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FORCED DEGRADATION STUDIES - A TOOL FOR DETERMINATION OF STABILITY IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Forced degradation is the process of subjecting drug compounds to extreme chemical and environmental conditions to determine product breakdown levels and preliminary degradation kinetics, and to identify degrading species. They are used to facilitate the development of analytical methodology, to gain a better understanding of active pharmaceutical ingredient (API) and drug product (DP) stability, and to provide information about degradation pathways and degradation products. It is particularly useful when little information is available about potential degradation products. These studies also provide information about the degradation pathways and degradation products that could form during storage. Forced degradation studies may help facilitate pharmaceutical development in areas such as formulation development, manufacturing, and packaging, in which knowledge of chemical behavior can be used to improve a drug product. In order to fulfill development and regulatory needs, this publication provides a roadmap for when and how to perform studies, helpful tools in designing rugged scientific studies, and guidance on how to record and communicate results.

Key Words: Drug stability, Stress degradation, Accelerated studies, Drug kinetics.

INTRODUCTION

Analytical procedures are used to assure that the drug product meets applicable standards of identity, strength, quality and purity during its expiration dating. cGMPs require stability indicating methods to monitor the drug product's stability profiles. Therefore, method development and validation significantly impact the drug development process. 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 (DP) stability, and to provide information about degradation pathways and degradation products. The stability indicating method can be defined as Validated Quantitative analytical method that an detect the change with time in the chemical, physical or microbiological properties of the drug substance and drug product, and that are specific so that the content of active ingredient, degradation can be accurately measured without interference (Kim HB and Mary AG, 2000).

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Critical role of drug stability

- Safety and efficacy of drug product are established during development via clinical studies.
- Quality is established for identify, strength, quality and purity
- Change of Drug Stability

-Would risk patient safety
-Quality of finished products decrease
- Potential sub-potent or over-dose products
- Potential toxic unknown impurities

Factors affecting drug stability

• Stability of the Active Pharmaceutical Ingredient (API) from storage
• Interaction between the API and excipient –during Formulation Development
• Selection of dosage form
• Manufacturing process of drug product
• Selection of container closure packaging system
• Effect of storage (temperature, humidity and light)
• Selection of marketing image
• Handling of the finished products

Objectives of stress studies

The best samples of product-related degradants for the specificity evaluation would be retrieved throughout the pharmaceutical stability study. The duration of most stability studies makes this ideal situation untenable. Thus, an analyst is faced with the necessity to artificially generate degraded samples (Jenke DR, 1996)

Forced degradation or stress testing studies are part of the development strategy and are also an integral component of validating analytical methods that indicate stability and detect impurities (ICH. Guidance, 2001; FDA.Guidance, 2000). It is important to recognize that forced degradation studies are not designed to establish qualitative or quantitative limits for change in drug substance (DS) or drug product (DP).

The main objectives of analytical techniques employed in stability studies include (Reynolds DW *et al*., 2002) near evaluate stability of DS and DP in solution

- to determine structural transformations of the drug substance 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 degradants
- to separate product-related degradants from those derived from excipients and intact placebo.

The forced degradation studies are also expected

- to elucidate possible degradation path-ways
- to identify degradation products that may be spontaneously generated during drug storage and use
- to facilitate improvements in the manufacturing process and formulations in parallel with accelerated pharmaceutical studies.

Stability testing program

Stability program are used in determining appropriate storage conditions and expiration date. The written program includes selection of sample size and test intervals, storage conditions for samples, reliable, meaningful and specific test methods, testing of drug product in marketed container, testing of drug product for reconstitution at dispensing time and reconstituted time. An adequate number of batches must be tested to determine an appropriate expiration date. A record of such data must be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates. Full shelf-life studies, if not available, are being conducted.

The current regulatory guidance governing forced degradation studies of biological pharmaceuticals are extremely general. They itemize broad principles and approaches with few practical instructions. There is no single document that comprehensively addresses issues related to stress studies such as objectives, timing, selection of stress conditions, and extent of degradation. However, the complexity of biological macromolecules when compared to small molecule therapeutics, differences in manufacturing, and the broad variety of potential degradation pathways lead to special requirements in quality assurance and analytical testing of pharmaceutical proteins (Ewing GW, 2000)

ICH Guidelines

The ICH guideline indicates that stress testing is designed to determine the intrinsic stability of the molecule by establishing degradation pathway in order to identify the likely degradation products and to validate the stability indicating power of the analytical procedure used.

The International Conference on Harmonization (ICH) guidelines ‘stability testing of new drug substances and products requires that stress testing should be carried out to elucidate the substance. It suggests that the degradation products that are formed under the variety of condition should include the effect of temperature, humidity where appropriate oxidation, photolysis and susceptibility to hydrolysis across a wide range of pH value (Vitthal V. Chopade, 2008). The ICH guidelines entitled ‘Impurities in New Drug Products emphasizes on providing documented evidence that analytical procedures are validated and suitable for the detection and quantitation of the degradation product. It is also required that analytical method should be validated to demonstrate that impurities unique to the new drug substance do not interfere with or are separated from specified and unspecified degradation products in the drug products.

The purpose of forced degradation testing studies is to evaluate the overall stability of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated they are not formed in the confirmatory studies, these degradation products need not be further examined (Skoog D, 2002).

Stability studies

1. Acid-Base Degradation

The hydrolytic degradation of a new drug in acidic and alkaline condition can be studied by refluxing the drug in 0.1 N HCl / 0.1 N NaOH. If reasonable degradation is seen, testing can be stopped at this point. However in case no degradation is seen under these conditions the drug should be refluxed in acid/alkali of higher strength & for longer duration of time. Alternatively if total degradation is seen after subjecting the drugs to initial condition, acid/alkali strength can be decreased with decrease in reaction temperature.

2. Oxidation Degradation

To test for oxidation, it is suggested to use hydrogen peroxide in the concentration range of 3 to 30 %. In some drugs extensive degradation is seen when exposed to 3% of hydrogen peroxide for very shorter time period at room temperature. In other cases exposure to high concentration of hydrogen peroxide, even under extreme condition does not cause any significant degradation. The behavior is on expected lines, as some drugs are in fact oxidisable, while there are others that are not. The latter are not expected to show any change even in the presence of high dose of oxidizing agent (Willard HH, 2000).

3. Photolytic Degradation

Sunlight: - The photolytic studies should cover the exposure of drug solution to sunlight. The drug solution should be exposed to sunlight for 4 days (Bichsel E, 1998).

4. UV Light Degradation

The drug solution should be exposed to UV radiation, in UV chamber for 4 days to study the photolytic stability of drug.

5. Neutral Degradation

Stress testing under neutral condition can be started by refluxing the drug in water for 12 hours. Refluxing time should be increased or decreased as per the degradation obtained in 12 hours.

6. Thermal Degradation

Dry heat

Heating the drug powder at high temperature in oven can carry out stress testing for dry heat degradation. The heating time can be increased up to 12 hrs and above if there is no sufficient degradation seen in initial studies.

Wet heat

Wet heat degradation can be studied by refluxing the drug solution for several hours.

Analytical Methods

The manufacturer should propose stability-indicating methodologies that provide assurance that changes in the identity, purity, and potency of the product will be detected. These methods will characterize potency, purity, and biological activity (Szepesi G *et al*., 1991) As examples, stability indicating methods may include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelec-trofocusing), high-resolution chromatography (e.g., reversed phase chromatography, SEC, gel filtration, ion exchange, and affinity chromatography), and peptide mapping.

The selected set of methods must be able to detect, separate, and quantitate all observed degradation products. New analytical technologies and modifications of existing technologies are continuously being developed and should be utilized when appropriate.

Extent of Degradation

The question of how much degradation is sufficient to meet the objectives of stress studies is widely discussed, especially with respect to conventional therapeutics. The apparent consensus among pharmaceutical scientists is that samples degraded ~10% are optimal for use in analytical method validation. These considerations apply to small organic pharmaceuticals for which stability is dictated by the typical pharmaceutical limit of 90% of label claim (Carr GP *et al*., 1990)

No such limits for physico-chemical changes, losses of activity, or degradation during shelf life have been established for individual types or groups of biological products. In general, international and national regulations for biological products provide little guidance with respect to stability-related issues. These issues should be considered on a case-by-case basis.

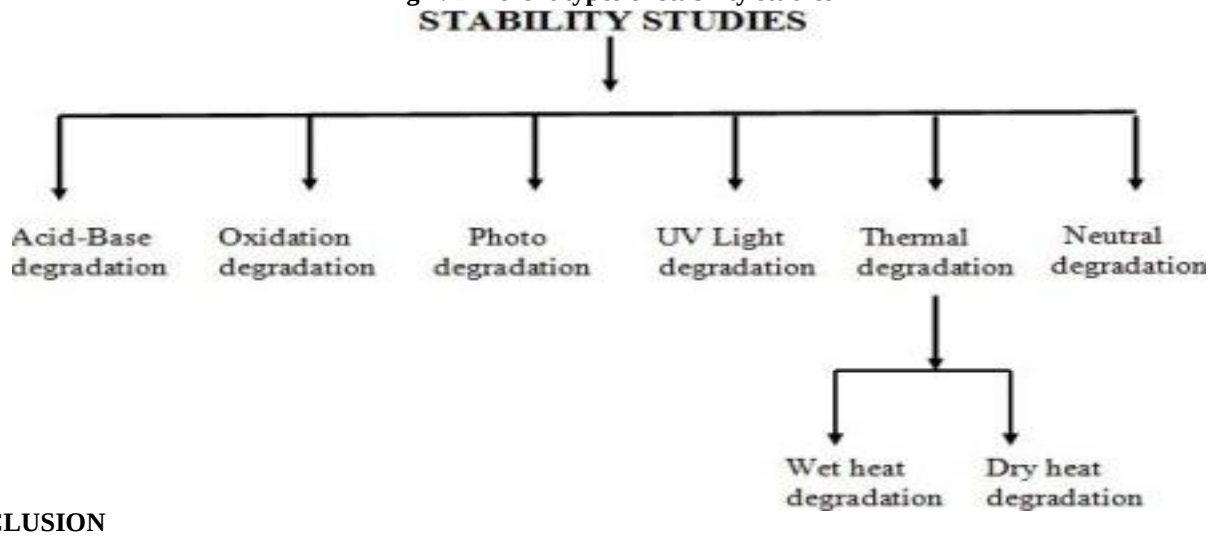
The forced degradation experiments do not necessarily result in product decomposition. The study can be stopped if no degradation is observed after drug sample or drug product has been exposed to a stress that exceeds conditions of accelerated stability protocol (Szepesi G *et al*., 1991).

JUDGEMENT OF RESULTS

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling. They should identify precaution nary measures needed in manufacturing or in formulation of the drug product, and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at time of use.

Fig 1. Different types of stability studies



CONCLUSION

Stability is a critical quality attribute of the API and the Drug Product. Stability profile needs to be established for drug product to assure safety, efficacy and quality. Stress testing studies are conducted to challenge the specificity of stability-indicating and impurity-monitoring methods as part of the validation protocol. Another major goal is to investigate degradation products and pathways.

REFERENCES

Bichsel E. Requirements for the quality control of chemically synthesized peptides and biotechnologically produced proteins. *Pharm Acta*. 1996; 71(6): 439-446.

Carr GP, Wahlich JC. A practical approach to method validation in pharmaceutical analysis. *J Pharm Biomed Anal*. 1990; 8(8): 613-618.

Ewing GW. Instrumental Methods of Chemical Analysis. 4th ed. London: Mc Graw Hill International Book Co; 1981; p. 1-7.

FDA. Guidance for Industry. Analytical Procedures and Methods Validation: Chemistry, Manufacturing, and Controls Documentation. *Draft Guidance*. 2000.

ICH. Guidance for Industry.Q1A Stability Testing of New Drug Substances and Products. *ICH-Q1A*. 2001.

Jenke DR. Chromatographic Method Validation: A Review of Current Practices and Procedures. II. Guidelines for Primary Validation Parameters. *J Liq Chromatogr Relat Technol*. 1996; 19(5): 737-757.

Kim HB, Mary AG. Stability fundamentals of drug product and API. *AAPS pharmaceutica*. 2000.

Reynolds DW, Facchine KL, Mullaney JF, Alsante KM et al. Available Guidance and Best Practices for Conducting Forced Degradation Studies. *Pharmaceutical Technology*. 2002; p. 48–56.

Skoog D, West DM, Holler FJ. Analytical Chemistry: An Introduction. 7th ed. Philadelphia: Saunders College Publishing; 2002; p. 3-4, 5-11.

Szepesi G, Gazdag M, Mihályfi K. Selection of high-performance liquid chromatographic methods in pharmaceutical analysis:III.Method validation. *J Chromatogr*. 1991; 464: 265-278.

Vitthal V. Chopade. Sensitive Analytical Methods for Determination of Stability of Drugs in Pharmaceutical Dosage Forms. *Pharma infonet.* 2008.

Willard HH, Merri LL, Dean JA. Instrumental Methods of Analysis. 6th ed. CBS Publisher; 2000; p. 82-83.