Kinetic Ratio as a Parameter for Product Stability Calculations

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Abstract □ A new parameter, the kinetic ratio, is suggested for estimating product potency during storage under ambient warehouse temperatures. Actual warehouse temperature data were integrated using Arrhenius kinetics, and the resulting potency errors, due both to the integration method and to temperature averaging, were evaluated. Kinetic ratios and virtual temperatures then were compared to show seasonal and Arrhenius constant effects. Equations interrelating the kinetic ratio and virtual temperature are given. Finally, sample calculations using typical vitamin A data were analyzed to demonstrate the calculational and interpretation characteristics of the kinetic ratio compared to the virtual temperature.

Keyphrases □ Stability—product potency, calculation, kinetic ratio parameter □ Drug potency—product stability, calculation, kinetic ratio parameter □ Expiration dating—product stability, calculation, kinetic ratio parameter □ Arrhenius equation—calculation of product stability, kinetic ratio parameter

The useful concept of a single measurement, virtual temperature, to reflect the pattern of changing temperatures in a warehouse was introduced in 1971 (1). Since then, virtual temperature has been used widely in stability calculations. Although the physical meaning of virtual temperature is easily understood, it tends to be misleading and difficult to use because it causes a change two exponentiations away from the focus of interest.

Because temperature is a misleading criterion for kinetic change and is difficult to use in calculations, and because reference potencies commonly were calculated based on a reference temperature anyway, a new parameter, the kinetic ratio, was defined. Compared to virtual temperature, the kinetic ratio appears to relate more directly to potency, to separate temperature effects more effectively, to reflect important changes more sensitively, and to yield calculated results more conveniently.

EXPERIMENTAL

Data obtained at a Dallas warehouse were selected for analysis because this location offered extreme temperature variation. Temperature readings were used weekly from a circular chart recorder at 6-hr intervals for 364 days (September 1, 1975 through August 31, 1976). The data were collected as part of an ongoing stability evaluation program by a quality assurance unit.

In addition to the temperature data, typical constants for vitamin A in multivitamin tablets at a reference temperature of 24° were obtained from the same source and used in sample calculations. These constants were: Arrhenius "activation" constant (b_1), 13185.0 °K; Arrhenius factor (b_0), 2.0361×10^{16} weeks^{-1}; reference rate constant (T_{ref}), 297.16 °K; reference rate constant (k_{ref}), 0.0010943 week^{-1}; initial potency (P_0), 7300 units; reference potency at 52 weeks (P_{52}), 6896 units; reference potency at 78 weeks (P_{78}), 6703 units; reference potency at 156 weeks (P_{156}), 6154 units; and reference shelflife (τ_{sl}), 442 weeks.

RESULTS

Definitions and Relationships—Virtual temperature is the fixed temperature that produces the same kinetic constant as that which results from evaluating temperature that changes with time[1]. The kinetic ratio is a ratio of a rate constant that results from evaluating temperature that changes with time to the rate constant at a fixed reference temperature.

Quantitative relationships are given in Table I, and the nomenclature is appended. Both virtual temperature and the kinetic ratio are independent of reaction order for the simple models used in most cases. In this paper, temperature response is assumed to follow Arrhenius's law (Eq. 1). Mathematical definitions of the virtual temperature and kinetic ratio (Eqs. 2*a* and 2*b*, respectively) allow for temperature variation with time. At a given location, the observed temperature values can be integrated numerically to yield values of the two parameters. The remaining relationships in Table I are the result of combining and relating kinetic-order effects with the Arrhenius equation. Because reference temperature constants are a common form of reporting stability data, these constants normally would be readily available for the indicated calculations.

The resulting equations for α may be verified by direct derivation using definitions and kinetic relationships. For example, if a ratio of the first-order kinetic equations, $\ln(P_\tau/P_0) = -k\tau$ and $\ln(P_\tau/P_0)_{ref} = -k_{ref}\tau$, is formed and the definition of the kinetic ratio, $\alpha = k/k_{ref}$, is substituted therein, Eq. 3*b* results after antilogs are taken.

Temperature Data—Many questions might be asked about the process of transforming temperature data into a potency change. How frequently must temperature be measured? What errors are introduced by averaging temperatures to daily, weekly, and monthly values? What methods might be used to convert temperature–time data into potency effects? These questions are not fully answered here, but an efficient approach to the problem is suggested and the relative importance of several factors is weighed.

Potency changes were evaluated for two sets of Arrhenius constants, one set typical of vitamin A in a multivitamin tablet and another set arbitrarily formulated to approach the upper temperature–instability limit likely to be encountered in products stored at ambient temperatures. The conventional Arrhenius equation and first-order kinetics were combined as in Eq. 3*a*, except that actual temperatures were used in place of virtual temperature. The result was integrated numerically over time. With temperature readings at 6-hr intervals, three numerical integration methods were compared: Simpson's rule, the trapezoidal rule, and a fifth-order quadrature method[2]. Although errors resulting from all methods were small (Table II), the fifth-order quadrature method was used for subsequent comparisons because it reduced integration errors to insignificantly small values.

The effect of temperature averaging on the observed error in potency also was considered. Results for averaged temperature values for each day, week, and month showed very small errors for moderately stable materials, but these values would be subject to noticeable errors at the limit of practical stability. This effect has a direct bearing on the use of virtual temperature, the kinetic ratio, or any other temperature-averaging method. Either correction factors or averages over smaller time intervals probably would be required to reflect accurately the potency of very heat-sensitive materials stored at ambient temperatures.

Daily averaged temperatures and fifth-order quadrature were used with Eq. 2*a* from Table I to evaluate virtual temperatures. Kinetic ratios were determined similarly from Eq. 2*b* with a reference temperature of 24°. Results are presented in Table III.

DISCUSSION

Virtual Temperature and Kinetic Ratio—Close examination of Eq. 3*b* reveals that, for first-order kinetics, the kinetic ratio has an interpretation similar to the elasticity in economics. For every small percent change in the reference potency, the actual percent potency changes by a factor of approximately α times. Thus, with reference to Table III, a compound with an activation constant of 15,000 will drop approximately 13.24% for a 10% annual loss observed at the reference temperature. Actual calculation from Eq. 3*b* yields 13.02%. Although this simple interpretation of α becomes subject to larger errors with larger potency

[1] This statement is a general application of Haynes' definition, which related virtual temperature to a monthly average temperature (1).

[2] Scientific Subroutine Package, IBM.

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Table I—Relationships of Virtual Temperature and Kinetic Ratio Parameters [Arrhenius's Law: $k = b_0 e^{-b_1/T}$ (Eq. 1)]

Definition	Virtual Temperature		Kinetic Ratio	
	$T_v = \dfrac{-b_1}{\ln\left(\frac{1}{\tau}\int_0^\tau e^{-b_1/T}\,d\theta\right)}$	(Eq. 2a)	$\alpha = \dfrac{\frac{1}{\tau}\int_0^\tau e^{-b_1/T}\,d\theta}{e^{-b_1/T_{ref}}}$	(Eq. 2b)
	where $T = g(\theta)$ is an unspecified function of time			
First-order potency	$P_\tau = P_0 e^{-(b_0 e^{-b_1/T_v})\tau}$	(Eq. 3a)	$P_\tau = P_0\left(\frac{P_\tau}{P_0}\right)^\alpha_{ref}$	(Eq. 3b)
First-order shelflife	$\tau_{sl} = \dfrac{\ln(P_0/P_\tau)_{sl}}{b_0 e^{-b_1/T_v}}$	(Eq. 4a)	$\tau_{sl} = \dfrac{\ln(P_0/P_\tau)_{sl}}{\alpha k_{ref}}$	(Eq. 4b)
Zero-order potency	$(P_0 - P_\tau) = (b_0 e^{-b_1/T_v})\tau$	(Eq. 5a)	$(P_0 - P_\tau) = \alpha(P_0 - P_\tau)_{ref}$	(Eq. 5b)
Zero-order shelflife	$\tau_{sl} = \dfrac{(P_0 - P_\tau)_{sl}}{b_0 e^{-b_1/T_v}}$	(Eq. 6a)	$\tau_{sl} = \dfrac{(P_0 - P_\tau)_{sl}}{\alpha k_{ref}}$	(Eq. 6b)
For equal cumulative time periods	$(-b_1/T_v)_\tau = \ln\frac{1}{\tau}\sum_{i=1}^{\tau}(e^{-b_1/T_{vi}})$	(Eq. 7a)	$\alpha_\tau = \frac{1}{\tau}\sum_{i=1}^{\tau}\alpha_i$	(Eq. 7b)
Conversion, T_v/α	$T_v = \dfrac{b_1}{b_1/T_{ref} - \ln\alpha}$	(Eq. 8a)	$\ln\alpha = b_1\left(\frac{1}{T_{ref}} - \frac{1}{T_v}\right)$	(Eq. 8b)
Conversion, reference T	$k_v = \alpha k_{ref}$	(Eq. 9a)	$\alpha_{T_2} = \alpha_{T_1} e^{-b_1(1/T_1 - 1/T_2)}$	(Eq. 9b)

Table II—Annual Percent Error in Potency Calculations Relative to the Best Estimate Based on a Dallas Warehouse

Constants		Percent Potency Remaining, $100\,(P_\tau/P_0)_y$	Percent Error in Fraction Potency Remaining[a] by Time Interval/Method[b]					
			6 hr			Daily	Weekly	Monthly
b_0	b_1		DQSF	SIMP	TRAP	DQSF	DQSF	DQSF
2.0361×10^{16}	13,185	93.1	0	<0.01	−0.02	0.06	0.18	0.50
8.46×10^{33}	25,000	74.3	0	0.09	−0.30	1.5	5.5	12.6

[a] Percent error = $100\,[(P_\tau/P_0)_y - (P_\tau^{\sim}/P_0)_y]/(P_\tau/P_0)_y$. [b] DQSF is a fifth-order quadrature subroutine from IBM's Scientific Subroutine Package, and SIMP and TRAP are mnemonics for Simpson's rule and the trapezoidal rule, respectively.

Table III—Yearly and Quarterly Arrhenius Kinetic Parameters for a Dallas Warehouse [T_{ref} = 297.16 (24°)]

	Kinetic Ratios					Virtual Temperatures				
b_1	α_y	α_1	α_2	α_3	α_4	T_{vy}	T_{v1}	T_{v2}	T_{v3}	T_{v4}
5,000	1.009	0.708	0.998	1.404	0.927	297.32	291.17	297.13	303.27	295.83
10,000	1.112	0.507	1.027	1.999	0.915	298.15	291.28	297.39	303.41	296.37
15,000	1.324	0.367	1.088	2.886	0.955	298.82	291.38	297.66	303.53	296.89
20,000	1.679	0.270	1.187	4.214	1.046	299.47	291.48	297.92	303.64	297.36
25,000	2.236	0.200	1.331	6.221	1.190	300.03	291.58	298.17	303.76	297.77

changes, it is a quick and easy estimator and has a readily understood relationship to potency.

Seasonal effects are relatively easy to discern in the kinetic ratio (Table III). A compound with an activation constant of 15,000 and a warehouse potency loss of 13% for the year will have experienced a cycle of changes relative to the constant-temperature reference. In the cold winter months of the first quarter, the α value of 0.367 suggests a change of slightly more than one-third of the change of the reference potency. During the spring and fall, the reference and warehouse potencies change by about the same amount. However, in the summer, the warehouse potency loss was just under three times the reference loss.

For zero-order kinetics, the kinetic ratio is directly proportional to the drop in potency (Eq. 5b). Thus, if the reference potency for the example drops 500 units in a year, that same compound would drop $1.324 \times 500 = 662$ units in the Dallas warehouse.

Comparison of Virtual Temperature and Kinetic Ratio—No obvious deductions regarding potency changes can be made from the virtual temperatures in Table III. Interpolation may be used to obtain intermediate values for both parameters. Linear interpolation in Table III produced a maximum positive error of ~0.01. Because of the additional exponentiation, virtual temperature calculations require greater care. The constancy of virtual temperature has been emphasized as offering a special advantage (1). This constancy is an artifact of double exponentiation and demonstrates the insensitivity of virtual temperature to changes that can significantly affect potency. For example, according to Eq. 3a, a relatively small change in T_v will, after being exponentiated twice, magnify into a substantial potency change.

The interrelationship between the kinetic ratio and virtual temperature is given by Eqs. 8a and 8b, which quantify the relative sensitivity of α observed in Table III. Specifically, the entire range of virtual temperatures here changes by only 4%, while the corresponding range of the kinetic ratio changes by 3100%. It is evident that numerous significant digits must be carried for virtual temperature and that the leading constant digits tend to screen information.

Computation of virtual temperature and the kinetic ratio is similar, except that a reference temperature must be declared for the latter (Eq. 2b). This requirement is the only price paid for later ease of use, and reference temperature calculations appear to be widely used throughout the pharmaceutical industry. Because both parameters are dependent on ambient temperatures, which, in turn, are a function of the specific

Table IV—Comparison of Calculations for Potency at a Dallas Warehouse

Calculation	Virtual Temperature	Kinetic Ratio	Number of Arithmetic Operations: Virtual Temperature	Number of Arithmetic Operations: Kinetic Ratio	Vitamin A Results
Potency after 3 years	Eqs. 1 and 3*a*	Eq. 3*b*	6	3	5914 units
Potency after 18 months (six quarters) using seasonal values	Eqs. 7*a*, 1, and 3*a*	Eqs. 7*b* and 3*b*	17	8	664 units
Potency after 18 months (six quarters) using annual values	Eqs. 1 and 3*a*	Eq. 3*b*	6	3	6570 units
Shelflife	Eq. 4*a*	Eq. 4*b*	6	4	358 weeks

warehouse location and construction, each company would have to determine its individual parameters. The inclusion of a reference temperature in these calculations is a small matter. In addition, conversion from one reference temperature to another, should this be necessary, is straightforward (Eq. 9*b*).

Sample Calculations—Constants and reference data were combined with the data from Table III for sample calculations. Twice as many arithmetic operations usually are required for calculations involving virtual temperature (Table IV). The use of reference potencies eliminates the need to calculate rate constants. The kinetic ratio reference potency and initial potency are all that are required for direct calculations. Once the reference values are calculated, they remain constant and may be used to calculate potencies at each warehouse with the appropriate α value. Virtual temperature calculations invariably require exponentiation to obtain a rate constant needed for subsequent calculations. As also can be seen from Table IV, the seasonal effect over six quarters is not significant for vitamin A in multivitamin tablets (1.5%). Shelflife calculations using the kinetic ratio are particularly easy because they only involve dividing a constant by a different α for each warehouse.

CONCLUSIONS

Although it is only a simple extension of a generalized virtual temperature definition, the kinetic ratio offers clear practical advantages. The parameter has a direct, easily understood physical relationship to potency, and commonly performed calculations are simplified greatly.

NOMENCLATURE

α = kinetic ratio (dimensionless)
b_0 = Arrhenius factor, defined by Eq. 1 (weeks^{-1})
b_1 = Arrhenius activation factor, E/R, defined by Eq. 1 (°K)
θ = time (weeks)
g = general unspecified function
k = Arrhenius kinetic constant (weeks^{-1})
P = potency or concentration variable (units)
τ = specific time (weeks)
T = temperature (°K)

Subscripts:

0 = initial value of a variable
1, 2, 3, 4 = either a specific value denoted by the number or values that relate to enumerated quarters of the year
ref = reference value of a variable or quantity enclosed in brackets
sl = value of variables corresponding to the shelflife
v = virtual value
y = cumulative annual value

REFERENCES

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Synthesis and Skeletal Muscle Relaxant Activity of Quaternary Ammonium Salts of Dantrolene and Clodanolene

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Received July 16, 1979, from the *Scientific Affairs Department, Norwich-Eaton Pharmaceuticals, Division of Morton-Norwich Products, Inc., Norwich, NY 13815.* Accepted for publication October 16, 1979.

Abstract □ A series of quaternary ammonium salts of dantrolene and clodanolene was prepared and evaluated for skeletal muscle relaxant activity. The quaternary ammonium salts exhibit greater aqueous solubility and, therefore, facilitate intravenous administration. One member of this series, although less effective orally, exhibited greater aqueous solubility than the sodium salt. When administered intravenously, it was a more potent antagonist of skeletal muscle contraction and yielded comparable therapeutic and muscle relaxant efficacy indexes.

Keyphrases □ Dantrolene—quaternary ammonium salts, synthesis, skeletal muscle relaxant activity □ Clodanolene—quaternary ammonium salts, synthesis, skeletal muscle relaxant activity □ Relaxants, skeletal muscle—dantrolene and clodanolene, quaternary ammonium salts, synthesis, activity

Several hydantoins have skeletal muscle relaxant activity (1). One member of this series, dantrolene[1], was shown subsequently to cause skeletal muscle relaxation by a unique mechanism involving direct action on the skeletal muscle (2, 3). Dantrolene sodium has been hypothesized to act by preventing the release of calcium ion (Ca^{2+}) from the sarcoplasmic reticulum (4, 5).

Dantrolene sodium recently was shown to have potential

[1] Dantrium, Morton-Norwich Products.

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