Estimation of Drug Shell-life Time Using Statistical Reliability Models

Ramón A. PONS MURGUÍA
PhD. Researcher.
Faculty of Industrial Engineering-University of Guayaquil.
Guayaquil 090150, Ecuador. rpons2015@gmail.com

Eulalia M. VILLA GONZÁLEZ DEL PINO
PhD. Researcher.
Faculty of Industrial Engineering-University of Guayaquil.
Guayaquil 090150, Ecuador. villaeulalia3@gmail.com

ABSTRACT

Stability is the property of a drug to keep its physical, chemical, and microbiological characteristics between the specified limits, during the time of storage and use. Its study should include the evaluation of those attributes that are susceptible to change and that is known they influence its quality, safety and fitness for use. Studies could be accelerated or natural aging. Accelerated aging i designed to increase the rate of chemical degradation and physical change under extreme conditions to predict drug shelf life in a short-term.

This research was aimed to make a comparison between the results obtained by both studies to determine whether the accelerated aging is a reliable tool to predict drug shell-life.

The natural stability study was developed over a period of 60 months under controlled conditions, meanwhile, the accelerated stability study was carried out over a period of 3 months, during which 3 pilot batches were tested. Comparison of both types of trials yielded similar results, but in less time and less batches with the application of accelerated trials.

Key words: drug shelf-life, stability, natural testing, accelerated testing, statistical reliability models

1. INTRODUCTION

During pharmaceutical development, the stability of the product has been assessed during long-term study. If any stability issues are discovered at this point of the process, it will result in re-formulation and important loss of time and cost. Therefore, important efforts are made to select the most stable product (1). Nevertheless, predicting the stability of the developed product at early stage of the development is challenging. Accelerated stability assessment based on Arrhenius equation approach, appears as an interesting tool allowing to evaluate stability and shelf-life of pharmaceutical product in a short period of time (2,5,6).

The application of Statistical Reliability has achieved significant advances in the field of stability studies of electronics, automation, home appliances, aircraft production and operations, and many other products. However, it has not been widely promoted into the pharmaceutical field, even considering the complexity of the stability tests, the socioeconomic impact of the drug shell-life and the variation effects associated to the drug manufacturing processes. among the new challenges involved in developing acceptable dosage forms for active pharmaceutical ingredients is demonstrating adequate chemical stability (8,9).

ISBN: 978-1-950492-60-2
ISSN: 2771-5914

https://doi.org/10.54808/IMCIC2022.01.166

Expiration dating is generally determined based on the time a drug remains within specification limits or total degradation at a recommended storage condition (3,4).

This paper introduces a procedure for stability assessments based on accelerated aging testing of drugs that provides credible predictions for product expiration understanding.

Hence, the objective of this research is to make a comparison between predicted and long-term data that were found accurate for a product, confirming the real interest of accelerated predicting stability approach for consistent determination of long-term stability shelf-life of pharmaceutical products.

2. MATERIALS AND METHODS

To make the comparison between the results obtained by the long term laboratory tests and the accelerated testing approach, to determine if the Mathematical Reliability Model is a reliable tool to predict the Shell-life of an oral diabetics drug, two different studies were conducted under the following conditions:

1. Conditions for the development of the natural stability study:

Study duration: Samples were followed for 60 months. Number of batches: The study was carried out on 2 batches manufactured in the same year.

Sampling times: The sampling was carried out in the following intervals 0, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months.

Temperature and relative humidity: 35 +2 ° C. 70% RH.

Data treatment: The concentration obtained vs time is plotted and the equation of the line for t90.

Sample totals per batch: During the 60 months, 3 were analyzed at each time. samples per lot that is 30 samples in total for each lot.

The value of the concentrations from beginning to time zero is made up of the data from initial quality control of each batch.

The studies were carried out in the same containers and packaging in which the product is marketed.

2. Conditions for the Development of Accelerated Stability Studies:

1. Study duration: Samples were followed for 3 months.
2. Number of lots: The study was carried out on 3 pilot lots.
3. Sampling time: Sampling was carried out at intervals of 0, 1, 2, 3, months.
4. Temperatures and relative humidity: 20 + 2 ° C, 35 + 2 ° C, 50 + 2° C, 70% RH
5. Data treatment: the concentration obtained vs. time is plotted and the
6. equation of the line for t_{90}.
7. The value of the concentrations from beginning to time zero is made up of the data initial quality control of each batch.
8. The studies must be carried out in the same containers and packaging in which the product is marketed.

Proposed Model for Natural Stability Analysis

1. Determine the 95% confidence limit.
2. Calculate the regression line from the logarithm of the mean of the remaining concentration obtained versus time.
3. Determine Useful Life: The intercept of the lower confidence limit curve of the 95% over the limit control value (90% of the concentration).

Proposed Model for Accelerated Stability Analysis

1. Determine the speed constant (k): To find the speed constant (K) of a reaction at a certain temperature.
2. *Diagram* reaction rate.
3. Calculate shelf life

Proposed model for Reliability analysis

Having carried out the laboratory tests according to the method described above, the results have been tabulated according to a laboratory scheme from which the pertinent information for the Reliability analysis was extracted.

STATGRAPHICS Statistical Software (7) was used for data processing of the conducted studies, considering the temperature in Kelvin, the observations (converted to hours), per cent of titration, lot number, and censorship specification. All tabulated data were considered as not censored, given that at the time of drug inspection and verification, they showed degradation. Model's comparisons were made by means of Weibull Analysis and Arrhenius Graphs.

3. ANALYSIS AND RESULTS

According to the natural stability model, it was obtained that the drug begins its degradation from 8 months at a regular average temperature of 20° C, through extrapolation. Considering the conditions applied to the test we have that for a temperature of 35 ° C the shelf life was 7,2 months, while for a temperature of 50 ° C it was shown in 6 months.

Table 1 shows the results of fitting a Weibull distribution to data values in time. The shape and scale parameters were estimated using maximum likelihood. The maximum value of the distribution was assumed to be located at 0.0. Distributions were adjusted separately for the 3 groups. All tabulated were considered as not censored, given that at the time of drug inspection and verification, they showed degradation.

Table 1 Maximun Likelihood Estimation of Weibull Distribution Parameters

	Sample	Number of	Shape	Estimated	Start
Group	Size	Failures	Estimation	Scale	Point
20	10	10	4,30138	6686,68	0,0
35	10	10	4,29587	5730,1	0,0
50	10	10	4,29587	4775,08	0,0

Figure 1 shows the goodness of fit for adjusted distributions of failure times of three lots at temperatures in which the tests were performed.

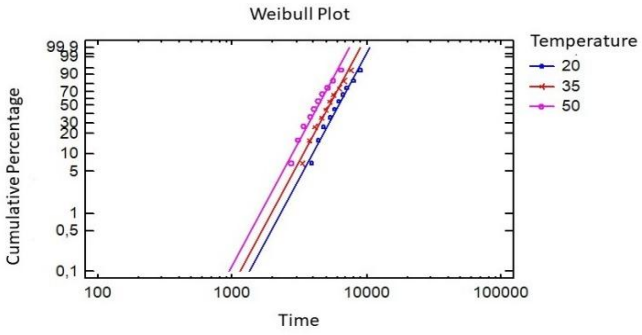

Figure 1 Weibull distributions of failures adjusted for different temperatures

Table 2 shows the estimates of percentiles through Weibull analysis. It is observed that the drug has 99% chance of 3-month, 2.7-month and 2.3-month sample survival for 20,35 and 50 ° C, respectively. Analogously, has 50% chance of 8.5, 7.3 and 6-month sample survival, respectively, and 1% chance of 13, 11 and 9.5-month sample survival, respectively.

Table 2 Time Critical Values

Temperature	X	Lower Tail Area (<)	Upper Tail Area (>)
20	2750,0	0,0216496	0,97835
	8960,0	0,970437	0,0295629
35	2750,0	0,0417939	0,958206
	8960,0	0,998912	0,00108757
50	2750,0	0,0892014	0,910799
	8960,0	1,0	3,26733E-7

Table 3 and Figure 2 show the Arrhenius Model for the estimation of the drug shell-life time and its graphical representation.

The mathematical model based on the observed formation of the degradant at all experimental conditions was built by using the Arrhenius equation obtained by the STATGRAPHICS Statistical Software.

Table 3 Arrhenius Model to Estimate the Drug shell-life Time

Adjusted model
P50 = 165,884*exp(0,0913583/k*KELVIN)
k = Boltzmann constant (8,617E-5 EV/degrees K)
Regression Statistics
Number of observations = 30
Intercept = 5,11129
Slope = 0,0913583
R-square = 99,4264%
Prediction
Temperature: 308,0 K
Estimated percentil: 5185,02
Lower limit 95,0%: 5164,12 h
Upper limit 95,0%: 5206,0 h

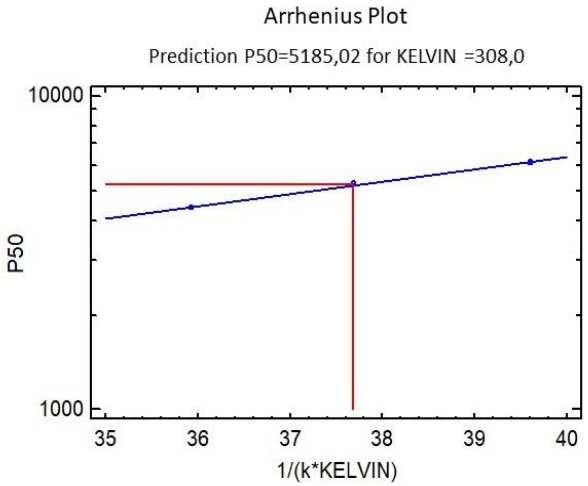

Figure 2 Arrhenius plot

The adjusted model was

P50 = 5,884*exp(0,0913583/k*KELVIN)

Where: k = Boltzmann constant (8,617E-5 EV/degrees K)

The comparison of the predicted versus experimental values, obtained by the long-term stability study, gave a mean deviation value of 1%, a R - square value of 0.994, and a p-value of 0.05.

The use of the Arrhenius equation modeling theory was found to be of value to set specifications and storage condition, using only few trials, with a good fit and resource saving.

4. CONCLUSIONS

The application of Reliability Statistical Models demonstrates the usefulness of their use because it is possible to obtain reliable results in terms of estimating the drug shell-life times, in a shorter time and with lower costs than those required by traditional methods.

On the other hand, if the stability of the product is assessed during long-term study and any stability issues are discovered at this point of the process, it will result in re-formulation and important loss of time and cost. Therefore, important efforts must be made to select the most stable product. Accelerated stability assessment program based on Arrhenius equation, appears as an interesting tool allowing to evaluate stability and shelf-life of a pharmaceutical product in a short period of time.

An accelerated approach utilizing the Arrhenius equation and STATGRAPHICS statistical software was utilized to quantitatively assess the stability of an oral diabetic's drug, under the influence of temperature. A mathematical model based on the observed formation of the degradant at all experimental conditions was built by using the Arrhenius equation and STATGRAPHICS statistical software. Comparison of the predicted versus experimental values gave a mean deviation value of 1%, a R - square value of 0.994, and a p-value of 0.05.

The use of the Arrhenius equation modeling theory was found to be of value to aid setting of specifications and storage condition selection. The model was also generated using only few trials, as an example from a resource saving perspective, which was found to provide a good fit to the entire set of data.

5. ACNOWLEDGMENTS

We are grateful to Professors Dayana Lozada and Freddie Steve Pincay, of the Guayaquil

University, for reviewing our paper and their valuable suggestions that contributed to its final presentation.

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