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Review Article

Biochemistry for Better Diagnosis and Therapy

Importance of LCMS in Forced Degradation Studies for new Chemical Entities

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Abstract: Forced degradation studies shows the chemical behaviour of the molecule which in turn helps in the development of formulation and package. In addition, the regulatory guidance is very general and does not explain about the performance of forced degradation studies. In pharmaceutical industry, mandatory degradation tests are important to determine the mechanisms and measure the potential degradants during the analysis of drug material and to help to elucidate the composition of degradation materials. The Liquid Chromatography/ Mass Spectrum analysis (L.C.M.S) is a short term widely established liquid chromatography and a methodology utilizing a natural fluid process. L.C.M.S. is commonly employed in the laboratories for qualitative testing of drug substances, drugs and biological samples. Degradation studies, metabolic screening, metabolite identity and in vivo drug screening, impurity identification, amide mapping, glycoprotein mapping were consistently used in pharmaceutical development by LCMS. The FDA and ICH guidelines sets out the requirement for stability testing data to understand how the quality of the drug substance and drug product changes over time under the influence of various environmental factors. Knowledge of molecular stability helps to select the correct formulation and package as well as to provide proper storage conditions and shelf life, which is essential for regulatory documentation. Active pharmaceutical ingredients (APIs) may form impurities when exposed to excipients or environmental variables such as light, high temperatures, acidic or basic conditions, humidity; and the oxidative atmosphere. Considering that these impurities may have an impact on safety and efficacy, it is necessary to know how these impurities are produced from the drug product and to establish the path of their formation. In this context, forced drug degradation studies have been used to characterize the physicochemical stability of APIs. These studies are also essential in the validation of analytical methodologies, in order to demonstrate the selectivity of methodologies. The API and its impurities and to develop strategies to avoid the formation of degradation products. The objective of this review is to demonstrate how forced degradation studies have been conducted and application of LCMS tools in related studies.

Keywords: FDS (Forced degradation studies), Forced Degradation; Drug substance; Stability; L.C.M.S/MS; Testing; I.C.H guidelines, F.D.A.

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1. INTRODUCTION

1.1 LC-MS / MS APPLICATION IN DRUG BASED IMPURITIES PROFILING

Most analytical techniques have a lack of sensitivity and are not capable to deduce the structure of the unknown impurities. LC-MS, therefore, is considered to be an essential and versatile tool for the structural elucidation of the impurity. It's handy and efficient because it's fast and an efficient separation process. Structures of unknown impurities characterization can be obtained on the basis of mass separations from the drug in the form of ions; molecular formulas may be determined from specific measurements of mass. As the instrument is highly sensitivity, it can detect impurities in trace levels up to femtogram level of bulk samples. Structural clarification with LC-MS, can help in the determination of the cause of the route Impurities, and thus helps to control the level of impurity in the drug substance or a drug product. Process-related impurities are potential impurities that emerge during the API manufacturing process which includes the starting material, intermediate material, and by-products, which may be organic or inorganic in nature[1-10].

1.2 IMPORTANCE OF LC-M.S / MS FOR THE ANALYSIS OF FORCED DEGRADATION STUDIES

Degradation studies are important for the determination of Inference of the route of degradation and stability of Pharmaceuticals under different stress conditions. Characterization of the degradants produced is usually performed in accordance with the ICH guidelines. Different, analytical equipment is used to determine the study of stability. Liquid ultraviolet chromatography (HPLC-UV) and HPLC-Photodiode array detector (PDA) is two common equipment to study stability indicating development and validation of the method (SIM) purpose. While, LC coupled to mass spectrometry (LC-MS) become an authentic technique for characterization of degrading products (DP). LC-MS has already won huge importance due to its high sensitivity to drug products (DP) and selectivity and, in addition, details are also provides Structural information for the different DP [25-30]. Degradation is the inability of a particular drug substance in a specific container to remain within a particular chemical, microbiological, therapeutically, physical, and toxicological specifications. The development of the degradation pathway can provide information on possible impurities that may arise in the drug substance. Forced degradation is performed to produce representative samples to develop methods for indicating stability for drug substances and drug products. Choosing stress conditions should be consistent with the decomposition of the product under normal conditions of manufacture, storage, and use which are specified in each case. A minimum list of stress factors suggested for forced degradation studies should include hydrolysis of the acid and base, thermal degradation, photolysis, oxidation. There is no specification regarding the conditions of pH, temperature and specific oxidizing agents to be used in regulatory guidelines [20-25]. Forced degradation studies are very necessary for the development of new drugs and new pharmaceuticals. Phase III of the Regulatory Proposal procedure is a prominent time for these studies, according to the FDA guidelines. Force degradation studies in various pH solutions, the presence of oxygen and light, and high humidity and temperatures should be carried out to establish the stability of drug substances. Forced studies of degradation are carried out in one batch. The stability studies include two types of long term (12 months) and accelerated (6 months) stability studies. But intermediate (6 month) studies can be conducted in less conditions than accelerated studies.

1.3 CHARACTERISATION OF DEGRADANTS BY LC-MS

Earlier reports have shown that multiple analytical techniques are available to isolate, identify, and characterize the impurities that are produced in the degradation studies even at a very low concentration. The degradants isolated in the study were identified and characterized by hyphenated methods such as LC–MS. More importantly, the structural characterization of the degradants/impurities become necessary as they play a vital role in the determination of shelf-life stability. Detection of impurities can be done by thin layer chromatography (TLC), electrophoresis, colorimetric, and gel filtration techniques, while separation and isolation of degradants in pure form can be done using reversed-phase HPLC, TLC, gas chromatography, and supercritical fluid chromatography. Notably, the determination of degradants pathways is carried out using LC-MS/MS technique. The degradative pathways can be determined based on fragmentation patterns that are observed. After determination of degradant pathways, structure elucidations of degradants are done by synthesizing or isolating methods and further characterized by employing LC-MS, LC-UV, and LC-NMR techniques[20-35].

1.4 OUTCOMES OF FORCED DEGRADATION

The following information is given in forced degradation studi es. [2,3,10]

a. Determining possible degradants,
b. Pathways of degradation determination,
c. Determination of endogenous drug molecule stability,
d. Validated stability determination suggesting analytical m ethods.

1.5 FORCED DEGRADATION STUDIES REGULATORY GUIDANCE BY LC-MS / MS

Different International agencies have been recommended to I.C.H Guidelines for forced degradation trials often refer only to new product and do not cover the portion during clinical development. The criteria for forced degradation applicable to I.C.H are[1,6,10]:

a. I.C.H Q1A: Safety Checking for New Drugs and Comp ounds,
b. I.C.H Q1B: New drug substances and products photos tability evaluation,
c. I.C.H Q2B: Analytical Process Validation: Methodology

1. I.C.H. Q1A: Suggests criteria for performing forced degradation studies of drug and drug. The recommendations are to inspect temperature results (especially for accelerated testing, i.e. > 50 ° C, humidity, oxidation and photolysis (75% relative humidity).

2. I.C.H Q1B: The photo stability of these methods are estimated Nature of drug molecules normally evolving

stage. These Guidelines provide insight to evaluate the photo stability of the molecules underneath study for studies on Stability. Forced degradation studies find application for detection of photolytic degradants in confirmatory studies.

3. I.C.H Q2B: The guidelines of ICH Q2B give information on Protocols to be followed when validating the other analytical protocols. Part II of ICH Q2B, Section 1.2.2 explains sample usage for studies were forced to degradation. It underlines the samples should undergo stress under different conditions accelerating humidity and heat conditions, and used further to determine its specificity. In furthermore, these guidelines are useful for quantitative purposes for determination of the produced degradants.

1.6 GOALS FOR FORCED DEGRADATION[5,14-19]

a. To develop drug substances and drug product degradation pathways.

b. To identify drug molecules' chemical characteristics.

c. To determine the intrinsic stability of a drug substance.

d. To detect drug substance and drug product degradation mechanisms.

e. To differentiate between degradation products related to drug products and products generated in formulation by non-drug products.

f. To make formulations more stable.

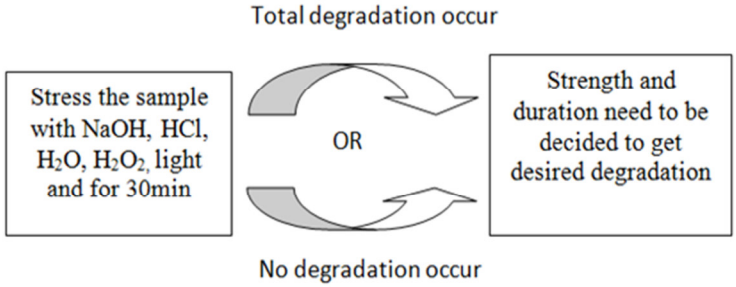

Fig 1: Approaches to Forced Degradation

1.7 CONDUCTING FORCED DEGRADATION STUDIES [11-19]

Forced degradation studies achieves improvements in the production process and provide proper choice for selecting of stability indicating analytical procedures (Figure-I). According to the FDA, forced degradation studies have been carried out during:

1.7.1 IN THE PRE-IND PERIOD

a. During formulation studies: Stability determination of quality features and degradation paths is carried out.
b. For preclinical studies: Degradants are determined and toxic components are identified.

1.7.2 DURING CLINICAL PROGRESS

a. Preclinical comparison with clinical quality
b. Comparison of changes before to after production
c. Stabilization in use

1.7.3 POST-MARKETING

Studies are usually not conducted but are considered for the following points

a. New stresses identified

b. Changes to production

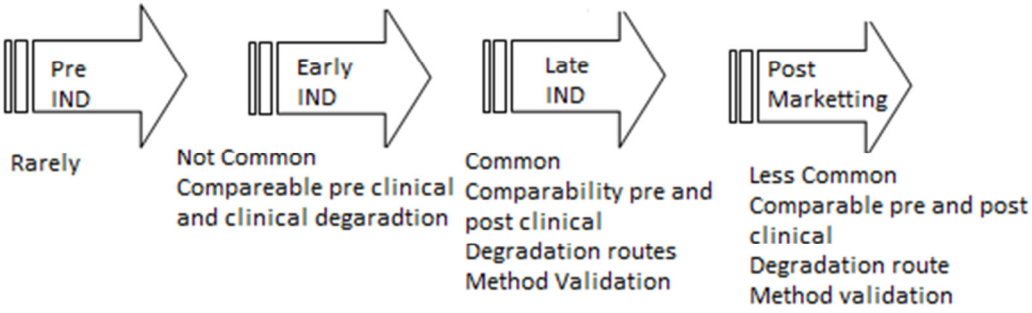

Fig 2: Forced Degradation Data Submitted

1.8 DIFFERENT CONDITIONS OF FORCED DEGRADATION [10-15]

Degradation is regarded as one of the principal sources for impurities. Beneath various stress conditions, that is, moisture, heat, pH, insulation, storage, and transport processes, drug molecules, due to chemical instability undergo degradation. Forced degradation can occur through different types of pathways including hydrolysis, heat, oxidation and Photolytic. It's also seen from various studies that it is possible, under different stress conditions produce all possible degrading agents (Table-I and Fig-1).

Table: 1: Parameters of Forced degradation			
Stress condition	**Strength of stress**	**Temperature**	**Duration**
Acid Hydrolysis	0.1M HCl	Ambient	72 h
Basic Hydrolysis	0.1M NaOH	Ambient	72 h
Oxidative/Peroxide degradation	3% v/v H2O2	Ambient	72 h
Thermal	NA	80°C	72 h
Photolytic Studies (UV-Light)	UV lamp (254 nm) at 1.2 million lux-hours	Ambient	72 h
Neutral (Water)	Water	Ambient	72 h

1.9 HYDROLYSIS[35-39]

Hydrolysis is one of the most common chemical degradation reactions over a wide range of pH. Hydrolysis is a chemical process comprising the decomposition of a chemical compound by water reaction. Under acidic and basic conditions hydrolytic study involves catalysis of functional ionisable groups present in the molecule. Acid or base stress testing involves forced degradation of a drug substance by exposure to acidic or basic conditions resulting in desirable primary degradants. The choice of acid or base type and concentrations depend on the drug substance's stability. Hydrochloric acid or sulfuric acids (0.1–1 M) for hydrolysis of acid and sodium hydroxide or potassium hydroxide (0.1–1 M) for base hydrolysis are suggested as suitable hydrolysis reagents. If the compounds are poorly soluble in water for stress testing, then co-solvents can be used in HCl or NaOH to dissolve these. Co-solvent selection is based on the structure of the medicinal substance. Stress testing is normally started at room temperature, and if no degradation occurs, elevated temperature (50–70° C) is used. Stress tests shouldn't exceed 7 days. To avoid further decomposition, the degraded sample is then neutralized using suitable acid, base, or buffering.

1.10 OXIDATIVE DEGRADATION[37-38]

Drug substance of oxidative degradation involves a mechanism for the electron transfer to form reactive anions and cations. Hydrogen peroxide is widely used in forced degradation studies for the oxidation of drug substances but other oxidizing agents such as metal ions, oxygen, and radical initiators may also be used. Selection of an oxidizing agent depends on the drug substance, its concentration, and conditions. It is reported that subjecting the solutions for seven days to 0.1–3 percent hydrogen peroxide at neutral pH and room temperature or up to a maximum degradation of 20 percent could potentially generate relevant degradation products.

1.11 PHOTOLYTIC CONDITIONS[37-38]

The photo stability testing of drug substances must be assessed to show that light exposure does not result in an unacceptable change. Photo stability studies are performed by exposure to UV or fluorescent conditions to produce primary drug substance degradants. Drug substance samples and solid/liquid drug product should be exposed to a light level of at least 1.2 million lx h and 200 W h / m^2. The most widely accepted wavelength of light is 300–800 nm in range to cause photolytic degradation. The recommended maximum luminance is 6 million l x h. The free radical mechanism can induce photo-oxidation by light stress conditions.

1.12 THERMAL DEGRADATION[39]

Thermal degradation (e.g., dry heat and wet heat) should be carried out under more stringent conditions than recommended accelerated test conditions for ICH Q1A. Samples of solid-state drug substances and drug products should be exposed to dry and humid heat while dry heat should be exposed to liquid drug products. Studies may be carried out over a shorter period at higher temperatures.

2. CONCLUSION

Rapid liquid chromatography tandem mass spectrometry is an important factor in preclinical and clinical trials. L.C.M.S / M.S has been widely used at present for the investigation of degradation studies and the determination of potential drug-drug interactions. The advantage of L.C.M.S / M.S is its high sensitivity and specificities, which makes it a powerful tool for monitoring drug degradation. FDS is an integral part of the lifecycle of product development. From early stages of development, FDS can be used to select the molecule with the most desirable developmental capabilities. These studies provide insights into possible ways in which the active ingredients may degrade and help to elucidate the degradant structure. These studies will also provide the information to improve the formulation process and determine the conditions for storage.

3. AUTHORS CONTRIBUTION STATEMENT

Dr. M.V. Kumudha Valli and Mrs. Anusha Kota designed the review. All authors read the Manuscript's published version and agreed.

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5. CONFLICT OF INTEREST

Conflict of interest declared none.

6. REFERENCES

1. ICH [guidelines:Q1A. (p. R2)]. Stability testing of new drug substances and products. 2nd revision, International Conference on Harmonization; 2003. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf
2. Reynolds DW, Facchine KL, Mullaney JF. Available guidance and best practices for conducting forced degradation studies. Pharm Technol. 2002;26(2):48-56. Google Scholar.
3. Brummer H. How to approach a forced degradation study. Life Sci. Technol. Bull. 2011;31:1-4.
4. FDA guidance for Industry, INDs for Phase II and III studies—chemistry, manufacturing, and Controls Information, Food and Drug Administration. 2003. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070567.pdf.
5. 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. 1999. Available from: http://www.fda.gov/ohrms/dockets/98fr/990674gd.pdf
6. ICH. Final guidance on stability testing of biotechnological/biological products availability, international Conference on Harmonization. 1996. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073466.pdf
7. ICH Guidance for Industry, Q1B: photo stability Testing of New Drug Substances and Product, International Conference on Harmonization. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073373.pdf1996.
8. ICH guidance for Industry, Q2B: validation of analytical procedures: methodology, international Conference on Harmonization. 1996. Available from: http://permanent.access.gpo.gov/LPS113764/LPS113764/www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM128049.pdf
9. EMA guideline on the limits of Genotoxic Impurities. Committee for Medical Products for Human Use (CHMP). 2007. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf
10. ICH Q. (R2): impurities in new drug substances, international Conference on Harmonization, Geneva. Vol. 3A. 2006. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2__Guideline.pdf
11. ICH Q. (R2): impurities in new drug products, international Conference on Harmonization, Geneva. Vol. 3B. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128033.pdf, 2006.
12. FDA guidance for Industry, ANDAs: impurities in drug substances [draft]. Rockville, MD: Food and Drug Administration. Available from: http://www.fda.gov/OHRMS/DOCKETS/98fr/1998d-0514-gdl0003.pdf, 2005.
13. FDA guidance for Industry, ANDAs: impurities in drug products [draft]. Rockville, MD: Food and Drug Administration. 2010. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072861.pd
14. ICH guidance for Industry, Q6B: specifications: test procedures and acceptance criteria for bio-technological/biological products, international Conference on Harmonization. 1999. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073488.pdf
15. Brummer H. How to approach a forced degradation study. Life SciTtechnol Bull:. 2011: 31. https://www.sgs.com/~/media/Global/Documents/Technical%20Documents/SGS-LSS-Forced%20Degradation-EN-11.pdf.
16. Alsante KM, Ando A, Brown R, Ensing J, Hatajik TD, Kong W, Tsuda Y. The role of degradant profiling in active pharmaceutical ingredients and drug products. Adv Drug Deliv Rev. 2007;59(1):29-37. Doi: 10.1016/j.addr.2006.10.006, PMID 17187892.
17. Hou S, Hindle M, Byron PR. A stability-indicating HPLC assay method for budesonide. J Pharm Biomed Anal. 2001; 24(3):371-80. Doi: 10.1016/S0731-7085(00)00424-6.
18. Bakshi M, Singh S. Development of validated stability-indicating assay methods-critical review. J Pharm Biomed Anal. 2002; 28(6):1011-40. Doi: 10.1016/S0731-7085(02)00047-X, PMID
19. Hewitt EF, Lukulay P, Galushko S. Implementation of a rapid and automated high performance liquid chromatography method development strategy for pharmaceutical drug candidates. J Chromatogr A. 2006;1107(1-2):79-87. Doi: 10.1016/j.chroma.2005.12.042, PMID 16406385.
20. Reynolds DW, Facchine KL, Mullaney JF, et al. Available guidance and best practices for conducting forced degradation studies Pharmaceutical Technology. p. 48-56; 2002. Available from: http://www.pharmtech.com [cited 9/11/2020].
21. Cione AP, Tonhi E, P. SilvaStability indicating methods. In:Tech (2011) Shoyama Y, editor. Available from: http://cdn.intechopen.com/pdfs/23465/InTech-Stability_indicating_methods.pdf, Quality control of herbal medicines and related areas. p. 25-36.
22. Thummar M, Patel PN, Kushwah BS, Samanthula G. Application of the UHPLC method for separation and characterization of major photolytic degradation products of trazodone by LC-MS and NMR. New J Chem. 2018;42(20):16972-84. Doi: 10.1039/C8NJ03545H.
23. Ortigara R, Steppe M, Garcia CV. Stability-indicating UPLC-PDA method for ambrisentan tablets and identification of a main degradation product by UPLC-MS/MS. CPA. 2019;16(1):55-63. Doi: 10.2174/1573412914666181003140449.
24. Raju B, Ramesh M, Srinivas R, Raju SS, Venkateswarlu YJ. Identification and characterization of stressed degradation products of prulifloxacin using LC-ESI-MS/Q-TOF, MSn experiments: development of a validated specific stability-indicating LC-MS method. J Pharm Biomed Anal. 2011 Nov 1;56(3):560-8. Doi: 10.1016/j.jpba.2011.06.021, PMID 21783336.
25. Purna Chander C, Raju B, Ramesh M, Shankar G, Srinivas R. Liquid chromatography/electrospray ionization tandem mass spectrometry study of

repaglinide and its forced degradation products. R.Rapid Commun Mass Spectrom. 2018 Aug 15;32(15):1181-90.
Doi: 10.1002/rcm.8151, PMID 29723439.

26. Jain D, Basniwal PKJ. Forced degradation and impurity profiling: recent trends in analytical perspectives. J Pharm Biomed Anal. 2013 Dec;86:11-35.
Doi: 10.1016/j.jpba.2013.07.013, PMID 23969330.
27. Narayanam M, Handa T, Sharma P, Jhajra S, Muthe PK, Dappili PK, Shah RP, Singh SJ. Critical practical aspects in the application of liquid chromatography-mass spectrometric studies for the characterization of impurities and degradation products. J Pharm Biomed Anal. 2014 Jan; 87:191-217.
Doi: 10.1016/j.jpba.2013.04.027, PMID 23706957.
28. Borkar RM, Raju B, Srinivas R, Patel P, Shetty SK. Identification and characterization of stressed degradation products of metoprolol using LC/Q-TOF-ESI-MS/MS and MS(n) experiments. Biomed Chromatogr. 2012 Jun;26(6):720-36.
Doi: 10.1002/bmc.1721, PMID 21989963.
29. Yang W, Yang X, Shi F, Liao Z, Liang Y, Yu L, Wang R, Li Q, Bi K. Qualitative and quantitative assessment of related substances in the Compound ketoconazole and clobetasol propionate Cream by HPLC-TOF-MS and HPLC. J Pharm Anal. 2019 Jun;9(3):156-62.
Doi: 10.1016/j.jpha.2018.08.006, PMID 31297292.
30. Žigart N, Časar Z. Development of a stability-indicating analytical method for determination of venetoclax using AQbD principles. ACS Omega. 2020 Jul 9;5(28):17726-42.
Doi: 10.1021/acsomega.0c02338, PMID 32715260.
31. Žigart N, Črnugelj M, Ilaš J, Časar Z. On the stability and degradation pathways of venetoclax under stress conditions. Pharmaceutics. 2020 Jul 7;12(7):639.
Doi: 10.3390/pharmaceutics12070639, PMID 32645956.
32. Kumar N, Sangeetha D, Reddy SP. UPLC and LC-MS studies on degradation behavior of irinotecan hydrochloride and development of a validated stability-indicating ultra-performance liquid chromatographic method for determination of Irinotecan hydrochloride and its impurities in pharmaceutical dosage forms. J Chromatogr Sci. 2012 Oct; 50(9):810-9.
Doi: 10.1093/chromsci/bms075, PMID 22661461.
33. Runje M, Babić S, Meštrović E, Nekola I, Dujmić-Vučinić Ž, Vojčić N. Forced degradation of nepafenac: development and validation of stability indicating UHPLC method. J Pharm Biomed Anal. 2016 May 10;123:42-52. doi: 10.1016/j.jpba.2016.02.003, PMID 26871279.
34. Roberto de Alvarenga Junior B, Lajarim Carneiro R. Chemometrics approaches in forced degradation studies of pharmaceutical drugs. Molecules. 2019 Oct 22;24(20):3804.
Doi:10.3390/molecules24203804.
35. Kamlesh Raju Chaudhari, Rajveer Bhaskar, Monika Ola, Amod Patil, Ankita Ambatkar, Tejaswini Mahajan, Comprehensive Review on Analytical Profile of Antidepressant Drug, Journal of Drug Delivery and Therapeutics. 2020,10(2).
36. Bhaskar R, Ola M, Agnihotri V, Chavan A, Girase H. Current Trend in Performance of Forced Degradation Studies for Drug Substance and Drug Product's. JDDT [Internet]. 15 Apr. 2020 [cited 17Sep.2020]; 10(2-s): 149-55.
37. Shubhangi V. Sutar, Veerendra. C. Yeligar, Shitalkumar S. Patil. Stability Indicating Forced Degradation Studies. Research J. Pharm. and Tech 2019; 12(1): 429-433. doi: 10.5958/0974-360X.2019.00078.7.
38. Jennifer Halley 1, Yite Robert Chou, et.al. An Industry Perspective on Forced Degradation Studies of Biopharmaceuticals: Survey Outcome and Recommendations. J Pharm Sci. 2020;109(1):6-21.
doi: 10.1016/j.xphs.2019.09.018.
39. G. Indira Priyadarshini et al. A Review on Forced Degradation And Stability Indicating Studies. Indo Am. J. P. Sci. 2020; 07(01).