Review Article CODEN: IJPRNK ISSN: 2277-8713
Amrita Panda, IJPRBS, 2013; Volume 2(6): 69-80 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

# STABILITY STUDIES: AN INTEGRAL PART OF DRUG DEVELOPMENT PROCESS

**AMRITA PANDA, SUKHADAKULKARNI, RAVI TIWARI**
Department of Pharmaceutical Chemistry, SVKM's NMIMS, School of Pharmacy and Technology Management Shirpur Dist. Dhule 425405 Maharashtra, India

**Accepted Date: 08/10/2013; Published Date: 27/12/2013**

**Abstract:** Stability testing is the systematic approach towards drug development process. This article provides an overview of types of stability testing, its application in pharmacy and the regulatory guidelines. The degradation of any drug product depends mainly on the chemical structure of active ingredient present in it, hence, stress stabilities studies are carried out to trace those degradation pathways. Stability testing is basically done to achieve a safer quality of drug product. Stability studies are performed at various stages of drug development process to assure efficacy of the drug.

**Keywords:** Stability Study, Drug Development

*PAPER-QR CODE*

**Corresponding Author: MS. AMRITA PANDA**

**Access Online On:**

www.ijprbs.com

**How to Cite This Article:**

Amrita Panda, IJPRBS, 2013; Volume 2(6): 69-80

## INTRODUCTION

Stability study is a vital stake of the drug development process. Stability is the only way that assures whether the drug is within acceptance criteria or not. Stability comes into focus when the quality and efficiency of the drug are concerned. literal meaning of stability is the capacity of a drug product to remain within specifications established to ensure its identity, strength quality and purity. Instability of the drug can cause undesired change in performance that causes product failures. Factors affecting drug stability are mainly classified as: Environmental factors such as temperature, light, oxygen, moisture, carbon dioxide; Drugs or excipients in the dosage form: particle size of drug, pH of the vehicle; Microbial contamination, trace metal contamination, etc.[1]

The main objective of stability study is to provide evidence for the report submitted on the effects of various factors (above mentioned) on the drug under different conditions and to establish shelf life for the drug and recommended storage conditions. Also it provides necessary data for the shipping and distribution of the drug product. It is intended to study basically three ensured stabilities i.e. physical, chemical and microbiological.[6]

Stability study is performed at various stages of the drug development process. At the early stage of drug development, accelerated stability studies are performed to find out the rate of degradation of the product if stored for longer period under specific conditions. After that, forced degradation study is carried out to check the effect of stressed external conditions on the drug product.[2]

International Conference on Harmonization (ICH) has given certain guidelines which give standards for how stability study should conducted. Regulatory guidelines are discussed further in this paper.

### Histological Background

The need arose when regional office organized a workshop for validation of expiry dates of drug in Amman. Jordan was the one to give the name for Stability testing in the pharmaceutical companies. The workshop ordered every medical authority to collaborate with every pharmaceutical company to guide them about the importance of drug stability and expiry date. Thus International Conference on Harmonization thus took a step to implement these guidelines. FDA issued its first stability guidance in 1987.Considerable efforts were taken, to harmonize the stability practices with in the ICH region then after in the early 1990. As a result to the efforts, International Conference on Harmonization (ICH) was established in 1991 and various guidelines for drug substance and drug product came into existence regarding their quality, safety and efficacy. These guidelines are called as quality, safety, efficacy and multi-

disciplinary (also called as Q, S, E and M) guidelines. Work on stability of pharmaceutical products was initiated by WHO in1998 and also the WHO Guidelines on stability testing for well-established Drug Substances in conventional Dosage forms were adopted in 1996 by WHO Expert Committee on Specifications for Pharmaceutical Preparations following extensive Consultation. In 2000, discussions began between the ICH expert working group Q1 (Stability) and the WHO to harmonize the number of stability tests and conditions employed worldwide.[3]

The main purpose of stability testing is to establish testing of about two or three batch of product shelf life and label storage instructions applicable to all the products. There is still a systematic information need to be provided for the adequate information of the physical, chemical, microbial test.

**Types of Drug stability studies**

Stability studies are mainly of following types:

- Long term stability
- Intermediate stability
- Accelerated stability
- In-use stability

**Long term stability**

Stability studies are intended for testing the drug product for longer periods under varying conditions of temperature and humidity. If the drug is to be distributed in different geographical regions and if shipping is required for transportation, in that case long term stability studies are of prime importance.[4] Long term stability studies are performed by testing the sample at specific time intervals and conditions of external parameters are changed accordingly. Main objective of this study is to determine shelf-life of the drug product.

30°C ± 2°C/65% RH ± 5% RH can be a suitable alternative long-term storage condition to

25°C ± 2°C/60% RH ± 5% in the following sections:

- Drug Substance - Storage Conditions - General Case
- Drug Product - Storage Conditions - General Case

**Intermediate stability**

Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

The intermediate storage condition has been changed between different temperature and relative humidity conditions in the following sections:

- Drug Substance - Storage Conditions - General Case
- Drug Product - Storage Conditions - General Case
- Drug products packaged in semi-permeable containers

**Accelerated testing**

These studies include use of exaggerated storage conditions designed to study increased rate of physical and chemical degradation. This is part of the formal stability studies. Data from these studies is uses to carry out long term stability studies i.e. to determine shelf-life of the drug product.[5]

Following table summarizes the storage conditions as per different types of stability studies:

| Study | Storage condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term | 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH | 12 months |
| Intermediate | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 months |

**In-use stability**

This type of stability studies is specifically for the drugs that are prescribed to be taken in more than one dose or multi-dose drugs. The chemical composition and physical stability of these drugs are such that due to repetitive opening and closing, it gets degraded due microbial

contamination. The purpose of in-use stability testing is to establish - where applicable - a period of time during which a multi-dose product can be used until retaining quality within an accepted specification once the container is opened.

**Application of Stability testing to Pharmaceutical method**

Pharmaceutical products are the one whose stability needed to be check which would otherwise affect the life of people. Hence stability study are included which test those attributes of drug which are susceptible to change during storage and are likely to influence quality, safety and efficacy.

The testing should cover the following important attributes,

1. Physical
2. Chemical
3. Biological / Microbiological

As described earlier, physical, chemical, and microbiological data are generated as a function of time and storage conditions (e.g., temperature and relative humidity). The stability of a pharmaceutical product is affected by the potential that is main drug interaction with its excipients; the manufacturing process, the dosage form, and the container/closure system. [16]The drug product stability are not only affected by above but also changes with time and environmental distribution. Seasonal changes, mode of transportation, and the number of drop-off points are the other variables that should be considered within the pharmaceutical supply chain. Not only physically but also chemically like oxidation, reduction, hydrolysis, or racemization play a vital role. Drug products which require the controlled-temperature storage conditions must be distributed in a manner that ensures that the product quality will not be adversely affected.[16]

**Physical stability** implies that the formulation is totally unchanged throughout it shelf life and has not suffered any changes in its appearance, organoleptic properties, and other physical properties (like hardness, brittleness, particle size etc in case if it is solid). The drug release nature (rate and mechanism) should not be altered. Different parameters are adapted for checking different stability criteria of different physical properties. Physical stability affect to drug uniformity and release rate hence it is important from safety and efficiency point of view.

**Chemical stability** implies that lack of chemical entity that is incorporated in formulation as the drug. The chemicals already present in formulation as preservative or excipients may also influence or alter the chemical stability of drug content. The Chemical stability of drug is of

great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic byproducts that are harmful to the patient.

**Microbiological stability** implies itself that the formulation has not suffered from any microbiological attack and is meeting the standards with respect to lack of sterility growth of microorganism. Microbiological instability of a sterile drug product could be hazardous.

**Strategies for development of stability indicating method**

Without knowing the stability testing of a drug, the drug formulation can cause a high risk of failure as it may cause loss of economy and also drug failure. Thus there are various steps while developing various stability methods:

- The structural and phytochemical properties of the API

With the help of the structure the degradation pathway of any compound can be predicted. The various physiochemical properties like pKa, pH, log P, solubility of API, molecular weight, λmax, etc. are the basic information required for the sample preparation techniques.[9] Whereas the chemical structure gives the idea of the molecular weight and the nature of functional group like acidic, basic and aromatic group taken into consideration. These functional group indicates the potential active sites for degradation of the drug to hydrolysis, oxidation and its thermal degradation.

- Setup the chromatographic Conditions

During initial method development, three steps are to be checked firstly mobile phase parameters [Percentage organic solvent (%B), buffer type and concentration, pH, solvent type], secondly Operating parameters [Flow (F), temperature (T), gradient range (Δϕ), gradient time (tG)], Column [Bonded phase type, length (L), column diameter (dc), particle size (dp)], thirdly Detector setting (monitoring wavelength) and sample amount.[13]

a) Selection of detector:

For an analyte having reasonable UV absorbance, the UV/Vis spectrophotometer is required. For analyte having no UV absorbance, Refractive index detectors are neccesary. Mass spectrometry (MS) is a possible choice for "ionizable" analytes.

b) Selection of mobile phase:

Solvents which are used for the HPLC that is high polarity liquid chromatography should have high solubility for API, noncorrosive to HPLC system, high purity, low cost, UV transparency, low toxicity, and non-flammability.[14]

The compounds which can be ionized are often separated by Reversed Phase Chromatography with buffered phase or with ion-pairing reagents. In RPC, acidic pH of 2.5–3 is used for many applications. The low pH suppresses the ionization of weakly acidic analytes, leading to higher retention.[13]

c) Selection of column:

Column efficiency (N) can be determined by the Column length (L), Particle size and size distribution not only it they also define analysis speed, and pressure drop. High surface area thus gives a bonded phase with higher density and retention. The nature and characteristic of column packing containing the stationary phase is considered the most delicate part to the column performance and success of the intended applications. Select columns packed with 3- or 5-µm high-purity silica-bonded phases from a reputable manufacturer. 3 µm packing is probably preferable due to its faster analysis since shorter column length can be used.

- Preparing sample for method development

Stability Indicating Methods is developed routinely for the API that are used differing from the one used for accelerated stability testing. Further along with demonstration of SIMs, stress testing, also referred to as force degradation, also can be used to provide information about degradation pathways and products that could form during storage and help in facilitating formulation development, manufacturing and packaging.[10] Force degradation study are conducted through thermolysis, hydrolysis, oxidation, photolysis, and or combinations. Each force degradation sample should be analyzed by using the HPLC detector.

In general, the "dilute and shoot" approach can be used for most drug substances and parenteral products.[10] A common process of "grind → extract → dilute → filter" is used for most solid dosage forms such as tablets or capsules. More complex dosage forms, such as suppositories, lotions, and creams, and physiological samples (serum or plasma) might require additional sample clean-up and extraction such as liquid-liquid extraction or solid-phase extraction.

- Developing separation method

After the sample is generated through the use of a properly designed and executed forced degradation, it can be used to develop the LC method. The goal of development of method is separation of API peak from degradable product and detection of same. The separation of peaks are depends on solvent type, mode of chromatograph, mobile phase pH, column type and temperature.

a. Solvent type

The choice of solvent is depend on the solubility of analyte, buffer used and UV value of solvent and safety of solvent. We first reject solvents whose physical properties (boiling point, viscosity, UV absorbance, etc.) are inappropriate for use in Liquid Chromatography. We select a solvent or solvent mixture of the right chromatographic strength.

b. Mode of chromatograph: Isocratic OR Gradient:

Isocratic elution means use of the same solvent throughout the separation. The main purpose of gradient elution is to move the retained components of the mixture faster, but having the least retained component well resolved. Gradient elution also increases quasi-efficiency of the column. In the isocratic elution, longer a component retained, the wider its peak.[15]

c. Column type:

HPLC column parameters such as column types (silica, polymer), modes, dimensions (preparative, analytical, narrow bore, micro LC), and packing characteristics (particle and pore size) are presented with key column development trends (high-purity silica, hybrid particles, novel bonding chemistries).[13] Nature of stationary phase has greater effect on capacity factor, selectivity, efficiency and elution and determine whether a column can be used for normal phase or reverse phase chromatography.

d. Column temperature:

Column temperature will affect selectivity. Use of a column oven eliminates variability due to normal fluctuations in the air temperature surrounding the column. The k' decreases with increases in temperature for neutral compound but less for partially ionized analysts.

- Method optimization

The experimental conditions regarding the stability indicating assay can be achieved through planned and systemic examination including pH, mode of chromatogram, flow rate of mobile phase, column type and column temperature, sample concentration and amount of sample injected, solvent used, detection wavelength, etc.[14]

Analytical method validation

The ICH guideline gives parameters to be considered when validating methods. These parameters include accuracy, precision, specificity, detection limit, quantitation limit, linearity, and range.1, 6 The specificity of the methods cannot be fully validated. It can be determined by using any known impurities samples. Precision or repeatability of the assay of API can evaluate

by preparing limit no of assay samples. An assay range might be from 50 % to 110% of normal sample concentration.

**Role of Regulatory**

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) was organized in order to harmonize stability testing requirements for new drug applications within the European Union (EU), the United States, and Japan.[17 18 19]

**Scope of the Guidelines**

The guideline addresses the information to be submitted in while registration of any new molecular entities and associated drug products is to be done. Further, they are used for guidance on biotechnological and biological products too that helps to test the stability studies of these products.[8]

**Limitations**

The guideline for drug stability does not give specific details of the sampling and testing for particular dosage forms in their proposed containers. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

Following are the guidelines given by ICH for the drug stability studies:[12]

| Guideline | Title |
|---|---|
| Q1A(R2) | Stability testing of new drug substance & product |
| Q1B | Stability Testing : Photo stability testing of New drug Substance & product |
| Q1C | Stability testing for new dosage form. |
| Q1D | Bracketing & Matrix Design for stability testing of new drug substance and drug product |
| Q1E | Evaluation of stability data |
| Q1F | Stability data package for Registration Application in Climatic Zones III and IV |
| Q5C | Stability Testing of Biotechnological/Biological Products |

**Stress Stability Studies:**

Basic purpose of this method is to develop and demonstrate specificity of stability- indicating methods and to find out both degradation pathway and product of the active ingredient present in the given drug product. The experimental protocol for degradation studies depends on the chemistry of active ingredients present in drug molecule. If the compound does not degrade in the given stressed conditions then no additional conditions are mentioned in such case.

The stability testing of samples under stressed conditions is required to demonstrate the following abilities of analytical techniques. [20]

- To evaluate stability of API and drug product in solution
- To determine structural transformations of the API and drug product
- To detect low concentrations of potential degradation products
- To detect unrelated impurities in the presence of the desired product and product-related substances causing degradation

**Conclusions**

Stability studies are capable of differentiating active drug ingredient from any degradation product formed under defined storage conditions. Further, they are used to find out degradation pathway (physical, chemical or microbiological). The types of stability allow analyst to study the degradation products formed under varying conditions of temperature and relative humidity. Regulatory provides standard guidelines for use of stability studies at different stages of drug development process. Forced degradation studies play an important role in development of Stability indicating assay method.

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