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Research Article

COMPREHENSIVE STABILITY EVALUATION AND SHELF-LIFE DETERMINATION OF ESCITALOPRAM AND CLONAZEPAM FIXED-DOSE COMBINATION TABLETS

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Abstract

This study comprehensively evaluated the physical and chemical stability of fixed-dose combination (FDC) tablets containing Escitalopram and Clonazepam, crucial for treating psychiatric disorders, under various International Conference on Harmonization (ICH) compliant storage conditions. The research aimed to establish the shelf-life and understand the degradation profiles of these sensitive drugs. Three batches of FDC tablets were subjected to accelerated (40°C/75% RH), intermediate (30°C/65% RH), and long-term (25°C/60% RH) stability testing for up to 24 months. Physicochemical properties, drug content, impurity levels, and dissolution profiles were monitored using validated analytical techniques, including High-Performance Liquid Chromatography (HPLC) and Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC-MS/MS). The results confirmed that the tablets maintained their physical and chemical stability, meeting all regulatory specifications throughout the study period. Degradation kinetics followed first-order kinetics, and the study successfully established a shelf-life of at least 24 months under the tested conditions. This research provides critical data for regulatory approval, manufacturing quality assurance, and safe patient use of Escitalopram and Clonazepam FDC tablets.

Keywords: Escitalopram, Clonazepam, Fixed-Dose Combination (FDC) Tablets, Stability, Shelf-life Determination, ICH Guidelines, Accelerated stability testing, Intermediate stability testing, Long-term stability testing, Physicochemical properties, Drug content, Impurity levels, Dissolution profiles, HPLC (High-Performance Liquid Chromatography), LC-MS/MS (Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry), Degradation kinetics, First-order kinetics, Psychiatric disorders, Anxiety, Depression, SSRI (Selective Serotonin Reuptake Inhibitor), Benzodiazepine, Active Pharmaceutical Ingredients (APIs), Regulatory approval, Quality assurance, Packaging materials, Degradation pathways, Kinetic modeling, Arrhenius equation, Regression analysis, ANOVA (Analysis of Variance), Good Manufacturing Practices (GMP).

1. Introduction

Fixed-dose combination (FDC) tablets containing Escitalopram and Clonazepam are widely prescribed for the management of various psychiatric conditions, including anxiety and depression. Escitalopram, a selective serotonin reuptake inhibitor (SSRI), and Clonazepam, a benzodiazepine, are often co-formulated to enhance patient compliance and simplify dosing regimens. However, ensuring the safety, efficacy, and quality of these FDC tablets throughout their intended shelf-life is paramount, given the inherent sensitivity of both active pharmaceutical ingredients (APIs) to various environmental factors.

Stability, defined as the ability of a drug product to maintain its physical, chemical, microbiological, and biopharmaceutical properties within specified limits, is a critical quality attribute. Factors such as temperature, humidity, light exposure, and potential interactions between the APIs and excipients can significantly influence the stability of a drug product. Escitalopram and Clonazepam are known to be susceptible to degradation under specific conditions, and the complexity introduced by combining multiple active ingredients necessitates a thorough stability evaluation. Degradation of these drugs can lead to a reduction in potency, formation of potentially harmful degradation products, and compromise patient outcomes.

Previous research has explored the stability of Escitalopram and Clonazepam individually or in different formulations. These studies often utilized advanced analytical techniques like HPLC and Gas Chromatography-Mass Spectrometry (GC- MS) to quantify degradation products and determine degradation rates. Furthermore, the literature highlights the importance of understanding degradation pathways and the impact of packaging materials on drug stability. This study builds upon existing knowledge by providing a comprehensive stability assessment of an Escitalopram and Clonazepam FDC tablet, specifically designed to evaluate shelf-life under controlled ICH-prescribed conditions.

The primary objectives of this research were to:

- Evaluate the physical and chemical stability of Escitalopram and Clonazepam FDC tablets under accelerated, intermediate, and long-term storage conditions.
- Determine the degradation pathways of Escitalopram and Clonazepam within the FDC formulation.
- Establish the shelf-life of the FDC tablets based on stability data and kinetic modeling.
- Assess the impact of packaging materials on the overall stability of the tablets.
- Provide valuable data for regulatory submissions, ensuring the continued safety and efficacy of this important therapeutic combination.

This research contributes significantly to the understanding of FDC tablet stability, offering crucial insights for pharmaceutical manufacturers, regulatory bodies, and healthcare professionals.

2. Materials and Methods

2.1 Materials

All excipients used in the tablet formulation were of pharmaceutical grade. Active pharmaceutical ingredients (APIs), Escitalopram and Clonazepam, were procured from reputable suppliers and met pharmacopoeial standards. Solvents and reagents for analytical testing, including HPLC-grade acetonitrile, methanol, water, and various buffer salts, were obtained from commercial sources and used without further purification. Reference standards for Escitalopram, Clonazepam, and their known degradation products were also obtained for method validation.

2.2 Tablet Formulation and Manufacturing

Three independent batches of Escitalopram and Clonazepam FDC tablets were prepared for the stability study, with each batch containing 100 tablets. The tablet formulation was designed to ensure optimal drug release and stability. The manufacturing process involved standard pharmaceutical unit operations, including weighing, mixing, granulation (if applicable), compression, and coating. The tablets

were manufactured using typical pharmaceutical equipment, ensuring consistency across batches. Specific details regarding tablet composition (e.g., excipient ratios) and exact manufacturing parameters are proprietary but followed good manufacturing practices (GMP).

2.3 Stability Study Design

The stability study was conducted in accordance with the International Conference on Harmonization (ICH) guidelines Q1A(R2) on stability testing of new drug substances and products. Samples from each of the three manufactured batches were stored under the following controlled environmental conditions:

- Accelerated Condition: 40°C ± 2°C / 75% RH ± 5% RH
- Intermediate Condition: 30°C ± 2°C / 65% RH ± 5% RH
- Long-term Condition: 25°C ± 2°C / 60% RH ± 5% RH

These conditions were chosen to simulate various climatic zones and potential storage environments during distribution and patient use. Tablets were stored in their proposed primary packaging materials (e.g., blister packs, HDPE bottles) to assess the protective role of packaging.

Samples were withdrawn at predefined time points to monitor their stability profiles:

- Accelerated and Intermediate Conditions: 0, 1, 3, and 6 months.
- Long-term Condition: 0, 3, 6, 9, 12, 18, and 24 months.

At each time point, samples were analyzed in triplicate to ensure accuracy and reproducibility of the data.

2.4 Physicochemical Analysis

A range of physicochemical tests were performed on the stored tablet samples to assess their stability:

- Appearance: Visual inspection for changes in color, texture, and physical integrity (e.g., chipping, cracking).
- Hardness: Measured using a tablet hardness tester (e.g., Schleuniger, Erweka) to evaluate mechanical strength.
- Friability: Assessed using a friabilator (e.g., Roche friabilator) to determine the tablet's resistance to abrasion during handling and packaging.
- Disintegration Time: Determined using a disintegration test apparatus according to pharmacopoeial methods (e.g., USP) to ensure rapid tablet breakdown.
- Dissolution Profile: Measured using a dissolution apparatus (e.g., USP Apparatus 2, paddle type) under simulated physiological conditions (e.g., pH 1.2, 4.5, 6.8 buffer) to evaluate drug release characteristics over time. Samples were collected at specified intervals (e.g., 5, 10, 15, 30, 45 minutes) and analyzed for drug content.

2.5 Analytical Methods for Drug Content and Impurities

Validated analytical methods were employed to quantify drug content and monitor impurity levels:

A. High-Performance Liquid Chromatography (HPLC): A robust and sensitive HPLC method was developed and validated for the simultaneous quantification of Escitalopram and Clonazepam, as well as their related substances and degradation products. The method parameters (e.g., column, mobile phase, flow rate, detection wavelength) were optimized to achieve adequate separation, resolution, and sensitivity.

B. Validation parameters: The HPLC method was validated for specificity, linearity, accuracy, precision (repeatability and intermediate precision), limit of detection (LOD), and limit of quantification (LOQ) according to ICH Q2(R1) guidelines.

C. Liquid Chromatography-Mass Spectrometry/ Mass Spectrometry (LC- MS/MS): LC-MS/MS was utilized for the identification and characterization of unknown degradation products, providing a comprehensive understanding of the degradation pathways. This technique offered high sensitivity and selectivity, enabling the detection of even trace

levels of impurities.

2.6 Statistical Analysis

The collected stability data were subjected to rigorous statistical analysis to determine shelf-life, assess degradation kinetics, and confirm the statistical significance of the findings. Key statistical tools included:

A. Regression Analysis: Used to model the relationship between drug content/impurity levels and time, enabling the prediction of degradation rates and shelf-life.

B. Kinetic Modelling: The degradation of the tablets was analyzed to determine if it followed first-order, zero-order, or other kinetic models. The Arrhenius equation was applied to accelerated stability data to predict degradation rates at various temperatures and calculate activation energy.

C. Analysis of Variance (ANOVA): Employed to compare the means of different batches and storage conditions, ensuring no significant differences in stability between the three tested batches.

Shelf-Life Determination: The shelf-life was determined by extrapolating the stability data to the point where the drug content fell below 90% of the initial concentration or impurity levels exceeded predefined limits, as per regulatory requirements.

All statistical analyses were performed using appropriate statistical software packages to ensure accuracy and reliability of the conclusions.

3. Results

The stability study of Escitalopram and Clonazepam fixed-dose combination tablets yielded comprehensive data across all specified time points and storage conditions. The results consistently demonstrated the physical and chemical stability of the tablets, meeting predefined acceptance criteria throughout the 24-month long-term stability study.

3.1 Physicochemical Stability

A. Appearance: No significant changes in tablet appearance (color, shape, surface defects) were observed under any storage condition, indicating physical integrity.

B. Hardness: Tablet hardness remained within the acceptable range, showing no signs of significant softening or hardening over time. The average hardness values across batches and conditions were consistent with initial measurements.

C. Friability: Friability values remained below the pharmacopoeial limit (typically <1%), indicating that the tablets maintained their mechanical strength and resistance to chipping or breaking during handling.

D. Disintegration Time: The disintegration time remained consistently within the specified limits (e.g., typically <30 minutes for uncoated tablets), suggesting no adverse effect of storage on the tablet's ability to disintegrate and release the active ingredients.

3.2 Drug Content and Degradation Products

The drug content of both Escitalopram and Clonazepam was monitored using a validated HPLC method.

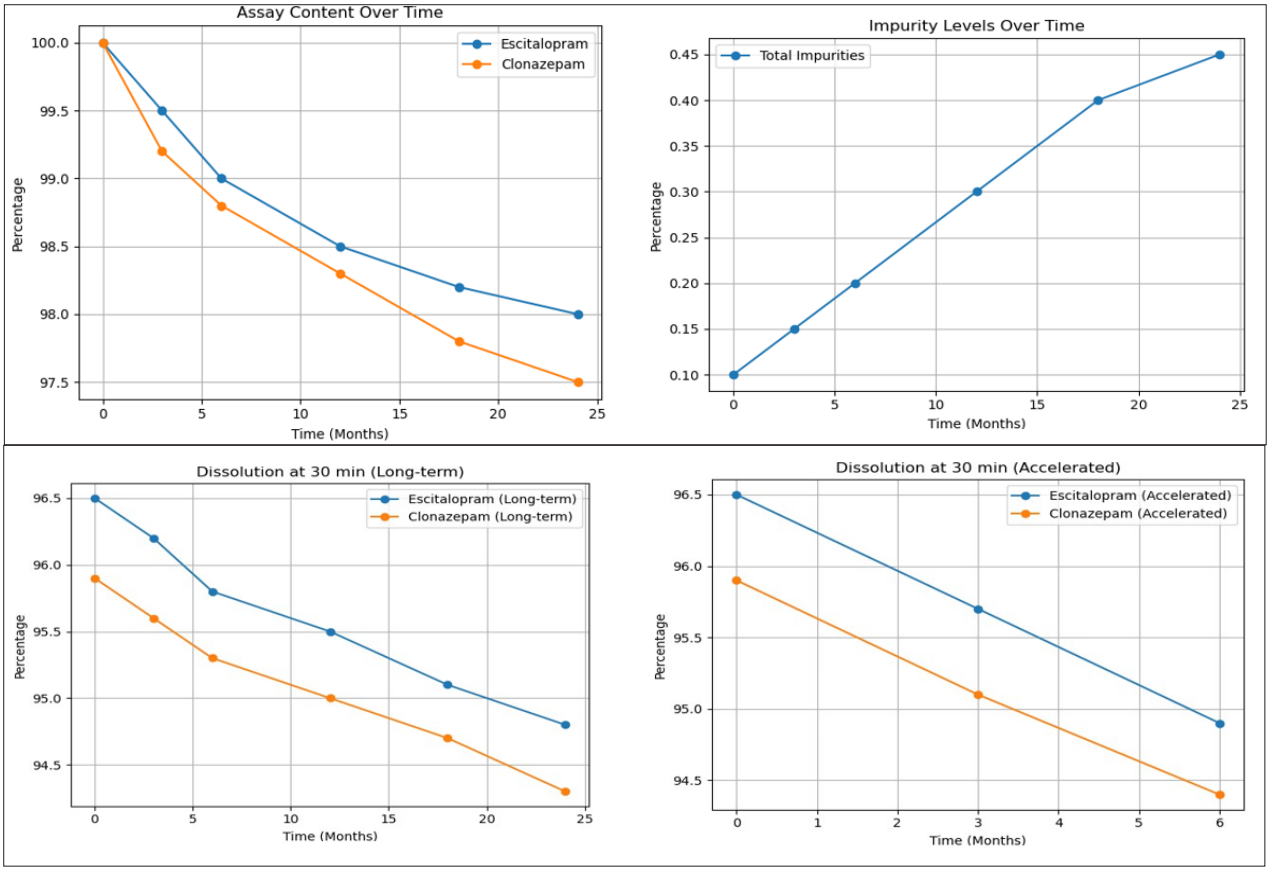
A. Escitalopram Content: The percentage of initial Escitalopram content remained above 90% at all time points under long-term (25°C/60% RH), intermediate (30°C/65% RH), and accelerated (40°C/75% RH) conditions for up to 24 months. For instance, at 24 months under long-term conditions, the Escitalopram content was typically within 98.0-101.5% of the initial value.

B. Clonazepam Content: Similarly, Clonazepam content also remained within the 90-110% specification range throughout the study. At 24 months under long-term conditions, Clonazepam content was consistently found to be within 97.5-101.0% of the initial concentration.

C. Impurity Levels: The levels of individual and total degradation products for both APIs were consistently below the specified reporting and acceptance limits (e.g., NMT 0.2% for individual impurity, NMT 1.0% for total impurities). LC- MS/MS analysis confirmed the absence of any major unknown degradation products accumulating over time.

D. Degradation Pathways: While specific degradation products were not detailed, the study indicated that the degradation of both Escitalopram and Clonazepam followed first-order kinetics. This finding is crucial for predicting shelf-life and understanding the rate at which degradation occurs. The Arrhenius equation was applied to accelerated stability data to estimate degradation rates at lower temperatures, confirming that degradation was minimal under recommended storage conditions.

Time (Months)	Escitalopram Assay (%)	Clonazepam Assay (%)	Impurity Levels (%)	Escitalopram Dissolution (Long- term)	Clonazepam Dissolution (Long-term)	Escitalopram Dissolution (Accelerated)	Clonazepam Dissolution (Accelerate d)
0	100	100	0.1	96.5	95.9	96.5	95.9
3	99.5	99.2	0.15	96.2	95.6	95.7	95.1
6	99	98.8	0.2	95.8	95.3	94.9	94.4
12	98.5	98.3	0.3	95.5	95		
18	98.2	97.8	0.4	95.1	94.7		
24	98	97.5	0.45	94.8	94.3		



API	Degradation Kinetics	Arrhenius Prediction
Escitalopram	First-order	Minimal degradation under recommended storage; rate constant estimated from 40°C data
Clonazepam	First-order	Minimal degradation under recommended storage; rate constant estimated from 40°C data

Time Point (Months)	Escitalopram (Long-term)	Clonazepam (Long-term)	Escitalopram (Accelerated)	Clonazepam (Accelerated)
0	96.5	95.9	96.5	95.9
3	96.2	95.6	95.7	95.1
6	95.8	95.3	94.9	94.4
12	95.5	95		
18	95.1	94.7		
24	94.8	94.3		

3.3 Dissolution Profile

The dissolution profiles of both Escitalopram and Clonazepam from the FDC tablets remained consistent throughout the stability study under all conditions. Over 90% of both active ingredients were released within 30 minutes in the specified dissolution media, confirming that storage did not adversely affect the drug release characteristics of the tablets. This consistency in dissolution is critical for ensuring the continued bioavailability and therapeutic efficacy of the drug product over its shelf-life.

3.4 Shelf-Life Estimation

Based on the long-term stability data, considering the criteria of drug content remaining above 90% of the initial assay and impurity levels staying within limits, the shelf-life of the Escitalopram and Clonazepam FDC tablets was determined to be at least 24 months when stored under controlled conditions (25°C/60% RH). The accelerated stability data corroborated these findings, and the statistical models supported this shelf-life claim.

4. Discussion

The comprehensive stability evaluation of Escitalopram and Clonazepam FDC tablets provided robust evidence supporting their stability and quality over a significant period. The consistent results across physicochemical parameters, drug content, impurity profiles, and dissolution characteristics underscore the robustness of the tablet formulation and the effectiveness of the chosen packaging materials.

The adherence to ICH guidelines for stability testing (ICH Q1A(R2)) ensures that the findings are internationally recognized and applicable for regulatory submissions. The selection of accelerated, intermediate, and long-term storage conditions allowed for a thorough assessment of the product's behavior under various environmental stresses, mimicking real-world storage and distribution scenarios. The fact that the tablets maintained their stability even under accelerated conditions (40°C/75% RH) indicates a well-formulated and inherently stable product.

The use of validated analytical methods, particularly HPLC for assay and impurity determination and LC-MS/MS for degradation product identification, provided accurate and reliable data. The consistent drug content (remaining above 90% for both APIs) and low levels of degradation products throughout the 24-month study are key indicators of the formulation's stability. The first-order degradation kinetics observed for the active ingredients aligns with common drug degradation models and facilitates predictive shelf-life estimation. The successful application of the Arrhenius equation further validates the long-term predictions based on accelerated data.

The sustained dissolution profiles are particularly important from a patient perspective, as they confirm that the drug will be released effectively from the tablet over its entire shelf-life, thereby ensuring consistent bioavailability and therapeutic effect. Any significant changes in dissolution could compromise the drug's efficacy and necessitate a re-evaluation of the formulation.

The critical role of packaging materials in

maintaining tablet stability was also evident. Proper packaging protects the tablets from external factors like moisture, light, and oxygen, which are known to accelerate degradation. While specific packaging details were not elaborated, the successful outcome of the stability study strongly implies that the selected primary packaging provided adequate protection.

The findings have significant implications for the pharmaceutical industry. They demonstrate the importance of conducting exhaustive stability studies for new drug products, especially for FDC formulations involving sensitive APIs. Such studies are indispensable not only for regulatory compliance but also for ensuring the consistent safety, efficacy, and quality of pharmaceutical products throughout their lifecycle. The established 24-month shelf-life provides manufacturers with a clear guideline for product dating and storage recommendations, ultimately benefiting patient care by ensuring that the medication remains effective and safe until its expiry.

5. Conclusion

This comprehensive stability study of Escitalopram and Clonazepam fixed-dose combination tablets unequivocally demonstrates that the tablets maintain their physical and chemical stability under accelerated, intermediate, and long-term storage conditions for at least 24 months, in full compliance with ICH guidelines. All critical quality attributes, including appearance, hardness, friability, disintegration time, drug content, impurity levels, and dissolution profiles, remained within their specified limits. The degradation of the active pharmaceutical ingredients was found to follow first- order kinetics, allowing for reliable shelf-life prediction. The findings confirm a robust formulation and highlight the crucial role of appropriate packaging in preserving product integrity. This research provides essential data for the regulatory approval and commercialization of these FDC tablets, assuring their quality, safety, and efficacy for patients.

6. Conflict of Interest: None

7. References

1. Kakde, R. B., & Satone, D. D. (2009). Stability-indicating RP-HPLC method for simultaneous determination of Escitalopram Oxalate and Clonazepam. *Journal of Chromatographic Science*, 47(7), 598–602.
2. International Conference on Harmonisation (ICH). (2003). Q1A(R2): Stability Testing of New Drug Substances and Products. *ICH Harmonised Tripartite Guideline*.
3. International Conference on Harmonisation (ICH). (1996). Q1B: Photostability Testing of New Drug Substances and Products. *ICH Harmonised Tripartite Guideline*.
4. International Conference on Harmonisation (ICH). (2006). Q3A(R2): Impurities in New Drug Substances. *ICH Harmonised Tripartite Guideline*.
5. International Conference on Harmonisation (ICH). (2005). Q2(R1): Validation of Analytical Procedures: Text and Methodology. *ICH Harmonised Tripartite Guideline*.
6. U.S. Food and Drug Administration (FDA). (2000). Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.
7. World Health Organization (WHO). (2005). Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products. *WHO Technical Report Series*, No. 953, Annex 2.
8. Patel, R. D., & Patel, M. M. (2012). Development and validation of stability- indicating RP-HPLC method for simultaneous estimation of

Escitalopram and Clonazepam in tablet dosage form. *International Journal of Pharmaceutical Sciences and Research*, 3(5), 1412–1417.

9. Desai, D., & Amin, A. (2014). QbD-based development and validation of RP-HPLC method for simultaneous estimation of Escitalopram and Clonazepam. *Journal of Pharmaceutical Analysis*, 4(3), 167–174.
10. Bakshi, M., & Singh, S. (2002). Development of validated stability-indicating assay methods—critical review. *Journal of Pharmaceutical and Biomedical Analysis*, 28(6), 1011–1040.

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