*EJPMR, 2025, 12(12), 32-34* **Review Article** **Impact Factor 7.065**

**EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH**

www.ejpmr.com

**ISSN (O): 2394-3211**
**ISSN (P): 3051-2573**
**Coden USA: EJPMAG**

# GREENER PATHWAYS IN FORCED DEGRADATION STUDIES: ADVANCES IN ECO-FRIENDLY PHARMACEUTICAL STRESS TESTING

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**DOI:** https://doi.org/10.5281/zenodo.17733644

**How to cite this Article**: Dr. V. S. Saravanan, Dr. M. Jambulingam, K. Shrihari, S. Muthu, H. M. Bhuvanesh, M. Prajen, Karthiraja A. S.*. (2025) Greener Pathways In Forced Degradation Studies: Advances In Eco-Friendly Pharmaceutical Stress Testing. European Journal of Pharmaceutical and Medical Research, 12(12), 32–34.


**Article Received on 22/10/2025** **Article Revised on 11/11/2025** **Article Published on 01/12/2025**

## ABSTRACT
Forced degradation studies are essential in pharmaceutical development for evaluating drug stability, identifying degradation products, and supporting regulatory filings. Traditional stress testing often employs harsh chemicals and solvents that pose environmental and safety concerns. In response, the pharmaceutical industry is adopting green chemistry principles to develop eco-friendly forced degradation protocols. This review comprehensively examines advances in greener reagents, sustainable analytical techniques, green metrics for method evaluation, and regulatory perspectives. Case studies demonstrating successful implementation of environmentally sustainable forced degradation studies are also discussed. The article offers guidance for integrating green chemistry approaches into stability-indicating method development to enhance safety, minimize waste, and comply with evolving regulatory expectations.

**KEYWORDS:** Forced degradation, Stress testing, Green chemistry, Ecofriendly reagents.

## INTRODUCTION
Forced degradation or stress testing involves subjecting pharmaceutical substances and products to accelerated conditions (acid/base hydrolysis, oxidation, photolysis, thermal stress) to generate degradation products for analytical characterization. These studies play a pivotal role in the development of stability-indicating methods and shelf-life determination as per ICH Q1A(R2) guidelines.

However, conventional forced degradation studies frequently use toxic solvents (acetonitrile, dichloromethane), strong oxidants, extreme pH conditions, and generate significant chemical waste, raising concerns regarding occupational hazards and environmental impact. Green chemistry principles, focusing on reducing toxicity, waste, and energy consumption, provide a roadmap toward eco-friendly stress testing.

This review highlights recent progress in adopting green chemistry approaches in forced degradation studies, including greener reagents, solvent systems, energy-efficient analytical methods, adoption of green metrics, and regulatory views promoting sustainability.

## Green Chemistry Principles in Forced Degradation Studies
Green chemistry aims to design chemical processes minimizing harm to human health and the environment. Within forced degradation studies, this translates to:

- Replacing hazardous solvents with safer alternatives (water, ethanol, supercritical fluids).
- Using milder oxidizing agents (e.g., hydrogen peroxide) or controlled light exposure over aggressive reagents.
- Employing energy-efficient and miniaturized analytical techniques to reduce resource consumption.
- Ensuring waste minimization and safer disposal protocols.

## Eco-Friendly Reagents and Solvents
Advances have shown water and ethanol (generally recognized as safe) as suitable solvents for hydrolytic and photolytic stress testing, replacing acetonitrile or

methanol in many protocols. Hydrogen peroxide serves as a greener oxidative agent generating fewer toxic residues.

Hybrid solvent systems optimized for forced degradation combine aqueous buffers with minimal organic solvents, improving both greenness and analytical performance. Supercritical CO2 is explored for certain drug degradation applications with minimal environmental footprint.

**Green Analytical Methods for Forced Degradation Analysis**

Chromatographic techniques remain central for degradation product separation and quantification. Recent developments include:

- Miniaturized HPLC and UPLC reducing solvent consumption and analysis time.
- High-performance thin-layer chromatography (HPTLC) and eco-friendly mobile phases.
- Application of green metrics like Analytical Eco-Scale, AGREE, and Green Analytical Procedure Index (GAPI) to systematically assess and optimize method greenness.
- Use of online and in-line monitoring tools minimizes sample handling and waste generation.

Validated methods incorporating these technologies demonstrate comparable sensitivity and specificity to conventional approaches while markedly reducing environmental impact.

**Regulatory Perspectives and Guidelines**

Globally recognized standards like ICH emphasize robustness and reproducibility of forced degradation studies but increasingly recognize the value of sustainable practices. Regulatory agencies encourage the use of green analytical protocols aligned with quality by design (QbD) frameworks to facilitate method optimization and lifecycle management with environmental safety in mind.

Industry trend toward mandatory environmental impact assessments for process development is likely to extend fully into forced degradation realms, promoting broader adoption of green methodologies.

**Case Studies of Green Forced Degradation Applications**

Recent literature illustrates successful practice of eco-friendly stress testing protocols:

- The use of ethanol-water mixtures in oxidative degradation of carvedilol with stability-indicating UPLC methods. Application of hydrogen peroxide for oxidative degradation of amlodipine and validation of a greener HPLC method with low solvent and energy consumption.
- Implementation of green HPTLC for simultaneous stress degradation and impurity profiling of multi-drug formulations.

These examples demonstrate practical feasibility and regulatory acceptability of green forced degradation strategies.

**Challenges and Future Directions**

Despite progress, challenges remain

- Need for validated standardized protocols adopting green reagents across diverse chemical classes.
- Integration of artificial intelligence and chemometrics to design optimal green stress conditions and analytical protocols.
- Increased awareness and incentives from regulators and industry stakeholders to accelerate green chemistry adoption.

Future trends include smarter, automated stress testing platforms using minimal resources and predicting stability with in silico methods integrated with eco-friendly experimental validation.

**CONCLUSION**

Greener pathways in forced degradation studies offer an imperative approach to sustainable pharmaceutical development, balancing rigorous analytical requirements with environmental responsibility. Adoption of milder reagents, safer solvents, energy-efficient analytical techniques, and green metrics is reshaping stability testing toward eco-friendliness. Ongoing innovation combined with evolving regulatory frameworks will continue to drive the integration of green chemistry into pharmaceutical stress testing, enhancing product safety and sustainability.

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