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AN OVERVIEW ON IMPURITY PROFILING OF DRUG AND PHARMACEUTICAL FORMULATIONS

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ABSTRACT

In the pharmaceutical world, an impurity is considered to be any other inorganic or organic substance. Today, not only purity profiles are mandatory, but also impurity profiles are also mandatory. Among impurities in the pharmaceutical world, there are any other inorganic or organic material, or residual solvents other than the drug ingredients or substances that arise after synthesis or unwanted substances that remain after the API processing. An impurity is an inorganic or organic substance other than the drug substances, or ingredients, that a result of synthesis or an undesirable chemical that remains in the drug product.

Key-words: Impurity, Drug, API, ICH, Guidelines

INTRODUCTION

There has been ever increasing interest in impurities present in Active Pharmaceutical Ingredient's (API's). Nowadays, not only purity profile but also impurity profile has become mandatory according to the various regulatory authorities. In the pharmaceutical world, an impurity is considered as an inorganic or organic material, or residual solvents other than the drug substances, or ingredients, arising out of synthesis or unwanted chemicals that remain with APIs. Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulation. [1] The control of impurities in Formulated products and API's were regulated by various regulatory authorities like ICH, USFDA, Canadian Drug, and Health Agency. Impurity profiling is very important in the modern pharmaceutical analysis due to the fact that unidentified, potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, impurities should be identified and determined by the selective method. Nowadays, it is a mandatory requirement in various pharmacopeias to know the impurities present in

APIs and finished drug products. Thus, impurity profiling can act as a Quality Control tool. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantitation of several organic and inorganic impurities, usually accompany with APIs and finished products. There is a strong requirement to have unique specifications/standards with regard to impurities. The major aim of bulk drug industries and pharmaceutical industries is to produce the best quality product. As drugs are meant for saving lives and even minute quantities of impurities are unacceptable. Hence, impurity profiling has become very important. Impurity can be defined as any substance that exists with the original drug; it can be starting material or intermediates that are formed due to any side reactions. Our aim is to provide details regarding impurity and its profiling, which is very important in the Pharmaceutical sector. As per the, International Conference on Harmonization (ICH), "any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product is considered an impurity.[2]

The bulk drug industry forms base of all pharmaceutical industries as it is the source of active pharmaceutical ingredients (APIs) of specific quality. Over the last few decades much attention is paid towards the quality of pharmaceuticals that enter the market. The major challenge for both bulk drug industries and pharmaceutical industries is to produce quality products. It is necessary to conduct vigorous quality control checks in order to maintain the quality and purity of output from each industry. Purity of active pharmaceutical ingredient depends on several factors such as raw materials, their method of manufacture and the type of crystallization and purification process. Concept about purity changes with time and it is inseparable from the developments in analytical chemistry. The pharmacopoeias specify not only purity but also puts limits which can be very stringent on levels of various impurities. Modern separation methods clearly play a dominant role in scientific research today because these methods simultaneously separate and quantify the components hence making the separation and characterization of impurities easier. Impurities in pharmaceuticals are unwanted chemicals that remain with the Active Pharmaceutical Ingredients (APIs) or develop during formulation or develop upon ageing of both APIs and formulated APIs to medicines [3-4]. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Different pharmacopoeias such as British pharmacopoeia (BP) and the United States pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations4. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents [5-7]. In addition, Ahuja and Gorog have published books covering different aspects of impurities including regulatory requirements, sources and types of impurities, isolation, characterization and monitoring of impurities found in drug products [5-7]. Impurity profile is description of the identified and unidentified impurities present in a typical batch of API produced by a specific controlled production process8-10. It is one of the most important fields of activity in contemporary industrial pharmaceutical analysis. The main reasons for the increasing interest of drug manufacturers and drug registration authorities in the impurity profiles of bulk drug substances are as follows [8]:

a) In the course of the development of a new drug or a new technology for manufacturing an existing drug it is essential to know the structures of the impurities: by possessing the information synthetic organic chemists are

often able to change the reaction conditions in such a way that the formation of the impurity can be avoided or its quantity reduced to an acceptable level.

b) Having suggested structures for the impurities, they can be synthesized and thus provide final evidence for their structures previously determined by spectroscopic methods.

c) The material synthesized can be used as an 'impurity standard' during development of a selective method for the quantitative determination of the impurity and the use of this method as part of the quality control testing of every batch.

d) In case of major impurities the synthesized or isolated material can be subjected to toxicological studies thus greatly contributing to the safety of drug therapy.

e) For drug authorities the impurity profile of a drug substance is a good fingerprint to indicate the level and constancy of the manufacturing process of the bulk drug substance.

REGULATORY GUIDELINES ON IMPURITIES IN AN ACTIVE PHARMACEUTICAL INGREDIENT: [9-15]

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. However monitoring impurities and controlling these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry. A unified terminology is necessary to assure that everyone uses the same vocabulary when addressing questions related to impurities. The United States Food and Drug Administration (US FDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations. The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines "stability testing of new drug substances and products"- Q1A
2. ICH guidelines "Impurities in New Drug Substances"- Q3A
3. ICH guidelines "Impurities in New Drug Products"- Q3B
4. ICH guidelines "Impurities: Guidelines for residual solvents"- Q3C
5. US-FDA guidelines "NDAs -Impurities in New Drug Substances"
6. US-FDA guidelines "ANDAs – Impurities in New Drug Substances"
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia

A. Common Terms of Impurities

Following terms are used by various regulatory bodies and ICH to describe the impurities

1. Intermediate
2. Penultimate intermediate
3. By-products
4. Transformation products
5. Interaction products
6. Related products
7. Degradation products

1. Intermediate:

The compounds produced during synthesis of the desired material or as a part of the route of synthesis.

2. Penultimate Intermediate:

It is the last compound in the synthesis chain prior to the production of the final desired compound.

3. By-products:

The compound produced in the reaction other than the required intermediates. They can occur through a variety of side reactions, such as overreaction, incomplete reaction, demonization and rearrangement, unwanted reactions between starting materials or intermediates with chemical reagents or catalysts.

4. Transformation Products:

They are related to theorized and nontheorized products that can occur in a reaction. They are similar to by-products except that more is known about these reaction products.

5. Interaction Products:

These products formed either intentionally or unintentionally interaction between various chemicals involved.

6. Related Products: These are chemically similar to drug substance and may even possess biological activity.

7. Degradation Products: They are formed by the decomposition of active ingredient or other material of interest by the effect of external factors like heat, light and moisture.

Classification of Impurity [16-20]

United States Pharmacopoeia (USP) According to USP impurities are classified into three sections

1. Impurities in Official Articles
2. Ordinary Impurities
3. Organic Volatile Impurities

The ICH Terminology According to ICH guidelines, impurities in drug substance produced by chemical synthesis can be broadly classified into following three categories

1. Organic Impurities (Process and drug-related)
2. Inorganic Impurities (Reagent, ligands, catalysts)
3. Residual Solvents (Volatile solvents)

1. ORGANIC IMPURITIES

These types of impurities arise during the manufacturing process and/or during storage of the drug substance. These include following sub-impurities.

Starting Materials or Intermediate Impurities

These types of impurities occur in almost every API unless a proper care is taken in every step during the multistep synthesis of drug product. Although the end products are always washed with solvents but there are chances of having the residual of unreacted starting materials unless the manufacturers are very careful about the impurities.

By-products

In synthetic organic chemistry, getting a single end product with complete yield is very rare; there is always a chance of having by products along with desired end product. **Degradation Products**

Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. This mainly occurs due to improper storage of formulation. Other Types of Organic Impurities [21-23]

A**. Synthesis Related Impurities**

New chemical entity generated during synthetic process from raw material, solvent, intermediate, byproduct. During synthesis process, if impurity present in trace or in significant amount in any of substance involved in reaction, that ultimately result in final product contaminated with one or more unwanted materials. Therefore, synthesis related impurity require upmost care during every step involved in synthesis process to minimize level of impurity that can arise.

B. Formulation Related Impurities:

Drug substance subjected to variety of conditions that leads to its degradation or other reactions. Solutions and suspensions are prone to degradation due to hydrolysis. Water used in formulation contribute to not only its impurity but also provide situation for hydrolysis and catalysis.

Factors Affecting On Formulation Related Impurities

a. Environment related

I. Exposed to adverse temperature: Substance which are labile to heat or in tropical temperature lead to degradation of active constitute and formation of impurity occurs. E.g. Vitamins are heat sensitive and its degradation lead to loss in potency.

II. Exposed to light: Photosensitive material when exposed to light / UV light undergo degradation which forms impurity.

III. Humidity: It can be detrimental to bulk powder and formulation containing solid dosage form. b. Formation of impurities on ageing: Mutual interaction: Interaction between ingredients involved in formulation leads to mutual interaction which causes impurity formation.

C. Functional Group Related Impurities

a) Ester hydrolysis: Drugs like aspirin, benzocaine, cefoxime, cocaine, ethyl paraben undergo ester hydrolysis.

b) Hydrolysis: Commonly drugs like benzyl penicillin, barbital, and chloramphenicol undergo hydrolysis.

c) Oxidative degradation: Drugs like hydrocortisone, methotrexate, heterocyclic aromatic ring, nitroso/nitrile derivative.

d) Photolytic cleavage: Product exposed to light while manufacturing or storage in hospital pending use or by consumer pending use.

e) Decarboxylation: Some dissolved carboxylic acid such as p-amino salicylic acid loose CO2 when heated.

2. INORGANIC IMPURITIES

Inorganic impurities are also obtained from the manufacturing processes which are used in bulk drug formulation. They are normally known and identified.

a. Reagent, Ligands and Catalysts: Rare chances of occurrence of these impurities. If during manufacturing procedure is not followed properly will create a problem.

b. Heavy Metals: Water is generally used in different manufacturing processes which act as the main source of heavy metals, like Ar, Cd, Cr, Na, Mg, Mn, etc., where acidification or acid hydrolysis takes place. By using demineralized water and glass-lined reactors heavy metal impurities can be easily avoided.

c. Other Materials (Filter Aids, Charcoal): The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants and in many cases, activated carbon is also used which also act as a source of impurity. Therefore to avoid the contamination, regular monitoring of fibers and black particles in the bulk drugs is essential.

3. RESIDUAL SOLVENTS Residual solvents are organic or inorganic liquids used during the manufacturing process. It is very difficult to remove these solvents completely by the work-up process. Some solvent that are known to cause toxicity should be avoided in the production of bulk drugs.

4. FORMULATION RELATED IMPURITIES (IMPURITIES IN DRUG PRODUCTS) Number of impurities in a drug product can arise out of inert ingredients used to formulate a drug substance. In the process of formulation, a drug substance is subjected to a variety of conditions that can lead to its degradation or other deleterious reaction. Solutions and suspensions are potentially prone to degradation due to hydrolysis. The water used in the formulation cannot only contribute its own impurities; it can also provide a ripe situation for hydrolysis and catalysis. Similar reactions are possible in other solvents that may be used. The formulation related impurities can be classified as follows: [24-25]

Method related

Environmental related

The primary environmental factors that can reduce stability include the following

I. Exposures to adverse temperatures II. Light-especially UV light III. Humidity

Dosage form related

I. Mutual interaction amongst ingredients

II. Functional group- related typical degradation

Ester hydrolysis

Hydrolysis

Oxidative degradation

Photolytic cleavage

Decarboxylation

Method related A known impurity, 1-(2, 6-diclorophenyl) indolin-2-one is formed in the production of a parenteral dosage form of diclofenac sodium if it is terminally sterilized by autoclave. It was the condition of the autoclave method (ie, 123 + 2°C) that enforced the intramolecular cyclic reaction of diclofenac sodium forming the indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on the initial pH of the formulation. The concentration of the impurity in the resultant product in the ampoule exceeds the limit of the raw material in the BP. Environmental related. The primary environmental factors that can reduce stability include the following: Exposures to adverse temperatures: There are many API's that are labile to heat or tropical temperatures. For example, vitamins as drug substances are very heatsensitive and degradation frequently leads to loss of potency in vitamin products, especially in liquid formulations. Light-especially UV light: Several studies have reported that ergometrine as well as methyl ergometrine injection is unstable under tropical conditions such as light and heat and a very low level of active ingredient was found in many field samples. In only 50% of the marketed samples of ergometrine injections tested did the level of active ingredient comply with the BP/USP limit of 90% to 110% of the stated content. The custom-made injection of ergometrine (0.2mg/mL) showed almost complete degradation when kept 42 hours in direct sunlight. Humidity: For hygroscopic products, humidity is considered detrimental to both bulk powder and formulated solid dosage forms. Aspirin and ranitidine are classical examples. Dosage form related [26-27] Although the pharmaceutical companies perform preformulation studies, including a stability study, before marketing the products, sometimes the dosage form factors that influence drug stability force the company to recall the product. Microbiological growth resulting from the growth of bacteria, fungi and yeast in a humid and warm environment may result in oral liquid products that are unusable for human consumption. Microbial contaminations may occur during the shelf life and subsequent consumer-use of a multiple-dose product due to inappropriate use of certain preservatives in the preparations or because of the semi permeable nature of primary containers.

APPLICATIONS OF ISOLATION AND CHARACTERIZATION OF IMPURITIES

Necessary to ensure the safety and efficacy of pharmaceutical product profiling of impurities in drugs is a regulatory expectation. Numerous applications have been sought in the areas of drug designing and monitoring. Quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterial, anticonvulsants, antidepressants, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, and so on.

CONCLUSION

The pharmaceutical ingredient must not only pass CGMP, QCP, and QA tests, but also meet the specified threshold for a new impurity. Impurities must be isolated and characterized in order to collect and evaluate data that establishes the new impurity threshold. In addition to the normal CGMP, QC, and QA tests, a pharmaceutical ingredient must meet the threshold of a new impurity. Isolation and characterization of impurities are necessary to obtain information that allows for establishing an impurity's significance. Besides passing CGMP, quality control, quality assurance, and water activity tests, pharmaceutical ingredients must also qualify for the specified threshold. Isolation and characterization of impurities are primary steps towards acquiring and evaluating the data. It is mandatory for pharmaceutical ingredients to pass not only CGMP, QC, QA tests, but to also meet the specified threshold of a new impurity, which is established by isolation and characterization.

REFERENCES

[1]. International Conference on Harmonization (1999) Specifications, Q6A: Test Procedures and Acceptance Criterial for New Drug Substances and New Drug Products. Chemical substances 65 (146):67488.

[2]. Keitel S. Impurity Profiles in Active Pharmaceutical Ingredients.EU / Swiss medic GMP Workshop Beijing University. 2006 Sep

[3]. Alsante KM, Hatajik TD, Lohr LL, and Sharp TR. Isolation and identification of process related impurities and degradation products from pharmaceutical drug Candidates. Part 1. American Pharmaceutical Review. 2001; 4(1):70-78.

[4]. Alsante K M, Boutres P, et al; 'Pharmaceutical Impurity Identification: A Case Study Using a Multidisciplinary Approach', Journal of Pharmaceutical Sciences (2004) 93 (9): 2296.

[5]. Ahuja S. impurities evaluation of pharmaceutical, Dekker, New York, 1998.

[6]. Connor KA, Amidon GL, Stella VJ. 2nd ed. New York: John Wiley and Sons; 1986. Chemical Stability of Pharmaceuticals- A Handbook for Pharmacists; pp. 182–4.

[7]. Jacobs P, Dewe W, Flament A. A new validation approach applied to the GC determination of impurities in organic solvents. J Pharm Biomed Anal. 2005;40:294–304.

[8]. Ahuja S. New York: Marcel Dekker; 1998. Impurities Evaluation of Pharmaceuticals; p. 142.

[9]. Gorog S., identification and determination of impurities in drugs, Elsevier, Amsterdam, 2000

[10]. Gimeno P, Besacier F, Bottex M, Dujourdy L, Chaudron-Thozet H. A study of impurities in intermediates and 3, 4 methylenedioxymethamphetamine (MDMA) samples produced via reductive amination routes. Forensic Sci Int. 2005;155:141–57. [PubMed]

[11]. International Conferences on Harmonization, Draft Revised Guidance on Impurities in New Drug Products.Q3B(R). Federal Register. 2000, 65(139), 44791-44797.

[12]. International Conferences on Harmonization, Impurities- Guidelines for Residual solvents Q3C. Federal Register. 1997, 62(247), 67377

[13]. Vijaylakshmi R, Kumaravel S, Anbazhagan S., Scientific Approaches for Impurity profiling in New Pharmaceutical Substances and its products- An Overview. International Journal of Pharmaceutical and Chemical Sciences 2012

[14]. Sapra A., Kakkar S., Narasimhan B., Sources of impurities: A Review. International Research Journal of Pharmacy. 2012; 3(1):57- 59.

[15]. Federal Register, International Conferences on Harmonization. Guidance for Industry: Impurities Residual Solvents, U.S. Department of Health and Human Services Food and Drug Administration, (CDER), Q3C, 1997: 1-13.

[16]. Roy, J., Islam, M., Khan, A. H., Das, S. C., Akhteruzzaman, M., Deb, A. K., Alam, A. H. M., J Pharm Sci. 2001, 90, 541-544.

[17]. Walker, G. J. A., Hogerzeil, H. V., Hillgreen, U., Lancet. 1988, 2, 393.

[18]. Hogerzeil, H. V., Battersby, A., Srdanovic, V., Stjernstrom, N. E., British Medical J. 1992, 304, 210-214.

[19]. Food and Drug Administration for immediate release consumer media: 888-Info-FDA. May 6, 1998.

[20]. Hoq, M. M., Morsheda, S. B., Gomes, D. J., Bang J. Microbiology. 1991, 8(1), 5-9.

[21]. Ahuja S, (1997) Chiral Separations by Chromatography, Oxford University Press, NY, p 365

[22]. Ahuja S (1992) Chromatography of Pharmaceuticals: Natural, Synthetic and Recombinant Products. ACS Symposium Series #512, Ame Chem Soc, Washington, DC, p. 14.

[23]. Ahuja S (1998) Impurities Evaluation of Pharmaceuticals. Marcel Dekker, NewYork, p. 142. 35. Peter J S, Ahmed A and Yan W (2006) An HPLC chromatographic reactor approach for investigating the hydrolytic stability of a pharmaceutical compound. J Pharm Biomed Anal 41: 883.

[24]. Radhakrishna T, Satynarayana J and Satynarayana A (2002) Determination of Loratidine and its Related Impurities by HPLC. Indian Drugs 39 (6): 342.

[25]. Radhakrishna T, Satynarayana J and Satynarayana A (2002) HPLC method for the Degradation of Celecoxib and its Related Impurities. Indian Drugs 40(3): 166.

[26]. Zawilla N H, Li B, Hoogmartens J and Adams E (2006) Improved RP-LC method combined with pulsed electrochemical detection for the analysis of amikacin. J Pharm Biomed Anal 42: 114.

[27]. Nisha M, Ismail M, Ismail R, Duncan F, Maili L, Jeremy K N and John C L (1999) Impurity profiling in bulk pharmaceutical batches using 19F NMR spectroscopy and distinction between monomeric and dimeric impurities by NMR-based diffusion measurements. J Pharm Biomed Anal 19:511.