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REVIEW ARTICLE

Forced Degradation Study: An Important Tool in Drug Development

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ABSTRACT:
Forced degradation studies are used to facilitate the development of analytical methodology, to gain a better understanding of active pharmaceutical ingredient (API) and drug product (DP) stability, and to provide information about degradation pathways and degradation products. The objective of the review article is to furnish comprehensive portrayal of the forced degradation studies as per the regulatory guidelines that are associated with various regulatory agencies. This article recapitulates the collective views of industry practices on the topic of forced degradation studies. This article reiterates a practical interpretation and summary of the available guidance and some suggestions for best practices for conducting forced degradation studies.

KEYWORDS: Active pharmaceutical ingredient (API), Drug product (DP), Forced Degradation, ICH, FDA guidance, Validation, Method Development

INTRODUCTION:
All pharmaceutical substances un-avoidably contain impurities and the role of ethical pharmaceutical industry is to define an impurity profile that is acceptable for the intended use of a given drug, without compromising its therapeutic safety and efficacy. The stability of a drug product or a drug substance is a critical parameter in which may affect purity, potency and safety.[1,2] Changes in drug stability can risk patient safety by formation of a toxic degradation product(s) or deliver a lower dose than expected. Therefore it is essential to know the purity profile and behavior of a drug substance under various environmental conditions which could be possible by stability testing.[1,2]

Stress testing is defined as the stability testing of drug substances and drug products undertaken to elucidate intrinsic stability attributes. Stress testing is performed by exposing drug substances and drug products to extreme conditions, such as pH, photolysis, oxidation and temperature, over a very short time period. It also referred to as forced degradation studies.[3,4]

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Pharmaceutical companies perform forced-degradation studies during preformulation to help select compounds and excipients for further development, to facilitate salt selection or formulation optimization, and to produce samples for developing stability-indicating analytical methods. Stress testing provides information about degradation mechanisms and potential degradation products. This information then can be used to develop manufacturing processes or to select proper packaging. It may also help in preparing reference material of identified degradation products. Although preformulation work is part of early-phase drug development, stress testing often is repeated when manufacturing processes, product composition, and analytical procedures are refined and reach a more final state.[5]

Forced degradation studies are carried out for the following reasons: [6]

- To develop and validate a stability indicating method
- To determine degradation pathways of drug substances and drug products (e.g., during development phase)
- To identify impurities related to drug substances or excipients
- To understand the drug molecule chemistry
- To generate more stable formulations

- To generate a degradation profile that mimics what would be observed in a formal stability study under ICH conditions
- To solve stability-related problems (e.g., mass balance)

Overview of Regulatory Guidance

Forced degradation studies are described in various international guidelines. The International Committee for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published a set of guidelines which have been discussed, agreed upon and adopted by the American, European and Japanese regulatory authorities. In the majority of cases, the ICH guidelines only apply to the marketing applications for new products, i.e., they do not apply during clinical development. However, since the conditions used for forced degradation are only defined in general terms, it is possible to apply them for developing stability indicating methods during clinical development. The same forced degradation conditions can then be applied to the drug substance during development and commercialization. The ICH guidelines that are applicable to forced degradation studies are:

- ICH Q1A – Stability Testing of New Drug Substances and Products [3]
- ICH Q1B – Photostability Testing of New Drug Substances and Products[4]
- ICH Q2B – Validation of Analytical Procedures: Methodology [7]

In ICH Q1A, section 2.1.2 (Stress Testing), there are recommended conditions for performing forced degradation studies on drug substances and drug products. The recommendations are to examine the effects of temperature (above that for accelerated testing, i.e., >50°C), humidity (≥75% relative humidity), oxidation and photolysis. Testing in solution should also be performed across a wide pH range either as a solution or suspension. These samples are then used to develop a stability-indicating method.

ICH Q1B gives recommended approaches to assessing the photostability of drug substances and drug products. Forced degradation conditions are specified in Section II (drug substance) and Section III (drug product). Exposure levels for forced degradation studies are not defined, although they can be greater than that specified for confirmatory (stability) testing. The actual design of photostability studies is left to the applicant; however, scientific justification is required where light exposure studies are terminated after a short time, e.g., where excessive degradation is observed. Photostability testing can be performed on the solid or in solution/suspension. These samples are then used to develop a stability indicating method.

ICH Q2B gives guidance on how to validate analytical methodology and in section B 1.2.2 (impurities not available) there is a recommendation to use samples from forced degradation studies to prove specificity. Specificity is a key factor in determining whether or not the analytical method is stability indicating. Co-elution of peaks or components being retained on the column will underestimate the amount of degradation products formed and could compromise quality and increase risk to the patient.

Timing of stress testing studies: [8]

The majority of companies perform studies on the drug substance and the drug product in the preclinical stage. The practice of repeating stress testing studies varies by stage of development. Studies are repeated on the drug substance between the preclinical and registration stages, and studies are repeated on the drug product between Phase I and registration as the final commercial formulation is developed.

Requirements[9,10]

IND stage:

The reporting of forced degradation study conditions or results is not required in Phase 1 or 2 INDs. However, preliminary studies are encouraged to facilitate the development of stability indicating methodology. Studies can be conducted on the API and developmental formulations to examine for degradation by thermolysis, hydrolysis, oxidation, and photolysis to evaluate the potential chemical behavior of the active. A draft guidance document suggests that results of one-time forced degradation studies should be included in Phase 3 INDs.

NDA stage:

Completed studies of the degradation of the API and DP are required at the NDA stage, including isolation and/or characterization of significant degradation products and a full written account of the degradation studies performed.

Selection of Stress Conditions:

In designing forced degradation studies, it must be remembered that more strenuous conditions than those used for accelerated studies (25°C/60% RH or 40°C/75% RH) should be used. A minimal list of stress factors suggested for forced degradation studies must include acid and base hydrolysis, thermal degradation, photolysis, and oxidation and may include freeze-thaw cycles and shear. However, some scientists have found it practical to begin at extreme conditions (80°C or even higher, 0.5N NaOH, 0.5N HCl, 3% H2O2) and testing at shorter (2, 5, 8, and 24 hrs, etc) multiple time points, thus allowing for a rough evaluation of rates of degradation.9 Testing at early time points may permit distinction between primary degradant and their secondary degradation products. This strategy allows for better degradation pathway determination. It must be noted that a forced degradation study is a “living process” and should be done along the developmental time line as long as changes in the stability-indicating methods, manufacturing processes, or formulation changes are ongoing. Forced degradation is only considered complete after the manufacturing process is finalized, formulations

established, and test procedures developed and qualified. The following conditions by no means exhaustive and should be adjusted by the researcher as needed to generate ~10% degradation of the API. The nature (inherent stability/instability) of the particular drug substance will determine in which direction to adjust the stress conditions.[11]

Acid and Base Hydrolysis:[12]
The hydrolytic degradation of a new drug in acidic and alkaline conditions can be studied by refluxing the drug in 0.1 N HCl/NaOH for 8 h. If reasonable degradation is seen, testing can be stopped at this point. However, in case no degradation is seen under these conditions, the drug should be refluxed in acid/alkali of higher strengths and for longer duration. Alternatively, if total degradation is seen after subjecting the drug to initial conditions, acid/alkali strength can be decreased along with decrease in the reaction temperature. In a similar manner, degradation under neutral conditions can be started by refluxing the drug in water for 12 h. Reflux time should be increased if no degradation is seen. If the drug is found to degrade completely, both time and temperature of study can be decreased.

Oxidative degradation:
Forced degradation studies designed to test the susceptibility of compounds to oxidative degradation. To test for oxidation, it is suggested to use hydrogen peroxide in the concentration range of 3–30%. [12] In some drugs extensive degradation is seen when exposed to 3% of hydrogen peroxide for very shorter time period at room temperature. In other cases exposure to high concentration of hydrogen peroxide, even under extreme condition does not cause any significant degradation. The behavior is on expected lines, as some drugs are in fact oxidisable, while there are others that are not. The latter are not expected to show any change even in the presence of high dose of oxidizing agent. [13]

Photolytic Degradation:
The photolytic studies should be carried out by exposure to light, using either a combination of cool white and ultraviolet fluorescent lamps, or one among the xenon and metal halide lamps. Exposure energy should be minimum of 1.2 million lux h fluorescent light and 200W h/m2 UV and if decomposition is not seen, the intensity should be increased by five times. In case still no decomposition takes place, the drug can be declared photostable. [12]

Thermal Degradation:
Thermal–humidity stress testing: forced degradation studies designed to test the stability of compounds by exposing them to different thermal and humidity conditions. Most companies perform thermal–humidity stress testing studies in both open and closed containers. Most companies typically test at a range of 51–70°C. If the drug substance does not degrade easily, some of companies stress solid-state samples at ≥ 90 ^{0}C, and few companies stress samples at 71–90°C [5]

Experimental Procedure: [12]
A minimum of four samples should be generated for every stress condition, viz. the blank solution stored under normal conditions, the blank subjected to stress in the same manner as the drug solution, zero time sample containing the drug which is stored under normal conditions and the drug solution subjected to stress treatment. The comparison of the results of these provides real assessment of the changes. Furthermore, it is advised to withdraw samples at different time periods for each reaction condition. By doing so, one can get a clear idea on the number of products formed, their relative strengths and whether they are stable or unstable, resulting further in newer products. This information is essential in establishment of SIAMs.

The studies should be initiated at a concentration of 1 mg/ml. If solubility is a limitation, varying amounts of methanol may be used to get a clear solution or even the testing can be done on a suspension. By using drug concentration of 1 mg/ml, it is usually possible to get even minor decomposition products in the range of detection. If several degradation products are formed in different conditions, the establishment of SIAM may involve a lot of development work. For this, repeat injections of reaction solutions might be required. Therefore, the volume of samples subjected to stress studies should be in sufficient quantity and also enough sample volume should be drawn at each period. The withdrawn samples can be stored in cold cabinets to stop further reaction. The aliquots might be diluted or neutralized before injecting into HPLC. Most companies attempt to induce at least 5–20% degradation of the drug substance before considering stress testing to be complete. The primary methods used to analyze stress testing studies are liquid chromatography (LC)–diode array (65%) and LC–UV (30%).

CONCLUSION:

Forced degradation studies of new drug substances and drug products are important to help develop and demonstrate specificity of stability-indicating methods and to determine the degradation pathways and degradation products of the active ingredients. Although stress testing has played a critical role in the drug development process, The ICH not provided any formal guidance. As a success to degradation study absolutely relies on skillfulness on researcher, It is indispensable to understand the precise objective of forced degradation study.

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