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**Review Article**

# Regulatory guidance on Forced degradation studies- A review

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**ABSTRACT**

Forced degradation studies are an integral part of drug development process. This is a method which promotes the intrinsic degradation rate of a product or material with applying extra stress conditions. It illustrates the chemical characteristics of the compound that aids in the creation of pharmaceutical formulation and packaging. The current study examines numerous regulatory considerations, forced degradation methods, and degradation characteristics for diverse pharmaceuticals. The drug substance and drug products are treated to extremely ambient condition throughout the forced degradation procedure to assess their stability. The stability in forced degrading circumstances should be determined in order to the applicability of stability methodologies. It is often used to establish storage conditions and enhance the formulation work flow.



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## 1. INTRODUCTION

Understanding the stability of a molecule assists in the selection of proper formulation and packaging, as well as the availability of required storage duration and shelf life, all of which are required for regulatory certification. Forced degradation is a process in which various stress conditions are performed to pharmaceutical compounds, resulting in the production of various breakdown products. These investigations are often known as stress testing or stress degradation studies. These approaches are mostly used to measure a molecule's stability under accelerated settings. The regulatory documentation procedure, the choosing of suitable storage and packaging parameters, and the formulation choice are all considered to be influenced by molecular stability (1). General circumstances such as light, heat, moisture, and oxidation are enhanced independently or in association with automated stress in the forced decomposition processes to accelerate component decomposition by physiochemical mechanisms. According to the International Council for Harmonization (ICH) requirements forced decomposition tests are used to assess the molecule's stability, numerous degradative pathways, and validation of the stated stability methods (2). The characteristics of drug molecules that deteriorate and the many products that are formed with reference to time changes under the impact of various environmental parameters, as well as the interpretation of stability data, are thoroughly explained using FDA and ICH guidelines. Forced degradation investigations are required by ICH guidelines in a variety of circumstances, involving pH, light, oxidation, heat, acidic, basic, hydrolysis, and so on. It also allows for the isolation of drug and decomposition products (3).

Each degradation product may be analysed using the designed and approved analytical technique. Moreover, there is limited research available on how to design truly selective forced degradation approaches. Temperatures, length, and intensity of deterioration, along with other things, are not appropriately stated in appropriate experimental circumstances for forced degradation investigations (4). This article gives an overview of the effects of forced deterioration due to a range of environmental variables. Stability studies of novel drug moiety are now required before submitting a registration dossier. Long-term (12-month) and expedited stability investigations are among the stability studies (6 months). However, intermediate research (6 months) can be conducted in less severe settings than expedited trials. Long-term studies facilitate the identification and isolation of

degraded products, but the primary disadvantage is that the study takes longer. The formation of degradation products occurs faster in forced degradation research than in stability test (5).

Forced decomposition studies are a technique for evaluating a drug's stability. These forced degradation studies can identify the drug's stability, which influences the purity, potency, and safety of the medicine. As a result, stability is regarded as a crucial feature. Any change in stability can result in a reduction in dose, making the dosage forms hazardous (6).

## 2. OBJECTIVES OF FORCED DEGRADATION

Studies on forced degradation of drug molecules are very important in the following aspects (7).

- To identify drug substance and drug product breakdown pathways.
- To distinguish between degradation products related to drug products and those produced by non-drug ingredients in a formulation.
- To resolve stability-related problems.
- To elucidate the structure of degradation products.
- To create formulas that are more stable.
- To create a deterioration profile that is comparable to what would be seen in a formal stability study conducted under ICH circumstances.
- To study the Chemical properties of molecules.
- For determination of intrinsic stability of drug in dosage forms.
- To tackle difficulties involving stability

## 3. REGULATORY GUIDELINES

When it comes to forced degradation, there are several guidelines to follow. The ICH has issued guidelines and instructions for performing these decomposition investigations, which have been adopted by various regulatory bodies (1, 2, 8-12).

**ICH Guidelines:**

ICH Q1A, Q1B, and Q2B, Q3A, Q3B, and M4Q are the ICH recommendations that describe forced degradation studies (R1).

**ICH Q1A (R2) (*testing of stability for new drug molecules and their products*):**

These guidelines will enable the development of drug stability measurement techniques. According to Q1A, degradation is determined by the type of the drug ingredients and drug products. These benchmarks are frequently used to determine the intrinsic stability of a drug. Section 2.1.2 of the Q1A guidelines is available here (under section

ICH Q1A-testing of stability for new drug molecules and their products). Under the following conditions, forced degradation investigations on drug compounds and drug products should be carried out. Several accelerated conditions were proposed in order to facilitate these forced decomposition studies on pharmaceutical substances and products. Temperature (>50°C), humidity (75 percent relative humidity), oxidation, photodegradation, and a wide pH range (solution/suspension) were among the factors considered (8-12).

**ICH Q1B (*photostability testing of new drug substances and drug products*)**: In the standard development stage, these approaches are employed to estimate the photostability of pharmacological compounds. These instructions explain how to evaluate the photostability of compounds that are being investigated for stability studies. In the sections on the necessity for forced degradation of pharmaceuticals and regulatory guidelines, respectively, forced breakdown of drug molecules and associated products were examined. In exploratory purposes, forced degradation investigations is being used to detect photolytic degradants (13-14).

**ICH Q2B (*validation of analytical procedures methodology*):** The ICH Q2B standards outline the steps to be taken in order to validate various analytical techniques. ICH Q2B, Part II, Section 1.2.2 describes the usage of samples during forced degradation investigations. It emphasises the importance of stressing the samples under various acceleration conditions such as humidity and heat before using them to evaluate specificity. Furthermore, these concepts may be used to calculate the number of degradants produced (15).

**ICH Q3A (*impurities in new drug substances*):** The ICH Q3A guidelines give information on determining contaminants in novel drug compounds. This section discusses many topics such as impurity identification, kinds, and specifications, analytical techniques, and report creation. More crucially, if impurities are either totally missing or present in tiny levels in a novel drug molecule batch, it is deemed beneficial to assure safety in clinical investigations (13).

**ICH Q3B (*impurities in new products*):** The ICH Q3B standard specifies analytical methodologies. An analytical process must validate the particular or non-specific degradation products under varied stress conditions (16-17).

**ICH M4Q (R1) (*the common technical document for the registration of pharmaceuticals for human use: Module 3: Quality*):** This report outlines the many sorts of research that have been conducted, the methodologies that have been employed, and the findings of the

investigations. Finally, it specifies the storage conditions, storage life, and the likely date of review. The findings should be presented in tabular, visual, or narrative fashion, and they should contain the analytical processes as well as the validation data (18).

The European Medicines Agency (EMA), the Food and Drug Administration (FDA), the United States Pharmacopeia (USP), the Japanese Pharmacopeia (JP), and the Agencia Nacional de Vigilancia Sanitaria (ANVISA) guidelines also include information on forced degradation research (19).

The **EMA guideline** includes information on the kind of investigations conducted, the processes employed, and the results received from the analysis. It provides information on the retest date and the expiry date of drugs. The development of an analytical technique, method validation, degradation routes, and intrinsic stability are all determined. The **FDA** has issued guidelines for analyzing the photostability of novel medication compounds and their derivatives (Q1B). These recommendations state unequivocally that no confirmatory tests for degradation products are required. Section 211.166(a) (3) requires that a SIM be extremely specific and capable of quantifying the quantity of active ingredient present, the kind of degradation products produced, and other components present in dosage form without interference. **Japanese Pharmacopoeia**, the suggested technique should be accurate, capable of identifying and estimating the amount of analyte present in the sample. If reference standard impurities are not accessible for comparison investigations, samples will be subjected to stress conditions, and degradation products may be employed for future research. The **National Health Surveillance Agency (ANVISA)** discusses the prerequisites for stability and forced decline. ANVISA was created to improve public health and safeguard against dangers associated with the manufacture and use of various pharmaceutical goods. ANVISA organizes states, districts, and municipalities in accordance with the principles of the Brazilian Unified Health System in order to improve people's quality of life (20).

## 4.TIME TO CONDUCT FORCED DEGRADATION STUDIES

Forced degradation analysis for novel drug compounds is regarded as critical since it affects the medication's stability and shelf-life. The FDA considers Phase III regulatory submission to be the appropriate time to conduct forced degradation research. Forced degradation experiments for specific batches will be done under various stress settings, according to the information provided.

Following the completion of the stability investigations, the identification, quantification, and isolation of degradants can be carried out (21).

Pre-clinical and Phase - I clinical trials allow enough time for the identification and structural elucidation of degradation products, which aids in the improvement of the manufacturing process. Determination of degradants and hazardous components can be conducted during pre-clinical testing. The degradation study may be performed at the clinical development stage, when the findings of pre-clinical and in-use stability stages can be compared. The recommendations also state that degradation studies can be conducted throughout the post-marketing period since new forms of stressors and changes that occur during manufacturing processes can be identified (22-23).

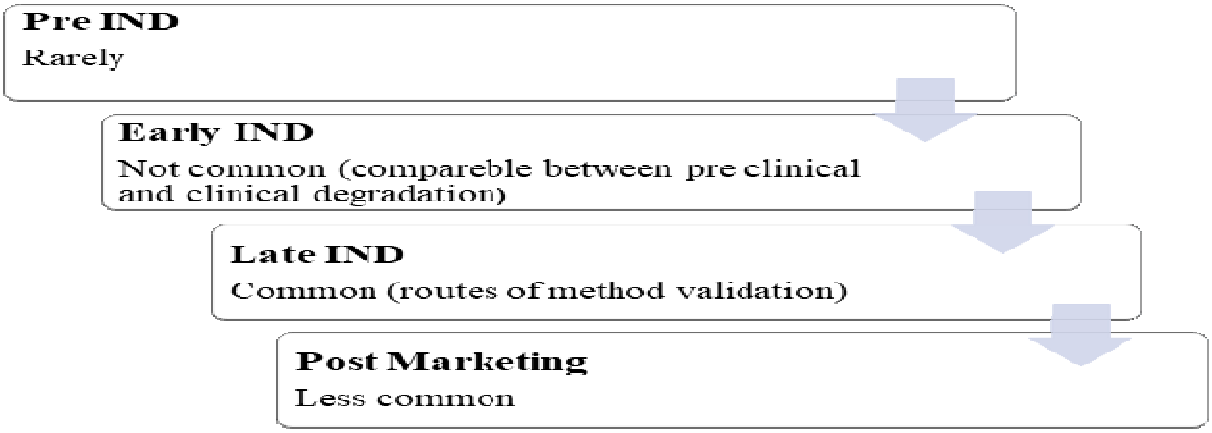


**Fig. 1: Forced Degradation Submitted Data**

1. During the pre-IND process Drug formulation Stability and quality aspects are studied, as are deterioration paths. Degradants and hazardous components identified for pre-clinical research.
2. During clinical development, the following factors must be considered:
    - comparing pre-clinical to clinical quality
    - comparing pre- to post-manufacturing alterations
    - in-use stability.
3. Post-marketing studies are not frequently conducted; however, the following aspects are taken into account.
    - discovered new stresses
    - Modifications to the manufacturing process
    - Additional indicators

## 5. KEY FEATUERS OF FORCED DEGRADATION

**Degradation Limit:**

Under these standards, regulatory bodies have specified the limitations of degradation products. It is said that 5–20% degradation is acceptable for chromatographic assay validation. In the case of tiny molecules, the stability limit should be more than 90%, implying that roughly 10% degradation is appropriate. In general, spiked samples of a mixture of known degradation products and drug substances are used to monitor drug product stability, which simplifies the process of determining the products that are detected throughout the degradation. If the physical and chemical character of the drug sample changes, or if the activity changes throughout the shelf life, the drug molecule is regarded to have degraded (20-21). When no such degradation is detected, the test will be terminated, or the relevant drug sample will be put to additional stress to determine the type of secondary degradants that are predicted to be produced throughout the study. However, as a result of the added stress, just a few or no degradants are formed, the drug material will be exposed to excess energy to evaluate the stability of molecules (24).

**Origin of Degradation Products:**

One of its major causes of contaminants is degradation. Drug molecules may degrade related to chemical instability in various stress conditions, like moisture, temperature, pH, separation, storage, and shipping processes. Forced deterioration can occur by a variety of mechanisms, including hydrolysis, oxidation, heat, and photodegradation. Certain investigations have also revealed that under several stress situations, this is feasible to manufacture most potential forms of degradants (25-26).

**Strategic Development of Forced Degradation:**

The structural diversity of drug compounds makes developing a general combination of events for a forced degradation investigation problematic. The chosen stress conditions must be compatible with the product's breakdown. The specified circumstance should encompass the product's characteristics along with its deterioration in regular production, storage, and usage situations. Protocol in general the methodology for forced deterioration is depicted in acid and base hydrolysis, heat degradation, photolysis, and oxidation are all needed forced degradation factors, as are freeze–thaw cycles and shear (27-29).

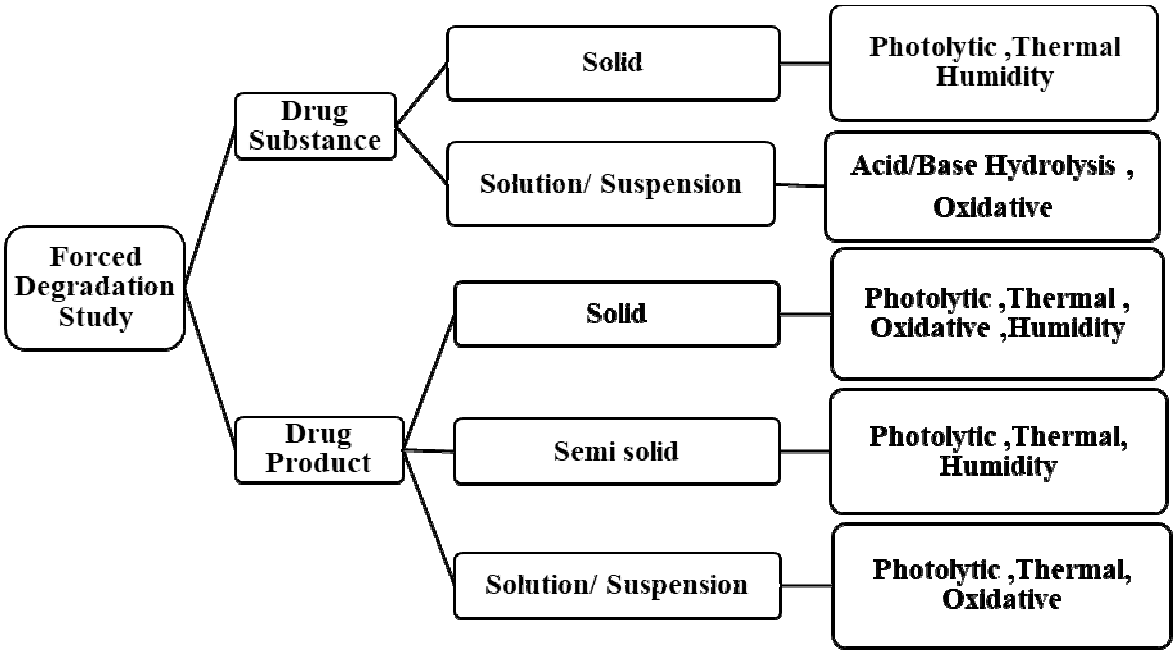


**Fig. 2: Common conditions used in conducting forced degradation study**

**FACTORS AFFECTING DEGRADATION:**

**I. Moisture**

Water-soluble compounds may dissolve in the presence of moisture. This causes physical and Chemical changes to occur within the molecule.

**II. Excipients**

Some excipients were discovered to have a high-water content. This moisture may cause a rise in the water level in the formulation, impacting the drug's stability. Chemical changes between excipients and medicinal substance may result in lower stability in some circumstances.

**III. Temperature**

Temperature fluctuations might have a negative impact on the drug's stability. When the temperature rises, the rate of drug hydrolysis rises as well.

**IV. pH**

The pH of the solution has a major influence on the rate of medication breakdown through hydrolysis. To mitigate this impact, the drugs are formulated using buffer solutions with the highest pH stability.

**V. Oxygen**

Oxidation of certain medications is accelerated in the presence of oxygen. Drugs that decompose faster in the presence of oxygen are stabilized by purging the storage container with nitrogen or carbon dioxide.

**VI. Light**

Some drugs are photolabile, meaning they disintegrate when

exposed to light. The sensitivity to photolytic breakdown can be determined by comparing the stability in the presence of light to the stability when kept in the dark (30).

## 1. VARIOUS DEGRADATION CONDITIONS

Before, typical circumstances such as high temperature and pH could be used to evaluate the inherent stability of medications. The drug molecules were then exposed to further stress to investigate their stability. The solution containing the drug sample was refluxed for a certain amount of time to examine the degradation. If any degradation products are detected at this time, the procedure will be halted; further isolation, identification, and characterization of the detected degradation products will be performed. If no evidence of deterioration were found, the response time would be extended to look for any signs of degradation caused by the passage of time (31).

**Hydrolytic Degradation:**

The drug interacts with water at various pH settings during hydrolysis (both acidic and alkaline). Hydrolytic research under acidic and basic circumstances covers catalysis of ionisable functional groups in the molecule. Acid or base stress testing includes forcing a pharmacological ingredient to degrade by exposing it to acidic or basic conditions, which produces primary degradants in an acceptable range. The kind and quantities of acid or base used are determined by the stability of the drug compound. As acceptable hydrolysis reagents, sodium hydroxide or potassium hydroxide (0.1–1 M) for base hydrolysis and hydrochloric acid or sulfuric acid (0.1–1 M) for acid hydrolysis are indicated. By refluxing the drug in 0.1 N HCl or 0.1 N NaOH, the hydrolytic breakdown of a novel drug in acidic and alkaline conditions may be examined. If there is reasonable decline, testing can be terminated at this stage. If no degradation is observed under these circumstances, the drug should be refluxed in a stronger acid/alkali for a longer period of time. Alternatively, if 100% degradation is seen after submitting the drugs to the initial conditions, acid/alkali strength and reaction temperature can be reduced (32).

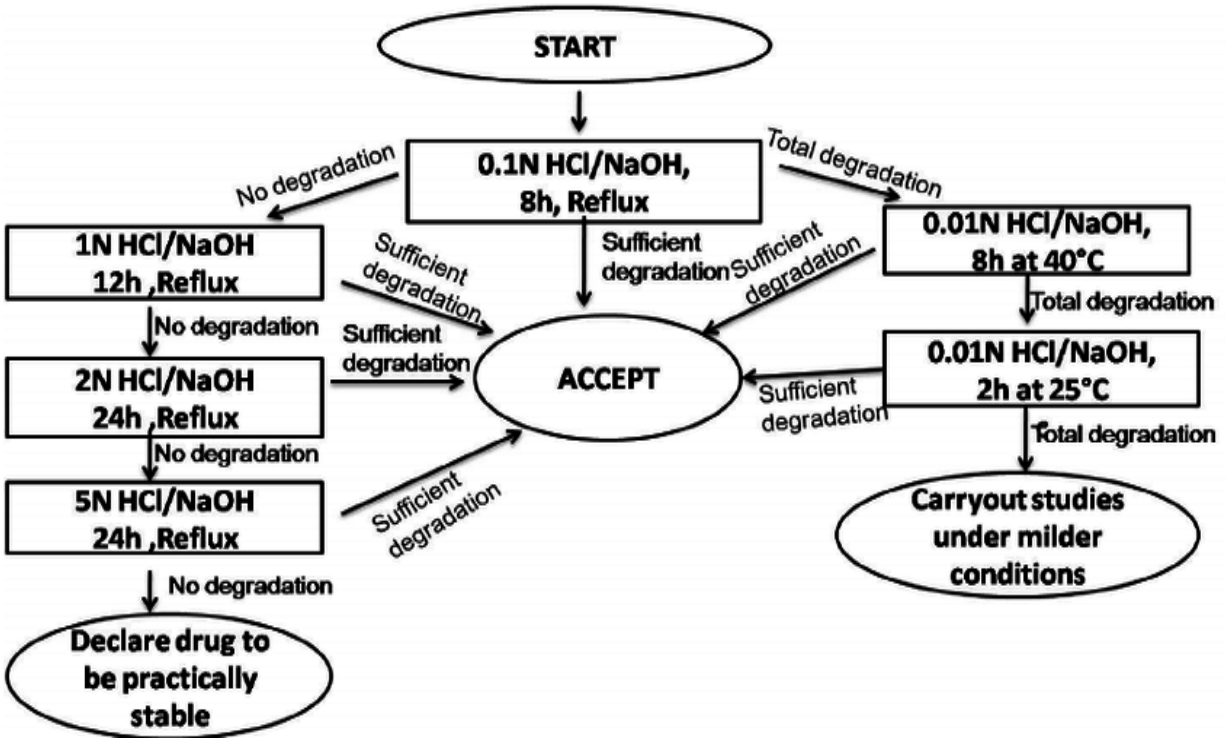


**Fig. 3: Flow chart for performing stress studies for hydrolytic Degradation under acid and alkali condition**.

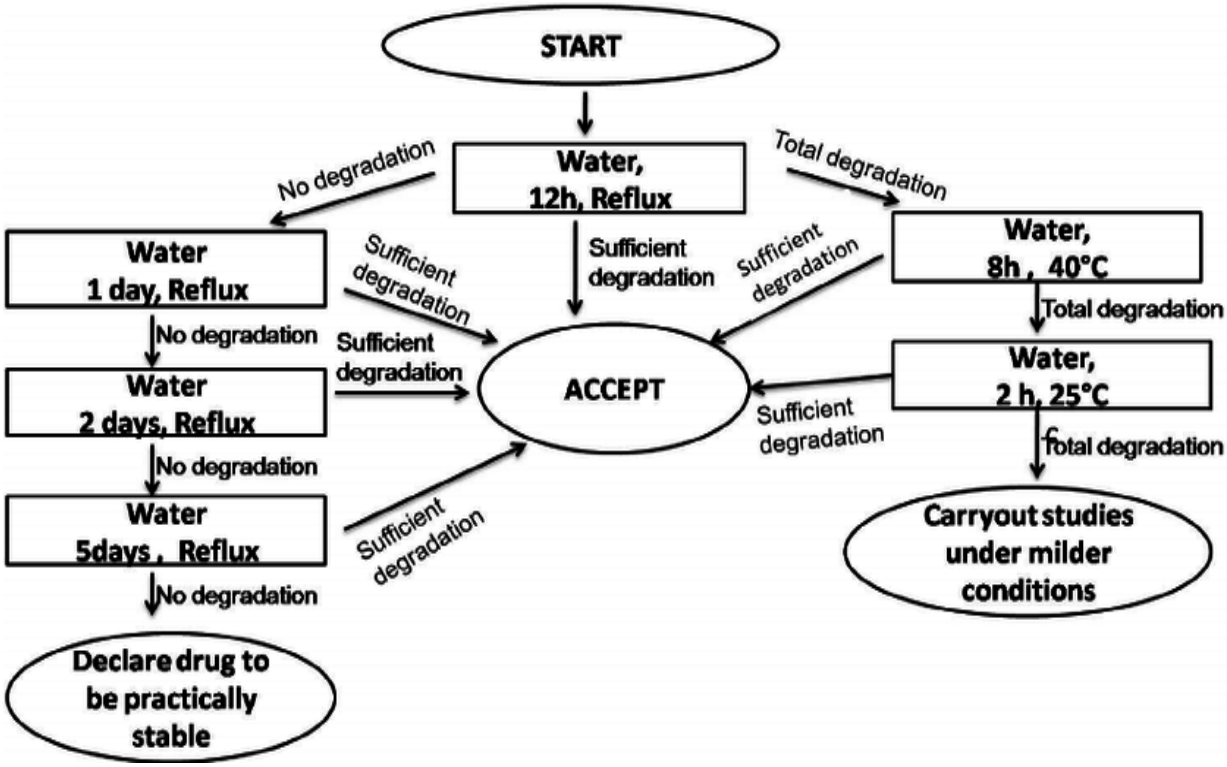


**Fig. 4: Flow chart for Hydrolysis in Neutral Condition for Drug Substance and Drug Product**

**Photolytic Degradation:**

The pharmaceutical compounds are exposed to UV or fluorescent light during photolytic degradation tests. The drug compounds or drug products (solid/liquid) are exposed to the light source in this investigation in accordance with the ICH Q1B guidelines. Samples of drug substance and solid/liquid drug product should be exposed to a minimum of 1.2 million lux h and 200-watt h per square meter light. The most commonly accepted wavelength of light is in the range of 300-800 nm to cause the photolytic degradation. The maximum illumination recommended is 6 million lux h. Degradation happens under photolytic conditions owing to oxidation via free radical mechanism or nonoxidation process. Non-oxidative degradation involves, among other things, isomerization, dimerization, and so forth. The oxidative photolytic process, on the other hand, utilizes a mechanism involving singlet/triplet oxygen states. Singlet oxygen combines with unsaturated molecules to form photooxidative breakdown products, whereas triplet oxygen reacts with free radicals to form peroxide. Significantly, it is demonstrated that light may also stimulate oxidation events. Several types of reactions are reported in non-oxidative processes, including homolytic breaking of C-X hetero bonds, deamination, and cleavage of C-S bonds (33).

**Oxidative Degradation**:

The majority of pharmaceutical components have been discovered to be auto oxidizers. For the oxidation process, they need free radical initiators. As free radical initiators, hydrogen peroxide, trace contaminants, and metal ions are present. The transport of electrons is involved in this form of deterioration. A popular initiator for oxidation driven degradation research is 0.1–3 percent hydrogen peroxide. These experiments should be carried out for 1–7 days at 40°C. If more than 20% degradants are created, it should be classified as abnormal (34).

**Thermal Degradation:**

Several drugs have been discovered to be thermolabile in nature. As the temperature rises, the rate of reaction rises as well, resulting in the formation of degradation products. These experiments should be carried out at temperatures ranging from 40 to 80 degrees Celsius. Thermal stress experiments typically last 1–2 months and are done at 70°C and heavy humidity. Solid drug molecules are treated to both dry and wet heat conditions, whereas liquids are exposed to dry heat for a shorter period of time. The drug molecule degrades as a result of the higher temperature, as predicted by the Arrhenius equation:

k = Ae-Ea/RT

where k: Specific reaction rate, A: Frequency factor, Ea: Energy of activation, R: Gas constant (1.987 cal/ deg/mole), and T: Absolute temperature in Kelvin (35).

**Moisture**:

Humidity is a crucial factor in the deterioration process. The drug ingredient is subjected to 90 percent humidity for one week in forced degradation trials, which causes deterioration. Humidity is an essential characteristic in determining the potential degradants in final products and API (36).

**Table 1 Conditions for Forced Degradation Studies**

| Degradation Type | Experimental Conditions | Storage Condition | Sampling Time (days) |
|---|---|---|---|
| Hydrolysis | Control API (no acid or base) | 40°C, 60°C | 1,3,5 |
| | 0.1M HCl | 40°C, 60°C | 1,3,5 |
| | 0.M NaOH | 40°C, 60°C | 1,3,5 |
| | Acid control (no API) | 40°C, 60°C | 1,3,5 |
| | Base control (no API) | 40°C, 60°C | 1,3,5 |
| | pH: 2,4,6,8 | 40°C, 60°C | 1,3,5 |
| Oxidation | 3% $H_2O_2$ | 25°C, 60°C | 1,3,5 |
| | Peroxide control | 25°C, 60°C | 1,3,5 |
| | Azobsisobutyronitrile (AIBN) | 25°C, 60°C | 1,3,5 |
| | AIBN control | 25°C, 60°C | 1,3,5 |
| Photolytic | Light 1 X ICH | NA | 1,3,5 |
| | Light 3 X ICH | NA | 1,3,5 |
| | Light control | NA | 1,3,5 |
| Thermal | Heat chamber | 60°C | 1,3,5 |
| | Heat chamber | 60°C/75% RH | 1,3,5 |
| | Heat chamber | 80°C | 1,3,5 |
| | Heat chamber | 80°C/75% RH | 1,3,5 |
| | Heat chamber | Room temperature | 1,3,5 |

## 7. STABILITY INDICATING METHOD

A stability indicating technique (SIM) is an analytical approach used to quantify the loss of active pharmaceutical ingredient (API) in a drug product owing to deterioration. The FDA describes the stability indicated method as a quantitative approach that measures how the concentration of the medicine changes over time. The reduction in drug concentration and drug product concentration will be determined. Significantly, the concentration of the drug molecules varies during the degradation experiments. During the degradation investigations, the concentration of the drug ingredient fluctuates; however, no influence from excipients or other degradation products is detected. As a result, the SIM aids in preformulation investigations as well as predicting drug storage conditions (37-38).

## 8. METHOD DEVELOPMENT AND VALIDATION

The early phase in designing a method is to ascertain the pKa value, log P, solubility, and $t_{max}$ of the respective drug. The establishment of a reverse phase technique for separating pharmaceuticals using HPLC is a frequent procedure. As mobile phases, frequently used solvents like as methanol, acetonitrile, and water are utilized in various ratios and quantities. The organic phase, such as methanol or acetonitrile, is chosen based on the drug's solubility profile. The mobile phase and its percentage are generally established by previous reports or by trial-and-error approaches (38). The organic and aqueous phases are kept 50:50 at the beginning of the experiment, and additional tuning of the solvent proportions for the mobile phase can be done to produce an optimal sharpness of the peaks. Buffers can also be employed in some circumstances to provide adequate baseline separation and peak symmetry. To achieve good repeatability of data, the column temperature is sometimes changed to 30–40°C. To get good resolution, degradant peaks are pushed in the chromatogram. Degradant peaks may elute with the drug peak or be obscured by drug peaks, requiring peak purity analysis. HPLC equipped with PDA detectors can be used for direct analysis (39).

## 9. OTHER METHODS

Potency, purity, and biological activity will be properties of stability-indicating procedures. The evaluations are designed depending on the products. Electrophoresis (SDS-PAGE, Western blot, isoelectrofoccusing), high-resolution chromatography (e.g., reversed phase chromatography, SEC, gel filtering, ion exchange, and affinity chromatography), and peptide mapping are some techniques

to measure stability. The analytical approach of consideration must be sensitive enough as to identify impurities at small concentration (i.e., 0.05 percent or less of the analyte of interest), and the peak responses should range within the detector's linearity range. At or under ICH acceptable limit, the analytical approach should be useful for collecting all impurities generated during a formal stability analysis. According to ICH, degradation component detection and characterization must be undertaken depending on established stability studies (46).

In order to identify and characterize the degradation products, conventional procedures (e.g., column chromatography) or hyphenated techniques (e.g., LC-MS, LC-NMR) can be utilized. LC-MS/MS play a vital part in the creation of complete degradation pathway of the drug molecule. The drug substance fragments will aid in the design of a degradation pathway (47).

It becomes simpler to resolve and evaluate the degradant peaks by adjusting the fraction of the mobile phase. If the degradants peak is detected where the area under the curve of the drug peak and its percentage are not modified, the technique established is called homogenous. These coeluting degradants are acceptable to a point; however, they were not seen in rapid or long-term storage trials. Moreover, the technique may be optimized by adjusting parameters such as the rate of mobile phase flow, the volume of sample injected, the type of column employed, and the fraction of mobile phase used in the investigation. Following the adjustment of these parameters, the technique established for the research will be validated as per ICH guidelines (40-42).

The generated SIM is then verified for linearity, accuracy, precision, specificity, quantitation limit, detection limit, ruggedness, and robustness in accordance with USP/ICH guidelines. It is essential to isolate, characterize, and quantify the degradants discovered to be over the identification threshold (about 0.1 percent). If the method somehow doesn't fulfill the validation admittance requirements, it is updated and revalidated (43-45).

## 2. CHARACTERIZATION OF DEGRADANTS

Prior research suggests that numerous analytical methods may be used to extract, identify, and describe the impurities created during degradation investigations, even at extremely low concentrations. LC–MS and LC–nuclear magnetic resonance spectroscopy (LC–NMR) were used to identify and classify the degradants isolated in the research. More significantly, structural characterization of

degradants/impurities is required since they play a crucial role in determining shelf-life stability (48). Thin layer chromatography (TLC), electrophoresis, colorimetric, and gel filtering methods may be used to detect contaminants, while reversed-phase HPLC, TLC, gas chromatography, and supercritical fluid chromatography can be used to separate and isolate degradants in pure form. Significantly, the degradant routes are determined using the LC-MS/MS approach. The observed fragmentation patterns can be used to determine the degradative processes. After determining degradant routes, degradant structures are elucidated using synthesizing or isolating procedures, and they are further characterized using LC-MS, LC-UV, and LCNMR techniques.

The application of these approaches can offer a better knowledge of the concept of the impurities, thereby expanding the understanding area of probable structural indications of genotoxicity and allowing for greater management of those impurities. It should be highlighted that molecular characterization of the degradation products is required for those contaminants that are produced during the formal useful life stability investigations and are over the qualifying level. UV and mass spectroscopy are two forms of detection that may be utilized to assess stressed substances. To detect the absence of spectral homogeneity, the detector must have 3D data capabilities, such as diode array detectors or mass spectrometers. The detection of diode arrays also allows for the verification of peak features for several wavelengths (49-51).

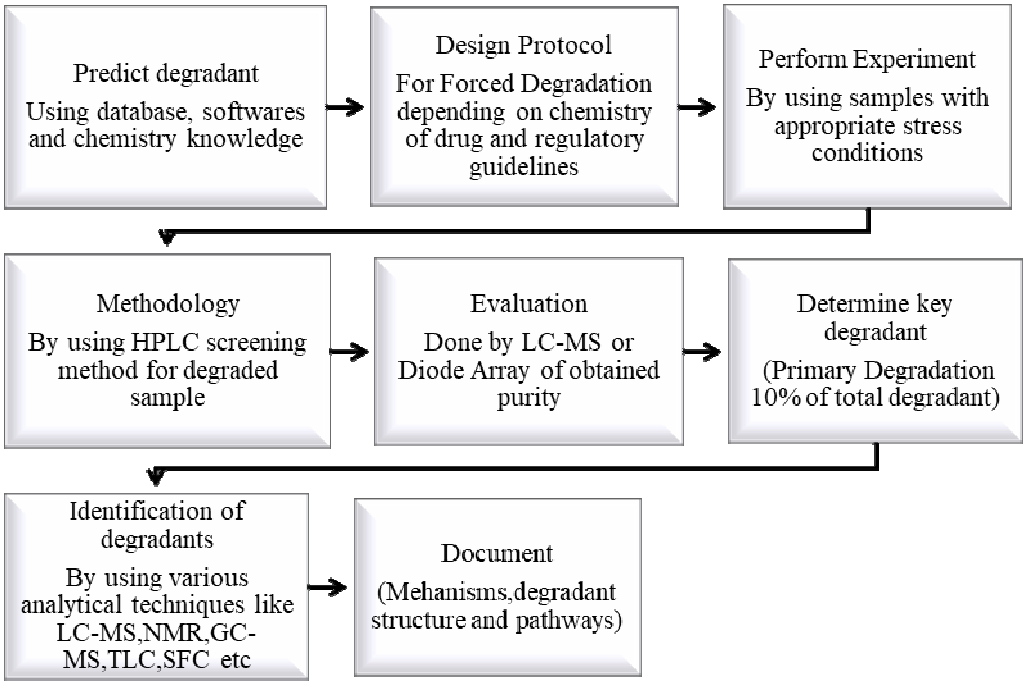


**Fig. No.5: Forced degradation process flow chart**

**Table 2: List of Degradation Products of Different Drugs:**

| Drug name | Stress Condition | Degradation Product |
|---|---|---|
| Deflazacort(52) | Alkaline condition | readily degraded and produced and 21-hydroxy deflazacort (21-OH-DFZ) |
| Nevirapine(53) | Acidic conditions | 2-(3-Amino-4-methylpyridine-2-ylamino) nicotinic acid impurity |
| Telmisartan(54) | Photo acidic | Form Tricyclic Lactone of drug (3-((1, 7-dimethyl-2_-propyl-1H, 3H2, 5-bibenzo[d]imidazol-3-yl) methyl)-6H-benzo[c]chromen-6-on |
| Tetracycline(55) | Heat, pH, and humidity | Undergo reversible Epimerization at positions C-4 and C-6 to form a mixture of degradation products |
| Glimepiride(56) | Alkaline conditions | [[4-[2-(N-carbamoyl) aminoethyl]phenyl]sulfonyl]-3-trans-(4-methylcyclohexyl)urea |

| | | |
|---|---|---|
| Metronidazole(57) | Photodegradation | Yellow photo degradation product |
| Metoclopramide(58) | Photodegradation | dechlorination and hydroxylation |
| Doxycycline(59) | Thermal | Metacycline and 6-epidoxycyline are Identified as degradation products at high temperatures. |
| Dicloxacillin(60) | Hydrolysis | Impurity-I. Penicilloic acids of dicloxacillin (dicloxacilloic acids). |
| Propranolol(61) | Photostability | (1)1-Naphthol<br>(2)N-Acetylpropranolol<br>(3)N-formylpropranolol |
| Valsartan(62) | Oxidative condition | 2-methyl-N-{[2'-(1H-tetrazol-5-yl)biphenyl3-yl]methyl}propan-1-amine and N-methyl-N- {[2'-(1H-tetrazol-5-yl)biphenyl-3-yl]methyl} butanamide were produced. |
| Enflurane(63) | Alkaline condition | N-acetyl-L-cysteine S-conjugates impurity was produced. |
| Hydrochlor Thiazide(64) | Hydrolysis | 4-amino-6-chloro-1,3-benzenedisulfonamide |
| Paclitaxel(65) | Acidic condition | 10-deacetyl paclitaxel Oxetane ring opened product |
| Diltiazem(66) | Oxidation | Diltiazem sulfoxide as a major degradation product, the drug was reduced to 43% on peroxide degradation. |

**CONCLUSION:**

Forced degradation studies disclose details on probable degradation products and routes of active substances, as well as aid in identifying the structure of degradants and contaminants. The outcomes of forced degradation studies are prospective degradation products which might or might not arise within suitable storage circumstances but lead to the development of the stability indication technique. It is preferable to begin degradation studies early in the phase of drug development so that more details relating the molecule's stability may be obtained. By using data, the production process may be carried out effectively, and the drug preparations can be stored in the most appropriate storage conditions. This overview has been condensed to the greatest extent possible in sequence to provide knowledge about various regulatory guidance available for forced degradation studies, methodologies to perform stress studies under various accelerated conditions, and stability and degradants produced under different stress conditions for several drugs.

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