STABILITY STUDIES OF FINISHED PRODUCT OF DRY MEDICAL CANNABIS FLOWER: ANALYSIS OF QUALITY AND CANNABINOID CONTENT

Chedomir Cekikj
Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
cedocekic@hotmail.com
Hristina Cekikj
Purely Plant GmbH, Skopje, North Macedonia, cekic.hristina@gmail.com
Blagoj Nikolov
Purely Plant GmbH, Skopje, North Macedonia, nikolov.blagoj@gmail.com
Bistra Angelovska
Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia,
bistra.angelovska@ugd.edu.mk

Abstract: With the increased therapeutic use of medical cannabis, ensuring quality, safety, and efficacy throughout shelf life is essential. This study evaluates stability of dry medical cannabis flower under different storage conditions, focusing on physicochemical quality and cannabinoid content changes over time. Three production batches (P050022, P050072, P050202) of THC-dominant dry cannabis flower (Chemotype I, Total THC >20%) produced at Purely Plant GmbH, were subjected to long-term stability studies (LTSS: 25°C ± 2°C, 60% ± 5% RH) and accelerated stability studies (ACCSS: 40°C ± 2°C, 75% ± 5% RH) over a 3-month period in accordance with ICH Q1A(R2) guidelines. Cannabinoid content was analyzed using validated HPLC-UV method based on German Pharmacopoeia (DAB) Cannabis flos monograph. Initial Total THC content was 23.84 ± 1.40% (n=3 batches). Under LTSS conditions, Total THC showed degradation of 7.27-9.40% after 3 months, while THCA decarboxylation reached 25-29%, with calculated half-lives of 21-28 months. Under ACCSS conditions, THCA decarboxylation was nearly complete (>97%) after 1 month, with Total THC degradation of 6.94-16.23%. Kinetic analysis revealed rate constants k = 0.025-0.033 month^{-1} for LTSS and Q10 factor of 1.37. CBN formation as oxidative degradation marker remained below specification (<1.0%) under all conditions, confirming effectiveness of nitrogen atmosphere packaging (PET/ALU/PE). Microbiological purity and heavy metal content remained within pharmacopeial limits. This study demonstrates acceptable stability under recommended storage conditions (≤25°C, RH 55-65%, protected from light, inert atmosphere), supporting minimum 12-month shelf life with potential extension to 24 months pending continued studies.
Keywords: stability studies, medical cannabis, cannabinoids, HPLC-UV, ICH Q1A(R2), GMP.

1. INTRODUCTION

Medical cannabis represents an increasingly significant therapeutic resource in contemporary pharmacotherapy, with demonstrated efficacy in treating various medical conditions including chronic pain, multiple sclerosis, epilepsy, and chemotherapy-induced nausea and vomiting (National Academies, 2017; Whiting et al., 2015). Cannabis sativa L. contains hundreds of bioactive compounds, among which the most significant are cannabinoids – a group of terpenophenolic compounds that exert their effects through the endocannabinoid system. The main therapeutically relevant cannabinoids include Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), and their acidic precursors THCA and CBDA (ElSohly et al., 2017; Pertwee, 2008).

Stability studies represent a fundamental part of pharmaceutical development and registration according to regulatory requirements of the European Medicines Agency (EMA) and International Council for Harmonisation (ICH). The recently revised ICH Q1 consolidated guideline (ICH Expert Working Group, 2025) provides updated stability testing requirements, while medicinal cannabis quality standards continue to evolve through European Pharmacopoeia monographs and GMP requirements (Kühn-Hebecker, 2025). For herbal medicinal products, including medical cannabis, stability studies are particularly important due to the complexity of the plant matrix and the sensitivity of active components to environmental factors such as temperature, humidity, light, and oxygen. Cannabinoids undergo several chemical degradation pathways: THCA undergoes thermally-induced decarboxylation to form psychoactive THC (activation energy ~85 kJ/mol), while oxidative degradation of THC leads to CBN formation through aromatization of the cyclohexene ring (Wang et al., 2016; Trofin et al., 2016).

The Republic of North Macedonia adopted medical cannabis legislation in 2016, enabling cultivation, production, and export under strict regulatory requirements aligned with EU GMP standards. Purely Plant GmbH is a certified facility producing dry medical cannabis flower for the European market. This study aims to establish and validate a

stability testing system for finished product from dry medical cannabis flower in accordance with ICH Q1A(R2) guidelines and EU GMP Annex 7 requirements, providing scientific basis for determining shelf life and defining optimal storage conditions.

2. MATERIALS AND METHODS

Materials. Three production batches of dry medical cannabis flower (Cannabis sativa L. var. indica, Chemotype I, THC-dominant >20%) were produced at Purely Plant GmbH, Skopje, North Macedonia: Batch P050022 (April 2025, 200.00 kg), P050072 (June 2025, 218.00 kg), and P050202 (September 2025, 300.00 kg). Plants were cultivated under controlled indoor conditions (temperature 24-26°C day/20-22°C night, RH 40-60%, LED lighting 600-900 μmol/m²/s, hydroponic system). Flowers were dried at 18-22°C, RH 50-60% for 7-10 days to moisture content <12%, cured for minimum 2 weeks, trimmed, and packaged in heat-sealed PET/ALU/PE laminated pouches under nitrogen atmosphere (N_2 >90%, O_2 <10%). Each unit contained 400 g of finished product.

Study Design. Stability studies were designed according to ICH Q1A(R2) and EU GMP Annex 7 requirements. Long-term stability studies (LTSS) were conducted at 25°C ± 2°C and 60% RH ± 5% RH (Climate Zone II conditions) with testing at 0, 1, 2, and 3 months (planned continuation to 24 months). Accelerated stability studies (ACCSS) were conducted at 40°C ± 2°C and 75% RH ± 5% RH with testing at 0, 1, 2, and 3 months. Calibrated and qualified stability chambers (Memmert HPP750eco) with continuous temperature and humidity monitoring were used. Three units (n=3) from each batch were removed at each time point for analysis.

Analytical Methods. Cannabinoid content was determined by validated HPLC-UV method based on DAB Cannabis flos monograph using Shimadzu Cannabis Analyser LC-2050C 3D system following validated HPLC-based quality control methodology for medicinal cannabis (Ahmad et al., 2022) with NexLeaf CBX column (150 × 4.6 mm, 2.7 μm). Certified reference standards (Cerilliant) for THCA, THC, CBDA, CBD, CBN, and CBG were used. Total THC was calculated as: Total THC = (THCA × 0.877) + Δ9-THC. Loss on drying was determined gravimetrically per Ph. Eur. 2.2.32 (105°C to constant mass, specification <12%). Microbiological testing followed Ph. Eur. 2.6.12/2.6.13 (TAMC ≤10^5 CFU/g, TYMC ≤10^4 CFU/g, specified pathogens absent). Heavy metals were determined by ICP-MS per Ph. Eur. 2.4.20 and ICH Q3D limits. Headspace gas analysis (O_2, N_2) verified packaging integrity.

Kinetic and Statistical Analysis. Degradation kinetics were analyzed assuming first-order kinetics. Rate constants (k) were calculated from the slope of $\ln(C/C_0)$ vs. time plots. Half-life was calculated as $t_{½} = \ln(2)/k$. Q10 factor was calculated as $Q10 = (k_{40}/k_{25})^{(10/15)}$. Statistical analysis included paired t-test for LTSS vs. ACCSS comparison, one-way ANOVA for time effect evaluation, and linear regression analysis.

3. RESULTS AND DISCUSSION

Initial Characterization. Initial characterization (Table 1) revealed high THCA content (25.00-28.27%) characteristic of Chemotype I cannabis, with low Δ9-THC (0.77-0.93%) indicating minimal decarboxylation during drying and curing processes. Total THC ranged from 22.89% to 25.45% (mean 23.84 ± 1.40%, RSD 5.87%), demonstrating good batch-to-batch consistency meeting EU GMP requirements. CBD, CBDA, and CBN were below the limit of quantification in all batches, consistent with THC-dominant chemotype. Loss on drying (6.11-6.64%) was well within specification (<12%). Microbiological analysis confirmed compliance with pharmacopeial limits for herbal preparations intended for inhalation, and heavy metals were within ICH Q3D specifications. Headspace analysis confirmed packaging integrity with O_2 <10% and N_2 >90%.

Table 1. Initial characterization of production batches at T=0

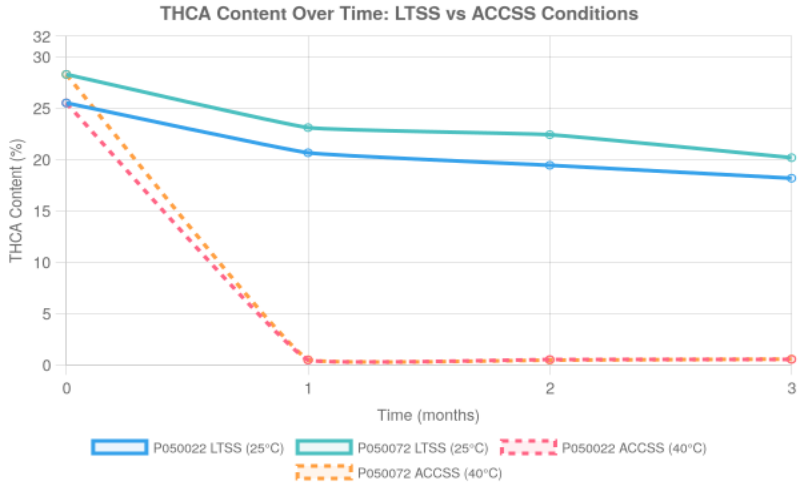
Parameter	P050022	P050072	P050202	Mean ± SD	RSD (%)
THCA (%)	25.49	28.27	25.00	26.25 ± 1.54	5.89
Δ9-THC (%)	0.93	0.77	0.77	0.82 ± 0.12	14.49
Total THC (%)	23.19	25.45	22.89	23.84 ± 1.40	5.87
Loss on drying (%)	6.54	6.64	6.11	6.43 ± 0.20	3.06

Source: Authors' elaboration

THCA Decarboxylation. The decarboxylation of THCA to THC showed dramatic temperature dependence (Figure 1). Under LTSS conditions (25°C), THCA decreased gradually from initial values of 25-28% to 18-20% after 3 months, representing 25-29% conversion. Under ACCSS conditions (40°C), decarboxylation was nearly complete (>97%) after only 1 month, with THCA decreasing to <0.5%. This is consistent with first-order to pseudo-zero-order kinetics observed for cannabinoid thermal degradation (Jaidee et al., 2022) and literature activation energy of approximately 85 kJ/mol (Wang et al., 2016). These findings have important implications for therapeutic use –

products intended for vaporization will complete decarboxylation during heating, while the THCA/THC ratio changes during storage should be considered for labeling.

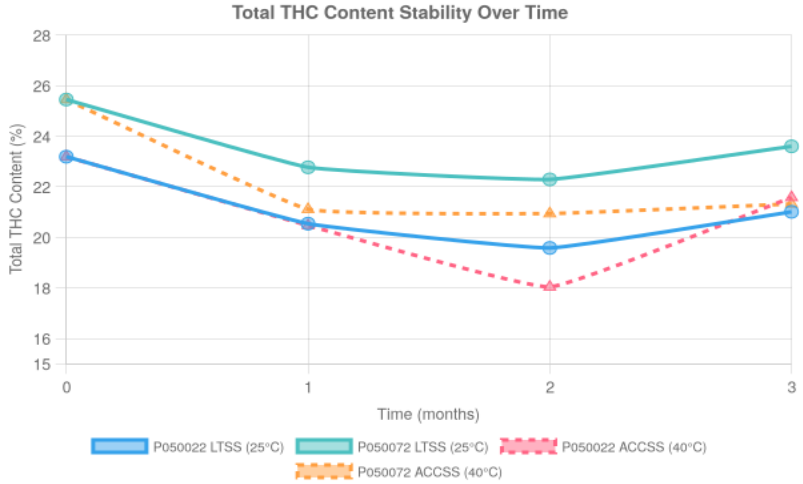
Figure 1. THCA decarboxylation under LTSS (25°C) and ACCSS (40°C) conditions over 3 months



Source: Authors' elaboration

Total THC Stability. Total THC, as the sum of THCA (converted to THC equivalent) and free THC, showed moderate degradation under both conditions (Figure 2, Table 2). Under LTSS, P050022 decreased from 23.19% to 21.01% (9.40% degradation) and P050072 from 25.45% to 23.60% (7.27% degradation). Under ACCSS, degradation was 6.94-16.23%. Calculated half-lives were 21-28 months (LTSS) and 13-18 months (ACCSS). Rate constants k = 0.025-0.033 month^{-1} for LTSS indicate good stability, supporting minimum 12-month shelf life with potential extension to 24 months pending continued studies. The greater variability under ACCSS may reflect differences in the initial plant matrix composition and its susceptibility to thermal stress.

Figure 2. Total THC content stability over time under LTSS and ACCSS conditions



Source: Authors' elaboration

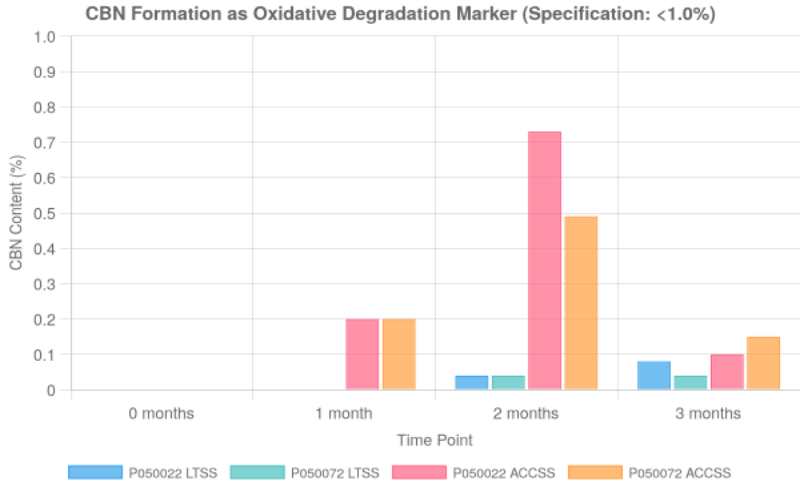
Table 2. Long-term stability study results (LTSS, 25°C/60% RH)

Batch	Parameter	0 months	1 month	2 months	3 months
P050022	THCA (%)	25.49	20.64	19.42	18.16
	Δ9-THC (%)	0.93	2.45	2.55	4.27
	Total THC (%)	23.19	20.54	19.58	21.01
P050072	THCA (%)	28.27	23.09	22.40	20.16
	Δ9-THC (%)	0.77	2.56	2.65	4.74
	Total THC (%)	25.45	22.77	22.29	23.60

Source: Authors' elaboration

CBN Formation and Oxidative Degradation. CBN, as the primary oxidative degradation product of THC, serves as a marker for product aging and improper storage (Figure 3). Under LTSS conditions, CBN reached only 0.04-0.08% at 3 months. Under ACCSS, maximum CBN was 0.73% (P050022, 2 months) and 0.49% (P050072, 2 months). All values remained well below the <1.0% specification, confirming effectiveness of nitrogen atmosphere packaging in preventing oxidative degradation. This is consistent with Lindholst (2010), who demonstrated that inert atmosphere significantly reduces CBN formation. The low oxygen environment (O_2 <10%) maintained by PET/ALU/PE laminated pouches effectively protects cannabinoid integrity.

Figure 3. CBN formation as oxidative degradation marker (specification <1.0%)



Source: Authors' elaboration

Kinetic Parameters and Shelf Life Prediction. Kinetic analysis (Table 3) revealed rate constants of 0.025-0.033 month^{-1} under LTSS, corresponding to half-lives of 21-28 months. The Q10 factor of 1.37 indicates moderate temperature dependence, favorable for practical handling – the product shows acceptable stability even under temperature excursions during transport. Average activation energy of 22.69 kJ/mol is consistent with literature data for oxidative degradation mechanisms. Based on ICH Q1E extrapolation principles and the demonstrated stability profile, a shelf life of 12 months is scientifically justified under the recommended storage conditions, with potential extension to 24 months pending confirmation from ongoing long-term studies.

Table 3. Kinetic parameters of Total THC degradation

Batch	Conditions	k (month^{-1})	t½ (months)	Q10
P050022	LTSS (25°C)	0.0329	21.1	-
P050022	ACCSS (40°C)	0.0376	18.4	1.09
P050072	LTSS (25°C)	0.0252	27.6	-
P050072	ACCSS (40°C)	0.0529	13.1	1.64

Source: Authors' elaboration

4. CONCLUSIONS

This study systematically evaluated the stability of dry medical cannabis flower through studies conducted in accordance with ICH Q1A(R2) guidelines and EU GMP requirements. Key findings demonstrate that THCA

decarboxylation is the primary chemical process during storage, with significant temperature dependence – approximately 25-30% conversion under LTSS (25°C) after 3 months versus >97% conversion under ACCSS (40°C) after 1 month. Total THC showed good stability under LTSS conditions, consistent with recent studies on cannabinoid transformation during long-term storage (El-Khoury et al., 2024). Total THC stability with 7-9% degradation after 3 months and calculated half-lives of 21-28 months, supporting a scientifically justified minimum shelf life of 12 months with potential extension to 24 months. CBN formation remained minimal (<0.1% under LTSS, <0.8% under ACCSS), well below the <1.0% specification, confirming effectiveness of nitrogen atmosphere packaging in protecting against oxidative degradation. Based on these results, recommended storage conditions are: temperature ≤25°C, relative humidity 55-65%, protected from direct light, in original sealed packaging. The kinetic parameters ($k = 0.025\text{-}0.033$ month^{-1}, $Q10 = 1.37$) indicate moderate temperature dependence favorable for practical handling and distribution. This study provides the scientific basis for defining shelf life and storage conditions for GMP-compliant medical cannabis products, contributing to ensuring quality, safety, and efficacy for patients.

ACKNOWLEDGEMENTS

The author expresses sincere gratitude to Prof. Dr. Bistra Angelovska, Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia, for her dedicated mentorship, guidance, and professionalism during the specialization studies. The author also thanks the team at Purely Plant GmbH for providing samples and access to laboratory equipment necessary for conducting this study.

REFERENCES

Ahmad, R., Rehman, M.U., Ahmad, M., & Arafah, A. (2022). Quality control of cannabis inflorescence and oil products: Response factors for the cost-efficient determination of ten cannabinoids by HPLC. Phytochem Anal Acta, 13(3), 1-9. doi:10.4172/2153-0769.1000293

El-Khoury, R., Mansour, R., Kfoury, M., Sarakbi, A., Maroun, R.G., Chidiac, F., Walrant, A., & Louka, N. (2024). Chemometric and predictive modeling of long term cannabinoid transformation in stored Cannabis sativa resin. Sci Rep, 14, 22860. doi:10.1038/s41598-025-03888-7

ElSohly, M.A., et al. (2017). Phytochemistry of Cannabis sativa L. Phytocannabinoids, Vol. 103, pp. 1-36. Springer. doi:10.1007/978-3-319-45541-9_1

ICH. (2003). Q1A(R2): Stability Testing of New Drug Substances and Products. ICH Harmonised Guideline.

ICH. (2005). Q1E: Evaluation of Stability Data. ICH Harmonised Guideline.

Pertwee, R.G. (2008). The diverse CB1 and CB2 receptor pharmacology of plant cannabinoids. Br J Pharmacol, 153(2), 199-215.

ICH Expert Working Group. (2025). ICH Q1 Stability Testing of Drug Substances and Drug Products (Draft). International Council for Harmonisation. Available from: https://database.ich.org/sites/default/files/ICH_Q1EWG_Step2_Draft_Guideline_2025_0411.pdf

Jaidee, W., Siridechakorn, I., Nessopa, S., Wisuitiprot, V., Chaiwangrach, N., Ingkaninan, K., & Waranuch, N. (2022). Kinetics of CBD, Δ9-THC Degradation and Cannabinol Formation in Cannabis Resin at Various Temperature and pH Conditions. Cannabis Cannabinoid Res, 7(4), 537-547. doi:10.1089/can.2021.0004

Kühn-Hebecker, A. (2025). New Quality Standards for Medical Cannabis and CBD. GMP Journal, February 20. Available from: https://www.gmp-journal.com/current-articles/details/new-quality-standards-for-medical-cannabis-and-cbd.html

Lindholst, C. (2010). Long term stability of cannabis resin and extracts. Aust J Forensic Sci, 42(3), 181-190.

National Academies. (2017). Health Effects of Cannabis and Cannabinoids. NAP. doi:10.17226/24625

Trofin, I.G., et al. (2016). Long-term storage and cannabis oil stability. Rev Chim, 63(3), 293-297.

Wang, M., et al. (2016). Decarboxylation study of acidic cannabinoids. Cannabis Cannabinoid Res, 1(1), 262-271.

Whiting, P.F., et al. (2015). Cannabinoids for medical use: A systematic review. JAMA, 313(24), 2456-2473.