A REVIEW ON QUALITY BY DESIGN (QbD) APPROACH TO FORCED DEGRADATION STUDY

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ABSTRACT
A thorough understanding of shelf life, expiration timelines, degradation behavior, stability characteristics, and impurity profiles is critical in pharmaceutical development. This review emphasizes the application of a Quality by Design (QbD) strategy to systematically optimize forced degradation conditions for effective impurity profiling. Analytical challenges encountered during the later phases of long-term stability testing are often associated with unforeseen impurities, which can interfere with the evaluation of known impurities and lead to significant regulatory concerns. Forced degradation studies, referred to as stress testing, or forced decomposition studies, are a critical component in establishing a regulatory-compliant stability program for both drug substances and drug products. Although these studies have been widely used in the pharmaceutical industry for many years, they were formally recognized as a regulatory requirement with the introduction of the ICH guideline Q1A: Stability Testing of New Drug Substances and Products. The impact of QbD on forced degradation studies is transformative. It converts FD studies into a powerful knowledge-generation tool that supports stability-indicating method development, risk management, and regulatory compliance, ultimately ensuring consistent product quality throughout the lifecycle. QbD-driven FD studies helps to ensure separation of drug substance from degradation products. Prove specificity and selectivity of the method. Establish method robustness and reliability.
KEYWORDS: Stress Testing, ICH, QbD, CQAs.
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INTRODUCTION:

This review emphasizes the application of a Quality by Design (QbD) strategy to systematically optimize forced degradation conditions for effective impurity profiling. Determination of impurity profiles using chromatographic analysis is an important aspect of proving quality and safety. Development of chromatographic methods mainly depends upon three concepts: quality, safety, and efficacy, representing the building blocks of such analysis due to their correlation with public health. However, development of chromatographic methods is time-consuming and also involves solvent wastage, hence it is important to follow an approach that can result in fast as well as robust development of high-performance liquid chromatography (HPLC) methods. A commonly used approach is one-factor-at-a-time (OFAT), but application of multivariate methods including design of experiments (DoE), chemometrics, etc. can help detect multiple factors at a time (MFAT). Quality by design is an approach which uses statistical experimentation to quantify system behavior accurately.

Forced degradation study is a complementary part of stability testing wherein the influence of environmental stress factors such as pH, temperature, humidity, oxygen, and light on drug substances and drug products is evaluated The use of a multivariate design of experiments (DoE) strategy for impurity classification can enhance process robustness while minimizing development time and cost. Considerable attention is also given to the implementation of ICH Q8 and Q9 guidelines to strengthen the quality, safety, and efficacy aspects of pharmaceutical studies.(1)

The implementation of the Quality by Design (QbD) approach ensures the development of a process that consistently achieves the desired performance, which is predefined based on a thorough understanding of the product and its characteristics. In forced degradation studies, key critical quality attributes (CQAs) associated with degradation behavior and analytical method performance are systematically identified and optimized to obtain reliable and reproducible outcomes.

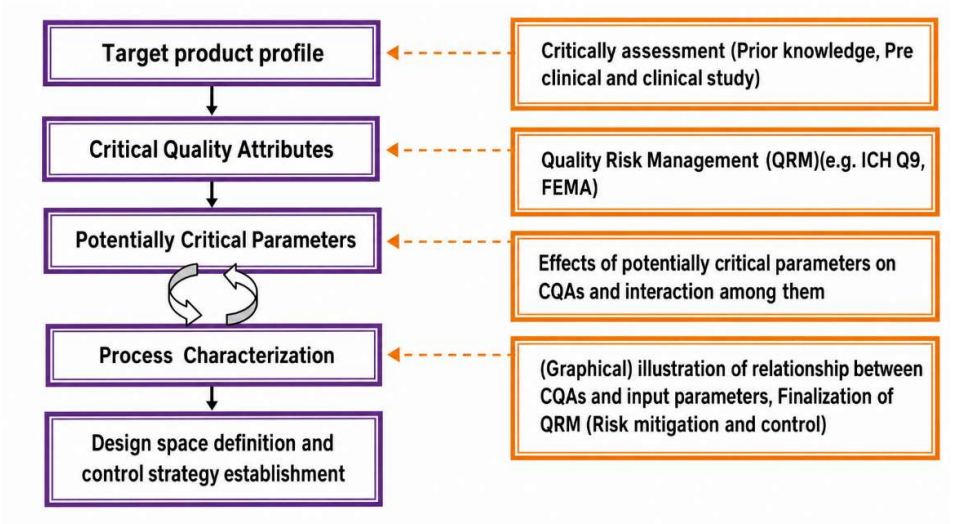

Fig. No. 01 Flow Chart of QbD Process

During the development of the UV spectrophotometric method and the execution of forced degradation studies under acidic, alkaline, oxidative, thermal, and photolytic conditions, QbD principles are applied by evaluating and optimizing critical parameters such as stress intensity, sample quantity, and exposure duration. These parameters are selected to produce degradation within an acceptable and predefined range in accordance with ICH recommendations. Additionally, the analytical method is validated following ICH guidelines, which ensures improved accuracy, precision, and robustness of the generated data. Overall, the integration of QbD principles enhances scientific understanding and control, leading to a more precise, accurate, and reproducible forced degradation process and analytical method. [2]

In accordance with International Council for Harmonisation (ICH) guidelines, forced degradation studies are conducted to evaluate the stability characteristics of drug molecules, identify potential degradation pathways, and assess the validity of established stability-indicating methods. These studies provide detailed information on the degradation behaviour of pharmaceutical compounds and the formation of degradation products over time when exposed to various environmental stress conditions. The interpretation and understanding of stability data, including the influence of factors such as temperature, light, moisture, and oxidative stress, are systematically addressed in line with Food and Drug Administration (FDA) and ICH regulatory requirements. [3,4]

Stability evaluation of pharmaceutical products is generally carried out through long-term and accelerated stability studies. Long-term stability studies are typically conducted for a period of approximately 12 months, whereas accelerated studies are completed within about 6 months. In addition, intermediate stability studies may be performed for around 6 months under conditions that are less severe than those used in accelerated testing. Long-term stability studies allow for the detection and separation of degradation products; however, their major limitation is the extended time required to obtain results. In contrast, forced degradation studies enable rapid generation of degradation products, facilitating quicker assessment of degradation

Degradation studies play a crucial role in understanding the degradation pathways and stability behavior of pharmaceutical compounds when exposed to various stress conditions. The identification and characterization of the resulting degradation products are generally performed in accordance with ICH regulatory guidelines. A range of analytical techniques is employed for stability assessment. Among these, high-performance liquid chromatography with ultraviolet detection (HPLC-UV) and HPLC coupled with a photodiode array detector (PDA) are commonly used for the development and validation of stability-indicating methods (SIMs). In contrast, liquid chromatography–mass spectrometry (LC-MS) has emerged as a powerful and reliable tool for the characterization of degradation products. The growing importance of LC-MS is attributed to its superior sensitivity and selectivity for degradation products, as well as its capability to provide detailed structural information. During the preliminary phase of method development, an Analytical Quality by Design (AQbD) approach was applied to develop and optimize an HPLC–UV method for the separation and quantitative determination of drug with the objective to establish a simple, rapid, cost-effective, and reliable analytical procedure. For this purpose, various chromatographic parameters such as column type, column temperature, mobile phase composition, flow rate, injection volume, and detection system were systematically evaluated. Based on the UV absorption characteristi

cs of drug and in accordance with the USP monograph, a detection wavelength has to be selected for analysis. [5]

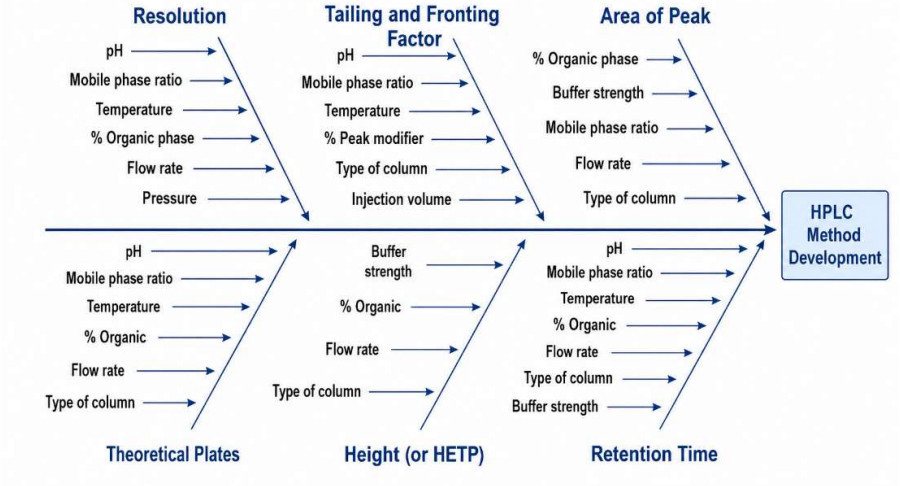

Fig. no. 02 HPLC Method Development

ICH Guidelines:

The ICH guidelines which discuss about forced degradation studies are ICH QIA, QIB, and Q2B, Q3A, Q3B, M4Q (R1)

ICH Q1A guidelines address the stability testing requirements for new drug substances and their finished pharmaceutical products and are used to evaluate the intrinsic stability of drug molecules. These guidelines assist in the systematic design of studies aimed at assessing the stability behavior of pharmaceutical compounds. According to ICH Q1A, the extent and nature of degradation are influenced by the chemical properties of the drug substance and the formulation characteristics of the drug product. To perform forced degradation studies on drug substances and products, the guidelines recommend exposure to various **accelerated stress** conditions, including elevated temperatures (above 50°C), high humidity levels (greater than 75% relative humidity), oxidative stress, photolytic exposure, and a wide pH range in solution or suspension.

2. ICH Q1B guidelines focus on the photostability testing of new drug substances and finished pharmaceutical products and are primarily applied during the early stages of drug development to evaluate the susceptibility of drug molecules to light. These guidelines describe the conditions required for inducing photolytic degradation of drug substances and products and outline the regulatory expectations for such studies. Forced degradation experiments conducted under photolytic stress are particularly useful for the identification and confirmation of light-induced degradation products. The ICH Q2B guideline on validation of analytical procedures provides comprehensive information on the protocols to be followed for validating analytical methods. Specifically, ICH Q2B highlights the use of stressed samples generated through forced degradation studies. It recommends subjecting samples to accelerated conditions such as elevated temperature and humidity to evaluate method specificity. Additionally, these guidelines support the quantitative estimation of degradation products, ensuring reliability and accuracy of analytical results. [6]

3. ICH Q3A guidelines address the evaluation and control of impurities in new drug substances and provide detailed guidance on the assessment of potential contaminants present in pharmaceutical compounds. These guidelines cover key aspects such as the classification, identification, and specification of impurities, along with recommended analytical approaches and documentation requirements. Importantly, demonstrating that impurities are either absent or present only at minimal levels in batches of new drug substances is critical for ensuring product safety and supporting progression into clinical studies. [7]

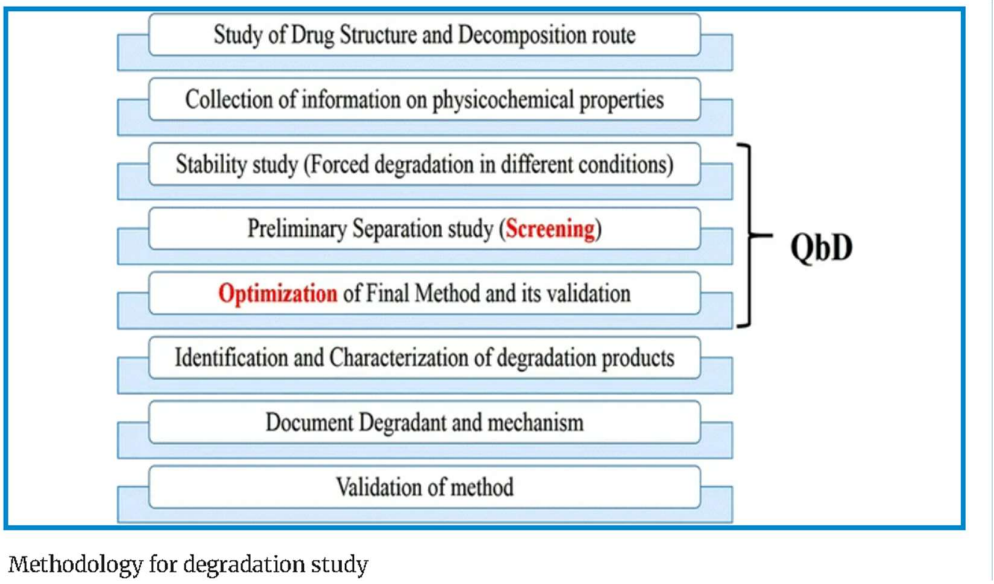

Fig. no. 02 Methodology of Forced Degradation Study

Stability studies:

Stability studies are generally based on two fundamental approaches: first, stability-indicating methods that quantify the active pharmaceutical ingredient in the presence of degradation products, excipients, and formulation additives; and second, selective stability-indicating methods that enable the determination of the drug along with its degradation products, excipients, and additives. Numerous methodologies for performing forced degradation studies have been reported in the scientific literature. (8, 9, 10)

System suitability evaluation forms an essential part of any analytical method:

system suitability parameters, including retention time, theoretical plate number, and tailing factor, were examined to verify the proper functioning and performance of the analytical system. The LOD and LOQ, specificity, linearity and range, Precision and Accuracy.

A Quality by Design with Design of Experiments approach to the development of an analytical method mainly involves two phases as follows: a) Screening Phase b) Statistical Analysis and Final Optimization.

This Screening Phase includes the following steps:

Selection of Critical Method Parameters

Critical Method Parameters are selected number of factors that impact on the analytical technique under development. So, the Critical Method Parameters selected for the study are Buffer pH, Organic Phase (% acetonitrile) and Organic Modifier (Methanol).

Selection of Critical Quality Attributes (CQAs)

Critical Quality Attributes are the responses that are measured to judge the quality of the developed analytical methods. So, the Critical Quality Attributes selected for the study are Retention time and Tailing Factor. These responses were monitored during the experimental trials. (11)

Benefits of Stress Testing in Stability Studies

i. Assessment of the overall vulnerability of a drug substance or product to individual stress factors and their combinations, including temperature, moisture, pH, oxygen, light exposure, and catalytic influences.

ii. Improved understanding of the intrinsic stability profile of the active pharmaceutical ingredient.

iii. Production of stressed samples necessary for the identification and characterization of degradation products formed under various stress conditions, along with clarification of possible degradation pathways.(12)

Factors Influencing Drug Degradation

Several factors contribute to the degradation of pharmaceutical substances, as outlined below:

- **Moisture:** Exposure to moisture can cause water-soluble drugs to dissolve, leading to both physical and chemical alterations that may compromise molecular stability.
- **Excipients:** Certain excipients may contain significant amounts of residual moisture, which can increase the overall water content of the formulation and negatively affect drug stability. Additionally, interactions between excipients and the active drug substance can sometimes result in chemical instability.
- **Temperature:** Variations in temperature can adversely influence drug stability. Elevated temperatures generally accelerate chemical reactions, particularly hydrolytic degradation.
- **pH:** The degradation rate of many drugs, especially through hydrolysis, is strongly dependent on pH. To minimize this effect, formulations are often prepared using buffer systems that maintain the drug at its optimum pH for stability.
- **Oxygen:** The presence of oxygen can promote oxidative degradation in susceptible drugs. Such instability can be reduced by replacing oxygen with

inert gases like nitrogen or carbon dioxide in the packaging environment.

- **Light:** Certain drugs are sensitive to light and may undergo photodegradation upon exposure, leading to loss of potency and product quality.

Stability indicating method:

According to the **Food and Drug Administration (FDA)**, a **stability-indicating method (SIM)** is a quantitative analytical technique designed to evaluate changes in the concentration of a drug substance or drug product over time. This method enables the determination of any reduction in drug content that occurs during stability and degradation studies. During such studies, variations in drug concentration are commonly observed; however, a properly developed SIM ensures that the measurement is free from interference caused by excipients, impurities, or degradation products. As a result, stability-indicating methods play a crucial role in preformulation studies and are valuable tools for predicting appropriate storage conditions and shelf life of pharmaceutical products.

Objective of forced degradation studies

1. Confirm that the drug maintains stability in its final dosage form.
2. Gain a thorough understanding of the chemical properties and composition of the drug.
3. Develop formulations with enhanced stability.
4. Produce stressed samples for the identification of degradation products under various conditions.
5. Study the degradation pathways to better understand how the drug breaks down under different environmental and stress conditions. [13]

Relation between forced degradation studies and stability data:

Forced degradation studies typically generate a greater number of degradation products compared to routine stability testing. During conventional stability studies, the low levels of degradation products often make their detection and identification challenging. Forced degradation experiments help overcome this limitation by intentionally accelerating degradation under controlled stress conditions. If no degradation products are observed, the drug substance may be considered stable under the applied stress, and the analytical method can be regarded as stability-indicating. In addition, forced degradation studies assist in identifying suitable storage conditions for pharmaceutical products and provide valuable insight into the **degradation mechanisms and pathways** of various drug substances. [14]

Method development and optimization:

Prior to analytical method development, it is essential to evaluate the physicochemical properties of the drug substance, including pKa, log P, solubility, and λmax. Reverse-phase high-performance liquid chromatography (RP-HPLC) is widely employed for the separation and analysis of pharmaceutical compounds. Commonly used mobile phase components include methanol, acetonitrile, and water, which are combined in varying ratios depending on the solubility characteristics of the drug. The selection of the organic solvent and its proportion is generally based on literature data or initial experimental trials.

At the initial stage of method development, equal proportions of organic and aqueous phases (50:50) are often employed, followed by systematic optimization to achieve adequate peak resolution. In some cases, the use of appropriate buffer systems improves baseline separation and peak symmetry. Adjustment of column temperature, typically within the range of 30–40 °C, may further enhance reproducibility. During forced degradation studies, special attention is given to the separation of degradation products, as these may co-elute with the parent drug or remain masked within the main peak. HPLC systems equipped with photodiode array (PDA) detectors facilitate peak purity assessment and identification of co-eluting degradants.

Modification of mobile phase composition often aids in resolving degradation peaks. A method is considered stability-indicating when the drug peak remains unaffected in terms of area and purity despite the presence of degradation products. Co-eluting degradants may be acceptable within defined limits, provided they are not detected in long-term or accelerated stability studies. Further optimization may involve adjusting parameters such as flow rate, injection volume, column type, and mobile phase ratio. Following optimization, the finalized analytical method is subjected to validation in accordance with ICH guidelines to ensure reliability and regulatory compliance.[15]

The key parameters of forced degradation studies are as follows

A. Stress conditions: Stress conditions represent external environmental factors that can influence the stability of a drug substance or drug product throughout its shelf life. These conditions commonly include hydrolytic stress (acidic, alkaline, and neutral), oxidative stress, photolytic exposure, thermal stress, and humidity-related stress. [16]

The major sub-parameters associated with stress conditions are as follows:

1. pH: The stability of a drug substance is strongly dependent on the pH of the medium.

Exposure to acidic or alkaline environments may promote hydrolysis or oxidation reactions.

2. Temperature: Changes in temperature can significantly impact drug stability. Elevated temperatures accelerate thermal degradation, whereas low temperatures may result in physical changes such as crystallization or freezing.

3. Light: Drug substances exposed to light may undergo photochemical degradation, leading to structural changes and loss of potency.

4. Humidity: High moisture levels can trigger hydrolytic or oxidative degradation, particularly in hygroscopic drug substances.

2. Degradation level:

The primary aim of forced degradation studies is to induce degradation within a range of approximately 5–30% under the applied stress conditions. Achieving degradation within this range confirms that the analytical method is stability-indicating and capable of effectively detecting and quantifying degradation products and related impurities.

The key sub-parameters influencing the extent of degradation include:

Time: The length of exposure to stress conditions plays a critical role in determining the degree of degradation observed.

Concentration: The strength or concentration of the stress-causing agent directly affects the rate and extent of degradation.

3. Analytical techniques

Analytical techniques are applied to identify, separate, and quantify degradation products and impurities generated during stability and forced degradation studies. The major sub-parameters associated with analytical techniques include:

- **Chromatographic Methods:** Techniques such as high-performance liquid chromatography (HPLC) and gas chromatography (GC) are commonly used to achieve effective separation and quantitative analysis of degradants and impurities.
- **Spectroscopic Methods:** Advanced techniques including mass spectrometry (MS) and nuclear magnetic resonance (NMR) are employed for the structural identification and detailed characterization of degradation products.

4. Mass balance: Mass balance is achieved when the combined quantity of the drug substance and all its degradation products equals 100%. This confirms the completeness of the degradation process and validates the accuracy and reliability of the analytical method used.[17]

5. Specificity and Selectivity

Forced degradation methods should be designed to be highly selective, ensuring that the peaks of the drug, its degradation products, and known impurities are well-resolved. This is essential for the accurate detection, identification, and quantification of all degradants and impurities.[17]

6. Forced degradation conditions optimization

When the extent of degradation is either too high or too low, it becomes necessary to adjust the stress conditions or the concentration of the stress-inducing agents. This ensures that the experimental setup is appropriate for achieving the targeted level of degradation.[18]

7. Stability-Indicating assay

The selected analytical method, commonly reverse-phase high-performance liquid chromatography (RP-HPLC), should be capable of detecting and quantifying all degradation products and impurities, thereby confirming that the method is truly stability-indicating.[18]

Most reported methods recommend the application of defined and controlled forced degradation conditions, including factors such as the intensity of the stressor, temperature, and duration of exposure. Traditionally, enhancement of degradation product formation is achieved by modifying these stress conditions through a trial-and-error approach. In contrast, a more advanced strategy in forced degradation studies involves assessing the combined effects and interactions of degradation variables using a Design of Experiments (DoE) framework. [19,20,21,22]

Regulatory guidelines

International guidelines suggest conducting forced degradation studies.

International regulatory frameworks recommend the **conduct of forced degradation studies** to evaluate the stability of drug substances and products. Guidelines from the **International** Council for Harmonisation (ICH) primarily address requirements for new product marketing applications and may not provide detailed instructions for the clinical development phase. The key ICH guidelines relevant to forced degradation studies include:

1. **ICH Q1A (Stress Testing):** Stability testing of new drug substances and products.
2. **ICH Q1B:** Photostability testing of new drug substances and products.
3. **ICH Q2B:** validation of analytical procedures

Additionally, the FDA recommends that forced degradation studies be conducted at multiple stages of drug development to ensure comprehensive evaluation of drug stability and degradation behavior.

Forced degradation studies are essential for evaluating drug stability and identifying potential degradation products. While some degradants may not form under normal storage, these studies help in selecting appropriate storage conditions and developing stability-indicating methods (SIMs). They involve subjecting drug substances to various stress conditions such as hydrolysis, oxidation, photolysis, thermal stress, and humidity. Key parameters include stress conditions, degradation levels, analytical techniques, mass balance, optimization, specificity, and selectivity. The objectives are to ensure drug stability, understand chemical properties, design stable formulations, and generate samples for degradant analysis. Regulatory guidelines, particularly from ICH and the FDA, recommend performing these studies at multiple stages of drug development. Factors like moisture, excipients, temperature, pH, oxygen, and light must be considered. Overall, forced degradation studies provide critical insights into degradation pathways, enabling the development of robust and reliable analytical methods.

Regulations by Guidelines

ICH guidelines are rigorously implemented in the three major regulatory regions, namely the European Union, Japan, and the United States, whereas their adoption is comparatively less stringent in many other countries. These guidelines represent prevailing regulatory and inspection practices. For instance, ICH guideline Q1A addresses stability testing requirements for new drug substances and finished pharmaceutical products, while ICH guideline Q3B focuses on impurity-related considerations. [23]

CONCLUSION:

Forced degradation studies are essential for understanding the stability behavior, degradation mechanisms, and impurity profile of therapeutic substances. The Quality by Design (QbD) methodology improves the development of resilient and reliable stability-indicating techniques through systematic optimization and risk assessment. The integration of ICH guidelines, Design of Experiments (DoE), and advanced analytical techniques such as HPLC and LC-MS ensures precise identification of degradation products and adherence to regulatory standards. Ultimately, QbD-based forced deterioration studies enhance product quality, safety, efficacy, and the reliability of analytical techniques throughout the product's lifespan.

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