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Forced Degradation Studies on Drug Products and Drug Substances and Stability Indicating Studies on Drugs – A Review

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ABSTRACT

Degradation of newer drug substances and drug products under conditions severe than those in which they degrade more rapidly is known as forced degradation. It is necessary to illustrate the specificity of stability-indicating methods. It also offers an understanding of the drug substance's degradation pathways and degradation products and aids in elucidating the structure of the degradation products. Studies on forced degradation reveal the molecule's chemical reactions, which is helpful in the formulation process and packaging processes.

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INTRODUCTION

Analytical method validation has been defined as a procedure used to prove that a test method consistently yields what it is expected to do with adequate accuracy and precision. Over recent years the Regulatory Authorities have become increasingly more aware of the necessity of ensuring that the data provided to them in applications for marketing (and perhaps clinical) authorizations have been acquired using validated analytical methodology. This has resulted in the publication of a series of requirements and guidelines by various authorities.

The stress testing methodology described in the International Conference on Harmonization (ICH) guideline Q1AR2 is expanding to include medication combinations. According to this ICH guideline, stress testing on API and drugs must be done to determine their intrinsic stability characteristics. These include susceptibility to a broad range of pH values, and the effects of temperature, humidity, light, and oxidizing agents. Additionally, it is advised that stability sample analysis be carried out using a proven stability-indicating testing procedure [1]. An analytical technique called the stability indicating method (SIM) [6] is used to measure how much of the active pharmaceutical ingredient (API) in a drug product is lost due to degradation. As per an FDA guideline document, a stability-indicating method is a quantitative analytical approach that has been validated and can be utilized to identify changes in the stability of drug substances and drug products over time. Without the influence of excipients, other degradation products, or contaminants, a stability-indicating approach precisely detects variations in the concentration of the active components.

In the pharmaceutical sector, stability samples are analyzed using the stability-indicating technique assay. The International Conference on Harmonization (ICH) rules have made it more imperative to establish a stability-indicating method assay before releasing a completed dosage form into the market. The guidelines notably demand the isolation of the medication from degradation products and the execution of forced decomposition tests in a range of environments, including pH, light, oxidation, dry heat, etc. The approach is expected to enable analysis of certain specific degradation products [9].

When there is limited information available regarding a potential degradation product, stress testing is done to show the specificity of the devised method to evaluate changes in drug

ingredient concentration. For pre-formulation research, stability studies, and the creation of appropriate storage requirements, a suitable stability-indicating method must be developed.

OBJECTIVE OF FORCED DEGRADATION STUDY

1. To ascertain a drug substance's inherent stability in a formulation.
2. To determine the processes by which drug compounds and drug products degrade.
3. To produce more stable formulations.
4. To clarify how degradation products are structured.
5. To disclose the drug substance's and drug product's breakdown processes, such as hydrolysis, oxidation, thermolysis, or photolysis [1][10].
6. To create a steadiness that demonstrates the nature of an established technique.
7. To comprehend how medication molecules are chemically constructed.
8. To distinguish between degradation products produced by non-drug goods in a formulation and those connected to drug products.
9. To develop a degradation profile that, in ICH guidelines, is comparable to what would be found in a standard stability study [2].
10. To deal with stability-related difficulties, a method and appropriate choice of stability-indicating analytical techniques should be developed [3].

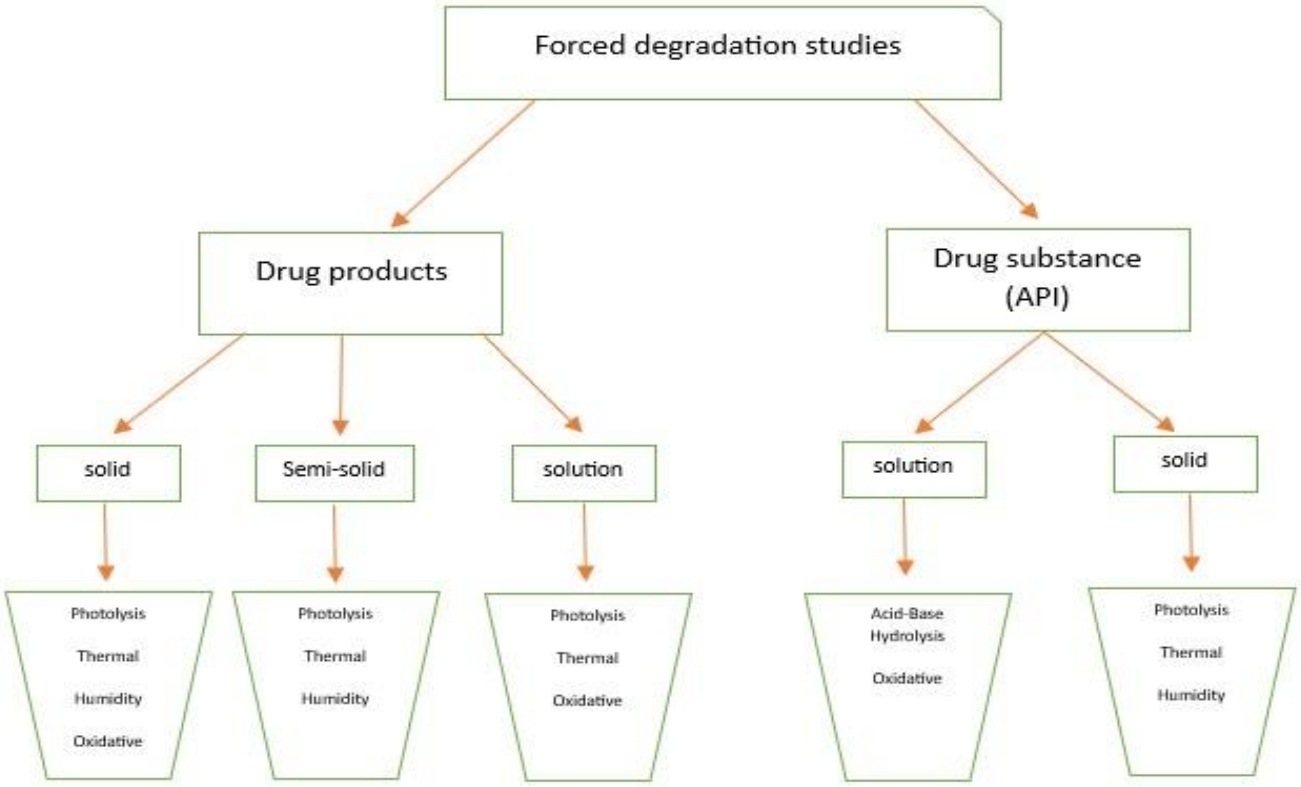

Fig.1. A typical flowchart that explains the different stress conditions that are employed to cause drug substance and drug product degradation

DEGRADATION CIRCUMSTANCES

The four primary degradation modes included in typical stress testing are thermal, hydrolytic, oxidative, and photolytic degradation. The ideal degree of degradation can be attained by choosing the right reagents, such as the acid, base, or oxidizing agent concentration, and altering the environment (such as temperature and exposure time) [4].

Under-stressing a sample can defeat the goal of stress testing while over-stressing it could result in the development of secondary degradants that are not observed in official shelf-life stability tests. Controlling the degradation to the desired degree is therefore essential. It has been suggested to use a general stress testing method to accomplish intentional degradation that is indicative of both accelerated and long-term storage conditions [6]. The range of typically advised degradation is 5 to 20% degradation. The stability limit for small molecule pharmaceutical drug products, which is 90%–110% of the label claim, is covered by this range, which also includes the normally allowed 10% degradation. While some literature

references suggest a higher suggested range (10–30%), results from elevated stress conditions are sometimes confused with secondary degradation products.

Regulatory guidance does not specify the medication concentration that should be used for the degradation research. It is advised that 1 mg/mL be the concentration at which the experiments are begun. It is typically achievable to obtain even little breakdown products within the detection range by employing a medication concentration of 1 mg/ml. Degradation studies at a concentration where the drug is anticipated to be present in the final formulations are also advised to be conducted [8]. The degradation conditions include.

1. Hydrolytic conditions
2. Oxidation conditions
3. Photolytic conditions
4. Thermal conditions

1. Hydrolytic condition.

One of the most frequent chemical breakdown processes across a broad pH range is hydrolysis. A chemical process called hydrolysis involves a chemical substance breaking down through an interaction with water. Studying hydrolysis in basic and acidic conditions entails catalyzing the molecule's ionizable functional groups [11]. Acid or base stress testing is the process of forcing a drug's deterioration by subjecting it to basic or acidic environments, which produces main degradants within a desired range.

The stability of the medication ingredient influences the choice of acid or base type and concentration.

Appropriate reagents for hydrolysis include sulfuric or hydrochloric acids (0.1–1 M) for acid hydrolysis and sodium or potassium hydroxides (0.1–1 M) for base hydrolysis. The chemicals for stress testing can be dissolved in HCl or NaOH using co-solvents if they are poorly soluble in water. The pharmaceutical active ingredient structure is taken into consideration when choosing a co-solvent [12]. Normally, a stress test trial is started at room temperature. If there is no degradation, the temperature is raised to 50–70 1C. A stress test shouldn't last longer than seven days. To stop further degradation, the degraded sample is subsequently neutralized with an appropriate acid, base, or buffer.

2. Oxidation condition.

In forced degradation investigations, hydrogen peroxide is frequently used to oxidize pharmacological compounds. However, other oxidizing agents, like metal ions, oxygen, and radical initiators (such as azobisisobutyronitrile, AIBN), can also be utilized. The drug ingredient determines which oxidizing agent to use, how much to use, and under what circumstances. According to reports, the solutions may produce relevant degradation products if they are exposed to 0.1–3% hydrogen peroxide at ambient temperature and neutral pH for seven days, or up to a maximum of 20% degradation [12].

An electron transfer process is involved in the oxidative breakdown of drug material, leading to the formation of reactive anions and cations. N-oxides, hydroxylamine, sulfones, and sulfoxide can be produced by electron transfer oxidation of amines, sulfides, and phenols. Functional groups containing labile hydrogen, such as benzylic, allylic, and tertiary carbons or α-positions relative to the hydrogen atom, are oxidizable to generate hydroperoxides, hydroxides, or ketone compounds [13].

3. Photolytic condition.

To prove that exposure to light does not cause undesirable changes, pharmacological compounds must undergo photostability testing. Photostability investigations are carried out to produce the drug substance's major degradants through exposure to UV or fluorescent light.

ICH guidelines specify some suggested conditions for photostability testing. A required minimum of 1.2 million lx h and 200 W h/m2 of light should be applied to samples of drug material and solid/liquid drug product [4]. The most widely acknowledged range of light wavelengths that can induce photolytic deterioration is between 300 and 800 nm. Free radical mechanisms can cause photo-oxidation in light-stress circumstances. Drug photosensitivity is likely to be introduced by functional groups such as carbonyls, nitro aromatic, N-oxide, alkenes, aryl chlorides, weak C–H and O–H bonds, sulfides, and polyenes.

4. Thermal condition.

It is recommended to conduct thermal deterioration (such as dry heat and wet heat) under more demanding conditions than those suggested by ICH Q1A accelerated testing settings [12]. Whereas liquid drug products shall be exposed to dry heat, samples of solid-state drug substances and drug products need to be exposed to both dry and wet heat. Studies may be

carried out for shorter periods and at higher temperatures. The Arrhenius equation is used to investigate the relationship between temperature and thermal deterioration of a substance [14].

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

Where k is the specific reaction rate, A is the frequency factor, Ea is the energy of activation, R is gas constant and T is the absolute temperature. Thermal degradation study is carried out at 40–80 ºC.

Degradation type	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid or base)	40 °C, 60 °C	1,3,5
	0.1 M 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% H_2O_2	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

Fig. 2. Most commonly used conditions in forced degradation studies. Ref. [5]

CONCLUSION

Stress testing, also known as forced degradation studies, is an essential approach in pharmaceutical research and development for the creation of stable formulations. In addition to helping to clarify the structure of the degradants, forced degradation experiments provide information regarding potential degradation pathways including degradation byproducts of the active components. To have enough time to learn more regarding the stability of the molecule, it is preferable to begin degradation studies early in the drug development process. As a result, the formulation process of manufacture and storage conditions can be improved with the use of this information. A well-planned and carried out forced degradation study will yield a suitable sample for developing of a stability-indicating technique.

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