ejpmr, 2018,5(8), 283-290

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

PHARMACEUTICAL IMPURITIES AND DEVELOPMENT OF STABILITY INDICATING METHOD (SIM)

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Article Received on 09/06/2018 **Article Revised on 29/06/2018** **Article Accepted on 18/07/2018**

ABSTRACT

There is an ever-increasing interest in impurities which are present in APIs. The presence of impurities in active pharmaceutical ingredients can have a significant impact on the quality, safety & efficacy of pharmaceuticals. Efforts should be made to identify, determine and characterize all unknown impurities in the drug, due to the increasing demand of regulatory agencies to manufacture and develop high-purity drugs. Drug impurity profiling, i.e. identification, structure elucidation and quantitative determination of impurities, degradation products in bulk drug materials is one of the most important fields of activities in pharmaceutical analysis and manufacturing. The degradation products may be provided through forced degradation studies, which enable development of indicators of stability methods with appropriate specificity and selectivity, provides information about possible degradation routes of a certain product, evaluation of the factors that may interfere in any way in the drug stability and critical analysis of the drug degradation profile. In this review, overview of forced degradation studies and description of different types and origins of impurities in relation to ICH guidelines, degradation routes including specific examples are presented. Also, discusses the current trends related to performance of forced degradation studies by providing a strategy for conducting studies on method development and on degradation mechanisms which is helpful for development of stability indicating method (i.e. SIAM).

KEYWORDS: There is an ever-increasing method (i.e. SIAM).

INTRODUCTION

Impurities in pharmaceuticals are the unwanted chemicals that mostly remain with the active pharmaceutical ingredients (APIs) or which are develop during formulation or upon aging of formulated APIs to medicines. The presence of such unwanted chemicals in small amounts may influence the quality and safety of the pharmaceutical products. Impurity profiling (i.e., the identity, quality and quantity of impurity in the pharmaceuticals), is now receiving important critical attentions from regulatory authorities.[4]

There is an ever-increasing interest in impurities which are present in APIs. Now days, not only purity profile but also the impurity profile has become mandatory as per various regulatory authorities.[1] Also, the International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances and products. According to the International Conference on Harmonization (ICH) guidelines "Impurities are substances in the product that are not Active Pharmaceutical Ingredients (API) itself or the excipient used to manufacture it". Impurity profile is a description of the identified and unidentified impurities present in drug products and drug substances.[7]

The safety and quality of pharmaceuticals is dependent not only on the intrinsic toxicological properties of the active pharmaceutical ingredient, but also on the impurities and some degradation products that it may contain. The presence of impurities in active pharmaceutical ingredients can have a significant impact on the safety and efficacy of pharmaceuticals.[2] Some efforts should be made to identify and characterize all unknown impurities in the drug due to the increasing demand of regulatory agencies to manufacture and develop high-purity drugs.[2]

Drug impurity profiling, i.e. identification, structure elucidation and quantitative determination of impurities, degradation products in bulk drug materials is one of the most important fields of activities in pharmaceutical analysis and manufacturing.[3] Impurity profile must contain the details of impurities both qualitatively and quantitatively.[8] An impurity profiling study of forced degradation samples of drug substance and products illustrates and explains the identification process and its potential impact on pharmaceutical development and manufacturing.[9]

A general scheme is set for the estimation and determination of the impurity of bulk drug substances by the rational use of chromatographic method, spectroscopic method and analytical techniques. The various parameters to be fulfilled in an impurity profile of drug substances are discussed and developed.[10]

Mainly chromatographic and non-chromatographic methods can be used for the isolation of impurities, which are intended to be characterized and determined by spectroscopic techniques. Nuclear Magnetic Resonance (NMR) spectroscopy, Raman spectroscopy and Mass spectroscopy techniques are the frequently used techniques for the elucidation of the impurities structure. Various extraction methods like Solid Phase Extraction (SPE), Liquid-Liquid Extraction (LLE), Supercritical Fluid Extraction (SFE), Accelerated Solvent Extraction (ASE), and Microwave Assisted Solvent Extraction (MASE) can be frequently used for the isolation of the impurities from the APIs.[11]

ICH guideline states that stress testing is intended to identify and determine the likely degradation products which further helps in determination and modification of the intrinsic stability of the molecule and establishing some of the degradation pathways, and to validate the stability indicating procedures and results used.[12]

Force degradation (stress testing) typically involves exposure of drug substance to heat, heat and humidity, and light for solid- states studies.[13]

Table 1: Acceptance criteria for Impurities (As per Indian Pharmacopoeia).

Criterion	For Drug Substances	For Drug Products
Each identified specified impurity	0.5 %	-
Each unidentified impurity	0.3 %	-
Total impurity	1.0 %	-
Each identified specific degradation product	-	1.0 %
Each unidentified degradation product	-	0.5 %
Total degradation product	-	2.0 %

Table 2: Regulatory guidelines.

Guideline	Depiction
Q1A	ICH guidelines "stability testing of new drug substances and products"
Q3A	ICH guidelines "Impurities in New Drug Substances"
Q3B	ICH guidelines "Impurities in New Drug Products"
Q3C	ICH guidelines "Impurities: Guidelines for residual solvents"
US-FDA	"NDAs -Impurities in New Drug Substances"
US-FDA	"ANDAs – Impurities in New Drug Substances"
Australian regulatory guideline	Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

Need for Impurity Profiling

While carrying out production process of any formulation it is a pre-requisite to analyse the presence of impurities in the raw materials used for production. These impurities may interfere with solubility of APIs. The presence of these unwanted substances or unwanted chemicals may also affect safety parameters of drug by producing adverse drug reactions or toxicities in the body has compromising safety and efficacy of APIs.[8]

Classification of Impurities (As per USP and ICH)

Impurities are classified based on their common names, ICH Terminology and USP. As per the common names impurities are mainly named as by-product, degradation products, intermediates, Penultimate intermediates, related and transformation product. As per USP, the impurities are mainly named as impurities in official articles, ordinary impurities and organic impurities.[7] ICH has defined impurities as organic impurities, inorganic impurities and residual solvents.[7]

Types of Impurities and Sources

Impurities can be broadly divided into four type[7], they are;

- Process related drug substance
- Process related drug product
- Degradation drug substance or drug product and
- Degradation drug product

There is a small variation in sources for impurities in each type. The details about the types and sources of impurities are shown in Figure 1.

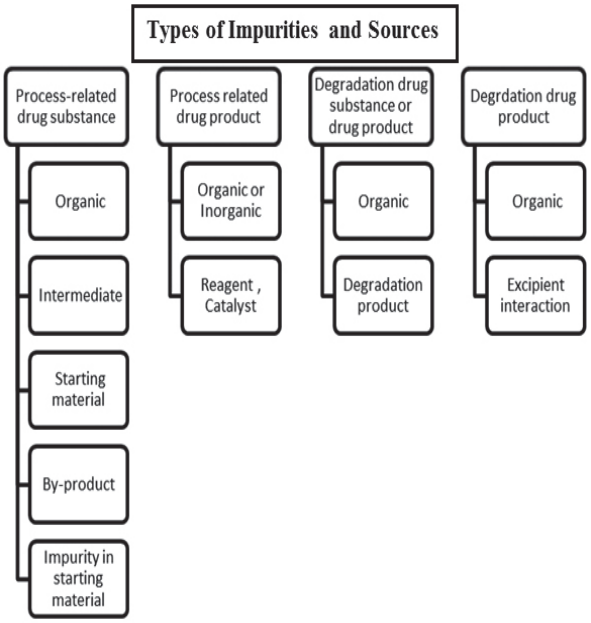


Figure 1: Types of Impurities and Sources.

Analytical Method for identification of Impurity

It becomes obligatory to isolate and characterize impurities to monitor them accurately, because estimations of impurities are generally made against the material of drug substance & drug products and can be uncorrected. These estimations assume that impurities are structurally related to the material of interest and therefore have the same detector response. Number of methods will be of significance for isolation, determination and characterization of impurities. The impurity can be identified by various analytical methods as shown in Figure 2. Many analytical techniques are used for separation and isolation of impurities and characterization of it.[7]

Techniques for separation and characterization of impurities

A general scheme is set up for the estimation and isolation of the impurity profile of bulk drug substances and drug products using chromatographic method, spectroscopic method and hyphenated techniques. Huge number of examples and results are showing the use and benefits of chromatographic methods such as Thin Layer Chromatography (TLC), Gas Chromatography (GC), High Performance Liquid Chromatography (HPLC), Supercritical Fluid Chromatography (SFC), High Performance Thin Layer Chromatography (HPTLC), Spectroscopic methods such as Mass Spectrometry (MS), NMR Spectroscopy, UV-Spectroscopy etc. Further, hyphenated techniques *viz* LC-MS-MS, LC-NMR, LC-NMR-MS, GC-MS and LC-MS have found to be of great significance and importance due to its simplicity and rapid way of analysis.

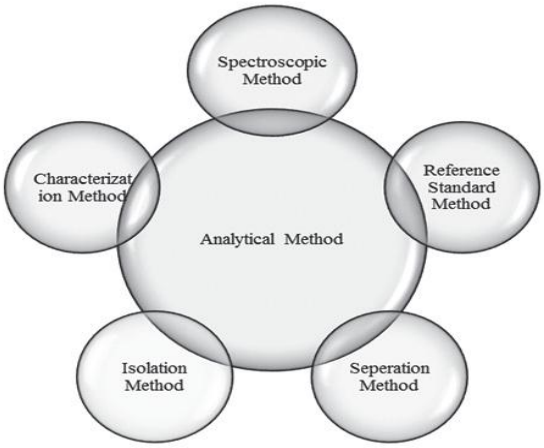


Figure 2: Analytical Method for identification of Impurities.

Forced degradation studies

Forced degradation studies are also known as stress testing or stress studies, stress decomposition studies or forced decomposition studies, etc. Forced degradation studies is a process that mainly involves degradation of drug products and substances at conditions that are more severe than accelerated conditions and thus it generates degradation products that can be studied to determine and identify the stability profile of the molecule. The ICH guideline implements that stress testing and degradation studies is intended to identify the likely degradation products which helps in determination and for development of the intrinsic stability of the molecule, establishing degradation pathways, to validate the stability indicating procedures and reports used. As these guidelines are very general and important in conduct of forced degradation, they do not provide details about the practical approach towards stress testing. Although forced degradation studies area, regulatory requirement and scientific necessity during drug development is not considered as a requirement for formal stability function.[14]

It has become mandatory to perform stability studies of new drug moiety before filing in registration dossier. FDA and ICH guidelines states all the requirements of stability testing profiles to understand how the quality, quantity and safety of a drug substance and drug product changes with time under the influence of various environmental and physical factors. The stability studies involve the long-term stability studies (12months) & accelerated stability studies (6months). Intermediate stability studies (6months) can be performed at conditions milder than that used in accelerated stability studies. Therefore, the study of degradation products like separation, identification and quantitation would take even more time. Compared to stability studies, forced degradation studies helps in generating and maintaining degradants in much shorter span of time.[9]

Knowledge and information of the stability of molecule helps in selecting proper formulation and API, Excipients and package as well as providing storage conditions

and shelf life, which is essential for regulatory documentation and maintenance of records. Forced degradation study is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated stability studies conditions and thus generates degradation products and substances that can be studied to determine and isolate the stability of the molecule.

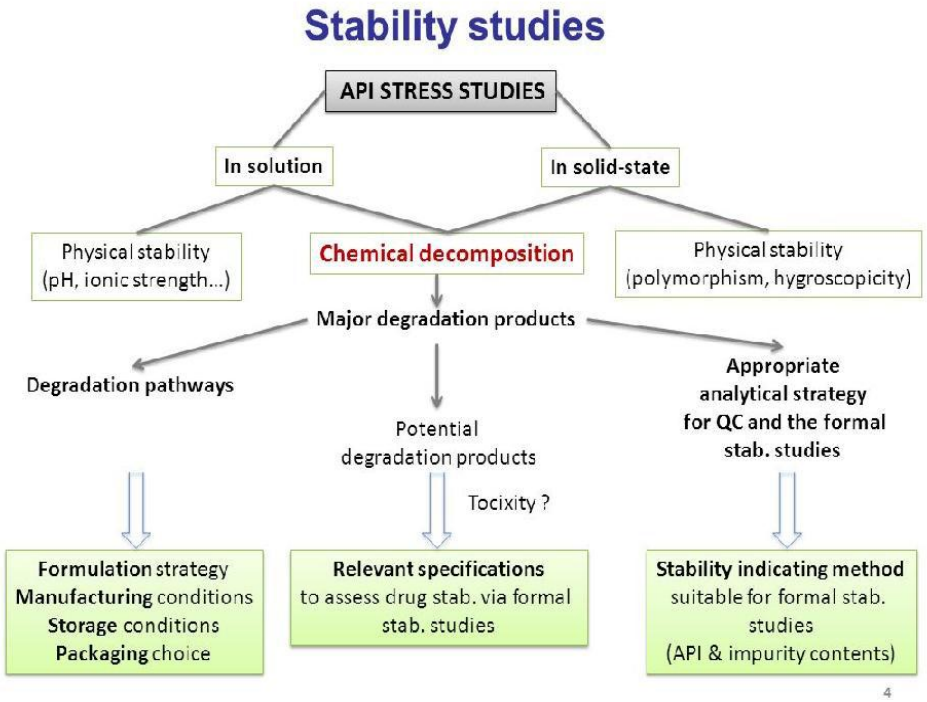


Figure 3: Stress Study.

Outcomes of forced degradation studies

Forced degradation studies offer the following information.[17]

a. Determination of likely degradants,
b. Determination of degradation pathways,
c. Determination of intrinsic stability of the drug molecule,
d. Determination of validated stability indicating methods.

Regulatory perspectives of forced degradation

A. Overview from a regulatory perspective, forced degradation studies provides data to support and maintain the following.[5]

- Identification of possible degradants
- Degradation pathways and intrinsic stability of the drug molecules
- Validation of stability indicating procedures.
- B. Issues addressed in regulatory guidance's include:
- Forced degradation studies are carried out using one batch of material.
- Forced degradation conditions are more severe than accelerated stability data testing such as >50 °C; ≥75% relative humidity; more than ICH light conditions; high and low pH, oxidation, etc.
- Photo stability should be an integral and important part of forced degradation study design.
- Degradation products that do not involve in accelerated or long term stability may not have to be isolated or may have their structure determined.
- Mass balance either should be considered.

C. Issues not specifically addressed in regulatory guidance

- Exact experimental conditions for degradation studies (temperatures, time and duration, and extent of degradation, etc.) are mostly not specified.
- Experimental designs is mostly left to the applicant's discretion.

Objective of forced degradation studies

Forced degradation studies are carried out to achieve the following purposes.[12]:

1. To establish degradation pathways of drug substances and drug products.
2. To differentiate degradation products and drug substances that are related to drug products from those that are generated from non-drug product in a formulation.
3. To elucidate the structure of degradation products.
4. To determine the intrinsic stability of a drug substance in formulation.
5. To reveal the degradation profile mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substances and drug products.
6. To establish stability indicating nature of a developed method.

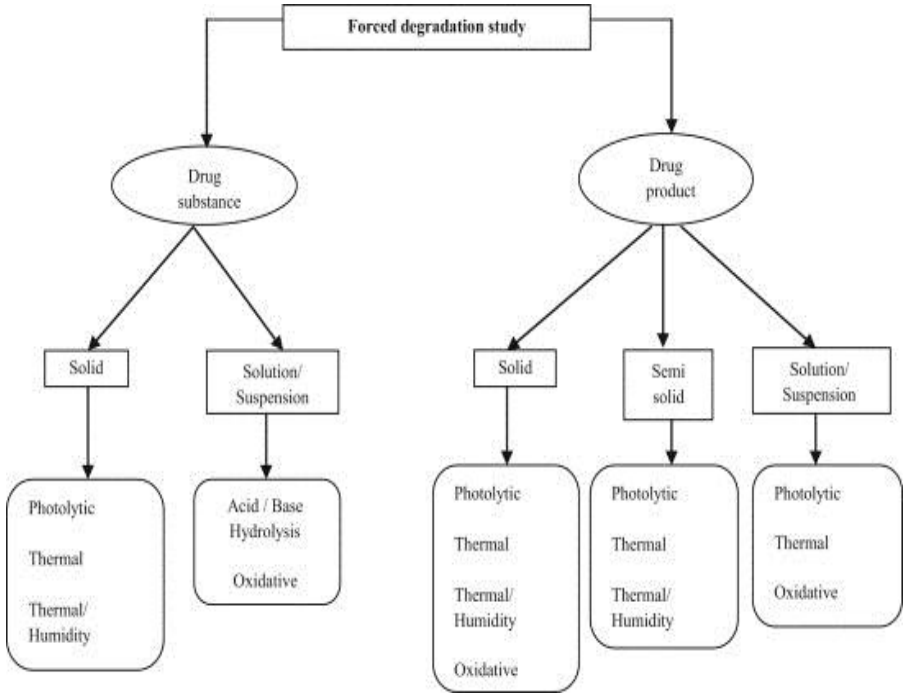
7. To understand the chemical properties of drug molecules.
8. To generate more stable formulations.
9. To produce a degradation profile like that of what would be observed in a formal stability study under ICH conditions.
10. To solve stability-related problems and errors.

Forced degradation in QbD paradigm

A well-designed, forced degradation study is indispensable for analytical method development in a QbD paradigm. It helps to establish and demonstrate the specificity of a stability indicating method or techniques and to predict potential degradation products that could form during formal stability studies and stability- related problems. Incorporating and maintaining all potential impurities in the analytical method and establishing the peak purity of the peaks of interest mostly helps to avoid all the unnecessary method re-development and re-validation.[15]

Strategy for selection of degradation conditions

Forced degradation is carried out to explore the representative samples for developing stability-indicating techniques for drug substances and drug products. The choice of stress conditions should be consistent with the product's decomposition under normal manufacturing, storage, and use conditions which are specific in each case. A general main protocol of degradation stability conditions used for drug substance and drug product is shown in Scheme 1.



Scheme 1: An illustrative flowchart describing various stress conditions used for degradation of drug substances and drug product.

Experimental Design

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.[16]

1. Acid and base hydrolysis,
2. Hydrolysis at various pH,
3. Thermal degradation,
4. Photolysis, and
5. Oxidation.

List of some common conditions and parameters used in conducting forced degradation studies for drug substances and drug products as shown in Table 3.

Table No. 3: Conditions Generally Employed for Forced Degradation.

Degradation Type	Experimental Condition Control API (No acid or base)	Storage condition 40°C, 60°C	Sampling Time 1,3,5 days
Hydrolysis	0.1N NaOH	40°C, 60°C	1,3,5 days
	Acid Control (no API)	40°C, 60°C	1,3,5 days
	Base Control (no API)	40°C, 60°C	1,3,5 days
	pH: 2,4,6,8	40°C, 60°C	1,3,5 days
	3% H2O2	25°C, 60°C	1,3,5 days
Oxidation	Peroxide control	25°C, 60°C	1,3,5 days

	Azobisisobutyronitrile (AIBN)	40°C, 60°C	1,3,5 days
	AIBN Control	40°C, 60°C	1,3,5 days
Photolytic	Light, 1X ICH	NA	1,3,5 days
	Light, 3X ICH	NA	1,3,5 days
	Light Control	NA	1,3,5 days
Thermal	Heat chamber	60°C	1,3,5 days
	Heat chamber	60°C /75% RH	1,3,5 days
	Heat chamber	80°C	1,3,5 days
	Heat chamber	80°C /75% RH	1,3,5 days
	Heat control	Room Temp.	1,3,5 days

1. Hydrolytic conditions

Hydrolysis study is one of the most common performed degradation chemical reactions over a wide range of pH. Hydrolysis is a chemical process that involves decomposition of a chemical compound by reaction with water. Hydrolytic study under acidic and basic condition involves catalysis of ionisable functional groups present in the molecule. Acid or base stress testing involves forced degradation of a drug substance and products by exposure to acidic or basic conditions which mainly generates primary degradants in desirable and wide range. The selection and choice of the type and concentrations of acid or base depends on the stability. Hydrochloric acid (HCL) or sulfuric acids (0.1–1 M) for acid hydrolysis and sodium hydroxide or potassium hydroxide (0.1–1 M) for base hydrolysis are used as suitable reagents for hydrolysis. If the compounds for stress stability testing are poorly soluble in water, then some quantity of co-solvents can be used to dissolve them in HCl or NaOH. The selection of co-solvents is based on the drug substance and product structure. Stress testing trial is normally started at room temperature and if there is no degradation, elevated temperature (50–70°C) is applied. Stress stability testing should not exceed more than 7 days. The degraded sample is then neutralized using suitable acid, base or buffer, to avoid further decomposition and impurities.

2. Oxidation conditions

Hydrogen peroxide is widely used for oxidation of drug substances and products in forced degradation studies. Other oxidizing agents such as metal ions, oxygen and radical initiators (e.g., Azobisisobutyronitrile) can be used. Selection of an oxidizing agent, its concentration and conditions depends on the drug substance and drug products. It is reported that subjecting the solutions to 0.1–3% hydrogen per-oxide at neutral pH and room temperature for seven days or up to a maximum 20% degradation could potentially generate relevant degradation products and substances. Oxidative degradation of drug substance and products involves an electron transfer mechanism to form reactive anions and cations. Amines, sulphides and phenols are more susceptible to electron transfer oxidation process to give the product as N-oxides, hydroxylamine, sulfones and sulfoxides. The functional groups with labile hydrogen like benzylic carbon, allylic carbon, and tertiary carbon or α-positions with respect to hetero atom is susceptible to oxidation to form the by-products as hydro peroxides, hydroxide or ketone.

3. Photolytic conditions

The photolytic stability testing of drug substances must be evaluated and isolated to demonstrate that a light exposure does not result in unacceptable change and results. Photo stability studies are performed only to generate some primary degradants of drug substance and drug products by exposure to UV or fluorescent conditions. Some conditions for photo stability testing are described in ICH guidelines. Samples and results of drug substance and solid/liquid drug product should be exposed to a minimum of 1.2 million lux hours and 200 Watt hours/m2 light. The commonly accepted wavelength of light is in the range of 300– 800 nm to cause the effect of the photolytic degradation. The maximum illumination recommended and observed is 6 million lux hours. Light stress conditions can induce photo oxidation by free radical mechanism and process. Functional groups mostly like carbonyls, nitro aromatic, N-oxide, alkenes and aryl chlorides, weak C–H and O–H bonds, sulphides and polyenes are likely to introduce and develop the drug photosensitivity.

4. Thermal conditions

Thermal degradation (e.g., dry heat and wet heat) should be carried and observed out at conditions which are recommended by ICH Q1A accelerated testing conditions. Samples of solid-state drug sub-stances and drug products should be exposed to dry and wet heat, while liquid drug products should be mostly exposed to dry heat only. Studies are conducted at higher temperatures for a shorter period intervals. Effect of temperature and time on thermal degradation of a substance is studied through the Arrhenius equation:

k ¼ Ae _Ea.=RT

Where k is the specific reaction rate, A is frequency factor, Ea. is energy of activation, R is the gas constant (1.987 cal/deg mole) and T is absolute temperature. Thermal degradation study is carried out at 40–80ºC.

Stability Indicating Method

Force degradation is mostly required to demonstrate and evaluate the specificity when developing SIMs and for this reason, it should be performed prior to implementing the stability studies. Force degradation of drug standard is carried out under different conditions to determine

whether the analytical method validated is stability indicating. The main contemporary goal of stability indicating methods validated and developed is to provide information about condition for stress testing to establish the stability of drug substances and product. This paper reviews the overview of regulatory aspects for development of stability indicating methods. SIMs are generally used to differentiate and evaluate the API from its potential decomposition product. Regulatory guidance in ICH Q1A (R2) and ICH Q3B (R2) Q6A and FDA 21 CFR section 211 requires validated stability indicating methods.[6]

Development of stability indicating method

Though the requirements with respect to stability study indicating method have been spelt out in regulatory affairs documents and information on the basic steps to be followed for the development, trials and validation of stability-indicating methods is neither provided in the regulatory guidelines and reports nor in the pharmacopoeias.[16] General steps in stability indicating method are as follows:

Step1: Critical study of the drug structure to assess the likely decomposition route

Much of the overall information can simply be gained from the structure, by study of the functional group and other key components. Definite functional group categories undergo various process like amides, esters, lactams, lactones, etc. that undergo hydrolysis, others like thiols, thioethers, etc. undergo oxidation and compounds like olefins, aryl halo derivatives, aryl acetic acids and compounds those with aromatic nitro groups and N-oxides undergo mostly photodecomposition.

Step 2: Collection of information on physicochemical properties

Before method development is taken up, it is generally important to know various physicochemical parameters like p*K*a, log *P*, solubility, absorptivity and wavelength maximum of the drug in question.

Step 3: Stress (forced decomposition) studies

As described above in forced degradation section, these studies should be carried out in accordance with ICH Q1A guideline. Stress conditions are as follows: (i) 10°C increments above the accelerated temperatures (e.g. 50°C and 60°C, etc.), (ii) humidity where mostly appropriate (e.g. 75% or greater), (iii) hydrolysis across a wide range of pH values, (iv) oxidation and (v) photolysis.

Step 4: Preliminary separation studies on stressed samples

The simplest way of separation is to start with a reversed-phase octadecyl column and perform the HPLC separation using UV/PDA detector system. Another way is to use the LC-MS separation technique. Using these chromatographic techniques, one should always follow the changes in all the stress stability samples at various time periods intervals. The results should be critically compared with the blank solutions which are been injected in a similar manner. Observe whether there is any type of fall in drug peak is quantitatively followed by a corresponding rise in the degradation product and substance peaks.

Step 5: Final method development and optimization

After preliminary chromatographic studies, the RT and relative retention times (RRT) of products formed should be tabulated and reported for each reaction condition. Special attention is being given to those components whose RT or RRT is very close. PDA spectra or LC-MS profile of such components are mainly obtained and critically evaluated to ascertain whether these products are same or different. To separate such close or co-eluting peaks, the method is optimized and developed by changing the mobile phase ratio and pH, gradient, flow rate, temperature and time, solvent type, column and its type.

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

For Identifying the resolved products, a conventional way is to isolate and evaluate them and determine the structure through spectral data (MS, NMR, IR, etc.) and elemental data analysis. However, this approach is mostly tedious and time consuming when multiple degradation products and reports are formed. The modern approach is used like hyphenated LC techniques coupled with mass spectrometry. This strategy mainly integrates in a single instrument approach, analytical HPLC, UV detection and full scan mass spectrometry (LC-MS) and tandem mass spectrometry (LC-MS-MS) provides a fair idea and knowledge on identity of resolving components. Further integrated approach is becoming popular nowadays, wherein LC-MS or LC-MS-MS is employed to obtain the molecular weight, peak purity and fragmentation information and lastly the detailed structural information is obtained through LC-NMR analysis.

Step 7*:* Validation

Validation of some analytical methods has been extensively covered in the ICH guidelines Q2A and Q2B and in the FDA guidance & by USP. The 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 and data.

ANALYTICAL TOOLS: DEGRADANT SEPARATION & IDENTIFICATION

1. Thin layer chromatography (TLC): TLC is fast, easy and inexpensive tool.
2. Solid phase extraction (SPE): fast way to enrich and to simplify a sample matrix.
3. Accelerated solvent extraction method (ASE).
4. Low-pressure LC (LPLC): Flash chromatography (FC) is the example.

5. Supercritical fluid extraction: Using carbon CO2 & counter current chromatography.
6. Mass Spectrometry (MS): Essential tool in all structure elucidation workflows.
7. Nuclear Magnetic Resonance (NMR): Extremely powerful tool.
8. High Performance Liquid Chromatography (HPLC): Routine technique.
9. GC-MS: First Hyphenated Technique.
10. LC-MS: LC-MS and its variants are most popular.
11. Capillary Electrophoresis-Mass Spectrometry method: Powerful technique.[6]

CONCLUSION

The present review article provides a viewpoint on the importance of forced degradation in drug development stage and impurities in drug substance and drug products. A properly designed and executed forced degradation study would mostly generate an appropriate sample for development and validation of stability indicating method. Forced degradation studies mainly provide knowledge about possible degradation stress pathways and degradation products of the active pharmaceutical ingredients and help elucidate and isolate the structure of the degradants. This data and knowledge is not only used primarily to develop and isolate stability- indicating analytical methods but also useful for other purposes such as formulation development, packaging development and the design of the official stability studies testings.

Recently in pharmaceuticals and development studies, impurity profiling has gained importance. Nowadays, it is mandatory and important requirements in various pharmacopoeias to know the impurities and degradations present in API's. It provides all valuable information about impurities types, its classification, various techniques and data for isolation and characterization, determination, safety and qualification of impurities. Isolation and characterization of impurities and degradants is required for acquiring and evaluating data that establishes and provide biological safety which reveals the need, importance and scope of impurity profiling of drugs in pharmaceutical research.

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