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Stability Testing Studies: A Review

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Abstract
Stability studies play an important role in pharmaceutical products. Stability studies ensure the product quality, efficacy and potency of the drug product. The main aim of the stability is to determine the product shelf life and its storage conditions. These stability studies follow the ICH and WHO guidelines. Importance of various methods followed for stability testing of pharmaceutical product, guidelines issued for stability testing and other aspects related to stability of pharmaceutical products have been presented in a concise manner in the present review.

Keywords
Stability studies, ICH guidelines, Types of stability studies, Conditions and factors affected.

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INTRODUCTION
A stability study is mainly used for in order to build quality, efficacy and safety. The stability – indicating assay is a method that is employed for the analysis stability samples in pharmaceutical industry [1,7]. With the advent of international Conference on Harmonisation (ICH) guidelines, the requirement of establishment of stability-indicating assay method (SIAM) has become more clearly mandated. The guidelines explicitly require conduct of forced decomposition studies under a variety of conditions, like pH, light, oxidation, dry heat, etc. and separation of drug from degradation products. The method is expected to allow analysis of individual degradation products. Stability studies thus evaluates the effect of environmental factors on the quality of the drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions & suggest labelling instructions.

Significance of stability testing method
- It is more important to determine the stability or shelf life of a product [2]
- To overcome the degradation of the product that may leads to loss of its therapeutic activity & resulting in death [2]

Factors effecting stability
The main factors affecting stability testing are [7]
- Interaction between active ingredients and excipients
- Manufacturing process
- Type of dosage form
- Container/closure system used for packaging
- Heat & moisture conditions encountered during shipment
- Storage & handling

Conditions effected the stability testing
They are-
- pH

- Catalysts
- Consistency
- Content uniformity
- Clarity
- Moisture content
- Particle size
- Package integrity

These physical and chemical changes of pharmaceutical product may lead to the degradation then loss of its activity and potency [10, 13].

Stability testing methods

Stability testing performed on different stages of the product development

Stability studies categorised into four types

- **Real-time stability testing**
- **Accelerated stability testing**
- **Retained sample stability testing**
- **Cyclic temperature stress testing**

Real-time stability testing

Real-time stability testing is done for longer duration of the test period. It is performed for laboratory batches i.e. Primary batches and the major factors of real time stability testing –Guidelines, stability protocol, storage conditions for samples, validated rest methods bracketing matrixing, evaluation of results [1,2].

Accelerated stability testing

Accelerated stability testing is performed at different high temperatures. The addition of temperature applied during accelerated stability testing are moisture, light, agitation, gravity and pH. This stability testing required high stress temperature and the duration of analysis is short; instability of these testing is reduced than real time stability testing. Stressed and unstressed sample recovery is expressed as per cent [1, 2].

The concept of accelerated stability testing is based upon the Arrhenius equation

$$lnK = lnA + \Delta E/RT$$

Where K=Degradation rate
A=Frequency factor
ΔE=Activation energy(kJ/mol)
R=Universal gas constant(0.00831Kj/mol)
T=Absolute temperature

Retained sample stability testing

This is performed on every marketed product. In this study, stability samples are stores at least one batch in a year are selected, if the number of batches marketed exceeds more than half, stability samples are recommended to be taken, repeat the procedure for every batch for later storage decreases 2% to 5%. In this study stability samples are tested at different intervals depends on the product shelf life, different test samples are taken up to few years. This conventional method of obtaining stability data on retained storage samples is known as constant interval method [1,2].

Cyclic temperature stress testing

This testing is performed marketed products and the period of life cycle mostly is 24hrs.The minimum and maximum temperatures are suitable for these testing and the factors like recommended storage temperature, physical and chemical degradation of the product. The test should normally have 20 cycles [1,2].

Regulatory guidelines for stability testing

The ICH guidelines have been incorporated as law in the EU, Japan and in the US, but in reality, besides these other countries are also using them. As these guidelines reflect the current inspectional tendencies, they carry the de facto force of regulation [3,5].

ICH defines stability studies as quantitative analytical methods that are based on the characteristic structural, chemical or biological properties of each ingredient of a drug product and that will distinguish each active ingredient from its degradation products so that the active ingredient content can be accurately measured [3,5].

USFDA defines stability testing as validated quantitative analytical methods that can detect the changes with time in the physical, chemical or microbiological properties of a drug substance and drug product and that are specific so that the contents active ingredient degradation products and other components of interest can be accurately measured without interference.

The ICH guideline Q1A on stability testing of new drug substances and products emphasizes that the testing of those features which are susceptible to change during storage and are likely to influence quality , safety and/or efficacy must be done by validated stability testing methods .It is also mentioned that forced decomposition studies (stress testing) at temperatures in 10c increments above the accelerated temperatures, extremes of p H and under oxidative and photolytic conditions should be carried out on the drug substance so as to establish the inherent stability characteristics and degradation pathways to support the suitability of the proposed analytical procedures.

The ICH guideline Q3B entitled Impurities in New Drug Products emphasizes on providing documented

evidence that analytical procedures are validated and suitable for the detection and quantification of degradation products. It is also required that analytical methods should be validated to demonstrate that impurities unique t5o the new drug substance do not interfere with or are separated from specified and unspecified degradation products in the drug product. The ICH guideline Q6A, which provides note for guidance on specifications, also mentions the requirement of stability-testing method under universal tests/criteria for both drug substances and drug products.

The same is also a requirement in the guidance Q5C on stability testing of Biotechnological/Biological products. Since there is no single assay or parameter that profiles that stability characteristics of such products, the onus has been put on the manufacturer to propose a stability-testing profile that provides assurance on detection of changes in identity, purity and potency of the product, Unfortunately, none of the ICH guidelines provides an exact definition of a stability testing method [16].

Elaborate definitions of stability testing methodology are however, provided in the united states-food and drug administration(US-FDA) stability guideline of 1987 and the draft guideline of 1998.Stability testing methods according to 1987 guideline were defined as the quantitative analytical methods that are based on the characteristic structural, chemical or biological properties of each active ingredient from its degradation products so that the active ingredient content can be accurately measured.

This definition I the draft guideline of 1998 reads as: validated quantitative analytical methods that can detect the changes with time in the chemical , physical or microbiological properties of the drug substance and drug product ,and other components of interest can be accurately measured without interference .Current ICH guideline on Good Manufacturing Practices for Active Pharmaceutical Ingredients(Q7A), which is under adoption by WHO, also clearly mentions that the test procedures used in stability testing should be validated.

Stability of pharmaceuticals

There is specification regarding quality and quantity attributes of pharmaceuticals, that's why change in those attributes with time can be used to quantify in terms of stability of that drug substance or drug product so related substances or shelf life of those. Generally, the maximum shelf life for any products 5 y.

- General pharmacopoeia limit for most of the drug substances (API):98-102%
- General pharmacopoeia limit for most of the drug products :95-105%

According to above general sentence, any API having active ingredient lesser than 98% or drug product having active ingredient lesser than 95%bare due to degradation of active ingredients.

Stability of pharmaceutical products checked for

- Loss of active ingredient
- Increase inactive ingredient
- Loss of content uniformity
- Change in biological activity
- Microbiological contamination
- Physical change leading to loss of elegance, performance and patient acceptability.
- Formation of toxic degraded product.
- Increase in side effects.
- Due to above reason, regular checking of stability of molecule is important.

Need for stability studies

- Provide evidence on how the quality of a drug substance or drug product varies with
- time under the influence of a variety of environmental factors such as temperature, humidity and light. Lack of drug substance or drug product stability may affect the purity, potency, and safety of the drug product.
- How each one of these factors has the capability to catalyse, accelerate or mediate one or more of the various degradation reactions like hydrolysis, oxidation, photolysis or some other unwanted conversion of the drug substance or product and understanding the degradation mechanism.
- To provide information of the drug substance /product characteristics. Identification of potential degradants.
- Establish a re-rest period for the drug substance or a shelf life for the drug product and recommended storage conditions.
- Process development, design and optimization of manufacturing process
- Design of formulation (including selection excipient for formulation).
- Packaging development.

Stability studies are used to provide data to support clinical trials, registration, submission, or commercialization [16,17].

Types of stability studies

Stability studies are used to provide data to support clinical trials, registration submission, or commercialization. There sis different types of stability studies during the development process. Each phase of drug development requires addressing

the time period that the drug product continues to maintain its specifications. This period is called expiration dating period of a drug product. Current GMP indicates that the purpose stability testing of the final packaged drug product is to assure that a drug product meets applicable standards of identity strength, quality, and purity at the time of use.

A.Stability of active pharmaceutical ingredient

Purity profile of API must be established and specifications set for the allowed levels of impurities. The change of impurities with storage time must be established by subjecting the API to various accelerated and stress storage conditions to establish conditions which minimise the formation of degradants. These early stability studies may determine that the API should store under non-ambient conditions such as low temperature, low humidity, and non-oxidizing and low light environments. These stability studies should be continued to determine the optimum storage conditions for holding the bulk API before actual processing.

Stability studies of the API will provide data to establish a retest time for the raw materials used in the process. Stability indicating methods must be developed to monitor the purity of the API as well as identification and quantification of impurities. If new impurities are developed, these are referred to as "degradants" or "degradation products", and analytical methods must be developed to monitor these degradants during stability studies.

B.Stability studies to support formulation development

Excipients or non-active constituents may be added to an API to develop a formulation which meets the intended performance criteria on the drug product. These excipients may be necessary for purpose of adding colour, controlling pH, moisture, oxygen content. Interaction of the excipients with one another or with the API will be determined, as well as the rates of these reactions, through stability studies. Data of these studies, so called excipient compatibility, will be used to determine the appropriate formulation for the drug product. If interactions occur, then the products of these interactions (degradants) must be evaluated for safety, and analytical procedures for identification and quantification must be developed [18].

C.Stability studies to support production and use of preclinical and clinical supplies During the formulation development studies, batches are made to support clinical studies. Pre-clinical stage formulations are usually used for testing in animals. Stability studies are performed to show that pre-clinical samples maintain their specifications over the entire time span of the animal study. The formulation being tested must be stable to assure that all animals receive the nominal dose and purity from start to finish of the study. As the drug product enters subsequent clinical phases, materials are needed to support these clinical evaluations. In most cases such studies would only require long-term storage; however, most companies conduct additional accelerated or stress studies on the clinical materials to gain more understanding of the drug product. This data set is also used to set expiry of clinical supplies.

D.Stability studies to support drug registration

Final packaged product must be shown to be stable up to at least the expiry date. These stability data are obtained by actual testing through the expiry date add beyond. Early term stability data may be submitted to FDA or other regulatory bodies to support preliminary expiry dating. These data as well as data obtained under accelerated storage conditions may be utilised to predict ultimate stability and to establish rates and kinetics of degradation. ICH requires at least 12-month long-term stability data of three batches of drug products as necessary for drug registration. In addition, accelerated and stress studies are also conducted to establish a tentative expiration date.

E.Stability studies to support marketed products

Expiry dating of a drug product must be determined on the actual packaged drug product over the period of time indicated by the expiry date. Although extrapolated stability data may be used to support registration, real time data must be established to support actual product dating. In addition, sampling of newly manufactured production lots of product must be monitored on a continuing basis, at least to the projected expiration date or beyond, and data submitted to FDA. After approval is received for the drug product, stability studies are continued to support commercialization of the drug product. Representative lots are put on stability station for annual product monitoring. In addition, post-approval studies would also be necessary if there is any change to the processing or packaging of the drug products.

Types of stability testing studies of pharmaceutical product [10, 13, 15]

The tests should follow the methods are - Physical

- Chemical
- Microbiological/ Biological
- Toxicological

Physical: Physical test includes parameters are appearance, uniformity, colour, odour, taste etc.

Chemical: Chemical test includes potency & therapeutic activity of the drug within the specified limits.

Microbiological/biological: Biological test includes the microbial activity of the drug within the specified limits.

Toxicological: Decreases the toxic activity.

Protocol for stability testing

The protocol of stability testing is a necessarily a written document. The protocol depends on the product are [2,3,8,11]

- Batches
- Containers and Closures
- Sampling time points
- Storage of containers
- Test parameters
- Test methodology
- Acceptance criteria

Climatic zone for stability testing

The whole world has been divided into four zones (I – IV) depending upon the environment conditions of the pharmaceutical product are likely to be subjected to during their storage. These conditions have been derived on the basis of the mean annual temperature and relative humidity [2,3,11,14].

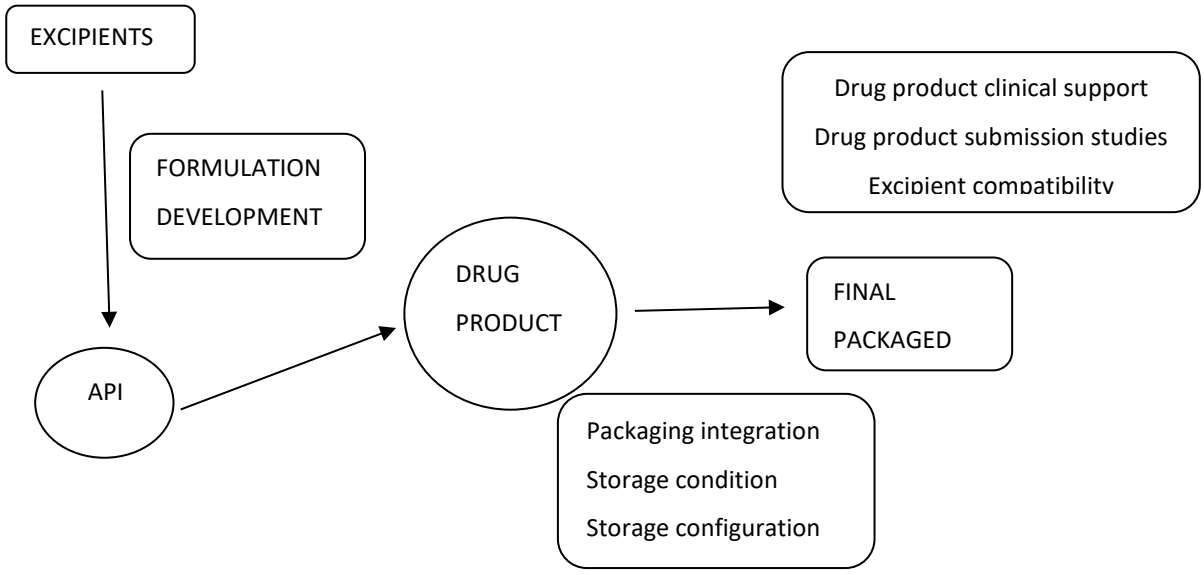
Table 1: Codes and Tables used in stability guidelines

List out the stability guidelines to be followed according to WHO and FDA.

Guideline	Title
Q1A(R2)	Stability testing of new drug substances and products
Q1B	Stability testing: photo stability testing of new drug Substances and products
Q1C	Stability testing of new dosage form
Q1D	Bracketing and matrixing designs for stability testing of New drug substances and products
Q1E	Evaluation for stability data
Q1F	Stability data package for registration applications in Climatic zone iii and iv

Figure 1: Types of stability studies

The stability studies are carrying through every step in the formulation related to API, marketed products, drug registration, formulation development, clinical and preclinical supplies.



CONCLUSION

The review work has been concluded that, proper storage conditions of the product, shelf life and the product is ensuring that safety and efficacy, decreases the side effects or lethal effects so, these testing is précised to be performed. The purpose of the stability testing is to provide evidence on how the quality of the drug substance varies with the time

under the influence of different environmental conditions.

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CONFLICT OF INTERESTS

There is no conflict of interest.

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