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COMMUNICATION

Effects of Temperature Excursions on Mean Kinetic Temperature and Shelf Life

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ABSTRACT

The international acceptance of the definition of controlled room temperature *(CRT) has given additional impetus to the use of mean kinetic temperature (MKT) as a method of quantifying temperatures during transport and storage and consequent possible effects on drug product stability. The present paper explores some of the implications of the MKT concept and considers the effect of temperature excursions on MKT values and hence on stability of drug products.*

INTRODUCTION

The USP definition of *controlled room temperature* (CRT) is:

> A temperature maintained thermostatically that encompasses the usual and customary working environment of 20°C to 25°C that results in a Mean Kinetic Temperature calculated to be not more than 25°C, and that allows for excursions between 15°C and 30°C that are experienced in pharmacies, hospitals, and warehouses.

The *mean kinetic temperature* (MKT) (1) is defined as the isothermal temperature that corresponds to the kinetic effects of a time-temperature distribution and is determined using Haynes' formula (2), into which temperature data obtained at defined intervals are entered. The MKT equation is

$$\text{MKT} = (\Delta H/R)/\{-\ln[(e^{-\delta H/RT1} + e^{-\delta H/RT2} + e^{-\delta H/RTn})/n]\}$$

The USP has proposed a method of calculating MKT for pharmacies and hospitals; the method uses the 52 weekly arithmetic means of the highest and lowest temperatures recorded over the preceding 52 weeks for the calculation of a yearly MKT. For other sites, electronic devices are used, and all the data are used to calculate MKT (3). The Food and Drug Administration (FDA) recommends that, for manufacturers, repackagers, and warehouses, all data points obtained be inserted directly into the equation. A minimum of 104 weekly high and low readings recorded over the preceding 52 weeks would be

inserted into the MKT equation to calculate a yearly MKT (4–7). It is unfortunate that, under some circumstances, the USP method of calculation will give lower values than the FDA method because of the use of an arithmetic average that is incorrect for an Arrhenius-type equation. The FDA method is therefore preferred.

In the present paper, we consider some of the implications of MKT for the stability of drug products. In particular, we explore the effect of temperature ''excursions'' on the shelf life (SL) of drug products.

THEORY

The USP definition of CRT is most useful. However, one question that has been raised by a number of persons, including some of the participants at the June 4, 1998, USP open conference on packaging, storage, and distribution, is: How long in time can the excursions in temperature up to 30°C be before it is likely that there will be a serious adverse effect on drug product stability? In particular: Is it likely that, for some products, the total effect of a number of temperature excursions will be such as to invalidate a previously assigned expiration date or beyond-use date? Further: What are the factors that may make some pharmaceutical products more sensitive than others to the adverse effects of temperature excursions of up to 30°C?

The form of the Arrhenius equation used by Grimm and Schepky (6) in their calculation of MKT assigns an energy of activation E_a of 83 kJ/mole. This value was obtained by Grimm and Schepky from a survey they made of literature reports of the energy of activation for a variety of drugs. Obviously, products with energies of activation that are significantly different from the average of Grimm and Schepky will show differing susceptabilities to changes in temperature such as are qualified by MKT determinations.

When solvolysis is the route of degradation, the Grimm value is probably more than reasonable, and, of course, hydrolysis is a very common mode of degradation. However, for drug products for which oxidation is the primary route of degradation, the energies of activation will be significantly less; values in the region of about 20 to 50 kJ/mol are not unlikely. Drug products that have lower than average energies of activation will be less sensitive to temperature stress than the average of Grimm and Schepky.

Conversely, there are drug products that degrade by mechanisms characterized by energies of activation substantially greater than 83 kJ/mol. Such products will be more sensitive than the Grimm and Schepky average to temperature stress.

The normal conventional method of determining a shelf life for a pharmaceutical product is to determine the intersection of the 95% confidence bound for the isothermal (storage temperature) regression line with the 90% potency value. The time given by such an exercise is the maximum that can be assigned as the shelf life. In practice, the period determined (defined by A. J. Smith) as the conformance period (CP) is often substantially greater than the SL. Thus, if we determined, for instance, that conformance periods were 1.1, 12.2, and 38.2 months, for three different products, it is likely that the respective shelf lives would be 1, 12, and 36 months. The difference between the conformance period and the assigned shelf life, in effect, provides an additional safety margin with respect to stability. Of course, since conformance periods are not normally publicly available, it is not easy to quantify the extent of this extra margin of safety for any given product.

METHODS

The data used in this paper were computer generated. In the studies of the effect of temperature excursions on MKT, and hence shelf life, we used idealized square-wave excursions such that temperature was deemed to rise instantaneously (Fig. 1). (Some limitations of this model are considered in the Results and Discussion sec-

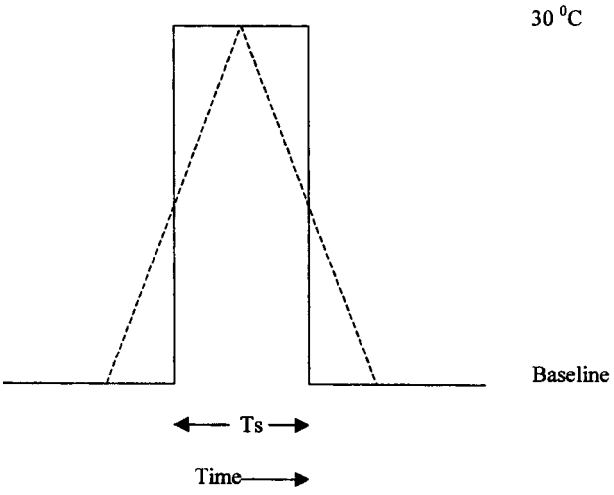

Figure 1. Variation of temperature with time for a spike (solid line = square wave; dotted line = spike).

tion). For example, for a 1-month excursion, we select a virtual product stored isothermally at exactly 25°C, and we cause the temperature to increase instantaneously to 30°C. At the end of 1 month, the temperature is required to revert instantaneously to the former value of 25°C. Knowledge of the time for which the product was subjected to 30°C allows us to calculate the MKT for products with different energies of activation, shelf lives, or conformance periods. With the new calculated MKT, we are able to determine whether or not the new MKT has adversely affected the shelf life of the product, assuming a first-order degradation process.

RESULTS AND DISCUSSIONS

Table 1 shows the effect of a 1-month, 30°C excursion on MKT values of systems that all have a baseline storage temperature of exactly 25°C and an activation energy of 83 kJ/mol. As can be seen, if the conformance period is slightly greater than the assigned shelf life, the excursion stress is not sufficient to invalidate the shelf life. However, when the shelf life is exactly equal to the conformance period, the MKT (calculated to include the effect of the excursion) is in excess of 25°C, and thus the assigned shelf life is now invalid.

Table 2 shows the effect of varying the energy of activation on excursion effects for two sets of system, one with an SL of 1 month and the second with SL values of 12 months. It can been seen that the excursion effects on MKT are indeed somewhat dependent on the value of activation energy; however, the effect is quite small. This suggests that, in most cases, the use of the Grimm average for the energy of activation is unlikely to lead to major error.

Table 3 shows the effect of increasing excursion stress from 0.01 months (i.e., about 7 hr) at 30°C to 2 months at 30°C. As can be seen for the smallest excursion, the effect on MKT values is almost negligible, even for products that only have a shelf life of 1 month. As the length of the excursion is increased, the effect on MKT values, especially for the systems with short shelf lives, becomes increasingly significant.

The data presented in Tables 1–3 are all derived for systems with a baseline storage temperature of exactly 25°C. This, of course, is a worst-case scenario. Table 4 shows results for various excursion stresses and shelf lives when the baseline temperature is 22.5°C (i.e., in the middle of the 20°C–25°C range). As can be seen, with the exception of two 1-month shelf-life systems, the MKT values all remain under 25°C, even with a 2-month 30°C excursion.

Table 5 shows comparable data for what might be termed a best-case scenario for systems with a baseline storage temperature of 20°C. As would be expected, such systems are especially resistant to the adverse effect of excursion stress, although even in this case, some of the 1-month shelf life products are affected adversely by the longer excursions.

In all the calculations presented in this paper, we assumed that the degradation process was governed by first-order kinetics. Calculations have shown that using zero-order degradation kinetics does not substantially affect the conclusions reported in this paper.

Obviously, the square-wave model used for the calculations reported in this paper is not likely to exist in actu-

Table 1

Effect of a 1-Month, 30°C Excursion on the Shelf Life of Drug Products with an Activation Energy of 83 kJ/mol

Conformance Period (CP) (Months)	Shelf Life (SL) (Months)	MKT Including Excursion (°C)	New CP (Months)	Shelf Life Still Acceptable?
1.000	1.000	30.000	0.575	No
12.00	12.00	25.532	11.31	No
24.00	24.00	25.270	23.37	No
28.00	24.00	25.232	27.29	Yes
36.00	36.00	25.181	35.28	No
39.00	36.00	25.167	38.21	Yes
41.00	36.00	25.159	40.28	Yes
62.00	60.00	25.105	61.28	Yes
65.00	60.00	25.100	64.28	Yes

Table 2

Effect of Activation Energy on the Shelf Life of Products Subjected to a 1-Month, 30°C Excursion

System	Activation Energy ΔH (kJ/mol)	MKT Including Excursion (°C)	New CP (Months)	Shelf Life (SL) Still Acceptable?
1.0-month SL and 1.1 month CP	55	29.608	0.785	No
	70	29.625	0.715	No
	95	29.650	0.611	No
	110	29.665	0.555	No
	120	29.674	0.521	No
12.0 months SL and 13.0 months CP	55	25.450	12.57	Yes
	70	25.472	12.43	Yes
	95	25.511	12.17	Yes
	110	25.537	12.00	Yes
	120	25.554	11.88	No

ality. However, it is suggested that, although the model has limitations, conclusions drawn from the use of this model are highly likely to be applicable to real storage conditions. In Fig. 1, we show a square-wave and a non-square-wave excursion that have the same amount of energy input (i.e., area under the temperature-time curve from the baseline). Because of the logarithmic nature of the Arrhenius relationship, the MKT of the square wave is slightly higher than that of the spike. However, the effect is small, and thus it is legitimate to use the square-wave model for studies of this type. Certainly, for investigations designed to elucidate the relative effects of such values as conformance periods, shelf lives, or energies of activation as described in this paper, this model is valid.

Table 3

Effect of Excursion Duration on Shelf Life for Products with an Activation Energy of 83 kJ/mol with a Baseline at 25°C

Excursion	Conformance Period (CP) (Months)	Shelf Life (SL) (Months)	MKT Including Excursion (°C)	New CP (Months)	Shelf Life Still Acceptable?
0.01 month at 30°C	1	1	25.065	0.993	No
	12	12	25.005	11.99	No
	24	24	25.003	23.99	No
	36	36	25.002	35.99	No
0.1 month at 30°C	1	1	25.635	0.931	No
	12	12	25.055	11.93	No
	24	24	25.027	23.93	No
	36	26	25.018	25.93	No
0.5 month at 30°C	1	1	27.820	0.731	No
	12	12	25.270	11.64	No
	24	24	25.136	23.64	No
	36	36	25.091	35.64	No
1 month at 30°C	1	1	30.000	0.576	No
	12	12	25.532	11.31	No
	24	24	25.270	23.29	No
	36	36	25.181	35.28	No
2 months at 30°C	12	12	26.035	10.69	No
	24	24	25.532	22.61	No
	36	36	25.358	34.59	No

Table 4

Effect of Excursion Duration on Shelf Life for Products with an Activation Energy of 83 kJ/mol with a Baseline at 22.5°C

Excursion	Conformance Period (CP) (Months)	Shelf Life (SL) (Months)	MKT Including Excursion (°C)	New CP (Months)	Shelf Life Still Acceptable?
0.01 month at 30°C	1	1	22.614	1.310	Yes
	12	12	22.510	15.91	Yes
	24	24	22.505	31.84	Yes
	36	36	22.503	47.77	Yes
0.1 month at 30°C	1	1	23.578	1.174	Yes
	12	12	22.595	15.76	Yes
	24	24	22.548	31.68	Yes
	36	26	22.532	47.61	Yes
0.5 month at 30°C	1	1	26.966	0.803	No
	12	12	22.965	15.11	Yes
	24	24	22.735	31.01	Yes
	36	36	22.657	46.94	Yes
1 month at 30°C	1	1	30.000	0.576	No
	12	12	23.407	14.37	Yes
	24	24	22.965	30.21	Yes
	36	36	22.812	46.11	Yes
2 months at 30°C	12	12	24.234	13.08	Yes
	24	24	23.407	28.73	Yes
	36	36	23.114	44.56	Yes

Table 5

Effect of Excursion Duration on Shelf Life for Products with an Activation Energy of 83 kJ/mol with a Baseline at 20°C

Excursion	Conformance Period (CP) (Months)	Shelf Life (SL) (Months)	MKT Including Excursion (°C)	New CP (Months)	Shelf Life Still Acceptable?
0.01 month at 30°C	1	1	20.177	1.734	Yes
	12	12	20.015	21.21	Yes
	24	24	22.007	42.45	Yes
	36	36	20.005	63.69	Yes
0.1 month at 30°C	1	1	21.632	1.466	Yes
	12	12	20.148	20.88	Yes
	24	24	20.074	42.12	Yes
	36	26	20.050	63.36	Yes
0.5 month at 30°C	1	1	26.258	0.869	No
	12	12	20.716	19.55	Yes
	24	24	20.365	40.73	Yes
	36	36	20.245	61.94	Yes
1 month at 30°C	1	1	30.000	0.576	No
	12	12	21.379	18.11	Yes
	24	24	20.716	39.10	Yes
	36	36	20.483	60.26	Yes
2 months at 30°C	12	12	22.579	15.79	Yes
	24	24	21.380	36.22	Yes
	36	36	20.942	57.15	Yes

It is recognized that temperatures recorded in a storage area, at some detector location, will not always necessarily reflect the actual temperature of pharmaceutical products stored in the area. Depending on the nature of the heating/air conditioning system and airflow efficiency in the area, there may be cold spots or hot spots. Certainly, if a storage area is overcrowded with packages, airflow will probably be seriously impaired. Thus, it is important that all warehouses or other storage areas used for pharmaceutical products should not be overloaded and should allow a free flow of air in all parts of the unit. The thermodetector used as the temperature probe for a warehouse or other unit should be placed at a location that may reasonably be regarded as representative of the average temperature. When there is any doubt on this point, a conservative approach should be used. Thus, place the detector higher in the room rather than closer to the floor.

When continuous monitoring of temperature is obtained, as for example, with chart recorders, there may be some quite transient excursions or spikes—caused perhaps by leaving a door open—that may have very little effect on the temperature of drug products stored in the area. All products have a finite thermal capacity; thus, for example, a 1-L glass bottle of aqueous injection has a specific heat of about 5 kJ per degree centigrade. A current of warm air at 30°C flowing over this bottle, even if it does not have an overwrap or other pack, would have little effect on the temperature of the product if the exposure to the warm air was for a short period.

A question that naturally comes to mind when we consider the effect of temperature excursions and spikes on drug product stability is whether a number of 30°C, 1-hr excursions have the same adverse effect on drug product stability as one 30°C excursion for a number of hours. Using the model developed in this paper, the answer is probably yes, at least in a semiquantitative way for chemical degradation. However, for some physical changes (e.g., loosening of a plastic cap), the answer to the question is no. Cap loosening and some other adverse physical changes are more affected by temperature change per se rather than MKT.

In this paper, we have only considered excursions up to 30°C. However, the same general approach may be used legitimately for spikes of higher temperatures, provided there is no change in reaction mechanism, no critical irreversible degradation temperature involved, and continued conformance to Arrhenius-type kinetics.

CONCLUSION

The effect of temperature excursions on MKT was evaluated. It appears that, for systems with a baseline storage temperature of 22.5°C, total excursions equivalent to 2 months at 30°C may be tolerated if the shelf life is 12 months or more. If the baseline storage temperature is more than 22.5°C or the shelf life is less than 12 months, then adverse effects on the validity of the assigned shelf life are more likely. It is highly improbable that a single 30°C excursion of 7 hr or less would adversely affect the shelf life of any otherwise normal product.

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