UNIVERSAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH (UJPSR)
Volume 10 Issue 1 Year 2026 Page No. 51 – 59
Estd. 1990

STABILITY-INDICATING METHODS IN FORCED DEGRADATION STUDIES: A CRITICAL REVIEW OF ANALYTICAL APPROACHES AND REGULATORY PERSPECTIVES

Usha Khanal*, Dawmit Lepcha
Himalayan Pharmacy Institute,Majitar,Sikkim(737136)

Article History
Received : 30th April 2026
Revised : 21st May 2026
Accepted : 31st May 2026
Published : 30th June 2026

Keywords
Forced degradation, HPLC, GC-MS, LC-MS, stability indicating methods, regulatory guidelines, analytical methods, and hyphenated techniques.

Abstract
Forced degradation studies are essential for evaluating the intrinsic stability, degradation pathways, and impurity profiles of pharmaceutical drug substances and drug products. These studies involve exposing pharmaceutical compounds to various chemical and environmental stress conditions to generate degradation products and develop stability-indicating analytical methods. Although regulatory guidelines such as ICH Q1A, Q1B, and Q2 provide general recommendations, the lack of standardized protocols often leads to variability in experimental approaches. This review critically discusses regulatory perspectives, common degradation conditions, and analytical techniques used in forced degradation studies, including UV spectrophotometry, HPLC, MS, NMR, and advanced hyphenated techniques such as LC-MS and GC-MS. The novelty of this review lies in the comparative evaluation of conventional and advanced analytical methods for degradant characterization and impurity profiling. The practical significance of forced degradation studies in method development, formulation optimization, quality assurance, and regulatory compliance is also highlighted. In addition, future perspectives involving advanced analytical technologies and automated approaches for pharmaceutical stability assessment are discussed.

INTRODUCTION

Chemical stability of pharmaceutical molecules is important because it directly affects the safety, efficacy, purity, and potency of drug products. Forced degradation involves exposing drug substances or drug products to stress conditions more severe than accelerated stability studies in order to generate degradation products and evaluate the intrinsic stability of the molecule. These studies help in understanding degradation pathways and developing stability-indicating analytical methods.

Accelerated stability studies and forced degradation studies differ in their objectives and conditions. Accelerated stability studies are performed under controlled temperature and humidity conditions to predict shelf life and storage conditions, whereas forced degradation studies use harsher conditions such as acid/base hydrolysis, oxidation, heat, light, and humidity to intentionally produce degradation products and study degradation behavior.

Several regulatory guidelines provide recommendations for forced degradation studies; however, no guideline specifies exact experimental conditions such as exposure time, pH, or oxidizing agents, leading to variability in approaches among pharmaceutical industries. International Council for Harmonisation (ICH) guidelines use different terminologies for these studies. ICH Q1A refers to “stress testing,” while ICH Q1B uses the term “forced degradation” (1). According to ICH guidelines, these studies help identify degradation products, establish degradation pathways, determine intrinsic stability, and validate stability-indicating analytical methods. Unlike confirmatory stability studies, forced degradation studies deliberately degrade the sample and are generally performed during the drug development stage.

OBJECTIVE OF FORCED DEGRADATION STUDIES (2)
The main objectives of forced degradation studies are:

1. To establish degradation pathways for drug substances and drug products.
2. To differentiate degradation products that is related to drug products from those that are generated from non-drug product in a formulation.
3. To elucidate the structure of degradation products.
4. To determine the intrinsic stability of a drug substance in formulation.

For correspondence: ushakhanal1996@gmail.com

5. To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product.
6. To establish stability indicating nature of a developed method.
7. To understand the chemical properties of drug molecules.
8. To generate more stable formulations.
9. To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
10. To solve stability-related problems.

OVERVIEW OF REGULATORY GUIDANCE (3)

Several international regulatory guidelines address forced degradation studies. The International Council for Harmonisation (ICH) has developed guidelines that are widely adopted by regulatory authorities in the United States, Europe, and Japan. Important guidelines related to forced degradation studies include ICH Q1A (Stability Testing of New Drug Substances and Products), ICH Q1B (Photostability Testing of New Drug Substances and Products), ICH Q1C (Stability Testing of New Dosage Forms), and ICH Q2B (Validation of Analytical Procedures: Methodology). These guidelines provide a general framework for stress testing, stability evaluation, and validation of stability-indicating analytical methods.

However, the current regulatory recommendations mainly provide broad guidance and do not specify exact experimental conditions such as stress duration, temperature, pH range, oxidizing agent concentration, or acceptable degradation limits. As a result, pharmaceutical industries often adopt different experimental strategies based on internal practices and product characteristics, leading to variability in degradation profiles and analytical outcomes. In addition, interpretation of regulatory expectations regarding the extent of degradation, impurity qualification, and validation requirements for stability-indicating methods may differ among laboratories and regulatory agencies. These limitations highlight the need for greater harmonization and clearer regulatory recommendations to improve consistency, reproducibility, and reliability in forced degradation studies.

REQUIREMENT OF FORCED DEGRADATION STUDIES (3)

It's very important to know when to perform forced degradation studies for the development of new drug substance and new drug product. As per FDA guideline that stress testing should be performed in phase III of regulatory submission process i.e., it should be carried out in to determine the stability of drug substance and drug product;

1. Different pH solutions like acid and alkali hydrolysis,
2. In presence of oxygen and light, and
3. At different temperature and humidity levels

These studies should be carried out on a single batch. The results should be summarized and submitted in an annual report. For obtaining the sufficient time and for the identification of the degradation products and structure elucidation as well as optimization of stress conditions, the starting stress testing of drug substance for preclinical phase or phase I of clinical trials is conducted. An early study also gives important guidance for improvements in manufacturing of the drug substance and process.

ORIGIN OF DEGRADATION PRODUCTS (3)

The main cause of development of impurities in drug substance or product is due to its degradation. The chemical instability of the drug substance under the conditions of heat, solvent, humidity, isolation, pH, an encountered during manufacture, drying, purification, storage, transportation is the main cause of its degradation. The chemical reactions like oxidation, hydrolysis, heat and photolysis occurred in the drug substance and main route of degradation.

LIMITS FOR DEGRADATION

Degradation of drug substances between 5% and 20% has been accepted as reasonable for validation of chromatographic assays. Some pharmaceutical scientists think 10% degradation is optimal for use in analytical validation for small pharmaceutical molecules for which acceptable stability limits of 90% of label claim is common (2).In the event that the experimental conditions generate little or no degradants due to the exceptional stability of the molecule, an evaluation should be made to verify if the drug substance has been exposed to energy in excess of the energy provided by accelerated storage (i.e., 40°C for 6 months). If the answer is yes, then the experiment can be stopped and a note of the stability of the drug substance can be made. Excessively overstressing the drug substance may produce deviant results(4).

STRATEGY FOR SELECTION OF DEGRADATION CONDITIONS

Forced degradation is carried out to produce representative samples for developing stability-indicating methods for drug substances and drug products. The choice of stress conditions should be consistent with the

product's decomposition under normal manufacturing, storage, and use conditions which are specific in each case (2). A general protocol of degradation conditions used for drug substance and drug product is shown in scheme 1(2). Stress factors suggested for forced degradation studies include acid and alkali hydrolysis, thermal degradation, photolysis, oxidation. There is no specification in regulatory guidelines about the conditions of pH, temperature and thermal condition and oxidizing agent used (3). General conditions used for forced degradation were illustrated in table 1(5).

SELECTION OF DRUG CONCENTRATION (3)

The concentration of drug to be used for degradation study has not been specified in regulatory guidance. The stress condition should be carried out in the concentration of 1 mg/ml. even in minor concentration drug should be degraded. It is suggested that degradation study should be carried out at a concentration which the drug is expected to be present in the final formulations.

VARIOUS DEGRADATION CONDITIONS

1. HYDROLYSIS(5)

Hydrolysis is one of the most common degradation pathways observed in pharmaceutical compounds over a wide pH range. It involves decomposition of a chemical compound through reaction with water. Drugs containing functional groups such as esters, amides, lactams, and carbamates are particularly susceptible to hydrolytic degradation. In acidic and alkaline hydrolysis, ionizable functional groups undergo acid- or base-catalyzed cleavage reactions, resulting in formation of primary degradants. Depending on the stability of the drug

Table 1: Conditions for forced degradation studies

Degradation type	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid or base) 0.1 M HCl 0.1 M NaOH Acid control (no API) Base control (no API) pH: 2,4,6,8	40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C 40°C, 60°C	1,3,5 1,3,5 1,3,5 1,3,5 1,3,5 1,3,5
Oxidation	3% H_2O_2 Peroxide control Azobisisobutyronitrile(AIBN) AIBN control	25°C, 60°C 25°C, 60°C 40°C, 60°C 40°C, 60°C	1,3,5 1,3,5 1,3,5 1,3,5
Photolytic	Light 1 × ICH Light 3 × ICH Light control	NA NA NA	1,3,5 1,3,5 1,3,5
Thermal	Heat chamber Heat chamber Heat chamber Heat chamber Heat control	60°C 60°C/75% RH 80°C 80°C/75% RH Room temp.	1,3,5 1,3,5 1,3,5 1,3,5 1,3,5

substance, suitable acids or bases and their concentrations should be selected. Hydrochloric acid or sulfuric acid (0.1–1 M) are commonly used for acidic hydrolysis, whereas sodium hydroxide or potassium hydroxide (0.1–1 M) are employed for alkaline hydrolysis. Co-solvents such as methanol or acetonitrile may be used for poorly water-soluble drugs. Forced degradation studies are generally initiated at room temperature and elevated further if no significant degradation occurs. For example, ester-containing drugs commonly undergo cleavage into corresponding acids and alcohols under alkaline conditions.

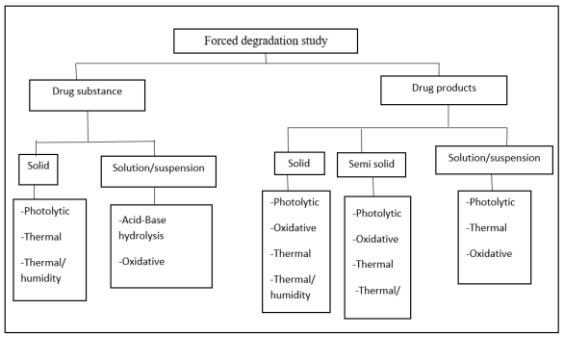

Fig. 1: Schematic Flow Chart for Forced Degradation Studies

2. PHOTOLYTIC DEGRADATION (4)

According to International Council for Harmonisation (ICH) Q1B guidelines, samples should be exposed to an overall illumination of not less than 1.2 million lux hours and an integrated near-ultraviolet energy of not less than 200 watt-hours/m² within the wavelength range of 320–400 nm. Exposure conditions are monitored using calibrated lux meters, radiometers, or validated actinometric systems. Photolytic degradation may occur through non-oxidative or oxidative pathways. Non-oxidative reactions include isomerization, dimerization, cyclization, rearrangement, decarboxylation, deamination, and bond cleavage reactions. Oxidative photolysis occurs through singlet oxygen ($^1O_2$) or triplet oxygen ($^3O_2$) mechanisms. Singlet oxygen reacts readily with unsaturated systems such as alkenes and aromatic hydrocarbons, while triplet oxygen participates in free radical oxidation reactions leading to peroxide formation. Thus, light may also act as a catalyst for oxidative degradation. Drugs containing conjugated double bonds and aromatic chromophores are particularly susceptible to photodegradation.

3. OXIDATIVE DEGRADATION(2)

Oxidative degradation is commonly induced using hydrogen peroxide, although other oxidizing agents such as metal ions, oxygen, and radical initiators like azobisisobutyronitrile (AIBN) may also be employed. Hydrogen peroxide concentrations ranging from 0.1–3% at neutral pH and room temperature are widely used to achieve controlled degradation. Oxidative degradation generally occurs through electron transfer mechanisms producing reactive intermediates such as free radicals, anions, and cations. Functional groups susceptible to oxidation include amines, sulfides, phenols, benzylic carbons, allylic carbons, and tertiary carbons adjacent to heteroatoms. Amines may form N-oxides or hydroxylamines, while sulfides are oxidized into sulfoxides and sulfones. Phenolic compounds may undergo oxidation to quinones. The extent of oxidative degradation depends on oxidant concentration, exposure time, pH, and molecular structure of the drug substance.

4. THERMAL DEGRADATION (6)

The rate of chemical degradation generally increases with temperature due to enhanced molecular motion and reaction kinetics. Consequently, many active pharmaceutical ingredients are susceptible to thermal degradation at elevated temperatures. Heat-sensitive compounds such as vitamins, peptides, and antibiotics may undergo degradation through pyrolysis, hydrolysis, decarboxylation, oxidation, rearrangement, isomerization, and polymerization reactions. Thermal degradation studies are commonly performed at temperatures between 40°C and 80°C under dry or humid conditions. The effect of temperature on degradation rate is explained by the Arrhenius equation:

K= Ae-Ea/RT

where k is the reaction rate constant, A is the frequency factor, E_a is activation energy, R is the gas constant, and T is absolute temperature. Although elevated temperatures accelerate degradation, excessively high temperatures (>80°C) may generate unrealistic degradation pathways that may not occur under normal storage conditions.

5. HUMIDITY(5)

Humidity is an important factor influencing the stability of pharmaceutical drug substances and finished products, especially hygroscopic compounds and solid dosage forms. High humidity conditions may accelerate hydrolysis, alter crystallinity, and enhance molecular mobility within formulations. Generally, forced degradation studies are conducted at approximately 90% relative humidity for one week to evaluate moisture sensitivity. Humidity-induced degradation is particularly significant in tablets and capsules where moisture uptake may lead to physical and chemical instability.

CHALLENGES AND LIMITATIONS OF FORCED DEGRADATION STUDIES

Forced degradation studies are associated with several scientific and analytical challenges. Small variations in stress conditions such as pH, temperature, oxidant concentration, and exposure duration may produce different degradation profiles, leading to reproducibility issues between laboratories. In formulation studies, excipients may interact with the drug substance and generate additional degradation products, resulting in matrix interference and increased complexity of analysis. Chromatographic techniques may also face co-elution problems, where degradants and impurities are insufficiently separated, and making accurate quantification difficult. Furthermore, identification and characterization of unknown degradants are often time-consuming and require advanced analytical techniques such as LC-MS/MS, LC-NMR, or high-resolution mass spectrometry. Another limitation is that degradation products formed under severe stress conditions may not always represent those generated during real-time storage studies, requiring careful interpretation of forced degradation data.

STABILITY INDICATING METHOD (3)

According to the FDA guidance document, a stability indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients. The development of a suitable stability indicating method provides background information of active ingredients about the solubility study, pre-formulation study, concentration changes with time, development of suitable storage conditions. The RP-HPLC is most widely used analytical tool for separation and quantifying the impurities and most important coupled with UV detector.

Using this process, a validated HPLC analytical assay, mechanisms of degradation, and the impurity/degradant information for filing can all be generated.

I. DEVELOPMENT OF STABILITY INDICATING METHOD

Though the requirements with respect to stability indicating method have been spelt out in regulatory documents, information on the basic steps to be followed for the development and validation of stability-indicating methods is neither provided in the regulatory guidelines nor in the pharmacopoeias. General steps in stability indicating method are,

STEP 1: CRITICAL STUDY OF THE DRUG STRUCTURE TO EVALUATE THE LIKELY DECOMPOSITION ROUTE.

This should be the first element whenever one takes up the project on establishment of a SIAM. Much information can simply be gained from the structure, by study of the functional groups and other key components. There are definite functional group categories, like amides, esters, lactams, lactones, etc. that undergo hydrolysis, others like thiols, thioethers, etc. undergo oxidation, and compounds like olefins, aryl halo derivatives, aryl acetic acids, and those with aromatic nitro groups, N-oxides undergo photodecomposition.

STEP 2: COLLECTION OF INFORMATION ON PHYSICOCHEMICAL PROPERTIES (4)

Before method development is taken up, it is generally important to know various physicochemical parameters like pKa, log P, solubility, absorptivity and wavelength maximum of the drug in question.

STEP 3: STRESS (FORCED DECOMPOSITION) STUDIES (7)

As described above in forced degradation section, these studies should be carried out in accordance with ICH Q1A guideline. Stress conditions are;

i. 10 °C increments above the accelerated temperatures (e.g. 50 °C, 60 °C, etc.),
ii. Humidity where appropriate (e.g. 75% or greater),
iii. Hydrolysis across a wide range of pH values,
iv. Oxidation and
v. Photolysis.

STEP 4: PRELIMINARY SEPARATION STUDIES ON STRESSED SAMPLES (4)

The simplest of separation way is to start with a reversed phase octadecyl column and perform HPLC separation using UV/PDA detector system. Another way is to go for LC-MS separation. Using these chromatographic techniques, one should follow the changes in all the stress samples at various time periods. The results should be critically compared with the blank solutions injected in a similar manner. It should be observed whether the fall in drug peak is quantitatively followed by a corresponding rise in the degradation product peaks.

STEP 5: FINAL METHOD DEVELOPMENT AND OPTIMIZATION (8)

Subsequent to preliminary chromatographic studies, the RT and relative retention times (RRT) of all products formed should be tabulated for each reaction condition. Special attention is then paid to those components whose RT or RRT is very close. PDA spectra or LC-MS profile of such components are obtained and critically evaluated to ascertain whether the products are same or different. To separate close or co-eluting peaks, the method is optimized, by changing the mobile phase ratio, pH, gradient, flow rate, temperature, solvent type, and the column and its type.

STEP 6: IDENTIFICATION AND CHARACTERIZATION OF DEGRADATION PRODUCTS, AND PREPARATION OF STANDARDS (4)

To identify the resolved products, a conventional way is to isolate them and determine the structure through spectral (MS, NMR, IR, etc.) and elemental analysis. However, this approach is tedious and time consuming when multiple degradation products are formed. Against it, the modern approach is to use hyphenated LC techniques coupled with mass spectrometry. This strategy integrates in a single instrument approach, analytical HPLC, UV detection, full scan mass spectrometry (LC-MS) and tandem mass spectrometry (LC-MS-MS) and provides a fair idea on identity of resolving components. These days a further integrated approach is becoming popular wherein LC-MS or LC-MS-MS is employed to obtain molecular weight and fragmentation information, and further detailed structural information is obtained through LC-NMR analysis.

STEP 7: VALIDATION

Validation of analytical methods, in general, has been extensively covered in the ICH guidelines Q2A and Q2B (7), (9) and in the FDA guidance (10) and by USP (11). The main focus of validation at this stage is on establishment of specificity/ selectivity, followed by other parameters like accuracy, precision, linearity, range, robustness, etc. The limits of detection and quantitation are also determined for degradation products to help in establishment of the mass balance.

II. SPECIFIC AND SELECTIVE STABILITY-INDICATING ASSAY METHODS (12)

There is lack of clarity on the terms used for differentiating the methods that measure quantitatively the component of interest in the sample matrix without separation, and the ones where separation is done of the drug as well all other degradation products. Thus 'Specific stability-indicating assay method (Specific SIAM)' can be defined as "a method that is able to measure unequivocally the drug(s) in the presence of all degradation products, excipients and additives, expected to be present in the formulation. The 'Selective stability-indicating assay method (Selective SIAM)' on the other hand can be defined as "a method that is able to measure unequivocally the drug(s) and all degradation products in the presence of excipients and additives, expected to be present in the formulation".

ANALYTICAL TOOLS FOR DEGRADANT SEPARATION AND IDENTIFICATION

A. CONVENTIONAL TECHNIQUES

MASS SPECTROMETRY (MS)(13),(14)

Mass spectrometry is a fundamental analytical tool for the structural elucidation of drug degradation products due to its high sensitivity, selectivity, and ability to generate fragmentation patterns. Advanced high-resolution instruments such as TOF and ion trap systems enable accurate mass determination and multi-stage fragmentation (MS^n), facilitating comparison between APIs and degradants. However, standalone MS generally requires prior chromatographic separation for complex mixtures.

NUCLEAR MAGNETIC RESONANCE (NMR) (15)

NMR spectroscopy provides detailed structural and stereo-chemical information and is commonly used alongside MS for confirmatory analysis. One- and two-dimensional NMR techniques enable molecular characterization and identification of unknown degradants. Although highly informative, NMR is comparatively less sensitive, requires relatively larger sample quantities, and involves high operational costs.

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)(16), (17)

HPLC is one of the most widely used techniques for separation and quantification of degradation products in pharmaceutical analysis. It offers good sensitivity, reproducibility, and applicability for stability-indicating methods. Multi-wavelength detection and peak purity assessment further improve selectivity. However, HPLC alone may not provide complete structural information for unknown degradants.

B. HYPHENATED TECHNIQUES

GAS CHROMATOGRAPHY–MASS SPECTROMETRY (16)(18)

GC-MS is highly sensitive and selective for the analysis of volatile and thermally stable compounds, particularly residual solvents and volatile impurities. Its major limitation

is that non-volatile, polar, or thermolabile degradants often require derivatization prior to analysis, limiting its applicability in pharmaceutical degradation studies.

LIQUID CHROMATOGRAPHY–MASS SPECTROMETRY (LC-MS) (13),(14)

LC-MS is one of the most powerful and widely applied hyphenated techniques for impurity profiling and degradant characterization. It combines the separation capability of HPLC with the structural elucidation power of MS, providing high sensitivity, selectivity, and accurate mass analysis. Advanced systems such as Q-TOF, Orbitrap, and FTICR support multi-stage fragmentation and detailed characterization of complex degradants. Despite its advantages, LC-MS requires expensive instrumentation and skilled operation.

CAPILLARY ELECTROPHORESIS–MASS SPECTROMETRY (CE-MS) (19)

CE-MS provides high-efficiency and orthogonal separation, particularly for ionic and polar compounds. It consumes very small sample volumes and offers high separation efficiency. However, limited robustness, reproducibility challenges, and complex interfacing systems have restricted its routine industrial application.

LIQUID CHROMATOGRAPHY–NMR (LC-NMR) (15),(18)

LC-NMR enables simultaneous chromatographic separation and structural characterization of degradation products in solution phase. It is especially valuable for stereochemical analysis and identification of structurally complex degradants. Nevertheless, lower sensitivity, high solvent consumption, and high operational costs limit its widespread use.

LIQUID CHROMATOGRAPHY–FTIR (LC-FTIR) (18)

LC-FTIR is useful for identifying functional groups and confirming structural modifications in degradants present at low concentrations. The technique provides complementary information to MS and NMR; however, its lower sensitivity and compatibility challenges with mobile phases reduce its routine applicability.

COMPARATIVE DISCUSSION OF ANALYTICAL TECHNIQUES

Different analytical techniques possess distinct advantages and limitations in forced degradation studies. HPLC remains the most commonly used technique for routine stability-indicating analysis because of its simplicity, reproducibility, and cost-effectiveness. LC-MS offers superior sensitivity and structural characterization capability, making it highly suitable for impurity profiling and identification of unknown degradants. GC-MS is particularly effective for volatile and thermally stable compounds but has limited applicability for non-volatile degradants. LC-NMR provides extensive structural and stereochemical information, whereas CE-MS offers high-efficiency separation for polar and ionic compounds. Selection of an appropriate analytical technique depends on the physicochemical properties of the drug, nature of degradation products, sensitivity requirements, availability of instrumentation, and regulatory expectations. Combining complementary analytical techniques often provides more reliable and comprehensive characterization of degradation products.

CHALLENGES AND LIMITATIONS OF FORCED DEGRADATION STUDIES

1. SELECTION OF APPROPRIATE STRESS CONDITIONS

Choosing suitable stress conditions (acidic, alkaline, oxidative, thermal, photolytic) is difficult. Over-stressing may lead to unrealistic degradation products, while under-stressing may not produce meaningful degradation.

2. LACK OF STANDARDIZED GUIDELINES

Regulatory bodies like International Council for Harmonisation (ICH) (e.g., Q1A, Q1B) provide general guidance but do not specify exact experimental conditions. This leads to variability in methodologies across laboratories.

3. COMPLEXITY OF DEGRADATION PATHWAYS

Drugs may undergo multiple degradation pathways simultaneously. Formation of secondary degradants complicates interpretation and identification.

4. ANALYTICAL METHOD LIMITATIONS

Techniques like HPLC, LC-MS, and UV may: Fail to separate closely related impurities and shows co-elution of degradants. Requires advanced tools like LC-MS/MS or NMR for confirmation.

5. IDENTIFICATION AND CHARACTERIZATION ISSUES

Structural elucidation of unknown degradants is time-consuming and resource-intensive. Requires sophisticated instrumentation and expertise.

6. RELEVANCE TO REAL-TIME STABILITY

Forced degradation conditions are much harsher than actual storage conditions. Degradants formed may not always reflect those formed during real-time or accelerated stability studies.

7. REPRODUCIBILITY ISSUES

Small changes in experimental parameters (pH, temperature, time) can lead to different degradation profiles. Makes reproducibility across labs difficult.

8. SAMPLE MATRIX INTERFERENCE

In formulation studies, excipients may:
Interact with the drug and form additional degradation products. This complicates analysis and interpretation.

9. TIME AND COST CONSTRAINTS

Requires multiple experiments under different stress conditions. Use of advanced analytical instruments increases cost.

10. REGULATORY INTERPRETATION CHALLENGES

While FDS is expected for stability-indicating methods, regulators may interpret results differently, especially regarding extent of degradation (typically 10–20%).

CONCLUSION

Forced degradation studies are essential for understanding degradation pathways and identifying degradation products of active pharmaceutical ingredients. These studies facilitate the structural elucidation of degradants and provide critical insights into the chemical and physical stability of drug substances and drug products. Furthermore, forced degradation supports the development of robust formulation strategies, optimization of manufacturing conditions, and establishment of appropriate storage conditions. It also plays a crucial role in determining the shelf life and expiry date of pharmaceutical formulations.

REFERENCES

1. Jayshree K Sonawane et.al. A Review of Stability Indicating Methods and Forced Degradation Studies. International Journal of Research Publication and Reviews. 4(5),2023,4703-4715.
2. Blessy M et.al. Development of forced degradation and stability indicating studies of drugs- A review. Journal of pharmaceutical analysis. 4(3), 2014, 159-165.
3. Mrs. Khushbu A. Thakor et.al.A review article-development of forced degradation and stability indicating studies for drug substance and drug product. International Journal of Research in Pharmacology & Pharmacotherapeutics. 5(4), 2016,291-297.
4. Uday Deokate et.al. Forced degradation and stability testing: Strategies and Analytical Perspectives. International Journal of Pharmaceutical Sciences Review and Research. 26(2), 2014, 242-250.
5. Akanksha Verma et.al. Development of Forced Degradation and Stability Indicating Studies of Drugs-A Review. Asian Journal of Pharmaceutical Research and Development 10(2),2022,83-89.
6. Trivikram Rawat et.al. Forced degradation studies for drug substances and drug products- scientific and regulatory considerations. Journal of Pharmaceutical Science and Research. 7(5), 2015, 238-241.
7. ICH Expert Working Group. Stability testing of drug substances and drug products Q1A(R2): Draft guideline. Geneva: International Council for Harmonisation; 2025 Apr 11.
8. Maryam Jahani et al. Recent Progress in Analytical Perspectives of Degradation Studies and Impurity Profiling in Pharmaceutical Developments (An Updated Review). Critical reviews in Analytical Chemistry. 2023;53(5).
9. ICH, Validation of Analytical Procedures: Methodology International Conference on Harmonisation, IFPMA, Geneva, 2023.
10. FDA, Guidance for Industry: Analytical Procedures and Methods Validation (Draft guidance). Food and Drug Administration, Rockville, MD, 2000.
11. The United States Pharmacopeia, 24th Revision, Asian Edition, United States Pharmacopeial Convention, Inc., Rockville, MD, 2000, 2149–2152.
12. Amitkumar J.Vyas et al. Review on stability indicating assay method or forced degradation study: Strategy and regulatory consideration. Asian Journal of Pharmaceutical Analysis. 2023;13(2):131–139.
13. Nagaraju Rajana et al. Review on LC-MS/MS methodologies for analysis of nitrosamine drug-substance-related impurities. Critical Reviews in Analytical Chemistry. 2025.
14. Jun-Ling Ren et al. Advances in mass spectrometry-based metabolomics and analytical applications. RSC Advances. 2018;8:22335-22350
15. Chowdhury SK (Ed.).Methods for metabolite generation and characterization by NMR. In: Identification and Quantification of Drugs, Metabolites and Enzymes. Elsevier; 2020.
16. Mohammed Al Saeedy et al. Advances in chromatography for drug impurity profiling. Critical Reviews in Analytical Chemistry. 2023;53(7):1455–1471.
17. Praveen Boppy et al. Stability-indicating HPLC method optimization using quality by design with design of experiments approach for quantitative

estimation of organic related impurities of Doripenem in pharmaceutical formulations. Journal of Applied Pharmaceutical Science.2025; 15(02):114-126.

18. Sukhwinder Singh. Recent trends in analytical techniques for impurity profiling. Biomedical journal of scientific and technical research. 2022;40(5):32191–32193.
19. Mansi Shah et al. Capillary electrophoresis methods for impurity profiling of drugs: A review. Journal of Pharmaceutical Analysis. 2022;12(1):15–28.