FORCED DEGRADATION STUDY: AN OVERVIEW

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Received: May 30, 2018 Accepted: July 18, 2018

ABSTRACT *Stability study is the organized approach towards drug development process. This article provides an summary of types of stability studies, strategies relevant to designing stability indicating HPLC method development for drug substance and and objective of forced degradation study. Forced degradation studies are used to facilitate the development of analytical methodology, to gain a better understanding of active pharmaceutical ingredient (API) and drug product stability, and to provide information about degradation pathways and degradation products. Practical recommendations are provided for developing forced degradation protocol. The ability to differentiate the active ingredient from closely related process and degradative impurities is usually the key requirement for stability indicating methods.*

Keywords: *Stability study, Forced degradation study, validation, HPLC*

INTRODUCTION

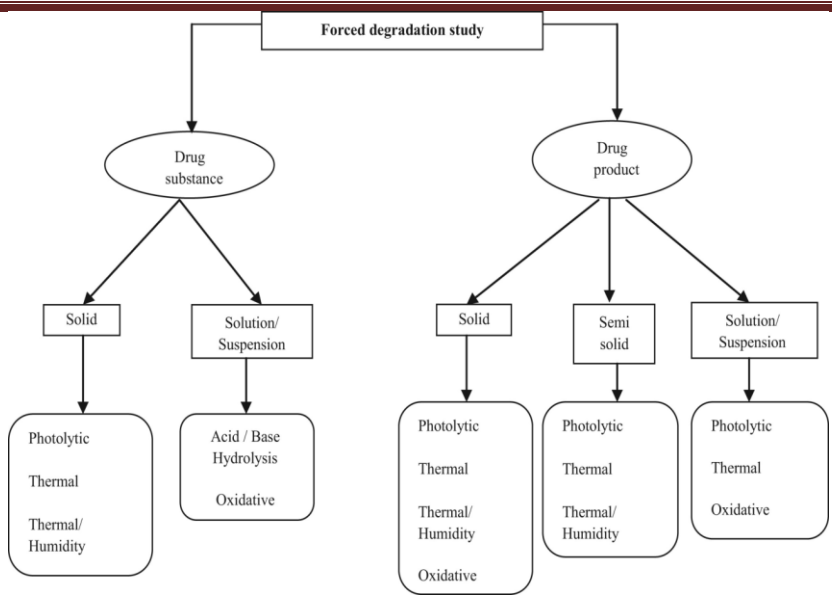
Stability:

Stability is defined as the capacity of a drug substance or drug product to remain within established specifications to maintain its identity, strength, quality, and purity throughout the re-test or expiration dating periods. Stability testing of an active substance or finished product provides proof on how the quality of a drug substance or drug product varies with time [1]. All stability study guidelines are mentioned in ICH, FDA, WHO and EMEA[2]. With the arrival of International Conference on Harmonization (ICH) guidelines, the condition of establishment of stability-indicating assay method (SIAM) has become more clearly mandated[3]. According to FDA guidance document a stability-indicating method is "a validated quantitative analytical procedure that can detect the changes with time in the relevant properties of the drug substance and drug product[4]. A stability-indicating method accurately measures the active ingredients without interference from degradation products, process impurities, excipients or other potential impurities[5].

High performance liquid chromatography (HPLC) is an integral analytical tool in assessing drug product stability. HPLC methods should be able to separate, detect, and quantify the various drug-related degradants that can form on storage or manufacturing, plus detect and quantify any drug-related impurities that may be introduced during synthesis[6].

Importance of stability testing

The most important reason for stability testing is the concern for the safety of the patient suffering from the disease for which the products is intended. Apart from degradation of the unstable product into toxic decomposition products, loss of activity up to a level of 85% of that claimed on the label may lead to failure of the therapy resulting in death e.g. nitroglycerine tablets for angina and cardiac arrest. Second important concern is to protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market. Other benefits of stability studies at the developmental stage or of the marketed products are to provide a database that may be of value in selection of satisfactory formulations, excipients and container closure systems for development of a new product, to determine shelf life and storage conditions for development of a new product, preparation of registration dossier, to confirm the claimed shelf life for the registration dossier and to verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product[7].



Scheme 1- An illustrative flowchart describing various stress conditions used for degradation of drug substance and drug product.

Types of drug stability studies[4]

Sr. No.	Study	Storage condition	Minimum time period Covered by data at Submission
1.	Long term	25^0 C ± 2^0C/ 60% RH ± 5% RH or 30^0 C ± 2^0 C/65% RH ± 5% RH	12 months
2.	Intermediate	30^0 C ± 2^0 C/65% RH ± 5% RH	6 months
3.	Accelerated	40^0 C ± 2^0 C/ 75% RH ± 5% RH	6 months

Stability indicating method development steps:

1. Understand the physiochemical properties and chemistry of the drug

The information of physicochemical properties of the APIs such as dissociation constant, partition coefficients, fluorescent properties, chromatographic nature, oxidation-reduction potentials, Spectrophotometric properties is important for setting the experimental conditions during the stability studies of the drug[5].

2. Set up preliminary HPLC condition

Literature search and officials or non-officials method usually used for the selection of preliminary experimental conditions for the stability studies. Experimental conditions are selected according to the properties of the API's[l8].

3. Sample preparation for method development

Stability indicating methods are developed by stressing the API under accelerated condition to degrade API up to 5-10% which is analysed by using the suitable preliminary HPLC condition with suitable detector[9].

4. Develop Stability indicating chromatographic conditions

The common separation variable includes flow mode, solvent types, mobile phase, pH, column type and temperature[10].

5. Method of Optimization

Experimental condition should be optimized to get desired separation and sensitivity after getting appropriate separation. Experimental condition should be achieved through the systematic examination on parameter including PH (ionic), mobile phase component and ratio, gradient, flow rate, temperature, injections volume and diluents sample type[11].

6. Validation of Analytical Method

Analytical methods have to be validated according to the ICH/USP guidelines. It is necessary to isolate, identify, characterize, and qualify degradation products if they are above the identification threshold (usually 0.1%)[9]. In validation accuracy, precision, linearity, range, specificity, limit of detection, limit of quantitation, ruggedness, and robustness of the method are done[12].

Table- 2 ICH Guidelines for the drug stability studies[4]

ICH code	Guideline title
Q1A	Stability testing of New Drug Substances and Products
Q1B	Stability testing : Photostability testing of New Drug Substances and Products
Q1C	Stability testing of New Dosage Forms
Q1D	Bracketing & Matrixing Designs for stability testing of Drug Substances & Products
Q1E	Evaluation of stability data
Q1F	Stability data package for Registration Applications in Climatic Zones III and IV
Q5C	Stability testing of Biotechnological/Biological Products

Forced degradation studies in stability-indicating method development:

Forced degradation is also referred as stress testing and it demonstrates specificity when developing stability indicating methods, especially when little is known about potential degradation products[11]. It is defined as the stability testing of drug substances and drug products undertaken to elucidate intrinsic stability attributes[13,14]. It is an fundamental step in the design of a regulatory compliant stability program for both drug substances and products, and was formalized as a regulatory requirement in ICH Guideline Q1A in 1993[15]. It is a powerful tool used regularly in pharmaceutical development in order to develop stability indicating methods that lead to quality stability data[16].

Table- 3 Condition generally employed for forced degradation[6]

Degradation type	Experimental condition	Storage condition	Sampling time
Hydrolysis	Control API (no acid or base)	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	0.1N HCl	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	0.1N NaOH	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	Acid Control (no API)	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	Base Control (no API)	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	pH: 2,4,6,8	40 ^{0}C, 60 ^{0}C	1,3,5 Days
Oxidative	3% H_2O_2	25 ^{0}C, 40 ^{0}C	1,3,5 Days
	Peroxide Control	25 ^{0}C, 40 ^{0}C	1,3,5 Days
	Azobisisobutyronitrile (AIBN)	40 ^{0}C, 60 ^{0}C	1,3,5 Days
	AIBN Control	40 ^{0}C, 60 ^{0}C	1,3,5 Days
Photolytic	Light, 1 × ICH	NA	1,3,5 Days
	Light, 3 × ICH	NA	1,3,5 Days
	Light Control	NA	1,3,5 Days
Thermal	Heat Chamber	60 ^{0}C	1,3,5 Days
	Heat Chamber	60 ^{0}C/ 75% RH	1,3,5 Days
	Heat Chamber	80 ^{0}C	1,3,5 Days
	Heat Chamber	80 ^{0}C / 75%RH	1,3,5 Days
	Heat Control	Room temp	1,3,5 Days

Objective of Forced Degradation Studies:

Forced degradation studies are carried out to accomplish the following purposes:

1. To establish the intrinsic stability of a drug substance in formulation[17].
2. To identify the chemical properties of drug molecules[17].
3. To produce more stable formulations[17].
4. Generation of samples required for identification of the degradation products formed under a different stress conditions[15].
5. To evaluate degradation pathways and mechanisms of a drug substance in formulation[15].
6. Study of drug-drug and drug-excipient interactions in formulation[15]

CONCLUSIONS:

Stability testing is now the key routine component in the pharmaceutical development program for a new drug as well as new formulation. Stability-indicating method (SIM) is an analytical method that is capable of differentiating between the active pharmaceutical ingredients (API) from any degradation product(s) formed during the defined storage conditions during the stability testing s period. Forced

degradation studies of new drug substances and drug products are important to develop and demonstrate specificity of stability-indicating methods and to determine the degradation pathways and degradation products of the active ingredients.

ACKNOWLEDGEMENT

The authors are thankful to the Principal Dr. S. S. Khadbadi and Associate Professor Dr. U. A. Deokate, Government College of Pharmacy, Aurangabad, Maharashtra, India for providing literature survey facilities for the review article.

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