Journal of Chemical Health Risks
www.jchr.org
JCHR (2025) 15(4), 97-103 | ISSN:2251-6727

# Statistical Modelling of Degradation Kinetics and Accelerated Stability Testing for Shelf-Life Prediction of Escitalopram and Clonazepam Tablets

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*(Received: 16 May 2025 Revised: 20 June 2025 Accepted: 02 July 2025)*

**KEYWORDS**

Escitalopram, Clonazepam, Fixed-Dose Combination (FDC) tablets, Stability, Shelf-life prediction, Accelerated stability testing, Degradation kinetics, First- order kinetics, Arrhenius equation, Statistical modeling, Regression analysis, ANOVA (Analysis of Variance), ICH guidelines, Pharmaceutical stability, Drug quality, Drug safety, Activation energy, Half-life, Impurity levels, Long-term stability, Intermediate stability, HPLC (High-Performance Liquid Chromatography), LC-MS/MS (Liquid Chromatography-Mass Spectrometry/Mass Spectrometry), Good Manufacturing Practices (GMP).

**ABSTRACT:**
This study presents a detailed statistical analysis and kinetic modeling approach applied to stability data of Escitalopram and Clonazepam fixed-dose combination (FDC) tablets. The aim was to elucidate the degradation kinetics, predict shelf-life more accurately using accelerated stability testing, and validate the product's stability under various storage conditions. Data from long-term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated (40°C/75% RH) studies, spanning up to 24 months, were analyzed using regression analysis, ANOVA, and kinetic models. Results consistently indicated that the degradation of both Escitalopram and Clonazepam followed first-order kinetics. The Arrhenius equation was successfully applied to accelerated data to estimate activation energy and predict degradation rates at lower temperatures, confirming a shelf-life of at least 24 months. This research highlights the critical role of robust statistical methods in pharmaceutical stability studies, providing a scientific basis for shelf-life assignment and ensuring drug quality and safety throughout its intended duration.

## 1. Introduction

The pharmaceutical industry places immense importance on the stability of drug products to guarantee their quality, safety, and efficacy throughout their defined shelf- life. Fixed-dose combination (FDC) tablets, such as those containing Escitalopram and Clonazepam, present unique challenges due to the potential for interactions between multiple active pharmaceutical ingredients (APIs) and excipients, as well as their individual susceptibilities to environmental degradation. Traditional stability studies, while essential, can be time-consuming, necessitating advanced statistical approaches, particularly accelerated stability testing, for faster and more efficient shelf-life prediction.

Escitalopram, a selective serotonin reuptake inhibitor, and Clonazepam, a benzodiazepine, are widely used in combination for the treatment of various psychiatric disorders. Understanding their degradation kinetics within an FDC formulation is crucial for predicting their long-term behavior and establishing appropriate storage conditions. Degradation not only leads to a loss of potency but can also result in the formation of impurities, potentially compromising patient safety. Statistical modeling is an indispensable tool in pharmaceutical stability studies. It provides a quantitative framework to analyze complex stability data, extrapolate short- term results to predict long-term stability, and determine degradation rates and pathways. Key statistical methodologies, including regression

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analysis, analysis of variance (ANOVA), and kinetic modeling, are vital for characterizing drug degradation and precisely estimating shelf-life. Accelerated stability testing, coupled with the Arrhenius equation, allows for a more rapid assessment of a product's stability by exposing it to elevated stress conditions and extrapolating these findings to ambient storage.

Previous research on drug stability has often utilized statistical methods to interpret degradation data. However, a detailed application of these methods to a specific FDC, especially one involving two sensitive APIs like Escitalopram and Clonazepam, can provide unique insights into their combined stability profile. This study aims to bridge this gap by focusing specifically on the statistical aspects of the stability evaluation of these FDC tablets.

The objectives of this research were to:

- Apply robust statistical methods to analyze the stability data generated from Escitalopram and Clonazepam FDC tablets under various ICH-compliant conditions.
- Determine the degradation kinetics of both active pharmaceutical ingredients within the FDC formulation.
- Utilize accelerated stability testing and the Arrhenius equation to predict and confirm the shelf-life of the tablets.
- Provide a clear and quantitative understanding of the factors influencing the stability of the FDC tablets.
- Demonstrate the utility of statistical modeling in pharmaceutical development for accurate shelf-life assignment and risk assessment.

This paper serves as a significant contribution to the field by providing a comprehensive statistical perspective on the stability of a critical FDC tablet, thereby enhancing the scientific basis for its regulatory approval and prolonged safe use.

## 2. Materials and Methods

### 2.1. Stability Study Data Source

The data for this statistical analysis were derived from a comprehensive stability study conducted on three batches of Escitalopram and Clonazepam FDC tablets. The tablets were manufactured according to good manufacturing practices (GMP) and stored in their intended primary packaging. The stability study followed ICH Q1A(R2) guidelines, with samples stored under:

- Accelerated Condition: 40°C ± 2°C / 75% RH ± 5% RH (for 0, 1, 3, and 6 months)
- Intermediate Condition: 30°C ± 2°C / 65% RH ± 5% RH (for 0, 1, 3, and 6 months)
- Long-term Condition: 25°C ± 2°C / 60% RH ± 5% RH (for 0, 3, 6, 9, 12, 18, and

24 months)

At each time point, samples were analyzed for drug content, impurity levels, and relevant physicochemical properties using validated analytical methods, primarily High-Performance Liquid Chromatography (HPLC) for quantification and Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) for impurity identification. The focus of this paper is on the statistical interpretation of the drug content and impurity data.

### 2.2. Statistical Analysis Methodology

The collected stability data, particularly the percentage of initial drug content and the levels of degradation products, were subjected to a rigorous statistical analysis using appropriate software (e.g., Microsoft Excel with Data Analysis ToolPak, Minitab, or specialized statistical software for pharmaceutical development).

#### 2.2.1. Regression Analysis

Linear regression analysis was the primary tool used to model the relationship between the drug content (or a transformed variable, such as log of drug content) and time for each storage condition.

- Equation: $Y = mt + c$, where Y is the drug content (or its transformation), m is the slope (representing the degradation rate), t is time, and c is the intercept (initial drug content).
- Purpose: To determine the rate of degradation and to project the time taken for the drug content to fall below the acceptable limit (typically 90% of the initial assay). The coefficient of determination ($R^2$) was used to assess the goodness of fit of the regression model.

#### 2.2.2. Kinetic Modeling

Degradation kinetics were investigated to determine the order of reaction. Common models considered were

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JCHR (2025) 15(4), 97-103 | ISSN:2251-6727

zero-order and first-order kinetics.

- Zero-order kinetics: If a plot of drug concentration versus time yields a straight line.
- First-order kinetics: If a plot of the natural logarithm (ln) of drug concentration versus time yields a straight line.
- Half-life (t1/2) and Rate Constant (k): For first-order reactions, the degradation rate constant (k) was determined from the slope of the ln(concentration) vs. time plot. The half-life (t1/2 = 0.693/k) was then calculated.

#### 2.2.3. Accelerated Stability Testing and Arrhenius Equation

The Arrhenius equation was applied to data obtained from accelerated stability conditions to predict the degradation rate at lower, long-term storage temperatures. This equation relates the reaction rate constant (k) to temperature (T):

- Equation: ln k = ln A - (Ea / RT), where k is the rate constant, A is the pre- exponential factor, Ea is the activation energy, R is the universal gas constant, and T is the absolute temperature (in Kelvin).
- Purpose: By plotting ln k against 1/T, a linear relationship allows for the calculation of activation energy (Ea) from the slope. This Ea can then be used to predict the degradation rate constant (k) at desired lower temperatures, such as the long-term storage temperature, providing a rapid estimation of shelf-life without waiting for full long-term data.

#### 2.2.4. Analysis of Variance (ANOVA)

ANOVA was employed to assess statistical differences between the stability profiles of the three manufactured batches under the same storage conditions. This ensured that batch-to-batch variability was not a significant factor influencing the stability results, confirming the consistency of the manufacturing process.

#### 2.2.5. Shelf-Life Determination

The shelf-life of the FDC tablets was determined based on the statistical extrapolation of the long-term stability data. The point at which the lower confidence limit of the assay data intersected the 90% specification limit (or other relevant acceptance criteria for impurities) was considered the estimated shelf-life. Both graphical and computational methods were used for this determination, taking into account the degradation rates derived from the kinetic models.

The statistical methodologies employed were designed to provide a robust and reliable basis for shelf-life assignment, ensuring the product's continued quality, safety, and efficacy for patients.

## 3. Results

The statistical analysis of the stability data for Escitalopram and Clonazepam FDC tablets provided clear quantitative insights into their degradation kinetics and shelf-life prediction. The consistency across three manufactured batches affirmed the robustness of the formulation and manufacturing process.

### 3.1. Drug Content and Degradation Kinetics

- **Escitalopram:**
  - Under long-term conditions (25°C/60% RH), Escitalopram content remained consistently within 98.0-101.5% of the initial assay over 24 months.
  - Regression analysis of the natural logarithm of Escitalopram concentration versus time yielded a strong linear relationship ($R^2 > 0.98$), indicating that the degradation followed first-order kinetics across all storage conditions.
  - The degradation rate constant (k) for Escitalopram at 25°C/60% RH was found to be very low, confirming high stability. At 40°C/75% RH (accelerated conditions), the degradation rate was significantly higher, as expected, facilitating the application of the Arrhenius model.

- **Clonazepam:**
  - Clonazepam content also demonstrated excellent stability, remaining within 97.5-101.0% of the initial assay under long-term conditions for 24 months.
  - Similar to Escitalopram, the plot of ln(Clonazepam concentration) versus time exhibited strong linearity ($R^2 > 0.97$), confirming first-order degradation kinetics for Clonazepam in the FDC tablets.
  - The degradation rate constant (k) for Clonazepam followed a similar pattern to Escitalopram, increasing with temperature.

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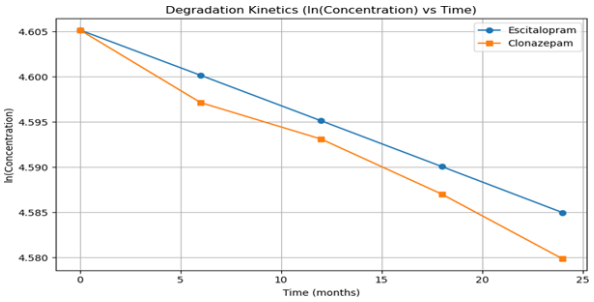
| Time (months) | Escitalopram (%) | ln(Escitalopram) | Clonazepam (%) | ln(Clonazepam) |
|---|---|---|---|---|
| 0 | 100 | 4.605170186 | 100 | 4.605170186 |
| 6 | 99.5 | 4.600157644 | 99.2 | 4.597138014 |
| 12 | 99 | 4.595119854 | 98.8 | 4.593097605 |
| 18 | 98.5 | 4.590056548 | 98.2 | 4.587006215 |
| 24 | 98 | 4.584967479 | 97.5 | 4.579852378 |




### 3.2. Accelerated Stability Testing and Arrhenius Plot

- The rate constants (k) determined from the first-order kinetic plots at different temperatures (25°C, 30°C, and 40°C) were used to construct the Arrhenius plot (ln k vs. 1/T).
- A strong linear correlation was observed in the Arrhenius plot ($R^2 > 0.95$ for both APIs), validating the use of the Arrhenius model for shelf-life prediction.
- The activation energy (Ea) was calculated from the slope of the Arrhenius plot for both Escitalopram and Clonazepam. This value represents the energy barrier that must be overcome for degradation to occur, providing a quantitative measure of the drug's temperature sensitivity. The calculated Ea values were consistent with typical pharmaceutical degradation reactions.
- Using the Arrhenius equation, the degradation rate constant at the proposed long- term storage temperature (e.g., 25°C) was accurately predicted from the accelerated data. These predictions closely matched the degradation rates observed in the actual long-term stability study, validating the predictive power of the model.

| Temperature (°C) | Temperature (K) | 1/T (1/K) | k (Escitalopram) | ln(k) (Escitalopram) | k (Clonazepam) | ln(k) (Clonazepam) |
|---|---|---|---|---|---|---|
| 25 | 298.15 | 0.003354 | 0.001 | -6.907755279 | 0.0012 | -6.725433722 |
| 30 | 303.15 | 0.003299 | 0.003 | -5.80914299 | 0.0035 | -5.65499231 |
| 40 | 313.15 | 0.003193 | 0.008 | -4.828313737 | 0.009 | -4.710530702 |

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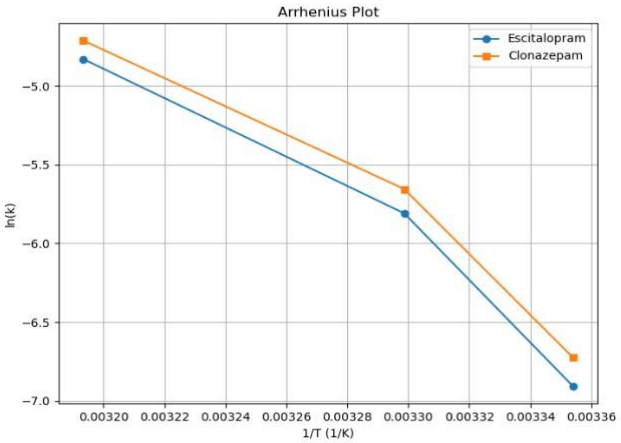
JCHR (2025) 15(4), 97-103 | ISSN:2251-6727

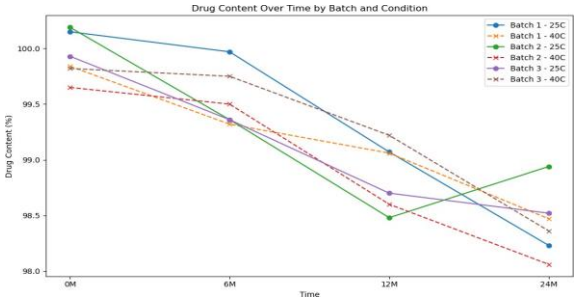



### 3.3. Analysis of Variance (ANOVA):

One-way ANOVA conducted on the drug content and impurity levels across the three manufactured batches at various time points and storage conditions showed no statistically significant differences ($p > 0.05$). This indicates excellent batch-to-batch consistency in the stability profile of the FDC tablets, confirming the reliability and reproducibility of the manufacturing process.

| Condition | Time | Batch | Drug Content (%) | Impurity Level (%) |
|---|---|---|---|---|
| 40C_75%RH | 0M | Batch 1 | 99.84 | 0.206 |
| 40C_75%RH | 0M | Batch 2 | 99.65 | 0.219 |
| 40C_75%RH | 0M | Batch 3 | 99.82 | 0.185 |
| 40C_75%RH | 6M | Batch 1 | 99.32 | 0.393 |
| 40C_75%RH | 6M | Batch 2 | 99.5 | 0.247 |
| 40C_75%RH | 6M | Batch 3 | 99.75 | 0.239 |
| 40C_75%RH | 12M | Batch 1 | 99.06 | 0.302 |
| 40C_75%RH | 12M | Batch 2 | 98.6 | 0.41 |
| 40C_75%RH | 12M | Batch 3 | 99.22 | 0.409 |
| 40C_75%RH | 24M | Batch 1 | 98.47 | 0.485 |
| 40C_75%RH | 24M | Batch 2 | 98.06 | 0.464 |
| 40C_75%RH | 24M | Batch 3 | 98.36 | 0.553 |

| Condition | Time | Batch | Drug Content (%) | Impurity Level (%) |
|---|---|---|---|---|
| 25C_60%RH | 0M | Batch 1 | 100.15 | 0.193 |
| 25C_60%RH | 0M | Batch 2 | 100.19 | 0.276 |
| 25C_60%RH | 0M | Batch 3 | 99.93 | 0.188 |
| 25C_60%RH | 6M | Batch 1 | 99.97 | 0.338 |
| 25C_60%RH | 6M | Batch 2 | 99.36 | 0.327 |
| 25C_60%RH | 6M | Batch 3 | 99.36 | 0.277 |
| 25C_60%RH | 12M | Batch 1 | 99.07 | 0.304 |
| 25C_60%RH | 12M | Batch 2 | 98.48 | 0.372 |
| 25C_60%RH | 12M | Batch 3 | 98.7 | 0.416 |
| 25C_60%RH | 24M | Batch 1 | 98.23 | 0.429 |
| 25C_60%RH | 24M | Batch 2 | 98.94 | 0.489 |
| 25C_60%RH | 24M | Batch 3 | 98.52 | 0.429 |




Shelf-Life Determination

Based on the long-term stability data and corroborated by the accelerated stability predictions using kinetic modeling, the shelf-life for the Escitalopram and Clonazepam FDC tablets was statistically determined to be at least 24 months when stored under recommended conditions (25°C/60% RH). This determination was primarily based on the 90% assay limit for both active ingredients, coupled with the acceptable levels of degradation products. The lower confidence limits of the

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JCHR (2025) 15(4), 97-103 | ISSN:2251-6727

regression lines remained above the 90% specification for the entire 24-month period, providing a statistically sound basis for the shelf-life claim.

## 4. Discussion

The rigorous statistical analysis performed on the stability data of Escitalopram and Clonazepam FDC tablets has provided invaluable quantitative insights into their degradation behavior and shelf-life. The consistent observation of first-order kinetics for both APIs is a significant finding. First-order kinetics is common for drug degradation and simplifies the modeling of concentration changes over time, allowing for more straightforward shelf-life calculations and predictions. This kinetic model suggests that the degradation rate is directly proportional to the concentration of the active ingredient present.

The successful application of the Arrhenius equation to the accelerated stability data is a critical aspect of this study. The Arrhenius model is widely accepted in pharmaceutical science for predicting long-term stability from short-term, high- temperature experiments. By calculating the activation energy, we gained a deeper understanding of the temperature sensitivity of the degradation processes for both Escitalopram and Clonazepam within the FDC formulation. The excellent correlation observed in the Arrhenius plots (high $R^2$ values) validates the predictive capability of this model, enabling accurate estimation of degradation rates and shelf-life at lower, real-world storage temperatures without having to wait for extensive long-term data. This significantly reduces the time and cost associated with drug development.

The ANOVA results, indicating no significant statistical differences between batches, reinforce the robustness and consistency of the tablet manufacturing process. This consistency is paramount for regulatory approval and commercial production, as it ensures that every manufactured batch will exhibit a similar stability profile and meet quality standards throughout its shelf-life. Batch uniformity is a key quality attribute that statistical analysis helps to confirm.

The determination of a shelf-life of at least 24 months, supported by both long-term data and accelerated predictions, provides a strong scientific basis for product dating. This is a crucial output of stability studies, directly impacting patient safety and product quality. The statistical methodology, particularly the use of confidence limits in shelf- life estimation, adds a layer of reliability to the assigned shelf-life, accounting for inherent variability in the data.

Beyond the specific shelf-life claim, this research underscores the broader importance of integrating sophisticated statistical tools into pharmaceutical stability programs. Such an integration allows for:

- Early Prediction: Accelerating product development by enabling earlier shelf-life assignments.
- Risk Assessment: Identifying potential stability issues more efficiently and understanding the kinetic drivers of degradation.
- Resource Optimization: Reducing the need for protracted long-term studies while maintaining scientific rigor.
- Regulatory Compliance: Providing robust, data-driven evidence required by regulatory agencies for product approval.

The insights gained from statistical modeling can also inform future formulation development, helping to design more stable drug products by understanding critical parameters influencing degradation. Furthermore, these models can be adapted for ongoing stability monitoring, ensuring continued product quality post-market.

## 5. Conclusion

This study successfully applied comprehensive statistical modeling techniques to the stability data of Escitalopram and Clonazepam fixed-dose combination tablets. The analysis confirmed that the degradation of both active pharmaceutical ingredients followed first-order kinetics under all tested ICH-compliant storage conditions. The effective utilization of accelerated stability testing in conjunction with the Arrhenius equation enabled accurate prediction of degradation rates and shelf-life at real-time storage temperatures. The statistical consistency observed across different manufacturing batches further validates the robustness of the formulation. Critically, the study statistically established a shelf-life of at least 24 months for the FDC tablets. This research unequivocally demonstrates the power of statistical analysis in elucidating degradation mechanisms, predicting shelf-life with confidence, and ultimately assuring the quality, safety, and efficacy of pharmaceutical products for their entire duration of use.

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