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Mean Kinetic Temperature and Ageing

Introduction

Good warehousing and distribution practice requires that warehouse temperatures are monitored and controlled and that appropriate actions are taken if temperatures exceed the specified storage conditions. Those actions are the calculation of the mean kinetic temperature as a verification of exceeded storage conditions and if conditions are exceeded a second calculation to determine the reduction of shelf life with the help of the Arrhenius equation. With the latest version of the data evaluation software from ELPRO-BUCHS AG, elproLOG it is now possible to do both calculations, the mean kinetic temperature and ageing.

Mean Kinetic Temperature (MKT)

The ICH stability testing guidelines[1] defines mean kinetic temperature (MKT) as „a single derived temperature which, if maintained over a defined period, would afford the same thermal challenge to a pharmaceutical product as would have been experienced over a range of both higher and lower temperatures for an equivalent defined period“. In other words, MKT is a calculated, fixed temperature that simulates the effects of temperature variations over a period of time. It expresses the cumulative thermal stress experienced by a product at varying temperatures during storage and distribution.

Calculation

Mean Kinetic Temperature refers to a datum, which can be calculated from a series of temperatures. It differs from other means (such as a simple numerical average or arithmetic mean) in that higher temperatures are given greater weight in computing the average. This weighting is determined by a geometric transformation, the natural logarithm of the temperature number.
Disproportionate weighting of higher temperature in a temperature series according to the MKT recognizes the accelerated rate of thermal degradation of materials at these higher temperatures. MKT accommodates this non-linear effect of temperature.

The formula for MKT is:

$$TK\left[K\right]=\frac{-\Delta H/R}{\ln\left(\frac{\sum_{1}^{n}\exp\left(\frac{-\Delta H}{R\cdot T_n}\right)}{n}\right)}$$

where ΔH is the activation energy, R is the universal gas constant (0.0083144 kJ/molK), T is the temperature in degrees K, n is the total number of (equal) time periods over which data are collected and *exp* is the natural log base.
The practical application of this equation is less complex than it first appears. For a huge range of pharmaceutics ΔH is within the range of 42 – 125 kJ/mol. In cases where an exact knowledge of the activation energy is important, it is possible to determine this factor with the help of a differential scanning calorimetry (DSC) analysis. T_1 is the average temperature recorded over the first time period and T_n is the average temperature recorded over the nth time period.

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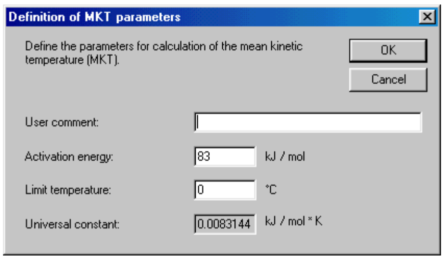
MKT Definition in elproLOG

The definition of the MKT parameters are done in the following screen of the elproLOG data logger evaluation software:



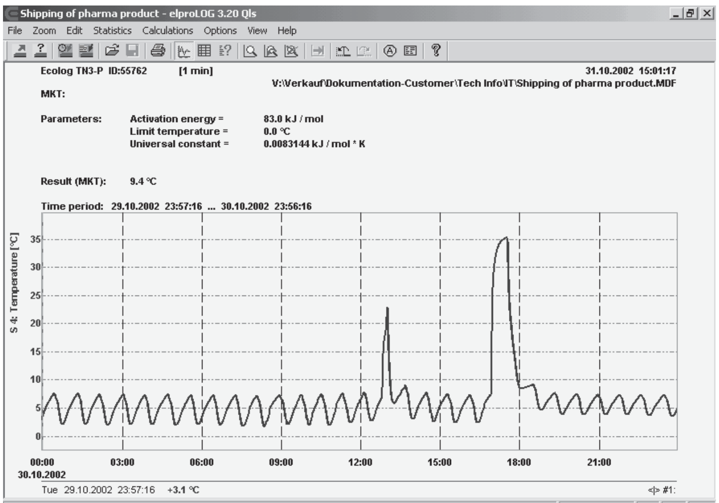
Activation energy:
As long as any detailed information about a proper activation energy is missing, the average value of 83 kJ/mol for pharmaceutics is a good choice. This value is set by default.

Limit temperature:
Temperature limit is used to suppress the effect of low storage temperature values in the MKT calculation.

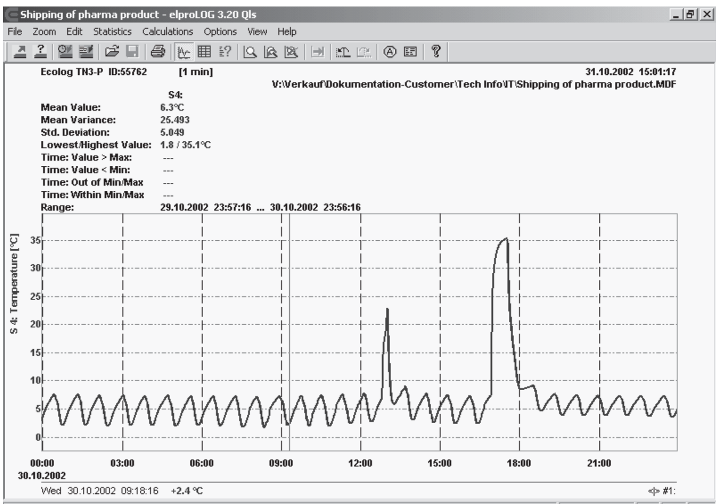
Effect and Calculation Example from elproLOG for Kinetic and Arithmetic Mean Temperatures

As an example of how the MKT calculation will affect an expressed mean for a calculation (important for the long term storage of critical drugs and chemicals), here is an illustration.
If the temperature is constant for a period of time, but is „out of specs“ for some moments of time, there will be a difference in the calculated arithmetic mean (the sum of all of the measurements divided by the number of measurements - a simple mean) and the kinetic mean. The following 2 screen shots show the different calculations for the MKT and the arithmetic mean temperature as it is done in the elproLOG evaluation software:

Mean Kinetic Temperature:
Value = 9.4°C



Arithmetic Mean Temperature:
Value = 6.3°C



Conclusion

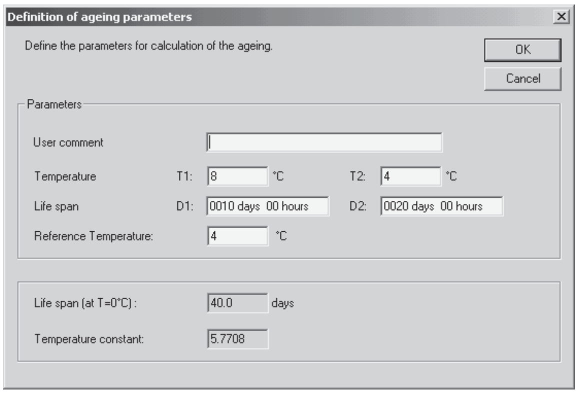
Depending on temperature conditions the effect may be dramatic, it is clear that the MKT method weights the higher temperatures in a series more than the lower temperatures. This is a more appropriate way of calculating an overall thermal effect because of the acceleration of thermally driven processes of degradation at higher temperatures.

Ageing

This calculation is used to determine the shelf life reduction due to incorrect storage conditions of a drug sub-stance or drug product. The formula for this calculation is based on the Arrhenius[2] life-stress model. To do this calculation the software elproLOG uses the following definition screen:

Ageing Definition in elproLOG

The definition of the Ageing parameters are done in the following screen of the elproLOG data logger evaluation software:



T1, D1 and T2, D2:
Storage conditions 1 and 2 for the monitored product

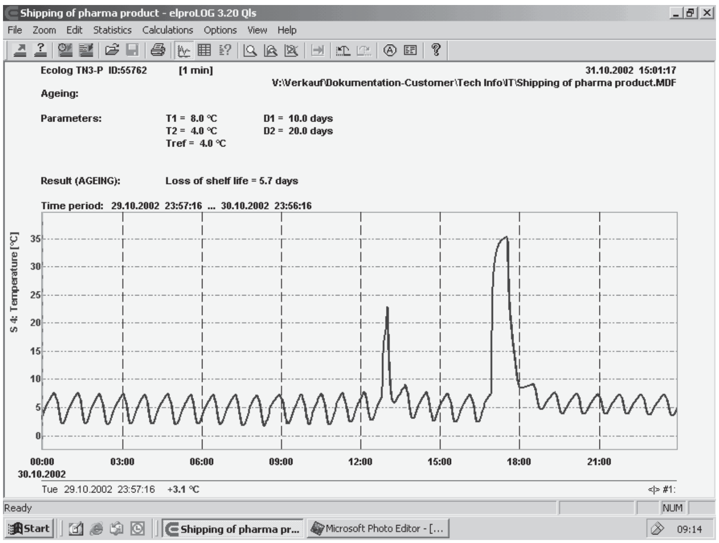
Reference Temperature:
Minimal recommended storage temperature

Life span [at T=0°C]:
Calculated storage time at 0°C
This value is used as a comprehension value for different products and their shelf life

Effect and Calculation Example from elproLOG for Ageing

As an example of how the Ageing calculation is going to reduce the shelf life time of a pharmaceutical product, here is an illustration.

Ageing:
Loss of shelf life = 5.7days



Conclusion

Due to the incorrect treatment during the unloading of this pharmaceutical product, its shelf life has been dramatically reduced from 10 days down to 4.3 days!

References

1. Note for guidance on stability testing: stability testing of new drug substances and products (ICH): CPMP/ICH2736/99 (revision of ICH/380/95)
2. Svandte Arrhenius, Swedish physical chemist, 1887