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STORAGE CONDITIONS IN THE SUDAN USING THE KINETIC MEAN TEMPERATURE CONCEPT.

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ABSTRACT.

The kinetic mean temperature concept introduced by Haynes (1971) and Grimm (e.g. 1993) is reviewed. The concept of climate zones is also dealt with, and its relevance to climactic conditions in the Sudan are shown. A more exacting equation for the acquisition of a kinetic mean temperature is developed.

INTRODUCTION.

The advantage of an Arrhenius plot, as pointed out by Carstensen (1972) is that knowledge of the activation energy and the collision number allows calculation of the anticipated loss at any (cyclic, uneven or constant) temperature stress. Since storage conditions are not at constant temperature and since testing temperatures in industrial stability programs are isothermal, the concept of virtual temperature or kinetic mean temperature (KMT) (Haynes, 1971) was developed. Grimm (1985,1986) surveyed

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temperature profiles in many parts of the world and arrived at temperature zones. One of these is the hot and arid zone, which is 30°C and 30% RH. KMT is the usual notation for kinetic mean temperature, but for notation purposes it is also referred to as T_{km} below.

The article to follow details the temperature profile experienced in the Sudan, and as seen it lies outside the definitions suggested in the recent Triparteid Harmonization Guidelines[1].

The principle of the concept of the KMT is as follows:

If one assumes that a product is stored in such a temperature profile, and is zero order, then in time element dt the loss is given by the differential equation:

$$dC = -kdt \qquad (2)$$

If the temperature dependence of k is given by the Arrhenius equation, then:

$$k = -Z\exp(-E/RT) \qquad (3)$$

where E is the activation energy, R is the gas constant, Z is the collision number and T is the absolute temperature. If Eq. 2 is inserted in Eq. 1, then Eq. 3 results:

$$dC = \{-Z\exp(-E/RT)\}dt \qquad (3)$$

If the sample of the product is exposed to a temperature profile, as e.g. the one shown in Fig. 1, then the absolute temperature, T, is a function of time, t, by the equation:

$$T = 273.15 + \tau = (\Phi(t)) \qquad (4)$$

where τ is the temperature in °C. Eq. 3 can now be integrated over the temperature profile the particular sample of a drug experiences and the result is that:

$$C = Co - \int_0^t Z\exp(-E/R(\Phi(t)))\, dt \qquad (5)$$

If one now exposes a sample of a pharmaceutical to a temperature

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[1] Issued on 10/17, 1993.

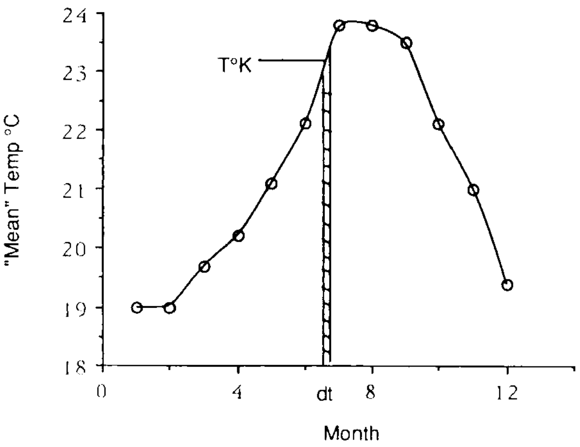

Fig. 1. Typical temperature profile in a location in the United states, running from January (Month 1) through December (Month 12).

profile as shown in Fig. 1, then the rate constants, depending on the magnitude of Z and E would be as shown in examples in Fig. 2.

It has been shown by Kennon (1964) that for many pharmaceutical reactions, the activation energy is close to 20 kCal/mole, and hence if E/R is assumed to be equal to 10,000°K, then Eq. 5 will take the form:

$$C = Co - \int_0^t Z\exp\{-10{,}000/(\Phi(t))\}\, dt \qquad (5)$$

Note that now the loss in potency (C_0-C) is now only a function of Z and (Φ(t)).

If we let the time interval be one year (12 months), then Eq. 6 becomes:

$$Co - C = \int_0^{12} Z\exp\{-10{,}000/(\Phi(t))\}\, dt \qquad (6)$$

We could trace the value of the potency, C, as a function of time, and this, of course, would not be a straight line, because the value of k (or rather (Φ(t))) is a function of time. A typical curve is shown in Fig. 3.

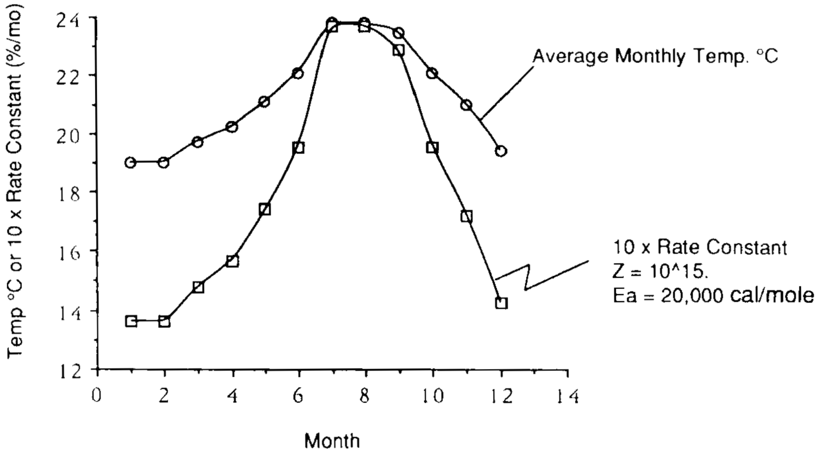

Fig. 2 Rate Constants with different values of Z and K in the temperature profile shown in Fig. 1.

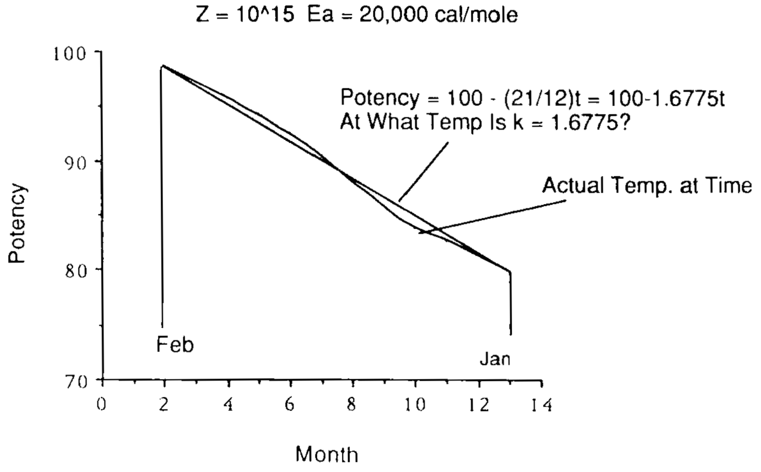

Fig. 3 Example of the concentration as a function of time, using the temperature profiles shown in Fig. 1 and 2, with the given values for activation energy and collision number.

If we draw the straight line between the two endpoints, then we have a zero order decomposition:

$$C = C_o - k^*t \qquad (7)$$

There is a given temperature, at which such an isothermal storage would produce this equation, i.e. produce the zero order rate constant k*. This temperature is obtained by the following argument: The loss in the 12 month period, C_o-C, is the same whether obtained from Eq. 6 or Eq. 7, hence

$$Co - C = \int_0^{12} Z\exp\{-10{,}000/(\Phi(t))\}\,dt = k^*t \qquad (8)$$

Since the Arrhenius equation holds, it follows that

$$k^* = Z\exp(-10{,}000/T_{km}) \qquad (9)$$

and combining Eq. (8) and (9) then gives:

$$Co - C = \int_0^{12} Z\exp\{-10{,}000/(\Phi(t))\}\,dt = 12Z(\exp(-10{,}000/T_{km}) \qquad (10)$$

For a first order reaction, the equation is exactly the same, except for the extreme left hand side which becomes

$$\ln[C_o/C] = \int_0^{12} Z\exp\{-10{,}000/(\Phi(t))\}\,dt = 12Z(-10{,}000/T_{km}) \qquad (11)$$

so that the equality presented by the middle and the right part of the equation holds true. It is noted that Z cancels out so that, in general, the KMT (T_{km}) is defined as:

$$\int_0^{12} \exp\{-10{,}000/(\Phi(t))\}\,dt = 12(\exp(-10{,}000/T_{km}) \qquad (12)$$

The principle of the kinetic mean temperature calculation hence is that the activation energy is assumed to be 20kCal/mole for all reactions.

This is not necessarily true, and it must be kept in mind, whenever the concept is used. There is a tendency, when using a concept, to remember the assumptions at the inception of the concept, but as it gets more commonly used, it is forgotten, and is assumed to be universal.

The function $(\Phi(t))$ is usually presented as a discrete function, e.g. an average monthly temperature, or a high and low for a particular month. The calculation then takes the form

$$\Sigma t_i \exp(-10{,}000T_i^{-1}) = 12\exp(-10{,}000/T_{km}) \qquad (13)$$

Taking logarithms on both sides then gives:

$$-10{,}000/T_{km} + \ln[12] = \ln\left[\Sigma t_i \exp(-10{,}000T_i^{-1})\right] \qquad (14)$$

and rearranging gives:

$$T_{km} = 10{,}000 \Big/ \left\{\ln(12) - \ln\left[\Sigma t_i \exp(-10{,}000T_i^{-1})\right]\right\} \qquad (15)$$

Limits are not stated at the summation sign, because these could be in days (i.e. the summation could be over 365 days), or in highs and lows for months (i.e. the summation would be over 24 periods of one half month), or for months (i.e. the summation would be over 12 monthly periods.

An example of such a calculation is given here, for the meteorological temperature in the Sudan, which is given in table 1.

A program for Eq. 15, written in BASIC the for monthly averages is shown below. The twelve average monthly temperatures are typed into line 400.

```
90      Print "Program Using Average Monthly Temperatures"
100     READ A
110     N = N + 1
120     X1 = A + 273.15
130     X2 = 10000/X1
140     X3 = EXP(-X2)
150     X4 = X4 + X3
160     IF N = 12 GOTO 500
170     GOTO 100
```

Table I. Temperature Profiles for the Years 1961-1990 in the Sudan (Shambat Station. Lat. 15 40'N, 32 32'E, Alt 380 Meters.

Month	Max	Min	Mean
Jan	30.2	14.1	22.1
Feb	32.3	15.1	23.7
Mar	36.4	18.3	27.3
Apr	39.6	21.2	30.4
May	41.6	25.2	33.4
Jun	41.0	26.4	33.7
Jul	38.3	25.6	31.9
Aug	37.5	25.0	31.3
Sep	38.7	25.2	31.9
Oct	39.0	23.9	31.5
Nov	34.6	19.6	27.1
Dec	31.2	15.7	23.5
Grand Averages	36.7	21.3	29.0

```
400     DATA 22.1, 23.7, 27.3, 30.4 33.4 33.7, 31.9, 31.3 31.9, 31.5, 27.1, 23.5
500     X5 = LOG(12)
510     X6 = LOG(X4)
520     X7 = X5 - X6
600     T1 = 10000/X7
610     T2 = T1 - 273.15
620     PRINT "KMT="; T2
```

A program for this, written in BASIC the for monthly averages is shown below. In this case the twelve highs are typed into the 400 line and the twelve lows into the 410 line.

```
90      Print "Program Using High and Low Monthly Temperatures"
100     READ A
110     N = N + 1
120     X1 = A + 273.15
130     X2 = 10000/X1
140     X3 = EXP(-X2)
150     X4 = X4 + X3
160     IF N = 24 GOTO 500
170     GOTO 100
```

```
400     DATA 22.1, 23.7, 27.3, 30.4 33.4 33.7, 31.9, 31.3 31.9, 31.5, 27.1, 23.5
410     DATA 14.1, 15.1, 18.3, 21.2, 25.2, 26.4, 25.6, 25.0, 25.2, 23.9, 19.6, 15.7
500     X5 = LOG(12)
510     X6 = LOG(0.5*X4)
520     X7 = X5 - X6
600     T1 = 10000/X7
610     T2 = T1 - 273.15
620     PRINT "KMT="; T2
```

When the table values are used in the first program a kinetic mean temperature of 29.7°C is obtained, when the second program is used, then a kinetic mean temperature of 32.4°C is obtained, demonstrating the fact that the "high" temperatures carry more weight (due to their exponential insertion), than the "low" values. The more correct second value is obviously in excess of the 30°C, 30%RH alluded to in the Harmonization Guidelines.

SUMMARY

1. The exacting equations for calculating kinetic mean temperature have been derived, and a program in BASIC shown for application of (a) average monthly temperature data and (b) for high/low monthly temperature data.

2. It is shown that it is the latter that should be used, rather than the former, whenever possible.

3. It is found that the kinetic mean temperature in the Sudan is 32.4°C, in excess of that stipulated for the "dry, hot" climate zone.

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