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Development of Specific and Sensitive Methods for Assay of Ozagrel and Its Pharmaceutical Formulation

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ABSTRACT
Pharmaceutical analysis is the integral part of the pharmaceutical sciences. Pharmaceutical analysis is the application of principles of analytical chemistry to drug analysis. The analytical chemistry may be defined as the science of developing accurate, precise and sensitive methods for determining the composition of materials in terms of elements or compounds which they contain. Qualitative Analysis: It deals with the identification and characterization of substances. Quantitative Analysis: It provides numerical information concerning the quantity of some species (the analyte) in a measured amount of the sample. Stability Indicating Assay Method (SIAM), Stress Testing / Forced Degradation Studies, Objectives of Stress Testing, Experimental Approach for Stress Studies.

Keywords : (SIAM), SENSITIVE METHODS, Stress Testing

I. INTRODUCTION

Pharmaceutical analysis is the integral part of the pharmaceutical sciences. Pharmaceutical analysis is the application of principles of analytical chemistry to drug analysis. The analytical chemistry may be defined as the science of developing accurate, precise and sensitive methods for determining the composition of materials in terms of elements or compounds which they contain.

In pharmaceutical analysis section, the research analyst is responsible for three important functions:

1) Development of analytical method for raw materials, active ingredients and chemical intermediates of the product.

2) Development of analytical methods for selective analysis of drug in presence of excipients, degradation products and impurities along with identification of degradation products, degradation pathway and extent of degradation when stored at ambient and accelerated conditions.

3) Development of analytical method for micro and semi micro quantities of drugs and its metabolites in biological system.

Analytical chemistry can be divided into two areas:

1) Qualitative Analysis: It deals with the identification and characterization of substances.

2) Quantitative Analysis: It provides numerical information concerning the quantity of some species (the analyte) in a measured amount of the sample.

Pharmaceutical analysis is the quantitative measurement of the active ingredient and related compounds in the pharmaceutical product. These determinations require the highest accuracy, precision, and reliability because of the intended use of the data: manufacturing control, stability evaluation, and shelf-life prediction.

Pharmaceutical analysis methods also play an important role to identify and quantify the drug in the formulated product, the rate at which drug is released from its formulation and stability of drug in the formulation. It is used to reveal identify and purity of drug substances and excipients to be used in the preparation of formulation and concentration of specified impurities in the pure drug substance. The key requisite for success in this field is a thorough knowledge of the various fields of chemistry and excellent interactions with the experts of various other disciplines.

The stability of the active component is a major criterion in determining the suitability of the dosage form. Several forms of instability can occur.

1) There may be chemical degradation of the drug, leading to substantial lowering of the quantity of the therapeutic agent in the dosage form. This is even of greater significance in the case of drugs with narrow therapeutic indices, where the patient needs to be carefully treated so that serum levels are neither so high that they are potentially toxic, nor so low that they are ineffective.

2) Although the degradation of the active drug may not be that extensive, a toxic degradation product may be formed in the decomposition process.

3) Instability of a drug product can lead to a decrease in its bioavailability, rather than to loss of drug or the formation of toxic degradation products. This reduction in bioavailability can result in a substantial lowering in the therapeutic efficacy of the dosage form. This can be caused by physical and chemical changes in the excipients in the dosage form, independent of whatever changes the active drug may have undergone.

4) There may be substantial changes in the physical appearance of the dosage forms.The prime necessity is to 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 and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. The Stability-Indicating Assay Method (SIAM) is a quantitative analytical procedure used to detect a decrease in the amount of the active pharmaceutical ingredient (API) present due to degradation. International Conference on Harmonization (ICH) Guidelines has made mandatory the requirement of SIAM. According to FDA guidelines, a SIAM is defined as a validated analytical procedure that accurately and precisely measures active ingredients (drug substance or drug product) free from potential interferences like degradation products, process impurities, excipients, or other potential impurities, and the FDA recommends that all assay procedures for stability studies be stability indicating.

Stability Indicating Assay Method (SIAM)

Stability is defined as the capacity of a drug substance or a drug product to remain within specifications established to ensure its identity, strength, quality, and purity throughout the retest period or expiration dating period. 7 According to ICH, the guidance is provided to design of stability studies for drug substances and drug products that should result in a statistically acceptable level of confidence for the established retest or expiration dating period for the formulation. An elaborate definition of stability-indicating methodology is, however, provided in the United States-Food and Drug Administration (US-FDA) stability guideline of 1987 and the draft guideline of 1998. Stability-indicating assay 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 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". 8 This definition in the draft guideline of 1998 reads as: 'validated quantitative analytical method that can detect the changes with time in the chemical, physical, or microbiological properties of the drug substance and drug product, and that are specific so that the contents of active ingredient, degradation products, and other components of interest can be accurately measured without interference'.

The major changes brought in the new guideline are with respect to:

- Introduction of the requirement of validation, and
- Requirement of analysis of degradation products and other components, apart from the active ingredient(s).

Two terms have been proposed in literature to differentiate the methods that measure quantitatively the component of interest in the sample matrix without separation, and the ones where separation of the drug as well as other degradation product is done.

1) Specific SIAM can be defined as "a method that is able to measure unequivocally the drugs in the presence of all the degradation products, excipients and additives, expected to be present in the formulation".

2) Selective SIAM can be defined as "a method that is able to measure unequivocally the drugs and all the degradation products in presence of excipients and additives, expected to be present in the formulation"

The development of the selective SIAM is of greater importance as it separates the active component along with all types of degradation products developed through different conditions guided by ICH Q1A [R2].

Stress Testing / Forced Degradation Studies

Stress testing is defined as the stability testing of drug substances and drug products under conditions exceeding those used for accelerated testing. It is an integral part of the information to be provided to regulatory authorities in registration application dossiers. 10 More recently, the ICH introduced an important distinction between the two terms accelerated testing and stress testing in the context of pharmaceutical stability. The ICH defined accelerated testing as "studies designed to increase the rate of chemical degradation or physical change of an active drug substance or drug product using exaggerated storage conditions as part of the formal, definitive, storage program". An important aspect of this definition is that the studies are part of the "formal, definitive, storage program". In contrast, ICH, in "Annex 1, Glossary and Information" of the revised stability guideline defined stress testing (drug substance) as "studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing". From the ICH definitions, it is clear that there is now a [regulatory] differentiation between "accelerated testing" and "stress testing". Stress testing is distinguished by both the severity of the conditions and the focus or intent of the results. Stress testing, which is often referred to as "forced degradation" is an investigation of the intrinsic stability characteristics of the molecule, providing the foundation for developing and validating analytical methods and for developing stable formulations. Stress testing studies are intended to discover stability issues, and are therefore predictive in nature. Stress testing of the drug substance can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug products involved. Stress testing is likely to be carried out on a single batch of the drug substance. It includes the effect of

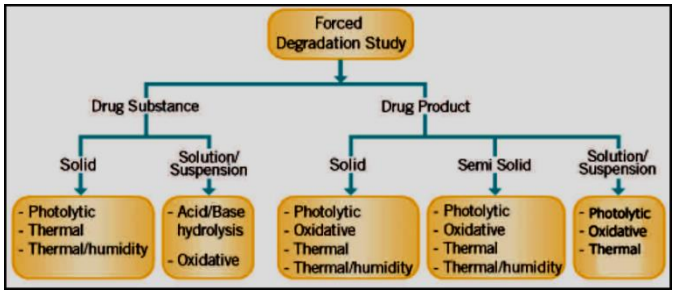
temperature (in 10ºC increments [e.g., 50ºC, 60ºC] above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation and photolysis on the drug substance. Testing evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photo stability testing is also an integral part of stress testing. Examining degradation products under stress conditions is useful for establishing degradation pathways and developing and validating suitable analytical procedures. It may not be necessary, however, to examine for specific degradation products. The stress conditions should result in approximately 5–20% degradation of the Active Pharmaceutical Ingredient (API) / Drug Substance (DS) or represent a reasonable maximum condition achievable for a given formulation. The specific conditions used will depend on the chemical characteristics of the Drug Product (DP). It is advisable to take kinetic time points along the reaction pathway for API and DP degradation studies for determining primary degradants and better understanding of the degradation pathway. 7 Photo stability testing should be conducted on at least one primary batch of the drug product. Standard conditions for photo stability testing are according to ICH Q1B guidelines.

Objectives of Stress Testing

The purpose of stability testing is to provide evidence on how the quality of DS or DP varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Stress testing studies are conducted to challenge the specificity of stability-indicating methods as part of validation protocol.

The forced degradation studies are carried out for the following reasons:

1. Development and validation of stability-indicating methodology;
2. Determination of degradation pathways of drug substances and drug products;
3. Discernment of degradation products in formulations that are related to drug substances versus those that are related to non-drug substances (e.g., excipients);
4. Structure elucidation of degradation products;
5. Determination of the intrinsic stability of a drug substance in solution and solid state and
6. To reveal the thermolytic, hydrolytic, oxidative, and photolytic degradation mechanism of the drug substance and drug product.



Overview of Forced Degradation Studies

Experimental Approach for Stress Studies

Forced degradation studies should be conducted whenever a stability-indicating method is required. Studies may need to be repeated as methods, processes, or formulations change. Alternatively, methods can be developed with a mixture of the known degradation products. Forced degradation studies should be performed on each unique formulation before formal stability studies begin.

Reynolds et al. have described that stress testing should include conditions to examine specifically for four main pharmaceutically relevant degradation mechanisms:

1) Hydrolytic,
2) Oxidative,
3) Thermolytic and
4) Photolytic.

The potential for these degradation pathways should be assessed in DS and DP (and/or drug– excipients mixtures). These mechanisms can be assessed in a

systematic way by exposure to stress conditions of heat, humidity, photo stress (UV and VIS), oxidative conditions, and aqueous conditions across a broad pH range.

Hydrolytic Degradation

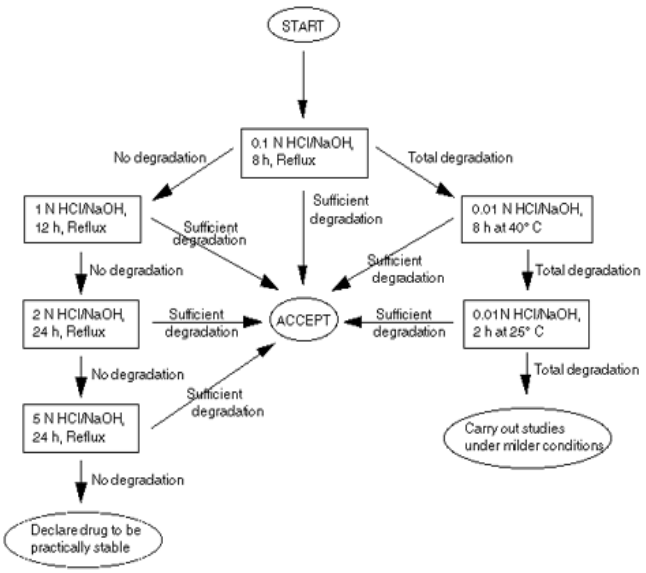
Drug degradation that involves reaction with water is called hydrolysis which is typically acid or base catalyzed. Acidic, neutral, and basic conditions should therefore be employed in order to induce potential hydrolytic reactions. This is especially important when the compound being tested has an ionizable functional group(s) and can exist in different ionization states under relevant aqueous conditions. It is particularly important to be sure to test hydrolysis at unique protonation states, unless there are a large number of ionizable functional groups as is often the case with peptides and proteins. In such cases, a practical approach is to simply expose the sample to a wide pH range in defined increments (e.g., 1 pH unit).

A major challenge in designing hydrolytic stress tests is compound solubility. Many small molecule drugs are not soluble in water at the concentrations typically used for analytical evaluation (i.e., 0.1– 1 mg/ml) across the entire pH range. Thus, either a slurry/ suspension must be used to examine the hydrolytic stability of a compound or a co-solvent must be added to facilitate dissolution under the conditions of low solubility. The two most commonly used co-solvents are acetonitrile and methanol. Because methanol has the potential of participating in the degradation chemistry (e.g., acting as a nucleophile to react with electrophilic sites or intermediates in the degradation pathways), it should be used with caution (especially under acidic conditions) if the compound being tested contains a carboxylic acid, ester, or amide as these groups may react with methanol. Acetonitrile is generally regarded as an inert solvent and is typically preferable to methanol in hydrolytic stress-testing studies. However, acetonitrile is not completely inert and can participate in the degradation reactions leading to artifactual degradation results. For example, acetonitrile is known to contribute to base-catalyzed epoxidation reactions in the presence of peroxides. Acetonitrile will also degrade, in the presence of base (e.g., pH 13) and/or acid (e.g., pH 1) under elevated temperatures, to detectable levels of acetamide and/or acetic acid, which can show up as early eluting peaks (when monitoring at low wavelengths) on RP-HPLC. In the presence of radicals [e.g., generated during prolonged sonication as part of the analytical workup or in the presence of free radical initiators such as 2, 2-azobisisobutyronitrile (AIBN)], acetonitrile can be oxidized to small amounts of formyl cyanide that will readily react with nucleophiles (such as amines), resulting in a “formylation” reaction.Other co-solvents recommended for hydrolytic studies are shown in Table:

Acidic pH	Neutral pH	Basic pH
Acetonitrile [a]	Acetonitrile [a]	Acetonitrile [a]
DMSO	NMP (N-Methylpyrrolidone)	DMSO
Acetic Acid	-	Glyme [a] (Glycol ethers)
Propionic Acid	-	Diglyme (Glycol diethers)
-	-	p-Dioxane

A Volatile solvent: may evaporate at higher temperatures Organic co-solvents that have been used for stress testing studies

Co-solvents have potential to affect the degradation rates and pathways. The apparent hydrolytic degradation rate of drug may be altered by the use of co-solvent used for facilitating dissolution. The overall hydrolytic degradation rate will depend on the specific mechanism(s) involved in the degradation pathway(s). The degradation reactions and rates involved will depend on a variety of factors such as the dielectric constant, solvent polarity, ionic strength, whether or not the solvent is protic or aprotic, the surface energy (i.e., of the solid–liquid interface in a slurry/ suspension), etc. For example, a degradation reaction involving acid-catalyzed hydrolysis with a cationic intermediate or a polarized transition state will be facilitated by a solvent with a high dielectric constant, and the addition of a co-solvent that reduces the effective dielectric constant will reduce the rate of such a reaction. Solvation of a compound in an aqueous co-solvent mixture may involve formation of a "solvent cage" of the more non-polar solvent around the compound, potentially leading to some protection from hydrolysis. Solvent composition can also affect tautomeric states of molecules, which in turn can affect both degradation rates and pathways. The effective pH of an aqueous solution will also change upon addition of a co-solvent, which can both affect the degradation rate and change the degradation pathway(s) e.g., by facilitating different protonation states. In conclusion, testing of the hydrolytic susceptibility of a DS should involve exposure to acidic, neutral, and basic conditions in the pH range of 1–13, preferably in 100% aqueous conditions. Elevated temperatures with an upper limit of 70ºC are recommended for accelerating the hydrolytic reactions. Higher temperatures can be used, but the risk of non-Arrhenius behaviour increases significantly and leads to unpredictable degradation pathways as temperature is increased further. The longest recommended time period for stressing at the highest temperature is 2 weeks, although longer times can certainly be used if desired.

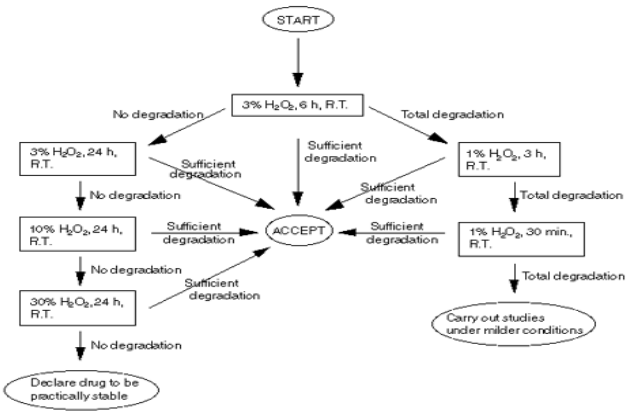


Performing stress studies for hydrolytic degradation under acid and alkali

Oxidative Degradation

Oxidative drug degradation reactions are typically auto oxidative, which is radical initiated. Radical-initiated reactions start with an initiation phase involving the formation of radicals, followed by a propagation phase and eventually a termination phase. The nature of oxidative reaction is complex. Oxidative intermediates are often thermally unstable and may decompose via alternate pathways at elevated temperatures. Increase in temperature, therefore, may not lead to predictable changes in degradation rates, and the observed oxidative rates and pathways may be different than those observed at lower temperatures. In solution, oxidative rates and pathways may be dependent on the dissolved oxygen concentration. Thus, the reaction rate in solution may actually be reduced at higher temperatures because of the decrease in oxygen content of the solvent. This may be partially overcome by bubbling oxygen or air through the solution while heating or by storing the solution under oxygen in an airtight vessel with high pressure (at least a few atmospheres). The susceptibility to oxidative degradation can be studied in solution using a radical initiator (e.g., AIBN, 40ºC,

up to 1 week) and exposure to hydrogen peroxide (e.g., 0.3% hydrogen peroxide, up to 1 week at room temperature, in the dark) in separate studies. As both of these oxidative susceptibility studies are in solution, it may be useful to control the pH such that all relevant protonation states of the drug are tested. The oxidative tests could be carried out at 1 pH unit above and below of the compound being tested. Room temperature storage is sufficient for the hydrogen peroxide test. The use of higher temperatures (e.g., >30ºC) with hydrogen peroxide should be done with caution because the O–O bond is a weak bond that will readily cleave at elevated temperatures to form hydroxyl radicals, a much harsher oxidative reagent. The use of transition metals [e.g., copper (II) and iron (III) at 1–5mM, 1–3 days] is also recommended for evaluation of oxidative susceptibility.



Performing stress studies for degradation under oxidative conditions

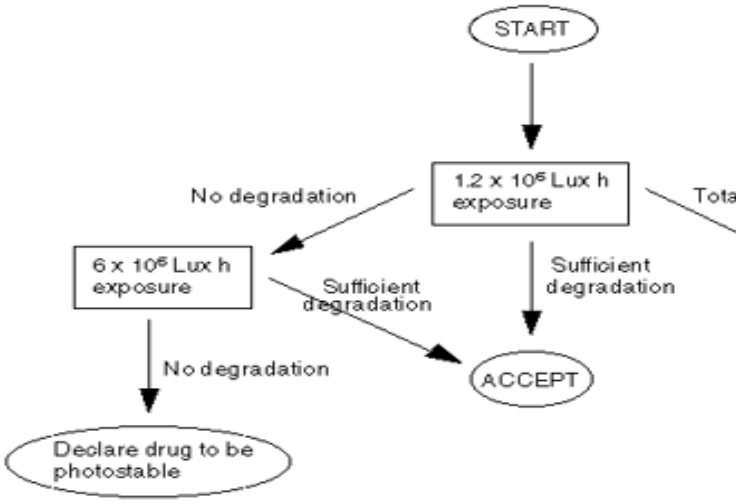
Thermolytic Degradation

Thermolytic degradation is usually thought of as degradation caused by exposure to temperatures high enough to induce bond breakage, that is, pyrolysis. For the purposes of simplification in the context of drug degradation, the term thermolytic describe reactions that are driven by heat or temperature. Thus, any degradation mechanism that is enhanced at elevated temperatures can be considered a "thermolytic pathway". Thermolytic pathways may lead to hydrolysis / dehydration, isomerization / epimerization, de-carboxylation, rearrangements and some kinds of polymerization reactions. Hydrolytic reactions are actually a subset of thermolytic pathways. The ICH stability guideline suggests studying the effect of temperatures in 10ºC increments above the accelerated temperature test condition (i.e., 50ºC, 60ºC, etc.). It is not clear why the guideline suggests 10ºC increments, but it may be related to the importance of understanding whether or not any degradation (in the solid state) mechanism change as a result of increasing temperature. Studies with such temperature increase would be useful for constructing Arrhenius plots to allow prediction of degradation rates in the solid state at different temperatures. Waterman and Adami12 have asserted that the relative humidity under which a solid drug product is stored is a critical variable when attempting to use the Arrhenius relationship. He showed evidence that degradation rates of formulated products (with pathways involving hydrolytic or oxidative degradation) often hold to the Arrhenius relationship if the relative humidity is held constant at the different elevated temperatures. Based on the literature and kinetic considerations temperatures up to 70ºC (at high and low humidity) should provide a rapid, reasonably predictive assessment of the solid-state degradation pathways and relative stabilities of most drug substances at lower temperatures.

Photolytic Degradation

Photolytic degradation is the degradation that results from exposure to ultraviolet or visible light in the wavelength range of approximately 300–800 nm. Exposure to radiation at wavelengths <300nm is not needed because a pharmaceutical compound would not experience such exposure during its life cycle. For photolytic degradation to occur, radiation must be absorbed either by the drug substance or by the formulation. Photo degradation rates are therefore directly dependent on the amount of incident radiation and on the amount of radiation that is absorbed by the compound or the formulation. It is

important to remember that a compound may undergo photolytic degradation even if it does not, itself, absorb radiation in the UV or visible region. This can only happen if there is some additional agent in the formulation, intentionally or adventitiously present, that facilitates absorption. The ICH photo stability guideline (Q1B) 11 refers to both forced degradation studies (stress testing) and confirmatory testing. As confirmatory photo stability testing is designed to be a part of the definitive, formal stability testing, it can be thought of as being analogous to an accelerated stability study. Thus, the minimum recommended exposure outlined in Q1B11 (i.e., 1.2 million lux-hr visible and 200W-hr/m2 UV) is not the exposure recommended for forced degradation studies. In fact, there is no mention of recommended exposures for forced degradation studies and the design is left open. A member of the original ICH Photo stability Expert Working Group recommended an exposure of three to five times the minimum ICH confirmatory exposure for forced degradation studies. Interestingly, early versions of the guideline (during Step 1 of the ICH process) suggested that forced degradation studies should use exposures in the range of five to 10 times the confirmatory exposure recommendations. A photo exposure in the range of three to 10 times the confirmatory exposure seems a reasonable amount of photo stress for forced degradation studies, remembering that photo degradation, of the compound being studied, beyond 20–30% would not be necessary or desired. It should be remembered that photo degradation products formed under stress conditions (i.e., "potential" photo degradation products) may not always be observed under confirmatory conditions. Such differences may be exacerbated by the use of different photon sources for stress testing and confirmatory studies.



Performing stress studies for photolytic degradation

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