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A COMPREHENSIVE REVIEW ON ADVANCEMENT IN FORCED DEGRADATION STUDIES

Vaibhav S. Adhao, Jaya P. Ambhore, Pranjal A. Dhoran*, Vaishnavi P. Wadodkar, Kalyani K. Malthane, Punam K. Satav

Department of Quality Assurance, Dr. Rajendra Gode College of Pharmacy Malkapur, Dist. Buldhana, M.S., India-443101.

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Corresponding Author: Pranjal A. Dhoran

Address: Department of Quality Assurance, Dr. Rajendra Gode College of Pharmacy Malkapur, Dist. Buldhana, M.S., India-443101. Email Id: pranjaldhoran12@gmail.com, adhao.vaibhav@gmail.com,

ABSTRACT

The advancement of analytical methodology, a better knowledge of the stability of active ingredients (API) and drug products (DP), and information regarding degradation pathways and degradation products are all made possible by forced degradation studies. This document describes the parameters of force degradation experiments, including the goals of ensuring drug stability, the time required to conduct drug degradation studies, and the factors—such as light, pH, and oxygen—that effect drug deterioration. The significance of the stability-indicating method and the connection between stability data and forced degradation investigations are emphasized in the study. Studying force degradation is crucial because it gives you the information and insight you need to create an analytical technique that indicates stability. The specifications and shelf life of a drug substance or drug product are established in part by this investigation.

KEYWORDS: Forced Degradation, Stability, Thermal, Photolytic, Stress testing.

INTRODUCTION

A forced degradation study, sometimes referred to as stress testing, examines how stable a chemical or medicinal product is under adverse circumstances. In this context, "stress" refers to any environmental or physical factors that a product may come into contact with that could result in a chemical alteration.[1-2] Forced degradation is the term used to describe the

breakdown of pharmacological compounds and goods under circumstances more severe than rapid degradation. Product degradation from this process can be investigated to determine the molecule's stability. The ICH recommendation states that stress testing should be used to verify the stability indicating methods used and to find the anticipated degradation products. This will help determine the molecule's intrinsic stability and pinpoint the degradation pathways.[3] The following goals are pursued by forced degradation studies:[3-9]

1. To identify drug substance and product degradation pathways.
2. To determine the processes by which drug compounds and products degrade.
3. To demonstrate the stability of a proposed method.

TYPES OF DEGRADATION

1. Hydrolytic Degradation

Hydrolysis is the term for drug degradation involving a reaction with water. Hydrolysis is influenced by PH, buffer salts, ionic strength, solvents, complexing agents, surfactants, and excipients. Usually, an acid or a base catalyses hydrolysis processes. The most frequent chemical degradation process across a broad pH range is hydrolysis. Most medications degrade when water, either as a solvent or as air moisture, comes into touch with medicinal dosage forms. In hydrolytic analysis, the molecule's ionisable functional groups are catalyzed in both basic and acidic environments.[10-14]

2. Oxidation Degradation

Under typical circumstances, many medicinal compounds undergo oxidation, including ground state elemental oxidation. One free radical reaction that needs a free radical initiator to start the chain reaction is autoxidation. Oxidation is initiated by hydrogen peroxide, metal ions, and trace amounts of contaminants in a medicinal component. The initial oxidative stress test is conducted for 6 hours at room temperature in 3% H2O; the duration can be adjusted to obtain adequate deterioration. With 1% H2O, the duration can also be shortened by 30 minutes or extended by 24 hours by 3%. An electron transfer process creates reactive anions and cations as part of the oxidative breakdown of medicinal substances. Substances Free radical oxidation is the most prevalent type of oxidative breakdown in the pharmaceutical industry.[14-17]

3. Photolytic Degradation

Any change or modification to the primary chemical component of a medication, food, paint, dye, ink, pesticide, etc. brought on by light or photon particles is known as photolytic

degradation. When sunlight and air interact with a product, they cause both oxidation and hydrolysis, which is why the phrase "photolytic degradation" was created.[11] Through the mechanism of free radicals, light stress conditions can cause photo-oxidation. Drug photosensitivity is likely to be introduced by functional groups such as carbonyls, nitro aromatic, N-oxide, alkenes, aryl chlorides, weak C H and O H bonds, sulphides, and polyenes.[18-20]

4. Thermal Degradation

More demanding conditions than the suggested ICH Q1A accelerated testing settings should be used for thermal deterioration (such as dry heat and wet heat). While liquid drug products should be exposed to dry heat, samples of solid-state drug substances and drug products should be exposed to both dry and wet heat. Higher temperatures may be used for shorter periods of time in studies.[21-24]

TIME TO PERFORM FORCED DEGRADATION

Knowing when to conduct forced degradation experiments is crucial for the creation of novel medicinal substances and products. According to FDA guidelines, phase III of the regulatory submission procedure is when stress testing should be carried out. To ascertain the stability of the drug material, stress tests should be conducted in various pH solutions, with oxygen and light present, and at high temperatures and humidity levels. A single batch is used for these stress tests. A yearly report summarising the findings should be submitted.[8] However, it is strongly advised to begin stress testing on medicinal substances early in the preclinical phase or phase I of clinical trials. This will allow enough time to identify degradation products, clarify structure, and optimise stress settings. Additionally, an early stress study provides prompt suggestions for manufacturing process enhancements and appropriate stability-indicating analytical procedure selection.[1,8-9]

FACTOR AFFECTING DEGRADATION

The several factors listed below contribute to the degradation of pharmacological compounds.

1. Moisture

Water-soluble compounds may dissolve when moisture is present. The molecule undergoes chemical and physical changes as a result.[7-9]

2. Excipients

It was noted that certain excipients can have high water content. This moisture could result in higher water content in the formulation, which would subsequently impact the drug's stability. Reduced stability is sometimes the result of chemical reactions between the medication substance and the excipients.[7-9]

3. Temperature

Temperature variations can occasionally have a negative impact on the drug's stability. Generally speaking, higher temperatures accelerate the rate of medication breakdown.[7-9]

4. pH

Drug hydrolysis breakdown rate is significantly impacted by pH. The medications are formulated using buffer solutions with the highest stability in order to lessen this effect.[7-9]

5. Oxygen

Some medications undergo increased oxidation when oxygen is present. Purging nitrogen or carbon dioxide from the storage container stabilises drugs that decompose more quickly in the presence of oxygen.[7-9]

6. Light

Certain medications have a tendency to break down when exposed to light because they are photolabile. Its stability in the presence of light and stability while stored in the dark can be used to test for photolytic decomposition susceptibility. It is important to keep in mind that the photolabile compounds ought to be kept in dark, amber glass containers.[7-9]

STABILITY INDICATING METHOD

An analytical technique called a stability indicating method (SIM) is used to measure how much of the active pharmaceutical ingredient (API) in a drug product has degraded.[1-2] A stability-indicating method is a validated quantitative analytical technique that can be used to identify changes in the stability of drug substances and drug products over time, per an FDA guidance document.[12-14] Without being influenced by other degradation products, contaminants, or excipients, a stability-indicating approach precisely monitors variations in the concentration of the active ingredient.[10] SIM is a quantitative technique that tracks variations in medication concentration over time, according to the FDA.[7-9] It guarantees that

excipients or other degradation products won't interfere with degradation investigations and aids in predicting storage conditions.[9]

RELATION BETWEEN FORCED DEGRADATION STUDIES AND STABILITY DATA Studying force degradation is crucial because it gives you the information and insight you need to create an analytical technique that indicates stability. The specifications and shelf life of a drug substance or drug product are established in part by this investigation. Compared to standard stability testing, forced degradation studies yield more degradation products. The drug compound is stable under specified stress conditions if no degradants are generated. Degradation pathways and storage conditions can be discovered with the help of forced degradation analysis.[7-9]

CONCLUSION

To sum up, studies on forced degradation are essential to the creation of analytical techniques for pharmacological compounds and products. In order to forecast degradant impurities during stability tests, these investigations entail exposing substances to a variety of stress conditions, including hydrolysis, oxidation, photolysis, thermal degradation, and humidity. Stress conditions, degradation levels, analytical methods, mass balance, optimization, specificity, and selectivity are some of the crucial variables. Assuring drug stability, comprehending its chemical composition, developing stable formulations, and producing samples for the detection of degradation products are the goals. The FDA highlights the significance of forced degradation studies throughout the pre-IND, clinical development, and post-marketing phases, whereas regulatory guidelines, especially those issued by the ICH, advise performing these studies at different stages of drug development. Degradation-influencing elements such moisture, excipients, temperature, pH, oxygen, and light need to be carefully taken into account. All things considered, studies of forced degradation offer important information about the stability and degradation processes of medicinal compounds, which aids in the creation of reliable and stability-indicating analytical techniques.

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Conflict of interest

The authors declare that there isn’t any conflict of interest.

REFERENCES

1. Adhao VS, Sharma J, Thakre M. Development and Validation of Stability Indicating RP-HPLC Method For Determination of Ceritinib. Indonesian Journal of Pharmacy. 2018 Jan 9;28(4):241.
2. Adhao V, Thenge R, Sharma J, Thakare M. Development and Validation of Stability Indicating RP-HPLC Method for Determination of Safinamide Mesylate. Jordan Journal of Pharmaceutical Sciences. 2020 May 8;13(2).
3. ICH guidelines, Q1A (R2): Stability Testing of New Drug Substances and Products (revision -2), International Conference on Harmonization. Available from: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm128204.pdf, 2003.
4. D.W. Reynolds, K.L. Facchine, J.F. Mullaney, et al. Available guidance and best practices for conducting forced degradation studies; Pharm. Technol., 26 (2) (2002), pp. 48-56
5. Brummer H.; How to approach a forced degradation study; Life Sci. Technol. Bull. 2011 Jan; 31:1-4.
6. Naveed S, Basheer S, Qamar F.; Stability of a dosage form and forced degradation studies. J Bioequivalence Bioavailab. 2016;8:191-3.
7. FDA Guidance for Industry, Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation, Draft Guidance, Food and Drug Administration.Availablefrom:⟨http://www.fda.gov/downloads/Drugs/…/Guidance's/ucm 122858. pdf⟩, 2000.
8. FDA Guidance for Industry, INDs for Phase II and III Studies—Chemistry, Manufacturing, and Controls Information, Food and Drug Administration. Available from:http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/ucm070567.pdf〉, 2003.Google Scholar
9. 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. Available from:〈http://www.fda.gov/ohrms/dockets/98fr/990674gd.pdf〉1999.
10. M. Kats Forced degradation studies: regulatory considerations and implementation BioPharm Int., 18 (2005), pp. 1-7

11. Venkataraman S, Manasa M.; Forced degradation studies: Regulatory guidance, characterization of drugs, and their degradation products-a review. Drug Invention Today. 2018 Feb 1;10(2).137-46
12. Adhao VS, Thenge RR. Development and validation of stability indicating high performance liquid chromatography method for determination of baclofen. American Journal of Pharmtech Research, 2017,7(5) 44-56.
13. Adhao VS, Ambhore JP, Thenge RR. Development And Validation of Stability Indicating High Performance Liquid Chromatography Method for Determination of Leflunomide. Asian Journal of Pharmaceutical Analysis. 2023;13(2):93-8.
14. Adhao VS, Ambhore JP; Reverse Phase-Liquid Chromatography Assisted Protocol for Determination of Molnupiravir Medication Used to SARS-CoV-2 Infection: An Investigative Approach; Int. J. Pharm. Sci. Rev. Res., 2024, 84(3), 204-210.
15. Adhao V. S., Chaudhari S.P. & Ambhore J. P.; Advancements and Insights in Forced Degradation Studies of Pharmaceuticals: A Comprehensive Review. World Journal of Pharmacy and Pharmaceutical Sciences. 2024, 13(3) 1084-1091.
16. Adhao, V.S., Chaudhari, S.R. and Ambhore, J.P.: Reverse phase-liquid chromatography assisted protocol for simultaneous determination of lamivudine and tenofovir disoproxil fumarate in combined medication used to control HIV infection: an investigative approach, Futur J Pharm Sci , 2021, 90(7)1-11.
17. Ambhore JP, Adhao VS, Cheke RS, Popat RR, Gandhi SJ. Futuristic review on progress in force degradation studies and stability indicating assay method for some antiviral drugs. GSC Biological and Pharmaceutical Sciences. 2021;16(1):133-49.
18. Adhao VS. RP-HPLC Method Development and Validation for the Simultaneous Estimation of Aceclofenac and Rabeprazole Sodium in the Bulk and Marketed Formulation. Indian Journal of Pharmacy and Pharmacology. 2016;3(3):146-51.
19. Adhao V.S., Chaudhari S.P., Ambhore J.P.; Stability Indicating RP-HPLC Method Development and Validation for Imeglimin HCL in Pharmaceutical Dosage form. Chem. Sci. Int. J.; 2024 Jun.; 33(4):1-10.
20. Ambhore J. P. and Adhao V. S.; Optimization of UPLC Method for Quantification of Molnupiravir: Stationary Phase, Mobile Phase, Organic Modifier, and Flow Rate Considerations. Biomed J Sci & Tech Res; 2024, 57(2), 48982-48997.
21. V. S. Adhao*, J. P. Ambhore, V. G. Akhand, V. M. Shejol; Comprehensive Method Development and Validation of RP-HPLC for Molnupiravir Quantification in Medicinal Dosage Forms; Journal of Xidian University; 2024, 18(8), 1015-102

22. Shinde NG, Bangar BN, Deshmukh SM, Sulake SP, Sherekar DP. Pharmaceutical forced degradation studies with regulatory consideration. Asian Journal of Research in Pharmaceutical Science. 2013;3(4):178-88.
23. Ahuja S, Scypinski S, editors. Handbook of modern pharmaceutical analysis. Academic press; 2001 Jul 26.
24. K.M. Alsante, A. Ando, R. Brown, *et al.* The role of degradant profiling in active pharmaceutical ingredients and drug products; Adv. Drug Deliv. Rev., 59 (1) (2007), pp. 29-37.