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REVIEW PAPER

Development of forced degradation and stability indicating studies of drugs—A review

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Abstract Forced degradation is a degradation of new drug substance and drug product at conditions more severe than accelerated conditions. It is required to demonstrate specificity of stability indicating methods and also provides an insight into degradation pathways and degradation products of the drug substance and helps in elucidation of the structure of the degradation products. Forced degradation studies show the chemical behavior 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. Thus, this review discusses the current trends in performance of forced degradation studies by providing a strategy for conducting studies on degradation mechanisms and also describes the analytical methods helpful for development of stability indicating method.

1. Introduction

Chemical stability of pharmaceutical molecules is a matter of great concern as it affects the safety and efficacy of the drug product. The FDA and ICH guidances state the requirement of stability testing data to understand how the quality of a drug substance and drug product changes with time under the influence of various environmental factors. Knowledge of the stability of molecule helps in selecting proper formulation and package as well as providing proper storage conditions and shelf life, which is essential for regulatory documentation. Forced degradation is a process that involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generates degradation products that can be studied to determine the stability of the molecule. The ICH guideline states that stress testing is intended to identify the likely degradation products which further helps in determination of the intrinsic stability of the molecule and establishing degradation pathways, and to validate the stability indicating procedures used [1]. But these guidelines are very general in conduct of forced degradation and do not provide details about the practical approach towards stress testing. Although forced

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degradation studies are a regulatory requirement and scientific necessity during drug development, it is not considered as a requirement for formal stability program.

It has become mandatory to perform stability studies of new drug moiety before filing in registration dossier. The stability studies include long term studies (12 months) and accelerated stability studies (6 months). But intermediate studies (6 months) can be performed at conditions milder than that used in accelerated studies. So the study of degradation products like separation, identification and quantitation would take even more time. As compared to stability studies, forced degradation studies help in generating degradants in much shorter span of time, mostly a few weeks. The samples generated from forced degradation can be used to develop the stability indicating method which can be applied latter for the analysis of samples generated from accelerated and long term stability studies. This review provides a proposal on the practical performance of forced degradation and its application for the development of stability indicating method.

2. Objective of forced degradation studies

Forced degradation studies are carried out to achieve the following purposes:

1. To establish degradation pathways of drug substances and drug products.
2. To differentiate degradation products that are related to drug products from those that are generated from non-drug product in a formulation.
3. To elucidate the structure of degradation products.
4. To determine the intrinsic stability of a drug substance in formulation.
5. To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product [1,2].
6. To establish stability indicating nature of a developed method.
7. To understand the chemical properties of drug molecules.
8. To generate more stable formulations.
9. To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
10. To solve stability-related problems [3].

3. Time to perform forced degradation

It is very important to know when to perform forced degradation studies for the development of new drug substance and new drug product. FDA guidance states that stress testing should be performed in phase III of regulatory submission process. Stress studies should be done in different pH solutions, in the presence of oxygen and light, and at elevated temperatures and humidity levels to determine the stability of the drug substance. These stress studies are conducted on a single batch. The results should be summarized and submitted in an annual report [4]. However, starting stress testing early in preclinical phase or phase I of clinical trials is highly encouraged and should be conducted on drug substance to obtain sufficient time for identifying degradation products and structure elucidation as well as optimizing the stress conditions. An early stress study also gives timely recommendations for making improvements in the manufacturing process and proper selection of stability-indicating analytical procedures [5,6].

4. Limits for degradation

The question of how much degradation is sufficient has been the topic of many discussions amongst pharmaceutical scientists. Degradation of drug substances between 5% and 20% has been accepted as reasonable for validation of chromatographic assays [7,8]. Some pharmaceutical scientists think 10% degradation is optimal for use in analytical validation for small pharmaceutical molecules for which acceptable stability limits of 90% of label claim is common [9]. Others suggested that drug substance spiked with a mixture of known degradation products can be used to challenge the methods employed for monitoring stability of drug product [2]. No such limits for physiochemical changes, loss of activity or degradation during shelf life have been established for individual types or groups of biological products [10].

It is not necessary that forced degradation would result in a degradation product. The study can be terminated if no degradation is seen after drug substance or drug product has been exposed to stress conditions than those conditions mentioned in an accelerated stability protocol [11]. This is indicative of the stability of the molecule under test. Over-stressing a sample may lead to the formation of a secondary degradation product that would not be seen in formal shelf-life stability studies and under-stressing may not generate sufficient degradation products [12]. Protocols for generation of product-related degradation may differ for drug substance and drug product due to differences in matrices and concentrations. It is recommended that maximum of 14 days for stress testing in solution (a maximum of 24 h for oxidative tests) to provide stressed samples for methods development [13].

5. Strategy for selection of degradation conditions

Forced degradation is carried out to produce representative samples for developing stability-indicating methods for drug substances and drug products. The choice of stress conditions should be consistent with the product's decomposition under normal manufacturing, storage, and use conditions which are specific in each case [9]. A general protocol of degradation conditions used for drug substance and drug product is shown in Scheme 1.

A minimal list of stress factors suggested for forced degradation studies must include acid and base hydrolysis, thermal degradation, photolysis, oxidation [5,14–16] and may include freeze–thaw cycles and shear [10]. There is no specification in regulatory guidelines about the conditions of pH, temperature and specific oxidizing agents to be used. The design of photolysis studies is left to the applicant's discretion although Q1B specifies that the light source should produce combined visible and ultraviolet (UV, 320–400 nm) outputs, and that exposure levels should be justified [11]. The initial trial should have the aim to come upon the conditions that degrade the drug by approximately 10%. Some conditions mostly used for forced degradation studies are presented in Table 1 [17].

Some scientists have found it practical to begin with extreme conditions such as 80 °C or even higher temperatures and testing at shorter (2, 5, 8, 24 h, etc.) multiple time points, so that the rate of degradation can be evaluated [18]. The primary degradants and their secondary degradations products can be distinguished by testing at early time points and thus help in a better degradation pathway