Review Article

A Review on Force Degradation Study for Pharmaceutical Product Development

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ABSTRACT

Force degradation helps in gauging the stability of a pharmaceutical product in a very early stage of product development. Thus this paper discusses about the regulatory guidelines for the stability of the new drug. The paper sheds light on the perspective of FDA regarding the scientific considerations with respect to force degradations studies.

I) 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 condition 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.

The study of the chemical stability of the drug in the adverse conditions is mandatory before the filing the registration dossier. The stability studies include the long term studies of 12 months as well as the accelerated studies of 6 months. Also the intermediate studies of 6 months can be performed in conditions milder than the conditions used in accelerated studies. Force degradation studies helps in generating the degradation products in short span of time such as few weeks. The samples generated from forced degradation can be used to develop stability indicating method which can be applied latter for the analysis of samples generated from accelerated and long term stability studies. This review tells about the various guidelines laid down by FDA and ICH for degradation studies and the conditions that the drug product and drug substance has to sustain during the testing.

II) Overview of the regulatory guidelines

2.1) ICH (International Committee for Harmonization) guidelines

The European, Japanese and American regulatory authorities have adopted the ICH (International committee for harmonization) guidelines for force degradation studies. The ICH gives the following guidelines in Q1A for stress testing new drug substance: *'Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.'* This section also provides recommendations for testing the new drug for temperature with increments of 10^0C and humidity. It also recommends testing the drug for hydrolysis in wide range of pH values in solution or suspension.

In Q1B ICH gives guidelines for photostability testing, which is as follows : '*Forced degradation testing studies are those undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.*' The exposure levels for force degradation studies are not defined. The study design for photostability is left to the applicant which can

be carried out on solid as well as solution/suspension.

The guideline Q2 by ICH which is titled as 'Validation of Analytical Procedures: Text and Methodology' has following mentions: '*If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure e.g.: pharmacopoeial method or other validated analytical procedure (independent procedure). As appropriate, this should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis and oxidation.*' Here it is recommended to use the samples from the force degradation for the specificity. The specificity is crucial factor in determining whether or not the analytical method is indicating stability.

The guideline Q3 which is titled as 'Impurities in New Drug Substances' requires identification of each and every impurity in the sample for chemical and safety perspective.

Apart from the ICH guidelines there are some other agencies that have created a draft of guidelines such as USFDA (United States food and drug authority), European medicines agency, WHO (World health organisation) etc.

2.2) FDA perspective and scientific considerations

Apart from ICH guidelines the united states food and drug authority brought the draft for guidelines for industry in June 1998 which was titled as 'Stability Testing of Drug Substances and Drug Products'. This draft of guidelines was never finalized but it is still available on the website of USFDA for reference.

Regarding scientific considerations in force degradation studies Ragine Maheshwaran has given a better perspective of FDA. According to this perspective if any drug does not show any degradation signs then the force degradation has to be continued under severe conditions to extract the degradation products but as the conditions under which the tests are carried out are too harsh, in which most of the drugs do degrade. The final analytical method should analyse both stressed and unstressed samples of force degradation to capture all the impurities. The purity determination should be done using the established software's only. Using photostability studies it should be determined whether the drug is sensitive to light or not. These things should be documented in the analytical method, manufacturing process, product handling etc.

III) Force degradation study

The force degradation is carried to establish degradation pathways of drug substances and drug products. It also elucidates the structure of degradation product. Force degradation reveals the degradation mechanism such as hydrolysis, oxidation, thermolysis or photolysis.

3.1) Origin of degradation

Degradation is the main reason for the cause of impurities in the drug substance. This degradation is caused due to the chemical instability in the drug substance which takes place because of heat, humidity, pH, light encountered during manufacturing, packaging, storage etc. Stress testing tries to form all the possible degradation products that can be formed during the exposure to environmental conditions.

3.2) Selection of experimental conditions

t is difficult to identify the generic set of condition to perform the experiment due to the structural multiplicity of the molecules of the drug. For molecule in the initial phase the set of normal conditions should be used as very little is know about the stability of the molecule, but if some data of the initial stability is know (e.g. temperature) then other conditions can be varied to test the instability of the molecule. As the set of conditions are determined they can be repeated each time the new stability-indicating method is required. For molecules which are in later phases the set of conditions are defined by the earlier work.

3.3) Conditions for degradation

The general stress conditions that are used for degradation of drug product or drug substance are shown below in Fig. 1.

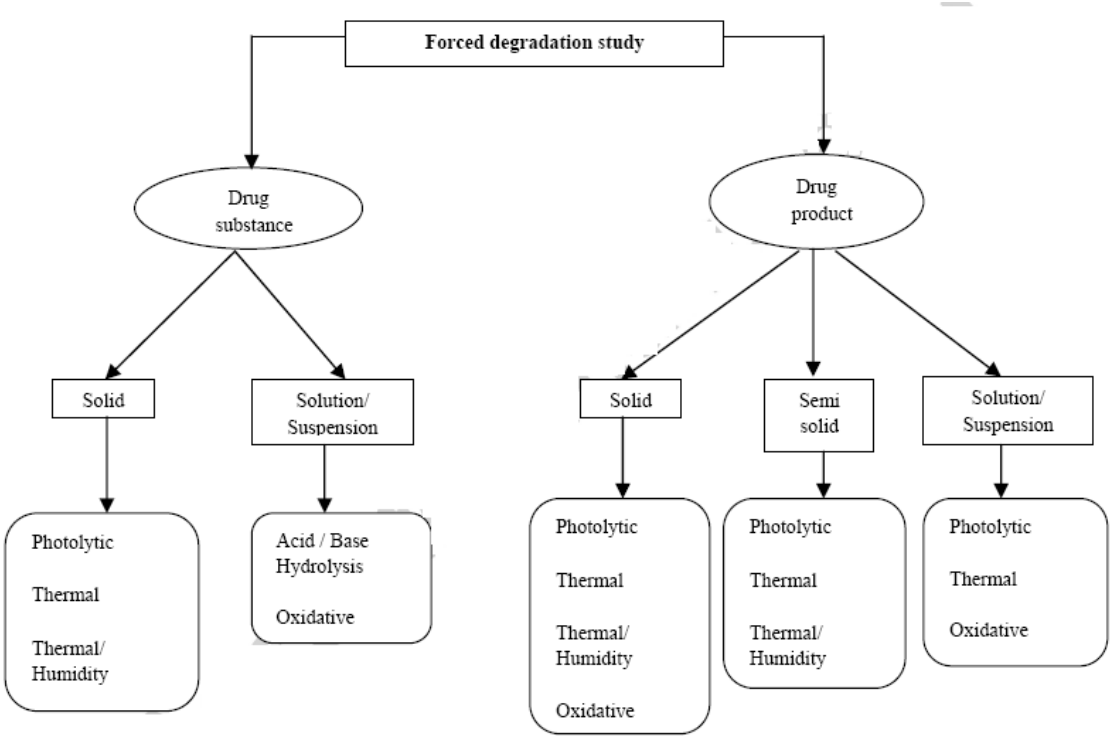

Fig. 1: Flowchart describing various stress conditions for the degradation of the drug substance and drug product

3.3.1) Hydrolytic Condition

Over a wide range of pH value the most common reaction for the degradation is hydrolysis. In hydrolysis the drug reacts with water to form the degradation products of different chemical compositions. Water in this reaction comes in contact with the drug either as a solvent or as moisture in the air. Under acidic and basic condition the hydrolytic process involves the catalyzation of the ionisable functional groups present in the molecule. HCL is used to generate acidic stress sample whereas NaOH is used to generate basic stress sample. The drug is refluxed in 0.1 N HCl for hydrolytic degradation of new drug in acidic and alkaline condition. If the degradation does not occur then the concentration is increased and if the drug is degraded in the initial condition then acid/alkali strength is decreased with decrease in reaction temperature. The refluxing is carried out for 30 minutes at about 60^0C temperature. Hydrolysis of most of the drug depend upon the concentration of hydronium and hydroxyl ions. Thus for the stable drug the pH can be found out.

3.3.2) Oxidative condition

In force degradation studies to carry out the oxidation reaction Hydrogen peroxide is mainly used but other oxidising agents such as metal ions, oxygen and radical indicators such as AIBN are also used for oxidation. Selection, concentration of the oxidising agent and experiment condition depend upon the drug substance. It is found that subjecting the drug to 0.1% -0.3% of hydrogen peroxide at room temperature and neutral pH when kept for seven days/20% degradation can form relevant degradation product. In oxidation reaction there is electron transfer which forms the reactive anions and cations.

3.3.3) Photolytic condition

In photostability testing the drug is called stable if it doesn't undergo any change when exposed to light. These studies are done by exposing the drug to the UV light or fluorescent light condition which can generate primary degradants. ICH has recommended that the drug substance or drug product should be exposed to at least 1.2 million lux h and 200 watt h per square meter light. To cause photolytic degradation the most commonly used wavelength of light is 300-800 nm. This photolytic condition causes photo oxidation by free radical mechanism. Functional groups like carbonyls, nitro aromatic, N-Oxide, alkenes, aryl chlorides, weak C-H and O-H bonds, sulphides are likely to introduce drug photosensitivity.

3.3.4) Thermal conditions

The thermal degradation process has to be carried out more severely than as described by ICH in Q1A. The drug substances and drug products in this process is exposed to dry as well as wet heat, where wet heat means exposing the drug to humidity as well as high temperatures. Effect of high temperatures on thermal degradation of a drug substance is studied by using Arrhenius equation:

$$K = A\, e^{-Ea/RT}$$

Where, K = Specific reaction rate
A = Frequency factor
Ea = Energy of activation
R= Gas constant
T= absolute temperature

The thermal degradation studies are generally carried out at temperature between 40^0C to 80^0C.

IV) CONCLUSION

Force degradation studies can help develop and demonstrate stability indicating methods of drug substances and drug product. It is also useful in determine the active ingredients in the drug. The information gained from the stability analysis helps improve the formulation, manufacturing and storage. As there are no specific set of conditions that can be used for all the drugs and the guidelines given by ICH does not provide any data for experimental conditions.

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