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Review Article

Development of Forced Degradation and Stability Indicating Studies of Drugs- A Review

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A B S T R A C T

Force degradation study is an essential study that provides the knowledge & judgement to develop a stability indicating analytical method. This study helps to establish the specification and shelf life of a drug substance or drug product. Force degradation study show the chemical behaviour of the molecule which in turn helps in the development of formulation and package. This helps to describe the analytical methods helpful for development of stability indicating method. In addition, the regulatory guidance is very general and does not explain about the performance of forced degradation studies. Thus, this review discusses the current trends in performance of forced degradation studies by providing a strategy for conducting studies on degradation mechanisms and also describes the analytical methods helpful for development of stability indicating method.

Keywords: Stability indicating method, stress testing, Force degradation, degradation conditions.

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INTRODUCTION

Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidances state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors [1].

A draft guidance document suggests that results of one-time forced degradation studies should be included in Phase 3 INDs (Investigational New Drugs). NDA (New Drug Application) registration requires data of forced degradation studies as forced degradation products, degradation reaction kinetics, structure, mass balance, drug peak purity, etc. This forced degradation study provides information about degradation pathways of API, alone and in drug product, any possible polymorphic or enantiomeric substances and difference between drug related degradation and excipient interferences[18].

Forced degradation studies play a central role during analytical method development, setting specifications and design of formulations under the quality-by-design (QbD) paradigm[25].Forced degradation involves the exposure of drug substance to heat, heat and humidity and light for solid state studies. For solution state studies the drug substance is exposed to range of pH values[6].Forced degradation, commonly known as stress testing, is carried out to demonstrate as specificity to developed a stability-indicating analytical method, using high-performance liquid chromatography (HPLC), i.e., a single analytic method that is capable of separating the degradant peaks from the drug substance/drug product peak[15].

Force degradation studies

Forced degradation or stress studies are undertaken to deliberately degrade the sample. These studies are used to evaluate an analytical method's ability to measure an active ingredient and its degradation products, without interference, by generating potential degradation products[13].

Forced degradation studies includes subjecting the drug substance to various stress conditions to observe the extent of degradation and rate of degradation which is likely to occur in the course of storage and/or after administration to body[23].

Purpose of Forced degradation testing

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 product involved[11].

Forced degradation studies are carried out for the following reasons: [26,11]

- To develop and validate a stability indicating method
- To elucidate the structure of the degradation products
- To determine degradation pathways of drug substances and drug products (e.g., during development phase)
- To identify impurities related to drug substances or excipients
- To understand the drug molecule chemistry
- To generate more stable formulations
- To generate a degradation profile that mimics what would be observed in a formal stability study under ICH conditions
- To solve stability-related problems (e.g., mass balance)
- To choose the correct storage conditions, appropriate packaging and better understanding of the potential liabilities of the drug molecule chemistry.

- Figure 1 shows the importance of forced degradation studies with respect to current pharmaceutical scenarios

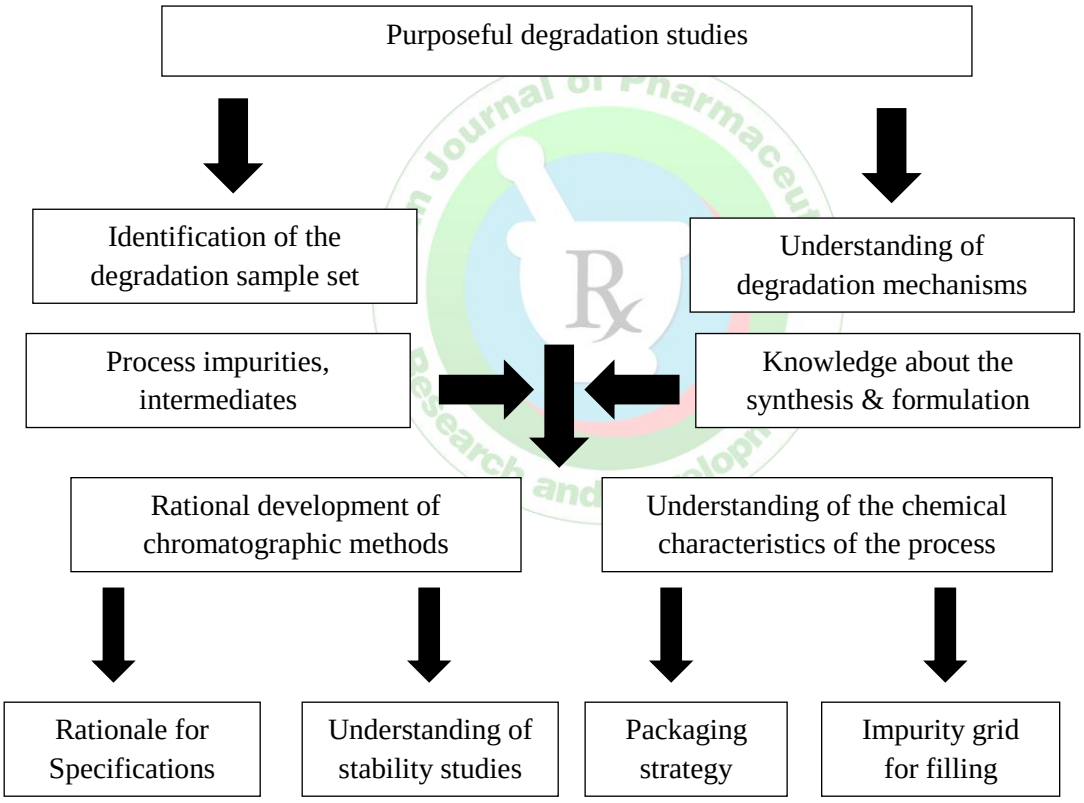

Figure-1: Importance of Force Degradation in Pharmaceuticals

Strategic development of Forced Degradation

Forced degradation is carried out to produce representative samples for developing stability indicating methodsfor drug substances and drug products. The criteria of selecting stress condition should be depend upon the products decomposition under normal manufacturing, uses condition and storage specifications which are specific and different for each drug substance and drug product. Stress factors suggested for forced degradation studies include acid and alkali hydrolysis, thermaldegradation, photolysis, oxidation. All force degradation condition mention Figure-2. There is no of specification in regulatory guidelines about the conditions of pH, temperature and thermal condition and oxidizing agent used[6].

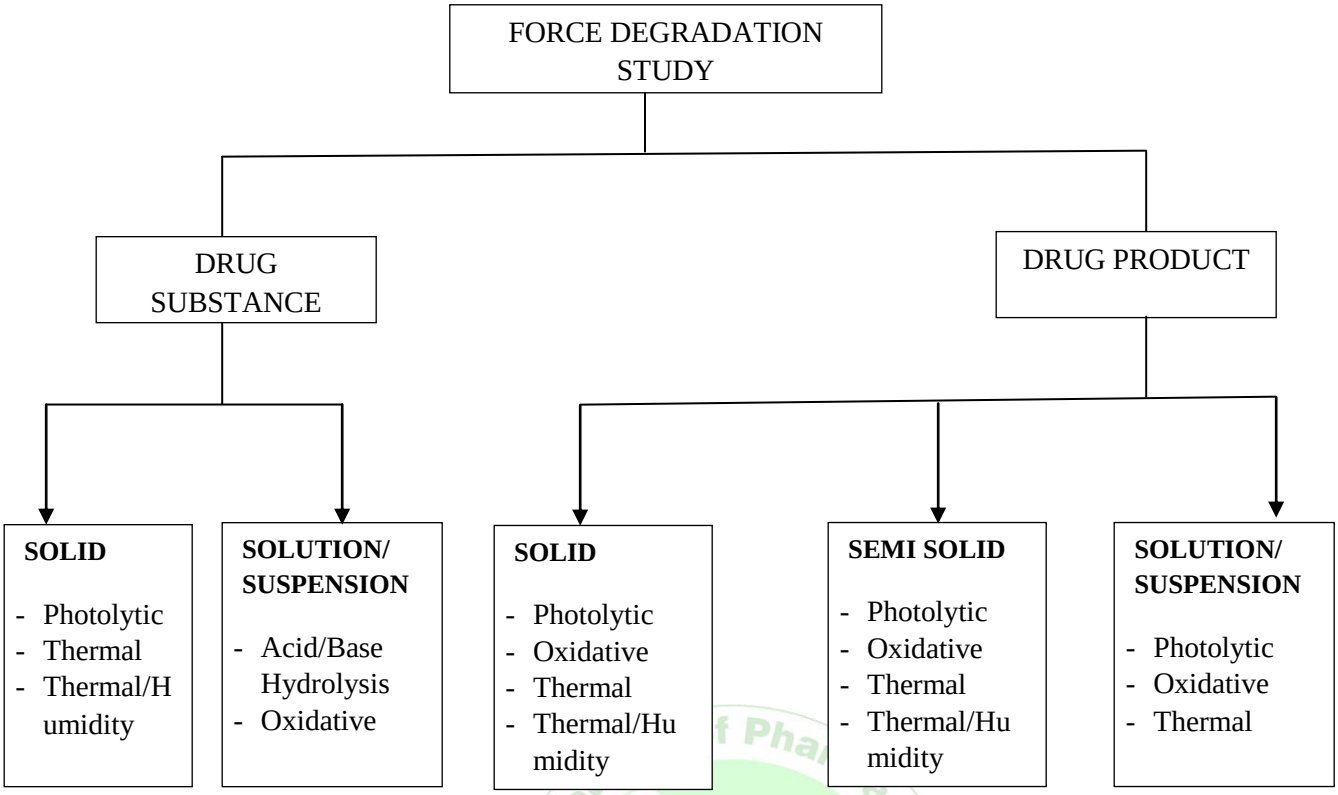

Figure 2: An illustrative flow diagram showing the different forced degradation conditions to be used for drug substances and drug products

Table-1: Condition generally employed for Forced Degradation study

Degradation type	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid or base)	40°C, 60°C	1,3,5
	0.1M HCl	40°C, 60°C	1,3,5
	0.1M NaOH	40°C, 60°C	1,3,5
	Acid control (no API)	40°C, 60°C	1,3,5
	Base control (no API)	40°C, 60°C	1,3,5
	pH: 2,4,6,8	40°C, 60°C	1,3,5
Oxidation	3%H_2O_2	25°C, 60°C	1,3,5
	Peroxide control	25°C, 60°C	1,3,5
	Azobisisobutyronitrile (AIBN)	40°C, 60°C	1,3,5
	AIBN control	40°C, 60°C	1,3,5
Photolytic	Light 1 x ICH	NA	1,3,5
	Light 3 x ICH	NA	1,3,5
	Light control	NA	1,3,5
Thermal	Heat Chamber	60°c	1,3,5
	Heat Chamber	60°c /75% RH	1,3,5
	Heat Chamber	80°c	1,3,5
	Heat Chamber	80°c /75% RH	1,3,5
	Heat Control	Room Temp.	1,3,5

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 that makes it not possible to identify a generic set of conditions for a forced degradation study[20].In designing forced degradation studies, it must be remembered that more strenuous conditions than those used for accelerated studies (25°C/60% RH or 40°C/75% RH) should be used. At a minimum, the following conditions should be investigated: (1) acid and base hydrolysis, (2) hydrolysis at various pH, (3) thermal degradation, (4) photolysis, and (5) oxidation. For the drug substance and drug product, the scheme shown in Figure 1 could be used as a guide [14].Excess degradation of a sample may lead to further degrade impurities and form secondary degradants that would not be seen in real-time stability studies. Excess degradation may mislead mass balance results also because of differences in response factors of unknown impurities[22].

The initial experiments should be focused on determining the conditions that degrade the drug by approximately 10%. The conditions generally employed for forced degradation are summarized in Table 1. However, some scientists have found it practical to begin at extreme conditions (80°C or even higher, 0.5N NaOH, 0.5N HCl, 3% H_2O_2) and testing at shorter (2, 5, 8, and 24 hrs, etc) multiple time points, thus allowing for a rough evaluation of rates of degradation[14].

Forced degradation studies used for degradation of drug product or drug substance are mentioned bellow:

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. For example, aspirin combines with water and hydrolyzed to salicylic acid and acetic acid [20].Hydrolytic study under acidic and basic condition involves catalysis of ionizable functional groups present in the molecule. Acid or base stress testing involves forced degradation of a drug substance by exposure to acidic or basic conditions which generates primary degradants in desirable range. The selection of the type and concentrations of acid or base depends on the stability of the drug substance. Hydrochloric acid or sulfuric acids (0.1–1 M) for acid hydrolysis and sodium hydroxide or potassium hydroxide (0.1–1M) for base hydrolysis are suggested as suitable reagents for hydrolysis[18].The hydrolytic stress testing normally is conducted at room temperature with or without co-solvent and if no degradation appears, continues under higher temperature of 50°C to 70°C. Stress testing normally should not exceed more than 7 days. The degraded sample is then neutralized before injection using suitable acid, base or buffer, to avoid further decomposition [1].

Oxidation condition:

For oxidative forced degradation, hydrogen peroxide is broadly used. Apart from this as metal ions, oxygen, and radical initiators: azobi-isobutyro-nitrile, AIBN can also be used. Drug structure will allow selecting concentration and condition of oxidizing agents. An electron transfer mechanism occurs in the oxidative degradation of drug substance[8].Many drug substances undergo auto-oxidation i.e. oxidation under normal storage condition and involving ground state elemental oxygen. Therefor it is an important degradation pathway of many drugs. Auto-oxidation is a free radical reaction that requires free radical initiator to begin the chain reaction. Hydrogen peroxide, metal ions and trace level of impurities in a drug substance act as initiators for drug substance. Selection of an oxidizing agent, its concentration and condition depends on the drug substance. It is mentioned that the drug solutions are subjecting to 0.1%-3% hydrogen peroxide at neutral pH and room temperature for seven days or upto a maximum 20% degradation could potentially generate relevant degradation products[10].

Photolytic condition:

The photo stability testing of drug substances must be evaluated to demonstrate that a light exposure does not result in unacceptable change. Photo stability studies are performed to generate primary degradants of drug substance by exposure to UV or fluorescent conditions. Some recommended conditions for photostability testing are described in ICH guidelines. Samples of drug substance and solid/liquid drug product should be exposed to a minimum of 1.2million lx h and 200 W h/m2 light. The most commonly accepted wavelength of light is in the range of 300– 800 nm to cause the photolytic degradation. The maximum illumination recommended is 6 million lx h. Light stress conditions can induce photo oxidation by free radical mechanism. Functional groups like carbonyls, nitroaromatic, Noxide, alkenes,aryl chlorides, weak C–H and O–H bonds, sulphides and polyenes are likely to introduce drug photosensitivity[7].

Thermal condition:

Thermal degradation (e.g., dry heat and wet heat) should be carried out at more strenuous conditions than the recommended ICH, Q1A accelerated testing conditions. Samples of solid state drug substances and drug products should be exposed to dry or wet heat, while liquid drug products should be exposed to dry heat. Studies may be conducted at higher temperatures for a shorter period. Effect of temperature on thermal degradation of a substance is studied through the Arrhenius equation:

$k=Ae^{-Ea/RT}$

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 40–80°C[16].

Factors affecting degradation

Below to the various factors which cause degradation of drug substances[17,27]

Moisture

Water soluble substances may get dissolved, if the presence of moisture .this leads to physical and chemical changes within the molecule.

Excipient

It was observed that some excipient may contain high content of water. This moisture may leads to increase water level in formulation which later affects the stability of the drug. In some cases, chemical photolytic decomposition can be tested by comparing its stability in the presence of light and stability when stored under dark. Photo labile compound should be stored in amber glass containers and should be stored in dark .interaction that occurs between the excipient and the drug material often results in decreased stability.

Temperature

Changes in temperature at time its show deleterious effect on the stability of the drug. Increase in temperature usually causes increase the rate of drug hydrolysis.

pH

pH shows a significant effect on the degradation rate of drugs by hydrolysis. To reduce this effect, formulation of the drug is carried out using buffer solution of pH with maximum stability.

Oxygen

In the presence of oxygen to increase the oxidation. In the presence of oxygen cause increased rate of decomposition .stabilized by using purging nitrogen or carbon dioxide in the storage in container.

Light

Some drug is photo labile and tends to decompose when they are exposed to light. Hydrolysis drug molecules are dissolved in 0.1-1 M of potassium hydroxide or sodium hydroxide. Sample treated 2 – 7 days at room temperature. Treated sample were neutralized with relevant acid or base to prevent additional degradation.

Sources of impurities and types of impurities[30]

A higher level of degradation will be out of the scope ofproduct stability requirements and therefore unrealistic. Thescope of the test is to generate degradation products in orderto facilitate a method development for determination of therelevant products.Therefore, samples will be stressed in asolid form and/or in solution. Typically, stress tests arecarried out on one batch of material. For drug products theplacebo should be stressed in a similar way in order toexclude those impurities that are not degradation products(e.g. impurities arising from excipients)

These ICH guidelines classify the impurities into the following categories:

1. Impurities associated with active pharmaceuticalingredient (APIs).
2. Impurities that are formed during formulation, formedwith ageing and that are related to formulation forms
3. Impurities associated with active pharmaceutical ingredients:

According to the ICH guidelines, impurities associated with APIs are classified into the following categories:

A. Organic impurities

B.Inorganic impurities

Organic impurities

- Starting material
- By products
- Intermediates
- Degradation products
- Residual solvents
- Reaction product with excipients
- Leachables from container closure system

Inorganic impurities

- Reagents, ligands, catalysts
- Heavy metals or residual solvents
- Inorganic salts

Other materials

- Filter aids
- Charcoal
- Formulation related impurities
- Dosage form related impurities
- Method related impurities
- Environmental related impurities
- Functional group related impurities

Stability indicating method

A stability indicating assay 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 assay accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities.

Force degradation plays an important role in the development of stability indicating analytical methodology. In addition to demonstrating specificity, force degradation studies can be used to determine the degradation pathways and degradation products of the APIs that could form during storage, and facilitate formulation development, manufacturing and packaging. Procedures for the preparation of specific degradation products needed for method validation often emerge from these studies[3].

General idea for designing stability indicating method[3]

Step-I Understand the chemistry/ physiochemical properties of drug

Obtaining suitable samples and analyzing them are crucial steps in establishing method specificity. They require thorough knowledge of the degradation chemistry and the physicochemical properties of the DS and its degradation products, as well as good scientific judgment to ensure that the samples truly contain all relevant degradation products. The ability of a SIM to monitor changes in the chemical properties of the drug over time, determines the need to perform forced degradation studies (stress and accelerated tests) on the DS and the DP, so these tests constitute a convenient alternative to generating samples containing the

analyte and its degradation products. According to the available regulatory guidance, they provide valuable information, including the determination of the degradation pathways of DSs and DPs, revealing the intrinsic stability of the API in the solid state and in solution and its susceptibility to hydrolytic, oxidative, thermolytic, and photolytic degradation. Furthermore, the resulting structural elucidation of the degradation products enables the discernment of compounds in formulations related to the DS from those arising from the excipients. Stress tests also fulfill the purpose of providing meaningful amounts of degradation products, which can be isolated and purified for complete physicochemical characterization and acquisition of impurity standards before carrying out the method development and validation[5]

Step-II Set up preliminary HPLC condition

Literature search and officials or non-officials method usually used for the selection of preliminary experimental conditions for the stability studies. Experimental conditions are selected according to the properties of the API's [9].Copious information about various HPLC columns is from catalogs of vendors and and it is possible to select a right column for any kind of API. Select the appropriate mobile phase combination and column for the separation. Computer assisted method development can be very helpful in developing the preliminary HPLC conditions quickly. A proper experimental condition at the beginning will save a lot of time in subsequent development stage[21].

Step-III Preparation of samples required for method development

SIMs is developed routinely by stressing the API under conditions exceeding those normally used for accelerated stability testing. In addition to demonstrating specificity in SIMs, stress testing, also referred to as a forced degradation, also can be used to provide information about degradation pathways and products that could form during storage and help facilitate formulation development, manufacturing and packaging. It is hard to get actual representative samples in the early stage of development. Stressing the API generates the sample that contains the products most likely to form under most realistic storage conditions, which is in turn used to develop the SIM. Generally the goal of these studies is to degrade the API 5-10%. Perform forced degradation study through thermolysis, hydrolysis, oxidation, photolysis, and or combination conditions. Each forced degradation sample should be analysed by using the preliminary HPLC conditions with suitable detector, more preferably PDA detector. While the typical dosage form- solid, semisolid or solution utilizes a solid phase extraction for sample preparation, especially for biosamples and as an alternative to liquid-liquid extractions in many U.S. Environmental Protection Agency (EPA) methods[3].

Step-IV Developing separation-stability-indicating chromatography conditions

In selecting initial chromatographic conditions for a SIM of a new entity, most important is to make sure that degradants are in solution, separated, and detected. To this effect, a diluents of 1:1 water: organic solvent is a good starting point as it will increase the likelihood of solubility of most related materials and ensure proper disintegration of solid dosage forms. The second step is to obtain separation conditions that allow the determination of as many distinct peaks as possible from the set of test samples. The most common separation variables include solvent type, mobile phase PH, column type and temperature[21].

Step-V Method optimization

Approach is enhanced to improve level of sensitivity after separation. The mobile phases as well as stationary stage compositions need to be considered. Note that the optimization of mobile phase criteria is always taken into consideration initially as this is much easier as well as convenient than fixed stage optimization. To minimize the variety of test chromatograms entailed, just the specifications that are most likely to have a considerable effect on selectivity in the optimization should be checked out[19].Forced degradation studies includes subjecting the drug substance to various stress conditions to observe the extent of degradation and rate of degradation which is likely to occur in the course of storage and/or after administration to body[3].

Step-VI Validation of analytical method

Method validation is done as per ICH guidelines. Accuracy, precision, linearity, LOQ, LOD, robustness, and ruggedness are the parameters tested on each novel method developed. RSD value should be less than 2% as per ICH guideline [2]. The main focus of validation at this stage is on establishment of specificity/selectivity, followed by other parameters like accuracy, precision, linearity, range, robustness, etc. The limits of detection and quantitation are also determined for degradation products to help in establishment of the mass balance[12].For assay procedures, that are intended do measure the analyte present in a given sample, typical validation items should be considered: Accuracy, Precision (repeatability and intermediate precision), Specificity, Detection and Quantitation Limits, Robustness, Linearity and Range[29].

Role of stability study in drug discovery[28]

Understanding the stability characteristics for both API and particularly Drug Product are critical for developing a safe and effective pharmaceutical agent. From the very start of production of API and Drug Product, samples are set aside under highly controlled storage conditions and using those samples,the stability of the product is evaluated. It is imperative that stability - measuring analytical methods be developed and validated to support all stability studies. Analytical studies are conducted on the product as it is exposed to accelerated decomposition conditions in order to identify the degradation byproducts likely to appear during longterm storage and to ensure the analytical methods can detect and quantify these byproducts.

Importance of stability indicating analytical methods[24]

The introductory section addresses the various attributes that define analytical methods as stability indicating as it relates to currently mandated regulatory testing of drug substances and drug products. Pharmaceutical considerations regarding when and why it is necessary to employ such specialized validated analytical procedures in the pharmaceutical laboratory are highlighted. Evaluation

of analytical methods used in formal drug substance and drug product stability programs is presented. A Stability-Indicating Method (SIM) is a quantitative analytical procedure used to detect a decrease in the amount of the Active Pharmaceutical Ingredient (API) present due to degradation. According to United States Food and Drug Administration (USFDA) guidelines, a SIM is defined as a validated analytical procedure that accurately and precisely measures active ingredients (drug substance or drug product) free from potential interferences like degradation products, process impurities, excipients, or other potential impurities, and the FDA recommends that all assay procedures for stability studies be stability indicating. The definition in the draft guideline of 1998 read as "Validated Quantitative analytical methods that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference". SIM are validated quantitative test methods that can detect changes with time in the chemical, physical, or microbiological properties of drug substances or drug products. They are specific so that the quantity of the active ingredient, degradation products and other components of interest may be accurately measured without interference in the material being tested. A degradation product is a molecule resulting from a change in the active ingredient brought about over time as a result of processing or storage (e.g. oxidation, hydrolysis).

The regulation requires a formal written stability testing program whose results are used to establish storage conditions and expiration dates of drug products and further mandates the use of "reliable, meaningful, and specific test methods". A drug application is expected to contain "a full description of the drug substance or drug product including its physical and chemical characteristics and stability" as well as "such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity and bioavailability of the drug product, and stability data with proposed expiration dating." If such documentation is generated to support a regulatory submission such as an Investigational New Drug Application (IND), Drug Master File (DMF) or an (A) NDA or generated to satisfy cGMP requirements for a non-application drug substance or drug product. These data are used to establish, confirm or extend retest intervals (usually) or expiration dating periods (if unstable) for drug substances and expiration dating periods for drug products.

CONCLUSION

Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method.Forced degradation is an essential study that provides the knowledge and judgment to develop a stability-indicating analytical method. This study also helps to establish the specification and shelf life of a drug substance or drug product. The information derived from the study will help to improve the formulation, manufacturing process, and storage conditions of the product. A properly designed and executed forced degradation study would generate an appropriate sample for development of stability indicating method. Therefore, the forced degradation study must be demonstrated at the time of method development and before submission of the regulatory dossier to the FDA.

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