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Review Article

Analytical Insights into Forced Degradation Studies: A Systematic Review of Methodologies, Applications, and Regulatory Implications

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ABSTRACT

Forced degradation, as a method to induce the breakdown of novel drug substances and products under harsher conditions than accelerated conditions, plays a critical role in demonstrating the specificity of stability indicating techniques. This process not only elucidates the degradation pathways and products of drug substances but also facilitates the elucidation of structural details of degradation products. Additionally, forced degradation studies provide valuable insights into the chemical behavior of molecules, aiding in formulation and packaging development. Despite its importance, existing regulatory guidelines often lack detailed explanations on the execution of forced degradation experiments, resulting in generic directives. This review aims to bridge this gap by delineating study methodologies, elucidating degradation mechanisms, and summarizing analytical techniques essential for the development of stability indicating methodologies. By addressing current trends in forced degradation research, this review contributes to the advancement of analytical methodologies in pharmaceutical development.

Keywords: Forced degradation, Accelerated conditions, Analytical techniques, Stability indicating methodologies, Formulation, Packaging.

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1.Introduction

Pharmaceutical molecule chemical stability is a serious problem since it influences the drug product's effectiveness and safety. Data from stability tests must be provided, according to FDA (Food and Drug Administration) and ICH (International council of Harmonisation) guidelines, to comprehend how a drug's content and product quality.

Over time while being influenced by different environmental circumstances. Understanding a molecule's stability aids in choosing the best formulation, packaging, storage conditions, and shelf life—all of which are crucial for regulatory paperwork. Through the process of forced degradation, drug compounds and products are broken down under more harsh conditions than during accelerated degradation, producing degradation products that may be analysed to ascertain the stability of the molecule. According to the ICH guideline, the purpose of stress testing is to discover potential degradation products, which aids in determining the molecule's inherent stability, developing degradation pathways, and validating stability. Naming the methods that were employed [1]. However, these standards cover forced degradation in a very basic way and don't go into specifics regarding how stress testing should be done in practice.

Forced degradation studies are not regarded as a prerequisite for a formal stability program, despite being a scientific and regulatory need during the medication development process. Stability studies of novel drug moiety must now be completed before submitting a registration dossier. The stability investigations consist of both rapid (6 months) and long term (12 months) tests. However, six-month trials can be conducted under certain circumstances.

Less harsh than that employed in quick studies. Therefore, it would take even longer to analyse degradation products such separation, identification, and quantification. Forced degradation studies, in contrast to stability studies, aid in the generation of degrades in a significantly shorter amount of time—typically a few weeks. Stability can be developed using the forced degradation samples. Demonstrating a technique that can be used in the future to analyse samples produced by both long-term and rapid stability investigations. This review offers a suggestion for the use of forced deterioration in practice and how to apply it to the creation of stability indicator methods.

1.1 Objective of Forced Degradation Studies

Forced degradation studies pursue multiple objectives, including elucidating degradation processes of drug substances and products, distinguishing between degradation products linked to the drug product and those from non-drug components, characterizing the structure of degradation products, assessing the inherent stability of drug substances, revealing breakdown mechanisms such as hydrolysis, oxidation, and photolysis, establishing stability indicating methods, understanding molecular compositions of pharmaceutical compounds, improving formulation stability, generating degradation profiles comparable to formal stability studies, and addressing stability-related issues within regulatory frameworks.

1.2 When to Execute Forcible Degrading

Knowing when to conduct forced degradation experiments is crucial for the creation of novel medicinal substances and novel drug products. According to FDA guidelines, stress testing needs to be done during Phase III of the regulatory submission procedure. To ascertain the stability of the drug material, stress studies has to be carried out in various

pH solutions, in the presence of oxygen and light, and at higher temperatures and humidity levels. One batch is used for these stress tests. An annual report containing a summary of the findings should be filed.

It is strongly advised to begin stress testing on pharmaceutical substances early in the preclinical phase or phase I of clinical trials. This will allow ample time for the discovery of degradation products, the elucidation of structure, and the optimisation of stress conditions early stress studies also provide helpful suggestions for enhancing the manufacturing process and choosing stability-indicating analytical techniques in a timely manner [4].

1.3. Limitation of Deterioration

Pharmaceutical experts have had numerous conversations about the issue of how much degradation is sufficient. It is considered normal for chromatographic tests to be validated when pharmacological compounds degrade by 5% to 20% [5,6]. When it comes to tiny pharmaceutical compounds, which typically have acceptable stability limitations of 90% of the label claim, some pharmaceutical professionals believe that 10% degradation is the best method to utilise for analytical validation [7]. Others proposed using drug material laced with a combination of recognised degradation products as a means of contesting the techniques used to track the stability of the drug product. For specific types or categories of biological products, no such restrictions have been defined for physiochemical changes, loss of activity, or degradation throughout shelf life.

2. Different Types of Degradation

2.1. Hydrolytic Degradation

Hydrolysis is one of the most common chemical breakdown reactions over a wide pH range. A chemical compound breaks down through an interaction with water, a process known as hydrolysis. Catalysing the molecule's ionisable functional groups is necessary to study hydrolysis in basic and acidic environments. The technique of driving a drug's degradation through exposure to basic or acidic environments which results in the production of primary degrades within a desired range is known as acid or base stress testing. The type and concentration of acid or base that is chosen depends on how stable the substance in the treatment is. acids that are sulphuric or hydrochloric (0.1 M to 1 M) For base hydrolysis and acid hydrolysis, sodium hydroxide or potassium hydroxide (0.1 M to 1 M) are suitable hydrolysis reagents [8,9].

If the compounds used for stress testing are not well soluble in water, they can be dissolved in HCl or NaOH with the use of co-solvents. The selection of a co-solvent considers the drug's substance composition. A stress test session is typically initiated at ambient temperature. The temperature is raised to 50–70°C if there is no deterioration. Seven days should be the maximum duration of a stress test. The degraded sample is subsequently neutralized with the appropriate acid, base, or buffer to prevent further degradation.

2.2 Oxidation Degradation

Hydrogen peroxide is widely used to oxidize pharmaceutical substances in forced degradation experiments. But you can also use other oxidizing agents, such oxygen, metal ions, and radical initiators (like AIBN, azobisisobutyronitrile). Selecting an oxidizing agent and determining its conditions, and dosage change based on the drug's ingredient. According to reports, the solutions can create relevant degradation products if they subjected to 0.1% – 3% hydrogen peroxide for seven days at room temperature and neutral pH, or up to 20% degradation. An electron

transport system is involved in the oxidative process. Medicinal material degradation, resulting in the production of reactive anions and cations. Electron transfer oxidation of amines, sulphides, and phenols can yield N-oxides, hydroxylamine, sulphones, and sulphide [10].

Functional groups having labile hydrogen, such as those with benzylic, allylic, and tertiary carbon positions with respect to the hetro atom, can be oxidized to produce hydro peroxides. Either 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.

It is possible to conduct research at higher temperatures and for shorter durations.

The influence of temperature on thermal deterioration of a chemical is studied using the Arrhenius equation, which is expressed as:

$$K = A\, e^{-Ea/RT} \qquad \text{.................. Eq. No. (1)}$$

where, T is the absolute temperature, R is the gas constant (1.987 Cal/deg mole), and k is the specific Reaction rate [16, 17]. A 40˚–80˚C thermal deterioration investigation is conducted. The frequency factor is represented by A, while the activation energy is represented by Ea.

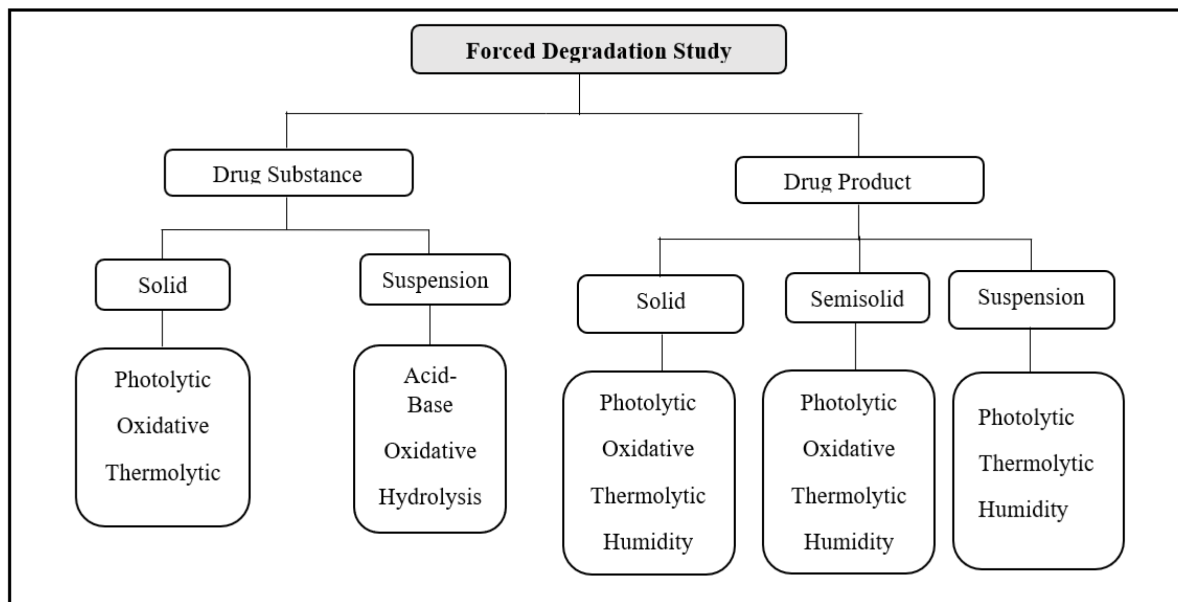

Fig.1: Conditions of Forced Degradation studies

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.

It seems that choosing a signal-to-noise ratio of 3:1 or 2:1 is a good starting point for figuring out the detection limit. Considering the standard deviation of the response and the slope. A detection limit can be stated in as per equation no (2)

$$LOD = 3.3\sigma/S \text{ …………Eq. no. (2)}$$

Where, σ represents the standard deviation. S represents slope in calibration curve's.

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.

A 10:1 signal-to-noise ratio is considered typical. Examine the Slope and the Standard Deviation of the Response. A Quantification limit can be stated in as per equation no (3)

$$QL = 10\sigma / S \text{……………Eq. no. (3)}$$

where σ is the response's standard deviation. S is representing the calibration curves slope.

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 foundation for developing an HPLC method is laid by understanding the drug's numerous physiochemical properties, such as its pKa value, log P, solubility, and maximum absorption. While pKa value aids in determining the pH of the mobile phase, log P and solubility aid in the selection of the mobile phase and sample solvent [25].

Since the degradation process is conducted in an aqueous solution, a reverse phase column is the recommended option to begin the separation of sample components. For the first phases of separation, acetonitrile, water, and methanol can be employed as the mobile phase in different ratios. The solubility of the analyte determines which of the two acetonitrile and methanol to choose for the organic phase. To get a satisfactory separation of peaks, the water: organic phase ratio can be started at 50:50 and adjusted as needed as experiments go on. If more buffer is needed to achieve improved peak symmetry and separation, it can be added. Mobile phase buffers such as trifluoracetic acid and ammonium format should be

MS compatible if the procedure is to be expanded to LC-MS. Mobile phase buffers such as trifluoracetic acid and ammonium formate should be MS compatible if the procedure is to be expanded to LC-MS. Because analytes react to temperature changes differently, variations in column temperature have an impact on the method's selectivity [26].

A temperature between thirty and forty degrees Celsius is ideal for achieving high repeatability. Since this leads to the separation of all degradation products, it is preferable to push the drug peak farther in the chromatogram. Additionally, enough time must pass after the drug peak in order to acquire the degradants peak eluting following the drug's peak. Throughout every step of the process, an impurity or degradant peak that co-elutes with the drug may be hidden by the drug peak. Peak purity analysis is required for this since it affects the specificity of the procedure [27].

Online direct analysis is possible using photo diode array (PDA) detection. PDA gives information about the spectral peak's homogeneity, but it is inapplicable to degradants with UV spectra comparable to those of drugs. Peak separation will be impacted by changes made to the chromatographic conditions, such as the mobile phase ratio, column, etc., in an indirect technique. Next, the original spectra and the spectrum of the modified chromatographic condition are contrasted. It can be established that the drug peak is homogenous if both the degradant peaks and the area % of the drug peak stay constant. If it is discovered that the degradant that co-elutes with the medication does not form under accelerated and long-term storage settings, then it is acceptable. After that, the technique is adjusted to separate closely eluting peaks by adjusting the injection volume, column type, mobile phase ratio, and flow rate.

6. Extent of Degradation

There is a lot of discussion around the subject of how much degradation is necessary to achieve the goals of stress studies, particularly in relation to traditional therapies. Pharmaceutical scientists seem to agree that samples with a degradation level of less than 10% are ideal for use in the validation of analytical methods. These factors pertain to small-scale organic medicines, whose stability is determined by the standard pharmaceutical limit of 90% of the claim on the label. No such restrictions have been set for specific types or groupings of pharmaceutical products about physico-chemical changes, loss of activity, or degradation during shelf life. National and international laws governing biological products do not offer much advice on matters pertaining to stability. These matters ought to be considered individually. It’s not always the case that the forced degradation trials lead to product breakdown. If, following exposure to a stress above the parameters of the accelerated stability procedure, no degradation is seen, the investigation may be terminated [20].

7. Other Analytical Method

Earlier reporters have shown that multiple analytical techniques are available to isolate, identify, and characterize the impurities that are produced in the degradation studies even at a very low concentrations. The degrades isolated in the study were identified and characterized by hyphenated methods such as LC–MS and LC–nuclear magnetic resonance spectroscopy (LC– NMR) [28]. More importantly, the structural characterization of the degradant’s impurities become necessary as they play a vital role in the determination of shelf-life stability. Detection of impurities can be done by thin layer chromatography (TLC), electrophoresis, colorimetric, and gel filtration techniques, while separation and isolation of degrades in pure form can be done using reversed-phase HPLC,

TLC, gas chromatography, and supercritical fluid chromatography.

When 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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