



FORCED DEGRADATION STUDIES: PRACTICAL APPROACH - OVERVIEW OF REGULATORY GUIDANCE AND LITERATURE FOR THE DRUG PRODUCTS AND DRUG SUBSTANCES

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ABSTRACT

The Objective of the review article is to give a detailed description of the forced degradation studies as per the regulatory guidelines that are associated with various regulatory agencies. This article summarizes the collective views of industry practices on the topic of forced degradation studies. The article includes an overview of existing guidance's and literature for best practices.

Keywords: Forced Degradation, ICH, FDA guidance, Validation, Method Development

INTRODUCTION

According to an FDA guidance document, a stability-indicating method is “a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product. A stability-indicating method accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities. “Forced Degradation (or stress testing) typically involves exposure of drug substances to heat, heat and humidity and light for solid-state studies. For solution-state studies the drug substance is exposed to a range of pH values. The experimental samples produced are then used to demonstrate that a proposed analytical method is “Stability Indicating,” i.e., the method is capable of detecting the loss in content of the active component and subsequent increase in degradation products. Ideally, loss in content of the active component and increase in degradation products should be monitored by a single analytical method. However, in some cases, this is not possible and separate assay and impurity methods have to be developed. This guidance document describes how forced degradation studies are used to develop stability-indicating methods ¹⁻¹⁰.

Requirements

This relates to the specificity section of the validation studies. It is important to recognize that forced degradation studies are not designed to establish qualitative or quantitative limits for change in drug substance or drug product. Testing of stressed samples is required to demonstrate the following abilities of analytical techniques employed in stability studies: Stress studies may be useful in determining whether accidental exposures to conditions other than normal ranges (e.g., during transportation) are deleterious to the product, and also for evaluating which specific test parameters may be the best indicators of product stability ^{1-2,11-15}. Figure-1 represents the complete flow of forced degradation.

- To estimate the stability of Drug Substance and Drug Product in solution
- To Identify structural transformations of the drug substance and drug product

- To detect if there are any low concentrations of potential degradation products
- To detect unrelated impurities in the presence of the desired product and product-related degradants
- To separate product-related degradants from those derived from excipients and intact placebo.
- To elucidate possible degradation pathways
- To identify degradation products that may be spontaneously generated during drug storage and use
- To facilitate improvements in the manufacturing process and formulations in parallel with accelerated pharmaceutical studies.

Overview of Regulatory Guidance

Forced degradation studies are described in various international guidelines. The International Committee for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published a set of guidelines which have been discussed, agreed upon and adopted by the American, European and Japanese regulatory authorities. In the majority of cases, the **ICH guidelines** only apply to the marketing applications for new products, i.e., they do not apply during clinical development. However, since the conditions used for forced degradation are only defined in general terms, it is possible to apply them for developing stability indicating methods during clinical development. The same forced degradation conditions can then be applied to the drug substance during development and commercialization. The ICH guidelines that are applicable to forced degradation studies are ^{1-2, 17-20}.

- ICH Q1A – Stability Testing of New Drug Substances and Products
- ICH Q1B – Photo stability Testing of New Drug Substances and Products
- ICH Q2B – Validation of Analytical Procedures: Methodology

In **ICH Q1A**, section 2.1.2 (Stress Testing), there are recommended conditions for performing forced degradation studies on drug substances and drug products. The recommendations are to examine the effects of temperature (above that for accelerated testing, i.e., >50°C), humidity

($\geq 75\%$ relative humidity), oxidation and photolysis. Testing in solution should also be performed across a wide pH range either as a solution or suspension. These samples are then used to develop a stability-indicating method. **ICH Q1B** gives recommended approaches to assessing the photo stability of drug substances and drug products. Forced degradation conditions are specified in Section II (drug substance) and Section III (drug product). Exposure levels for forced degradation studies are not defined, although they can be greater than that specified for confirmatory (stability) testing. The actual design of photo stability studies is left to the applicant; however, scientific justification is required where light exposure studies are terminated after a short time, e.g., where excessive degradation is observed. Photo stability testing can be performed on the solid or in solution/suspension. These samples are then used to develop a stability indicating method. Both guidance's, **Q1A** and **Q1B**, note that some of the degradation products formed during forced degradation studies may not actually be observed to form during stability studies, in which case they need not be examined further. **ICH Q2B** gives guidance on how to validate analytical methodology and in section B 1.2.2 (impurities not available) there is a recommendation to use samples from forced degradation studies to prove specificity. Specificity is a key factor in determining whether or not the analytical method is stability indicating. Co-elution of peaks or components being retained on the column will underestimate the amount of degradation products formed and could compromise quality and increase risk to the patient. **Q3A (R2)** requires identification of each impurity with respect to both chemistry and safety perspectives. The chemistry perspectives include classification and identification of impurities, report generation, listing of impurities in specification and a brief discussion of analytical procedures while the safety perspectives include specific guidance for qualifying those impurities that were not present or were present at substantially lower levels in batch of a new drug substance and used in safety and clinical studies^{1-15, 25-34}.

FDA perspectives and scientific considerations

Ragine Maheswaran provided a clear perspective on FDA regarding the scientific considerations with respect to forced degradation studies. If the substance does not show any degradation under any of the stress conditions then the Stress studies shall be repeated to obtain adequate degradation. If degradation is not achievable, rationale shall be provided. The conditions employed for stress study are too harsh and that most of the drug substance has degraded. The stress studies using milder conditions or shorter exposure time to generate relevant degradation products. Stressed samples shall be performed as per the assay method conditions. For the related substances method to be stability indicating, the stressed samples should be analyzed using related substances method conditions. The attempts shall be made to ensure that all the impurities including the degradation products of the unstressed and the stressed samples are captured by the final analytical method. Summary of the amount of degradation products (known and unknown) in the stressed samples shall be provided. The purity determinations shall be performed as per the established software. Mass imbalance of the stressed samples shall be justified. The degradation products shall be identified that are formed due to drug-excipients interactions. Photo stability studies shall be determined whether the drug product is very sensitive to light or not. This shall be

documented in the analytical method, manufacturing process, product handling, and etc.

Origin of degradation products

The main reason of appearance of impurities in drug substance or product is due to its degradation. The chemical instability of the drug substance under the conditions of heat, humidity, solvent, pH, and light encountered during manufacture, isolation, purification, drying, storage, transportation, and/or formulation is main cause of its degradation. It is governed by inherent chemical stability of the drug substance. The major routes of degradation of any drug substance include hydrolysis, oxidation, heat and photolysis. The stress testing helps in generation all possible degradation products that may form under different conditions¹.

Selection of experimental conditions

There are many examples in the literature of experimental conditions for conducting forced degradation studies and the structural multiplicity of drug molecules makes it not possible to identify a generic set of conditions for a forced degradation study. For an early phase molecule, using a set of normal conditions by first intention makes sense since very little may be known about the intrinsic stability. If early stability data are available which suggest the molecule is labile at a particular condition (e.g., high pH), the conditions can be modified to take into account the instability (e.g., reduced temperature or time of study). Once a set of conditions have been found, they may be repeated whenever a new stability-indicating method is required during development. Therefore, for later-phase molecules, the forced degradation conditions are defined by the earlier work. By reprocess the same forced degradation conditions throughout development a consistent approach is maintained^{1-2, 30-34}.

Conditions for degradation

Hydrolytic condition

Hydrolysis is one of the most common degradation chemical reactions over wide range of pH. Hydrolysis is a solvolytic process in which drug reacts with water to yield breakdown products of different chemical compositions. Water either as a solvent or as moisture in the air comes in contact with pharmaceutical dosage forms is responsible for degradation most of the drugs. Hydrolytic study under acidic and basic condition involves catalyzation of ionisable functional groups present in the molecule. HCl and NaOH are employed for generating acidic and basic stress samples, respectively. The hydrolytic degradation of a new drug in acidic and alkaline condition can be studied by refluxing the drug in 0.1 N HCl / 0.1 N NaOH. If reasonable degradation is seen, testing can be stopped at this point. However in case no degradation is seen under these conditions the drug should be refluxed in acid/alkali of higher strength and for longer duration of time. Alternatively if total degradation is seen after subjecting the drugs to initial condition, acid/alkali strength can be decreased with decrease in reaction temperature. In general temperature and pH are the major determinant in stability of the drug prone to hydrolytic decomposition. Hydrolysis of most of the drugs is dependent upon the relative concentration of hydronium and hydroxyl ions. Hence pH at which each drug is optimally stable can be determined¹⁷⁻³⁴.

Procedure for conducting hydrolytic degradation

Conduct the following forced degradation studies to obtain degraded samples wherever degradation possible from about 1% to 30%. For Acid stress Reflux with 0.1N HCL at 60°C for 30 minutes. For Base stress Reflux with 0.1N NaOH at 60°C for 30 minutes. For water stress Reflux with water at 60°C for 30 minutes. Stress agent can be changed to achieve degradation if necessary Co-solvent can be used to dissolve and extract the drug, where necessary. Figure-2 represents the flow of hydrolytic degradation.

Oxidative Condition

Many drug substances undergo autoxidation i.e., oxidation under normal storage condition and involving ground state elemental oxygen. Therefore it is an important degradation pathway of many drugs. Autoxidation is a free radical reaction that requires free radical initiator to begin the chain reaction. Hydrogen peroxide, metal ions, or trace level of impurities in a drug substance act as initiators for autoxidation. The mechanism of oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anions and cations. Amines, sulphides and phenols are susceptible to electron transfer oxidation to give N-oxides, hydroxylamine, sulphones and sulphoxide. The functional group with labile hydrogen like benzyl carbon, allylic carbon, and tertiary carbon or α - positions with respect to hetro atom is susceptible to oxidation to form hydro peroxides, hydroxide or ketone. Products could be rationalized with free radical-mediated autoxidation reactions involving alkene and alcohol sites. Hydrogen peroxide is very common oxidant to produce oxidative degradation products which may arise as minor impurities during long term stability studies. It can be used in the concentration range of 3-30% at a temperature not exceeding 40 °C for 2-8 days.

Procedure for conducting oxidative degradation

Conduct the following forced degradation studies to obtain degraded samples wherever degradation possible from about 1% to 30%. For oxidation stress: Treat with 1% H_2O_2 at less than 30°C for 30 min. The oxidative stress testing is initially carried out in 3% H_2O_2 at room temperature for 6 hr and it can be increased/ decreased to achieve sufficient degradation. Stress agent can be changed to achieve degradation if necessary. Co-solvent can be used to dissolve and extract the drug, where necessary. Figure-3 represents the flow of oxidative degradation.

Thermal Condition

In general, rate of a reaction increase with increase in temperature. Hence, the drugs are susceptible to degradation at higher temperature. Many APIs are sensitive to heat or tropical temperatures. For example, vitamins, peptides, etc. Thermal degradation 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: $K = Ae^{-E_a/RT}$ Where k is specific reaction rate, A is frequency factor, Ea is energy of activation, R is gas constant (1.987 cal/deg mole) and T is absolute temperature. Thermal degradation study is carried out at 40°C to 80°C. The most widely accepted temperature is 70°C at low and high humidity for 1-2 months. High temperature ($>80^\circ C$) may not produce predictive degradation pathway. The use of high-temperatures in predictive degradation studies assumes that the drug molecule will

follow the same pathway of decomposition at all temperatures. This assumption may not hold true for all drug molecules, and therefore great care must be taken in using the extreme temperatures easily accessible in a sealed-vessel microwave experiment for predictive degradation studies.

Procedure for conducting thermal degradation

Conduct the following forced degradation studies to obtain degraded samples wherever degradation possible from about 1% to 30%. Preferably, the following stress conditions are recommended for specificity study, however stress condition can be decided based on experimental data, or physical properties of the analyte based on literature. If melting point of API is less than 150°C, stress at 105°C or 40°C less than melting point whichever is higher. If melting point of API is more than 150°C stress at the nearest melting point and at 105°C. Figure-4 represents the flow of thermal degradation.

Photolytic Condition

Exposure of drug molecules may produce photolytic degraded products. The rate of photo degradation depends upon the intensity of incident light and quantity of light absorbed by the drug molecule. Photolytic degradation is carried out by exposing the drug substance (in solid as well as in the solution form) or drug product to a combination of visible and UV light. The most commonly accepted wavelength of light is in the range of 300-800 nm to cause the photolytic degradation. The photolytic degradation can occur through non oxidative or oxidative photolytic reaction. The non-oxidative photolytic reaction include isomerization, dimerization, cyclization, rearrangements, decarboxylation and hemolytic cleavage of X-C hetero bonds, N-alkyl bond(de alkylation and deamination), SO_2 -C bonds etc. and while oxidative photolytic reaction occur through either singlet oxygen(1O_2) or triplet oxygen(3O_2) mechanism. The singlet oxygen reacts with the unsaturated bonds, such as alkenes, dienes, poly nuclear aromatic hydrocarbon to form photo oxidative degradation products whereas triplet oxygen react with free radical of the drug molecule, which than react with a triplet oxygen molecule to form peroxide. Hence, light can also act as a catalyst to oxidation reactions. Hence, the characterization of photo degradation process involves the study of the transient species and the interaction between precursor and products, is a crucial way to understand the potential Photo-toxicity of a drug and determining it.

Procedure for conducting photolytic degradation

Conduct the following forced degradation studies to obtain degraded samples wherever degradation possible from about 1% to 30%. Expose the tablet powder contents of capsule to ultraviolet radiation up to minimum of 200 watts hour/m² and minimum of 1.2 million lux hour for visible light and photo stability chamber. If photo stability chamber is not available, expose the tablet powder/content of capsule to intense ultraviolet radiation (both at longer and shorter wavelengths) up to minimum of 7 days in UV cabinet. Figure-5 represents the flow of photolytic degradation

Humidity

Humidity is the Key factor in establishing the potential degradants in the finished product and active pharmaceutical ingredient. Normally 90% Humidity for duration of one week shall be recommended for the establishment of forced degradation samples.

Selection of samples

The strength and duration of the stress conditions need to be decided by experimenting to get the sample with required degradation. Simultaneously subjects the Placebo (Excipients mixture) as per the manufacturing formula to all the above stress conditions. For multi-drug product placebo formulation containing one drug substance each shall be subjected to forced degradation. Prepare test solutions using unstressed sample, placebo and the stressed samples, as per the test method and inject into the HPLC system with diode array detector. Record the chromatograms and calculate the Percentage degradation and percent net degradation as per acceptance criteria. In case of stable molecules, percent net degradation may be difficult to achieve as per acceptance criteria. Hence based on the experiments, study can be concluded and summary of the experiments shall be documented. Demonstrate the effective separation of the analyte from the degradation product and peaks if any due to components of placebo mixture¹⁻¹⁵. Ensure that response of analyte peak in test solution is equal to or less than 1AU (absorbance unit). If it is more, dilute the test solution accordingly and repeat the analysis.

Acceptance Criteria

All requirements of the software are to be met while evaluating peak purity. The purity angle should be less than purity threshold. The peak should not have any flag in purity result table. Mass balance of all stressed samples shall be verified by calculating Mass balance: (% assay of stressed sample + % impurities) X 100/ % assay of unstressed sample.

Selection of analytical method in identification and characterization of drug products

The preferred method of analysis for a stability indicating assay is reverse-phase high-performance liquid chromatography (HPLC). Reverse-phase HPLC is preferred for several reasons, such as its compatibility with aqueous and organic solutions, high precision, sensitivity, and ability to detect polar compounds. Separation of peaks can be carried out by selecting appropriate column type, column temperature, and making adjustment to mobile phase pH. Poorly-retained, highly polar impurities should be resolved from the solvent front. As part of method development, a gradient elution method with varying mobile phase composition (very low organic composition to high organic composition) may be carried out to capture early eluting highly polar compounds and highly retained non polar compounds. Stressed samples can also be screened with the gradient method to assess potential elution pattern. Sample solvent and mobile phase should be selected to afford compatibility with the drug substance, potential impurities, and degradants.

Stress sample preparation should mimic the sample preparation outlined in the analytical procedure as closely as possible. Neutralization or dilution of samples may be necessary for acid and base hydrolyzed samples. Chromatographic profiles of stressed samples should be compared to those of relevant blanks (containing no active) and unstressed samples to determine the origin of peaks. The blank peaks should be excluded from calculations. The

amount of impurities (known and unknown) obtained under each stress condition should be provided along with the chromatograms (full scale and expanded scale showing all the peaks) of blanks, unstressed, and stressed samples. Additionally, chiral drugs should be analyzed with chiral methods to establish stereo chemical purity and stability. The analytical method of choice should be sensitive enough to detect impurities at low levels (i.e., 0.05% of the analyte of interest or lower), and the peak responses should fall within the range of detector's linearity⁹⁻¹⁵.

The analytical method should be able to capture all the impurities produced during a formal stability study at or below ICH threshold limits. Degradation product identification and characterization shall be performed based on stability results in accordance with ICH requirements. Conventional methods (e.g., column chromatography) or hyphenated techniques (e.g., LC -MS, LC -NMR) can be used in the identification and characterization of the degradation products. Use of these techniques will provide better insight into the structure of the impurities that could add to the knowledge space of potential structural alerts for genotoxicity and the control of such impurities with tighter limits. It should be noted that structural characterization of degradation products is necessary for those impurities that are formed during formal shelf-life stability studies and are above the qualification threshold limit. The detector should contain 3D data capabilities such as diode array detectors or mass spectrometers to be able to detect spectral non-homogeneity. After the method finalization test method on different detectors like RI/ELSD/CE detector with the suitable method parameters and compare the data with other detectors like UV, Fluorescence etc. The UV inactive compounds can be found with this exercise. If any such type of components are there these shall be addressed based on the process and cross checking to be made by using LC-MS technique²⁰⁻²⁷.

Use the analytical mode of fraction collections for major impurities /degradants and check the mass numbers or develop chromatographic conditions suitable to LC-MS and identify the mass of major degradant which are found to be forming greater than 1.0% during stress studies. Try to establish the structures of the major degradant, if possible and compare the synthetic process for justification. Diode array detection also offers the possibility of checking peak profile for multiple wavelengths. The limitation of diode array arises when the UV profiles are similar for analyte peak and impurity or degradant peak and the noise level of the system is high to mask the co-eluting impurities or degradants. Compounds of similar molecular weights and functional groups such as diastereoisomers may exhibit similar UV profiles. In such cases, attempts must be made to modify the chromatographic parameters to achieve necessary separation. An optimal wavelength should be selected to detect and quantitation of all the potential impurities and degradants. Use of more than one wavelength may be necessary, if there is no overlap in the UV profile of an analyte and impurity or degradant peaks. A valuable tool in method development is the overlay of separation signals at different wavelengths to discover dissimilarities in peak profiles¹⁸⁻³⁴.

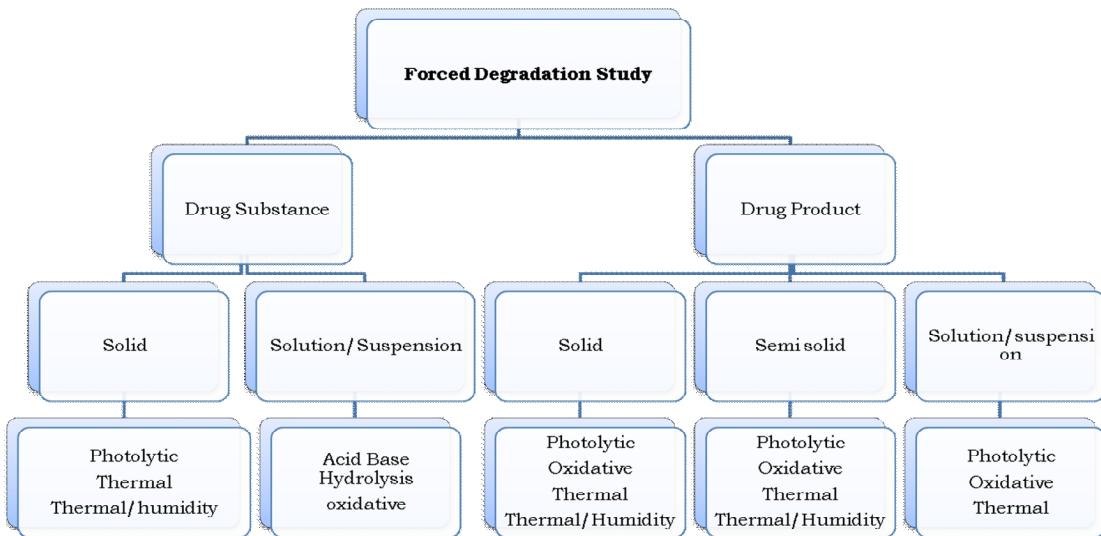


Figure 1: Overview of forced degradation

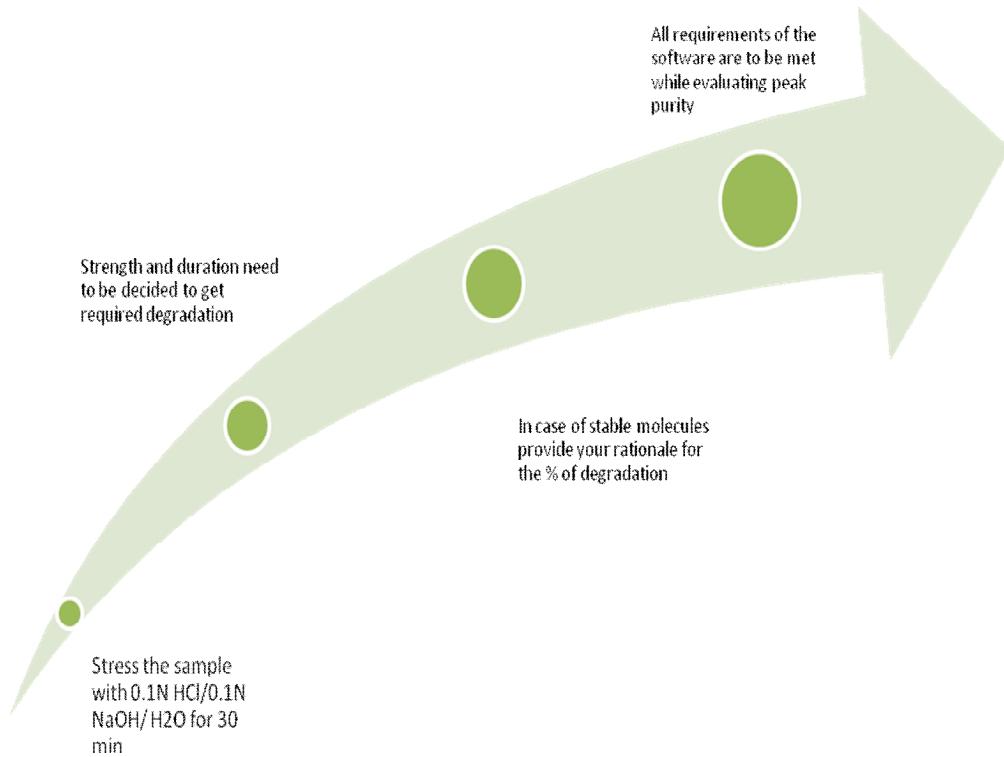


Figure 2: hydrolytic degradation

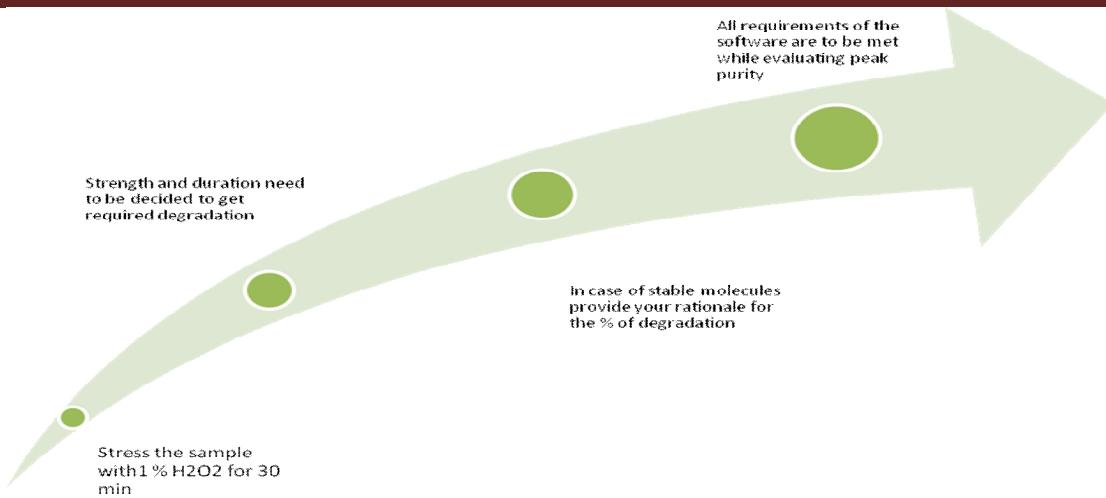


Figure 3: Oxidative Degradation

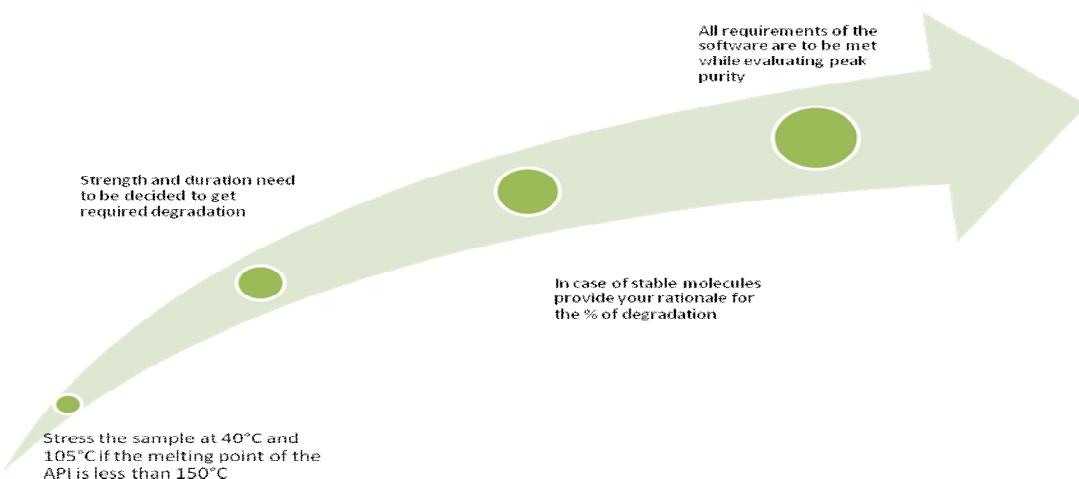


Figure 4: Thermal Degradation

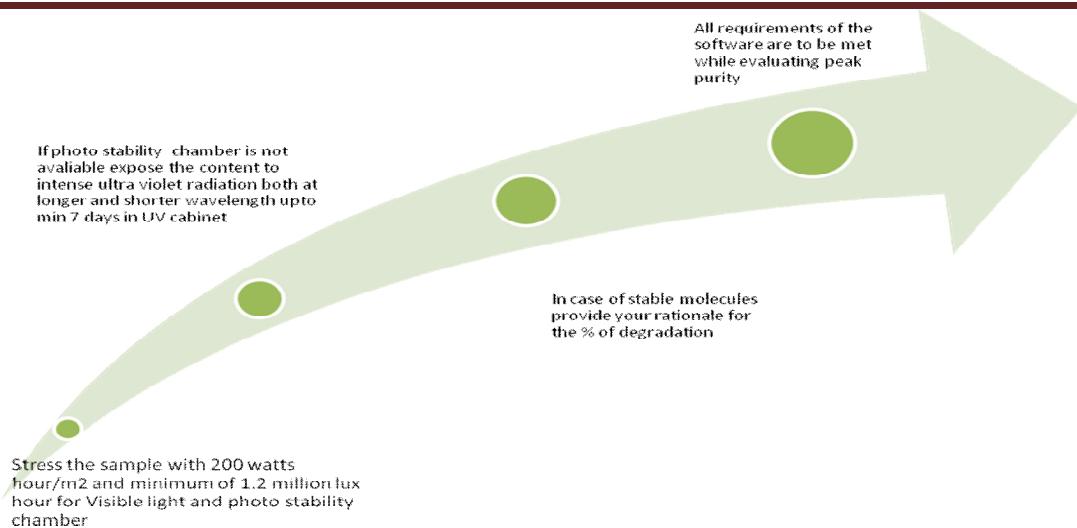


Figure 5: Photolytic Degradation

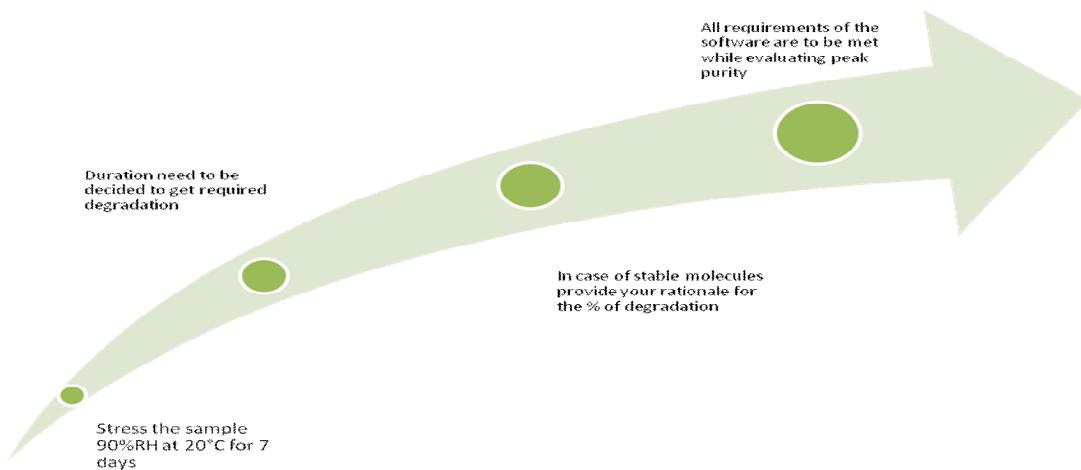


Figure 6: Humidity Degradation

CONCLUSION

Forced degradation studies of new drug substances and drug products are important to help develop and demonstrate specificity of stability-indicating methods and to determine the degradation pathways and degradation products of the active ingredients. They were also useful in the investigation of the chemical and physical stability of crystal forms, the stereochemical stability of the drug substance alone and in the drug product and mass-balance issues, and for differentiating drug substance-related degradation products in formulations. The ICH not provided any formal guidance. Adequate degradation required to understand the probable degradants for the evaluation of stability indicating method.

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