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Review Article

Forced degradation studies for Drug Substances and Drug Products- Scientific and Regulatory Considerations

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Abstract-

Forced degradation is the process of subjecting drug compounds to extreme chemical and environmental conditions to determine product breakdown levels and preliminary degradation kinetics, and to identify potential degradation products. They 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. It is particularly useful when little information is available about potential degradation products. In addition to develop stability- indicating analytical methods, these studies also provide information about the degradation pathways and degradation products that could form during storage, transportation. Forced degradation studies may help facilitate pharmaceutical development in areas such as formulation development, manufacturing, and packaging, in which knowledge of chemical behavior can be used to improve a drug product. This publication provides information about regulatory needs and scientific guidance to perform forced degradation.

INTRODUCTION

Forced degradation studies are also known as stress testing, stress studies, stress decomposition studies, forced decomposition studies, etc. 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.

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[2].

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

OVERVIEW OF REGULATORY GUIDANCE

According to the available guidance, forced degradation studies are carried out for the following reasons:

1. Development and validation of stability-indicating methodology.
2. Determination of degradation pathways of drug substances and drug products.
3. Discernment of degradation products in formulations that are related to drug substances versus those that are related to non–drug substances (e.g., excipients).
4. Structure elucidation of degradation products.
5. Determination of the intrinsic stability of a drug substance molecule. Degradation studies have several defining characteristics.
6. They are carried out in solution and/or the solid state.
7. Involve conditions more severe than accelerated testing (e.g., 40 C; 75% relative humidity; in excess of ICH light conditions; high and low pH, oxidation, etc.) (1, 2).
8. Are typically carried out on one batch of material (1, 2).
9. Include conditions that analyze thermolytic, hydrolytic, oxidative, and photolytic degradation mechanisms in the drug substance and drug product (as appropriate) (1, 2).
10. Is not part of the formal stability program.

FDA PERSPECTIVES AND SCIENTIFIC CONSIDERATIONS

Ragine Maheswaran provided a clear perspective on FDA regarding the scientific considerations with respect to forced degradation studies. If the substance does not show any degradation under any of the stress conditions then the Stress studies shall be repeated to obtain adequate degradation. If degradation is not achievable, rationale shall be provided. The conditions employed for stress study are too harsh and that most of the drug substance has degraded. The stress studies using milder conditions or shorter exposure time to generate relevant degradation products. Stressed samples shall be performed as per the assay method conditions. For the related substances method to be stability indicating, the stressed samples should be analyzed

using related substances method conditions. The attempts shall be made to ensure that all the impurities including the degradation products of the unstressed and the stressed samples are captured by the final analytical method. Summary of the amount of degradation products (known and unknown) in the stressed samples shall be provided. The purity determinations shall be performed as per the established software. Mass imbalance of the stressed samples shall be justified. The degradation products shall be identified that are formed due to drug-excipients interactions. Photo stability studies shall be determined whether the drug product is very sensitive to light or not. This shall be documented in the analytical method, manufacturing process, product handling, and etc [3].

Forced degradation in QbD paradigm

A systematic process of manufacturing quality drug products that meet the predefined targets for the critical quality attributes (CQA) necessitates the use of knowledge obtained in forced degradation studies.

A well-designed, forced degradation study is indispensable for analytical method development in a QbD paradigm. It helps to establish the specificity of a stability indicating method and to predict potential degradation products that could form during formal stability studies. Incorporating all potential impurities in the analytical method and establishing the peak purity of the peaks of interest helps to avoid unnecessary method re-development and revalidation.

Knowledge of chemical behavior of drug substances under various stress conditions can also provide useful information regarding the selection of the excipients for formulation development. Excipients compatibility is an integral part of understanding potential formulation interactions during product development and is a key part of product understanding. Degradation products due to drug-excipient interaction or drug-drug interaction in combination products can be examined by stressing samples of drug substance, drug product, and placebo separately and comparing the impurity profiles. Information obtained regarding drug-related peaks and non-drug-related peaks can be used in the selection and development of more stable formulations. For instance, if a drug substance is labile to oxidation, addition of an antioxidant may be considered for the formulation. For drug substances that are labile to acid or undergo stereo-chemical conversion in acidic medium, delayed-release formulations may be necessary. Acid/base hydrolysis testing can also provide useful insight in the formulation of drug products that are liquids or suspensions.

Knowledge gained in forced degradation studies can facilitate improvements in the manufacturing process. If a photostability study shows a drug substance to be photolabile, caution should be taken during the manufacturing process of the drug product. Useful information regarding process development (e.g., wet versus dry processing, temperature selection) can be obtained from thermal stress testing of drug substance and drug product. [3]

In addition to develop stability indicating methods, forced degradation studies provide information for degradation pathways and degradation products that could form during storage and transportation. Forced degradation studies may help facilitate pharmaceutical development as well in areas such as formulation development, manufacturing, and packaging, in which knowledge of chemical behavior can be used to improve a drug product.

Selection of experimental conditions

There are many examples in the literature of experimental conditions for conducting forced degradation studies and the structural multiplicity of drug molecules that makes it not possible to identify a generic set of conditions for a forced degradation study. For an early phase molecule, using a set of normal conditions by first intention makes sense since very little may be known about the intrinsic stability. If early stability data are available which suggest the molecule is labile at a particular condition (e.g., high pH), the conditions can be modified to take into account the instability (e.g., reduced temperature or time of study). Once a set of conditions have been found, they may be repeated whenever a new stability-indicating method is required during development. Therefore, for later-phase molecules, the forced degradation conditions are defined by the earlier work. By reprocess the same forced degradation conditions throughout development a consistent approach is maintained [4]. Some conditions mostly used for forced degradation studies are presented in Table 1.

Table 1. Conditions generally 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
	0.1 M 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	40°C, 60°C	1,3,5
Oxidation	3%H2O2	25°C, 60°C	1,3,5
	Peroxide control	25°C, 60°C	1,3,5
	Azobisisobutyronitrile (AIBN)	40°C, 60°C	1,3,5
	AIBN control	40°C, 60°C	1,3,5
Photolytic	Light 1 × ICH	NA	1,3,5
	Light 3 × ICH	NA	1,3,5
	Light control	NA	1,3,5
Thermal	Heat chamber	60°C	1,3,5
	Heat chamber	60°C /75% RH	1,3,5
	Heat chamber	80°C	1,3,5
	Heat chamber	80°C /75% RH	1,3,5
	Heat control	Room temp.	1,3,5

DEGRADATION CONDITIONS

Typical stress tests include four main degradation mechanisms: heat, hydrolytic, oxidative, and photolytic degradation. Selecting suitable reagents such as the concentration of acid, base, or oxidizing agent and varying the conditions (e.g., temperature) and length of exposure can achieve the preferred level of degradation. Over-stressing a sample may lead to the formation of secondary degradants that would not be seen in formal shelf-life stability studies and under-stressing may not serve the purpose of stress testing. Therefore, it is necessary to control the degradation to a desired level. A generic approach for stress testing has been proposed to achieve purposeful degradation that is predictive of long-term and accelerated storage conditions [5]. The generally recommended degradation varies between 5-20% degradation [5-8]. This range covers the generally permissible 10% degradation for small molecule pharmaceutical drug products, for which the stability limit is 90%-110% of the label claim. Although there are references in the literature that mention a wider recommended range (e.g., 10-30%), the more extreme stress conditions often provide data that are confounded with secondary degradation products.

1. Hydrolytic condition

Hydrolysis is one of the most common degradation chemical reactions over wide range of pH. Hydrolysis is a solvolytic process in which drug reacts with water to yield breakdown products of different chemical compositions. Water either as a solvent or as moisture in the air comes in contact with pharmaceutical dosage
forms is responsible for degradation most of the drugs. For example, aspirin combines with water and hydrolyzed to salicylic acid
and acetic acid [9-10]. Hydrolytic study under acidic and basic condition involves catalyzation of ionisable functional groups present in the molecule. HCl and NaOH are employed for generating acidic and basic stress samples, respectively [11]. The hydrolytic degradation of a new drug in acidic and alkaline condition can be studied by refluxing the drug in 0.1 N HCl / 0.1 N NaOH. 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 strength and for longer duration of time. Alternatively if total degradation is seen after subjecting the drugs to initial condition, acid/alkali strength can be decreased with decrease in reaction temperature. In general temperature and pH are the major determinant in stability of the drug prone to hydrolytic decomposition. Hydrolysis of most of the drugs is dependent upon the relative concentration of hydronium and hydroxyl ions. Hence pH at which each drug is optimaly stable can be determined.

2. Oxidation conditions

Hydrogen peroxide is widely used for oxidation of drug substances in forced degradation studies but other oxidizing agents such as metal ions, oxygen, and radical initiators (e.g.,azobisisobutyronitrile, AIBN) can also be used. Selection of an oxidizing agent, its concentration, and conditions depends on the drug substance. It is reported that subjecting the solutions to 0.1–3% hydrogen per oxide at neutral pH and room temperature for seven days or upto a maximum 20% degradation could potentially generate relevant degradation products [12]. The mechanism of oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anions and cations. Amines, sulphides and phenols are susceptible to electron transfer oxidation to give N-oxides, hydroxylamine, sulphones and sulphoxide [13]. The functional group with labile hydrogen like benzylic carbon, allylic carbon, and tertiary carbon or α – positions with respect to hetro atom is susceptible to oxidation to form hydroperoxides, hydroxide or ketone [14, 15].

3. Photo degradation

According to ICH Q1B guideline for photo degradation, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter with spectral distribution of 320-400nm to allow direct comparisons to be made between the drug substance and drug product. Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters [16]. The photolytic degradation can occur through nonoxidative or oxidative photolytic reaction. The nonoxidative photolytic reaction include isomerization, dimerization, cyclization, rearrangements, decarboxylation and hemolytic cleavage of X-C hetero bonds, N-alkyl bond (dealkylation and deamination), SO2- C bonds etc and while oxidative photolytic reaction occur through either singlet oxygen (1O2) or triplet oxygen (3O2) mechanism. The singlet oxygen reacts with the unsaturated bonds, such as alkenes, dienes, polynuclear aromatic hydrocarbon to form photoxidative degradation products whereas triplet oxygen react with free radical of the drug molecule, which than react with a triplet oxygen molecule to form peroxide. Hence, light can also act as a catalyst to oxidation reactions [17, 18].

4. Thermal condition

In general, rate of a reaction increase with increase in temperature. Hence, the drugs are susceptible to degradation at higher temperature. Many APIs are sensitive to heat or tropical temperatures. For example, vitamins, peptides, etc. Thermal degradation involves different reactions like pyrolysis, hydrolysis, decarboxylation, isomerization, rearrangement and polymerization. Effect of temperature on thermal degradation of a substance is studied through Arrhenius equation:

$K = Ae^{-Ea/RT}$

Where k is specific reaction rate, A is frequency factor, Ea is energy of activation, R is gas constant (1.987 cal/ deg mole) and T is absolute temperature.

Thermal degradation study is carried out at 40˚C to 80˚C. The most widely accepted temperature is 70˚C at low and high humidity for 1-2 months. High temperature

(>80˚C) may not produce predictive degradation pathway. The use of high-temperatures in predictive degradation studies assumes that the drug molecule will follow the same pathway of decomposition at all temperatures. This assumption may not hold true for all drug molecules, and therefore great care must be taken in using the extreme temperatures easily accessible in a sealed-vessel microwave experiment for predictive degradation studies [19].

CONCLUSION

Forced degradation is important part of the drug development process as it provides knowledge about the degradation chemistry of drug substances and drug products. This knowledge is used primarily to develop stability- indicating analytical methods but also useful for other purposes such as formulation development, packaging development and the design of the official stability studies. As there is no formal regulatory guidance for forced degradation, it is recommended to use appropriate conditions to achieve 5-20% degradation.

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