Contents lists available at UGC-CARE

International Journal of Pharmaceutical Sciences and Drug Research

[ISSN: 0975-248X; CODEN (USA): IJPSPP]

journal home page : http://ijpsdronline.com/index.php/journal

Research Article

Forced Degradation Profiling of Cilnidipine: A Multi-technique Characterisation using UHPLC–MS, HRMS, Prep-HPLC, and NMR

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ARTICLE INFO

Article history:
Received: 07 June, 2025
Revised: 14 October, 2025
Accepted: 26 October, 2025
Published: 30 November, 2025
Keywords:
Cilnidipine, method development, NMR, HRMS
DOI:
10.25004/IJPSDR.2025.170601

ABSTRACT

Currently, no forced degradation studies for Cilnidipine are available. Therefore, it is essential to monitor its stability under various conditions. The main medical disorders that Cilnidipine is used to treat are hypertension, which is high blood pressure, and angina, also known as chest discomfort. Cilnidipine underwent forced degradation experiments, and sample analysis was performed by liquid chromatography-mass spectrometry (LC–MS). As per regulatory guidelines, the sample was subjected to hydrolytic, oxidative, thermal, and photolytic stress conditions. The drug remained stable when exposed to oxidative, thermal, and photolytic conditions; however, it underwent degradation under acidic and alkaline environments. The major deterioration, Impurity components formed during the forced degradation investigation, have been isolated to identify and quantify compounds. In alkaline conditions, three degradation products, designated as DP-1, DP-2, and DP-3, were formed, whereas acidic conditions yielded only one product (DP-4). A semi-preparative HPLC purification technique was used to isolate the identified degradation components. The compounds were characterised through high-resolution mass spectrometry (HRMS) and nuclear magnetic resonance (NMR) analyses, which included ^{1}H NMR, ^{13}C NMR, heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) techniques.

Introduction

One of the main causes of death globally is disease. Cilnidipine (CDP) serves as a therapeutic agent for individuals with heart-related disorders, including hypertension and angina.[1,2] It is a member of the group of medications called calcium channel blockers. [3,4] By inhibiting both N-type and L-type calcium channels, cilnidipine induces dilation of arterioles and venules, thereby lowering capillary bed pressure.[5,6] Consequently, it seems that continuous treatment of vital hypertension with N-type calcium channel antagonists is safe and effective.[7,8] Cilnidipine's distinct qualities, in particular, might offer a fresh approach to treating a sympathetic hyperactivity-related cardiovascular disease. [9,10] India, Japan, Nepal, China, and Korea have approved the use of CDP to treat hypertension.[11-14]

Cilnidipine's physical appearance is a powdery white solid, and it is marketed in dosages of 5 mg, 10 mg, and 20 mg. It retails in India under Clinblue, Cilacar, and Cinod, among others. [15,16] The IUPAC name of the CDP is 3-cinnamyl 5-(2-methoxyethyl) 2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate.

Pharmaceutically active compounds (APIs) are susceptible to deterioration due to their reactivity in different conditions.[17-19] Hence, a detailed investigation is necessary to understand forced or stressed degradation, the process

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

by which drugs break down under different conditions. [20,21] These studies' findings help clarify the generation of degradation products (DPs) and the breakdown route by contributing new guidance on both. The study also clarifies how API maintains its stability. Further to the ingredients used, this information is helpful in the formulation and storage of the medication. Additionally, the guidelines Q1A, Q1B, and Q2B issued by the International Council for Harmonisation (ICH) highlight the significance of stressed or forced degradation. [22,23]

A comprehensive literature review shows that similar investigations were conducted on many different APIs utilising modern analytical techniques. [24,25] However, no research of this kind has been done on CDP. The DPs were recognised and isolated, a method was developed, and examined through various analytical procedures for characterisation. Accordingly, the present study aimed to employ UHPLC-MS, HRMS, and NMR (1D and 2D) investigations to demonstrate in a straightforward way how the DPs are structured, evaluate the molecule's stability, and gain insight into drug packaging and storage.

Materials And Methods

Chemicals and Reagents

One of the pharmaceutical companies in Hyderabad provided a gift sample of Cilnidipine (API). Analytical-grade solvents and reagents were selected for the experiments. HPLC-grade methanol, acetonitrile, and formic acid, as well as AR-grade hydrochloric acid, sodium hydroxide, and hydrogen peroxide, were purchased from Merck India Ltd. At the same time, dimethyl sulfoxide-d6 was sourced from Cambridge Isotope Laboratories. Water was filtered and utilized using the Millipore Milli-Q lab water purification system.

Instrumentation and Software

UHPLC with DAD was coupled to a dual polarity electrospray ionisation (ESI) mode Waters SQD mass detector, with a detection range of 100–1500 m/z. Key parameters: 3.5 kV capillary voltage, 140°C source, 350°C desolvation, gas flow rates were adjusted to 650 L/h for desolvation and 50 L/h for the cone. Chromatography run time was 4 min with 0.5 µL injection at 10°C, controlled by MassLynx 4.2 software. Isolation of degradation products was achieved using Waters modules (pump 2545, autosampler 2707, detector 2489) operated with ChromScope 2.1 software. HRMS was performed on a Thermo Fisher Q Exactive Orbitrap coupled with a Dionex Ultimate 3000 LC system using Xcalibur software. NMR spectra were acquired on a Bruker Avance Neo 400 MHz spectrometer with Topspin 4.11 software. A Shimadzu AP-AD balance was employed for sample weighing.

Method development

To optimise resolution between degradation products and Cilnidipine (CDP), various UPLC columns (YMC Triart C18, Acquity BEH C18, etc.) and buffer combinations (formic acid, trifluoracetic acid, ammonium bicarbonate) with organic solvents like acetonitrile and methanol were tested.

Table 1: HRMS data for CDP and all DPs.

Product name	Molecular formula	Calculated mass (m/z)	Obtained mass (m/z)	Fragments (m/z)
Cilnidipine	$C_{27}H_{28}N_2O_7$	493.1930	493.1971	434.1478, 376.1271, 117.0704, 59.0497
DP-1	$C_{14}H_{12}N_2O_4$	273.0831	273.0884	-
DP-2	$C_{18}H_{20}N_2O_7$	377.1304	377.1348	317.0774, 59.0497
DP-3	$C_{24}H_{22}N_2O_6$	435.1511	435.1554	317.0774, 117.0704
DP-4	$C_{17}H_{18}N_2O_5$	331.1249	331.5300	273.0875, 59.04977

High-Resolution Mass Spectrometry

Thermo Fisher Q Exactive Orbitrap mass spectrometer with an ESI source, in combination with a Dionex Ultimate 3000 LC system fitted with a PDA detector, was employed for HRMS analysis and operated via Xcalibur software. The instrument was operated with a spray voltage of 3500 V, a capillary temperature of 270°C, an auxiliary gas flow rate of 14, an auxiliary heater temperature of 440°C, a sheath gas flow rate of 53, and sweep gas 3. Chromatographic conditions were consistent with those used for UHPLC–MS, with the exception of a flow rate set at 0.7 mL/min. The mass fragmentation profiles of all DPs are summarised in Table 1.

Method of Degradation

In accordance with ICH stability guidelines, the drug was exposed to acid, alkali, oxidative, thermal, and photolytic stress conditions to evaluate its degradation profile. A 10 mg/mL CDP stock solution in 100% ethanol was prepared for acid and base degradation using 1.0 N hydrochloric acid (HCl) and 1.0 N sodium hydroxide (NaOH). The solution was stirred at room temperature and 70°C, and samples were extracted, neutralised, and diluted to 100 µg/mL for analysis. Oxidative degradation was carried out by diluting CDP with 30% hydrogen peroxide, and the mixture was stirred at room temperature. Thermal degradation was performed by exposing 20 mg of CDP to 100°C for 48 hours. Photodegradation was studied by exposing 20 mg of CDP to UV light at 254 nm for 48 hours.

Table 2: Gradient program for isolation of basic degradation products

Time (min)	*Flow (mL/min)*	*% of pump A*	*% of pump B*
00.01	15	90	10
02.00	15	90	10
12.00	15	40	60
12.50	15	2	98
15.00	15	2	98
15.50	15	90	10
20.00	15	90	10

Table 3: Gradient program for isolation of acidic degradation products

Time (min)	*Flow (mL/min)*	*% of pump A*	*% of pump B*
00.01	18	90	10
02.00	18	90	10
12.00	18	10	90
12.50	18	2	98
15.00	18	2	98
15.50	18	90	10
20.00	18	90	10

Optimisation of Chromatographic Conditions

Evaluation across multiple trials revealed that 0.05% formic acid in water and acetonitrile, together with YMC Triart C18, Acquity BEH C18, and Cortex UPLC C18 columns, achieved desirable results, while other columns showed unsatisfactory peak shapes or lower resolution. The YMC Triart C18 (30 × 2.1 mm, 1.9 µm) column was tested under various gradient settings and flow rates. Resolution of CDP along with all degradation products was achieved under a binary gradient elution of 0.05% formic acid in water and acetonitrile at a flow rate of 0.6 mL/min and a column temperature of 35°C. The eluents were monitored by PDA detection.

Sample Preparation for Purification

CDP was subjected to heat, light, oxidation, acidic, and alkaline conditions, with degradation observed in both acidic and basic environments. The alkaline-degraded sample was neutralised using 5 N hydrochloric acid (HCl) and lyophilized to produce a free solid. Following neutralization with saturated ammonium bicarbonate, the acid-degraded sample was lyophilized, yielding a crude solid. Both stress samples were dissolved in 3–4 mL of mobile phase and subjected to preparative HPLC purification.

Isolation of Degradation Products

Under basic stress, degradation resulted in 3, 7, and 9% impurity levels. An XSelect CSH Phenyl-Hexyl (250 × 19 mm, 5 µm) column was employed for isolation, utilising

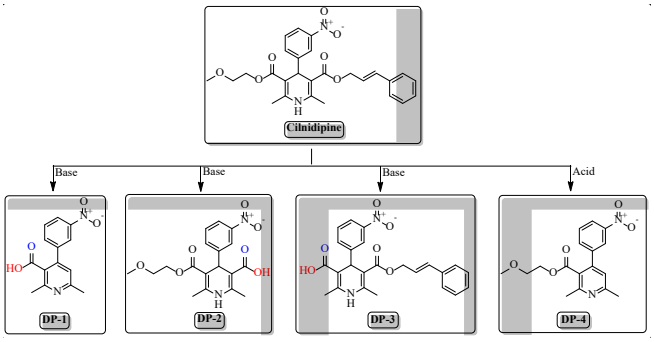

Fig. 1: Structures of cilnidipine and its degradation products.

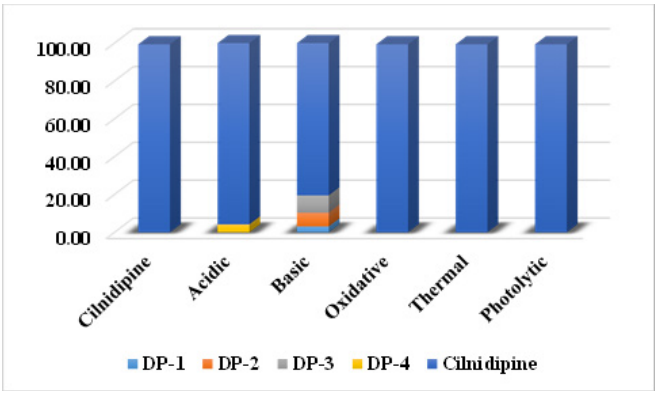

Fig. 2: Degradation trend of cilnidipine.

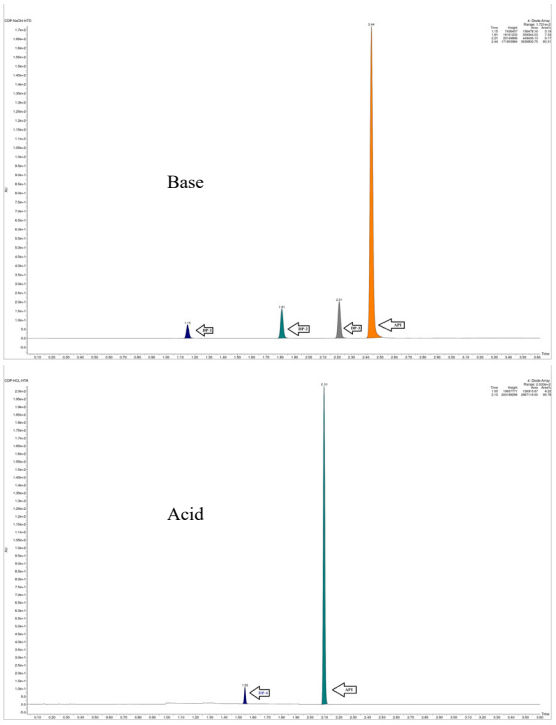

Fig. 3: Degradation behaviour of cilnidipine in acid hydrolysis.

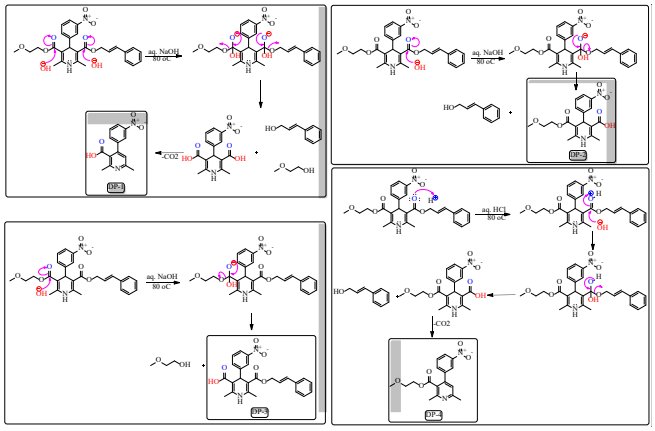

Fig. 4: Feasible mechanism under base and acid degradation.

Table 4: Degradation conditions and outcomes.

Conditions	*% of degradation products and Cilnidipine*				
	DP-1	*DP-2*	*DP-3*	*DP-4*	*Cilnidipine*
Cilnidipine	-	-	-	-	99.37
Acidic (1N HCl stirring at 70°C up to 48 h)	-	-	-	4.22	95.78
Basic (1N NaOH stirring at 70°C up to 48 h)	3.14	7.27	9.10	-	80.49
Oxidative (30% H2O2 stirring at rt up to 48 h)	-	-	-	-	99.37
Thermal (exposed to 100 ◦ C up to 48 h)	-	-	-	-	99.37
Photolytic (exposed at 254 nm for 48 h)	-	-	-	-	99.37

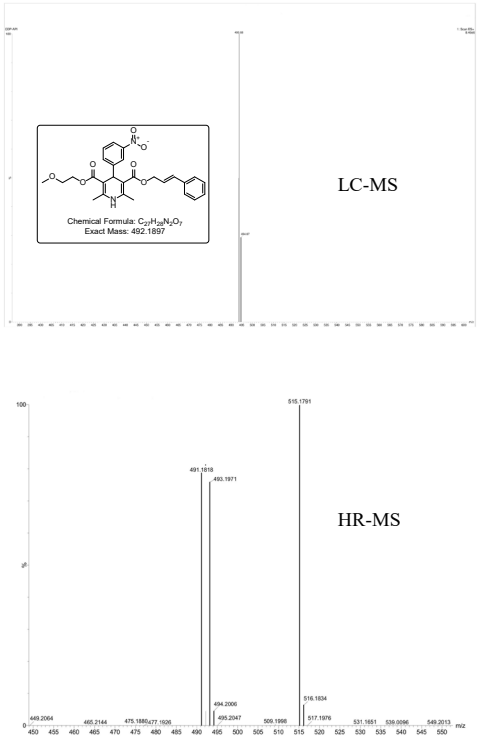

Fig. 5: LC-MS and HR-MS data of cilnidipine.

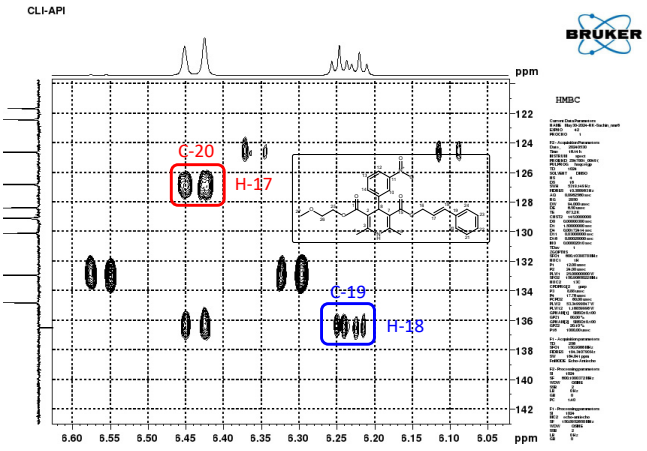

Fig. 6: Heteronuclear multiple bond correlation (HMBC) spectrum of cilnidipine.

10 mM ammonium bicarbonate in water and acetonitrile as the mobile phase, following the gradient in supporting information Table 2. Exposure to acidic stress led to 4% degradation. The corresponding degradation product was isolated on an Inertsil ODS-3 (250 × 20 mm, 5 µm) column with 0.1% formic acid in water and acetonitrile as the mobile phase, as detailed in Supporting Information Table 3. After successive injections, fraction collection was carried out according to the UV detector response, and UHPLC-MS confirmed the molecular weights. The collected fractions were lyophilised.

Results And Discussion

The outcomes of each stress study were carefully determined by analysing individual samples using mass spectrometry (MS), specifically UHPLC-MS and HRMS, to track the formation of the degradation products over time. Detailed analysis revealed four significant DPs, which were

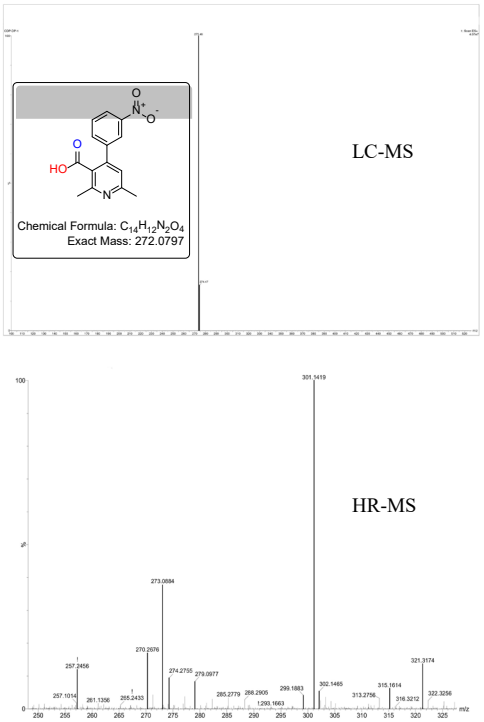

Fig. 7: LC-MS and HR-MS data of DP-1.

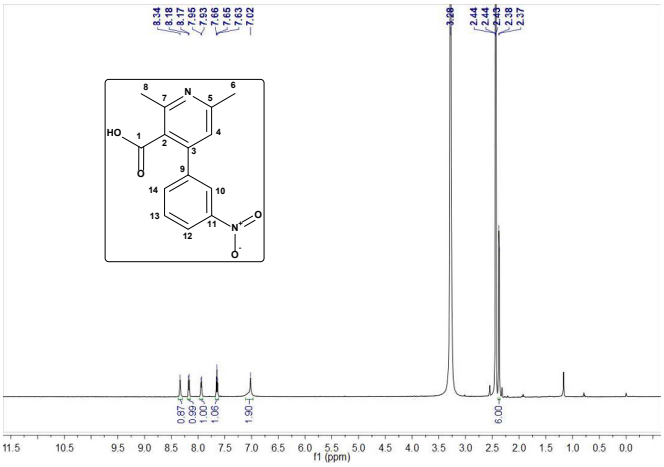

Fig. 8: [1]HNMR data of DP-1.

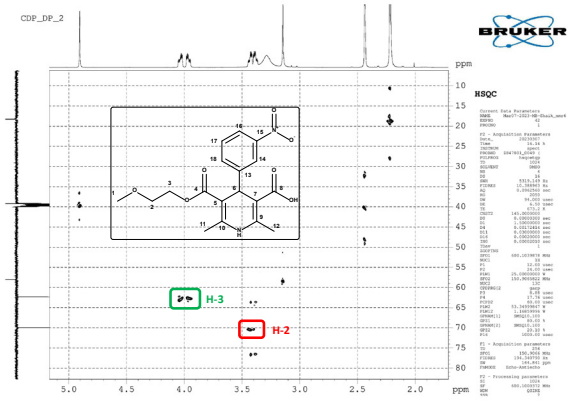

Fig. 10: HSQC data of DP-2.

separated and characterised using multiple analytical techniques: UHPLC-MS for their initial identification, HRMS for high-resolution mass analysis, and NMR (both 1D and 2D) for detailed structural elucidation.

The degradation studies showed that the acid and base stress conditions resulted in the formation of four major DPs. These conditions were particularly effective in promoting degradation, with noticeable shifts in molecular structures. Isolation of four DPs was achieved, followed by structural confirmation through comparison with the standard CDP molecule and using their mass fragmentation patterns. Each of these degradation products showed distinct chromatographic behaviour, with varying MS data providing retention times and corresponding m/z ratios. Fig. 1 provides a visual representation of the proposed structures by which acid and base degradation of the CDP leads to the formation of these four DPs. The reaction pathways suggest that the degradation of CDP involves cleavages at specific sites of the molecule, leading to products with different molecular weights. The identified DPs could potentially serve as markers for stability testing and could provide insights into the degradation pathway of the compound, which is essential for pharmaceutical development and formulation stability studies.

The stability of the CDP molecule was evaluated under various stress conditions, revealing that it was found to be resistant to degradation under oxidative, thermal, and photolytic conditions, as no significant degradation occurred under these conditions. This supports the conclusion that CDP maintains its integrity in oxidative, heat, and UV-exposed environments. However, the CDP molecule exhibited hydrolyzability under acidic and basic conditions, where degradation was observed.

When CDP was stirred in solutions of 1.0 N hydrochloric acid and 1.0 N sodium hydroxide maintained at 70°C for up to 48 hours, the degradation was more pronounced in the alkaline environment. The base hydrolysis resulted in 20% degradation, while the acid hydrolysis led to only

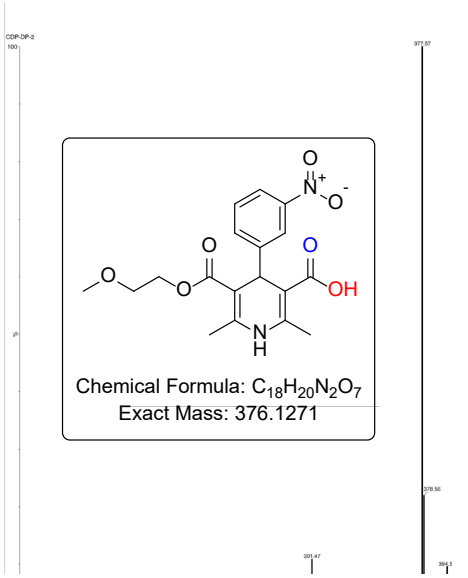

Fig. 9: LC-MS and HR-MS data of DP-2.

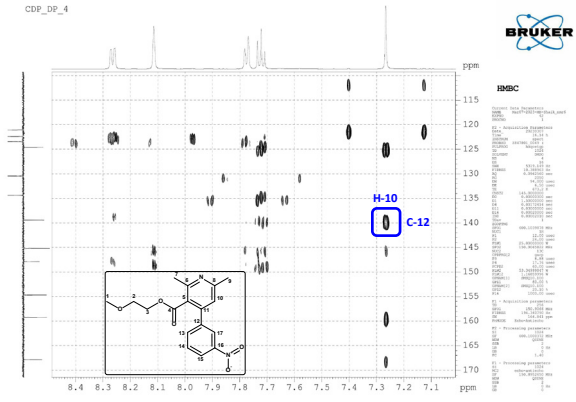

Fig. 11: HMBC data of DP-2.

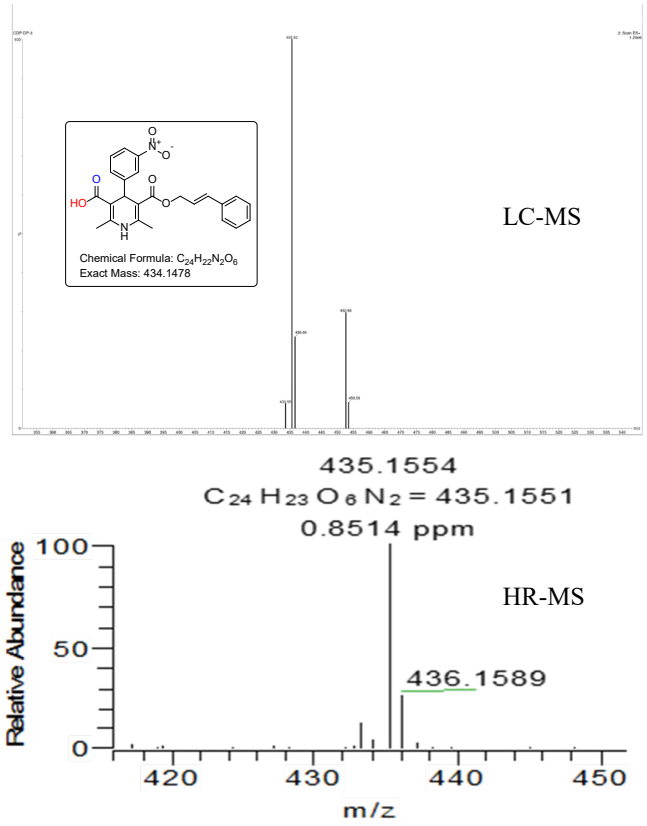

Fig. 12: LC-MS and HR-MS data of DP-3.

4% degradation, as shown in Fig. 2. In the supporting information, Table 4 summarises the degradation conditions and outcomes. The degradation chromatograms for base and acid hydrolysis are depicted in Fig. 3.

Under alkaline stress, three degradation products (DP-1, DP-2, and DP-3) were observed, while acidic conditions yielded a single product (DP-4). These findings suggest that the degradation mechanism under acidic and basic stress differs. Furthermore, temperature was found to influence the degradation rate significantly. An increase in temperature led to a higher degradation rate and greater formation of degradation products, indicating that higher temperatures accelerate the degradation process.

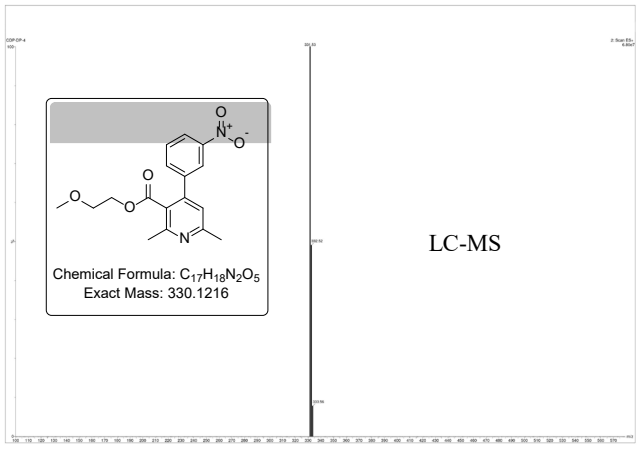

Fig. 14: LC-MS and HR-MS data of DP-4.

Structural Confirmations of Degradation Products

All analytical data, including MS, HRMS, and the degradation product structures, were confirmed through NMR spectral analysis. In the supporting information, Fig. 4 suggests a mechanism underlying the generation of DP-1 to DP-4 under basic and acidic conditions. The degradation pathway illustrates how the CDP molecule undergoes structural changes, as supported by the observed mass fragmentation patterns and NMR chemical shifts.

CDP Characterization

Mass spectrometry and high-resolution mass spectrometry confirmed the mass of CDP, yielding $[M+H]^+$ ions at m/z 493.68 and 493.1971, respectively, consistent with the molecular formula $C_{27}H_{28}N_2O_7$ (see Supporting Information, Fig. 5). The full structural characterisation

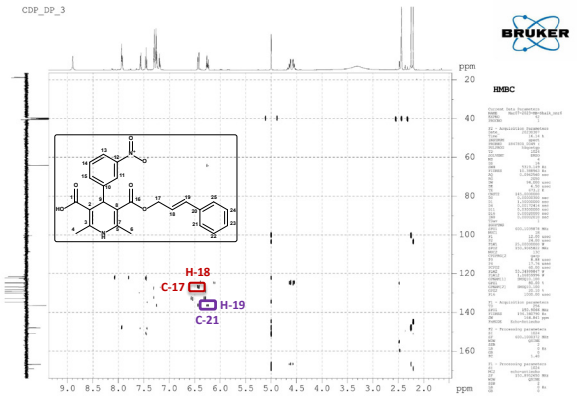

Fig. 13: HMBC data of DP-3.

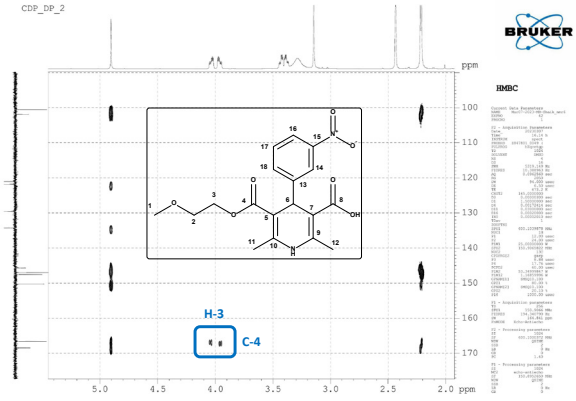

Fig. 15: HMBC data of DP-4.

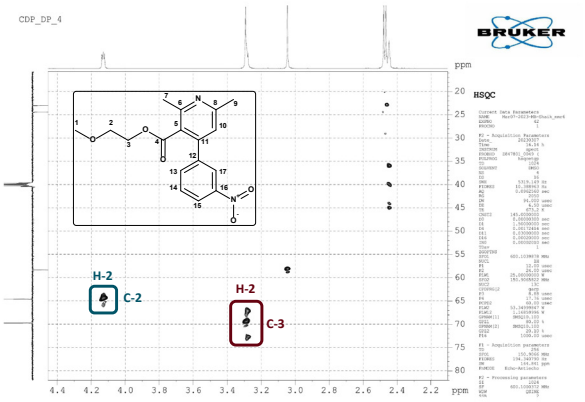

Fig. 16: HSQC data of DP-4.

of CDP was achieved using NMR spectroscopy, with the sample dissolved in DMSO-d_6 for analysis. The ^{1}H NMR spectrum revealed a total of 28 protons: 16 protons in the aliphatic region (2.23–4.64 ppm) and twelve protons were observed in the aromatic region (δ 6.20–9.05 ppm). HMBC spectroscopy (Fig. 6) indicated the absence of a ^{3}J correlation from the NH proton to C-2 and C-6. However, H-18 exhibited a ^{3}J correlation to C-16 and C-19, as well as a ^{4}J correlation to C-19, C-24, and C-21. Additionally, H-17 showed a ^{3}J correlation to C-19 and a ^{4}J correlation to C-20 and C-24.

DP-1 Characterization

When CDP was treated with a base, it produced the degradation product DP-1. The isolated compound was characterised by LC-MS and HR-MS, which yielded an $[M+H]^+$ ion at m/z 273.48 and 273.0884, respectively, corresponding to the chemical formula $C_{14}H_{12}N_2O_4$ (In supporting information Fig. 7). The full structural characterisation of DP-1 was elucidated using NMR spectroscopy. For the analysis, the sample was dissolved in DMSO-d_6. The ^{1}H NMR spectrum in Fig. 8 revealed a total of 12 protons: Six protons were observed in the aliphatic region (δ 1.5–4.0 ppm) and six protons in the aromatic region (δ 6.5–8.5 ppm).

DP-2 Characterization

Base-induced degradation of CDP produced DP-2. The isolated compound was characterised by mass LC-MS and HR-MS, which yielded an $[M+H]^+$ ion at m/z 377.57 and 377.1295, respectively, consistent with the chemical formula $C_{18}H_{20}N_2O_7$ (In supporting information Fig. 9). The sample was dissolved in DMSO-d_6 for NMR spectroscopy analysis. The ^{1}H-NMR spectrum revealed a total of 20 protons: Thirteen protons were observed in the aliphatic region (δ 1.5–4.0 ppm), while four protons were detected in the aromatic region (δ 6.5–8.5 ppm), one quaternary proton, and two D_2O-exchangeable protons observed at 8.9 ppm and 11.8 ppm. In the gradient heteronuclear multiple bond correlation (HMBC) spectrum, a ^{3}J correlation was absent between H-14 and C-13/C-6, whereas H-18 showed a ^{3}J correlation to C-16. Figs 10 and 11 present the HSQC and HMBC spectra, respectively.

DP-3 Characterization

The base treatment of CDP led to the formation of degradation product DP-3. The isolated compound was characterised by LC-MS and HR-MS, which yielded an $[M+H]^+$ ion at m/z 435.62 and 435.1554, respectively, consistent with the elemental formula $C_{24}H_{22}N_2O_6$ shown in supporting information Fig. 12. The ^{1}H NMR spectrum revealed a total of 21 protons: the aliphatic region (δ 1.5–4.0 ppm) exhibited six proton signals, while the aromatic region (δ 6.5–8.5 ppm) displayed nine protons, 2 between 4.5–5.0 ppm, 2 between 6.0–6.5 ppm, 1 quaternary proton, and 1 proton at 8.9 ppm, which was identified as D_2O-exchangeable. The HMBC spectrum (Fig. 13) showed the absence of a ^{3}J correlation from the NH proton to C-2 and C-6. However, H-18 exhibited a ^{3}J correlation to C-17 and C-20. Additionally, H-19 showed ^{3}J relationship to C-20, C-21, and C-25, while H-17 displayed a ^{3}J correlation to C-16.

DP-4 Characterization

Exposure of CDP to acidic conditions led to the formation of the degradation product DP-4. The isolated compound was characterised by LC-MS, which yielded an $[M+H]^+$ ion at m/z 331.53, corresponding to the elemental formula $C_{17}H_{18}N_2O_5$ (In the supporting information, Fig. 14). The ^{1}H NMR spectrum revealed a total of 18 protons: Eleven protons were observed in the aliphatic region (δ 1.5–4.0 ppm), five protons in the aromatic region (δ 6.5–8.5 ppm), and 2 additional protons around 4.1 ppm. In the gHMBC spectrum, a ^{3}J correlation was notably absent between H-10 and C-12. Figs 15 and 16 present the HMBC and HSQC spectra, respectively.

Conclusion

The stability of cilnidipine under various stress conditions was evaluated following ICH recommendations. While remaining stable under oxidative, thermal, and photolytic conditions, cilnidipine degraded when exposed to acidic or alkaline environments. Four distinct degradation products (DPs) were identified, with DP-1 and DP-4 forming due to ester hydrolysis and CO2 loss, and DP-2 and DP-3 resulting from ester hydrolysis. These DPs were fully characterised using 1D and 2D NMR and HRMS. While DP-1 and DP-4 are newly identified, DP-2 and DP-3 have been documented in the literature but were not characterised before this study. This investigation constitutes the first detailed structural characterisation of cilnidipine and its associated degradation products using advanced spectroscopic methods, supported by well-developed UHPLC-MS techniques for effective separation.

Acknowledgments

We would like to sincerely thank Aragen Life Sciences Pvt. Ltd. management for their invaluable assistance and for providing the laboratory facilities essential to this research.

References

1. Aoki S, Hosomi N, Nezu T, Teshima T, Sugii H, Nagahama S, et. al. Effects of Cilnidipine, an L/N-Type Calcium Channel Blocker, on Carotid Atherosclerosis in Japanese Post-Stroke Hypertensive Patients: Results from the CA-ATTEND Study. Journal of Atherosclerosis and Thrombosis. 2018;39:225–234. Available from: 10.5551/jat.42101
2. Kario K, Ando S, Kido H, Nariyama J, Takiuchi S, Yagi T, et. al. The effects of the L/N-type calcium channel blocker (cilnidipine) on sympathetic hyperactive morning hypertension: results from ACHIEVE-ONE. The Journal of Clinical Hypertension. 2012;15:133–142. Available from: 10.1111/jch.12042
3. Tsuchihashi T, Ueno M, Tominaga M, Kajioka T, Onaka U, Eto K, et. al. Antiproteinuric Effect of an N-Type Calcium Channel Blocker, Cilnidipin. Clinical and Experimental Hypertension. 2005;27:583–591. Available from: 10.1080/10641960500298558
4. Kadian R, Nanda A. A Comprehensive Insight into the Pharmacological Properties of Cilnidipine: A Fourth-generation Calcium Channel Blocker.
5. Cardiovascular & Haematological Agents in Medicinal Chemistry. 2024;22:40–50. Available from: 10.2174/1871525721666230224111518
6. Murakami M, Nakagawasai O, Fujii S, Hosono M, Hozumi S, Esashi A, et. al. Antinociceptive effect of cilnidipine, a novel N-type calcium channel antagonist. Brain Research. 2000;868:123–127. Available from: 10.1016/s0006-8993(00)02295-2
7. Kanaoka T, Tamura K, Wakui H, Ohsawa M, Azushima K, Uneda K, et. al. L/N-Type Calcium Channel Blocker Cilnidipine Added to Renin-Angiotensin Inhibition Improves Ambulatory Blood Pressure Profile and Suppresses Cardiac Hypertrophy in Hypertension with Chronic Kidney Disease. International Journal of Molecular Sciences. 2013;14:16866–16881. Available from: 10.3390/ijms140816866
8. Wermeling DP. Ziconotide, an intrathecally administered N-type calcium channel antagonist for the treatment of chronic pain. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2005;25:1084-1094. Available from: 10.1592/phco.2005.25.8.1084
9. Wu H, Wang Y, Wang G, Qiu Z, Hu X, Zhang H, et. al. A bivalent antihypertensive vaccine targeting L-type calcium channels and angiotensin AT1 receptors. British Journal of Pharmacology. 2020;177:402–419. Available from: 10.1111/bph.14875
10. Iyer RP, Lindsey ML, Chilton RJ. A Two-for-One Bargain: Using Cilnidipine to Treat Hypertension and Its Comorbidities. The Journal of Clinical Hypertension. 2013;15:455–457. Available from: 10.1111/jch.12112
11. Takahara A. Cilnidipine: A New Generation Ca2+ Channel Blocker with Inhibitory Action on Sympathetic Neurotransmitter Release. Cardiovascular therapeutics. 2009;27:124–139. Available from: 10.1111/j.1755-5922.2009.00079.x
12. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nature Reviews Nephrology. 2020;16: 223–237. Available from: 10.1038/s41581-019-0244-2
13. Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and medical care to cardiovascular mortality trends. Nature Reviews Cardiology. 2015;12:508–530. Available from: 10.1038/nrcardio.2015.82
14. Laatikainen T, Nissinen A, Kastarinen M, Jula A, Tuomilehto J. Blood Pressure, Sodium Intake, and Hypertension Control: Lessons From the North Karelia Project. Global Heart. 2016;11:191-199. Available from: 10.1016/j.gheart.2016.04.011
15. Ibrahim MM, Damasceno A. Hypertension in developing countries. The Lancet. 2012;380:611–619.
16. Oda S, Oda T, Takabuchi S, Nishi K, Wakamatsu T, Tanaka T, et. al. The calcium channel blocker cilnidipine selectively suppresses hypoxia-inducible factor 1 activity in vascular cells. European Journal of Pharmacology. 2009;606:130–136. Available from: 10.1016/j.ejphar.2009.01.012
17. Rose GW, Kanno Y, Ikebukuro H, Kaneko M, Kaneko K, Kanno T, et. al. Hypertension Research. 2001;24:377-383. Available from: 10.1291/hypres.24.377
18. Alsante K, Ando A, Brown R, Ensing J, Hatajik T, Kong W, et. al. The role of degradant profiling in active pharmaceutical ingredients and drug products. Advanced Drug Delivery Reviews. 2007;59:29–37. Available from: 10.1016/j.addr.2006.10.006
19. Jain D, Basniwal PK. Forced degradation and impurity profiling: Recent trends in analytical perspectives. Journal of Pharmaceutical and Biomedical Analysis. 2013;86:11–35. Available from: 10.1016/j.jpba.2013.07.013
20. Baena-Nogueras RM, González-Mazo E, Lara-Martín PA. Degradation kinetics of pharmaceuticals and personal care products in surface waters: photolysis vs biodegradation. Science of The Total Environment. 2017;590–591:643-654. Available from: 10.1016/j.scitotenv.2017.03.015
21. Singh S, Junwal M, Modhe G, Tiwari H, Kurmi M, Parashar N, et. al. Forced degradation studies to assess the stability of drugs and products. TrAC Trends in Analytical Chemistry. 2013;49:71-88. Available from: 10.1016/j.trac.2013.05.006
22. Zelesky T, Baertschi SW, Foti C, Allain LR, Hostyn S, Franca JR, et. al. Pharmaceutical Forced Degradation (Stress Testing) Endpoints: A Scientific Rationale and Industry Perspective. Journal of Pharmaceutical Sciences. 2023;112:2948–2964. Available from: 10.1016/j.xphs.2023.09.003
23. ICH. ICH Guideline Q1A(R2) Stability Testing of New Drug Substances and Products (QIAR) International Conference on Harmonisation. 2000.
24. ICH Expert Working Group, in Int. Conf. Harmon, 2003.
25. Jahani M, Fazly Bazzaz BS, Akaberi M, Rajabi O, Hadizadeh F. Recent Progress in Analytical Perspectives of Degradation Studies and Impurity Profiling in Pharmaceutical Developments: An Updated Review. Critical Reviews in Analytical Chemistry. 2023;53:1094-1115. Available from: 10.1080/10408347.2021.2008226

HOW TO CITE THIS ARTICLE: Kore AG, Kashid LM, Gharbude DS, Mohite SB, Singamsetti JM. Forced Degradation Profiling of Cilnidipine: A Multi-technique Characterisation using UHPLC–MS, HRMS, Prep-HPLC, and NMR. Int. J. Pharm. Sci. Drug Res. 2025;17(6):487-494. **DOI:** 10.25004/IJPSDR.2025.170601