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REVIEW ON OBJECTIVE OF FORCED DEGRADATION STUDIES ITS IMPORTANCE AND OVERVIEW OF REGULATORY GUIDANCE

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ABSRACT
Force Degradation study is most important tool in pharmaceutical research and development to develop stable formulation. It provides information about the degradation pathway and degradation product of the drug substance and helps in the elucidation of the structure of drug products. This review article discusses about regulatory guideline and factor affecting degradation to provide knowledge of the current trends in performance of force degradation studies and also helpful for development of stability indicating method.

KEYWORD: Force degradation, Regulatory Guideline, Degradation Product, Degradation Condition.

INTRODUCTION

The safety and efficacy of the drug product is affected by the chemical stability of the pharmaceutical molecules. Thus FDA and ICH have stated the various requirements that have to be followed for the stability testing to know the quality of the drug product and to find out how the environmental changes affect the drug product. Proper formulation and storage conditions can be identified by using the stability data. In forced degradation the drug products are degraded in more severe conditions and the degraded products are studied for the chemical stability of the molecules.[1] 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.[2] International Conference on Harmonisation (ICH) guidelines, make it essential to organize the forced degradation studies and it is evidently mandated to perform forced degradation of new drug products. These studies offer the information to support detection of potential degradants. It also illustrates the degradation pathways of pharmaceutically active molecules. The drug molecule intrinsic stability can be estimated by forced degradation studies. Probable polymorphic or enantiomeric substances and variation between drug related degradation and excipients interferences can also be evaluated by forced degradation studies.[3]

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 those 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.[4]
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.[1]

NEED FOR FORCED DEGRADATION OF DRUGS

Studies on forced degradation of drug molecules are very important in the following aspects.[5]

1. To develop methods to determine stability.
2. To determine the degradation pathways.

3. For determination of intrinsic stability of drug in dosage forms.
4. To study the chemical properties of molecules.
5. For production of stable formulations.
6. To determine the structure of decomposition products.
7. To solve problems related to stability.
8. To generate a degradation profile under ICH conditions

OVERVIEW OF REGULATORY GUIDANCE

Regulatory and Various International guidelines recommended forced degradation studies. ICH guidelines sometimes apply only to the marketing applications for new products and do not cover the part during clinical development. The ICH guidelines that are applicable to forced degradation studies are

- ICH Q1A: Stability testing of new drug substances and products.
- ICH Q1B: Photo stability testing of new drug substances and products.
- ICH Q1C- Stability Testing of New Dosage Forms
- ICH Q2B: Validation of analytical procedures: Methodology.[6, 7]

ICH Q1A (Stress testing):testing of stability for new drug molecules and their products Recommended conditions for performing forced degradation studies on drug substances and drug products. The recommendations are to inspect the results of temperature (above that for accelerated testing, i.e., >50 C), humidity (75% relative humidity), oxidation and photolysis. Wide pH range should be considered in the testing of solution or suspension. Ultimately the stability-indicating method developed by these samples.[3,6]

ICH Q1B: photo stability testing of new drug substance and drug product

gives recommended approaches to assessing the photo stability of drug substancesand 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 photo stability 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. Photo stability testing can be performed on the solid or in solution/suspension. These samples are then used to develop a stability indicating method. Both guidances Q1A and Q1B, note that some of the degradation products formed during forced degradation studies may not actually be observed to form during stability studies, in which case they need not be examined further.[2,3]

ICH Q2B: validation of analytical procedure: methodolody

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.

ICH Q3A: impurities in new drug substances

requires identification of each impurity with respect to both chemistry and safety perspectives. The chemistry perspectives include classification and identification of impurities, report generation, listing of impurities in specification and a brief discussion of analytical procedures while the safety perspectives include specific guidance for qualifying those impurities that were not present or were present at substantially lower levels in batch of a new drug substance and used in safety and clinical studies.[2,3]

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.[8] Some conditions mostly used for forced degradation studies are presented in following table and figure.

Table. 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 Hydrochloric acid	40°C, 60°C	1,3,5
	0.1M Sodium hydroxide	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
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

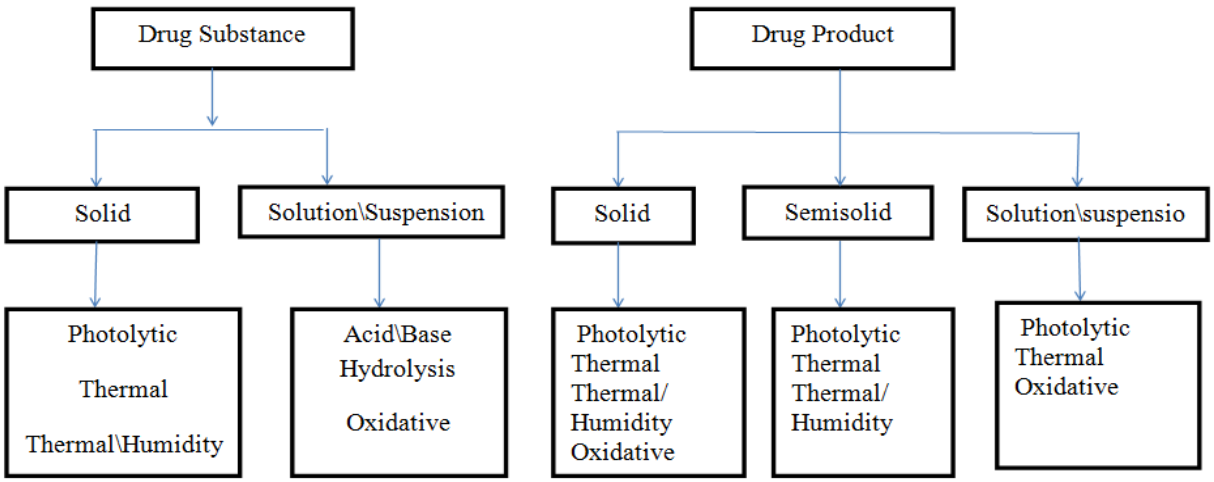

Fig: Schematic representation of degradation studies of drugs and drug products under different stress conditions.

FACTORS AFFECTING DEGRADATION

Following are the different factor which causes degradation of drug substances. They are.

Moisture

In the presence of moisture, water-soluble substances may get dissolved. This leads to physical and chemical changes within the molecule.

Excipients

It was observed that some excipients may contain high content of water. This moisture may lead to increased water level in formulation which later affects the stability of the drug. In some cases, chemical interactions that occur between the excipients and the drug material often results in decreased stability.

Temperature

Changes in temperature at times show deleterious effect on the stability of the drug. Increase in temperature usually causes increases the rate of drug hydrolysis.

PH

pH shows a significant effect on the degradation rate of drugs by hydrolysis. To reduce this effect, formulation of the drugs is carried out using buffer solutions of pH with maximum stability.

Oxygen

Presence of oxygen increases the oxidation in some drugs. Drugs with increased rate of decomposition in the presence of oxygen are stabilized by purging nitrogen or carbon dioxide in the storage container.

Light

Some drugs are photo labile and tend to decompose when they are exposed to light. The susceptibility to

photolytic decomposition can be tested by comparing its stability in the presence of light and stability when stored under dark. It is to be remembered that the photo labile compounds should be stored in amber glass containers and should be stored in the dark.[9,5]

Degradation conditions

Hydrolytic conditions

Hydrolysis is one of the most common degradation chemical reaction over wide range of ph. Hydrolysis is a solvolytic process in which drug react with water to yield breakdown products of different chemical compositions. Acid or base stress testing involves forced degradation of a drug substance by exposure to acidic or basic condition which generate primary degradents in desirable range. The selection of the type and concentrations of acid or base on the stability of drug substance. Hydrolytic acid or sulfuric acids (0.1-1 M) for acid hydrolysis and sodium hydroxide or potassium hydroxide (0.1-1M) for base hydrolysis are suggested as suitable reagents for hydrolysis. If the compound for stress testing are poorely soluble in water, then co-solvents can be used to dissolve them in HCL or NaOH. The selection of co-solvent is based on the drug substance structure. Stress testing trial is normally started at room temperature and if there is no degradation, elevated tempreture (50-70 oc) is applied. stress testing should not exceed more than 7 days. The degraded sample is then neutralized using suitable acid, base or buffer, to avoid further decomposition.[10-11]

Oxidative Condition

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. azobisisobutyro –nitrile, 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 peroxide at neutral pH and room temperature for seven days or up to a maximum 20% degradation could potentially generate relevant degradation products. The oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anion and cations. Amines, sulfides and phenols are susceptible to electron transfer oxidative to give N-oxides, hydroxylamine, sulfones and sulfoxide. 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 hydro peroxides, hydroxide or ketone.[4,8,11]

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 320-400 nm 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. In photolytic degradation studies, the drug substances are exposed to UV or fluorescent conditions. In this study, the drug substances or drug products (solid/ liquid) are exposed to the light source according to the ICH Q1B protocols. The commonly used radiation range for degradation studies is about 300–800 nm. In photolytic condition, the degradation occurs due to oxidation through free radical mechanism or non- oxidation process. Non-oxidative degradation process involves with isomerization, dimerization, etc among others. On the other hand, oxidative photolytic reaction involves mechanism involving singlet/triplet oxygen states. Singlet oxygen reacts with unsaturated compounds to produce photo oxidative decomposition products, while triplet oxygen follows free radical mechanism, to produce peroxide. Notably, it is shown that light also catalyzes oxidation reactions.[1,9,12]

Thermal degradation

Thermal degradation (e.g., dry heat and wet heat) should be carried out at more strenuous condition than recommended ICH. Q1A accelerated testing conditions. Sample of solid-state drug substance and drug product should be exposed to dry and wet heat, while liquid drug products should be exposed to dry heat. Studies may be conducted at higher temperatures for a shorter period. Effect of temperature on thermal degradation of a substance is studied through the 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 40-80^{0}C.[2, 11]

CONCLUSION

Force degradation is important part of the drug development process as it provide knowledge about the degradation of drug substance and drug product. The information gained from stability analysis helps to improve the formulation, manufacturing and storage condition and determine the expiry date of the drug formulation.

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