (e.g., 42 and 55 °C) with unspecified RH, and the Joel Davis test (40 °C, 75% RH); the latter, of course, is with a specified RH. As pointed out above, at the high temperature stations RH is usually not controlled. However, it is usually low, so that nonhermetically packaged drug products will dry out, preventing rational data treatment.

In addition to the accelerated data, there are room temperature data (somewhere between 22 and 25 °C) and, sometimes, 4 and 30 °C data. If one of these latter as well as the two accelerated temperature stations were maintained at a constant, controlled RH, then there would be four T and P conditions allowing evaluation of the four parameters in eq 1. This would not be a system with zero degrees of freedom since there are usually more than one data point per temperature. With such a system, there would be a rational basis for extrapolation of stress data of non-bottled solid dosage forms to a defined room temperature condition. It should be noted that there is one factor which has been added to this rational viewpoint; namely, that the room temperature condition to which the extrapolation is carried out is not only a temperature, but also a RH.

The method requires the assessment of the CRH at each temperature or, rather, it requires that the humidity condition at each temperature be above this value. To insure this, it suffices to place a unit of the dosage form at the condition and observe that it gains weight. If it does not, then the RH at the storage condition is too low for the use of the formula.

A system which is quite close to present-day practices uses RH values below the CRH. A modification of eq 1 applies to the system below the CRH:[8]

$$x = k' P^s t^n \qquad (2)$$

or

$$x = x_0 (P/17.8)^s (t/100)^n \qquad (3)$$

where x_0 is the percent decomposed at t = 100 days and P = 17.8 mmHg (25 °C, 75% RH). Equation 2 contains only three parameters; hence, if three stability stations (e.g., 25, 42, and 55 °C) were kept at controlled, fairly low RH values, it would be possible to extrapolate stabilities to any temperature and RH below the CRH. It is noted that for the latter approach, the only difference between what is done in present-day practice and what is suggested is that the RH at the three stations be controlled and known.

An example (meclofenoxate hydrochloride[8]) is used to illustrate this latter principle (Table I). The parameters x_0, s, and n in eq 3 are found by nonlinear regression to be 0.063, 9.26, and 3.17; that is, eq 3 takes the following form:

$$x = 0.063\, (P/17.8)^{9.26} (t/100)^{3.17} \qquad (4)$$

If, for example, it is desired to know what the percent decomposition would be after 180 days at 25 °C and 60% RH, it is noted (from a water vapor pressure table[9]) that $P = 23.8 \times 0.6 = 14.3$. Inserting this value and 180 in eq 4 gives the following:

Table I—Example of Data at Relative Humidities below the Critical Relative Humidity

Temperature, °C	RH, %	*P*, mmHg	*t*, day	*x*, %
60	49.9	74.7	3	0.5
			4	1.3
			5	2.7
70	22.0	51.4	10	0.8
			15	2.8
			20	7.0
80	22.6	80.3	3	1.1
			4	2.7
			5	5.4

$$x = 0.05\ (\%) \qquad (5)$$

This is the estimated decomposition if the accepted "room temperature condition" to which extrapolations are made is 25 °C and 60% RH. In this case, supportive data are associated with a figure which can be compared with actual figures obtained at room temperature and lend credence to actual room temperature data or room temperature data extrapolated beyond the longest assay time. It is noted from Table I that there is no "routine" time interval, and this would vary from dosage form to dosage form. In fact a general scenario would be to "try" a time point at each of the stations and, from this first "try", decide on a rational set of pull-times. In the example the RH values are seemingly rather high and they could be lowered to give longer times for a given decomposition.

References and Notes

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SUMIE YOSHIOKA*x
J. T. CARSTENSEN‡
*National Institute of Hygienic Sciences
1-18-1, Kamiyoga, Setagaya-ku
Tokyo 158, Japan
‡School of Pharmacy
University of Wisconsin
Madison, WI 53706

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