International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 85-93 www.ijprajournal.com ISSN: 2456-4494

Impact of Forced Degradation Studies on the Formulation and Stability of Topiroxostat: A Comprehensive Review

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Date of Submission: 05-03-2025 Date of Acceptance: 15-03-2025

ABSTRACT: Topiroxostat, a selective xanthine oxidase inhibitor used in the treatment of gout and hyperuricemia, plays a critical role in regulating purine metabolism by reducing serum urate levels. However, especially when developing formulations, its stability is essential to preserve the therapeutic efficacy. In order understand Topiroxostat degradation routes and ensure its stability in pharmaceutical formulations, forced degradation studies are important. By purposefully simulating extreme conditions, these experiments aid in the identification of degradation products and mechanisms, including oxidation, hydrolysis, photolysis, and thermolysis, that break down the therapeutic ingredient. The influence of forced degradation on Topiroxostat is thoroughly examined in this review, which also outlines the factors that affect its stability, such as temperature, pH, moisture, and light.The study also addresses the regulatory significance of forced degradation study, including FDA, WHO, and ICH guidelines, as well as the significance of creating stability-indicating methods (SIM) to monitor degradation products. The article also describes the Topiroxostat forced degradation settings and the analytical methods (HPLC, LC-MS, and NMR) utilized to detect and isolate degradation products. To guarantee the stability and effectiveness of Topiroxostat in its therapeutic uses, it is essential to understand the degradation mechanisms and optimize formulations considering the implications of these studies

KEYWORDS: degradation, stability, analytical method,topiroxostat

I. INTRODUCTION

Topiroxostat is a selective xanthine oxidase inhibitor used to treat and control gout and hyperuricemia. Purine metabolism is regulated by xanthine oxidase, also known as xanthine oxidoreductase (XOR), and serum urate levels can be effectively decreased by inhibiting the enzyme. 4-(5-pyridin-4-yl-1H-1,2,4-triazol-3-yl) pyridine-2-carbonitrile is the IUPAC name of Topiroxostat and 248.24 g/mol. [1] Topiroxostat is available as a crystalline solid which is soluble in organic solvents such as DMSO and Dimethyl formamide. The solubility with this solvent is approximately 10 and 20 mg/ml, respectively. It is sparingly soluble in aqueous buffer, to increase the solubility of Topiroxostat in aqueous buffer it should be first dissolved in DMF and then diluted with the aqueous buffer of choice.[2]

Forced degradation study are of great importance in the pharmaceutical product development, these studies are used to intentionally designed degrade drug substances and products under more rigorous conditions than standard accelerated conditions. In these studies, the drug substance undergoes various stress conditions to reveal degradation pathways and identifies degradation product [3]

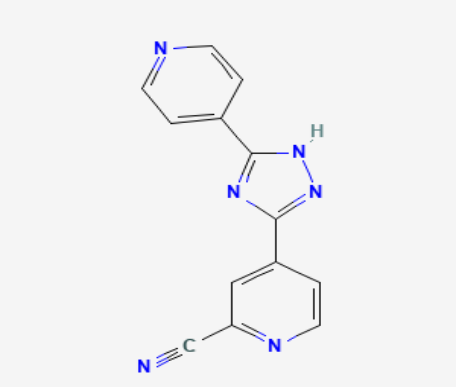

Figure no.1 Chemical Structure of Topiroxostat

I. Role of Forced Degradation Studies in Pharmaceutical Development:

In order to help researchers select compounds and excipients for additional research, to make salt selection or formulation optimization easier, and to provide samples for the development

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar – Apr 2025, pp: 85-93 www.ijprajournal.com ISSN: 2456-4494

of stability-indicating analytical techniques, pharmaceutical companies conduct forced-degradation experiments during pre-formulation. Degradation mechanisms and possible degradation products are discovered using stress testing. The development of manufacturing procedures or the choice of appropriate packaging can then be done using this knowledge. It might also be useful for creating reference materials for degradation products that have been discovered. Stress testing is often repeated when manufacturing processes, product composition, and analytical procedures are improved and attain a more final state, even if pre-formulation work is a part of early-phase drug development [4]

II. Purpose and objective of Forced degradation study:

1. To determine the mechanisms by which pharmaceutical ingredients and products degrade.
2. To separate degradation products connected to drug products from those generated from the non-drug product in a formulation.
3. To determine the inherent stability of a pharmaceutical ingredient within the formulation.
4. To determine the degradation mechanisms of the drug material and drug product, including photolysis, oxidation, hydrolysis, and thermolysis
5. To generate a deterioration profile that is comparable to that of an official stability study conducted in accordance with ICH principles.
6. To identify the drug's molecules' chemical characteristics.
7. To clarify the breakdown products' structure.
8. To deal with issues related to stability to determine a pharmacological substance's natural stability inside the formulation.
9. To create formulations that are more stable. It also aids in figuring out when a specific formulation expires.
10. To provide a degradation profile under ICH conditions that is similar to what would be seen in an official stability study. [5,6]

III. Regulatory Significance:

General guidelines for Good Manufacturing Practices (GMPs) in the industry have been produced by the compendia of numerous countries or regions. The World Health Organization (WHO), the European Medicines Agency (EMA), the Japanese Pharmacopoeia (JP), the Food and Drug Administration (FDA), the International Conference on Harmonization (ICH) has provided stability testing guidelines for new drug substance. A written testing procedure aimed at determining the stability characteristics of a drug component or drug product must be in place, according to 21 CFR part 211 Section 166, which contains the requirements for the US. [7]

ICH Guidelines:

Forced degradation studies are necessary as part of the drug development process, particularly for novel molecular entities like Topiroxostat, according to ICH guidance. By identifying the degradation routes, these investigations help guarantee that the medication satisfies stability requirements and retains its therapeutic efficacy over the course of its shelf life.

Guidelines	Title
Q1A(R2)	Stability testing of new drug substance and products
Q1B	Photostability testing of new drug substances and products
Q2(R1)	Validity of analytical procedures: Text and methodology
Q3A(R2)	Impurities in new drug substances
Q3B(R2)	Impurities in new drug products
M4Q(R1)	The common technical document for the registration of pharmaceuticals for human use

Table no.1 ICH Guidelines for forced degradation study.

Recommendations for conducting forced degradation tests on drug compounds and drug products are included in ICH Q1A, section 2.1.2 (Stress Testing). It is advised to investigate the

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effects of oxidation, photolysis, humidity (75% relative humidity), and temperature (above that for accelerated testing, i.e., >50°C). It is also important to do testing in solution, either as a suspension or a solution, over a broad pH range. Then, a stability-indicating technique is developed using these samples. ICH Q1B outlines recommended methodologies to evaluate the photo stability of medicinal ingredients and therapeutic products.

Sections II (drug substance) and III (drug product) outline requirements for forced degradation. Although they may be higher than those allowed for confirmatory (stability) testing, exposure levels for forced deterioration studies are not specified. The applicant is in charge of designing the actual photo stability experiments, however in cases where light exposure studies are stopped early on—for example, when severe degradation is noticed—scientific reason is needed. Testing for photo stability can be done on a solid or in a suspension or solution.

Guidelines for validating analytical methods are provided by ICH Q2B, and section B 1.2.2 (impurities not accessible) suggests using samples from forced degradation tests to demonstrate specificity. When evaluating whether or not the analytical approach is stability signalling, specificity is a crucial consideration. The quantity of degradation products produced will be underestimated by co-elution of peaks or components that are kept on the column, which could jeopardize quality and raise patient risk. The amount of deterioration needed in forced degradation investigations is not specified in the ICH recommendations. The capacity of the approach to identify and track degradation products during stability testing would not be challenged if too little stress was applied since some degradation pathways might not be seen. [8]

IV. Forced Degradation Conditions for Topiroxostat:

The four main degradation mechanisms are heat, hydrolytic, oxidative, and photolytic degradation. Typical stress tests include the following: choosing appropriate reagents, such as the concentration of acid, base, or oxidizing agent, and adjusting the conditions (e.g., temperature) and duration of exposure to achieve the desired level of degradation. Excessive stressing of a sample may result in the formation of secondary degradants that would not be observed in formal shelf-life stability studies, and under-stressing may not be useful for stress testing.[9]

Hydrolytic degradation:

One of the most common chemical breakdown processes across all pH levels is hydrolysis. Drug and water react during the solvolytic process of hydrolysis to produce breakdown products of various chemical compositions. The majority of medications degrade with water, either as a solvent or as airborne moisture when comes in contact with pharmaceutical dosage forms. A novel medicine can be refluxed in 0.1 N HCl / 0.1 N NaOH to study its hydrolytic breakdown in acidic and alkaline conditions.

Testing might end at this stage if a reasonable level of degradation is seen. However, the medication should be refluxed in an acid/alkali of greater strength and for a longer period of time if no degradation is observed under this situation.

Alternately, if complete breakdown is observed after first treatment condition, a drop in reaction temperature can result in a decrease in acid/alkali strength. In general the main factors influencing a drug's stability that is susceptible to hydrolytic breakdown are pH and temperature.[10]

Oxidative Degradation:

Oxidation can occur in the presence of peroxides or in an oxygen atmosphere. An oxygen-based model is more realistic. Oxidation can be accelerated by using free radical initiators. All of the primary oxidation degradation products shown on real-time stability are typically produced by a free radical initiator and peroxide. Therefore, at every stage of development, conditions involving hydrogen peroxide and/or free radicals are highly advised. Use a suitable solvent to dissolve the API at solution state stress conditions, then add 5–20% of a free radical initiator at atmospheric pressure. The reaction can be carried out using molecular oxygen in a reaction vessel pressured at 50–300 psi to improve the solubility of oxygen in the solution**.** To accelerate degradation, the system is also heated. The choice of free radical initiator affects the temperature. Up to 30% hydrogen peroxide reagent can be utilized for peroxide conditions. Depending on API solubility, the addition of a suitable co-solvent can be required. In Drug Product investigations when hydrogen peroxide is an impurity in an excipient, hydrogen peroxide stress testing may be helpful. Placing the API in appropriate closed containers with an oxygen head space versus an argon or nitrogen control head space allows for a similar investigation of solid-state stress conditions. Moreover, depending on the API's heat sensitivity,

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Volume 10, Issue 2 Mar – Apr 2025, pp: 85-93 www.ijprajournal.com ISSN: 2456-4494

the sample may be heated for a predetermined amount of time or temperature to hasten breakdown. When metal ions are added to API solutions, it can reveal whether the API has a propensity to undergo catalytic oxidation. APIs and formulation excipients frequently contain iron and copper ions. In a Fenton-type reaction, transition metal ions can also decrease peroxide to produce hydroxyl radicals. Furthermore, oxidation reactions can also be impacted by light. A photosensitiser's absorption of light can cause molecular oxygen to react with singlet oxygen species, which are more reactive.[11]

Photolytic degradation:

Samples should be exposed to light that has a spectral distribution of 320–400 nm, an integrated near ultraviolet energy of at least 200-watt hours/square meter, and an overall illumination of at least 1.2 million lux hours in order to allow for direct comparisons between the drug substance and drug product.

Samples can be exposed side by side utilizing a validated chemical actinometric system for the appropriate amount of time when conditions have been tracked with calibrated radiometers, lux meters, or both to confirm that the intended light exposure is generated. Hydroperoxides, hydroxides, and ketones can be created by oxidizing functional groups having labile hydrogens, such as benzylic, carbon, allylic, and tertiary carbons. Photolytic breakdown can result from both oxidative and nonoxidative photolytic processes.[12]

Thermal Degradation:

Generally speaking, a reaction's rate increases as its temperature increases. As a result, the medications are prone to degradation at elevated temperatures. A lot of APIs are susceptible to tropical or high temperatures. For instance, peptides, vitamins, etc. Several processes, including pyrolysis, hydrolysis, decarboxylation, isomerization, rearrangement, and polymerization, are involved in thermal degradation. Using the Arrhenius equation, which states K=Ae-Ea/RT, where k is the specific reaction rate, A is the frequency factor, Ea is the energy of activation, R is the gas constant (1.987 cal/deg mole), and T is the absolute temperature, the effect of temperature on the thermal degradation of a chemical is investigated. Research of thermal degradation is conducted between 40 and 80 degrees Celsius. For one to two months, 70˚C with low and high humidity is the most commonly recognized temperature. Over 80˚C may not result in a predictable degradation pathway. It is assumed that the drug molecule will decompose along the same pathway at all temperatures when high temperatures are used in predicted degradation experiments. It is important to use the extremely high temperatures readily available in a sealed-vessel microwave experiment for predicted degradation studies because this assumption might not apply to all pharmacological compounds.[13]

V. Stability of Topiroxostat depends on many factors which majorly includes:

Temperature: High temperatures increase the reactions of oxidation, reduction, and hydrolysis that result in the decomposition of drugs.

pH: The rate at which most drugs break down is influenced by an acidic or alkaline pH. Drug degradation rises in proportion to the degree of ionization.

Moisture: The deterioration process is catalysed by water.

Light: Impacts drug stability by causing oxidation of components by energy or thermal heat.

Drugs incompatibility: Reactions between components or between components and the container lid may occur when additional components are present in the final pharmaceutical medication product.[14]

Connection Between Stability Data and Forced Degradation Studies

Compared to standard stability testing, a number of stuffs are produced in forced degradation investigations. Because of its poor potential, stability testing makes it challenging to identify the real degradation products. From this angle, studies on forced degradation minimize this issue. The procedure can be shown as a stability indicating process if no degradants were generated, indicating that the drug ingredient is stable under the specified stress conditions. Analyzing forced degradation also aids in finding the ideal storage conditions for certain drugs. More significantly, studies on forced degradation can be used to identify the breakdown mechanism of different medicinal compounds.[15]

Stability Indicating Methods for Topiroxostat:

In the pharmaceutical sector, stability samples are analyzed using the stability-indicating assay method. The need to establish a stability indicating assay method (SIAM) has been

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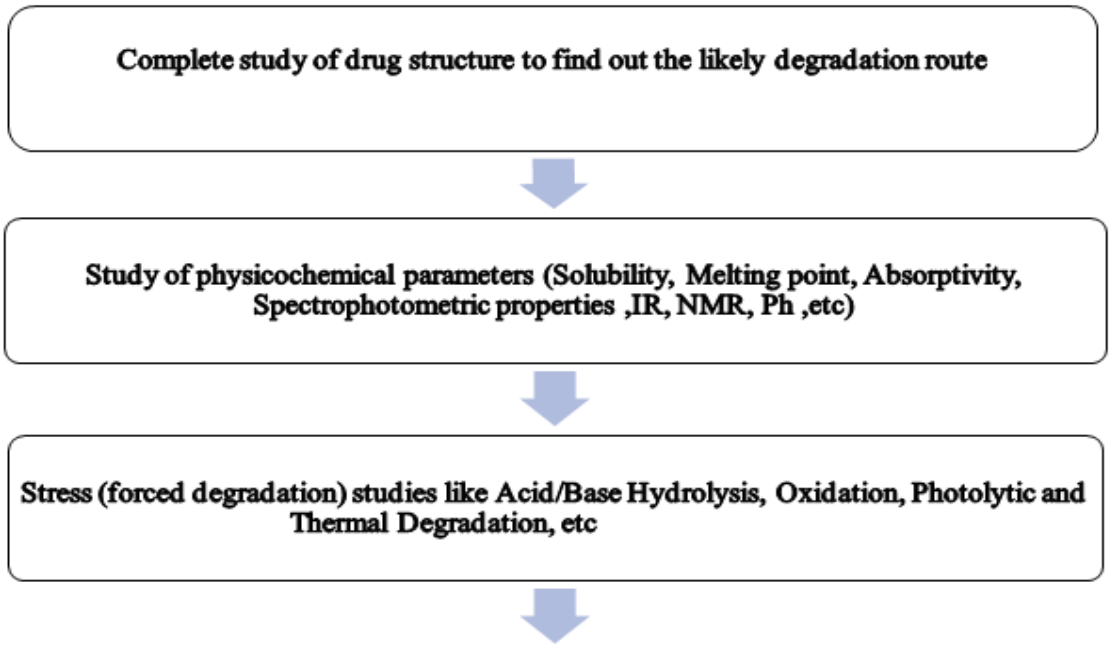
increasingly urgent since the introduction of ICH recommendations. The rules specifically call for action of investigations on forced decomposition in a range of settings, including light, oxidation, dry heat, pH, etc., and the extraction of the medication from the breakdown products. According to the FDA, the stability indicated method is a quantitative approach that monitors how the drug's concentration changes over time. It will decided how much the drug product and present concentrations have decreased. Notably, the degradation investigations reveal variations in the medication molecules' concentrations. During the degradation experiments, it is noted that the drug substance's concentration varies; significantly, no influence from excipients or other degradation products is detected. Thus, the SIM aids in preformulation research and forecasts the drug's storage conditions. [11]

Method Development and Optimization:

Determining the drug's pKa value, log P, solubility, and λmax is the initial step before developing a method. It is standard procedure to develop a reverse phase method for drug separation using HPLC. Common solvents including water, acetonitrile, and methanol are employed as mobile phases in various ratios and combinations. The organic phase, such as methanol or acetonitrile, is selected based on the drug's solubility profile. Usually, prior reports or trial-and-error techniques are used to choose the mobile phase and its proportion. The aqueous and organic phases are kept at a 50:50 ratio at the beginning of the experiment, and the solvent proportions for the mobile phase can be further optimized to provide the best peak resolution.

VI. Stability Indicating Method (SIM)

Buffers can be utilized in some situations to provide peak symmetry and adequate baseline separation. The column temperature is occasionally set between 30 and 40°C to achieve good repeatability of the results. To get good resolution, degradant peaks are pushed in the chromatogram. Peak purity analysis results when degradant peaks occasionally elute alongside or are covered by drug peaks. It is possible to perform direct analysis with HPLCs that have PDA detectors installed.Resolving and analysing the degradants' peaks is made simpler by altering the percentage of the mobile phase.If the degradants peak is seen where the drug peak's area under the curve and its percentage remains unaffected, the established approach is considered uniform.



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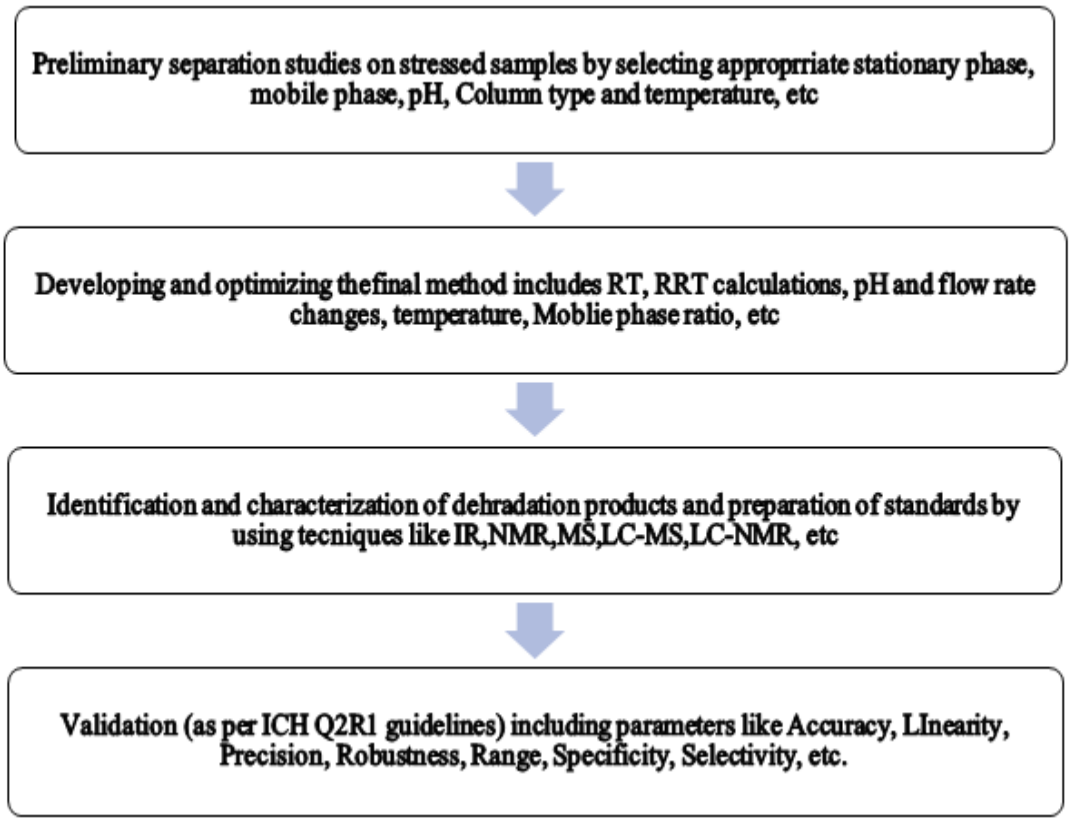

Figure no.2 Steps Involved in development of SIM established approach is considered uniform. These degradants, which coelute with the medicine, are somewhat acceptable as long as they weren't seen in somewhat acceptable as long as they weren't seen in trials on long-term and rapid storage.Additionally, the technique can be improved by altering the parameters, such as the mobile phase flow rate, sample volume injected, column type, and the percentage of mobile phase employed in the analysis. Following the optimization of these variables, the study's methodology will be validated as the ICH guidelines.[15]

VII. Analytical Instruments for Identifying And Separating Degradants:

A.Traditional Methods:

1. TLC, or thin layer chromatography: For many years, it has been demonstrated that preparative thin-layer chromatography (TLC) is highly advantageous. TLC is quick, easy, and reasonably priced; however, it has a poor throughput in terms of the quantity of material that can be extracted for structural analysis. It is often only applied to MS-proposed structures. [16]

2. Solid phase extraction (SPE): This rapid method enriches and simplifies a sample matrix before isolation. Because SPE is so easy to use, it can be used in the post-isolation process to de-salt and extract significant amounts of water from collected semi-preparative chromatographic fractions.

3. Accelerated solvent extraction (ASE): This method uses organic solvents to rapidly extract API and impurities from a solid matrix. One of the limitations was the potential for the extracted compounds to degrade due to the application of high pressures and temperatures.

4. Low-pressure LC (LPLC): Flash chromatography (FC), one of the low-pressure chromatography techniques, is the conventional method of choice when NMR analysis is needed to support the identification of a degradant. FC is a low-priced technique that is suitable for separations requiring only a modest level of resolution and can process milligram-to-gram amounts of material rapidly.

5. Supercritical fluid extraction (SFE): Counter-current chromatography (CCC) and the use of carbon dioxide in structural elucidation processes have found application in both the pharmaceutical

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and natural product industries. CCC is a high-resolution chromatographic method that does not require a solid stationary phase, making it unusually appropriate for unstable compounds.

6. Mass Spectrometry (MS): MS is necessary for all structural elucidation workflows. This approach has several advantages, including high sensitivity, wide dynamic range, information richness, and the capacity to provide structural information "on the fly" and connect directly to LC separations.[17]

7.Nuclear Magnetic Resonance (NMR): NMR spectroscopy is a highly efficient technique for examining medication breakdown products. Combining a molecular formula and additional structural knowledge from MS fragmentation studies with the rich structural data from NMR spectroscopy can significantly improve the process for medication degradation products. In order to do NMR-based structural elucidation of drug degradation products, it is standard practice to separate sufficient material (>1 mg) for NMR analysis. By assembling associated fragments of the molecule using one- and two-dimensional NMR observations, the chemical structure is then established. Due to developments in NMR-probe technology, these tests may now be performed on isolated materials in the microgram range.[18]

8. High-Performance Liquid Chromatography (HPLC): HPLC is commonly used to isolate degradants. These days, most UV HPLC detectors can measure multiple wavelengths simultaneously, and some can even create ratio graphs at two separate wavelengths. This approach has also been endorsed for peak purity testing during the development of SIMs.[19]

B.HyphenatedTechniques

1. GC-MS

GC-MS was the first hyphenated approach and remains crucial for verifying the existence of organic volatile IMPs and residual solvents in samples (45–48).

However, the properties of analytes required for GC-MS, such as volatility and thermal stability, are unknown in advance for the vast majority of organic contaminants and degradants. The application of this technology in the characterization of pollutants that are pertinent to the pharmaceutical business is therefore only seldom documented in the literature.[20]

2. LC-MS

LC-MS and its variants are the most often utilized hyphenated procedures for identifying impurities because they can yield nearly definitive structural data even when employed alone.[21]

3. Capillary Electrophoresis-Mass Spectrometry (CE-MS):

Capillary electrophoresis (CE) and capillary electrochromatography (CEC) are important orthogonal techniques for the separation of contaminants and degradation products. CEC is a hybrid method that combines the high efficiency of CE with the mobile and stationary phase selectivity of LC. Systems where CE and CEC are hyphenated with MS are progressively becoming more important for the characterization of degradants, even though they are still in the exploratory stage and restricted to the development of separation techniques, the study of the utility of various CE modes, and the evaluation of the benefit of various types of mass spectrometers for the purpose.[22]

II. CONCLUSION:

Forced degradation studies are an essential part of the pharmaceutical development process, particularly for drug such as Topiroxostat. In order to guarantee the stability and effectiveness of the medication throughout its shelf life, these studies are essential in identifying degradation processes and products. These studies help in defining the drug's chemical stability and offer insights into formulation optimization across a variety of stress situations, including oxidation, hydrolysis, thermal, and photolytic destruction.

For Topiroxostat, forced degradation aids in understanding its stability under different situations and helps predict possible degradation routes. It also facilitates the development of more stable formulations. Guidelines from organizations like the FDA, ICH, and WHO that specify medication stability testing protocols highlight the regulatory importance of these investigations. In addition to ensuring that Topiroxostat continues to be effective for the duration of its shelf life, the application of stability-indicating techniques helps in the development of reliable analytical methods for tracking degradation.

Through involve of forced degradation studies in the drug development process, drug stability fears are reduced and patients receive a more dependable product. Pharmaceutical businesses may efficiently evaluate degradation products and optimize formulations to satisfy regulatory criteria and improve drug safety and

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Volume 10, Issue 2 Mar – Apr 2025, pp: 85-93 www.ijprajournal.com ISSN: 2456-4494

performance by employing modern analytical techniques such as HPLC, MS, and NMR.

REFERENCES:

[1]. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 136232987, Topiroxostat-d4. Retrieved February 5, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Topiroxostat-d4.

[2]. Product information CYMAN CHEMICL Cayman Cemical. Product information, Topiroxostat, Item No 21267. Retrieved 16 May 2024 from https://cdn.caymanchem.com/cdn/insert/21267

[3]. Tayde A. Forced Degradation Studies: Analytical Methodologies, Applications, and Regulatory Insights–A Systematic Review. Journal of Drug Delivery and Biotherapeutics. 2024 Oct 25;1(02):13-23.

[4]. Roge AB, Tarte PS, Kumare MM, Shendarkar GR, Vadvalkar SM. Forced degradation study: an important tool in drug development. Asian Journal of Pharmaceutical Research. 2013;3(4):198-201.

[5]. Iram F, Iram H, Iqbal AZ, Husain A. Forced degradation studies. Journal of Analytical & Pharmaceutical Research. 2016 Dec 14;3(6):73.

[6]. Sonawane JK, Chavan SM, Narkar IP, Jale SC, Tendulkar NV, Jadhav V, Jain A. A review of stability indicating methods and forced degradation studies. Int. J. Res. Publ. Rev. 2023;4:4703-15.

[7]. Somase K, Rishipathak D. A review on forced degradation studies, stability indicating method and stability profile of few antiviral drugs. Journal of Pharmaceutical Negative Results. 2022 Oct 3:1315-31.

[8]. Patel NN, Kothari CS. Critical review: Significance of Force degradation study with respect to current Pharmaceutical Scenario. Asian Journal of Research in Chemistry. 2013;6(3):286-96.

[9]. 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.

[10]. Singh R, Rehman ZU. Current trends in forced degradation study for pharmaceutical product development. Journal of Pharmaceutical Education and Research. 2012 Jun 1;3(1):54.

[11]. Sonawane JK, Chavan SM, Narkar IP, Jale SC, Tendulkar NV, Jadhav V, Jain A. A review of stability indicating methods and forced degradation studies. Int. J. Res. Publ. Rev. 2023;4:4703-15.

[12]. Quadri SS, Sonwane LV, Poul BN, Kamshette SN. Review on stability indicating assay methods (SIAMs). PharmaTutor. 2014 Aug 1;2(8):16-31.

[13]. 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).

[14]. Ravisankar P, Swathi V, Srinivasa Babu P, Shaheem Sultana Md GS. 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.

[15]. Simon R, Hicks H. Forced degradation to develop stability-Indicating methods. Pharmaceutical Outsourcing. 2012.

[16]. Blessy MR, Patel RD, Prajapati PN, Agrawal YK. Development of forced degradation and stability indicating studies of drugs—A review. Journal of pharmaceutical analysis. 2014 Jun 1;4(3):159-65.

[17]. Vyas AJ, Jadav CD, Patel AI, Patel AB, Shah SR, Sheth D, Dholakia S. Review on Stability Indicating Assay Method or Forced Degradation Study: Strategy and Regulatory Consideration. Asian Journal of Pharmaceutical Analysis. 2023;13(2):131-9.

[18]. Malet-Martino M, Holzgrabe U. NMR techniques in biomedical and pharmaceutical analysis. Journal of pharmaceutical and biomedical analysis. 2011 Apr 28;55(1):1-5.

[19]. Malviya R, Bansal V, Pal OP, Sharma PK. High performance liquid chromatography: A short review. Journal of global pharma technology. 2010 Jun 9;2(5):22-6.

[20]. Bochkareva NL, Glazkov IN, Revelsky IA. Combination of supercritical fluid extraction and gas chromatography-mass

spectrometry: determination of impurities extracted from tablet preparations of the benzodiazepine series. Journal of Analytical Chemistry. 2006 Nov;61:1082-9.

[21]. Trabelsi H, Hassen IE, Bouabdallah S, Bouzouita K, Safta F. Stability indicating LC method for the determination of pipamperone. Journal of pharmaceutical and biomedical analysis. 2005 Oct 4;39(5):914-9.

[22]. Aleksenko SS, Gareil P, Timerbaev AR. Analysis of degradation products of chemical warfare agents using capillary electrophoresis. Analyst. 2011;136(20):4103-18.