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ADVANCED DEVELOPMENTS IN THE CONDUCT OF ACCELERATED STABILITY AND DRUG DEGRADATION STUDIES

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Abstract

The deterioration of new drug materials and drug compounds in forced conditions is more intense than the deterioration observed in accelerated conditions. The specificity of stability indicating techniques must be demonstrated. Stability studies are a common practice to ensure that pharmaceutical products remain safe, of high quality, and effective throughout their shelf life. In pharmaceutical research, forced degradation is a powerful technique often employed to investigate how drug ingredients and products break down, and to develop stability testing procedures that generate reliable stability data. It is crucial to understand the impurities that arise when medicines are stored under different environmental conditions. Therefore, comprehending a drug's purity profile and its performance of various environmental conditions is vital. The goal is to gather evidence on how different environmental conditions, such as temperature, light, and humidity, affect the quality of a drug substance or product as it ages. By subjecting the drug material to stress testing, it is possible to identify the predictable degradation products, which helps in understanding the degradation pathways and inherent stability of the molecule. This also validates the effectiveness of the analytical techniques used to assess stability. The specific approach to stress testing will vary depending on the type of drug materials and product being evaluated. The results of forced degradation research shed valuable insights in the analytical field.

Keywords: Stability, Environmental, Chemical reaction, accelerated degradation, Shelf life.

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Introduction

Stability testing evaluates how the environment affects the quality of drug materials or formed products in order to estimate their shelf life, identify the best conditions for storage, and recommend labeling guidelines. Additionally, regulatory approval of any medicine or formulation heavily depends on the data collected during stability testing (1). Changes in drug stability have the potential to endanger patient safety by producing harmful degradation products or delivering a lower dose than intended. Thus, it is critical to understand the purity profile and behavior of drug materials under various environmental conditions. Stability-indicating methods that detect changes over time in the microbiological, physical, or chemical characteristics of drug materials or products require the use of established quantitative test procedures (2). These methods are designed to allow reliable measurement of the amount of the active ingredient, degradation products, and other relevant components without affecting the material being tested. A molecule that results from the active component changing over time as an outcome of processing or storage is called a degradation product (3).

Stress testing

The ICH guideline Q1A serves as an example of the fundamental stability requirements. Verified Selective Ion Monitoring (SIM) should perform tests on properties that are susceptible to alteration during storage and can impact the quality, safety, and effectiveness of the drug. Additionally, to confirm the inherent stability traits and degradation pathways of the drug substance and support the appropriateness of the proposed analytical methods, it is recommended to conduct forced decomposition studies on the drug substance at temperatures incremented by 10°C above the accelerated temperatures, extreme pH values, and under oxidative and photolytic conditions (4).

Photostability testing should be a crucial component of stress investigations, according to the ICH Q1B. In order to assess the potential photostability issues of the provided drug ingredient and products, it is commonly recommended to utilize an ICH dose of 1.2×10^6 and 2.4×10^6 lux-hours of fluorescent light, as well as 200 watt-hours per square meter (wh/m^2) of UV light (5). The ICH guideline Q3B places a strong emphasis on providing documentation to support the validity and suitability of analytical techniques for the detection and quantification of degradation materials. The guideline provides a comprehensive understanding of the reporting, identification, and quantification thresholds for degradation products in pharmacological compounds (6). The ICH guideline Q6A emphasizes the importance of stability-indicating assays that adhere to Universal Tests/Criteria for both Drug Substances and Drug Products, and provides guidance on specifications. Similar requirements are outlined in the ICH Q5C guideline on Stability Testing of Biotechnological/Biological Products. The text clarifies that the identification, purity, and potency of the product should be monitored for changes, as these attributes are characteristic and defining parameters (7).

As per FDA recommendations, a stability indicating test method is a validated quantitative analytical procedure that is capable of detecting changes in the quality attributes of a drug substance and drug product during storage (8). The stability-indicating approach can be used to identify any changes in product potency, purity, and the production of degrading contaminants. An extremely important phase in the validation of a stability indicating approach is a forced deterioration or stress research (9). Not all impurities must always be generated in real time. Stability studies will also be

produced via stress tests, although forced degradation tests allow for the quick production of degradation contaminants. These samples are employed to forecast long-term stability and provide a technique for identifying stability. There is no other instruction for doing stress testing in the ICH (The International Conference on Harmonization) Q1B standard other than photo stability stress testing (10).

Stability Testing

The objective of stability testing is to determine the re-test period for a drug substance or the shelf life for a drug product, along with the recommended storage conditions. This is achieved by gathering data on the changes in the quality of the drug substance or drug product over time, considering the impact of different environmental factors such as humidity, temperature, and light (11).

Stability Indicating Method

A stability-indicating methodology is an analytical approach that accurately measures the active components of a drug while minimizing interference from potential impurities such as degradation products, process impurities, excipients, or other sources (12). If a method is able to accurately quantify significant degradation products, it may also be considered as stability indicating. Typically, the process of forced degradation is outlined, as shown in Figure 1.

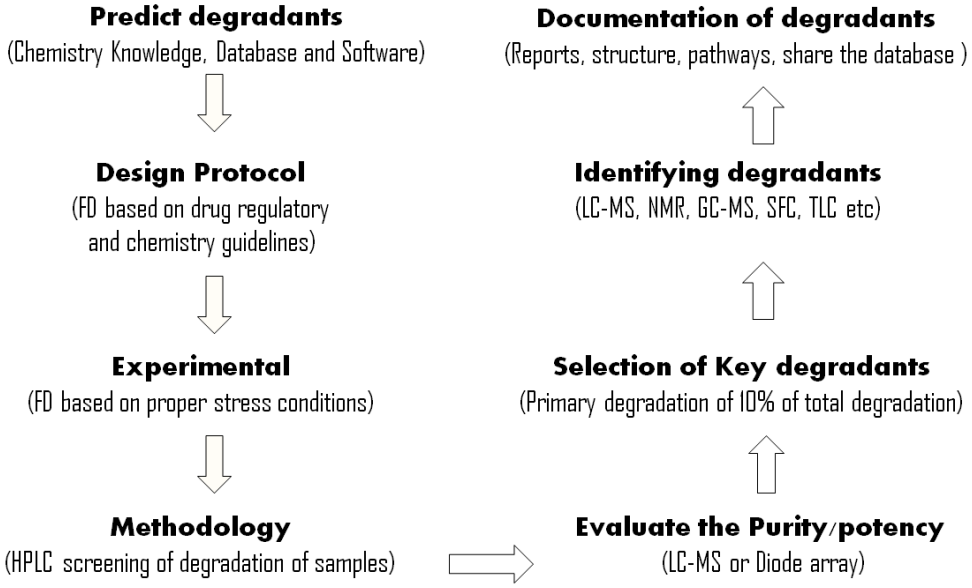

Figure 1. Flow map of forced degradation process for stability study

Forced Degradation

Forced degradation refers to the process of accelerating the degradation rate of a material or product through the application of external forces such as oxidation, reduction, elevated temperatures, increased humidity, intensified light, and so on. The objectives of forced degradation include identifying the degradation pathways of drug materials and products, differentiating degradation materials specific to the drug product from those originating from the placebo in a formulation, determining the structures of degradation products, and evaluating the inherent stability of a drug substance in a formulation (13). Additionally, this technique is employed to uncover the degradation mechanisms, such as hydrolysis, oxidation, thermolysis, or photolysis, of the drug substance and product. Furthermore, it aids in establishing the stability-indicating properties of a developed method and in creating more stable formulations. By generating a degradation profile that simulates the conditions of a formal stability study under ICH guidelines,

forced degradation can be utilized to address stability-related issues (14).

Forced degradation studies are valuable during formulation studies as they can help establish the stability-indicating nature of a developed analytical method and facilitate the comparison of pre-manufacturing and post-manufacturing changes. During pre-clinical studies, forced degradation studies can assist in identifying degradants, toxic components, and body conjugates. In clinical development, forced degradation studies can aid in comparing pre-clinical and clinical quality (15).

Having a clear understanding of the stability of a molecule is essential for making informed decisions on formulation, packaging, storage conditions, and shelf life, which are necessary for regulatory documentation (16). Forced degradation is a technique that involves exposing drug products and substances to conditions that are more severe than accelerated conditions, resulting in the generation of degradation products that can be analyzed to assess the stability of the molecule.

Step1: Critical study to determine the probable pathway of decomposition

While embarking on a project to establish a Stability-Indicating Method (SIM), it is important to begin with Step 1, which involves closely examining the drug's structure. Valuable insights can be gained by analyzing the functional groups and other important components of the drug. For instance, certain functional group categories such as esters, amides, lactams, and lactones are prone to hydrolysis, while others like thiols and thioethers are susceptible to oxidation (17). Compounds such as aryl halo, olefins derivatives, aryl acetic acids, and those containing aromatic nitro groups and N-oxides, endure photodecomposition.

Step 2: Group of evidence on physicochemical characteristics

Before undertaking method development, it is typically crucial to have an understanding of various physicochemical parameters, such as the pKa of drug, log P, absorptivity, solubility, and maximum wavelength (18).

S**tep 3: Studies of forced decomposition**

As previously mentioned in the section on forced degradation, it is recommended to conduct these studies following the ICH Q1A guideline (Figure 2). Stress conditions typically involve (i) increasing temperatures by 10 °C higher the accelerated conditions (e.g., 50, 60°C, etc.), (ii) applying appropriate humidity levels (e.g., 75% RH or higher), (iii) conducting hydrolysis across a broad range of pH values, (iv) performing oxidation, and (v) carrying out photolysis (19).

Step 4: Preliminary studies of separation

One of the simplest approaches for separation involves utilizing a reversed-phase octadecyl column and conducting HPLC separation with a PDA/UV detector system, or alternatively, LC-MS separation. It is crucial to monitor the changes in all the stress samples at various time points during these chromatographic methods. The results obtained should be thoroughly compared with blank solutions that are injected in a similar manner (20, 21). It is noteworthy to observe if the decrease in the drug peak is consistently accompanied by an increase in the degradation material peaks.

Step 5: Final optimization and method development

Following initial chromatographic investigations, it is important to document the relative retention times (RRT) and retention time (RT) of each product formed under different reaction conditions and organize them in a table. Special attention should be given to components that have similar RT or RRT values. LC-

MS profiles or PDA spectra of these components should be obtained and analyzed to determine if they are identical or distinct (22). If necessary, optimization of the separation method can be carried out by modifying factors such as pH, mobile phase ratio, gradient, temperature, flow rate, solvent type, column properties and column type, in order to effectively separate closely eluting peaks (23).

Step 6: characterization and Identification of degradation products, and preparation of standards

Determination of the structure of separated products, a traditional method is to isolate and analyze them using spectral and elemental analysis. However, this can be time-consuming when multiple degradation products are present (24). A contemporary approach involves utilizing hyphenated liquid chromatography (LC) techniques in conjunction with mass spectrometry (MS), which combines analytical UV detection, HPLC, full scan MS (LC-MS), and tandem MS (LC-MS-MS). This integrated approach offers valuable insights into the identity of the separated components. Another innovative approach involves combining LC-MS-MS or LC-MS for molecular weight and fragmentation information, and LC-NMR analysis for detailed structural information (25).

Step 7: Validation

The validation of analytical technique has been thoroughly discussed in various procedures such as FDA guidance, ICH Q2A and Q2B, and USP. During this stage, the primary emphasis is on specificity/selectivity, with accuracy, precision, linearity, range, robustness, and other parameters following suit (26). To establish the mass balance, the quantitation and detection limits are also determined for degradation products.

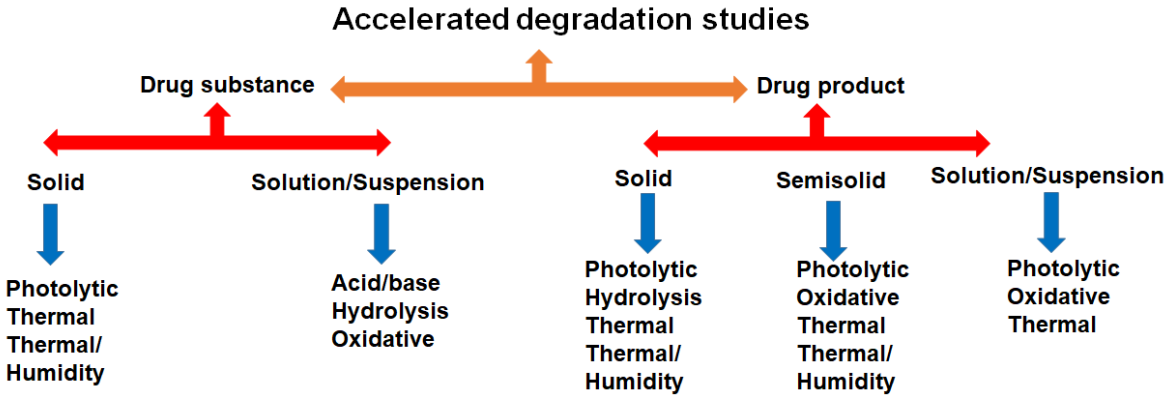

Figure 2. Schematic diagram of accelerated stability study on drug and drug products

Pharmaceutical scientists have debated how much stress is sufficient for forced degradation studies. Typically, a degradation range of 5 to 20% of the drug substance is viewed as acceptable and reasonable for validating chromatographic assays. Pharmaceutical scientists have reached a consensus that around 10 % degradation is the most suitable amount for analytical validation of minor pharmaceutical molecules, which typically have adequate stability limits of 90% of the labeled claim (27, 28). If the experimental conditions result in minimal or no degradation products owing to the exceptional stability of the molecule, it is necessary to check if the drug substance was exposed to energy beyond what was provided during accelerated storage (e.g. 40 °C for 6 months; Figure 2). If the response is positive, the trial can be stopped, and a record can be made regarding the stability of the drug compound, as excessive stress may result in unexpected results.

Storage Conditions

The basic rule is that a pharmacological molecule should be assessed under storage condition (with suitable limits) that test its thermal stability and, if necessary, its sensitivity to moisture (29). Research should be conducted for a sufficient duration to include storage, shipping, and usage as per the recommended conditions (as indicated in Table 1). When submitting the findings, long-term testing should have been carried out for a minimum of 12 months on at least three main batches, and the testing period should be long enough to cover the proposed re-test period of 30 days (30).

Table 1. Conditions generally employed for forced degradation

Degradation type	**Experimental conditions**	**Storage condition (ºC)**	**Sampling time (days)**
Oxidative	3% H_2O_2	25 and 40	1,3 and 5
	peroxide control		
	Azobisisobutyronitrile (AIBN)	40 and 60	
	AIBN Control		
Hydrolysis	Control API (no acid or base)	40 and 60	
	0.1N NaoH		
	0.1N HCl		
	Base control (no API)		
	Acid control (no API)		
	PH: 2, 4, 6, 8		
Thermal	Heat chamber	60 ºC	
	Heat chamber	60 ºC/75%RH	
	Heat chamber	80 ºC	
	Heat chamber	80 ºC/75%RH	
	Heat control	Room Temperature	
Photolytic	Light control	NA	
	Light, 1 X ICH NA	NA	
	Light, 3 X ICH NA	NA	

If required, further information gathered during the registration application's evaluation period should be sent to the authorities. To assess the impact of brief excursions outside the label storage circumstances, data from the accelerated storage condition and, if appropriate, the intermediate storage condition can be employed (such as might occur during shipping). The parts below go through long-term, rapid, and, when necessary, interim storage settings for pharmacological compounds (Table 2). If a later section does not address the drug substance specifically, the general case is applicable. If necessary, alternative storage conditions may be used (31).

Table 2. Various terms of storage conditions

Study	**Storage Conditions**	**Minimum time period covered by data at submission (Months)**
Long Term	25 ± 2 °C/60 RH ± 5% RH or 30 ± 2°C/65% RH ± 5% RH	12
Intermediate**	30 ± 2 °C/65 RH ± 5% RH	6
Accelerated	40 ± 2 °C/75 RH ± 5% RH	6

*The choice between conducting long-term stability studies at either 25 ± 2 °C/60 RH ± 5% RH or 30 ± 2 °C/65 RH ± 5% RH is at the discretion of the applicant. **If the selected long-term condition is 30 ± 2 °C/65 RH ± 5% RH, then there is no intermediate condition essential.

If there is a notable difference observed during the first three to six months of testing in the accelerated storage state, the recommended re-test period should be determined based on the actual data obtained from the long-term storage condition (as indicated in Table 3). If a significant change is noticed within the initial three months of testing in the accelerated storage condition, a discussion on the potential impact of temporary deviations from the labeled storage conditions, such as those occurring during shipping or handling, should be included (32).

Table 3. Pharmaceutical coumpound meant for refrigerated storage

Study	**Storage condition**	**Minimum time period covered by data at submission (months)**
Long term	5 ± 3 °C	12
Accelerated	25 ± 2 °C/60 RH ± 5% RH	6
Pharmaceutical compounds designed for storage in a freezer		
Long term	- 20 ± 5°C	12

Various degradation Conditions

Hydrolysis

One of the most frequent chemical degradative processes occurs during hydrolysis over a broad pH range. A chemical process called hydrolysis involves breaking down a chemical molecule by an interaction with water (33). Catalysis of the molecule's ionizable functional groups occurs during hydrolytic studies conducted in acidic and basic conditions. By subjecting a drug substance to acidic or basic conditions that result in the production of desired primary degradants within a specific range, the drug substance is intentionally degraded. Depending on how stable the drug ingredient is, different types and amounts of acid or base must be used. For conducting base hydrolysis, we suggest using sodium hydroxide or potassium hydroxide at concentrations ranging from 0.1 to 1 M. For acid hydrolysis, hydrochloric acid or sulfuric acid at concentrations of 0.1 to 1 M are recommended (34). Co-solvents can be used to dissolve compounds for stress testing in HCl or NaOH if they are not easily dissolved in water. The selection of a co-solvent for stress testing of the drug substance is guided by its molecular

structure. The initial stress testing trials are conducted at room temperature, and if no degradation is observed, higher temperatures ranging from 50 to 70 °C are then employed. The stress testing period should not exceed seven days. To stop further degradation, the degraded sample is subsequently neutralised with the appropriate buffer or acid, base (35).

Oxidation

Hydrogen peroxide is commonly utilized as an oxidizing agent in forced degradation studies to oxidize pharmacological compounds, although other oxidizing agents like metal ions, oxygen, and radical initiators such as azobisisobutyronitrile (AIBN) can also be employed. The selection of the oxidizing agent, its concentration, and the conditions for the investigation, including pH and temperature, are determined by the nature of the drug substance (36). Studies have shown that treating solutions with hydrogen peroxide at neutral pH and room temperature for seven days, or up to a maximum of 20% degradation, at concentrations ranging from 0.1% to 3%, could potentially yield significant degradation products (37)**.**

An electron transfer mechanism is used in the oxidative breakdown of pharmacological material to create reactive anions and cations. Electron transfer oxidation can transform phenols, sulphides, and amides into hydroxylamine, N-oxides, sulfoxide, and sulfones (38). The functional group with labile hydrogen, such as allylic carbon, benzylic carbon, tertiary carbon, or -positions with regard to hydrogen atom, is oxidizable and can result in hydroperoxides, hydroxide, or ketone (39).

Photolysis

To show that a light exposure does not cause an unacceptable alteration, photo stability testing of pharmacological compounds must be assessed. Through exposure to UV or fluorescent light, photostability tests are carried out to produce major degradants of medicinal material(40). According to ICH recommendations, there are a few suggested conditions for photostability testing.A minimum of 1.2 million lx h and 200 W h/m^2 of light should be applied to samples of drug material and solid/liquid drug product. The photolytic deterioration is most frequently attributed to light with a wavelength between 300 and 800 nm.By using a free radical pathway, light stress conditions can cause photo oxidation. Drug photosensitivity is likely to be introduced by functional groups such as nitro aromatics, carbonyls, N-oxide, aryl chlorides, alkenes, weak O-H and C-H bonds, polyenes and sulphides (41).

Thermal conditions

The accelerated testing conditions outlined in ICH Q1A should not be utilized for assessing thermal degradation (e.g., dry heat and wet heat). Unlike liquid drug products, solid-state drug substances and drug products should be subjected to both dry and moist heat during testing. Studies might be carried out for a shorter amount of time at a higher temperature. The Arrhenius equation, $K= Ae^{-Ea/RT}$, is used to analyse how temperature affects a substance's ability to withstand heat. R is the gas constant (1.987 cal/deg. mole), **Ea** is the energy of activation, and T is the absolute temperature (42, 43). At 40–80 °C, thermal degradation studies are conducted.

Evaluation techniques

Various analytical techniques and equipment can be used to separate and quantify the expected degradant compounds during forced degradation investigations. Common methods employed in the pharmaceutical industry for stability-indicating method development and validation include High-Performance Liquid Chromatography with photodiode array detector (HPLC-PDA), and High-Performance Liquid

Chromatography with UV detector (HPLC-UV) as stated in reference (44). Additionally, gas chromatography with mass detector (GC-MS), nuclear magnetic resonance (NMR) spectroscopy, and high-performance liquid chromatography with mass detector (LC-MS) are important techniques used for determining the structure of degradants, as mentioned in reference (45).

Conclusion

Forced degradation studies are conducted to elucidate the structure of degradants and gain insights into potential degradation pathways and products of the active components. These studies generate potential degradation products that may or may not occur under normal storage conditions, but they are valuable in the development of stability-indicating methods. In order to have enough time to learn more about the molecule stability, it is preferable to begin degradation investigation earlier in the drug development process. By determining the storage conditions and enhancing formulation manufacture, this knowledge will help. This study necessitates the experimenter using common sense because no single set of parameters is appropriate to all drug goods and drug ingredients, and the regulatory guidance is ambiguous regarding the conditions to be used. The aim of a forced degradation technique is to achieve the desired level of degradation, typically ranging from 5-20%. A well-planned and meticulously executed forced degradation study can yield samples suitable for the development of stability-indicating methods. Although the degradation impurities produced during stress studies may or may not occur during real-time stability studies, this step is essential for the development of analytical methods that can accurately assess stability. It is highly advisable to initiate these studies early in the drug development process to gather valuable information that can be used to evaluate the inherent stability of the drug and make necessary improvements to formulation and manufacturing processes.

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