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Statistical evaluation for stability studies under stress storage conditions

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Abstract

During the pharmaceutical development of a new drug, it is necessary to select as soon as possible the formulation with the best stability characteristics. The current International Commission for Harmonisation (ICH) regulations regarding stability testing requirements for a Registration Application provide the stress testing conditions with the aim of assessing the effect of severe conditions on the drug product. In practice, the well-known Arrhenius theory is still used to make a rapid stability prediction, to estimate a drug product shelf life during early stages of its pharmaceutical development. In this work, both the planning of a stress stability study to obtain a correct stability prediction from a temperature extrapolation and the suitable data treatment to discern the reliability of the stability results are discussed. The study was focused on the early formulation step of a very stable drug, Mitonafide (antineoplastic agent), formulated in a parenteral solution and in tablets. It was observed, for the solid system, that the extrapolated results using Arrhenius theory might be statistically good, but far from the real situation if the stability study is not designed in a correct way. The statistical data treatment and the stress–stability test proposed in this work are suitable to make a reliable stability prediction of different formulations with the same drug, within its pharmaceutical development.

Keywords: Statistical evaluation; Stability; Stress test; Data treatment; Formulation step

1. Introduction

Within the pharmaceutical development of a new drug, during the early formulation step, several preparations, both liquid and solid dosage forms, are studied. In this step, it is necessary to select as soon as possible the formulation with the best stability characteristics. The degradation of a drug included in a solid dosage form usually runs very slowly. For this reason, it is usual to choose stress storage conditions, in order to get a fast stability prediction.

There has always been much controversy over the prediction of the stability of the drugs and drug products, both for the design of the stability study and for the statistical evaluation [1–5]. The current regulations for stability tests, drafted by the International Commission for Harmonisation (ICH) [6], propose to carry out, on a single batch, this stress testing including the effect of temperature in 10 °C increments above the accelerated temperature test condition (e.g. 50, 60 °C, etc.). The aim of this ICH stress testing is to assess the effect of severe conditions on the drug product. In practice, nowadays, several pharmaceutical industries or work groups still use the well-known Arrhenius theory, which applies a temperature extrapolation for the stability prediction. The aim of using Arrhenius theory is to obtain a shelf-life prediction of the drug product rapidly.

The objective of this work is to propose a suitable stress–stability test and a correct statistical data treatment in order to make a reliable stability prediction of different formulations with the same drug within its pharmaceutical development. In order to check the extrapolated t_{90} parameter from this stress testing, a long-term testing was planned (25 ± 2 °C/60% $\pm$ 5% RH), with duration equal to the extrapolated shelf life.

The design proposed was confirmed in both a liquid formulation (parenteral solution) and a solid formulation (tablets) using an antineoplastic drug, Mitonafide,

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within the early formulation step of its pharmaceutical development.

2. Experimental

2.1. Materials

Parenteral solution: Mitonafide (CAS 54824-17-8, Lab. Knoll S.A.), in a dose of 100 mg; acetate buffer solution (pH 4.61–4.64). It was packed in 10 ml white glass ampoules.

Tablets: Mitonafide, in a dose of 100 mg; 65 mg of Ludipress®, granulate constituted by lactose monohydrate (93.4%), povidone K30 (3.2%) and povidone CL (3.4%); 1.6 mg of Explotab® or sodium starch glycolate; 2.4 mg of Kollidon®30 or povidone K30 as such; 1.4 mg of magnesium stearate Eur. Pharm. grade. The total weight of the tablet was 170 mg. The package used was a PVC blister.

SIMFIT computer package 3.2 (W.G. Bardsley).

2.2. Stability storage conditions and testing frequency

In the preformulation studies, an aqueous solution of Mitonafide was stored at 70 °C. After 20 days of storage, a drug degradation value of only 3% was statistically detected [7]. For this reason, in order to accelerate the degradation of the drug, high temperatures may be used. Therefore, a stability study was planned at 60, 70, 80 and 90 °C (± 2 °C) of this drug formulated in both parenteral solutions [8] and tablets elaborated by direct compression [9]. The relative humidity (RH) for all the studied conditions was 60% (± 5%), obtained with saturated salt aqueous solutions. One batch of both parenteral solution and tablets was elaborated. The frequency of testing was initially determined according to the results of the drug stability study in the preformulation step. From the early results obtained in the present work, the frequency of testing was checked.

Also planned was a long-term stability study to verify the extrapolated t_{90} parameter from the stress testing. The storage conditions were 25 ± 2 °C/60% $\pm$ 5% RH. The duration of the study was as long as the expected shelf life obtained from the t_{90} at 25 °C, extrapolated in the short-term stability study.

The samples were analysed by a validated high-performance liquid chromatographic method [10].

2.3. Mathematical data treatment

The following mathematical treatment was applied to the results of the short-term stability study.

At each temperature, it was evaluated if there was a statistically significant correlation between the two variables compared, drug content in the samples and storage time, through the values of the correlation coefficient '*r*':

1. If a significant correlation did not exist, it was concluded that the samples had not undergone chemical alteration during the storage at the temperature studied.
2. If it was not so, the kinetic model of the degradation reaction was identified: the experimental data were fitted to a zero- or first-order kinetic equation through a weighted linear regression or a weighted non-linear regression, respectively. If both models were reliable (ANOVA for zero order and chi-square test for first order), their variances were compared with the *F*-Snedecor test:
   - -if a significant difference was detected, the kinetic model with the lowest variance value was selected;
   - -if no significant difference was detected, the kinetic model chosen was the same as that selected for the other temperatures of the study due to Arrhenius theory requirements (the kinetic model should be the same for all of the temperatures studied).

It is possible that both degradation kinetic models (zero and first order) are statistically valid for all the studied temperatures. In this case, for the parenteral solution, first order was chosen. It is well known that the drug degradation reaction usually follows this order kinetics in liquid preparations [11]. For the tablets, zero order was chosen. The decomposition of most solid dosage forms stored under controlled relative humidity appears zero order, i.e. is pseudo-zero order [12–14].

Attempts were made to fit, through a weighed non-linear regression, the rate constants of the degradation reaction obtained at the different storage temperatures (k_T) to the Arrhenius equation:

$$k_T = A\,e^{-E_a/RT}$$

where k_T is the rate constant of the degradation reaction obtained at the different storage temperatures, A is the frequency factor, E_a is the energy of activation, R is the gas constant and T is the storage temperature in Kelvin.

An evaluation was made to check if there was statistically significant correlation between the two variables compared: degradation reaction constant (k_T) and the inverse of the storage temperature ($1/T$):

1. If a significant correlation did not exist, the mathematical treatment could not be applied because the Arrhenius equation cannot be applied.
2. If it was not so, the goodness of fit of the weighed non-linear regression was evaluated by a chi-square test. If the fitting was statistically valid, the rate constant of the degradation reaction at 25 °C ($k_{25\ ^\circ C}$) was calculated by extrapolation. The t_{90} parameter at 25 °C, time to reduce the drug content

to 90% of the initial content, was calculated from the 95% one-sided upper confidence limit of the $k_{25\ °C}$ extrapolated value. The stability of the different formulations was compared through each t_{90} parameter at 25 °C.

Finally, if a statistically significant drug degradation was detected, the remaining drug content (in percentage) in the formulations after the long-term stability study was compared with the theoretical remaining drug content or 90%, through a suitable Student's t-test. Theoretically, the remaining drug content in the formulations after the long-term stability study should be 90% of the initial one.

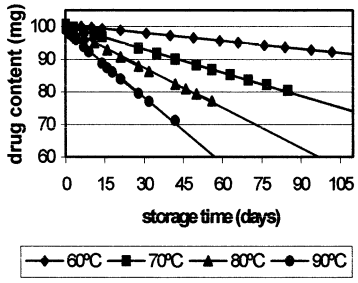

Fig. 1. Mitonafide parenteral solutions. Drug content versus storage time at the studied temperatures.

Table 1
Mitonafide in parenteral solutions

	60 °C	70 °C	80 °C	90 °C
N	36	36	36	36
r	−0.924 [a]	−0.952 [a]	−0.982 [a]	−0.958 [a]
Goodness of fit ANOVA-F (zero order)	0.99	1.51	1.31	1.17
χ^2 (first order)	12.98	16.22	22.53	6.72
Msq zero order	1.461	5.267	2.682	7.208
Msq first order	1.451	4.928	2.345	6.039
F	1.01	1.07	1.14	1.19
Best fitting	0/1	0/1	0/1	0/1

Correlation between the variables: drug content versus storage time. Degradation reaction kinetic fitting. The number of samples assayed each time was three. N, sample size; r, coefficient of correlation; ANOVA-F, F value of the ANOVA; χ^2, chi-square test; Msq, mean of square variance; F, Snedecor test.

[a] $P<0.01$.

Table 2
Mitonafide in parenteral solutions

	60 °C	70 °C	80 °C	90 °C
Model selected	$Q = Q_0\ e^{(-kt)}$			
Q_0 (mg)	100.6	100.5	100.0	99.1
SD_{Q_0} (mg)	0.6	1.1	0.7	1.0
k (days^{-1})	8.5×10^{-4}	2.53×10^{-3}	4.61×10^{-3}	7.60×10^{-3}
SD_k (days^{-1})	1×10^{-5}	2×10^{-5}	2×10^{-5}	6×10^{-5}

Parameters of the degradation kinetic equation selected. Q_0, initial drug content; SD_{Q_0}, standard deviation of Q_0; k, degradation rate constant; SD_k, standard deviation of k.

3. Results

3.1. Parenteral solutions

The Mitonafide content in the parenteral solution decreased as storage time increased, for all the studied temperatures (Fig. 1).

Table 1 shows the correlation between the variables drug content in the solutions versus the storage time. The results of the degradation reaction kinetic fitting are also shown in Table 1.

The parameters of the degradation kinetic equation selected are listed in Table 2.

Table 3 shows the correlation between the degradation rate constant versus inverse of the storage temperature (K), the Arrhenius equation fitting and the parameters of the equation. Fig. 2 illustrates the Arrhenius equation: degradation reaction constant against the inverse of the storage temperature (K). In Table 4, the results of statistical evaluation of the possible drug degradation are summarised: number of solutions analysed, mean drug content and standard deviation, F-Snedecor test and Student's t-test. Also shown are the results of comparing the remaining drug content in the parenteral solution after 1.5 years of storage with the theoretical one (90%): Student's t-test.

3.2. Tablets

The Mitonafide content in the tablets also decreased with storage time, under all the storage conditions studied (Fig. 3).

Table 5 summarises both the correlation between the variables drug content in the tablets versus the storage time and the results of the degradation reaction kinetic fitting.

The parameters of the degradation kinetic equation selected are listed in Table 6.

Table 7 lists the correlation between the degradation rate constant versus inverse of the storage temperature (K), the Arrhenius equation fitting and the parameters of the equation. Fig. 4 shows the plot of the Arrhenius equation: degradation reaction constant against the inverse of the storage temperature (K).

In Table 8, the results of comparing the drug content in the tablets at initial time with the remaining one after 2 years of storage (statistical evaluation of the possible drug degradation) are summarised: number of tablets analysed, mean drug content and standard deviation, F-Snedecor test and Student's t-test.

Table 3
Mitonafide in parenteral solutions

Correlation		Goodness of fit		Arrhenius equation parameters	
N	r	Msq	χ^2	A (days^{-1})	E_a (kJ/mol)
4	−0.986 [a]	0.024	0.05	2.3853×10^8	72.58

Arrhenius equation fitting.
Correlation between the variables: degradation rate constant versus inverse of the storage temperature (K). Parameters of the equation. N, sample size; r, coefficient of correlation; Msq, variance of the regression; χ^2, chi-squared test; A, frequency factor; E_a, activation energy.
[a] $0.01 < P < 0.05$.

4. Discussion

4.1. Parenteral solutions

The Mitonafide content in the parenteral solution decreased as storage time increased. A statistical correlation between the remaining content of Mitonafide and the storage time at all the temperatures used in this study (Fig. 1) was detected through the values of 'r' (Table 1).

Statistically, it was not possible to discern which was the best kinetic model (zero or first order), after fitting the experimental data, for all of the four temperatures used in this study (Table 1). First-order kinetics was selected for all of the temperatures, since, as mentioned above, the drug degradation reaction follows this kinetics in liquid preparations.

Thus, taking into account the first-order kinetics for the degradation of Mitonafide in the parenteral solution, the parameters, initial amount of drug (Q_0) and rate constant (k), with their standard deviations were calculated by non-linear regression (Table 2). It was observed that the higher the storage temperature, the larger the degradation rate constant values obtained. The small standard deviation values of the degradation rate constant for all of the temperatures studied can also be highlighted (the values of the coefficient of variation of the degradation rate constant at 60, 70, 80 and 90 °C were 1.18, 0.79, 0.43 and 0.79%, respectively).

Then, the results were fitted to the Arrhenius equation through a non-linear regression weighted by the inverse of the corresponding variances (Table 3 and Fig. 2). A significant correlation was detected, through the value of 'r', between the degradation reaction constant and the inverse of the storage temperature in degrees Kelvin. The fitting was statistically good according to the chi-squared test for a probability of 0.05. So, the parameters of the Arrhenius equation (frequency factor and activation energy) were calculated.

Extrapolation to 25 °C gave a value of 4.45×10^{-5} days^{-1} for $k_{25\,°C}$ (rate constant of the degradation reaction at 25 °C) with a 95% one-sided upper confidence limit of 1.884×10^{-4} days^{-1}. The value for t_{90} was of 559.24 days $\cong$ 1.5 years.

The remaining content of drug in the parenteral solution after 1.5 years of storage under long-term storage conditions was 93.83 ± 1.82 mg. From the Student's t-test value (Table 4), it can be seen that there was a statistically significant drug degradation (difference between this content and that obtained at initial time). It can be stressed that the remaining content (93.78%) after the long-term study with duration equal to the extrapolated shelf life was a little higher than 90%. It was so, since the t_{90} value was calculated from

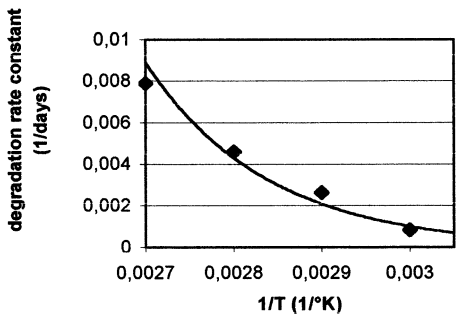

Fig. 2. Mitonafide parenteral solutions. Plot of Arrhenius equation: degradation reaction constant against the inverse of the storage temperature (K).

Table 4
Mitonafide in parenteral solutions

	Initial time	Long-term test (1.5 years)
N	20	20
$\bar{X}$ (mg)	100.05	93.83
SD (mg)	0.69	0.91
Significant drug degradation?		
F-Snedecor	3.85 [a]	yes
t-Student	24.35 [a]	
Comparison to theoretical 90% drug content		
t-Student	18.82 [b]	

Statistical evaluation of the significance of drug degradation. Remaining drug content after 1.5 years under long-term storage conditions versus drug content at initial time: Student's t-test. Experimental drug content after 1.5 years under long-term storage conditions versus theoretical one: Student's t-test. N, sample size; $\bar{X}$, mean drug content; SD, standard deviation of the mean drug content.
[a] $P < 0.05$.
[b] $P < 0.01$.

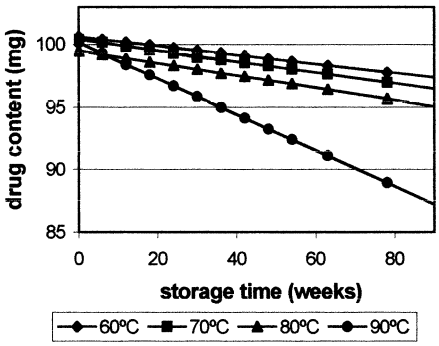

Fig. 3. Mitonafide tablets. Drug content versus storage time at the studied temperatures.

Table 5
Mitonafide in tablets

	60 °C	70 °C	80 °C	90 °C
N	42	39	36	36
r	−0.873 [a]	−0.974 [a]	−0.939 [a]	−0.994 [a]
Goodness of fit ANOVA-F (zero order)	0.36	0.49	0.34	0.99
χ^2 (first order)	3.66	2.51	11.02	12.73
S^2 zero order	0.362	0.256	1.086	1.207
S^2 first order	0.366	0.251	1.102	1.273
F	1.01	1.02	1.02	1.06
Best fitting	0/1	0/1	0/1	0/1

Correlation between the variables: drug content versus storage time. Degradation reaction kinetic fitting. The number of samples assayed each time was three. N, sample sizes; r, coefficient of correlation; ANOVA-F, F value of the ANOVA; χ^2, chi-square test; Msq, mean of square variance; F, Snedecor test.

[a] $P<0.01$.

Table 6
Mitonafide in tablets

	60 °C	70 °C	80 °C	90 °C
Model selected	$Q=Q_0-kt$			
Q_0 (mg)	102.6	102.4	101.5	102.2
SD_{Q_0} (mg)	0.3	0.2	0.2	0.3
k (mg/weeks)	3.6×10^{-2}	4.4×10^{-2}	5×10^{-2}	0.144
SD_k (mg/weeks)	6×10^{-3}	3×10^{-3}	6×10^{-3}	5×10^{-3}

Parameters of the degradation kinetic equation selected. Q_0, initial drug content; SD_{Q_0}, standard deviation of Q_0; k, degradation rate constant; SD_k, standard deviation of k.

the 95% one-sided 'upper' confidence limit of the $k_{25\ °C}$ extrapolated value.

Therefore, it may be said that both the stability study and the data treatment proposed were suitable for the stability prediction of the drug in parenteral solutions.

4.2. Tablets

The Mitonafide content of the tablets also decreased with storage time. A correlation was detected statistically, through the values of the correlation coefficient (Table 5), between the remaining content of Mitonafide and the storage time at all of the temperatures used in this study (Fig. 3).

Statistically, it was not possible to discern which was the best kinetic model (zero or first order), after fitting the experimental data, for all of the four temperatures used in this study (Table 5).

Zero order was selected for all of the temperatures, because, as mentioned above, drug degradation reaction usually follows this kinetics in solid systems.

Thus, taking into account zero-order kinetics for the degradation of Mitonafide in the solid dosage form, the parameters were calculated (Table 6). The higher the storage temperature was, the larger were the degradation rate-constant values (k) obtained, pointing out the very high k value obtained at 90 °C versus those obtained at the other temperatures. The standard deviation values of the degradation rate constant for all of the temperatures studied were higher than those obtained for the parenteral solution. The values of the coefficient of variation of the degradation rate constant at 60, 70, 80 and 90 °C were 16.67, 6.82, 12.00 and 3.47%, respectively.

When an attempt was made to fit the results to the Arrhenius equation through a non-linear regression weighted by the inverse of the variance, a significant correlation between the degradation rate constant and the inverse of the storage temperature was not obtained ($r=0.870$). On plotting these variables (Fig. 4), the lack of correlation can be observed. In the same figure, it can be also observed that the degradation rate constant value at 90 °C ($k_{90\ °C}$) did not allow a good correlation because it was too high.

Therefore, extrapolation to 25 °C cannot be done. In other words, stability prediction for Mitonafide in tablets was not possible under these study conditions.

Then, it may be thought that for the same drug, it was possible to apply the Arrhenius theory to get a stability prediction for liquid systems (parenteral solution), but not for solid ones (tablets).

One of the most common causes for the invalidity of the Arrhenius law is that the degradation mechanism changes above a critical temperature [12]. In Mitonafide tablets, it may be thought that 80 °C is the critical temperature up to which Arrhenius law does not hold. A quite similar event (large difference in degradation rates at 80 and 90 °C) was also detected and studied in phenylbutazone tablets [15]. Other problems that have been encountered in other works are that there are two or more simultaneous decay mechanisms with different rate constants and heats of activation (some pharmaceutical products which are hydrates) [5,12,16,17]. It is clear that a specious relationship is not being drawn between thermodynamics and kinetics. Situations are possible wherein thermodynamic characteristics mirror kinetic behaviour [18].

Table 7
Mitonafide in tablets

Correlation		Goodness of fit		Arrhenius equation parameters	
N	r	Msq	χ^2	A (mg/week)	E_a (kJ/mol)
3	−0.998 [a]	0.064	0.06	9.24	15.27

Arrhenius equation fitting.
Correlation between the variables: degradation rate constant versus inverse of the storage temperature (K). Parameters of the equation. N, sample size; r, coefficient of correlation; Msq, variance of the regression; χ^2, chi-squared test; A, frequency factor; E_a, activation energy.
[a] $P<0.05$.

In order to solve the problem of Mitonafide in solid systems, the k values may be fitted to the Arrhenius equation, but without the k value at 90 °C, since it did not allow a good correlation (Fig. 4) (it was over the critical temperature). Elimination of isotherm data for prediction of the drug product stability is not unusual [5,15,16]. It seems appropriate to comment on a different method of data elimination proposed by Gneuß and Biberach [5]. They used five temperatures for the stress stability testing: 50, 60, 70, 80 and 90 °C. Their procedure was conditioned on the temperature-independence of the A and E_a parameters. For this reason, data from the 60 and 80 °C isotherms were not used, since they did not allow identical Arrhenius parameters to be obtained. The authors justified from the mathematical point of view the elimination of data from intermediate temperatures of the stability study. In the present work, the elimination of data from the highest temperature due to a possible decay kinetic change is fully justified from both mathematical and theoretical points of view.

On fitting the k values at 60, 70 and 80 °C to the Arrhenius equation (Table 7), a statistically significant correlation between them and the inverse of the storage temperature was obtained ($r=0.998$). According to the chi-squared test ($\chi^2=0.06$), the fitting was statistically good, for a probability of 0.05. Then, the Arrhenius equation parameters (E_a and A) were calculated. The low E_a value obtained is highlighted (15.27 kJ/mol). The heat of activation is related to reaction rate constant so that a rate-constant change with temperature is shown by the value of heat of activation. Therefore, this low value of E_a obtained for tablets may mean that the catalytic effect of temperature on the degradation rate of Mitonafide in tablets was not very acute.

The value of the rate constant of the degradation reaction extrapolated to 25 °C ($k_{25\ °C}$) was 0.018 mg/week, with a 95% one-sided upper confidence limit of 0.097 mg/week. The value for t_{90} was of 103.09 weeks $\cong$ 1.91 years.

It may be highlighted that the coefficient of variation of this $k_{25\ °C}$ parameter extrapolated from three temperatures presented a value of 150%.

Taking into account that the value of t_{90} at 25 °C obtained from accelerated storage conditions was of 1.91 years, the long-term stability study was planned with a duration of 2 years.

The remaining content of drug in the tablets after 2 years of storage under long-term storage conditions was 101.44 ± 2.10 mg. From the Student's t-test value, it can be detected that there was no statistical difference between this content and that obtained at initial time (Table 8). Therefore, it may be said that after 2 years under long-term storage conditions a significant degradation of Mitonafide was not detected.

For this reason, the value of t_{90} at 25 °C obtained by extrapolation from accelerated storage conditions was

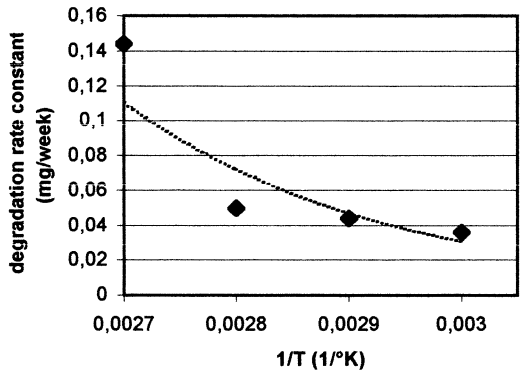

Fig. 4. Mitonafide tablets. Plot of Arrhenius equation: degradation reaction constant versus the inverse of the storage temperature (K).

Table 8
Mitonafide in tablets

	Initial time	Long-term test (2 years)
N	20	20
$\bar{X}$ (mg)	101.50	101.44
SD (mg)	1.95	1.05
Significant drug degradation?		
F-Snedecor	3.44 [a]	no
t-Student	0.121	

Statistical evaluation of the significance of drug degradation. Remaining drug content after 2 years under long-term storage conditions versus drug content at initial time: Student's t-test. Experimental drug content after 1.5 years under long term storage conditions versus theoretical one: Student's t-test. N, sample size; $\bar{X}$, Mean drug content; SD, standard deviation of the mean drug content.
[a] $P<0.05$.

not correct. It was not a surprise since the larger the variance of the extrapolated value is, far more than the real situation, the coefficient of variation of the $k_{25\ °C}$ parameter extrapolated from three temperatures presented a value of 150%. So the 95% upper confidence interval of the predicted room-temperature rate constant is quite high resulting in a short expiration period, as seen in others reports [12].

The design of the present work allowed realising that the results were a clear indication of the lack of accuracy that an extrapolation with the Arrhenius equation can present if the stability study is not planned in a correct way.

A way of avoiding the problems encountered is decreasing the difference between the lowest temperature of this study (60 °C) and the temperature of the long-term stability study (25 °C). In this way, narrowing the dispersion of the values obtained by the Arrhenius extrapolation can be achieved. Therefore, it is not only important to choose the number of temperatures for the stability study, but also to choose the appropriate lowest temperature which complies both to get a significant drug degradation in a short period of time and to be near the long-term storage temperature. This idea is mathematically supported [19]. The formula of the variance of the estimated value presents the term $(x_{\text{average}} - x_{\text{extrapolated}})^2$ in the numerator. So, with a short extrapolation, the confidence bands gets narrower because this term becomes smaller.

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