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FORCED DEGRADATION STUDY - A NEW APPROACH FOR STRESS TESTING OF DRUG SUBSTANCES AND DRUG PRODUCTS

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ABSTRACT: Forced degradation studies are a vital tool in pharmaceutical research and development to predict long-term stability. Stress studies should be performed in method development to know drug behavior but can also be performed with method validation for regulatory filling predict stability, and measure impurities. It is especially valuable when little data is free about potential degradation products. Forced degradation studies may help encourage drug advancement in regions like formulation development, manufacturing, and packaging, in which information on substance conduct can be utilized to improve a medication item. Hence it is important to realize the purity profile and conduct of a medication substance under various natural conditions. For stable formulation development, comprehension of synthetic conduct forced degradation pathways and degradants of drug substance and drug product is very important. Therefore, by using different regulatory guidelines in the present review paper, we described the broad overview of forced degradation studies by determining the system to perform stress studies & its methods for isolation and identification of degradation.

INTRODUCTION: Forced degradation may be a degeneracy of the latest drug substance and drug product at conditions more severe than forwarding conditions. Forced degradation studies show the chemical performance of the molecule, which successively helps with the development of formulation and package. As analysis of dosage forms under stability study is crucial. Forced degradation studies appearance the chemical performance of the molecule, which in turn use within the development of formation and collection.

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Additionally, the regulative guidance was very broad and doesn't explain the work of forced degradation studies [1]. Force Degradation study to found the force degradation profile and to develop whether the analytical method for evaluation is stability demonstrate, the Tablet composition of ATN and CTN applied to separate stress conditions to handling forced degradation studies. Stress studies were drifting out under the condition of acid/alkali hydrolysis, oxidation, neutral and thermal degradation in conformation with ICH Q1A (R2) guideline. The collection of stress conditions essentially depends on the literature review and drug profile [2].

The most important considerations in the drug discovery are safety-related, not only of the drug but also impurities and degraded products present in them. Impurities present in the drug may lead to cytotoxicity, carcinogenic or teratogenic effects.

For diseases like hypertension or diabetes, which are related to changes in body physiology, the patient, for the rest of his life, is going to be on medication. Though the amount of impurities is very min still prolong exposure to them may be hazardous. Hence identification and the check on the presence of a specific amount is a must. Drug produce degradation profiles essential to establish to monitor the stable formulation and provide appropriate drug shelf life valuation. Structural description of impurities and degradation products in bulk API has become an integral part of pharmaceutical product development [3].

The analysis of these low-level unidentified impurities and degradant is very challenging. Various regulatory bodies like ICH, USFDA, Canadian Drug and Health Agencies have started insisting on characterization and development of complete impurity profile of Active Pharmaceutical Ingredient's (API's) as well as pharmaceutical formulations. Structural elucidation of impurity and degradants is a collaborative effort involving spectral analysis as well as analytical method development Identification of the degradation in samples may give a clue about the mechanism of degradation.

In the present state, development within the traditional instrumental methods that aid in fast description of impurities and related substances /degradation products spectral analysis and isolation, using new analytical techniques, like UPLC, LC-MS, LC-NMR, GC-MS, SFC-MS, CE-MS *etc.* has become easy. The conventional method included the separation and identification of impurities or related substances by an appropriate method. Eventually, they are isolated and characterized using various spectroscopic techniques.

Impurity is something whose presence is unwanted and makes the pure compound impure. An impure substance may be defined as a substance mixed with a substance of interest. The desired compound may be impregnated with extraneous or usually inferior substance [4]. The number of positions has been normally used to define organic impurities. The number of positions has been normally used to define organic impurities that are intermediates, starting material, penultimate intermediate (final intermediate), transformation Products by-products, interaction products related products and degradation products. The United States Pharmacopoeia (USP) has many parts for impurities involving impurities in official articles, ordinary impurities and organic volatile impurities. That is described as foreign substances, concomitant components, toxic impurities, signal impurities, organic volatile impurities and ordinary impurities. ICH guidelines categories impurities as organic impurities (starting materials, process-related impurities, intermediates and degradation products); inorganic impurities (salts, catalysts, ligands and heavy metals); other materials (filter aids and charcoal) and residual solvents (organic and inorganic liquids) ICH guidelines give simple divided the impurities while few are unable to describe enantiomeric (chiral) impurities. Chiral impurities have an identical formula and therefore, the same connectivity between various atoms, and that they differ only in the three-dimensional arrangement of their atoms within the space. The differences in pharmacological/toxicological profiles have been seen with chiral impurities *in-vivo* [5].

Forced degradation readings give information to support identification of thinkable degradant; degradation paths and vital stability of the drug molecule and validation of stability representing analytical processes. A draft guidance document recommends results of one-time forced degradation studies should include in Phase 3 INDs (Investigational New Drugs). NDA (New Drug Application) registration needs data of forced degradation studies as forced degradation products, degradation reaction kinetics, structure, drug peak purity, and mass balance, etc. This forced degradation study offers data about API's debasement pathways, alone and in a sedate item, any conceivable polymorphic or enantiomeric substances and adjust between drug-related degradation and excipient obstructions [6]. The percentage degradation is calculated by the subsequent formula.

% Degradation = Area of unstressed – Area of stressed/ Area of unstressed × 100

General Principle on Forced Degradation Studies: The demonstration of specificity and therefore the capability of the tactic to watch

changes within the chemical properties of the drug Over time consistently involves a forced degradation study to be complete on the drug substance and drug product [7]. Investigating degradation products under stress conditions is beneficial in establishing pathways and developing and validating the proper analytical method. In contrast, such investigation might not be needed surely degradation products if it's demonstrated that they're not formed under accelerated or future storage conditions. Degradation products formed during stress conditions are called as "Potential" degradation products. Therefore, the general strategy of stress testing is to predict potential problems associated to stability of the molecule, either the drug substance alone or the formulated product. The many and relevant degradation products are formed during accelerated or future stability testing's [8]. Forced degradation on the drug substance and merchandise will provide the subsequent information:

- Determination of forced degradation pathways of drug substances and drug products.
- Structure elucidation of the degradation product.
- Discernment of degradation products in formulations that are associated with drug substances against people who are associated to non-drug substances (*e.g.,* excipients)
- Assurance of the intrinsic stability of a drug substance molecule in solution and solid-state

The ICH Guideline Q1A Advises the Subsequent Conditions to be employed:

- 10°C increments above the accelerated temperatures (*e.g.,* 50 °C, 60 °C, *etc.*),
- Humidity where appropriate (*e.g.,* 75% or greater),
- Hydrolysis across a good range of pH values
- Oxidation and
- Photolysis.

Development of Validated Degradants: Practical steps involved within the development of degradants, functional group categories.

Step I: Study of the Drug Structure To Assess the Likely Decomposition Route (S): It is the most component to be considered whenever one takes up the project on the establishment of a degradant. The extra information is often easily gained from the structure by the study of the functional groups and other main components. There are certain, like esters, amides, lactams, lactones, *etc.*, that undergo hydrolysis, others like thiols, thioethers, *etc.*, undergo oxidation, and compounds like olefins, aryl ethanoic acid, aryl halo derivatives, and people with aromatic Nitro groups, N-oxides undergo photodecomposition [9].

Step II: Physicochemical Properties of Drug: Before carried out method development, it is vital to know various physicochemical parameters like-

pKa: pKa is vital as a number of the pH-related variations in retention occur at pH values within 1.5 units of the pKa value.

Log P: log P for the drug and the known degradation products provides a good understanding of the separation behavior likely to be obtained on a certain stationary phase.

Solubility: For the choice of the sample solvent and the mobile phase, the availability of the solubility data in organic, aqueous and commonly used HPLC solvents and their mixtures is a very useful tool.

Absorptivity and Wavelength Maximum of the Drug under Study: As the HPLC analysis using a UV detector is usually carry out at the wavelength maximum or at a wavelength where all components give good absorbance.

Step III: Stress (Forced Degradation) Studies: The demonstration of specificity and the capability of the method to monitor changes in the chemical properties of the drug over time consistently calls for a forced degradation study to be complete on the drug substance and drug product. Investigating degradation products under stress conditions is useful in establishing pathways and developing and validating proper analytical methods.

While such investigation may not be needed for certain degradation products if it has demonstrated that they are not formed under accelerated or long-term storage conditions. Degradation products formed during stress conditions are called "Potential" degradation products. The overall strategy of stress testing is, therefore, to predict potential problems associated with the stability of the molecule, which is either the drug substance alone or the formulated product. The significant and relevant degradation products are formed during accelerated or long-term stability testing's. Forced degradation on the drug substance and product will provide the following information [10].

- Determination of forced degradation pathways of drug substances and drug products.
- Structure elucidation of the degradation product.
- Discernment of degradation products in formulations that are related to drug substances against those that are associated to non-drug substances (*e.g.*, excipients)
- Assurance of the intrinsic stability of a drug substance molecule in solution and solid-state

- **The ICH Guideline Q1A Advises the Following Conditions to be Employed [11]:**
  - 10 °C increments above the accelerated temperatures (*e.g.*, 50°C, 60°C, *etc.*).
  - Humidity where appropriate (e.g., 75% or greater).
  - Hydrolysis across a wide range of pH values.
  - Oxidation
  - Photolysis

- **Experimental Design:**

In scheming forced degradation studies, it must be retained that more strenuous conditions than those used for accelerated studies (25 °C/60% RH or 40 °C/75% RH) should be used. At a minimum, the following conditions should be measured.

- Acid and base hydrolysis
- Hydrolysis at various pH
- Thermal degradation
- Photolysis
- Oxidation

List of some common conditions and parameters used in regulating forced degradation studies for drug substances and drug products as shown in **Table 1** [12].

TABLE 1: CONDITIONS GENERALLY EMPLOYED FOR FORCED DEGRADATION

Degradation type	Experimental Condition Control API (No acid or base)	Storage condition 40 °C, 60 °C	Sampling time 1, 3, 5 days
Hydrolysis	0.1N NaOH	40 °C, 60 °C	1,3,5 days
	Acid Control (no API)	40 °C, 60 °C	1,3,5 days
	Base Control (no API)	40 °C, 60 °C	1,3,5 days
	pH: 2,4,6,8	40 °C, 60 °C	1,3,5 days
		25 °C, 60 °C	1,3,5 days
Oxidation	3% H2O2 Peroxide control	25 °C, 60 °C	1,3,5 days
	Azobisisobutyronitrile (AIBN)	40 °C, 60 °C	1,3,5 days
photolytic	Light, 1X ICH	NA	1,3,5 days
	Light, 3X ICH	NA	1,3,5 days
	Light Control	NA	1,3,5 days
Thermal	Heat chamber	60°C	1,3,5 days
	Heat chamber	60 °C /75% RH	1,3,5 days
	Heat chamber	80 °C	1,3,5 days
	Heat chamber	80 °C /75% RH	1,3,5 days
	Heat control	Room Temp.	1,3,5 days

A. Hydrolytic Degradation: Forced degradation studies to get degraded samples wherever degradation possible from about 1% to 30%. For Acid stress Reflux with 0.1N HCL at 60 °C for half-hour. For Base stress Reflux with 0.1N NaOH at 60 °C for half-hour. For water stress Reflux with water at 60 °C for 30 min. Stress agents are often changed to realize degradation if necessary Co-solvent are often inclined to dissolve and extract the drug necessary represents the flow of hydrolytic degradation [13].

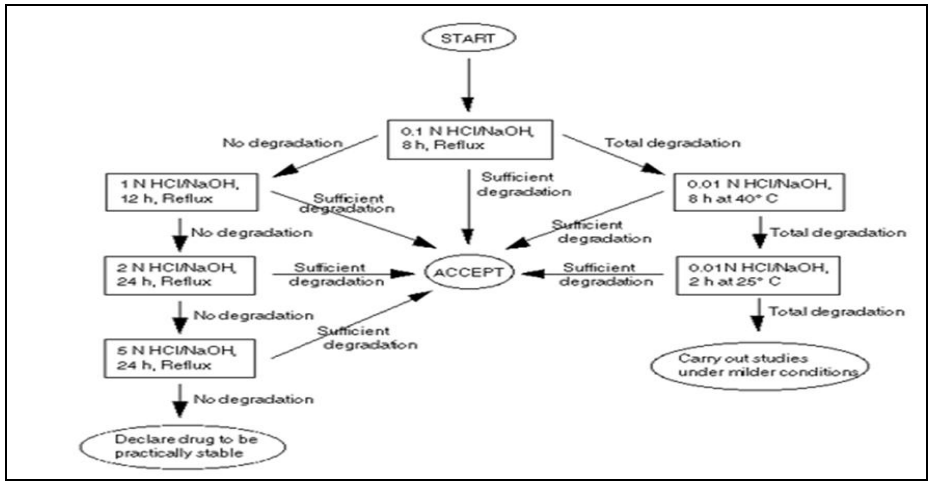

FIG. 1: FLOW CHART OF HYDROLYTIC DEGRADATION

B. Oxidative Degradation: Many drug substances undergo autoxidation, *i.e.*, oxidation under normal storage conditions and involving state elemental oxygen. Therefore it's a crucial degradation pathway of the many drugs. Autoxidation may be a radical reaction that needs a radical initiator to start the chain reaction. Hydrogen peroxide, metal ions, or trace level of impurities during a drug substance act as initiators for autoxidation. The mechanism of oxidative degradation of drug substance involves an electron transfer mechanism to make reactive anions and cations. Amines, sulphides and phenols are vulnerable to electron transfer oxidation to offer N-oxides, hydroxylamine, sulphones and sulphoxide. The functional group with labile hydrogens like benzyl carbon, allylic carbon, and tertiary carbon or α – positions with reference to hetro atom is vulnerable to oxidation to make hydroperoxides, hydroxide or ketone.

Products may be supported with free radical-mediated autoxidation responses, including alkene and liquor sites. Hydrogen peroxide is an incredibly basic oxidant to produce oxidative degradant, which can emerge as minor polluting influences during term stability studies. It are often utilized in the concentration range of 3-30% at a temperature not exceeding 40 °C for 2-8 days [13].

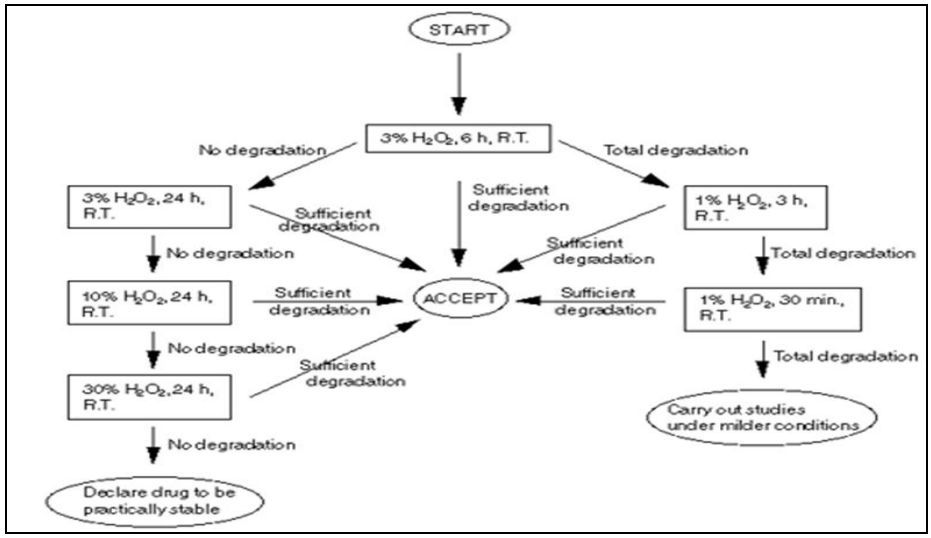

FIG. 2: FLOW CHART OF OXIDATIVE DEGRADATION

C. Photolytic Degradation: Exposure of light on drug molecules may produce photolytic degraded products. The rate of photodegradation depends upon the intensity of incident light and the quantity of sunshine absorbed by the drug molecule. Photolytic degradation is administered by exposing the drug substance (in solid also as within the solution form) or drug product to a mixture of visible and UV light. The most normally acknowledged wave-length of sunshine is inside

the scope of 300-800 nm to cause photolytic degradation. The photolytic degradation can happen through non-oxidative or oxidative photolytic reaction. The non-oxidative photolytic reaction consolidates dimerization, isomerization, changes, decarboxylation, cyclization and homolytic cleavage of X-C hetero protections, N-alkyl security (deamination and dealkylation), SO_2-C and so forth and remembering that oxidative, photolytic response occur through either singlet oxygen ($1O_2$) or triplet oxygen ($3O_2$) instrument. The singlet oxygen reacts with the unsaturated bonds, similar to alkenes, dienes, polynuclear hydrocarbon to make photooxidative corruption items though triplet oxygen reacts with the radical of the medication atom, which then reacts with a triplet oxygen particle to make peroxide. Henceforth, light can likewise go about as a catalyst to oxidation reactions. For example, photodegradation of Barnidipin includes the plausible formation of singlet oxygen, which will alter or decimate tissues causing noteworthy harms and loss of therapeutic activity.[13]

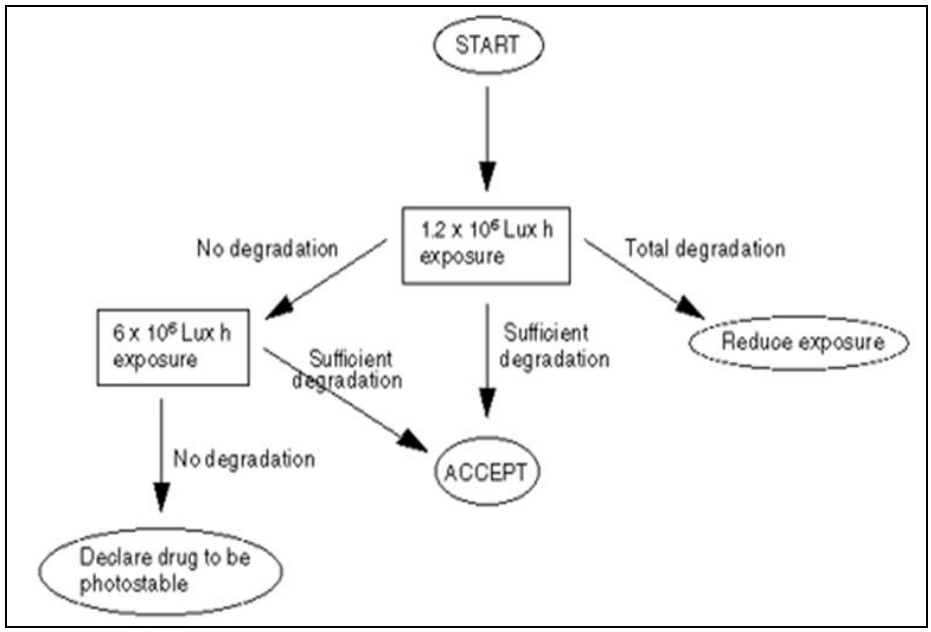

FIG. 3: FLOW CHART OF THERMAL DEGRADATION

D. Thermal Degradation: The drugs are vulnerable to degradation at a higher temperature. Many Active pharmaceutical Ingredients are sensitive to heat or tropical temperatures. For example, vitamins, peptides *etc.* Thermal stress study involves different reactions like pyrolysis, hydrolysis, decarboxylation, Isomerization, rearrangement and polymerization. Effect of temperature on thermal degradation of a substance is studied through Arrhenius equation: K= Ae-Ea/RT Where k is restricted reaction rate, A is frequency factor, Ea is the energy of activation, R is the universal gas constant (1.987 cal/deg mole), and T is temperature. Thermal degradation study is administered at 40 °C to 80 °C. The most widely succeeded temperature is 70 °C at low and high humidity for 1-2 months. High temperature (>80 °C) might not produce a predictive degradation pathway [13].

Step IV: Preliminary Separation Studies on Stressed Samples: The many stress samples obtained are subjected to preliminary analyses to review the amount and sorts of degradation products formed under different conditions. It must be preferred to use water-methanol or water–acetonitrile because the mobile introduces the initial stages. By Using different chromatographic conditions, (*e.g.* Selection of wavelength, Selection of mobile phase, flow in HPLC analysis), one should follow the variations altogether the strain samples at a special interval. The obtained results should be critically compared with the blank solutions injected in a similar manner.

Step V: Final Method Development and Optimization: Subsequent to preliminary chromatography studies, the RT and relative retention times (RRT) of all products formed

should be tabulated for every reaction condition. PDA spectra or LC-MS profile of such components is obtained and critically calculated to determine whether the products are similar or different. To separate close or co-eluting peaks, the tactic gets improved; by make change the mobile phase proportion, gradient, pH, flow rate, solvent type, temperature, and therefore the column and its type.

Methods for Isolation and Identification of Degradation: A number of the process are often used for confine impurities. Three of the foremost utilized techniques are thin-layer chromatography (TLC), flash chromatography (column chromate-graphy) and preparative high-performance liquid chromatography (HPLC).

The certain technique to be used depends upon the character of the impurity and/or degradant. The extent is present within the original component from which it must be isolated. Extraction systems are sometimes used for isolation of impurities, on the idea of variation within the solubility of impurity and drug substance in several solvents. it had been potential to extract impurities separated on the idea of acidity, basicity, or neutrality of impurities . The method usually influences liquid-liquid extraction where one form was aqueous while the opposite was non-polar organic aspect. By appropriate regulation of pH of aqueous phase, one can extract acidic, basic or neutral impurities [14, 15, 16, 17, 18, 19, 20].

Separation Methods: The following separation methods are often used.

- Thin-layer chromatography (TLC)
- Gas chromatography (GC)
- High-pressure liquid chromatography (HPLC)
- Capillary electrophoresis (CE)
- Supercritical fluid chromatography (SFC)

TLC: By appropriate a variety of different plates and mobile phases. The primary difficulties relevant to this method are defined resolution, detection and ease of quantification. The greatest advantages are the serenity of use and low cost.

Gas Chromatography: It was a very advantageous technique for quantification. It can produce the desired resolution, selectivity and ease of quantification. However, the primary limitation was that the sample must be volatile or has to be built volatile by derivatization. This method was very advantageous for volatile organic impurities.

High-Pressure Liquid Chromatography: It was generally referred to as high-performance liquid chromatography today. Both of these terms can be abbreviated as HPLC and they are advantageous by chromatographers. This was a helpful method with applications that have been accordingly extended for the pharmaceutical chemistry by the need of a variety of detectors such as fluorescence, electrometric, MS *etc.*

Capillary Electrophoresis: It was a helpful method when a very low volume of samples are available and the high resolution was required. The primary hazard was assuring reproducibility of the injected samples.

Supercritical Fluid Chromatography: It offers a few of the advantages of GC in terms of detection, and HPLC are the conclusion of separations, in that volatility of the sampling was not of are amount importance. This method was still evolving, and its greatest application has been formed in the extraction of samples [21].

Hyphenated Methods: The following hyphenated methods are often used effectively to watch impurities [22, 23]:

- GC–MS
- LC-MS
- LC–DAD–MS
- LC–NMR
- LC–DAD–NMR–MS
- LC–MS–MS [15]

Outcomes of Forced Degradation Studies [24]: Forced degradation studies provide the following information.

- Resolution of acceptable degradants
- Resolution of degradation pathways
- Resolution of intrinsic stability of the drug molecule
- Resolution of validated stability-indicating method.

Importance of Forced Degradation Studies [25, 26]:

- Forced degradation studies produce learning about probable degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants.
- To determine the particularity when expanding the stability-indicating method.
- To stimulate the analysis reactions that induce degradation of a pharmaceutical product.
- As a portion of method development system.
- As acreate to generate product related modification.
- Resolution of intrinsic stability of the drug molecule.
- Resolution of degradation pathways.
- Resolution of certifies the stability-indicating analytical method.
- Forced degradation studies produce learning about probable degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants.
- To determine the particularity when expanding the stability-indicating method.
- To stimulate the analysis reactions that induce degradation of a pharmaceutical product.
- As a portion of method development system.
- As acreate to generate product related modification.
- Resolution of intrinsic stability of the drug molecule.
- Resolution of degradation pathways.
- Resolution of certifies the stability-indicating analysis.

CONCLUSION: Forced degradation studies consider giving information about conceivable degradation pathways and degradation results of the dynamic fixings and help clarify the structure of the degradants. Degradation products generated from forced degradation studies are potential degradation products that will or might not be formed under relevant storage conditions, but they assist within the developing stability-indicating method. It's better to start out degradation studies earlier within the drug development process to possess sufficient time to realize more information about the steadiness of the molecule. This information will successively help to improve the formulation manufacturing process and determine the storage conditions. As no specific set of conditions is applicable to all or any drug products and drug substances and therefore the regulatory guidance doesn't specify the conditions to be used, this study requires the experimenter to use sense.

The aim of any strategy used for forced degradation is to supply the specified amount of degradation, *i.e.,* 5-20%. An appropriately structured and executed forced degradation study would produce a fitting example for the advancement of stability indicating technique.

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