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CYCLIC TESTING IN STABILITY PROGRAMS

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ABSTRACT

It is shown that accelerated testing can be used to predict losses at given times of storage in cycled testing. This is useful, since temperatures of storage are never totally constant, and the concept has been illustrated by assuming an average temperature of 25°C and a fluctuation of 5°C.

INTRODUCTION

It was customary, up until 1984, to base expiration dating on stability studies carried out at "room temperature". The definition of this in the United States was, in the past, interpreted as about 25°C[1], and it was recognized that there would be fluctuations about this in storage. Most studies aimed at expiration period determination were, nevertheless, carried out at constant temperature. The F.D.A. guidelines of March 1984 state, however, that

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"stability studies....stored at the temperature stated on the label are ordinarily required but are not usually adequate without other information (e.g., stress testing) for assignment of an expiration date."

One reason for carrying out accelerated stability programs is to obtain an estimate of the apparent activation energy for the drug in the dosage form. There may be no theoretical justification for this, in fact the directly obtained Arrhenius plot may not be linear, but it will be sufficiently linear in narrow temperature intervals (± 5-8°C), so that it can be of value in the assessment of stability at extended room temperature. This, by U.S.P. definition is 15-30°C. To make this claim the best direct way of testing would be to test at both 15 and at 30°C. As mentioned, a common (more economic) practice is to test at or about 25°C, since this constitutes an average ambient temperature in pharmacies and/or warehouses in the U.S.[1]. If extended stability data were only obtained at 25 (± 0.5)°C, then only this temperature, not extended room temperature, could be claimed on the label. For this reason it is a practice to (a) acquire an extended data collection at 25°C, (b) to test at 37°C up to 6 months, and (c) if the latter is not "bad", to apply for expiration periods calculated at 25°C, but to claim extended room temperature on the label.

From a philosophical point of view, (a) the fact that 25°C is the average room temperature in the U.S., or (b) the fact that 22.5°C is the mean of the extended room temperature definition should make one or the other the logical temperature for testing.

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If the philosophy of the extended room temperature definition is to allow for fluctuations in temperatures about a mean, then it might be worthwhile to examine the possible effect of such fluctuations in realistic situations. For instance if, instead of placing the dosage form at constant 25°C it were placed at this average temperature, and fluctuations of ±5°C were allowed, then what would be the difference in stability? For such an undertaking, the activation energy is, of course, crucial, and one of the advantages of performing accelerated studies is exactly the fact that such calculations can be carried out. Here all that is assumed is that the Arrhenius plot is linear in the 10°C range in question (or if 22.5°C is used, the 15°C range).

THEORY

The magnitude that the described temperature fluctuations have on the stability of a dosage form is calculated below for 5 activation energies, 15, 20, 25 and 30 kcal/mole. This covers the span of activation energies usually encountered in drug dosage forms (but not for drug substance itself. This latter will be covered at a later point).

To carry out such a calculation, the following considerations have been made: The drug is assumed to experience an actual loss of 10% in three years of storage at constant room temperature (25°C). This[2] means that the reaction can be considered to be zero order, so that, denoting by C the potency at time t, and by C_0 the

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initial concentration, the value of C will be given by

$$C = C_0 - k\ t \qquad \text{(Eq. 1)}$$

where the rate constant, k, is a function of temperature by the Arrhenius equation:

$$\ln k = -(E_a/\{RT\}) + \ln P \qquad \text{(Eq. 2)}$$

here, E_a is the activation energy, R is the gas constant, T is absolute temperature, and P is the pre-exponential factor. T is allowed to fluctuate in a regular fashion about the average temperature T_1, and the amplitude of this fluctuation is denoted T_2. A rational function for this would be a sinusoidal function as shown in Fig. 1.

The dependence of T on time, t, is therefore given by

$$T = T_1 + T_2 \sin(2\pi t) \qquad \text{(Eq. 3)}$$

Although the calculations below are carried out based on daily fluctuations, it should be pointed out that this is no limitation in general. If, for instance, the fluctuation were within a year, i.e., if it were anticipated that the winter temperature were 20°C and the summer temperature were 40°C, then t would be inserted in units of a year. In the just cited example, T_1 would be 30°C and T_2 would be 10°C, and the unit for k would be in reciprocal years. If both yearly and daily fluctuations are included, then a function describing this would be:

$$T = [T_1 + T_2\sin(2\pi t)] + T_3(\sin \underline{a}t) \qquad \text{(Eq. 4)}$$

where a is tied into the yearly cycle and in the simplest case would be (2π/365). On the other hand, as mentioned if the fluctuation were only the fluctuations experienced within one day, then T_1

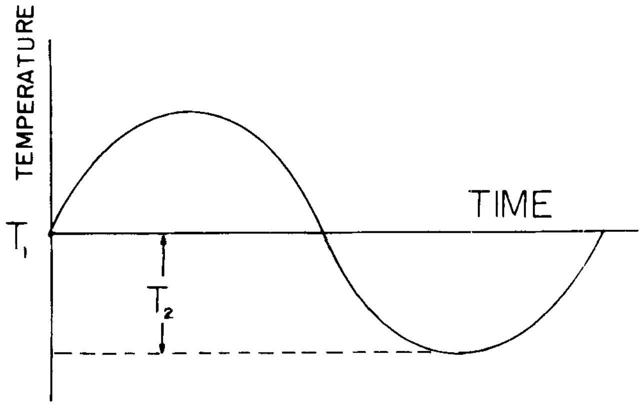

FIGURE 1

Sinusoidal Temperature Fluctuation about a Mean

could be assumed to be 25°C, T_2 would be (assumed to be) 5°C at the most, and the unit for k would be reciprocal days.

Combining equations 1 to 3 gives

$$C = C_0 - \int_0^t P\exp[-E/(T_1+T_2\sin\{2\pi t\})]\,dt \qquad \text{(Eq. 4)}$$

This has been solved by computer. The number of steps used in the integration has been such that 0.1 minute is the interval employed for the considerations at room temperature, i.e., the sinusoidal period has been divided up into 14,400 intervals, to render the integration accurate. The program will print out only 10 of these (or any other number desired). If done for other periodicity it is advisable to use a similar number of steps for each period. In general the effect can be gauged well by simply considering one period, and the manner in which the data are shown below is done in exactly this manner.

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RESULTS AND DISCUSSION

The data are shown in Table I and the table lists (a) the rate constant for the constant temperature storage at 25°C, and (b) the rate constant obtained for the cyclic storage with the activation energy employed.

It should be noted that, in general, the "average" accepted activation energy is that proposed by Kennon[3], namely 14 kCal/mole. But this average is by no means a safe assumption, since many solid dosage forms have higher activation energies. In fact pure solids, when they decompose into a solid plus a non-liquid, will have activation energies of the order of 80-100 kcal/mole. This may, at first glance, seem to be alarming, but what it actually means is that there is practically no decomposition before a "reaction temperature" is reached, and then the decomposition is rapid. This is synonymous with the "decomposition range" implied in melting point tables for many organic compounds. It is only if this "reaction temperature" is very low (e.g., below 50°C) that this should be of concern, and this is rare.

When the statistical parameters[4] are included, then cyclic conditions could result in substantial decreases in expiration dating, if the energy of activation is above 20 kcal/mole.

For this activation energy the rate constant at 37°C is 3.7 times that at room temperature (i.e., it is 0.037 %/day in the example shown in the table). This would correspond to a loss of 6.6% after 6 months at 37°C, so that if losses are higher than

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TABLE I

Cyclic Versus Constant Temperature Room Temperature Data. k = 0.01% per day.

Activation Energy E_a, kCal/mole	k(static) %/day	k(cyclic) %/day	Loss after 3 years static	Loss after 3 years cyclic	% Increase
10	0.01	0.01019	10.95	11.16	10.2
15	0.01	0.01041	10.95	11.38	10.4
20	0.01	0.01075	10.95	11.77	10.7
25	0.01	0.01120	10.95	12.27	11.2
30	0.01	0.01177	10.95	12.89	11.7

that, then there should be cause for concern regarding the cyclic versus static room temperature predictions.

It would be a good assumption, based on the data in the table, to assume, in general, that if the average loss in strength after the (constant temperature) expiration period is m, then cyclic storage, such as described, would cause a loss in strength of 1.1m.

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