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Review Article

Forced Degradation Studies: Analytical Methodologies, Applications, and Regulatory Insights – A Systematic Review

Ashwini Tayde, Mukesh Patil, Ashish Jain

* Department of Quality Assurance, Shri D.D Vispute College of Pharmacy and Research Centre, Devad, New Panvel, India

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ABSTRACT

Forced degradation studies are an essential component of pharmaceutical development, designed to intentionally degrade drug substances and products under conditions more rigorous than standard accelerated conditions. These studies play a pivotal role in validating the specificity of stability-indicating analytical methods. By exposing drug substances to various stress conditions, forced degradation reveals degradation pathways and identifies degradation products, providing critical insights into the molecular stability and chemical behavior of active pharmaceutical ingredients. These insights are instrumental in guiding formulation design, packaging development, and shelf-life determination. However, despite its significance, regulatory guidelines on forced degradation often lack comprehensive instructions, leaving the execution and interpretation of these studies to the discretion of researchers. This review aims to address this gap by providing a systematic examination of forced degradation methodologies, elucidating degradation mechanisms, and summarizing analytical techniques integral to stability-indicating method development. Additionally, it highlights current trends and challenges in forced degradation research, contributing to the advancement of robust and reliable analytical approaches in pharmaceutical science.

Keywords: Forced degradation, Accelerated conditions, Analytical techniques, Stability-indicating methods, Formulation development, Packaging stability.

Corresponding Author:

Ashwini Tayde

Department of Quality Assurance, Shri D.D Vispute College of Pharmacy and Research Center, Devad, New Panvel

Email id: tashwini90@gmail.com

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1.Introduction

Chemical stability of pharmaceutical molecule is an issue of significant concern because it impacts on the drug product's efficacy and safety. The way of content and product quality of a certain drug must be determined from the data of stability tests, if such data should be submitted as follows: The FDA and ICH.

As they are subjected to the various environmental trends for some time. Knowledge of a molecule's stability assists in conclusion of the proper formulation, package, storage and shelf life, all which are important in preparing the necessary paperwork. Compared to the accelerated degradation, drug compounds and products are forced to degenerate under worse conditions of degradation in order to determine the stability of the molecule based on the degradation products obtained. But as per ICH guideline the qualification of stress testing is to identify the potential degradation products which in turn helps to understand the stability of the molecule, identifying the degradation mechanisms and validating the stability. Specifying the employed methods of this research [1]. Nevertheless, these standards describe forced degradation in a limited manner and do not address question of what the concrete stress testing should look like.

Despite forced degradation studies being scientific and having a regulatory element during the medication development process they are not considered less as a formal stability program. The clinical files of a new drug moiety must now undergo Stability studies before one can prepare and submit a registration dossier. The stability tests include the significant stability test which is a six months test and the further test that is the twelve months test. However, there would be six months trials if some conditions will be met.

Not as severe as that used in the fast-paced analyses. Consequently, even longer time would have been required to assess degradation products such as separation, identification and quantification. Unlike stability studies, forced degradation studies help to create degrades in a comparatively shorter period of time, say, a few weeks. With the help of the forced degradation samples, stability can be developed. Illustrating a method that may be applied in the future to evaluate samples resulting from both short and long studies. This review actually presents not only a practical tip on the use of forced deterioration in practice but also how to employ this issue to generate methods for stability indicators.

1.1 Objective of Forced Degradation Studies

The forced degradation studies are aimed at the following goals: to study degradation processes of drug substances and products, to identify the relation between degradation products and the drug product, to clarify structures of degradation products, to determine inherent stability of drug substances, to reveal breakdown mechanisms such as hydrolysis, oxidation, and photolysis, to develop stability indicating methods, to study molecular compositions of pharmaceutical compounds, to enhance formulation stability, to obtain degradation profiles matched to

1.2 When to Execute Forcible Degrading

It is of significant importance to determine the occasions on which forced degradation analyses should be performed to anticipate new medicinal substances as well as new drug products. In keeping with FDA rules on stress testing, it is only possible during the third phase of the regulatory submission procedure. Stress studies must be conducted at different pH cases, in presence of oxygen and light, also at higher temperatures and humidity. This one batch is used for those stress tests. It should be useful

to prepare an annual report in the form of the brief of the findings.

The use of stress testing in the evaluation of pharmaceutical substances should as much as possible be initiated at the onset of the preclinical stage or in the clinical trial phase I. This will enable enough time to discover the degradation products, the elucidation of structure and the optimisation of stress conditions Moreover, the early stress studies also offer useful tips on how to improve the manufacturing process and how to select stability indicating methods in time [4].

1.3. Limitation of Deterioration

Drugs and pharmaceuticals professionals have engaged in many discussions that, among other things, has concerned when enough degradation is enough. Many consider it okay for chromatographic tests to have been validated when the pharmacological compounds in questions degrade to the tune of 5% to 20% [5,6]. With small drug molecules, which are usually associated with reasonable stability losses of 90% of the label claim, some pharmaceutical personnel still think that 10% degradation is the most appropriate approach to use for analytical verification [7]. Some suggested the use of drug material where one of the components is a mixture of recognised degradation products, as a strategy for challenging methodologies applied in identifying the stability of the drug product. Specifically for particular types or categories of biological products there are no such limitations for physiochemical changes, inactivation or degradation throughout shelf life.

2. Different Types of Degradation

2.1. Hydrolytic Degradation

This picture considers the hydrolysis and is among the most popular chemical vigorous reactions crosswise under a large pH scale. Hydrolysis is a process by which a chemical compound disintegrates because of the effect created by water combined with it. Activating the molecule's ionisable functional groups is required to examine the extents of hydrolysis in basic and acidic conditions. The technique of forcing a drug compound to decompose by exposing its formulation to acidic or basic conditions that produce the first degradation byproducts falls under the category known as acid or base stress testing. The amount of acid or base which is to be used depends on a stability of a substance in the treatment process Sample preparation Substances that are used in hydrolysis depend on the level of base or acid stability They include hydrochloric or sulphuric acid of 0.1M to 1M Base hydrolysis reagents include sodium or potassium hydroxide of about 0.1M to 1M

When the used compounds used for stress testing are insoluble in water, they can be dissolved in HCl or NaOH in the presence of co-solvents. The co-solvent alternative takes into account the substance composition of the drug. A stress test session can be usually started at ambient temperature. If there is no degrading, the temperature is then increased to 50-70°C. According to the results of the present study, it suggested that seven days should be the maximum time in a stress test. The degraded sample is then washed with the right acid, base or buffer to stop further degradation of the samples.

2.2 Oxidation Degradation

Hydrogen peroxide is extensively used to oxidize pharmaceutical substances in forced degradation studies. However, other oxidizing agents can be employed for the same purpose, the examples are oxygen, metal ions and radical initiators (for instance AIBN-azobisisobutyronitrile). Choosing the oxidizing agent and its conditions and dosage change depending on the component of the medicine. Afterwards, the evaluated solutions were

found to generate corresponding degradation products if exposed to 0.1% – 3% hydrogen peroxide for one week at ambient temperature and near neutral pH, or up to 20% degradation. They also indicated that an electron transport system is used in the oxidative process. Dispelling into environment of medicinal material through the conversion of organic substance into ash and further getting broken down into anions and cations. Oxidation involving electron transfer of amines, sulphides, and phenols may produce N-oxides, hydroxylamine, sulphones and sulphide can be obtained [10].

Those functional groups that contain labile hydrogen, including benzylic, allylic, tertiary carbon atoms in relation to the hetero atom, can be oxidized to yield hydro peroxides. It is acceptable to have hydroxide or ketone [11, 12].

2.3 Photolytic Degradation

Pharmacological substances must go through photo stability testing to demonstrate that exposure to light do not result in unfavourable alterations. To produce the primary degrades of the medicinal substance through exposure to UV or fluorescent light, photo stability investigation is conducted recommended parameters for photo stability testing are described in the ICH recommendations.

Samples of pharmaceutical businesses' material and solid/liquid medicinal objects should be exposed to a minimum of 1.2 million lux hours and 200-watt hours per square meter of light.

Six million lux hours per hour is the maximum quantity of lighting that is recommended [13]. The most known range of light wavelengths for photolytic degradation is between 300 and 800 nm [14].

Free radical pathways may cause photo oxidation when there is a light stress. Functional groups such as sulphides, polygenes, weak C-H and O-H bonds, alkenes, nitro aromatic, N-Oxide, and carbonyls are predicted to introduce medication photosensitivity [15].

2.4 Thermal Degradation

Thermal deterioration (dry heat and wet heat) should be performed under more rigorous conditions than those specified by the ICH Q1A accelerated testing settings. Dry and wet heat should be applied to samples of solid-state drug ingredients and drug products, but only dry heat should be applied to liquid drug products

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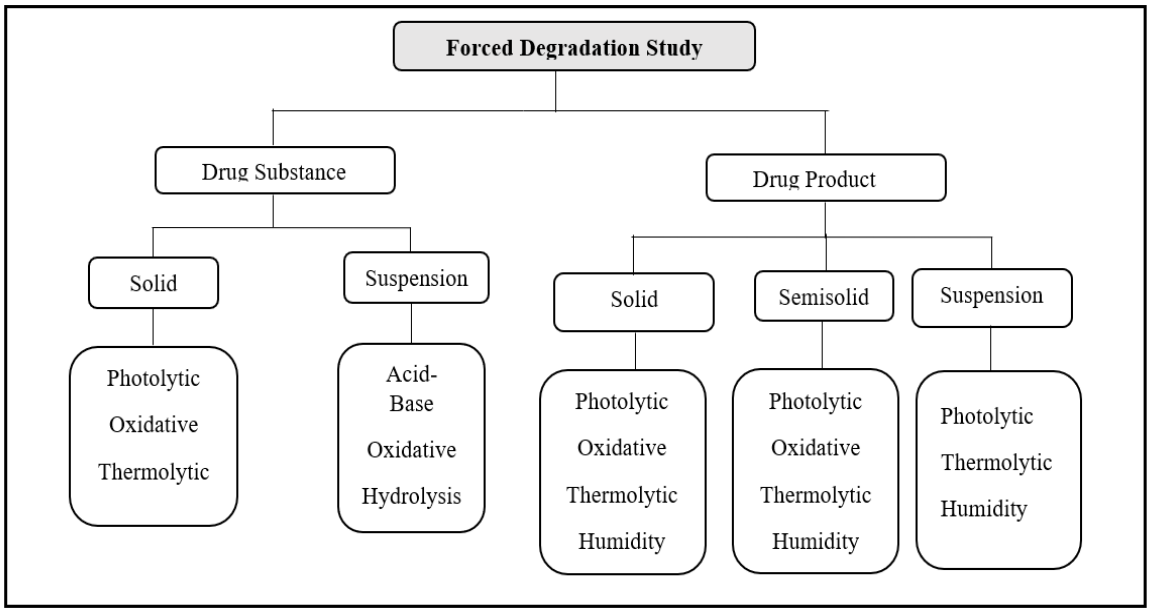

Fig.1: Conditions of Forced Degradation studies

3. Factors Affecting of Degradation

The several factors listed below lead to the deterioration of pharmacological compounds. They are as follows:

3.1 Excipient: Wetness Substances that are soluble in water may dissolve when wet. The molecule experiences both chemical and physical changes as a result. Recipients it has been noted that certain excipients could have a high-water content.

3.2 Moisture: moisture may cause the formulation's water content to rise, which would then impact the drug's stability. Decreased stability can occasionally be the result of chemical reactions between medicated substance and excipient

3.3Temperature: Temperature variations can occasionally have a negative impact on the drug's stability. The rate at which drugs hydrolysed normally rises with warmth.

3.4 pH: The pH has a major impact on how quickly medications hydrolyse and break down. In order to mitigate this effect, buffer solutions with the highest stability are used during the drug formulation process

3.5 Oxygen: Air certain medications oxidize more when oxygen is present. Nitrogen or carbon dioxide purging in the storage container stabilizes drugs that break down more quickly in the presence of oxygen.

3.6 Light: Some drugs are photo labile and tend to decompose when they are exposed to light. How vulnerable its stability under light and stability when stored in the dark can be used to test the photolytic decomposition process.

It is to be remembered that the photolabile compounds should be stored in amber glass containers and should be stored in the dark [18].

4. Method Validation Parameter [19-24]

After that, the created SIM is verified for linearity, accuracy, precision, specificity, quantitation limit, detection limit, ruggedness, and robustness of the technique in compliance with USP/ICH requirements. The method is adjusted and revalidated if it doesn't satisfy the validation

acceptance criteria. Degrades need to be isolated, recognized, and quantified (usually at 0.1%), if they are found to be above the identification threshold.

4.1 Specificity

In order to develop an HPLC separation process, specificity—the capacity to evaluate without reservation in the presence of potentially present components—must be demonstrated. These possible sample components typically consist of matrix, synthesis intermediates, excipients, degradation products, and placebo formulation. Other supporting analytical procedures may make up for a particular analytical procedure's lack of specificity. Identification: To confirm an analyst's identity. Purity tests: To make sure that every analytical technique used enables an accurate description of an analyst's impurity content, such as the content of residual solvents, heavy metals, and related compounds. Assay (content or potency): to yield a precise result that permits a precise declaration of the analyst's content or potency in a sample.

4.2 Accuracy

Trueness is another word for accuracy. The percentage difference between the expected and observed concentrations can be used to define percentage accuracy. To make sure that other components don't interfere with the analytical method, accuracy is typically measured by measuring a known amount of standard material under various conditions. Ideally, this is done in the formulation, bulk material, or intermediate product. Spiked samples are made in triplicate at three different levels ranging from 50% to 150% of the desired concentration for use in assay (dissolution sample) procedures. Next, the recovery percentage needs to be computed. The mean recovery at each concentration within the range of 50–150 percent of the target concentration is the accuracy requirement for an assay procedure. According to ICH methodology recommendations, data collection should be done from a minimum of nine determinations over a minimum of three concentration levels that cover the defined range (e.g., three concentrations, three replicates each) in order to document accuracy.

4.3 Precision

To be precise, an analyst's readings should all be quite near to one another. Every quantitative result need to be highly precise, with an assay system variance of no more than ± 2%. One helpful metric is the coefficient of variation (CV), or relative standard deviation, which indicates how inaccurate the system is. Precision should be carried out at two distinct levels, according to the ICH: repeatability and intermediate precision. Repeatability measures how simple it is for a lab operator to use the same procedure, same tools, and same reagents to get the same result for the same batch of material at different times.

4.4 Detection limit (LOD)

An analytical technique's detection limit is the lowest concentration of analyse in a sample that can be identified, albeit it may not necessarily be measured as a precise quantity. Signal-to-Noise claims that only analytical procedures exhibiting baseline noise can use this technique. Signal-to-noise ratios and the limited intensity at which the substance under study can be reliably recognized can be computed by comparing recorded signals from blank samples with analyse concentration that is known to be low.

4.5 Quantification limit (LOQ)

The quantitation limit of a method of analysis is the lowest concentration of analyte in a sample that can be accurately and precisely determined

quantitatively. Based on the Signal-to-Noise Technique This approach is only applicable to analytical processes with baseline noise. The measurement of the signal-to-noise ratio involves comparing the observed signals of samples that have low analyse concentrations with blank samples. Furthermore, the lowest level of concentration at which the analyse may be reliably detected can be determined.

4.6 Linearity and range

The capability of a test process to yield results that are exactly proportionate to the analyte concentration in the sample (within an established range) is known as linearity. The range is the space between the highest and lowest analyte levels that have been precisely, accurately, and linearly determined using the prescribed procedure. A minimum of five concentration thresholds and a few minimum specified ranges are required by ICH suggestion. The y-intercept of the linear regression line for the response versus concentration plot and the correlation coefficient are frequently utilized to assess the acceptability of linearity data. When the regression coefficient (r2) is 0.999, it is typically seen as proof that the data fit the regression line rather well. It is necessary to compute the slope, intercept, and percentage relative deviation from the mean (RSD).

4.7 Robustness

Measures an analytical method's ability to stand up to minor but intentional changes in parameters including temperature, buffer concentration, injection volume, mobile phase composition, and pH. It additionally offers some insight into how reliable an analytical method is under usual circumstances. It is crucial to compare the chromatography obtained using the adjusted parameter(s) with the chromatographic produced using the target parameter for a sample comprising representative impurities.

5. Method Development & Optimization

The prerequisites for creating the HPLC method are its many physiochemical parameters, including the pKa, log P, solubility, and a maximum absorption. Thus, pKa value assist in the identification of pH of the mobile phase, while log P and solubility assist in identification of the mobile phase and sample solvent [25].

Because the sample degradation is done in an aqueous solution, the first choice of the column loading is reverse phase column to start separation of the components of a sample. Initially, the separation steps can be made using acetonitrile, water and methanol as the mobile phase in combination with each other. The choice of which of the acetonitrile and methanol to use in the organic phase depends on solubility of the analyte. To get a satisfactory separation of peaks, the water: The organic phase to aqueous phase ratio may be set to start on a 1:1 and altered according to the successive experimental results. Whereas in the case of requiring better peak symmetry and separation, more of the buffer can be used. General, all of the mobile phase buffers used in this procedure, including trifluoracetic acid and ammonium formate, ought to be MS compatible if the methods are to be extended to include LC-MS. Furthermore, because analytes exhibit different response to changes in temperature, column temperature affects the selectivity of the method [26].

It showed that reprocessing at a temperature that ranges from 30-40 degrees Celsius would give the best repeatability. The presence of all of the degradation products at this point allows for easier separation of each peak, so it is better to shift the drug peak further along the chromatogram. Further,

time must elapse after the drug peak in order to get the degradants peak eluting after the drug's peak. At any single stage throughout the process of analysis, impurity or degradant peak may be masked underneath the drug peak. This is important because it is needs peak purity analysis that is different from conventional purity in the procedure as beginners will only measure abs.

PDA detection enables online direct analysis. PDA provides information about homogeneity of the spectral peak; however, it cannot be used for degradants whose UV spectra are similar to the spectra of drugs. Therefore, in an indirect technique, an attempt to alter a chromatographic condition, such as the ratio of the mobile phase, column, etc., shall affect the degree of peak separation. Subsequently, there is a comparison of the original spectra with that of the modified chromatographic condition. And it can be concluded that the drug peak is homogenous if the degradant peaks and the % area of the drug peak remains unchangeable. If it can be seen that the degradant that elutes together with the medication does not form under accelerated and long-term storage conditions then it is okay. Subsequently, more or less similar peaks are resolved by modifying the injection volume, type of column, ratio of the mobile phase, and flow rate.

6. Extent of Degradation

He agreed that more arguments arise apropos to how much degradation is needed for stress study goals aside from the traditional therapies. It appears that pharmaceutical scientists consider samples with degradation level of less than 10% as suitable for use in method validation. These factors relate to small scale organic medicine that has shelf stability has to do with the standard pharmaceutical limit of 90 percent of the claim on the label. Unlike what has been done for types or classifications of pharmaceutical products regarding physico-chemical alterations, inactivation, or degradation during shelf life. Similarly, the national and international laws on biological products do not provide much guidance on issues concerning stability. Such matters should be given special attention separately. To the extent that the forced degradation trials are carried out the result is not necessarily total product malfunction. If, after having experienced a stress beyond the limits to the accelerated stability procedure, none of the products demonstrate any sign of degradation, the investigation might end [20].

7. Other Analytical Method

Prior reporters have demonstrated that there is a possibility of employing several analytical approaches to extract, recognize and quantify the impurities generated during the degradation studies even below detectable levels. The degrades isolated in the study were identified and characterised using hyphenated techniques comprising of LC-MS and LC- nuclear magnetic resonance spectroscopy (LC-NMR) [28]. More importantly, the structural characterization of the degradant's impurities becomes relevant since it contributes to eligibility in shelf-life stability. Impurities can be detected with thin layer chromatography (TLC) and its modified forms, electrophoresis, colorimetric, and gel filtration techniques; and degrades in pure form may be isolated with reversed-phase HPLC, TLC, gas chromatography, and supercritical fluid chromatography. After separation when the eluting degradant cannot be isolated in pure form HPLC – DAD and LC-MS are used to compare the RRT(relative retention time),UV spectra mass spectra (MS/MS or MSN) [29, 31].

Conclusion

Forced degradation studies have clarified the structures of degradants and provided insights into

potential degradation pathways and products of active components. The hypothetical compounds generated through forced degradation studies may or may not occur under normal storage conditions, but they aid in developing stability indicating methods. Initiating degradation studies early in the drug development process allows sufficient time to understand molecule stability, thereby enhancing formulation manufacturing processes and determining optimal storage conditions.

This study underscores the importance of employing common sense, as no single set of conditions applies universally to all drug substances and products, and regulatory guidance lacks specificity on required criteria. The objective of any forced degradation strategy is to achieve a targeted level of degradation, typically between 5% and 20%. A well-planned and executed forced degradation investigation yields a suitable sample for developing a stability indicating method.

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Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authorship contribution statement

Mukesh Patil: Supervision, Validation, Methodology, Investigation, Writing – original Draft, Ashwini Tayade: Conceptualization, Administration, Ashish S Jain: Funding, Data Curation.

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