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A Review on Forced Degradation and Its Regulatory Guidelines - A Reliable and Necessary Tool in Stability Studies and Development of Stability Indicating Methods

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ABSTRACT

Forced degradation is also known as,"Stress Testing" and "Purposeful Degradation" and it has long been recognized as an important part of the drug development process. Recent efforts by the International Conference on Harmonization (ICH) with regard to impurities and photo stability have brought an increased regulatory scrutiny of impurities, requiring identification and toxicological classification at very low levels. Efforts to improve and streamline processes related to early identification of potential problems are important to the goal of providing new, safe medicine, faster. Stress testing is the main tool that is used to predict stability problems, develop analytical methods, and identify degradation products/ pathways. Forced degradation studies also play a central role during analytical method development, setting specifications and design of formulations under the quality-by-design (QbD) paradigm. This review paper will provide the readers with a single source reference that bench marks the current best practices in stress testing and answers to questions like, " How hot, How long, "How much humidity", "What pH values to be used?," " What reagents/conditions for oxidative studies to be used", What conditions are appropriate", and topics such as mass balance, photo stability, oxidative susceptibility and the chemistry of drug degradation are addressed in an objective, detailed scientific manner, with an overview of the relevantguidelines governing stress testing. Prior to appropriate guidelines on stress testing coming into force, the stress testing had evolved into an artful science that was highly dependent on the experience of the company or the individuals directing the studies.

Keywords: Shelf-Life, Stability Studies, Stability Indicating Methods, Degradation Pathways, Degradation Products, Forced Degradation.

INTRODUCTION

Stability of a pharmaceutical product may be defined as, "the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications". The fact that the product is stable should be decided by collection of valid data in its commercial package. These stability data involve selected parameters that, taken together, form the stability profile. Pharmaceutical products are expected to meet their specifications for identity, purity, quality, and strength throughout their defined storage period at specific storage conditions. The stability of a pharmaceutical product is

investigated throughout the various stages of the development process. The stability of a drug substance is first assessed in the preformulation stage. At this stage, pharmaceutical scientists determine the drug substance and its related salt stability/compatibility with various solvents, buffered solutions, and excipients considered for formulation development. Optimization of a stable formulation of a pharmaceutical product is built upon the information obtained from the preformulation stage and continues during the formulation development stages. The impact of a drug product with a poor stability profile could delay approval, affect the safety and efficacy of the drug and/or cause product recall[1].

Stress testing is the main tool that is used to predict stability-related problems, develop analytical methods, and identify degradation products and pathways. Stability-related issues can affect many areas, including the following:

- Analytical methods of development,
- Formulation and package development,
- Appropriate storage conditions and shelf-life determination,
- Safety/ toxicological concerns,
- Manufacturing/processing parameters,
- Absorption, Distribution, Metabolism and Excretion (ADME) studies,
- Environmental assessment[2].

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical methods. However, such examination may not be necessary for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions. Therefore, the degradation products formed during stress testing can be thought of as "potential degradation products". Overall strategy for the protection, identification and control of stability-related issuesare shown in Figure-1 below[2].

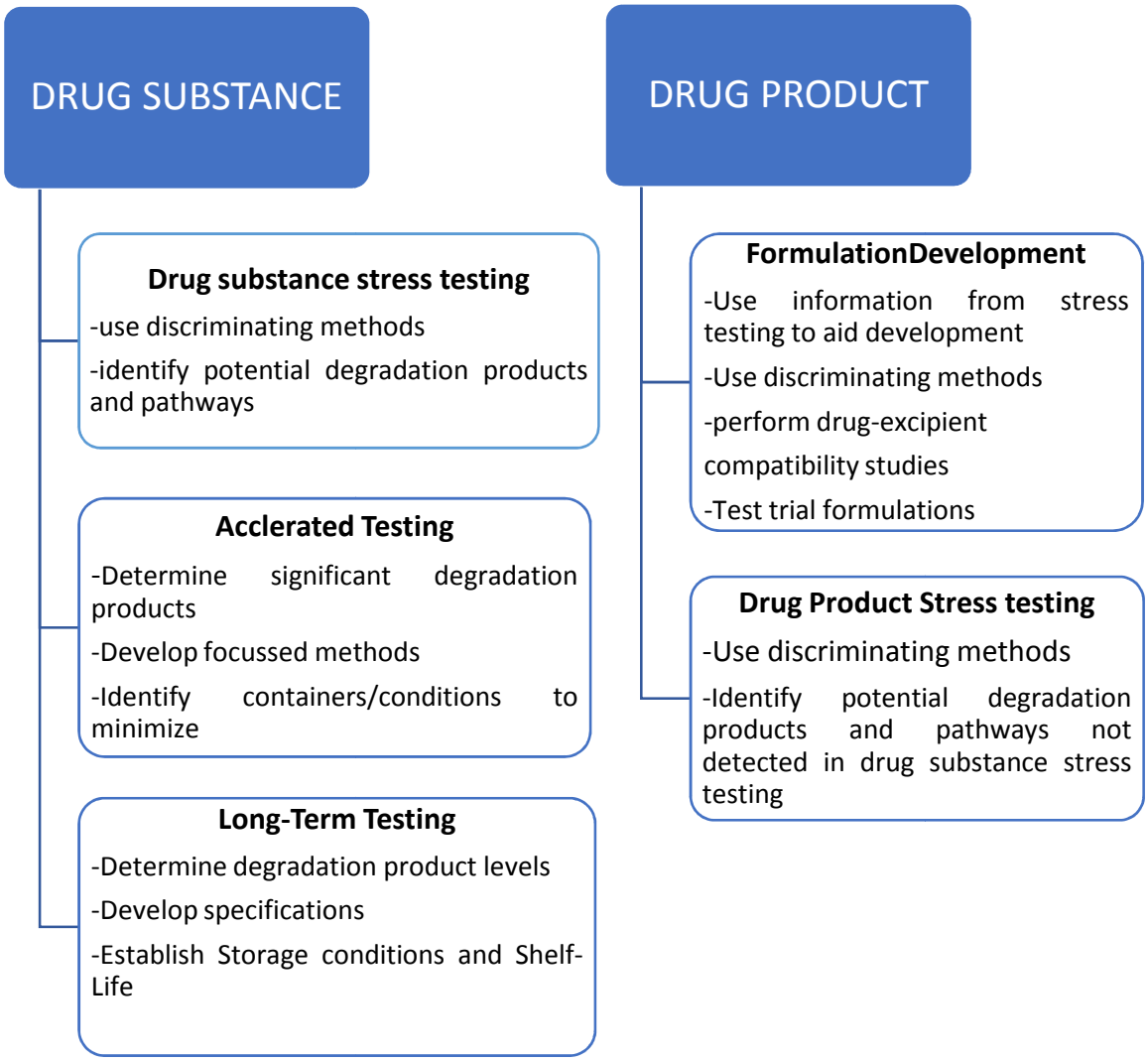


Figure-1: Overall Strategy for the Protection, Identification and Control of Stability-Related Issues[2]

A Glance at Factors Affecting Drug Stability

Many factors affect the stability of a pharmaceutical product and include the stability of the active ingredients, the potential interaction between active and inactive ingredients, the manufacturing process, the dosage form, the container-linear closure system, and the environmental conditions encountered during shipment, storage and handling, and length of time between manufacture and usage. Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations[1].

Physical factors, such as heat, light, and moisture, may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound. The primary environmental factors that can reduce stability include exposure to adverse temperatures, light, humidity, oxygen, and carbon dioxide. The major dosage form factors that influence drug stability include particle size (especially in emulsions and Suspensions), pH, solvent system composition (i.e., percentage of "free" water and overall polarity), compatibility of anions and cations, solution ionic strength, primary container, specific chemical additives, and molecular binding and diffusion of drugs and excipients. In dosage forms, the following reactions usually cause loss of active drug content, and they usually do not provide obvious visual or olfactory evidence of their occurrence[3].

The chemical causes of drug deterioration have been classified as Hydrolysis, Oxidation Reduction, Autoxidation, Racemization, Epimerization, Polymerization, Decarboxylation, Interionic Compatibility, Photo degradation and Incompatibilities[1].

Force Degradation Studies

Synonyms of Forced Degradation

Forced degradation studies are also known as, "Forced Decomposition Studies, Stress Studies, Stress Decomposition Studies, Stress Testing, Purposeful Degradation etc[4, 5].

Historical Context of Forced Degradation/Stress Testing Studies

History says that, "Stress Testing" was somewhat vague and undefined term and was often used interchangeably with the term accelerated stability testing in the pharmaceutical industry. Usually, these topics were discussed as part of overall discussions of drug stability and or prediction of shelf-life, although in some cases the focus was on the degradation pathways or chemical reactivity /stabilization. Accelerated stability was defined in an article in 1980 as,**"**the validated method or methods by which product stability may be predicted by storage of the product under conditions that accelerate change in a defined and predictable manner. The united states FDA definition of Accelerated testing in the 1987 guidelines states that, the term, "Accelerated testing", is often used synonymously with "stress testing". Here the term stress testing is used in many industries to describe testing intended to measure how a system functions when subjected to an applied force or system of forces[6]**.**

More recently ICH introduced an important distinction between the two terms, "Accelerated stability testing" and "Stress testing". ICH defined "Accelerated stability testing" as, studies designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product using exaggerated storage conditions as part of the formal, definitive, storage program. These data in addition to long term stability may be used to assess longer-term chemical effects at non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes and the studies are part of the formal, definitive, storage program[6]."

Stress testing was defined by ICH as, "Studies under taken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing. In Stability guideline, under the drug substance heading, a more detailed description of stress testing is provided, "stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug productinvolved[6].

The latest definitions of stress testing for the drug substance and stress testing for the drug product:

Stress Testing for the Drug Substance

Stress testing is conducted to provide data on forced decomposition products and decomposition mechanisms for the drug substance. The severe conditions that may be encountered during distribution can be covered by stress testing of definitive batches of drug substance.

Stress Testing for the Drug Product

Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photo stability testing and specific testing on certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products)

From the ICH definition, it is clear that there is now a differentiation between the Accelerated Testing and The Stress Testing.

- Stress testing is distinguished by both the severity of the condition and the focus or intent of the results.
- Stress testing which is also often referred to as, "Forced Degradation" is an investigation of the "intrinsic stability" characteristics of the molecule providing the foundation for developing and validating analytical methods and for developing stable formulations.
- Stress testing studies are intended to discover stability issues and are therefore predictive in nature. Stress testing studies are not a part of the validated formal stability program.

Pharmaceutical stress testing is a research investigation requiring scientific expertise and judgement[6].

Table-1: Stress Testing Recommendation for Drug Substance and Drug Products[4]

Active Drug Substance	
Temperature	50,60,70 °C etc.
Humidity	25 □/75% RH and 25□/90 % RH
Oxidation	Over a wide range of pH

Light	Based on Q1B Exposed and in the Drum
Drug Product	
Temperature/ Humidity	40□/75% RH and 25□/80 % RH
Temperature	50 or 60□ for 1 month
Light	Based on Q1B Exposed and in the Package

Definition of Forced Degradation/Stress Testing Studies

According to the ICH Guidance on the stability testing (ICH 2003), the definition provided is that, "Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the "intrinsic stability" characteristics of the molecule and validate the stability indicating power of the analytical procedure used." This is an important definition because it distinguishes stress testing also known as forced degradation from two other types of stability-related studies: Accelerated stability testing and long-term stability studies. Thus, stress testing is a predictive research tool that is used to discover stability issues with a drug molecule, providing the scientific foundation for developing stability-indicating methods. Accelerated stability testing and long-term stability testing can then utilize the stability- indicating methods in a more formal manner to generate the specific and quantitative information needed for estimation/ Determination of shelf-life as part of a regulatory submission[7].

The Intrinsic Stability encompasses four main aspects:

- Conditions leading to degradation,
- Rates of degradation (relative or otherwise)
- Structures of the major degradation products, and
- Pathways of degradation[7].

Experimental Approach to Forced Degradation/Stress Testing Studies

Best Time for Conducting Forced Degradation Studies

Starting forced degradation studies at early stage is highly recommended. There are good reasons for initiating forced degradation studies on drug substances at phase 1. The most important reason is to support the development of a preliminary method that would be highly discriminating due to its ability to detect most if not all of the potential degradation products. Such method would have stability indicating power and would require only minimal validation at this stage. Another reason is to further understand degradation pathways and mechanisms occurring in the drug substance and drug product. A good understanding of degradation early in development avoids having to change the method in later development stages. If stability issues arise. This results in a smoother transition between development phases. In summary, the decision to start forced degradation early or late in development is one that should be driven by quality risk assessment and depends, among other factors, on the chemistry of the molecule, the formulation approach, material availability and portfolio prioritization[8].

Study Protocol for Conducting Forced Degradation/Stress Testing Studies

A general protocol for conducting forced degradation studies based upon the protocol described in Available Guidance and Best practises for conducting forced degradation studies is shown in the **Table-2** below[8].

Table-2: **General protocol for forced degradation studies (stress studies) of a drug substance and drug product[8]**

	Drug Substance		Drug Product	
Stress Conditions	**As Solid**	**As Solution/ Suspension**	**As Solid Dosage form (Tablet capsules, blends)**	**As Liquid**
Hydrolysis (Acid, Base & Thermal	-	✓	-	✓
Oxidative	X	✓	✓	✓
Photo-Degradation	✓	✓	✓	✓
Thermal	✓	-	✓	✓
Thermal/Humidity	✓	-	✓	-

Design of Forced Degradation /Stress Testing Studies

The design of stress testing studies should take into consideration the following aspects:

Manufacturing Conditions, Analytical Handling, Storage and Distribution, and Patient "in use".Since conditions can vary depending upon the location of storage facilities and means forDistribution /transport, consideration should also be given to how patients might reasonably beexpected to handle or mishandle their medicine once it is in their hands. Thus, the design ofstress conditions should anticipate temperature excursions during shipping, elevated humidities, exposure to direct or window-filtered sunlight and exposure to oxidation sources such asperoxides and other autoxidation initiating sources[8].

Conditions for Forced Degradation/Stress Testing Studies

Conditions for Stress Testing to Predict Degradation

Stress testing needs to be conducted to investigate four main degradation pathways of a typical drug. These pathways are:

Hydrolytic: This can be accomplished by storing the drug in solutions or suspensions from pH 1 to 13, up to a temperature of 70□ for up to 1 week.

Thermolytic: This can be accomplished by storing the drug at temperatures up to 70□ in both high humidity conditions (75%) and low humidity conditions (e.g., 10-20%), typically for 3-6 weeks.

Photolytic: This can be accomplished by exposing the solid and solutions to both visible and UV light in excess of ICH minimum confirmatory exposure this can be done by either exposing the drugs to a combination UVA lamp and cool white fluorescent either sequentially or simultaneously, and secondly by exposing to simulated solar radiation behind window glass.

Oxidative: Oxidative degradation can be difficult to mimic because of the different reactive oxygen species and complex oxidative mechanisms that are possible[7].
Specific parameters for stress testing of drug and drug products are shown in the **Table-3[8].**

Table-3: Stress Conditions for Drug Substance[8]

Type of study	Conditions	Time
Acid hydrolysis	0.1 N- 1.0 N HCl, RT or higher	1-7 days
Base hydrolysis	0.1 N- 1.0 N NaOH, RT or higher	1-7 days
Thermal hydrolysis	Aqueous solution, 70°C	1-7 days
Oxidative/solution	O2 + Initiator (AIBN) in CAN/ H2O; 80/20,40°C 0.3-3.0 % H2O/ Ambient in the dark	1-7 days Few hours to 7 days
Thermal solid,	70°C	Up to 3 weeks
Thermal/ Humidity solid,	70°C/ 75% RH	Up to 3 weeks
Photo degradation Solid,	fluorescent and UV light	>2× ICH

Drug Product Stress testing

Stress testing studies should also be conducted on the formulated product because drugs can and often do degrade differently in specific dosage forms and in the presence of specific excipients.for solid oral dosage forms like capsules and tablets, stress testing can involve exposure to elevated temperatures, humidities , and to light i.e., photostability testing. For lyophilized powder products, the same conditions are recommended plus reconstitution studies at elevated temperature and in the presence of light. For liquid formulations, in addition to exposure to elevated temperature and humidity and to light, acid/basehydrolysis studies are recommended because of the potential for changes in the degradation profile as a function of the pH and the components of the liquid formulation[7].

There commended Stress Conditions for Drug Product are shown in Table-4[8].

Table-4: Recommended Stress Conditions for Drug Product

Stress Type	Conditions	Time
Thermal	70□	Up to 3 Weeks
Thermal/ Humidity	70□/75% RH	Up to 3 Weeks
Photo-degradation	Fluorescent and UV Light	>2 x ICH

Using Quality-by-Design (QbD) Concepts

The concepts of Quality-by-Design(QbD) can provide a useful construct for understanding how stress testing can provide the scientific foundation for analytical method development and the development of control strategies for stability. QbD is defined by ICH as a, " Systematic approach to pharmaceutical development that begins with predefined objectives and emphasises product and process understanding based on sound science and quality risk management[7].

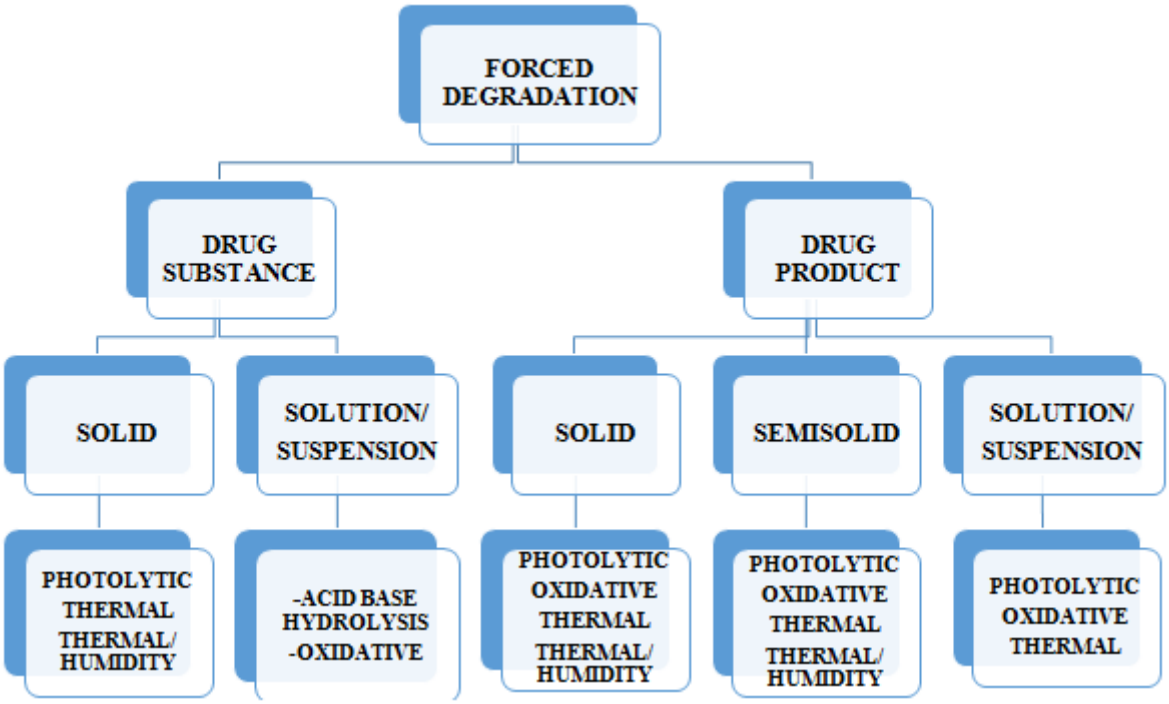


Figure-2: An illustrative flow diagram showing the different forced degradation conditions to be used for drug substanceand drug products.

Evaluation of Results

The evaluation for all the degradation products formed under all the stress conditions is done by chromatographic techniques, the most commonly used are HPLC, UPLC, UHPLC, and CE. The major concern here is the successful separation of all the degradation products from the drug and from each other, viz development of stability-indicating method. The developed analytical method should be good enough to detect impurities at low levels. During the method development it may happen that the drug peak may hide a degradation impurity peak that co-elutes with the drug. All known and unknown impurities should be well separated from main component peak and all unknown impurities should be well separated from known impurities. Sometime two merged unknown impurity may lead to out of specification results in real time stability therefore analytical method should have capability to resolve any unknown impurities higher then unknown impurity specification level from merging with each other[9]

Analytical method

The preferred method of analysis for a stability indicating assay is reverse-phase high-performance liquid chromatography, which is the method of choice for several reasons, such as its compatibility with aqueous and organic solutions, high precision, sensitivity, and ability to detect 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. 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[10].

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 linearity. The analytical method should be capable of capturing all the impurities formed during a formal stability study at or below ICH threshold limits. Degradation product identification and characterization are to be performed based on formal 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 can 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. Various detection types can be used to analyze stressed samples such as UV and mass spectroscopy[10].

Peak Purity or Peak Homogeneity Analysis

Peak purity is used as an aid in stability indicating method development. The spectral uniqueness of a compound is used to establish peak purity when co-eluting compounds are present. Peak purity or peak homogeneity of the peaks of interest of unstressed and stressed samples should be established using spectral information from a diode array detector. When instrument software is used for the determination of spectral purity of a peak, relevant

parameters should be set up in accordance with the manufacturer's guidance. Attention should be given to the peak height requirement for establishing spectral purity. UV detection becomes nonlinear at higher absorbance values. thresholds should be set such that co-eluting peaks can be detected. Optimum location of reference spectra should also be selected. The ability of the software to automatically correct spectra for continuously changing solvent background in gradient separations should be ascertained[8, 9].

Mass balance

When degradation occurs ideally, the measured amount of parent drug lost should correlate well with the measured increase in degradation products. This correlation is known as "Mass Balance". The ICH has defined mass balance, also known as material balance as, "the process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical precision". This concept is a useful scientific guide for evaluating data, but it is not achievable in all circumstances. Mass balance in pharmaceutical analysis is important for several reasons. It not only establishes adequacy of a stability indicating method, but is also useful in method validation. In order to demonstrate that analytical methods are stability indicating, unstressed and stressed materials are often compared. An increase in degradation products that correlates well with loss of parent drug aids in demonstrating that the methods can be accurately assess degradation. Mass balance is also important in understanding alternative degradation pathways. Mass balance can be calculated and expressed in a variety of ways. The amount of parent compound lost and of degradation products formed can be expressed in terms proportional either to weight or to number of moles. The mass balance is suggestive of a straight forward correlation of mass or weight lost and gained. If all starting materials and degradation products are accounted for, then a correlation in terms of weight is appropriate. It is important to remember that the goal of stress testing is not primarily to achieve mass balance in the analytical results, but to achieve a full understanding of the degradation chemistry[11]

When to Terminate of study

Termination of the forced degradation studies should be carried out after ensuring adequate exposure to stress conditions. A compound may not necessarily degrade under every single stress condition. In circumstances, where some stable drugs do not show any degradation under any of the stress conditions, specificity of an analytical method can be established by spiking the drug substance or placebo with known impurities and establishing adequate separation Typical activation energy of drug substance molecules varies from 12–24 kcal/mol[12].

Guidelines on Forced Degradation/Stress Testing Studies

There are various regulatory guidelines on forced degradation/stress testing studies which are listed in the **Table-5** below.

Table-5 various regulatory guidelines on forced degradation/ Stress Testing

Serial number	Title of the Guideline	Guideline Reference	References
1	Stability Testing of New Drug Substance and Products	Q1A(R2)	**13**
2	Stability Testing: Photo stability Of New Drug Substances and Products.	Q1B	**14**
3	Evaluation of stability data	Q1E	**15**
4	Validation of Analytical Procedures: Methodology	Q2(R1)	**16**
5	Impurities in New Drug substances	Q3A(R2)	**17**
6	Impurities in New Drug Products.	Q3B (R2)	**18**
7	Stability Testing of Biotechnological/Biological Products.	Q5C	**19**
8	Specifications: New Chemical Drug Substances and Products.	Q6A	**20**
9	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	Q7	**21**
10	Impurities in official Articles	USP (1086)	**22**
11	USP Reference standards	USP (11)	**23**
12	Pharmaceutical stability	USP (1150)	**24**
13	Stability Considerations in Dispensing Practice	USP (1191)	**25**
14	Pharmaceutical Compounding-Sterile Preparations-Storage and Beyond -Use Dating	USP (797)	**26**
15.	Note for Guidance on In-Use Stability Testing of Human Medicinal Products	EMEA-March 2001	**27**
16	Guideline on The Chemistry of New Active Substances	EMEA-February 2004	**28**
17	Analytical Procedures and Method Validation	FDA-Guidance for Industry (Draft) February 2014	**29**
18	INDs for Phase II and Phase III Studies, Chemistry Manufacturing, and Controls Information	FDA-Guidance for Industry 2003	**30**

CONCLUSION

Forced degradation i.e., stress testing studies are foundational to develop an understanding of real time stability. It is used to establish the potential degradation products of a drug, which can be used to develop valid stability indicating methods. Thus, stress testing is a predictive tool, used to discover the intrinsic stability characteristics of a molecule[7].

Forced degradation/stress testing is also an important tool for the prediction of stability related problems. The results of stress testing can be useful to many areas of pharmaceutical research and development beyond the obvious areas of analytical, formulation, and packaging development. Well-designed stress testing studies can lead to a thorough understanding of the intrinsic stability characteristics of the drug molecule[2].

Forced degradation is required to demonstrate specificity of stability indicating methods. 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 under defined storage condition. A stability-indicating assay method accurately measures the active ingredient(s) without interference from other peaks and is sensitive enough to detect and quantify the degradation products/impurities. To develop a stability-indicating method, stress testing, in the form of forced degradation and a photo stability study, should be carried out at an early stage so that impurities and degradation products can be identified and characterized. Stability-indicating assay analytical methods must be discriminating and validated to ensure the accuracy of the long-term stability study trending[31].

Forced degradation studies show the chemical behaviour of the molecule which in turn helps in the development of formulation, package and Storage. Degradation impurities generated in forced degradation studies may or may not be generated in real time stability studies, but this important step is used primarily to develop stability-indicating analytical methods. It is strongly recommended that these studies should be started as early as possible to be able to provide valuable information that can be used to assess the inherent stability of a drug and to improve formulation and the manufacturing process. A thorough knowledge of degradation, understanding of potential degradation pathways, stress conditions etc. are essential for success of these studies. It is important to perform stress testing for generic drugs due to allowable qualitative and quantitative differences in formulation, selection of manufacturing process, processing parameters, and packaging materials[7].

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Conflict of Interest: The authors declare no conflict of interest.

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