ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4

Journal of Coastal Life Medicine

An Extensive Comprehension of Forced Degradation Studies of New Drug Substances and Products

Received: 19 October 2022, **Revised:** 23 November 2022, **Accepted:** 28 December 2022

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Keywords
Forced degradation, degradation pathway, ICH guidelines, hyphenated techniques, stability indicating assay method.

Abstract
Forced degradation tests are a method used in the pharmaceutical industry to assess the stability of medication samples. Stress examination of degradation products is beneficial in determining the pathways of degradation as well as designing and testing appropriate analytical techniques. Forced degradation experiments reveal chemical behavior of the molecule, which aids in formulation & package creation. According to the studies, the majority of researchers and reviewers claim to use ICH recommendations, Q1A-Q1F, for the degradation analysis and impurity profiling of drug substances & drug products. A variety of spectroscopic and chromatographic techniques like as UV spectroscopy, RP- HPLC, Gas Chromatography, and others may be used for regular analysis of pharmacological compounds and products. Forced degradation studies of medicinal compounds and products have found a significant application for hyphenated approaches. The current research also provides significant insights into the stability indicating assay techniques and their importance in determining medication stability. The study also discusses the role of excipients in the deterioration of pharmaceuticals.

Introduction

Forced degradation studies provide the approach to analyse the stability of drug samples in pharmaceutical industries. Drug □□□□□□□□□ □□□□□□□□ □□□□ □□□□□□□□□□ □□□□ □□□□□□□□□□ □□□□□□□□ □□□□□□□□□□ □□□□□□□□□□ of the molecule. Stability of molecule information provides the data for selecting proper formulation, package, proper storage □□□□□□□□□□□□ □□□□ □□□□□□ □□□□□□ □□□□□□ □□□□□□ □□□□□ □□□□□ □□ □□□□□□□□□□□□□ □□□□□ □□□□□□□□□□□□□□□□□□□□□□□□□□ □□□□□□□□□□□□□□□□□□□□□□□□□□ □□□□□□□□□□□□□□□□□□□□ registration dossier it is obligatory to execute stability studies of new drug molecules

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Forced degradation tests are a method used in the pharmaceutical industry to review stability of medication samples. Chemical stability of molecule influences drug product safety & efficacy. The information provided by molecular stability is used to identify the best formulation, package, shelf life & storage conditions. These statistics are especially important because they are required in regulatory documents. Stability studies of novel medicinal compounds are required before completing out the registration dossier [1,2].

The forced degradation research is a vital and important phase in the investigation of drug compounds and pharmacological products. Stress testing is another term for forced degradation investigations. It is a significant study that must be carried out in accordance with standard regulatory criteria. Stability studies are undertaken in accordance with ICH recommendations (Q1A) to recommend the shelf life of novel drug substances and/or pharmaceutical products. Shelf life studies are also included in a variety of regulatory filings to the USFDA. When a formulation is created, it must be tested for stability because the degradation products that arise are responsible for the loss of the drug's medicinal efficacy. Physical, chemical, and biological deterioration can be caused by a variety of environmental conditions [3,4].

Forced breakdown Analysis is an operation that involves determining the stability of the active medicinal ingredient by assessing its breakdown products generated by exposing it to rapid and high stress conditions. As illustrated in Figure 1, drug material or drug product degradation can be Physical, Chemical, or Biological.

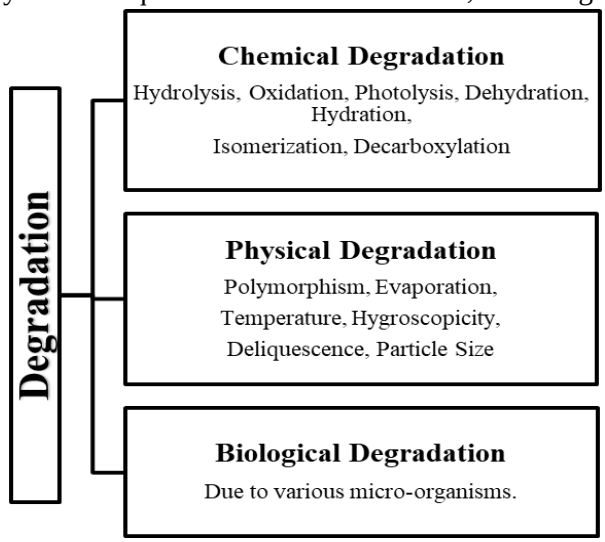

Figure 1: Types of degradation

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Stress testing a drug substance can help to detect the expected degradation products, which can help to establish the degradation pathways and intrinsic stability of the molecule. It can also help to validate the analytical procedures' ability to identify stability. The specific drug chemical and drug product will define the kind of stress testing [5,6].

The drug ingredient will probably be the subject of a single round of stress testing. Considerations for the pharmaceutical molecule should include oxidation, photolysis, humidity (e.g., 75% RH or higher), and temperature (in 10 C increments [e.g., 50 C, 60 C] above that for accelerated testing). When in solution or suspension, the drug substance's sensitivity to hydrolysis should be assessed across a broad pH range. Photo stability testing should be a part of stress tests [7,8,9].

Determining degradation pathways and developing and testing suitable analytical techniques can both benefit from looking at degradation products under stressful conditions. However, it might not be necessary to look for certain degradation products if prior studies [10,11,12] have demonstrated that they do not appear under expedited or long-term storage conditions.

The two stages of photo stability testing should be forced deterioration and confirmatory testing. Assessment of the material's overall photosensitivity for technique development and/or elucidating the degradation process is the aim of forced-degradation testing. The drug material may be examined either alone or in simple solutions and suspensions to validate the analytical methods. Depending on the photosensitivity of the therapeutic ingredient and the strength of the light sources, different exposure conditions may be used, and the samples in these tests should be in transparent, chemically inert containers. It is appropriate to minimise exposure and end the studies for development and validation if significant breakdown takes place. Once an appropriate exposure level has been used, studies on photostable materials may be concluded. Although the exposure levels used in these tests must be justified, the applicant is free to design them as they see fit. [13,14,15]

Under forcing conditions, decomposition products that are unlikely to form under the conditions used for confirmatory investigations may be seen. The creation and validation of appropriate analytical techniques may benefit from this data. These degradation products don't need to be further explored if it has been demonstrated in practise that they are not produced in confirmatory testing. [16,17]

The behaviour and characteristics of the drug substance, the results of stability studies on the drug substance, and clinical formulation expertise should all be taken into consideration when designing formal stability studies for a drug product. It is important to outline the anticipated changes in storage conditions as well as the rationale behind choosing the features that will be examined in formal stability studies. Testing for photostability should be done on at least one initial batch of the medicinal product, if applicable. The normative testing circumstances are outlined in ICH Q1B. [18,19,20]

Any review should consider the test results, as well as the degradation byproducts and other pertinent characteristics. When appropriate, the sufficiency of mass balance, stability, and performance degradation should be taken into account. [21,22]

Stability Testing

According to the definition of the stability indicating method, it is "a validated quantitative analytical method that can detect changes in the chemical, physical, or microbiological properties of the drug substance and drug product over time, and that

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is specific enough that the active ingredient and degradation product content can be accurately measured without interference." [23,24,25]

Stability testing is the process of gathering data in order to create stability information (including, if necessary, results of physical, chemical, biological, and microbiological tests) and a retest period applicable to all upcoming batches of the medication material produced under similar conditions. The testing of at least three batches of the drug ingredient served as the foundation for it. Confidence that a subsequent production batch will remain within specification for the designated retest period is impacted by individual batch variability. The results of the stability tests show that:

1. How environmental factors like temperature, humidity, and light affect a drug substance's or product's quality over time.
2. Establish the drug substance's retest window or the drug product's shelf life.
3. Recommendations for storage circumstances. [26,27,28]

Objectives Of Stability Study

The various explanations for the performance of the stability testing are:

1. Determination of the drug's expiry date.
2. Stability is regarded as a critical quality trait.
3. Gathering stability data and product specifications.
4. Determination of container closure system compatibility.
5. Evaluation of comparability following manufacturing adjustments.
6. The requirement for regulatory agency approval. [29,30]

Factors Affecting Stability

i) Physical aspects

Pharmaceuticals are handled in many ways. As a result, they are susceptible to several types of deterioration, and a product may undergo multiple simultaneous decomposition reactions. Possible physical factors include:

1. Warm up the oxygen and light.
2. Transport and storage conditions.
3. Container that can be leached and extracted.

It generally causes volatile constituent loss, water loss, water absorption, polymorphism alterations, crystal formation, and colour changes. Stress testing is used to combat such an issue. It aids in:

1. Determining the most likely degradation product.
2. Aids in the establishment of degradation pathways & intrinsic stability of molecules. [31,32,33]

Although frequently not in the context of stress testing, numerous advice materials address a variety of stress testing challenges. For instance, the published guideline discusses mass balance, polymorphism and crystal forms, parenteral combination product stability, stereochemical stability, and degradation product identification thresholds, but does not address these topics in the context of degradation investigations.

ii) Chemical elements

Variability in pharmaceutical product composition causes chemical breakdown of active substances in formulation. The following are the primary parameters that contribute to degradation:

1. formulation pH.
2. The concentration of the formulation.
3. Excipients used in formulation.

Chemical breakdown pathways include:

1. **Hydrolysis:** It is defined as a compound's reaction with water. Acidic and basic species catalyse hydrolysis.
2. **Oxidation:** Oxidation of a chemical refers to the removal of an electropositive atom, radical, or electron or the addition of an electronegative atom or radical.
3. **Polymerization:** This is the process by which two or more identical molecules

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combine to produce a larger and more complicated molecule.

4. **Decarboxylation**: It is the process of removing carbon dioxide from a molecule. This is especially common in parenteral solutions.

Stability Indicating Assay Method (SIAM)

According to guidelines issued by the US Food and Drug Administration (USFDA), a stability indicating assay method (SIAM) is defined as a validated analytical procedure that accurately and precisely measures active ingredients (drug substance or drug product) free of potential interferences such as degradation products, process impurities, excipients, or other potential impurities. The FDA recommends that all assay procedures used in stability studies be stability indicating.

An active pharmaceutical ingredient (API) reduction brought on by degradation is detected using a SIAM, a quantitative analytical procedure. In the pharmaceutical industry, SIAM is frequently used to examine stability sample data. [34,35,36]

Objectives Of SIAM

Because there is no one stability test that profiles product's stability features, it is recommended for suggesting a stability signaling profile that guarantees change in identity, purity & potency. It assures that each product maintains within set limits for safety, purity, and potency during the clinical trial's intended life. Furthermore, it provides useful alternative standards for release and stability, which is to be supported by data to verify that clinical performance, is not harmed. [34,35,36]

Types Of SIAM

1) **Specific SIAM-** Analyses the drug(s) objectively in the presence of all excipients, additives, and breakdown products.
2) **Selective SIAM-** Analyses beyond a doubt the drug(s) and all degradation products, including excipients, additives, and degradation products.

Developing a stability indicating assay requires contemplation of three aspects of the method:

1) Obtaining a representative sample

Getting all the components that might be present in the drug ingredient before it is synthesised is one technique to prepare samples. The choice of molecules in the synthetic scheme that may be present in trace amounts in the finished product will be aided by knowledge of the drug's synthetic pathway. One or more of the drug's precursors might be a suitable choice to include in the combination of test compounds because it is sometimes possible to anticipate that chemical degradation will occur in the reverse sequence of manufacture. Placing the pure drug material under stress on purpose is another method for obtaining samples for creating stability indicating assays. Every laboratory has its own methods for this procedure, which is also known as forced degradation or planned degradation. However, the general strategy remains the same. The medication is exposed to heat, light, heat, acid, base, or oxidation. The target is typically to degrade the parent medication by 10% to 20%. Secondary degradants that could impede the development process could be produced by degradation that is much higher than 10–20%. [37,38,39,40]

2) Choosing the separation technique

Because the samples are prepared in aqueous solutions, RP- LC is method of choice for stability indicating tests. Polarity of deteriorated samples can vary significantly. Solvent type, mobile phase pH, column type, and temperature are the most frequent separation variables. Alterations in variables should be made at the start of the method development process to cause major changes in the separation. [37,38,39,40]

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3) Selecting detector

Particularly for drug detection in biological materials, the mass spectrometer is quickly replacing other detectors as the detector of choice for many LC techniques. However, for stability indicating experiments, the UV detector continues to be the detector of choice. The sample components must be identifiable by stability-indicating assays over a concentration range of 1000-fold, from 100% to 0.1-0.05% of the parent drug. UV detectors are more than capable of detecting this area. Diode array UV detectors are widely employed in the design of a stability indication test. A variable wavelength detector may be used for routine applications, however the diode array detector offers an advantage during development. In stability indicating studies, the wavelength with the parent chemical's maximum absorbance is frequently employed as the detecting wavelength. [37,38,39,40]

Chromatographic Techniques Employed For Siam

Because of the demand for separating numerous components during stability sample analysis, chromatographic methods have assumed dominance over conventional approaches. Aside from the ability to separate different components, chromatographic procedures provide improved accuracy & sensitivity for even very small quantities of degradation products created. One characteristic of the technique's adaptability is that the analysis can be performed on a very expensive and complex equipment at one extreme and on a basic, affordable thin layer plate at the other. [41,42,43]

As a result, there are limited reports on the usage of GC for the aim of establishing SIAM. SIAM is commonly used in comparison to GC, HPLC, and HPTLC. Its high resolution capability, sensitivity, and specificity have made it popular in stability investigations.

High Performance Liquid Chromatography, Gas Chromatography, Thin Layer Chromatography, High Performance Thin Layer Chromatography, & Capillary Electrophoresis are some of the chromatographic procedures employed.

The use of hyphenated approaches in the performance of forced degradation studies of medicinal substances & products has recently grown. The hyphenated techniques combine a chromatographic approach with an analytical method to obtain separation of mixture and spectra at the same time. It offers a wide range of uses, including increased reproducibility, reduced analytical time and contamination, and much more. The hyphenated approaches are characterised as double or triple hyphenated based on the combination of two or more instruments. [44,45] Figure 2 displays some of the most frequent hyphenated approaches used in drug forced degradation investigations.

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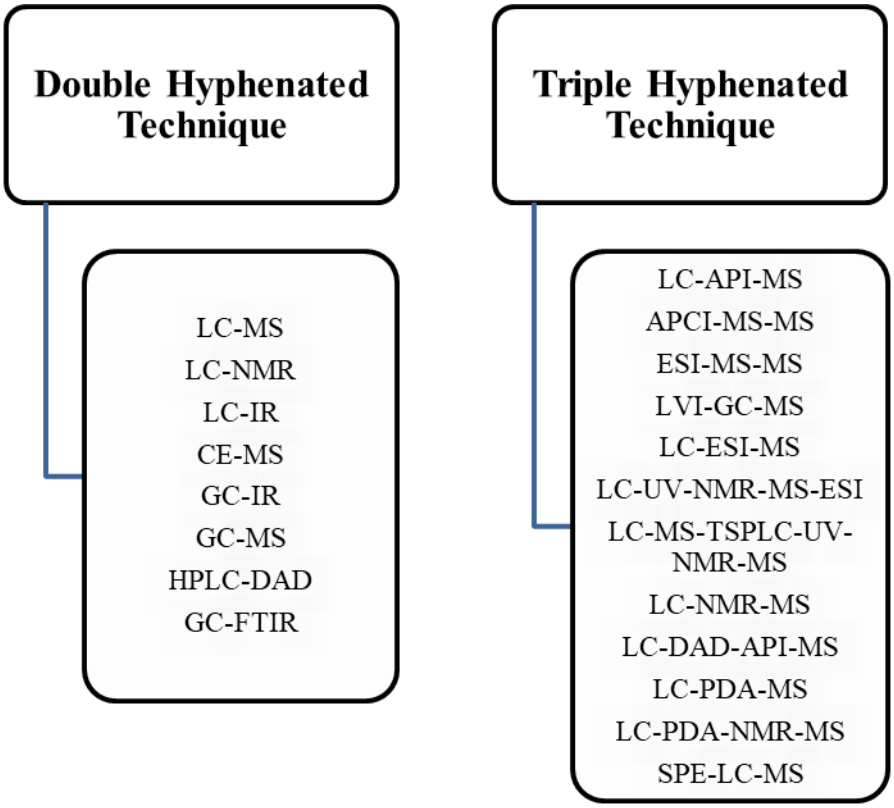

Figure 2: Examples of hyphenated techniques used for forced degradation analysis

Approaches For Conducting Forced Degradation Studies

While the prerequisites for SIAM have been described in regulatory papers, neither the regulatory guidelines nor the pharmacopoeias detail the fundamental steps that must be taken for the development and validation of stability-indicating methods. As a result, the steps in SIAM development that are actually viable are described here. The stages are intended to be followed in order to produce a SIAM that satisfies the regulatory requirements. [46,47,48]

Start the trials at 1.0 mg/ml of concentration. Aqueous solutions will be used to conduct these stress testing. The interest-generating pharmaceutical molecule's solubility, however, might play a role. Variable amounts of co-solvents can be employed to provide a clear solution when the drug is hydrophobic or has a poor solubility, or the testing can be carried out on a suspension. It is typically possible to acquire even tiny breakdown products within the detection range with a medication concentration of 1.0 mg/ml. Establishing SIAM may need a large amount of development work if various degradation products are produced under various circumstances. For this, repeated injections of reaction solutions may be necessary. As a result, appropriate sample volume should be drawn at each interval and the volume of samples submitted for stress tests should be sufficient. The extracted samples can be kept in cool cabinets to stop further reaction. The aliquots produced by acid and alkali hydrolysis may be neutralised and diluted before injection into HPLC. [49,50]

1. **Degradation:** By refluxing a known concentration of a novel medicine (API) in 0.1 N HCl/NaOH for 8 hours, taking samples at various intervals for each reaction state, and neutralising them, it is possible to study the hydrolytic breakdown of the drug in both acidic and

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ISSN: 2309-6152 (Online)
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alkaline conditions. Once a reasonable amount of degradation (5–20%) is seen, testing can be stopped. The drug needs to be refluxed in stronger acid or alkali for a longer period of time if no degradation is seen when it is being used under these circumstances. Alternately, acid/alkali strength and reaction temperature can be decreased if 100% degradation is seen after exposing the drug to the initial conditions. After separating these peaks in the chromatogram, peak purity is assessed using PDA and/or mass spectrometry to see if any significant degradation products are co-eluting and to check the homogeneity of the main component's (API) spectra. It is safe to assume that the chemical is resistant to acid/base hydrolysis if no deterioration has been found.

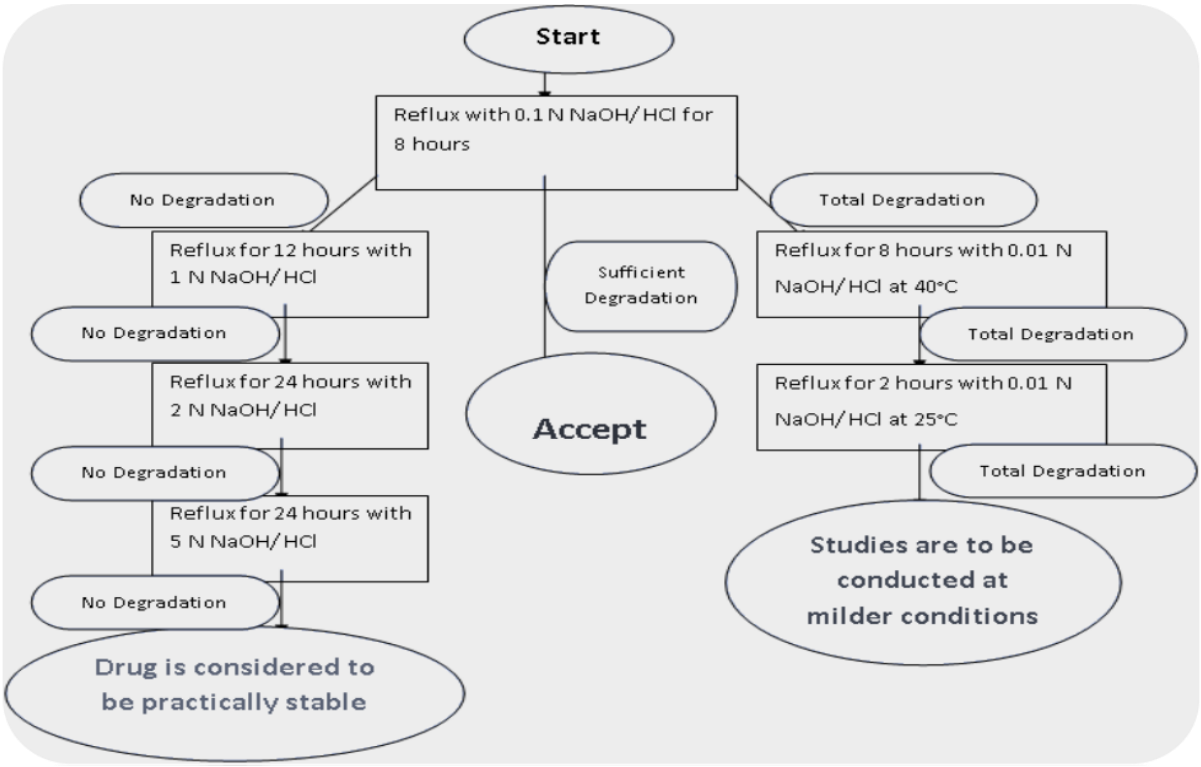

Figure 3: Flow chart for stress studies degradation under acidic and alkaline conditions [1]

2. Neutral Degradation: The same as with hydrolytic degradation, refluxing the drug in water for 8 hours might start deterioration under neutral conditions. The reflux time should be extended if no worsening is shown. The trial's duration and temperature can be decreased if it turns out that the medicine completely declines.

3. Oxidative Degradation: Free radicals are produced during oxidation reactions, which can be catalysed by oxygen, heavy metals, or light (initiation). Free radicals then combine with oxygen to form peroxy radicals, which then combine with the oxidative substrate to create more complex radicals (propagation), and finally the reaction comes to an end (termination).

The following is an example of an experimental setup for investigating oxidative degradation:

A pre-weighed excipient combination, API, and API + excipients are included in each crimped headspace vial. There are two more iterations of this process. This will lead to the storage of three sets of vials under three stress conditions (air, nitrogen, and oxygen

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ISSN: 2309-6152 (Online)
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headspace): excipients, API, and API + excipients. Two needles would be put into the rubber septa, one to let gas into the headspace and the other to let gas out, to produce the nitrogen (control) and oxygen stress conditions. In set one, nitrogen is transferred into vials; in set 2, pure oxygen is transferred into vials for a short period of time before the input and exit needles are removed. The set with pure oxygen in the headspace vials would exhibit the most oxidative degradation if molecular oxygen were involved in the production of degradation products. The third set's headspace, which is made up of air (which consists primarily of 78% nitrogen and 21% oxygen), has the next-highest amount. Given that set number one's headspace vials contain nitrogen, oxidative degradation is expected to be minimal. It is safe to assume that molecular oxygen is not causing any oxidative degradation of excipients, APIs, and API + excipients if the degradation profiles and number of main degradation peaks for all three sets of conditions are remarkably comparable. The aforementioned experiment can be carried out again using liquid or solid dose forms as long as the liquid bubbles with the gas passed through the needles. The example before shows how oxidative degradation can happen when molecular oxygen is present, but it can also happen when trace metal contaminants or radical initiation (peroxide residues from excipients in the presence of light) are present. All feasible trials must be conducted in order to ascertain how and what is causing the degeneration. It is best to conduct all experiments as early as feasible in the development phase. The clinical programme can be delayed as a result, particularly if the degradation product(s) needs to be discovered and/or certified.

Oxidative degradation can be performed by immersing the drug (API) in 3% H2O2 for 8 hours at room temperature and then removing samples at different time intervals during the process. Testing can be terminated at this particular point if reasonable degradation (i.e. 5-20%) is observed. If no degradation is observed under these conditions, the H2O2 strength and duration of exposure may be reduced to 30%. The oxidative deterioration is sufficient under the ambient storage condition. Higher temperatures >30°C are not suggested since the reaction rate in solution may be lowered due to a decrease in the oxygen content of the solvent. However, some compounds may degrade at higher temperatures due to the commencement of a free radical reaction. Higher temperatures (> 30°C) should be used with caution since the O-O bond is weak bond that would rapidly cleave at greater temperatures and thus creating hydroxyl radicals.

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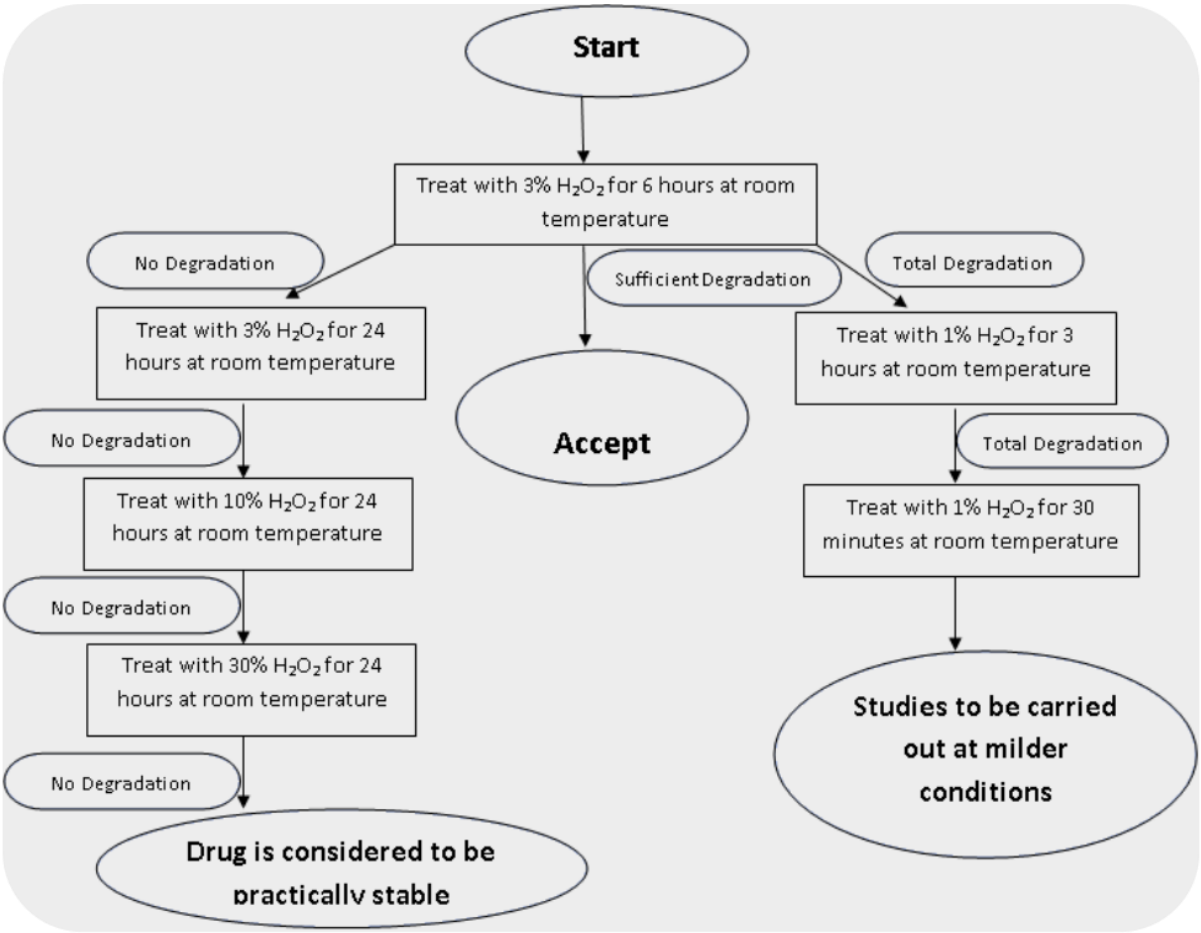

Figure 4: Flow chart for stress studies under oxidative conditions [1]

4. Thermolytic Degradation: The drug ingredient (API) will most likely be the subject of stress testing on a single batch. Thermolytic degradation can lead to hydrolysis, dehydration, isomerization, epimerization, decarboxylation, rearrangements, and several kinds of polymerization reactions. Thermolytic degradation studies should be carried out in accordance with ICH criteria at temperatures (in 10° increments, for example, 50°C, 60°C, etc.) higher than those used for accelerated testing, and samples should be taken at various points during the reaction condition. If a reasonable amount of degradation (5–20%) is seen, testing can be stopped at this time. If no degradation is seen in these circumstances, the investigation should be repeated at a higher temperature and for a longer period of time.

It has also been suggested in the literature that the thermolytic settings be chosen based on the melting point of the medicinal component.

• For drugs with a melting point of 150°C, stress the drug substance at 70°C or approximately 40°C below the melting point, whichever is greater.

• For drugs with a melting point more than 150°C, stress the drug ingredient at 105°C.

If no degradation occurs even under even severe stress, the molecule can be considered stable.

5. Photolytic Degradation: tests that purposefully degrade the sample are referred to as forced degradation testing tests. These studies, which are frequently carried out on pharmaceutical compounds throughout the development phase, are used to evaluate the material's overall photosensitivity for method

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development and/or the clarification of the degradation route.

A phenomena exists called surface-mediated photo degradation. For photolytic study, light exposure should be employed using either a xenon and metal halide lamp or a combination of cool white and UV fluorescent lights. In order to see signs of decomposition, the exposure energy must be at least 200W/m2 of UV and 1.2 million Lux/h of fluorescent light. If no signs of decomposition are seen, the intensity should be increased fivefold. The medication is referred to as photostable if there is no breakdown. A Lux/Watt metre is used to calculate the total amount of light that a pharmaceutical ingredient has been exposed to.

Photo stability can be measured using the light sources that are detailed below.

• Any light source made to produce an output similar to the D65/ID65 emission standard, such as a metal halide lamp, a xenon lamp, or a fluorescent lamp mixing visible and ultraviolet (UV) outputs. D65 is referred to as the acknowledged worldwide standard for outdoor daylight in ISO 10977 (1993). ID65 is the corresponding indoor indirect daylight standard. A light source that emits a significant amount of radiation below 320 nm may have the radiation removed by the proper filter or filters.

• Apply cool white fluorescent and near ultraviolet lamps to the same sample.

• A cool-white fluorescent lamp producing an output corresponding to that specified in ISO 10977(1993).

• A near ultraviolet fluorescent lamp with a spectral distribution from 320 nanometers to 400 nanometers and a maximum energy emission from 350 nanometers to 370 nanometers; a sizeable amount of UV should be present in both bands of 320 to 360 nanometers and 360 to 400 nanometers.

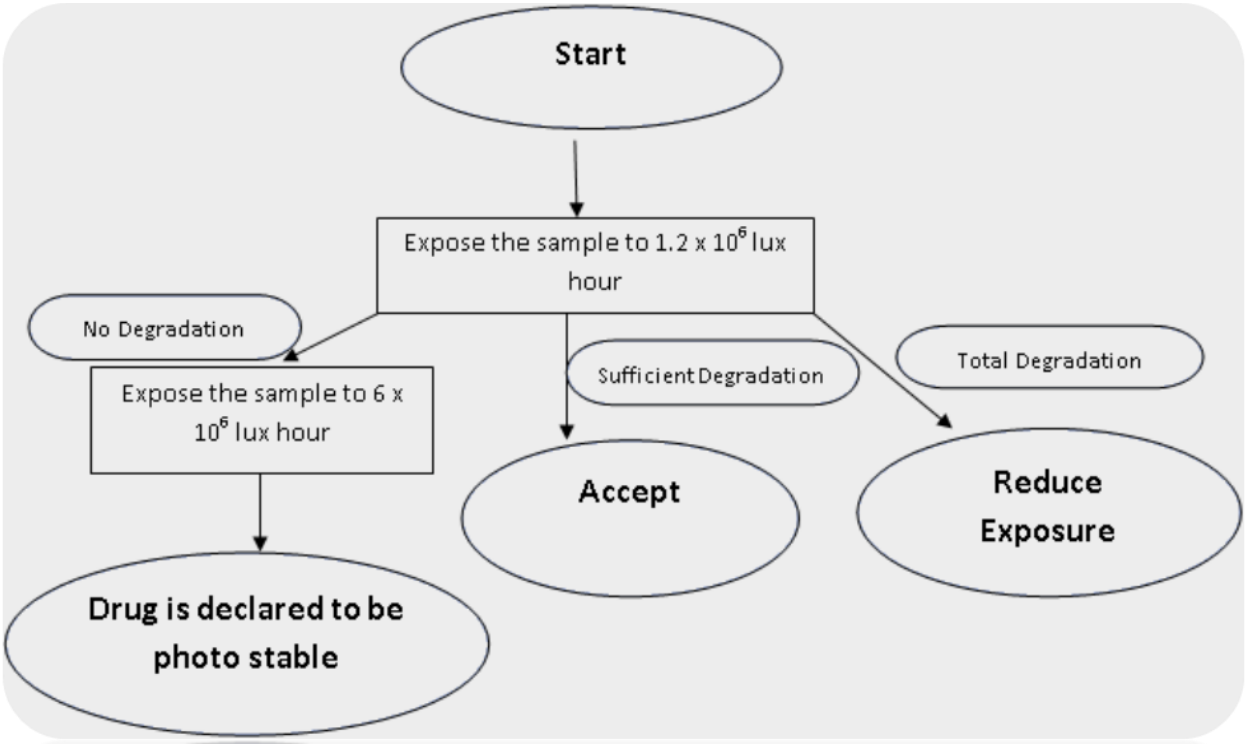

Figure 5: Flowchart for stress studies for photolytic degradation [1]

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Impact Of Excipients On Api(S) Degradation

Chemical substances with functional groups are called excipients. The functional group on the excipients may interact with the API in certain circumstances. Both accelerated storage and normal storage may be affected by these conditions. For these reasons, excipients shouldn't be considered inactive. The degradation product that results from an API's interaction with any of the RP-HPLC excipients may be bigger in molecular weight than the API itself. Because component retention in RP-LC is influenced by their relative hydrophobicity and interactions with the stationary phase, this does not necessarily imply that it will elute after API. It is common for RP-HPLC to work this way when neutral species are present, but it isn't always the case when ionizable species are present. If a more hydrophobic degradation product is produced, it will elute after the API peak. [51,52,53,54] The typical procedure for stress testing medicinal compounds and pharmaceutical goods is shown in Table 6.

Table 1: Stress testing procedures for drug chemicals and drug products [14]

Stress condition	Drug substance		Drug product		
	As pure solid	As solution or suspension	Solid dosage form	Liquids	Semi solids
Hydrolysis (Acid, Base & Thermal)	No	Yes	No	Yes	No
Oxidative	No	Yes	No	Yes	No
Photo degradation	Yes	Yes	No	Yes	Yes
Thermal	Yes	No	Yes	Yes	Yes
Thermal/Humidity	Yes	No	Yes	No	Yes

Conclusion

The current review highlights forced degradation studies and their importance in the stability assessments of new medicinal compounds and products. Every novel medicine molecule and formulation undergoes forced degradation studies to ensure its stability and storage conditions. To establish the degradation pathway and identify potential breakdown products of the medicinal molecule, the sample is exposed to severe temperatures, relative humidity, and light. The forced deterioration investigations are carried out in accordance with the ICH Q1 criteria. According to the regulatory standards, the fundamental forced degradation studies comprise hydrolytic degradation, thermal degradation, oxidative degradation, and photolytic degradation. Various hyphenated techniques like HPLC-MS, HPTLC-MS, GC-MS, and others, are used in the forced degradation analysis of pharmacological compounds and products. The current study also included the stability indicating assay methodologies, their goals, development, and importance. Excipients can sometimes cause drug molecule degradation, and its stress testing criteria are also included.

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ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
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