JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue

JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)

An International Scholarly Open Access, Peer-reviewed, Refereed Journal

AN INTRODUCTION TO FORCED DEGRADATION STUDIES FOR DRUG SUBSTANCE & DRUG PRODUCTS.

Ms. Shreya M. Durgule*, Ms. Pranoti M. Patil[1], Ms. Ankita P. Kore[2], Ms. Muskan T. Singh[3], Mr. Sandeep D. Kadam[4].

Department of Pharmaceutical Sciences, Sanjay Ghodawat University, Kolhapur, India.*

Department of Pharmaceutical Sciences, Sanjay Ghodawat University, Kolhapur, India.[1]

Department of Pharmaceutical Sciences, Sanjay Ghodawat University, Kolhapur, India.[2]

Department of Pharmaceutical Sciences, Sanjay Ghodawat University, Kolhapur, India.[3]

Department of Pharmaceutical Sciences, Sanjay Ghodawat University, Kolhapur, India.[4]

Corresponding author,

Miss. Shreya Manohar Durgule

Near Rankala, Kolhapur. Pin 416012.

Contact No. - 9021938072.

Abstract-

Forced degradation is basically degradation studies of may drug substances and drug products which are generally available in pharmaceutical industry. Forced degradation studies also known as stress testing studies, carried out to demonstrate developed stability indicating method by using high performance liquid chromatography i.e. HPLC . Forced degradation is a powerful tool used routinely in pharmaceutical development in order to develop stability indicating methods that lead to quality stability data and to understand the degradation pathways of the drug substances and drug products. This review discuss the trends in forced degradation studies. Forced degradation studies ensure appropriate stability of final pharmaceutical products in very early stages of pharmaceutical development.

Keywords- forced degradation studies, HPLC, stress testing.

Introduction

Pharmaceutical analysis is branch of practical chemistry that involves a series of process for identification, determination, qualification and separation of components of any solution or type of mixtures or it can be determine structural chemical compounds.

The substances may be a single compounds or a mixture of compounds and it may be in any of dosage forms. For example – substances that are used in pharmaceuticals are animal, plants, micro organisms or various synthetic products.[2]

The sample to be analyzed is called 'analyze' and it based on size of sample i.e. as macro, semi macro, micro, sub micro, ultra micro , trace analysis.

Forced degradation studies is a type of mechanism which is utilized in pharmaceutical development so that to create or perform stability studies of different types of drug substances and drug products. This method can express various forced degradation pathways which can be help to learn stability studies of various drug substances and drug products.

Forced degradation studies are carried out to bring off following purposes:

1. To create degradation pathways of drug substances and drug products.
2. To elucidate structure of degradation products.
3. To establish stability of drug substances in various formulations.
4. To affirm degradation mechanism such as hydrolysis, oxidation, photolytic, thermolytic of drug substances and drug products.
5. To solve stability related problems.
6. To understand chemical properties of developed method.
7. To produce more stable formulation.
8. To improve packaging system , storage conditions and shelf life.

The FDA and ICH guidance's 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.

Regulation guidelines

Many guidelines are available to explain forced degradation studies which includes ICH , EMA, FDA, USP etc. ICH guidelines provides informative data about degradation or stability guidelines on various types of substances of drug products as well as other guidelines also represents forced degradation studies.

ICH Guidelines The ICH guidelines which discuss about forced degradation studies are ICH Q1A, Q1B, and Q2B, Q3A, Q3B, M4Q (R1).[1]

ICH Q1A – *testing of stability for new drug molecules and their products*

Intrinsic stability of drug is determined using these guidelines. Q1A Guidelines of Section 2.1.2 of Q1A guidelines. (under section ICH Q1A-testing of stability for new drug molecules and their products). These guidelines are helpful in designing methods for determining the stability of drugs. According to Q1A, degradation depends on respective drug molecules and the nature of drug products. In this various types of conditions are explained such as humidity (≥75% relative humidity), oxidation, photolysis, and diverse range of pH (solution/suspension).[1][3][5]

ICH Q1B – *photo stability testing of new drug substances and drug products*

These methods are used to estimate the photo stability nature of drug molecules normally in the development stage. These guidelines provide knowledge about how to assess the photo stability of molecules that are under study for stability studies.

ICH Q2B – validation of analytical procedures: Methodology

The ICH Q2B guidelines provide information about the protocols to be followed for the validation of different analytical protocols.[4][6]

ICH Q3A- impurities in new drug substances

ICH Q3A guidelines provide information about the determination of contaminants present in new drug molecules.[4][6]

ICH Q3B- *impurities in new products*

ICH Q3B provides information about analytical procedures. It is important for an analytical procedure to validate the specific or non-specific degradation products under various stress conditions.[4][6]

ICH M4Q (R1) – The common technical document for the registration of pharmaceuticals for human use: Module 3: Quality This document provides information about types of studies performed, procedures used, and outcomes of the studies.[4]

EMA Guidelines

It is a guideline used in chemistry of active substances. It covers the data for type of studies performed, procedures used, and outcomes thus obtained from the analysis. This explains about the stability testing for API and dosage forms. It contains the data of retest date and expiry date of substances. Development of analytical method, validation of method, degradation pathways, and intrinsic stability are also determined. It also mandate on conducting stability studies for sensitive compounds such as photosensitive and hygroscopic drug.[1] [5][4][7]

FDA Guidelines

FDA is providing guidelines for photo stability analysis of newer drug molecules and their products (Q1B). According to the FDA, degradation studies should be conducted using normal development conditions. It covers the degradation pathway of samples when they exposed are to light. These guidelines help to develop SIM and also summarize the data of validation which are in turn helpful for confirmatory studies. These guidelines insist on the fact that there is no necessity to carry out the confirmatory studies for degradation products.[4][6]

USP Pharmacopoeia: Validation of Compendia Procedures

According to these guidelines, if degradation standards or contaminants are not available, the specificity can be estimated in comparison of the data with the results obtained from the analytes (containing the

contaminants or degradative products) using an alternative procedure under the same accelerated conditions.[4]

Origin of degradation products-

Degradation studies are based on impurities. Under various conditions humidity, pH, heat, isolation, storage conditions and transportation process drug molecules may have chances to undergo chemical stability so to avoid this degradation studies are generally carried out. [10]

Forced degradation studies can be carried out by many pathways given in figure 1 and table 1.

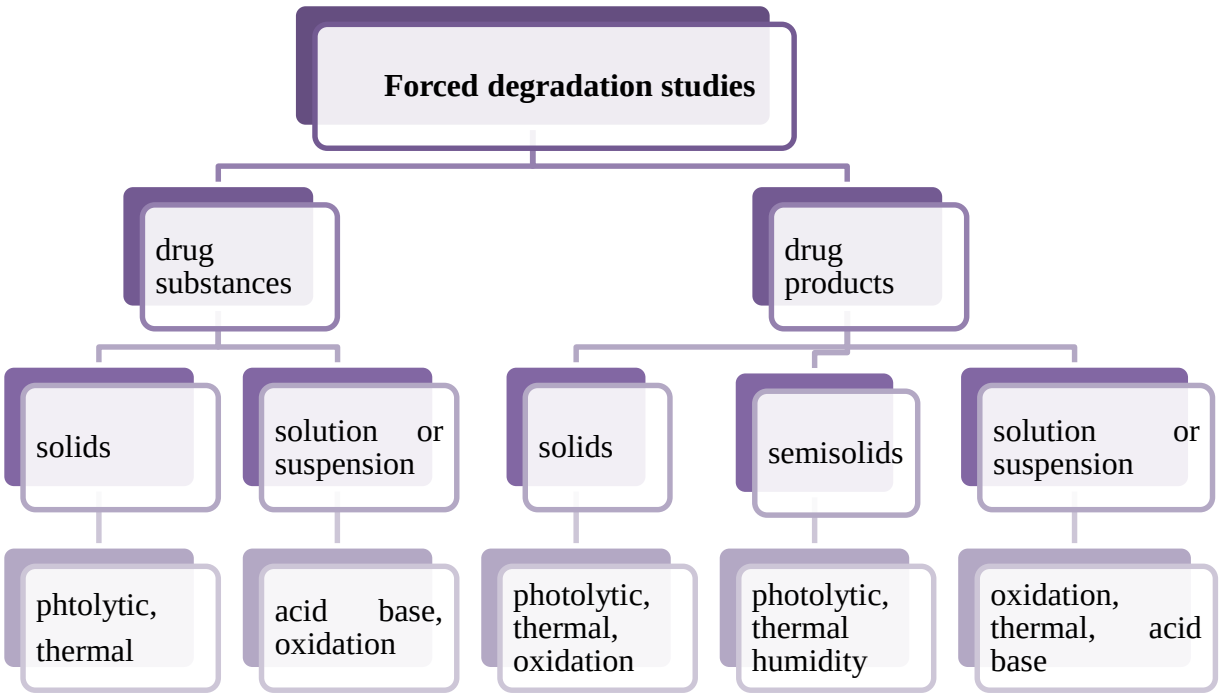

Figure 1: Schematic represents of degradation of drug substances and drug products under various conditions.

DEGRADATION PATHWAYS

1. **Hydrolysis-**

   Over a wide range of pH most common degradation, chemical reactions are Hydrolysis The decomposition of a chemical or drugs or drug substances by reaction with water is called Hydrolysis. There are two types of degradation pathways of hydrolysis such as , In acidic and basic hydrolysis the catalysis of ionisable functional groups present in the molecule occurs. Forced degradation of a drug substance occurs when the drug interacts with acid and base. It produces primary degradants in the desirable range. Depending on the stability of the drug substance the class

and concentrations of acid or base taken should be decided. For acid hydrolysis hydrochloric acid or sulphuric acids (0.1-1 M) considered to be most suitable whereas sodium hydroxide or potassium hydroxides (0.1-1M) for base hydrolysis are suggested.[8]

2. **Oxidation**

For oxidative forced degradation, hydrogen peroxide is broadly used. Apart from this as metal ions, oxygen. Drug structure provide guidance to select concentration and different condition of oxidizing agents. An electron transfer mechanism occurs in the oxidative degradation of drug substance.[8]

3. **Photolytic-**

The light exposure does not affect the drug substance for this purpose photo stability is conducted. Photo stability studies are performed to produce primary degradants of drug substance by exposure to UV or fluorescent conditions. In ICH guidelines some recommended conditions for photo stability testing are described. 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, 300-800 nm is the most commonly accepted wavelength of light to cause the photolytic degradation. million lxh is the maximum illumination recommended. Photo oxidation can be caused by light stress conditions by the free radical mechanism.[9]

4. **Thermal**

Thermal degradation (e.g., dry heat and wet heat) should be carried out at more strenuous conditions than recommended ICH Q1A accelerated testing conditions. Samples of solid-state drug substances and drug products should be exposed to dry and wet heat. Liquid drug products should be exposed to dry heat. For a shorter period studies may be conducted at higher temperatures. Through the Arrhenius equation the effect of temperature on thermal degradation of a substance can be studied.[8][10]

table 1- protocol of forced degradation pathways.

Degradation type	**Experimental conditions**	**Storage conditions**	**Sampling time(days)**
Hydrolysis	0.1 M HCL 0.1 M NaOH	40°C, 60°C 40°C, 60°C	1,3,5 1,3,5
Oxidation	Hydrogen peroxide Azobisisobutyronitrile (AIBN)	25°C, 60°C 25°C, 60°C	1,3,5 1,3,5
Photolytic	Exposure to UV or fluorescent conditions	NA	1,3,5
Thermal	Heat chamber	40°C-100°C	1,3,5

When to perform degradation studies?

It is necessary to know that when to perform stability studies. Hence according to FDA guidelines phase III of regulatory submission process is eminent time to perform these stability studies. To perform degradation studies of drug substances and drug products. So this forced degradation studies can be performed on a single batch. So the outcome should be checked and summarized and submitted in annual report. Stability studies can be carried in two ways such as long term studies (12 months) and accelerated studies (6 months) intermediate studies require less time than accelerated stability studies.[13][14]

This forced degradation studies in pre-clinical and phase I of clinical trials can be encourage to perform which further can help to identify degradation products its pathways, structural elucidation. This lead to improve manufacturing process as well as packaging system of different types of dosage forms.[13][14]

According to FDA forced degradation studies can be perform:

During pre-IND

During formulation Studies: stability indicating quality attributes, degradation routes. For pre-clinical studies: degradants, identification of toxic components

During clinical development:

a. Comparing pre-clinical to clinical quality

b. Comparing pre- to post- manufacturing changes

c. In-use stability.

Post-marketing: usually studies are not performed but following points considered-

a. Identified new stresses

b. Manufacturing changes

c. Additional indications.[13][14]

Characterization of forced degradation studies by analytical approaches-

Forced degradation studies can be developed by using different techniques. Most convenient method which is opt is HPLC method i.e. High performance liquid chromatography. RP-HPLC is mostly chosen due to its compatibility with many aqueous and organic solutions , high precision, high accuracy, high sensitivity and have ability to obtain or detect polar compounds.

While developing stage of degradation study suitable column type is choose, column temperature , pressure with selecting appropriate/ suitable mobile phase pH .

Role of HPLC-DAD

HPLC-DAD provides diagnostic information about the structure of impurity, but HPLC-DAD is not as informative as LC-MS and LC-NMR. The photodiode array ultraviolet detector (DAD) has proven to be an important tool in identification of compounds as it allows on-line acquisition of their UV spectra. One of the strengths of HPLC-DAD is that oxidation does not alter to some extent the chromophores of a drug/impurity, so the drug can be easily identified. If the UV spectrum of an unknown impurity is identical to that of the drug substance, it is likely that the impurity has the same chromophores as that of the drug substances. On other hand, if the impurity has a different UV spectrum from the drug substances, it is an indication that chromophores have been changed in the impurity. [11]

Role of LC-MS

By suitable LC-MS conditions, the mass numbers of impurities/ degradants get confirm and further identify the mass of major degradants which are found to be forming greater than 1.0% during stress studies. LCMS help to illustrate the structures of the major degradants. Similar molecular weights compound may exhibit similar UV profiles, in such cases; attempts must be made to modify the chromatographic parameters to achieve necessary separation. To detect and quantization of all the potential impurities and degradants an optimal wavelength should be used. [11][12]

Conclusion

Forced degradation is an essential step in the drug development process. Forced degradation studies are required to develop stability indicating methods (to determine the intrinsic stability of drug product in formulation to solve stability related problems), to generate more stable formulations, to establish degradation pathways of drug products, to elucidate the structure of degradation products, to reveal the degradation mechanisms such as hydrolysis, thermolysis, photolysis and oxidation of drug product, to understand the chemical properties of drug molecules.

References

1. Dharti Patel, Miral Patel, Keyur Ahir , Sumer Singh 2019. A Review Article on Development of Forced Degradation and Stability Indicating Studies for Drug Substance and Drug Product. Journal of Pharmaceutical Sciences and bio scientific Research**,** 9 (2):165-172 **.**

2. ICH Harmonised Tripartite Guideline stability testing: Photostability testing of new drug substances and products Q1 B.
3. ICH guidelines, Q1A (R2): Stability testing of New drug substances and products, International council On Harmonization.
4. Von V, Helene J, Aus S. 2015. Forced degradation studies - comparison between ICH, EMA, FDA and WHO guidelines and ANVISA's resolution RDC 53/2015; 2015.
5. Kumar HK, Reddy SP, Raju VK, Ravindranath LK. 2013. Forced degradation studies: Practical approach-overview of regulatory guidance, and literature for the drug products and drug substances. Int Res J Pharm 4: 78-85.
6. Harde MS, Kumar J, Velankiwar AS, Chakole RD.2013. Review: Development of forced degradation studies of drugs. Int J Adv Pharm.34-9.
7. Sowmyalakshmi Venkataraman, Merugu Manasa.2018, Journal of Pharmacy Research Solutions,vol 10: 137-146.
8. Farah Iram, Huma Iram, Azhar Iqbal .2016.Forced Degradation studies. Journal of Analytical & Pharmaceutical Research, 3(6): 00073:1-5.
9. M.Kats.2005.Regulatory Considerations and implementation .Biopharm International, 18(7):32-42.
10. Blessy M, Ruchi D. 2014. Development of forced degradation and stability indicating studies of drugs- A review. Journal of pharmaceutical analysis. 4, 2014, 159-165.
11. Qiu F Norwood DL, 2007. Identification of pharmaceutical 12. impurities. J Liq Chromatogr R T 30: 877-935.
12. Barvwick V, Langlay J, Mallet T, Stien, Webb K. 2006. Best Practice 36. for Generating Mass Spectra. ISBN: 9780948926242, 2006.
13. FDA Guidance for Industry, INDs for Phase II and III Studies—Chemistry, Manufacturing, and Controls Information, Food and Drug Administration.
14. FDA Guidance for Industry, INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products, Draft Guidance, Food and Drug Administration.