Force Degradation for Pharmaceuticals: A Review

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***Abstract*- Studies on forced degradation involve the breakdown of novel pharmacological substances and drug products under conditions that are more demanding than accelerated conditions. These investigations demonstrate the molecule's chemical stability, which makes it easier to create stable formulations with proper storage conditions. According to ICH recommendations, some factors might cause degradation, such as light, oxidation, dry heat, acidic or basic environments, hydrolysis, etc. The forced deterioration experiments are best illustrated by ICH Q1A, QIB, and Q2B. The strategic philosophies and developments in forced degradation studies are surveyed in this article.**

Keywords: **Degradation, Stability, Safety, ICH guidelines.**

1. INTRODUCTION

Forced degradation studies are also known as stress testing, stress studies, stress decomposition studies, forced decomposition studies. Forced degradation is a procedure where drug products and drug compounds are broken down under settings that are harsher than accelerated conditions. This process creates degradation products that may be examined to find out how stable a molecule is. According to the ICH guidelines, stress testing is meant to detect potential degradation products, which aids in determining the molecule's intrinsic stability, developing degradation routes, and validating the employed stability indicating methodologies [1].

In the pharmaceutical industry, forced degradation studies offer a method for analyzing the stability of medication samples. The chemical stability of the molecule has an impact on the safety and effectiveness of drug products. Information on molecule stability offers the information needed to choose the best formulation, container, storage environment, and shelf life. These data are crucial for the regulatory documentation and also play a big part in it. It is required to carry out stability studies on novel therapeutic compounds prior to filling out the registration dossier [2, 3]. Before submitting a registration dossier, stability tests of novel drug moieties are now required. Long term (12 months) and expedited (6 months) stability investigations are both included in the stability studies. However, intermediate studies (6 months) can be carried out under more hospitable circumstances than those employed in rapid studies. Therefore, it would take considerably longer to analyze degradation products using methods like separation, identification, and quantification. Forced deterioration studies, as opposed to stability studies, assist in creating in a considerably shorter period of time, typically a few weeks. The samples produced by forced deterioration can be utilized to create a stability indication technique that will later be used to analyze materials produced by accelerated and long-term stability tests. This evaluation offers a suggestion regarding the forced degradation's practical performance and its use in the creation of stability indicating methods.

1.1 Objective of forced degradation studies

The following goals are pursued through forced deterioration studies:

1. To identify the processes by which drug compounds and drug products degrade.
2. To distinguish degradation products generated from non-drug compounds in a formulation from those connected to drug products.
3. To clarify the degradation products' structure.
4. To ascertain a pharmacological substance's inherent stability in formulation.
5. To identify the drug substance and drug product's degradation mechanisms, such as hydrolysis, oxidation, thermolysis, or photolysis.
6. To demonstrate the stability of a proposed method.
7. To comprehend the chemistry of medication compounds.
8. To produce formulations those are more stable.
9. To create a degradation profile that resembles what would be seen in an official stability study conducted under ICH guidelines.
10. To address issues with stability.

1.2 Outcomes of forced degradation studies

The following details are provided via forced degradation investigations [3,4,5] .

a. Identifying potential degraders.
b. Identifying degradation pathways.
c. Identifying the drug's intrinsic stability, and
d. Identifying verified stability-indicating analytical techniques.

2. REGULATORY GUIDELINES

Forced degradation researches were advised by many international standards. Sometimes, ICH guidelines only address the portion of clinical development that occurs during the marketing applications for new products. The following ICH recommendations [2,5,8] apply to forced deterioration studies:

a. Stability testing of new drug substances and products is covered by ICH Q1A,
b. Photo stability testing is covered by ICH Q1B, and
c. Methodology validation of analytical procedures is covered by ICH Q2B.
d. ICH Q3A (R2)

a. ICH Q1A (Stress testing): Recommendations for conducting studies on drug compounds and drug products under forced deterioration. The advice is to carefully examine the findings of oxidation, photolysis, humidity, and temperature (above that for accelerated testing, i.e., >50 C). When testing a solution or suspension, a wide pH range should be taken into consideration. In the end, these samples' stability-indicating methodology [3, 9] was created.

b. ICH Q1B: Methods for evaluating the photo stability of drug ingredients and medicinal products. Sections II and III, respectively, detail the forced degradation conditions for drug material and drug product. Exposure levels in investigations of forced deterioration are not specified. Testing for photo stability is possible in solid, solution, or suspension forms. The development of a stability indicating method then uses these samples. It may not actually be experiential for some of the degradation products to occur during stability testing, in which case further research is not necessary [2,10].

c. ICH Q2B: provides direction for confirming the analytical methods. Section B 1.2.2 (impurities not accessible) suggests using samples from forced degradation trials to demonstrate specificity. 'Specificity' is an important consideration when determining whether an analytical procedure indicates stability [8].

d. ICH Q3A (R2): It is necessary to identify each contaminant with regard to chemistry and safety concerns. Chemical possibilities include a succinct description of analytical techniques, report preparation, cataloguing of impurities in the specification, and classification and identification of impurities. The safety possibilities provide detailed instructions for classifying contaminants that were absent or present in very small quantities in a batch of a new medicinal ingredient [9–11].

3. WHEN TO PERFORM FORCED DEGRADATION STUDIES?

Knowing when to conduct forced degradation experiments is crucial for the creation of new medication substances and new medicinal products. Stress testing should be carried out in Phase III of the regulatory submission procedure, according to FDA guidance. To ascertain the stability of the drug material, stress experiments should be carried out in various pH solutions, with oxygen, light, and at elevated temperatures and humidity conditions. These stress analyses are carried out on a single batch. An yearly report should be submitted with a summary of the findings [12]. To give yourself enough time to identify degradation products, elucidate the structure of the drug molecule, and perfect the stress conditions, stress testing should be initiated early in the preclinical phase or phase I of clinical trials. Early stress studies also provide pertinent advice on how to enhance the manufacturing process and choose the best stability-indicating analytical techniques [13, 14].

3.1 Selection of experimental condition

There are many examples of experimental conditions for forced degradation studies in the literature, and the structural diversity of drug molecules prevents the identification of a universal set of parameters for a forced degradation study. Utilizing a set of typical circumstances makes sense for an early-phase molecule because the intrinsic stability may not be well understood. The settings can be changed to account for the molecule's instability if early stability data are available and indicate that it is labile under a certain circumstance (for example, a high pH). Whenever a new stability-indicating approach is necessary during development, a set of conditions can be used again. The prior work thus defines the forced degrading conditions for molecules in the subsequent phases. A consistent approach is maintained by repeatedly processing the same forced degradation situations during the course of development. Table 1 lists some of the most common conditions for studies on forced deterioration.

Table 1 Conditions mostly used for forced degradation studies

Degradation type	Experimental conditions	Storage conditions	Sampling time(days)
Hydrolysis	Control API (no acid or base)	40˚C, 60˚C	1,3,5
	0.1M HCL	40˚C, 60˚C	1,3,5
	0.1M NaOH	40˚C, 60˚C	1,3,5
	Acid control (no API)	40˚C, 60˚C	1,3,5
	Base control (no API)	40˚C, 60˚C	1,3,5
	pH: 2,4,6,8		1,3,5
Oxidation	3% H2O2	25˚C, 60˚C	1,3,5
	Peroxide control	25˚C, 60˚C	1,3,5
	Azobisisobutyronitrile(AIBN)	25˚C, 60˚C	1,3,5
	AIBN control	25˚C, 60˚C	1,3,5
Photolytic	Light 1 × ICH	NA	1,3,5
	Light 3 × ICH	NA	1,3,5
	Light 3 × ICH	NA	1,3,5
Thermal	Heat chamber	60˚C	1,3,5
	Heat chamber	60˚C /75% RH	1,3,5
	Heat chamber	60˚C	1,3,5
	Heat chamber	60˚C /75% RH	1,3,5

3.2 Various degradation conditions

3.2.1 Hydrolytic conditions: Over a broad pH range, hydrolysis is one of the most prevalent chemical processes for degradation. In the chemical process of hydrolysis, a chemical substance is broken down by interaction with water. Ionizable functional groups included in the molecule are catalyzed during a hydrolytic research in acidic and basic conditions. Acid or base stress testing entails

exposing a pharmacological material to acidic or basic conditions in order to force degradation that produces primary degradants in a desired range. The stability of the drug material determines the kind and quantities of the acid or base. As acceptable reagents for hydrolysis, sodium hydroxide or potassium hydroxide (0.1-1M) is indicated for base hydrolysis and hydrochloric acid or sulfuric acids (0.1-1 M) for acid hydrolysis [15, 16]. Co-solvents can be employed to dissolve the minimum HCl or NaOH if the compounds for the stress test are not easily dissolved in water. The structure of the drug substance is used to guide the choice of co-solvent. Normal stress testing trials begin at room temperature, and if no degradation occurs, higher temperature (50–70 °C) is next applied. A maximum of seven days should be allowed for stress testing. To stop further degradation, the deteriorated sample is then neutralized with the appropriate acid, base, or buffer.

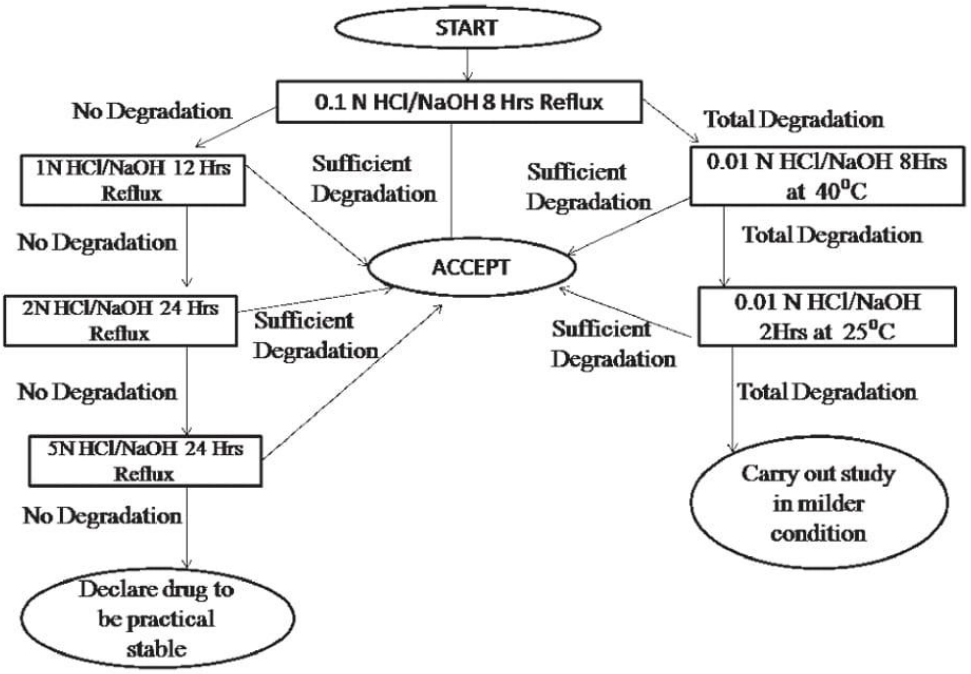

Figure 1: Flow chart for performing hydrolytic degradation [30]

3.2.2 Thermal conditions: Thermal deterioration should be tested under more demanding settings than those suggested by ICH Q1A accelerated testing (for example, dry heat and wet heat). Samples of dry and wet heat should be applied to solid-state drug ingredients and drug products. Drug items in liquid form should be exposed to dry heat. Studies may be carried out at higher temperatures for a shorter time. The Arrhenius equation can be used to study how temperature affects a substance's ability to withstand heat [21].Where k is the specific reaction rate, A the frequency factor, Ea the activation energy, R the gas constant (1.987 cal/deg mol), and T the absolute temperature. At 40 to 80 C, thermal degradation studies are conducted.

3.2.3 Oxidative conditions: The substance hydrogen peroxide is frequently employed for oxidative forced degradation. In addition to these, other radical initiators include metal ions, oxygen, and azobis-isobutyro-nitrile (AIBN). The structure of the drug will enable the choice of oxidising agent concentration and state. When a drug ingredient oxidises, an electron transfer mechanism takes place [17].

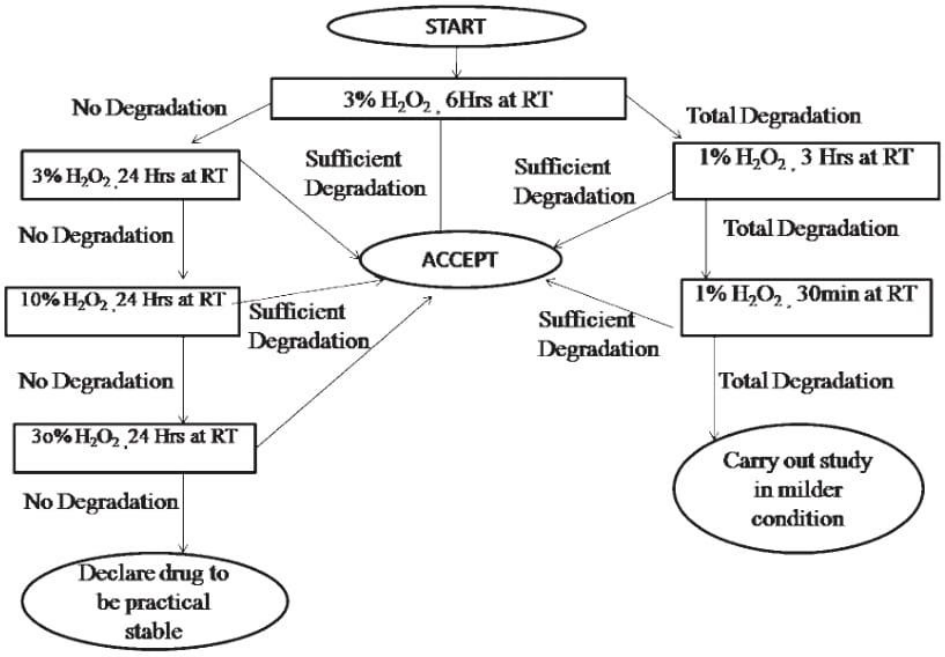

Figure 2: Flow chart for performing oxidative degradation [30]

3.2.4 Photolytic conditions: To show that a light exposure does not cause an unacceptable alteration, the photo stability testing of pharmacological compounds must be assessed. The principal degradants of a pharmacological substance are produced by photo stability tests when exposed to UV or fluorescent light. In ICH guidelines, several suggested circumstances for photo stability testing are listed [18]. Drug material and solid/liquid drug product samples need to be subjected to 200 W h/m2 and 1.2 million lx per hour of light, respectively. The most widely accepted wavelength of light to cause photolytic deterioration is between 300 and 800 nm [19, 20]. The suggested maximum lighting is 6 million lx h. By using a free radical pathway, light stress conditions can cause photo oxidation. Drug photosensitivity is likely to be introduced by functional groups including carbonyls, nitro aromatics, N-oxide, alkenes, aryl chlorides, weak C-H and O-H bonds, sulphides, and polyenes.

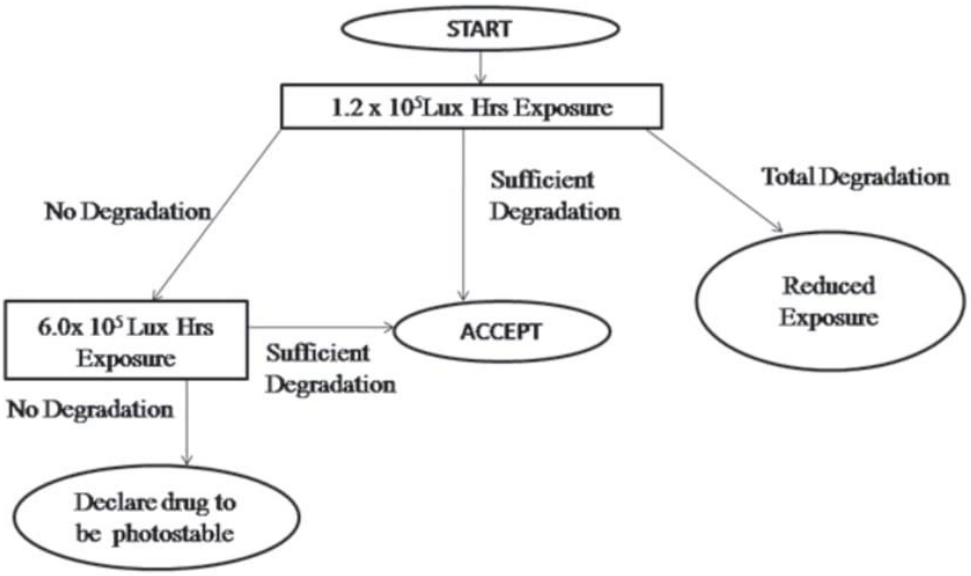

Figure 3: Flow chart for performing photolytic degradation [30]

3.2.5 Humidity: The main determinant of the potential degradants in the final product and the active medicinal ingredient is humidity. The normal recommendation for the establishment of forced deterioration samples is 90% humidity for a week.

4. SELECTION OF SAMPLES

To get the sample with the requisite deterioration, the strength and duration of the stress conditions need to be determined by experimentation .Subjects the Placebo (combination of excipients) in accordance with the manufacturing formula to all the aforementioned stress conditions simultaneously. For placebo formulations including one medication component each in multi-drug products, forced degradation shall be applied. As directed by the test method, prepare test solutions using the unstressed sample, the placebo, and the stressed samples. Inject the solutions into the HPLC system with the diode array detector. Calculate

the percentage deterioration and percent net degradation in accordance with the acceptance criteria after recording the chromatograms. According to acceptance criteria, % ne degradation may be challenging to attain in the case of stable compounds. Therefore, the study can be concluded based on the trials, and a summary of the experiments must be recorded. Show how the analyte is effectively separated from the degradation product and, if necessary, from peaks caused by components of the placebo mixture. Make sure the analyte peak response in the test solution is 1 AU (absorbance unit) or less. If the amount is higher, repeat the analysis after dilution of the test solution.

5. CHARACTERIZATION BY ANALYTICAL TECHNIQUES

The identification and characterization of forced degradation products can be done using a variety of techniques. Reverse-phase high-performance liquid chromatography (HPLC) is the most popular method of analysis for a stability indicating assay [22]. Due to its compatibility with both aqueous and organic solutions, high precision, sensitivity, and capacity to identify polar molecules, RP-HPLC was chosen. Additionally, a well-known approach is developed by choosing the proper column type, column temperature, and modifying the pH of the mobile phase [23, 24]. [Gradient elution was used to produce early elution of highly polar molecules and retention of non-polar chemicals. Gradient elution can also be used to elute samples that have undergone various environmental stresses. The pharmacological substances should be compatible with the solvents and mobile phase [25]. Stressed samples that are acidic or basic should be neutralized before analysis. Depending on the analytical procedure being utilized, samples should be diluted. Blank spaces shouldn't be used in the calculation. Based on stability data, ICH standards for product identification and characterization must be followed [8, 25]. The identification and characterization of the degradation products can be done using conventional techniques (like column chromatography) or hyphenated techniques (like LC MS, LCNMR). The development of the entire drug molecule breakdown pathway depends heavily on LCMSMS. The drug substance's fragments will make it easier for the degradation pathway to grow [26]. The mass numbers of impurities and degradants are confirmed by appropriate LC-MS settings, and these results are used to further determine the mass of major degradants that are discovered to be generating at a rate more than 1.0% during stress studies. The principal degradants' structures are better understood thanks to LCMS. When compounds with similar molecular weights display similar UV profiles, efforts must be taken to change the chromatographic settings to achieve the required separation. An ideal wavelength should be used to identify and quantify all probable contaminants and degradation products. The created method needs to be approved in accordance with ICH rules [27–29].

CONCLUSION

In order to refine analytical methods, better understand the stability of active pharmaceutical ingredients (API) and drug products (DP), and learn more about the pathways and end products of degradation, forced degradation studies are used. The importance of pharmaceutical impurity profiling is rising as the public and the media pay more and more attention to drug safety. The technique-oriented and chemistry-guided approaches to pharmaceutical DRI profiling will both be improved in the coming years. . Significant advancements in analytical methods will speed up DRI profiling and significantly lower the danger of "missing" the crucial DRIs as technology develops at an accelerated rate. Pharmaceutical development and impurity profiling are two areas where multi-dimensional techniques, such as coupled analytical separator with numerous detectors, are likely to play a major role. Faster technology for structural elucidation, better computational tools, and enhanced processes for stress testing and mechanistic studies will all lead to advancements in chemistry-guided techniques.

ACKNOWLEDGMENTS:

The author expresses my gratitude to the Principal, Government College of pharmacy, Karad for providing experimental facilities. This work was financially supported by the All India council for technical Education, New Delhi.

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