ejpmr, 2018,5(10), 159-166

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

FORCED DEGRADATION STUDIES: REGULATORY CONSIDERATIONS AND IMPLEMENTATIONS IN ANALYTICAL METHOD DEVELOPMENT AND VALIDATION

Prasad P. Talekar[1#,2*], Chetan M. Bhalgat[3*], Zhang Wei[2], Huang Zhengyi[2], Yang Hai Yang[2], Chen FangFang[2], Kiran Pokharkar[1], Anil Nakade[1], Naresh Jambhale[1], Niket Gharat[1], Nitin Bhoir[1], Ramesh Ambule[1], Subodh Gambhir[1], Jayvant Harlikar[1] and Manish Gangrade[1]

[1]Analytical R & D (API-IPD), Cipla Ltd, Vikhroli (W), Mumbai-400083, Maharashtra, India.
[2]Anhui Biochem United Pharmaceutical, Taihe Industrial Research Park, Anhui Province, China.
[3]Analytical R & D, Rubicon Research Pvt. Ltd, Thane (W), Mumbai-400604, Maharashtra, India.

***Corresponding Author: Prasad P. Talekar**
Anhui Biochem United Pharmaceutical, Taihe Industrial Research Park, Anhui Province, China. E mail: prasad.@bcpharm.com, talekar.prasad88@gmail.com (PT), chetanbhalgat2004@gmail.com (CB) Contact No: +8613866256527 (PT), +91-9036080540 (CB)

Article Received on 22/08/2018 **Article Revised on 13/09/2018** **Article Accepted on 04/10/2018**

ABSTRACT

This review discusses forced degradation methodology and validation as per regulatory aspects of investigations of degradation of active pharmaceutical ingredients. It also highlights the prediction of degradants of drug substances and degradation pathways and development of stability indicating analytical methods. Furthermore, review discusses analytical methodology of various conventional and hyphenated techniques for degradant separation and characterizations are summarized in detail. Forced degradation is a degradation of new drug substance and drug product at conditions more severe than accelerated conditions. It is required to demonstrate specificity of stability indicating methods and also provides an insight into degradation pathways of degradation products of the drug substance and helps in elucidation of the structure of the degradation products. Forced degradation studies show the chemical behavior of the molecule which in turn helps in the development of formulation and selection of packaging material. In addition, the regulatory guidance is very general and does not explain about the actual performance of forced degradation studies. Thus, this review also discusses the comparative study in between International Conference on Harmonisation, Food and Drug Administration and World Health Organization's guidelines which highlights 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: Forced degradation study, High Performance Liquid Chromatography, Retro synthesis, Mass Spectrometry, Nuclear Magnetic Resonance Spectroscopy, Infra-red Spectroscopy.

1. INTRODUCTION

Forced degradation is the evaluation of drug substances or drug products which are subjected to exposure to more severe conditions than accelerated studies which results into generation of relevant degraded product. This degradation study is carried out purposefully to understand the intrinsic property of molecule as well as it helps to indicate stability of drug substance and drug product.

The stability has impact on safety, purity and potency. Therefore it is fundamental to understand the behavior and purity profile of particular molecule in various conditions. Presently many guidelines provide guidance on forced degradation study but none of the recommendations give complete information and detail instructions about each individual aspects. For example, exact time for exposure or exact conditions in acidic and basic hydrolysis or oxidation. This leads to different approaches which results into disagreements and uncertainty among pharmaceutical industries. Internationally, there are different terminologies to describe forced degradation even within International Conference on Harmonisation (ICH) guideline; more than one term is used to describe forced degradation. As like ICH Q1A (Stability testing of new drug substances and products) uses term Stress testing and ICH Q1B (Photostability testing of new drug substances and products) uses term Forced degradation.[1,2] According to ICH Q1A, Stress testing of drug substances helps to identify the likely degradation products which can in turn help to establish the degradation pathways and intrinsic stability of the molecule and validate the stability indicating power of analytical procedure used. The nature of stress testing will depend on nature of drug substance and type of drug product involved. ICH Q1B

outlines that Forced degradation studies is to evaluate overall photosensitivity of the material for the method development purpose and/or elucidation of degradation pathway. But, both the guidelines have accepted that under forced or stressed condition, degradants may be observed that are unlikely to be formed under the conditions used for confirmatory studies. ICH Q1B distinguishes between forced degradation testing and confirmatory testing. In forced degradation testing, the studies are undertaken to degrade the sample deliberately. This study may be carried out under development phase normally on drug substances while photostability studies are carried out under standardized conditions.

1. Forced degradation aspects

As per the overview of World Health Organization (WHO) guideline on Stability testing, it has been brought in consideration that, for submission, when available, it is acceptable to provide the relevant data in scientific literature to support identified degradation products but if the data is not available then stress testing should be performed.[3] Most of the requirements of WHO are similar with ICH Q1A.

The guidance document suggests that result of one time forced degradation study should be included in phase 3 of Investigational new drugs (INDs).[4] The data required for registration of New Drug Application (NDA) are forced degradation products, degradation reaction kinetics, peak purity of drug, structure and mass balance etc. of forced degradation study. Thus, forced degradation study provides useful information about degradation pathways of API alone, and in drug product, possible polymorphic or enantiomeric substances and differences between drug related degradations and excipients interferences.[5,6] USP pharmacopoeia, general chapter <1225>, suggests that, if an impurity or degraded standards are unavailable, the specificity should be demonstrated by comparing the test results of sample containing impurities or degradation products to a second well characterized procedure.[7]

The chemical stability of pharmaceutical molecule provides knowledge which helps in selecting proper formulation, proper packaging and storage conditions and its shelf life.[8] Hence the drug substances and drug products are purposefully involved in the process in order to get degradants. The conditions employed in this process are more severe than that of accelerated conditions to generate degradation products. To know the degradation pathways, analytical techniques such as High Performance Liquid Chromatography, Mass Spectrometry, Infra-red Spectrometry and Nuclear Magnetic Resonance Spectrometry are found more useful for scientists to describe the impurity or degradant, identification, quantification and their controlling. But, if too much stress is applied then unrealistic degradation products may be observed and the resulting analytical method may be unsuitable to detect actual degradation products formed during stability testing.[9] The actual condition needs to be chosen carefully so that the amount of degradation of drug substances produced during degradation is neither too excessive nor too less. It is recommended that degradation must be achieved within 5% to 20%.

In particular, analytical procedure should be validated to demonstrate specificity for the specified and unspecified degradation products. This validation should include sample stored under relevant stress conditions: light, heat, humidity, acid and base hydrolysis and oxidation. According to ICH Q3A (new impurities in drug substances) and ICH Q3B (new impurities in drug product), when identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.[10-11]

Evaluation should be done under all investigated stress conditions so that the observed unknown degradation products are sufficiently separated from the drug substance peak or the peaks of identified organic impurities.

2. Generation or source of degradation products

Theoretically, one can understand the possible or probable degradation products along with their respective structural information on the basis of Retro Synthetic Approach. As in case of practical approach, the forced degradation ideally involves the exposure of drug substances to heat, humidity and light in case of solid. However, to demonstrate analytical method as stability indicating; the same drug substances is studied at different pH. The generation of the known as well as unknown impurities is due to the degradation of its parent drug. The appearance of these impurities provides great information to the scientist to study the chemical instability of the parental drug, which is treated under the condition of heat and/or humidity and/or solvent and/or light encountered during its manufacturing, isolation, purification, drying, storage, transportation, formulation, etc.

The loss in content of parent drug (active component) and increase in the degradation product should be monitored on single analytical method. However, in some cases, it is impossible to monitor on single method hence, assay and impurity methods need to be developed separately.[12]

3. Typical stress test conditions for forced degradation studies

The evaluation of currently relevant regulatory requirements, forced degradation studies comprise a series of physical stress tests. Following are the typical stress tests condition

1) Heat (thermal stress with dry heat or wet heat)
2) Photostability

3) Hydrolytic stress-chemical stress (acid and base hydrolysis)
4) Oxidation (oxidizing solution)

The general approach for use of degradation conditions used for drug substance and drug product of forced degradation studies can be distinguished. For drug substances, the forced degradation study can be worked out for solid and solution / suspension. In case of solid; photolytic, thermal and thermal/humidity can be studied whereas in case of solution/suspension, acid/base hydrolysis and oxidation reactions can be applied.

Forced degradation study for drug product may be achieved for solid, semisolid as well as solution/suspension. Photolytic and thermal studies are applicable to all type of drug products. But oxidative degradation can be applied only if the drug product is solid or solution/suspension but not for semi solid drug product.[13]

3.1. Thermal stress (Dry heat and wet heat)

Solid drug substance and drug products should be exposed to both thermal stress conditions dry and wet heat, while liquid drug product should be exposed to dry heat only. According to ICH Q1A, degradation studies should be conducted at more stringent conditions than introduced and recommends accelerated experimental testing conditions. Thermal degradation study is normally conducted in the range 40 °C to 80 °C. The most widely accepted temperature is 70 °C at low and high humidity for 1 to 2 months. The temperature higher than 80 °C may not produce predictive degradation pathway.[14,15] Wet heat can be applied to drug solution for several hours to know how much degradation occurs. However, the recommendation is that, the effect of temperature be studied in 10 °C increments above that for routine accelerated testing and humidity at 75% relative humidity or greater. It is also recommended that these studies can be carried out for higher temperature but for shorter exposure time.[15,16]

Effect of temperature on thermal degradation of a substance is studied through Arrhenius equation.[14]

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

Where,
K = specific reaction rate
A = frequency factor
Ea = energy of activation

Humidity is seen as a key factor in establishing potential degradants in finished product and API. Degradation study can be achieved normally at 90% humidity for the duration of one week. Testing at several time points could provide the information on primary and secondary degradation rate. Many literatures also suggest that stress conditions sometimes produces minor or no degradation due intrinsic stability of drug molecule. Before terminating stress study, one should ensure that stress is applied in excess of the energy applied by accelerated conditions i.e. 40 °C for 6 months.

3.2. Photolytic degradation

Regulatory guidance does not specify the number of freeze-thaw cycles, or specific wavelengths and light intensities. The design of photolysis studies is left to the applicant's discretion although Q1B recommends that the light source should produce combined visible and ultraviolet (UV, 320-400 nm) outputs, and exposure levels should be justified on case by case studies.[17]

Sample may be exposed to 1.2 million lux hours, 2.4 million lux hours, 200 watt hours/square, 400 watt hours/square meter with spectral distribution of 320 nm to 400 nm to allow direct comparisons to be made between drug substances and drug product. The most commonly accepted wavelength of light is between the range of 300 nm to 800 nm in order to cause photolytic degradation. The photostability testing is accepted as an integral part of stress testing, especially when the drug substance and drug product are photosensitive. It must be confirmed that, when a drug substance and drug product experiences exposure to light and this does not result in a not acceptable change. The photolytic degradation can occur through oxidative photolytic reaction. The photolytic reaction include isomerization, dimerization, cyclization, rearrangements, decarboxylation and hemolytic cleavage of C-X hetero bonds, N-alkyl bond that are dealkylation and deamination, SO_2- C bonds and while oxidative photolytic reaction occur through either singlet oxygen ($1O_2$) or triplet oxygen ($3O_2$) mechanism. The singlet oxygen reacts with the unsaturated bonds, such as alkenes, dienes, polynuclear aromatic hydrocarbon to form photoxidative degradation products whereas triplet oxygen react with free radical of the drug molecule, which then react with a triplet oxygen molecule to form peroxide. Hence, light can also act as a catalyst for oxidation reactions.

Furthermore, sample can be exposed simultaneously/ side-by-side with a validated actinometric system to make sure that specified light exposure is obtained for the appropriate duration of time when condition have been monitored using calibrated radiometers/lux meters.[2,18,19]

For example, consider the photolysis of O_3 which produces molecular oxygen and atomic oxygen, either or both of which may be in electronically excited states, depending on the excitation energy. For example, the primary photochemical process in principle requires light corresponding to $\lambda = 310$ nm. (whereas, the production of O (1D) has been observed experimentally to be at least 336 nm).

$$O_3 + hv \rightarrow O_2\ (\Delta g) + O\ (D)$$

In addition to energetic considerations, however, there are other factors such as spin conservation that also

determines the importance of various sets of products. Ground state of O_3 is a singlet, dissociation into either two singlet states or into two triplet states is expected to predominate. However, as discussed shortly, both hot-band absorption by rovibrationally excited O_3 and by a spin-forbidden process are believed to contribute significantly to the atmospheric photochemistry of O_3.[20]

3.3. Hydrolytic degradation

Reaction of analyte with water is a common chemical degradation reaction. Apart from this, water hydrolysis, acid catalyzed and base catalyzed hydrolysis reactions are recommended to be carried out in stress degradation approach. The typical example for hydrolysis reaction is shown in figure 1.

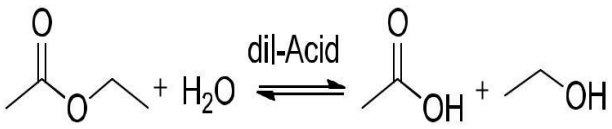

Figure 1: Hydrolysis reaction of ethyl acetate.

Forward reaction: Ethyl acetate is treated with dilute acid to form hydrolysed product as Acetic acid and Ethanol.

Backward reaction: Ethyl acetate is the resultant product, when dilute acid is employed as catalyst in the reaction of Acetic acid and Ethanol.

The hydrolysis testing is normally carried out at room temperature with or without co-solvent and if in case, no degradation is observed, then study can be extended with higher temperature of 50 °C to 70 °C. Testing should not exceed 7 days. The degraded sample needs to be neutralized with suitable acid or suitable base or buffer before injection in order to avoid further decomposition. In actual routine practice, scientists in pharmaceutical industries select 0.1 M to 1.0 M concentration of acid and base to initiate activity of degradation. Hydrochloric acid and sodium or potassium hydroxide are found suitable reagents for testing.[16,19]

3.4. Oxidative degradation

There is always a common suggestion for oxidative treatments to use hydrogen peroxide in the concentration range of 3% to 30%. Other oxidizing agent can be used for example Azobisisobutyronitrile (AIBN), metal ions, oxygen and radical inhibitors. In some study, it is observed that oxidative degradation has been achieved up to 20% by monitoring reactions having 3% to 10% concentration of Hydrogen peroxide for shorter time. It has been addressed that these conditions could potentially generate the relevant degradation products.

It has also been communicated that no significant transformation is observed even when the reaction is worked out under extreme conditions. The behavior is on expected lines, as some drugs are in fact oxidizable while some of the drugs are not.[21]

The typical example is shown below in figure 2 to understand the oxidation of alkene in which the oxidizing agent is H_2O_2.[22]

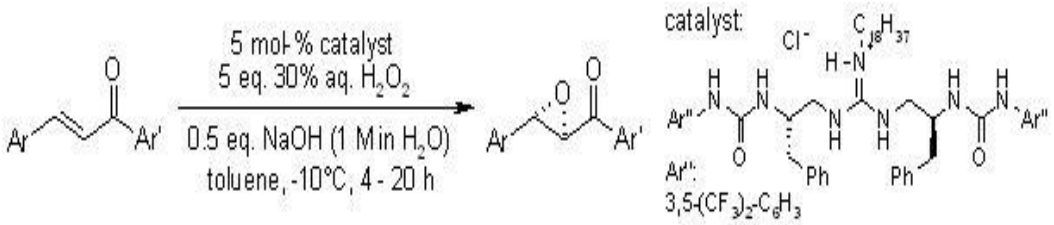

Figure 2: Oxidation of alkene.

4. Mass balance and peak purity considerations

Mass balance establishes adequacy of a stability indicating method though it is not achievable in all circumstances. It is performed by adding the assay value and the amounts of impurities and degradants to evaluate the closeness to 100% of the initial value (unstressed assay value) with due consideration of the margin of analytical error. Mass balance correlates the measured loss of a parent drug to the measured increase in the amount of degradation products. It is the best quality control check on analytical methods to display that all degradation products are adequately detected and they do not interfere with quantitation of the parent drug (i.e., stability-indicating methods).

It is observation that under certain circumstances, it is not appropriate to estimate mass balance directly from the amount of degradation products formed but rather the percent parent drug lost. This percentage, which corresponds to the amount of degradant formed, is the ultimate quantity that should be used to reconcile mass balance. The amount of degradant is converted to the corresponding percent of parent drug degraded by means of the ratio of molecular weight of the parent drug relative to that of the degradant.[23,34] Thus, the operative entity used in reconciling mass balance is the percent of parent drug degraded. Some attempt should be made to establish a mass balance for all stressed samples. Mass imbalance should be explored and an explanation should be provided. Varying responses of analyte and impurity peaks due to differences in UV absorption should also be examined by the use of external standards. Potential loss of volatile impurities, formation of non-UV absorbing compounds, formation of early eluents, and potential retention of compounds in the column should be explored. Alternate detection techniques such as RI

LC/MS may be employed to account for non-UV absorbing degradants.

Peak purity is used as an aid in stability indicating method development.[25] The spectral uniqueness of a compound is used to establish peak purity when co-eluting compounds are present.

The typical chromatogram of Drug substance indicating peak purity (match factor) shown below in figure 3

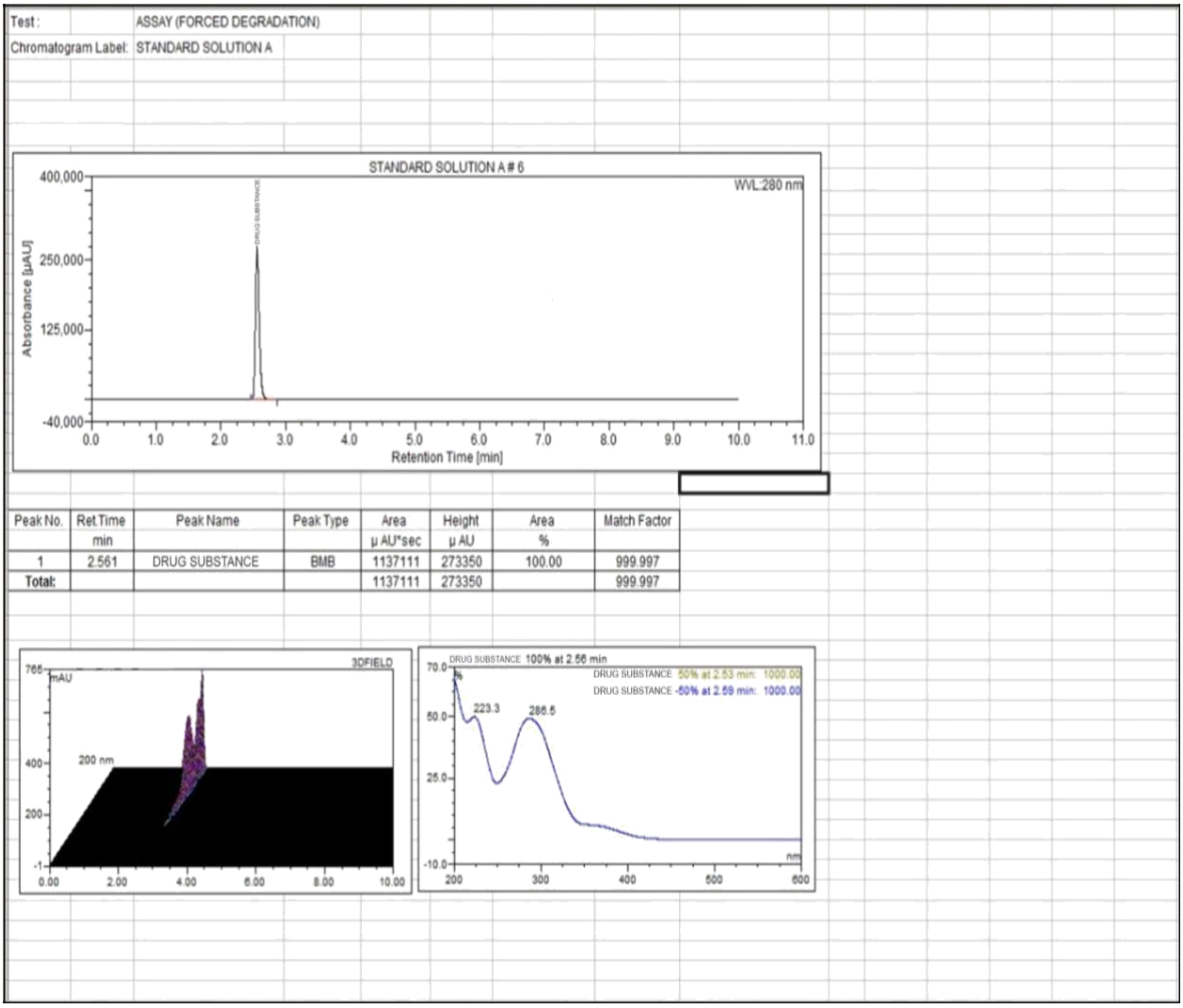

Figure 3: Typical chromatogram of Drug substance indicating peak purity.

Peak purity or peak homogeneity of the peaks of interest of unstressed and stressed samples should be established using spectral information from a diode array detector. When instrument software is used for the determination of spectral purity of a peak, relevant parameters should be set up in accordance with the manufacturer's guidance. Attention should be given to the peak height requirement for establishing spectral purity. UV detection becomes nonlinear at higher absorbance values. Thresholds should be set such that co-eluting peaks can be detected. Optimum location of reference spectra should also be selected. The ability of the software to automatically correct spectra for continuously changing solvent background in gradient separations should be ascertained.

Establishing peak purity is not an absolute proof that the peak is pure and that there is no co-elution with the peak of interest. Limitations to peak purity arise when co-eluting peaks are spectrally similar, or below the detection limit, or a peak has no chromophore, or when they are not resolved at all.

The most valuable tool in peak purity analysis is the overlay of separation signals at different wavelengths to discover dissimilarities of peak profiles. The availability of spectral data in three-dimensional matrix generated by the diode-array detector enables signals at any desired wavelength to be selected and reconstructed for peak purity determination after the analysis.

The typical three-dimensional matrix generated by the diode-array detector of Drug substance shown below in figure 4.

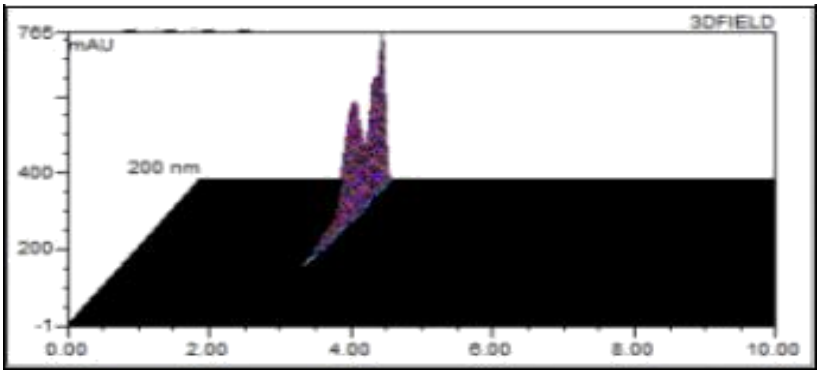

Figure 4: The typical three-dimensional matrix generated by the diode-array detector of Drug substance.

A set of signals can be best interpreted by the observer when, before being displayed, it is normalized to maximum absorbance or to equal areas. A good overlap, where peak shape and retention or migration time match, indicate a pure peak while a poor overlap indicates an impure peak.[26]

The Normalized signals are shown below in figure 5 and figure 6 for pure and impure peak respectively. Peak observed in signal A (highlighted in blue colour) and signal B (highlighted in red colour) are perfectly matched in normalized signals for pure peak. Peak observed in signal A (highlighted in blue colour) and signal B (highlighted in red colour) are not matched perfectly in normalized signals for impure peak.

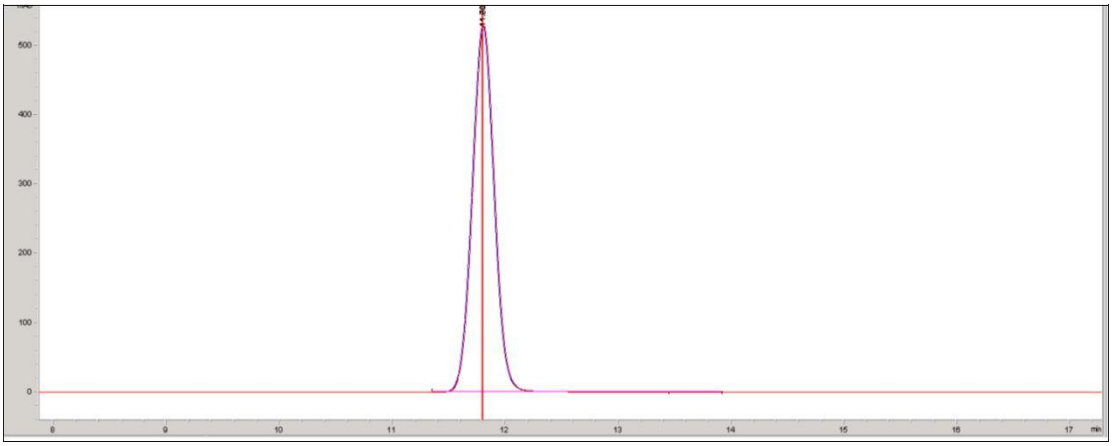

Figure 5: The Normalised signals for pure peak.

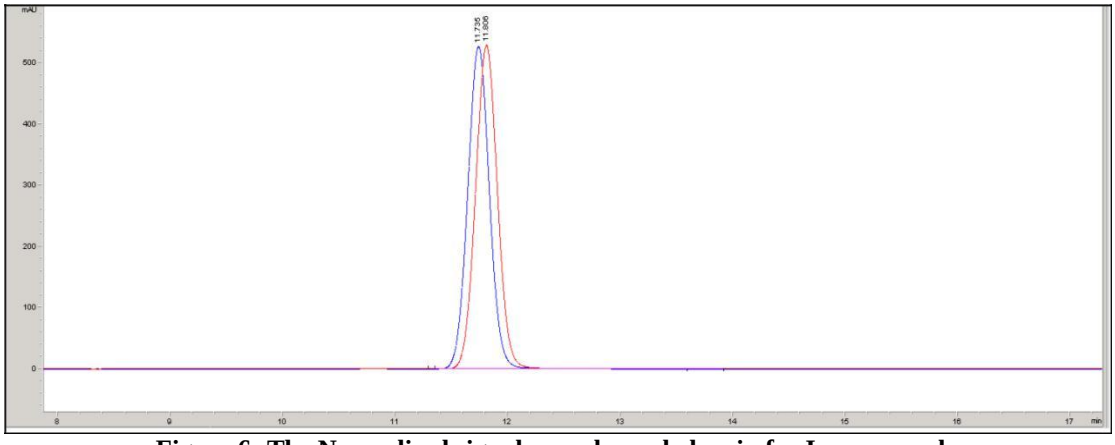

Figure 6: The Normalised signals are shown below in for Impure peak.

Tools in chemical analysis and analytical methods for identification of degradation pathways

When any changes happen with the drug substance or drug product stability then it may result in risk for safety of patients life as degradation product can be formed. In order to monitor possible changes analytical tools and analytical methods are found most useful for scientists to study the degradations. According to Food and Drug Administration

(FDA) guideline, Analytical procedures and method validation for drugs and biologics, guidance for industry,[27] if stability indicating procedure is validated then it can detect changes in quality attributes of the drug substance and drug product during storage. Analytical method must be validated to provide reliable data for regulatory submissions. Hence the analytical method development and method validation plays a key role to study the stability of molecule which has a significant impact on drug development process.

In reversed phase chromatography is the term utilizes to describe the state in which the stationary phase is less polar than the mobile phase. Chemically bonded Octadecylsilane, an n-alkane with 18 carbon atoms, is mainly utilized as stationary phase. C8 and shorter alkyl chains and also cyclohexyl and phenyl groups provide other alternatives as stationary phase. Phenyl groups are more polar than alkyl groups. The reverse of the above applies that the stationary phase is very non-polar and mobile phase is relatively polar. So, non-polar drugs are eluted later than polar drugs.[28]

Reversed phase HPLC is found as universal analytical tool to describe the forced degradations followed by detecting and quantifying the degradants or impurities. Hence forced degradation study became as an integral part of HPLC. Infrared spectroscopy helps to know the probable kinds of bondings within the molecule before and after the degradation. When sample undergoes for LC-MS study, it gives useful information of what sort of fragment is generated in process. Nuclear magnetic resonance (NMR) is found highly powerful interpreter to understand the structure of degraded impurity. The combination study of all gives a documentary evidence and support for assessment of the drug molecule.

5. FDA recommendations

a. If the drug substance does not show any kind of degradation under any stress condition, then repeat the stress studies to obtain adequate degradations. If degradation is not achievable then provide relevant rationale.
b. Note that, conditions in stress testing are too much harsh and therefore most of drug substance can be degrade. Repeat the study by keeping mild conditions having short exposure time to ensure the adequate degradant.
c. Analyze stress samples as per assay method condition. For related substance analyze stress sample as per related substance method to be stability indicating.
d. Attempts which are made to ensure all impurities including degradation products of the unstressed and stressed samples must be captured by analytical method.
e. Provide a list of summarizing amount of degradations known and unknown in stressed samples.
f. Verification must be done of peak height requirements in software for peak purity determinations in samples.
g. Provide information about mass balance of stressed samples.
h. Identification of degradants formed due to interaction between drug molecule and excipients.
i. Whenever the photostability study shows the drug product or drug substance is photosensitive to light, provide its reflections in analytical method, product handling and in manufacturing process.[29,30,31]

7. CONCLUSION

The study is used to facilitate the development of analytical methodology to gain a better understanding of API and drug products. The major objective of the stability indicating study is to monitor and to ensure the safety, efficacy and quality. Therefore, forced degradation is important part of the drug development process as it provides knowledge about the degradation chemistry of drug substances and drug products. This knowledge is used primarily to develop stability-indicating analytical methods but also useful for other purposes such as formulation development, packaging development and design of official stability studies. As there is no formal regulatory guidance for forced degradation, it is recommended to use appropriate conditions to achieve 5-20% degradation.

ACKNOWLEDGEMENT

The authors would like to thank, Srikant Bhandare, Nitish Suryawanshi, Ramdas Waghmale, Ashwin Malvankar and Mrs. Sampada Sutar for supportive role in development and validation. The authors also would like to acknowledge the management of Cipla Ltd, Mumbai/Patalaganga (MH, India), Rubicon Resaerch Pvt Ltd, Thane (MH, India) and Anhui Biochem United Pharmaceutical Co. Ltd. (Anhui, China) for support and facility.

REFERENCES

1. International Conference on Harmonisation Guideline for Stability Testing of New Drug Substances and Products. Current Step 4 version ICH Q1A (R2), 2003.
2. International Conference on Harmonisation Guideline for Stability Testing: Photostability Testing of New Drug Substances and Products. Current Step 4 version ICH Q1B, 1996.
3. World Health Organization's, WHO Technical Report Series, No. 953. Annex 2. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, 2009.
4. Draft Guidance for Industry on IND's for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format; Availability Federal Register (Notices). Food and Drug Administration, 1999; 64(76): 19543-19544.

5. Rao RN, Raju and Narsimha R Isolation and characterization of process related impurities and degradation products of bicalutamide and development of RP-HPLC method for impurity profile study. Journal of Pharmaceutical and Biomedical Analysis, 2008; 46: 505–519.
6. Jain D and Basniwal PK Forced degradation and impurity profiling: Recent trends in analytical perspectives. Journal of Pharmaceutical and Biomedical Analysis, 2013; 86: 11–35.
7. United States Pharmacopeia, USP 41-NF 36. United States Pharmacopieal Convention Inc. Rockville, MD, USA, 2018.
8. Blessy M, Patel RD, Prajapati PN and Agrawal YK Development of forced degradation and stability indicating studies of drugs: A review. Journal of Pharmaceutical Analysis, 2013; 09: 003.
9. Hicks SRJ Forced Degradation to Develop Stability-indicating Methods. Pharmaceutical Outsourcing, 2012; 13.
10. International Conference on Harmonisation Guideline for Impurities in New Drug Substances. Current Step 4 version ICH Q3A (R2), 2006.
11. International Conference on Harmonisation Guideline for Impurities in New Drug Products. Current Step 4 version ICH Q3B (R2), 2006.
12. Hotha KK, Reddy SPK, Raju VK and Ravindranath LK Forced degration studies: practical approach - overview of regulatory guidance and literature for the drug products and drug substances. International Research Journal of Pharmacy, 2013; 4(5): 78-85.
13. Jenke DR Chromatographic method validation: a review of common practices and procedures. II. Guidelines for
14. primary validation parameters. Journal of Liquid Chromatography, 1996; 19: 737-757.
15. Shinde NG, Bangar BN, Deshmukh SN, Sulake SP and Sherekar DP Pharmaceutical Forced Degradation Studies with Regulatory Consideration. Asian Journal of Research in Pharmarceutical Sciences, 2013; 3(4): 178-188.
16. Dorman DE, Lornez LJ, Occolowitz JL, Spangle LA, Collins, MW, Bashore FN and Baertschi SW Isolation and structure elucidation of the major degradation products of Cefaclor in the solid state. Journal of Pharmaceutical Science, 1997; 86(5): 540-549.
17. Alsante KM, Ando A, Brown R, Ensing J, Hatajik TD, Kong W and Tsuda Y The role of degradant profiling in active pharmaceutical ingredients and drug products. Advanced Drug Delivery Reviews, 2007; 59: 29-37.
18. Kats M Forced Degradation Studies: Regulatory Considerations and Implementation. Bio Pharm International, 2005; 18(7): 32-42.
19. Baertschi SW and Alsante KM Stress testing: The chemistry of the drug degradation, In: Pharmaceutical Stress Testing, Baertschi SW, editors, Taylor & Francis, New York, 2005; 99.
20. Singh R and Rehman ZU Current trends in forced degradation study for pharmaceutical product development. Journal of Pharmaceutical Education and Research, 2012; 3(1): 54-63.
21. Speight JG Chemical Transformations in the Environment, In: Environmental Organic Chemistry for Engineers, Butterworth-Heinemann, Oxford, 2017.
22. Willard HH, Merri LL and Dean JA Instrumental Methods of Analysis 6th Edition, CBS Publisher: New Delhi, 2000; 82-83.
23. Tanaka S, Nagasawa K Guanidine-Urea Bifunctional Organocatalyst for Asymmetric Epoxidation of 1,3-Diarylenones with Hydrogen Peroxide. Synlett, 2009; (4): 667-670.
24. Lukulay P and Hokanson G Reconciling Mass Balance in Forced Degradation Studies. Pharmaceutical Technology, 2005; 29(10): 106-112.
25. Reynolds DW, Facchine KL, Mullaney JF, Alsante KM, Hatajik TD and Motto MG Available Guidance and Best Practices for Conducting Forced Degradation Studies. Pharmaceutical Technology, 2002: 48-56.
26. Maheswaran R FDA Perspectives: Scientific Considerations of Forced Degradation Studies in ANDA Submissions. Pharmaceutical Technology, 2012; 36(5): 73-80.
27. Stahl M Peak Purity Analysis in HPLC and CE Using Diode-Array Technology. https://www. agilent.com/cs/library/applications/5988-8647EN pdf, 2003.
28. FDA Guidance for Industry, Analytical Procedures and Methods Validation for Drugs and Biologics, http://academy.gmp-compliance.org/guidemgr/files /UCM386366. PDF, 2015.
29. Ravisankar P, Swathi V, Babu PS, Sulthana MS and Gousepeer SK Current Trends in Performance of Forced Degradation Studies and Stability Indicating Studies of Drugs. IOSR Journal of Pharmacy and Biological Sciences, 2017; 12(6): 17-36.
30. Draft Guidance for Industry on Analytical Procedures and methods Validation Chemistry, Manufacturing, and Controls Documentation Federal Register (Notices). Food and Drug Administration, 2000; 65(169): 52776-52777.
31. FDA Guidance for Industry, ANDAs: Impurities in Drug Substances, https://www.fda.gov/downloads/ Drugs/Guidances/UCM172002.pdf, 2009.
32. FDA Guidance for Industry, ANDAs: Impurities in Drug Products, https://www.fda.gov/downloads/ drugs/guidancecomplianceregulatoryinformation/guidances/ucm072861.pdf, 2010.