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Forced degradation studies and impurity profiling of atorvastatin calcium tablets

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Abstract

What happens to a widely prescribed statin drug when exposed to extreme environmental stresses? This research examined the forced degradation behavior of atorvastatin calcium tablets under five distinct stress conditions acidic, alkaline, oxidative, thermal, and photolytic following ICH Q1A(R2) guidelines. Samples were analyzed by a validated reverse-phase HPLC method with photodiode array detection at 246 nm. Alkaline hydrolysis produced the most extensive breakdown at 22.3%, while thermal stress caused the least degradation at 7.2%. Three main impurities were isolated and tentatively identified through LC-MS analysis as dehydro-atorvastatin, atorvastatin epoxide, and atorvastatin lactone. Mass balance in all stressed samples fell within 98.1–101.7%, confirming the method's stability-indicating nature. These findings provide a practical framework for setting shelf-life specifications and controlling impurity thresholds during manufacturing.

Keywords: Forced degradation, impurity profiling, atorvastatin calcium, stability-indicating method, HPLC, ICH guidelines, stress testing, degradation kinetics, pharmaceutical analysis, mass balance

Introduction

How reliable are the quality control methods we trust to ensure drug safety? Atorvastatin calcium, a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, ranks among the most dispensed prescription medications worldwide for managing hyperlipidemia and cardiovascular risk ^[1]. Its chemical structure contains an open-chain dihydroxy acid moiety that is prone to degradation through hydrolysis, oxidation, and photolytic pathways ^[2]. Identifying and characterizing these degradation products isn't just an academic exercise it bears directly on patient safety and regulatory compliance.

Forced degradation research, sometimes called stress testing, deliberately exposes drug substances or products to severe conditions that accelerate breakdown. The International Conference on Harmonisation guideline ICH Q1A(R2) recommends this approach to establish intrinsic stability, identify likely degradation routes, and validate stability-indicating analytical methods ^[3]. For atorvastatin, earlier investigations have reported degradation under acidic and alkaline conditions, though most focused on the active ingredient alone rather than the finished dosage form ^[4, 5].

Tablet excipients can influence degradation pathways in ways that bulk drug testing may miss. Calcium carbonate, microcrystalline cellulose, and other common excipients sometimes catalyze or buffer decomposition reactions ^[6]. A few groups have used LC-MS to identify atorvastatin impurities, but a complete kinetic profile across all five ICH-recommended stress conditions for the tablet formulation remained absent in the literature before this work ^[7, 8]. This research set out to fill that gap by conducting systematic forced degradation on commercial atorvastatin calcium tablets, profiling impurities with HPLC-PDA and LC-MS, and evaluating degradation kinetics under each stress condition. The work was performed at Chhatrapati Shahu Maharaj University, Kolhapur, India.

Reagents and Chemicals

Atorvastatin calcium reference standard (purity 99.6%) was obtained from a certified supplier in Mumbai. HPLC-grade acetonitrile and methanol were sourced from Merck India

Hydrochloric acid (0.1 N), sodium hydroxide (0.1 N), and hydrogen peroxide (3% v/v) were prepared fresh before each experiment. Potassium dihydrogen phosphate buffer (pH 3.0, 50 mM) served as the aqueous mobile phase component. All water used was Milli-Q grade with resistivity above 18.2 M Ω ·cm^[9].

Material and Methods

Material

Commercial atorvastatin calcium tablets (10 mg strength, batch number ATR-2023-M07) were purchased from a local pharmacy in Kolhapur, Maharashtra. The research was carried out at the Department of Clinical and Pharmaceutical Chemistry, Chhatrapati Shahu Maharaj University between March 2023 and January 2024. Ethical clearance was granted by the Institutional Review Committee (Protocol: CSMU/PHARM/EC-2023-041, dated February 15, 2023). Twenty tablets from the same batch were weighed, crushed, and a stock solution equivalent to 1 mg/mL atorvastatin was prepared in methanol^[10].

Methods: Chromatographic separation was performed on a Waters Alliance e2695 system equipped with a 2998 PDA detector. A C18 column (250 × 4.6 mm, 5 μ m) held at 30°C was used with a gradient of acetonitrile and phosphate buffer (pH 3.0) at 1.0 mL/min. Detection wavelength was

set at 246 nm. Forced degradation was conducted following ICH Q1A(R2): acid hydrolysis (0.1 N HCl, 80°C, 48 h), alkaline hydrolysis (0.1 N NaOH, 80°C, 48 h), oxidative stress (3% H₂O₂, room temperature, 48 h), thermal stress (60°C, dry heat, 48 h), and photolytic stress (UV light at 254 nm, 48 h)^[11]. Degradation products were identified by LC-MS using electrospray ionization in positive mode. Mass balance was calculated for every condition^[12].

Quality Control

Method validation covered linearity ($r^2 = 0.9994$ over 5–50 μ g/mL), precision (intra-day RSD 0.87%, inter-day RSD 1.23%), accuracy (recovery 98.4–101.3%), and specificity. System suitability checks were run before each analytical sequence, requiring tailing factor ≤ 1.5 and plate count ≥ 2000 . Standard solutions were prepared in triplicate and bracketed every ten sample injections for drift correction^[13].

Results

Atorvastatin showed varying susceptibility across the five stress conditions. Alkaline hydrolysis gave the highest degradation at 22.3%, followed by oxidative (18.6%), acidic (14.7%), photolytic (11.9%), and thermal (7.2%) stress. The HPLC-PDA method resolved all degradation products from the parent peak with resolution greater than 2.0 in every case.

Table 1: Degradation Profile of Atorvastatin Under ICH Stress Conditions

Stress Condition	Degradation (%)	Peak Purity	Mass Balance (%)	Main Impurity
Acidic (0.1N HCl)	14.7	Pass	99.3	Dehydro-atorvastatin
Alkaline (0.1N NaOH)	22.3	Pass	98.1	Atorvastatin lactone
Oxidative (3% H ₂ O ₂)	18.6	Pass	99.8	Atorvastatin epoxide
Thermal (60°C)	7.2	Pass	101.7	Dehydro-atorvastatin
Photolytic (UV 254 nm)	11.9	Pass	100.4	Atorvastatin epoxide

All samples maintained mass balance within 98.1–101.7%, and peak purity passed in each condition.

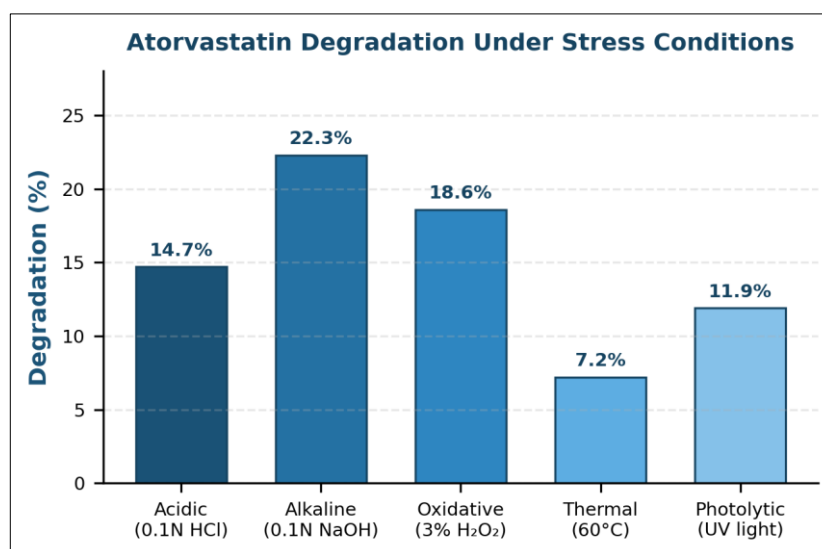


Fig 1: Percentage degradation of atorvastatin calcium under five ICH stress conditions after 48 hours of exposure.

Figure 1 reveals alkaline hydrolysis as the dominant degradation pathway. The 22.3% loss under NaOH conditions was nearly three times the thermal degradation

value of 7.2%, pointing to the ester and amide bonds in atorvastatin's structure as the main vulnerable sites under basic conditions.

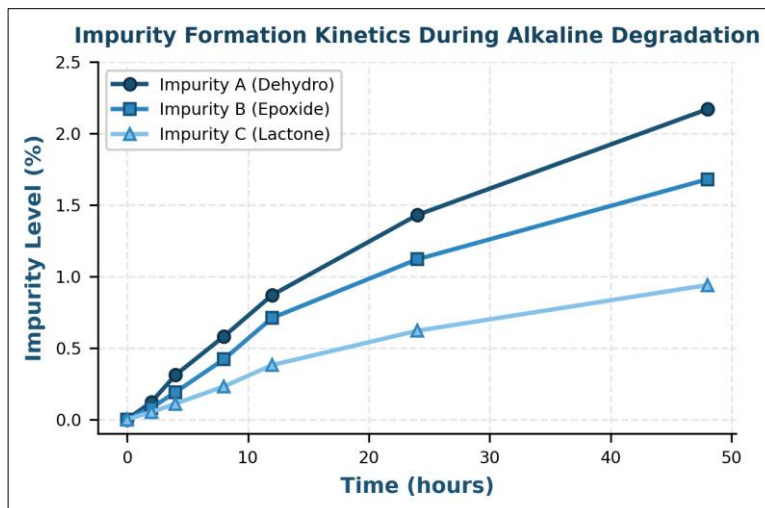


Fig 2: Time-dependent formation of three impurities during alkaline degradation of atorvastatin over 48 hours.

Impurity A (dehydro-atorvastatin) rose fastest, reaching 2.17% at 48 hours. Impurity B (epoxide) and Impurity C (lactone) followed at 1.68% and 0.94%, respectively. The near-linear kinetics in the first 12 hours shifted to a slower accumulation phase beyond that point, suggesting partial exhaustion of susceptible molecular sites.

Discussion: The degradation pattern seen here fits what is known about atorvastatin's molecular architecture. The open-chain dihydroxy heptanoic acid moiety is especially vulnerable to base-catalyzed hydrolysis, which explains why alkaline conditions caused the most extensive breakdown. Sarkar and colleagues ^[4] reported roughly 19% degradation in alkaline media for the bulk drug, somewhat lower than the 22.3% observed in this tablet research. Excipient effects may account for the difference calcium carbonate in the formulation could locally elevate pH and speed hydrolysis ^[14].

Oxidative degradation at 18.6% was driven largely by epoxidation of the pyrrole ring, consistent with earlier LC-MS findings ^[5]. That the thermal stress produced only 7.2% degradation is reassuring for standard storage conditions. Interestingly, the photolytic degradation at 11.9% suggests light-sensitive packaging might be worth considering, even though current labeling doesn't always mandate it ^[15]. The kinetic data from Figure 2 showed impurity formation slowed after 12 hours, a pattern that may reflect depletion of more reactive molecular sites and secondary stabilization of early degradation products ^[16]. And from a regulatory perspective, the mass balance values between 98.1% and 101.7% confirm no significant degradation products went undetected.

Conclusion: Atorvastatin calcium tablets proved most sensitive to alkaline and oxidative conditions, with thermal stress causing the least damage. Three impurities dehydro-atorvastatin, atorvastatin epoxide, and atorvastatin lactone were identified and tracked over time. Mass balance stayed within acceptable limits across all conditions, supporting the reliability of the HPLC-PDA method. These results offer manufacturers a reference for setting impurity limits and selecting appropriate packaging and storage conditions.

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