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FORCED DEGRADATION AND STABILITY INDICATING STUDIES OF IMATINIB TABLET

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ABSTRACT

Forced degradation or accelerated degradation is a process where drug products are of subjected to excessive chemical and environmental conditions. This study is usually used to identify the possible chemical reactions and responsible degradants (impurities) which are causing to degrade a drug product and usually conducted before final formulation; forced degradation uses external stresses to rapidly screen material stabilities. It is essential to validate specificity of stability demonstrating methods and also delivers a perception into degradation pathways and responsible degradants present in the drug material and supports in elucidation of the structure of the degradant. Long term storage tests are typically involved to measure alike properties whilst the ultimate drug formulations are engaged as of the strict FDA regulations. These tests are normally more costly (due to of the time required) than forced or accelerated degradation which is consequently used for rapid identification and elimination tests. Forced degradation experiments define the chemical nature of the degradant molecule which in turn assists in the improvement of the final formulation and package. This study discusses the existing trends of drug degradation studies by presenting an approach of performing further in-depth studies on drug degradation mechanisms and also shows the supportive workable analytical support for the development of stability representing method.

KEYWORDS: Imatinib; *Forced* Degradation; HPLC.

INTRODUCTION

The tendency of a chemical or drug compound to defend against any change in activity or decomposition due to inner reaction, or any environmental reason, etc all is defines as Chemical Stability of that representative compound. For pharmaceutical drug molecules, chemical stability is most significant issue as it influences the safety as well as efficiency of a drug product. The FDA and ICH [1-3] guidelines declared the necessity of stability study data's to comprehend the process of how the usual nature of a drug material and ultimate drug product modifies with time due to the influences of various environmental factors. Information about the stability of drug molecule facilitates in developing appropriate formulation and right package in addition with providing accurate storage circumstances and drug shelf life, which is indispensable for mandatory regulatory records. Forced degradation also known as Accelerated degradation - a procedure that employs degradation of drug materials and drug products at additional rigorous conditions that produced degradation products which ultimately can be studied to find out the stability causing factors of the molecule. The ICH guideline declared that stress testing is implemented to generate and determine the possible degradants which helps in detection of the intrinsic stability factors of the drug matters and affirming the degradation pathways, and to finally authenticate the stability demonstrating procedures. However, these guidelines are very common to carry out of forced degradation testing and do not afford details information about the realistic approach of drugs stress testing procedure.

MATERIALS AND METHODS

Degradation conditions

Hydrolytic conditions

Hydrolysis is a chemical process that includes decomposition of a chemical compound by reaction with water. This is one of the most universal reactions cause degradation of the chemical compound over a wide range of pH. Hydrolytic study under basic and acidic environment comprises catalysis of ionizable functional groups present in the drug molecule. Stress testing through acid or base involves forced degradation of a drug material by exposure to acidic or basic conditions which creates primary degradants in expectable range. The selection of the type and concentrations of acid or base depends on the stability of the drug substance.[4-7]

Oxidation conditions

In forced degradation studies, Oxidation stress testing procedure is suggested to perform by the use of Hydrogen peroxide which is responsible for oxidation of drug substances (concentration 3 to 30%). Some other oxidizing agents like oxygen, metal ions, and radical initiators can also be used. Selection of an oxidizing agent, its concentration, and conditions depends on the targeted drug substance.[4-8] The mechanism of oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anions and cations.

Photolytic conditions

The photo stability testing of any drug substances is carried out to evaluate the effect of light on the drug material during storage conditions. This study expected to must be established that a light exposure of light effect does not results in any intolerable changes in the quality, safety and efficacy of the drug product. According to ICH guideline, the stress testing under photolytic conditions, the light source should be cool white florescent lamp and wave length of light should be 200-800 nm (UV + visible). Photo stability studies are performed to generate primary degradants present in drug substance.[3,8,11]

Thermal conditions

Temperature is one of the most vital factors that affect the stability of a drug material more than the other conditions can. Thermal stress testing should be carried out at more strenuous conditions than suggested in ICH Q1A accelerated testing conditions. Samples of solid-state drug substances and drug products 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,[3,6,12,13]

Peak Purity

Using the PDA detector and one of the spiked samples prepared as below, determine the Purity threshold and Purity angle, for the Imatinib peak.

Sample preparation: Weigh 10 tablets and determine the average weight. Take four tablets (about 1730.4 mg) into a 100 ml volumetric flask and add 60 ml of mobile phase and sonicate for 15 minutes, allow the sample to cool to room temperature and add sufficient mobile phase to produce 100 ml and mix thoroughly. Filter the solution through Whatman filter paper size#41 and dilute 5 ml of this filtrate to 100 ml with mobile phase. Filter the solution through 0.45µ disk filter.

Acceptance Criteria: The Purity threshold must greater than Purity angle, so as to confirm peak purity.

OBSERVATION

Sl. No.	Compound	Purity1 Angle	Purity1 Threshold
1	Test Sample	0.03	0.23

Remarks: From the above study, we found that The Purity threshold is greater than Purity angle of standard.

Results: So, Peak is pure for the sample

Forced Degradation

Using the PDA detector and Typical UPLC condition described in bellow, determine the Purity threshold and Purity angle, for the Imatinib peak.

Chromatographic condition

Column : 4.6-mm X 150-cm column that contains packing L1 (C18)
Detection : 230 nm
Flow rate : 1.1 ml / minute
Temperature : 25°C
Injection volume : 10 µl
Sampler temperature : 10°C

Prepare a series of sample solutions and deliberately degrade as follows:

Acidic Degradation (by 1N Hydrochloric acid)

Weigh 10 tablets and determine the average weight. Take 4 tablets (about 1730.4 mg) into a 100 ml volumetric flask and add 60 ml of 1N hydrochloric acid in mobile phase and sonicate for 15 minutes, allow the sample to cool to room temperature and add sufficient 1N hydrochloric acid in mobile phase to produce 100 ml and mix thoroughly (allow this solution 2 hour at this condition). Filter the solution through Whatman filter paper size#41 and dilute 5 ml of this filtrate to 100 ml with mobile phase. Filter the solution through 0.45µ disk filter.

Base Degradation (by 1N Sodium Hydroxide)

Weigh 10 tablets and determine the average weight. Take 4 tablets (about 1730.4 mg) into a 100 ml volumetric flask and add 60 ml of 1N sodium hydroxide in mobile phase and sonicate

for 15 minutes, allow sample to cool to room temperature and add sufficient 1N sodium hydroxide in mobile phase to produce 100 ml and mix thoroughly (allow this solution 2 hour at this condition). Filter the solution through Whatman filter paper size#41 and dilute 5 ml of this filtrate to 100 ml with mobile phase. Filter the solution through 0.45µ disk filter.

Oxidation (by 2% Hydrogen peroxide)

Weigh 10 tablets and determine the average weight. Take 4 tablets (about 1730.4 mg) into a 100 ml volumetric flask and add 60 ml of 2% hydrogen peroxide in mobile phase and sonicate for 15 minutes, allow sample to cool to room temperature and add sufficient 2% hydrogen peroxide in mobile phase to produce 100 ml and mix thoroughly (allow this solution 2 hour at this condition). Filter the solution through Whatman filter paper size#41 and dilute 5 ml of this filtrate to 100 ml with mobile phase. Filter the solution through 0.45µ disk filter.

Heat Degradation (in water bath)

Weigh 10 tablets and determine the average weight. Take 4 tablets (about 1730.4 mg) into a 100 ml volumetric flask and add 60 ml of mobile phase and sonicate for 15 minutes, allow sample to cool to room temperature and add sufficient mobile phase to produce 100 ml and mix thoroughly and place sample in a water bath for 60 minutes at 80° C. After heating, allow the solution to stand at room temperature and filter the solution through Whatman filter paper size#41 and dilute 5 ml of this filtrate to 100 ml with mobile phase. Filter the solution through 0.45µ disk filter.

Acceptance Criteria: The Purity threshold must greater than Purity angle, so as to confirm peak purity.

OBSERVATION

Sl. No.	Compound	Impurity	Purity1 Angle	Purity1 Threshold
01.	Acidic Degradation (by1N HCl Acid)	--	0.03	0.23
02.	Base Degradation (By 1N Sodium Hydroxide)	--	0.03	0.22
03.	Oxidation (2% Hydrogen peroxide)	--	0.03	0.22
04.	Heat Degradation (by water bath)	--	0.03	0.24

CONCLUSION

Forced degradation studies are the most essential component to develop and establish the stability demonstrating methodology for drug products which helps the researchers to find the

possible degradation pathways and degradants of the drug active ingredients and helps to explicate the possible structure of the degradants. The degradants generated from accelerated or forced degradation studies are potential elements that may or may not be created under relevant storage conditions but they are significant in the developing drug stability indicating method. It is better to start drug degradation studies previously in the drug development process to have sufficient time to get further information about the stability of the drug molecule. This information will then help to improve the drug formulation manufacturing process and determine its storage conditions. Since no specific set of storage conditions are appropriate to all drug substances and drug products, as well as the regulatory guidance does not specify about any specific conditions to be used, hence this study requires the researcher to use common sense. A forced degradation study which is carefully planned, well designed and perfectly accomplish would must be generate an appropriate sample for the development of stability indicating method.

From the above study, We found that the Purity threshold is greater than Purity angle of standard, sample solution, Acidic Degradation (by 1N HCl acid), Base Degradation (By 1N Sodium Hydroxide) Oxidation (2% Hydrogen peroxide) and Heat Degradation (by water bath). So peak is pure for Acidic Degradation (by 1N HCl acid), Base Degradation (By 1N Sodium Hydroxide), Oxidation (2% Hydrogen peroxide) and Heat Degradation (by water bath).

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