A Review on Industrial Applicable Stability Indicating Assay

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ABSTRACT

In this article forced degradation is a degradation of drug product and new drug substance at different condition more severe accelerated condition. The forced degradation studies ensure chemical behavior of the molecule which in turn helps the development of formulation and packaging. The HPLC is an essential analytical tool in assessing drug and product stability. It insists various conditions like humidity, temperature, light and environmental factors which may affects the drug substance and drug product.

Keywords: Stress testing, Stability indicating assay, Development, Regulatory status.

INTRODUCTION

The degradation of drug substances between 5% and 20% has been accepted as reasonable for validation of chromatographic assays [14, 15]. The study can be terminated if no degradation is seen after drug substance or drug product has been exposed to stress conditions than those conditions mentioned in an accelerated stability protocol [16]. The limits for physiochemical changes, loss of activity or degradation during shelf life have been established for individual types or groups of biological products not be considered. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients [17].

Concept of Stability Indicating Method [2, 3]

The stability indicating assay method is a analytical method based on structural and chemical properties of each active ingredients of drug product and that will distinguish each active ingredients from its degradation products hence contents most be accurately analyzed. The ICH stability testing guideline specifies the storage condition like temperature and time. The number and size of batches testing frequency etc. stability indicating assay comes in to the picture when pharmaceutical industries and scientist began to recognize the need for specificity in stability assay method.

Types of Stability Indicating Assay

There are three types of stability under consideration which gives an idea about the stability of drug.

1. Long term stability studies
2. Accelerated stability studies
3. Forced degradation stability studies

Long term stability studies

It is also called as real time testing. The length of studies and storage condition should be sufficient to cover storage, shipment and subsequent use. The storage for long term testing is as follows:

$$25\,^{\circ}C \pm 2\,^{\circ}C/\ 60\ \%\ RH \pm 5\%\ RH$$

The minimum time period for submission is 12 Month.

Accelerated stability testing

These studies are designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product by using exaggerated storage condition as part of the formal, definitive storage programmers.

The condition of storage for accelerated testing $40\,^{\circ}C \pm 2\,^{\circ}C$/ 75 % RH $\pm$ 5% RH The minimum time period for submission is 6 Month.

Forced degradation studies

The stress testing is different from accelerated testing since the studies are carried out under more severe condition. The stress testing is conducted to provide data on forced decomposition mechanism for the drug substance. The condition that may be encountered during distribution can be covered by stress testing of definite batches of drug substance. The study normally include exposure of the drug to elevated temperature or humidity ,light and oxidizing agent as well as susceptibility to hydrolysis across a range of pH values .

Objective of Forced Degradation Studies [1]

1. To solve stability related problem
2. To establish degradation pathway of drug substance and drug products
3. To elucidate the structure of degradation products
4. To determine intrinsic stability of drug substance in formulation
5. To establish stability indicating nature of developed method
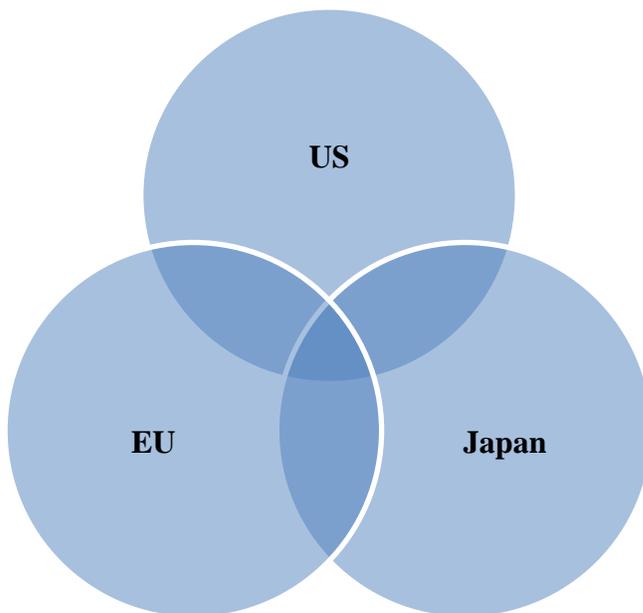6. To generate more stable formulation

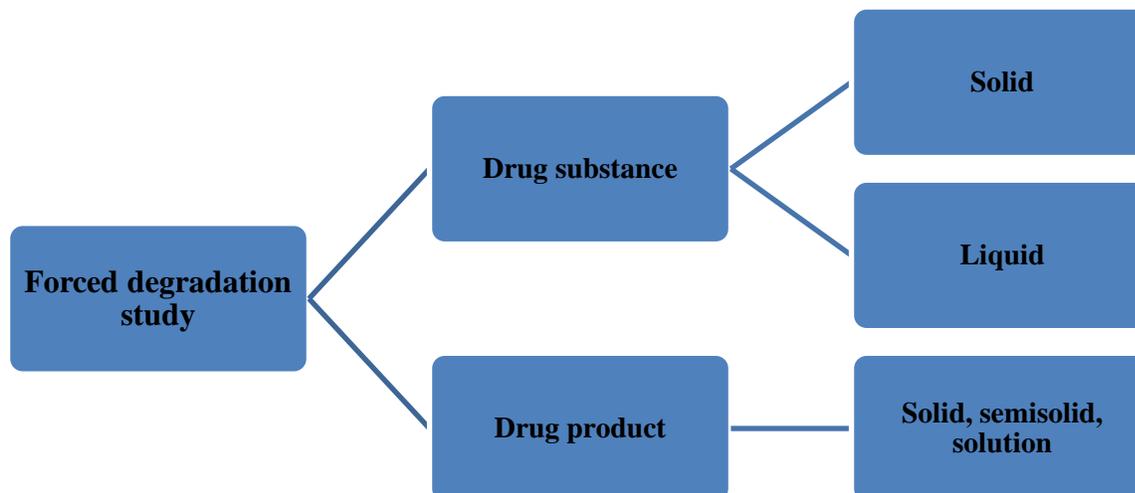**Figure 1: Regulatory three parties (ICH)**

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                                              ┌──────────────┐
                                              │    Solid     │
                              ┌──────────────┐└──────────────┘
                              │Drug substance│
                              └──────────────┘┌──────────────┐
┌──────────────────┐                          │   Liquid     │
│Forced degradation│                          └──────────────┘
│      study       │
└──────────────────┘┌──────────────┐          ┌──────────────────┐
                    │ Drug product │          │ Solid, semisolid,│
                    └──────────────┘          │    solution      │
                                              └──────────────────┘
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Figure 2: Forced degradation illustration study

Stability Indicating Method Development Strategies [2]

The method of process can be high level process map achieving the end product stability, stability indicating method. The following discussion steps indicating the analytical method:

1. Understand the chemistry/ physicochemical properties of drug

2. Set up preliminary HPLC condition

3. Preparation of sample required for method development

4. Developing separation stability indicating chromatography condition

5. Method optimization

6. Validation of analytical method

Stability Indication [4]

Developing a stability indicating assay requires consideration of three aspects of the method

1. The sample

2. The separation

3. The detector

The stability indicating assay requires condition of three aspects of the method obtaining a representative sample, choosing separation technique and selecting the detector.

The sample

A good deal of developing a stability indicating assay is generating a sample that can be used for method development. Another way to obtain sample for developing stability indicating assay is to place the pure drug substance under the stress intentionally.

The separation

The reverse phase LC is the method of choice for stability indicating assay because the sample are generated in aqueous solution. The most common separation variable includes solvent type, mobile phase pH, column and temperature.

The detector

The mass spectrometer is becoming the detector choice for many LC methods particularly for determining drugs in biological samples. The UV detector remains the detector of choice for stability indicating assay.

Table 1: Condition of forced degradation studies [1]

Types	Conditions	Storage condition	Sampling time
1.Thermal	Heat chamber	60 º C	1,3,5
-	Heat chamber	60 º C/ 75 % RH	1,3,5
-	Heat chamber	80 º C	1,3,5
-	Heat chamber	80 º C/ 75 % RH	1,3,5
-	Heat chamber	RT	1,3,5
2. Photolytic	Light 1 X 1 CH	NA	1,3,5
-	Light 3 X 1 CH	NA	1,3,5
-	Light	NA	1,3,5
3. Oxidation	3 % H2O2	25º C 60 º C	1,3,5
	Peroxide control	25º C 60º C	1,3,5
	Azobisiso butyronitrile	40º C 60º C	1,3,5
	AIBN	40º C 60º C	1,3,5
4. Hydrolysis	Control API	40º C 60º C	1,3,5
	0.1 M Hcl	40º C 60º C	1,3,5
	0.1 NaOH	40º C 60º C	1,3,5
	Acid control	40º C 60º C	1,3,5
	Base control	40º C 60º C	1,3,5

Table 2: Stability indicating method development strategies for solid state [2]

Stress	Condition	Period
Heat	60º C	1 M
Humidity	75 % RH	1 M
Photostability	3 mm (powder)- control	ICH Q1B

Table 3: Reports of stability indicating methods employed stress condition

Stress condition	Drugs	Methodology	References
Acid	Lisinopril	Derivative UV	8
Alkali	Allantoin	HPLC	9
Neutral	Physostigmine HCl	HPLC	10
Oxidation	Nortryptiline HCl	UV spectroscopy	11

Light	Atenolol	HPLC	12
	Danazol	HPLC	13

Different Methods for Stability Indicating Assay [5]

1. Tritrimetric and spectrometric
2. Chromatographic assay
3. Advanced technique

Tritrimetric and spectrometric method

These methods are analyzed by single drug of interest with excipients, additives, degradation products, impurities and in combination products. These methods are used in quantitative determination of analyte.

Chromatographic assay

The difference technology is used in SIAM like TLC, HPLC, HPTLC, Capillary electrophoresis and GC. These techniques are sensitive and accurate than others and produced small quantities of degradation products.

Advanced technique

The advanced stability indicating assay methods includes the use of proton nuclear magnetic resonance (H^1 NMR) spectroscopy. There are many hyphenated techniques includes LC-MS, LC-MS-MS used for structural information and molecular weight determination.

Regulatory Status of Stability Indicating Assay [6]

The ICH guideline Q6A, which provides note for guidance on specifications, the same is also requirements in the guidelines Q5C on stability testing of biotechnological/ Biological products. The ICH guidelines have been incorporated as law in EU, US and Japan, but in reality besides these other countries are also using them. The ICH guideline Q1A on stability testing of new substance and products, even the United States of pharmacopeia (USP) has requirement listed under stability studies in manufacturing which says that sample of the products should be assayed for potency by the use of stability indicating assay.

CONCLUSION

Forced degradation studies provide knowledge about possible degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants. Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method. It is better to start degradation studies earlier in the drug development

process to have sufficient time to gain more information about the stability of the molecule. This article could help in designing and developing methods for stability studies of different types of drug. Stress tests for developing a stability indicating method should always be designed and evaluated with common sense and chemical knowledge, keeping in mind the manufacturing process and the nature of the final drug product. The stability profile needs to be established for drug product to assure safety, efficacy and quality.

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