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INTERFERENCE STUDY IN ANALYTICAL METHOD DEVELOPMENT -A CRITICAL REVIEW

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ABSTRACT
The primary focus of this paper is that evaluation criteria of interference in the development of chromatographic methods for separation, identification, and quantification of pharmaceutical compounds, which may be applied within the various functions in the drug development continuum. The paper aims at critical review of forced degradation study & also discusses the issues and parameters that must be considered in the validation of analytical methods. Authors also reviewed the residual solvent analysis and its quantification and significance in the safety, efficacy and potency of pharmaceutical products.

KEYWORDS: Separation, identification, and quantification of pharmaceutical compounds.

1. INTRODUCTION

The figure for drugs that are introduced in the market is increasing every day. The API introduced can be totally new ones or already existing ones with some modifications. Very often there is a time lag from the introduction of the drug into the market and introduction in pharmacopoeias. This occurs due to certain problems that give rise due to prolonged or continuous use of a drug, reporting of new toxicities, and development of resistance in the patient, the introduction of new drugs into the market which is having more activity, less adverse effects. All the above situations may lead to the withdrawal of the drug from the market. Under such conditions, there are no standard or analytical methods available in pharmacopoeias. Here comes the scope for development of analytical methods for such drugs.[1-6]

2. Description

2.1. Basic criteria for new method development of drug analysis

- ✓ The drug or drug combination may not be official in pharmacopoeias.
- ✓ Due to patent regulations a proper analytical procedure may not be available for the drug in the form of the formulation.
- ✓ Analytical method may not be available to study involvement caused by excipients used in the formulation.
- ✓ Analytical method for determining the quantity of drug in biological fluids are not available.
- ✓ Analytical method for the drug in combination with other drug is not available.
- ✓ The present procedures of analysis may require sophisticated reagents and solvents and also extraction and purification procedures may be complicated to perform.

2.2. Method validation

The validation of the analytical method is very important in the pharmaceutical industry on a daily basis. This is because validation method is necessary for regulatory filing for approval.[7-9]

2.3. Pharmaceutical impurities

According to ICH Guidelines, an impurity is any component that is not a chemical substance defined as API or excipients in the drug formulation. The safety of drug products depends on the toxicity of active pharmaceutical ingredient as well as on the impurities it contains. Thus spotting, quantification and management of impurities in the drug product and substance is a vital part of the development.[10-16]

2.4 Impurities classification: The safety, activity and quality of API in the generic product can be disturbed by the existence of impurities. The nature and quantity of

these impurities can be observed by a number of factors like reaction conditions, the quality of raw material, reagents, solvents purification step, excipients, drug manufacturing process, purification, storage of the formulation.[17-21]

According to Q3A drug impurities can be as

1. Organic impurities
2. Impurities (inorganic)
3. Residual solvents

Impurities especially organic can invade during the manufacturing process of medicine or during storage of drug substance. They can be identified or unidentified and include

1. Degradation products
2. Intermediated
3. Starting substances
4. By-products
5. Reagents, ligands and catalyst

Inorganic impurities include

1. Reagents or ligands or catalyst
2. Heavy metals or other residual metals
3. Inorganic salts
4. Other materials (filter aids, charcoal)

2.5 Control of impurities

A specification is defined as the list of references, tests to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the tests described. It gives a set of criteria to which the drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug product or substance, when tested according to given procedures, will meet listed acceptance criteria. Specifications are the standards that are proposed by the manufacturer and approved by regulatory authorities.[22-27]

2.6 Listing of impurities in the drug substance specifications

The specification of the API includes a list of impurities along with their limits. The methods to foretell contaminants likely to occur in the drug product may include stability testing, chemical development studies, routine batch analysis of degradation pathways. Where applicable, the list of following types of contaminants can be included in drug substance specifications.[28-32]

1. Impurities (organic)
2. Specified and identified impurity
3. Specified and unidentified impurity
4. Whole impurities
5. Residual solvents
6. Impurities (inorganic)

3. Forced degradation

Physical and chemical stability of the drug is of eminent concern as it affects the efficacy and safety of the drug. FDA and ICH guidelines give the requirements of stability testing and also an idea of how time and environmental factors influence the changes in the drug product.

3.1 Purpose of forced degradation studies

1. To know the pathway of degradation of the drug product.
2. To differentiate the degradation products of an active constituent and non- drug product.
3. To determine the chemical structure of the degradation product.
4. To elucidate the native stability of the drug in the drug formulation.
5. To uncover the mechanism of degradation like hydrolysis, photolysis, oxidation or thermolysis of the drug.
6. To introduce more stable forms of the formulation.
7. To note the chemical properties of the drug substance.

3.2 Limits for degradation

The topic of many discussions among the pharmacist is the question of how much degradation is adequate in the formulation without affecting its activity. For validation of chromatographic assays degradation of the drug must be between 5-20% for its acceptance. According to some pharmacist, 10% degradation of drug substance is optimum.

3.3 Plan for selection of degradation conditions

The main aim of forced degradation studies is to develop stability-indicating methods for drug products. The selection of stress conditions should be comparable with the product's decomposition under conditions specified in each case. Hydrolysis, oxidation and photolysis are the stress factors.[32-34]

3.4 Degradation states

I). Hydrolytic condition

Hydrolysis is nothing but a reaction between water and a chemical compound. The most commonly occurring degradation reaction over a wide range of pH is a hydrolytic reaction. Hydrolysis involves acidic and basic hydrolysis. This hydrolysis involves forced degradation of drug or API which produce primary degradation products if exposed to an acidic or basic environment. Stability of the drug decides the selection method and concentration of base or acid. For acidic hydrolysis, HCL and sulphuric acid are suitable reagents and for basic hydrolysis, NaOH and KOH are considered suitable. Co – solvents can be added to increase the solubility of the drug if it is insoluble in water. Seeing the drug structure solvent should be selected. Forced testing is carried at room temperature and if there is zero degradation then it should be carried at elevated temperature (50-70^{o}C). Stress testing should not exceed 7 days. The degradation of the product should be neutralised to avoid further degradation.

II). Oxidation conditions

The most commonly and widely used agent for the oxidation of drug is hydrogen peroxide, but other oxidising agents can also be used like oxygen, metal ions can also be used. The procedure for choosing oxidising agents depends on the structure of API. This oxidative degradation of the drug involves electron transfer to form anions and cations. These anions and cations are reactive. Sulfoxide, sulfones, hydroxyl amine, N-oxide are produced when amides, phenols, sulphides undergo electron transfer. Hydroxide or ketone, hydrogen peroxide are formed when functional groups that contain liable hydrogen-like tertiary carbon, allylic carbon, benzylic carbon with respect to hereto atom is susceptible to oxidation.

III). Photolytic conditions

Photo-stability testing is performed to know if there are any undesired products formed after degradation. This has to be performed by exposing a drug to Fluorescent or UV light. There are certain conditions given in ICH guidelines to perform this test. The sample is subjected to a minimum of 1.2 million 1x h and 200 W h / m^2 light. 300-800nm has generally used wavelength during photodegradation. Functional groups like carbonyl, acyl chlorides, nitroaromatic, alkenes, N-oxide, weak CH and OH bonds, sulphides and polyenes are likely to introduce drug photosensitivity.

IV) Thermal situations

Thermal degradation should be carried out in more exertion states. Solid samples should be subjected to both wet as well as dry heat, while liquid samples can be subjected to dry heat only. To complete the study in a shorter period of time they must be conducted at an elevated temperature. The Arrhenius equation gives the effect of temperature on thermal degradation.

4. CONCLUSION

Forced degradation studies provide knowledge about possible degradation pathways and degradation products of the active ingredients and help elucidate the structure of the degradants. Degradation products generated from forced degradation studies are potential degradation products that may or may not be formed under relevant storage conditions but they assist in the developing stability indicating method. It is better to start degradation studies earlier in the drug development process to have sufficient time to gain more information about the stability of the molecule. This information will in turn help improve the formulation manufacturing process and determine the storage conditions. As no specific set of conditions is applicable to all drug products and drug substances and the regulatory guidance does not specify about the conditions to be used, this study requires the experimenter to use common sense. The aim of any strategy used for forced degradation is to produce the desired amount of degradation i.e., 5–20%. A properly designed and executed forced degradation study would generate an appropriate sample for development of stability indicating method.

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