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Advance approaches for the impurity profiling of pharmaceutical drugs: A review

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Abstract

In the pharmaceutical world, an impurity is considered as any other organic material, besides the drug substance, or ingredients, arise out of synthesis or unwanted chemicals that remains with API's. The impurity may be developed either during formulation, or upon aging of both API's and formulated API's in medicines. The presence of these unwanted chemicals, even in small amount, may influence the efficacy and safety of the pharmaceutical products.Any material that affects the purity of the material of interest viz. active ingredient or drug substance. The impurities are not necessarily always inferior. From the standpoint of its usage, the drug substance is compromised in terms of purity even if it contains another material with superior pharmacological or toxicological properties. Highly sophisticated instrumentation, such as mass spectra meters attached to a Gas Chromatography or HPLC, are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices.

Key-Words: Impurity profiling, HPLC, Hyphenated Methods, ICH guidelines.

Introduction

Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or that is formed, due to any side reactions. Impurity can be of three types: - (1) Impurities closely related to the product and coming from the chemical or from the biosynthetic route itself, (2) Impurities formed due to spontaneous decomposition of the drug during the storage or on exposure to extreme conditions, (3) The precursors that may be present in the final product as impurities. Impurities present in excess of 0.1% should be identified and quantified by selective methods. The suggested structures of the impurities can be synthesized and will provide the final evidence for their structures, previously determined by spectroscopic methods. Therefore, it is essential to know the structure of these impurities in the bulk drug in order to alter the reaction condition and to reduce the quantity of impurity to an acceptable level. Isolation, identification and quantification of impurities help us in various ways, to obtain a pure substance with less toxicity and, safety in drug therapy.

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Quantitative determination of these impurities could be used as a method for the quality control and validation of drug substances. Regulatory authorities such as US FDA (United States Food and Drug Administration), CGMP (Current Good Manufacturing Practice), TGA (Thermo Gravimetric Analysis), and MCA (Ministry of Corporate Affairs) insist on the impurity profiling of drugs. Impurities in new drug substances can be addressed from two perspectives:-(1) The chemical aspect, which includes classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures. (2) The safety aspect, which includes specific guidance for quantifying impurities, present, substantially at lower levels, in a drug substance used in clinical studies. [1]

Impurity profile

There is no precise definition for impurity profile. It gives an account of impurities present in it. Impurity profile is a description of the identified and unidentified impurities present in a typical batch of API (Active Pharmaceutical Ingredient) produced by a specific controlled production process. It includes the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and type of each identified impurity.Impurity profile of a substance under investigation gives maximum possible types of impurities present in it. It also estimates the actual amount of different kinds of

impurities present in it. For each API there should be an impurity profile describing the identified and unidentified impurities present in a typical batch. The impurity profile is normally dependent upon the process or origin of the API.

Sources of impurities in drug products

In general, the various types of impurities that may be present in pharmaceutical substances can come from

Drug	Impurity	Method
AmphotericinB	Tetraenes	Ultra violet spectroscopy
Atropine sulphate	Apo atropine	Ultra violet spectroscopy
Cloxacillin	N,N dimethyl aniline	Gas chromatography
Dextrose	5 hydroxy methyl fulfural	Ultra violet spectroscopy
Doxorubicin hydrochloride	Acetone and ethanol	Gas chromatography
Ethambutol hydrochloride	2 amino butonol	Thin layer chromatography
Fluorescene sodium	Dimethyl formamide	Gas chromatography
Framycetin sulphate	Neamine	Thin layer chromatography
Mercaptopurine	Hypoxanthine	Ultra violet spectroscopy

the following sources:

1. The raw materials used.
2. The method of manufacture adopted.
3. Due to the instability of product and
4. From the atmospheric contaminants.

Classification of impurities

Impurities can be classified as Organic impurities (process- and drug-related), Inorganic impurities and Residual solvents. Organic impurities may arise during the manufacturing process or storage of the new drug substance, which include starting materials, by-products, intermediates, degradation products, reagents, ligands, and catalysts. Inorganic impurities include, reagents, ligands and catalysts, heavy metals or other residual metals, inorganic salts, filter aids, charcoal etc. Residual Solvents are organic or inorganic liquids used during the manufacturing process. Since these are, generally of known toxicity, the selection of appropriate controls can be accomplished easily. [4]

Types of impurities in organic medicinal substances

Organic medicinal substances are contaminated in exactly the same manner as inorganic substances during their manufacturing processes. Since the organic substances belong to a very wide range of chemical groups and at the same time the contaminating impurities being of varied nature the task of detecting the impurities becomes a difficult job. Therefore, the contaminating impurities for organic medicinal compounds can be classified into –

(1) Inorganic impurities.
(2) Organic impurities.
(3) Contamination by chemical intermediates.[2, 3]

Sources of impurities in pharmaceutical chemicals

Knowledge of those impurities, which occur in pharmaceutical substances in general use, is readily from actual batch analysis and stabilities studies. Experience in the manufacture any one particular substance often shows that not all the expected impurities are present in practice. A list of the possible impurities can be readily compiled from knowledge of the raw materials used, the method of manufacture and the stability of the product. To these must be added impurities, which may arise from physical contamination or inadequate storage conditions.[4]

Indian pharmacopoeia specifies qualitative, quantitative or semi quantitative tests for limiting known impurities in certain drugs. The list of few such drugs and corresponding impurities is as follows:

Table 1:- List of few drugs and corresponding impurities[5]

I.C.H. Guidelines for impurity profile

Impurities in New Drug Substances and drug products are dealt with new approaches to quantification and qualification. Regulatory requirements for the identification, quantification and control of impurities in drug substances and their formulated products are now being increasingly explicitly defined, particularly through the I.C.H. (International Conference of Harmonization). The implications of recent are important both from their regulatory impact and the impact upon analytical technology.This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered.Biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation and semi-synthetic products derived there from, herbal products, and crude products of animal or plant origin are not covered under it.

In I.C.H. Guidelines impurities in new drug substances are addressed from two perspectives

(1) Chemistry Aspects includes classification and identification of impurities, report generation, setting

specifications, and a brief discussion of analytical procedures.

(2) Safety Aspects includes specific guidance for qualifying impurities that were not present in batches of new drug substance used in safety and clinical studies and/or impurity levels substantially higher than in those batches. Threshold limits are defined at or below which, qualification is not needed.[6]

Significance of the research

The studies conducted to characterize the structure of actual impurities present in the new drug substance at a level greater than (>) the threshold given in Attachment 1 of ICH guidelines (e.g., calculated using the response factor of the drug substance) should be described. All specified impurities at a level greater than (>) the identification threshold in batches manufactured by the proposed commercial process should be identified analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacologic effects at a level less than or equal to the identification threshold. All impurities should be qualified as described in guide. The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantization of impurities (see ICH Q2A and B guidelines for analytical validation). Specifications and analytical procedures used to estimate identified or unidentified impurities are often based on analytical assumptions (e.g., equivalent detector response, etc.). Analytical results should be provided for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Impurities should be designated by code number all impurities at a level greater than (>) the reporting threshold should be summed and reported as Total Impurities. When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. The applicant should ensure that complete impurity profiles (i.e., chromatograms) of individual batches are available if requested.[7,8]

Current good manufacturing practices

Current Good Manufacturing Practices (cGMPs) have become a way of life for those of us in the healthcare industry. With cGMPs, The trend toward paperless will continue. New product FDA submissions will routinely be electronic. QC laboratory management systems (LMS) will be routine with a dramatic reduction in manual transcriptions. The industry has not yet grasped the significance of the FDA´s Process Analytical Technology (PAT) initiative. PAT is the clearest view of the future among published FDA guidelines.[9] What future manufacturing and QC testing will look like is written on (and between) the lines of that guideline. The vision of a monitored and controlled manufacturing process that moves significantly away from a batch production system is at the center of PAT. Based on the results of in/on/at line testing, processing decisions will be made without subjective human intervention (i.e. art gives way to science). With the ever shrinking world in this global economy, the quest to harmonize rules, regulations, guidance documents, and pharmacopeias will continue along with the frustration of getting so many different world organizations and national bureaucracies to agree.[10]

Background of study

The actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance should be summarized ,based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the drug substance. The spectroscopic studies (NMR, IR, MS etc.) conducted to characterize the structure of actual impurities present in the drug substance above an apparent level of 0.1% (e.g., calculated using the response factor of the drug substance) should be described. All recurring impurities above an apparent level of 0.1% in batches manufactured by the proposed commercial process should be identified of these studies. According to I.C.H., the maximum daily dose qualification threshold to be considered is as follows; $\leq$ 2g/day 0.1 % or 1 mg per day intake (whichever is lower) $\geq$2g/day 0.05% Inorganic impurities are normally detected and quantified using Pharmacopoeia or other appropriate standards. Carryover of catalysts to the drug substance should be evaluated during development.[11]

Qualification of impurities

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER) in January 2005 has given a draft for Guidance for Industry on “ANDAs: Impurities in Drug Substances ”. This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. One can use an alternative approach

if the approach satisfies the requirements of the applicable statutes and regulations.[12]

New impurities

During the course of drug development studies, the qualitative degradation profile of a new drug product may change, resulting in new degradation products that exceed the identification and/or qualification threshold. In this event, these new degradation products should be identified and/or qualified. Such changes call for consideration of the need for qualification of the level of the impurity unless it is below the threshold values as noted.[13]

Characterization of impuities

It is important that the authentic sample should be used for estimations, when it is available. If the estimations indicate that a given impurity content is greater than 0.1% then it must be characterized as per the FDA requirements. Hyphenated methods such as gas chromatography, mass spectroscopy, or liquid chromatography, mass spectrometry or the number of other chromatographic-spectroscopic configuration are perfectly suitable for initial characterization of the impurities.

Characterization methods

Highly sophisticated instrumentation, such as MS attached to a GC (Gas Chromatography) or HPLC (High Performance Liquid Chromatography), are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices. For characterization of impurities, different techniques are used; which are as follows;

(1) N.M.R. The ability of NMR (Nuclear Magnetic Resonance) to provide information regarding the specific bonding structure and stereochemistry of molecules of pharmaceutical interest has made it a powerful analytical instrument for structural elucidation.The ability of NMR- based diffusion coefficient determination to distinguish between monomeric and dimeric substances was validated using a standard mixture of authentic materials containing both monomers and dimers. Unfortunately, NMR has traditionally been used as a less sensitive method compared to other analytical techniques. Conventional sample requirements for NMR are on the order of 10 mg, as compared with MS, which requires less than 1 mg.

(2) M.S. MS (Mass spectroscopy) has an increasingly significant impact on the pharmaceutical development process over the past several decades. Advances in the design and efficiency of the interfaces, that directly connect separation techniques with Mass Spectrometers have afforded new opportunities for monitoring, characterizing, and quantification of drug-related substances in active pharmaceutical ingredients and pharmaceutical formulations. If single method fails to provide the necessary selectivity, orthogonal coupling of chromatographic techniques such as HPLC-TLC and HPLC-CE (High Performance Liquid chromatography coupled with Capillary Electrophoresis), or coupling of chromatographic separations with information rich spectroscopic methods such as HPLC-MS or HPLC-NMR may need to be contemplated, but hopefully only as a development tool rather than a tool for routine QC (Quality control) use.

Hyphenated Methods

1. LC-MS-MS
2. HPLC-DAD-MS
3. HPLC-DAD-NMR-MS
4. GC-MS
5. LC-MS

An example of reverse-phase LC-MS analysis in gradient elution with two distinct soft ionization techniques is the Atmospheric Pressure Ionization with Electrospray Source (API-ESI) and the chemical ionization of d-allethrine. The popularity of LC-MS-MS systems for complex mixture analysis of thermally labile and biologically relevant molecules, *viz* mosapride, is largely attributed to the "soft" nature of Atmospheric Pressure Chemical Ionization (APCI), and Atmospheric Pressure Ionization (APPI). HPLC-DAD-MS (HPLC coupled with a Diode Array UV Detector and a Mass Spectrometer), and such other techniques are almost routinely used. NMR has now been added to this combination to provide HPLC-DAD-NMR-MS capabilities in instruments.

General scheme for drug impurity profiling

Highly sophisticated instrumentation, such as mass spectra meters attached to a Gas Chromatography or HPLC, are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices.NMR spectroscopy, which involves complete structure elucidation, which may require the isolation of larger components (usually by preparative HPLC). Since Mass and NMR are very expensive and in the latter case very time consuming UV rapid scanning using the diode-array detector attached to HPLC is better alternative. But the UV-HPLC method to determine impurity profile only, provi0ded the impurity is spectrophotometrically active. Although the successful application of HPLC/DAD (Diode-Array UV Detectors) in the identification of the above mentioned minor components is restricted to those cases where the components is spectrophotometrically active and its

spectrum differs sufficiently from that of the main components (parents drugs) and from other small components, this technique can be successfully used in the impurity profiling of drugs.

Purposeful degradation studies

This technique helps in identification of impurities especially of a new drug or a chemical. Degradation product, a molecule resulting from a chemical change in the substance brought about over time and/or by the action of, e.g., light, temperature, pH, or water or by reaction with an excipient and/or the immediate container/closure system (also called decomposition product) is described in a Degradation Profile and is then subjected to a known degradation process and the products thus obtained are identifies. As we know the degradation process (may be oxidation or hydrolysis) we have an idea what could be the degradation products. These can be listed and kept as a reference library of degradation products. Then routinely doing an impurity profile one can take help from this library and trace the nature and structure of the impurity.[14, 15]

Analytical challenges to current methods and potential new methods

While the threshold for identification and qualification of organic impurities is set at 0.1% for the majority of compounds, it is important to recognize that the implication is that a Limit of Quantification (LOQ) of approximately 0.05% will be required: For a compound that is 98% pure, the 2% impurities could be composed of between 10 and 20 components at a level of scrutiny of 0.05%. In future, it may become essential to increase selectivity through the use of gradient separation, both in HPLC and TLC, or through the use of alternative technologies.[16] However, gradient HPLC is the more usual technique, If single methods fail to provide the necessary selectivity, orthogonal coupling of chromatographic techniques such as HPLC-TLC and HPLC-CE, or coupling of chromatographic separations with information rich spectroscopic methods such as HPLC-MS or HPLC-NMR may need to contemplated, but hopefully only as a development tool rather than a tool for routine QC use. The further may see the significantly increased use of spectroscopic techniques for impurity measurement. NMR has shown values for stereo isomers and for process related impurity, but still does not quite show the sensitivity required. Near-infrared spectroscopy in rapidly increasing in use and can detect impurities, although more demonstrations of true validation for low levels of impurities are required.[17] One single method that is showing great promise in pharmaceutical analysis is Capillary Electrophoresis (CE). With its much increased efficiency and great variety of separation modes it may provide sufficient peak capacity, and indeed CE is finding increasing favour for pharmaceutical analysis. CE also adds speed to selectivity, and many of the concerns over the robustness and transferability of CE separations have been dispelled recently through a number of collaborative studies. Additionally, while enantiomers are outside the scope of the current ICH guidelines, there is no doubt that, when they are potential impurities, their level(s) must be controlled. CE-MECC can provide the necessary detectabilty to control enantiomers to the 0.1% level.[18]

Acceptance criteria for impurities

For newly synthesized drug substances, the specification should include acceptance criteria for impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. A rationale for the inclusion or exclusion of impurities in the specification should include a discussion of the impurity profiles observed in batches under consideration, together with a consideration of the impurity profile of material manufactured by the proposed commercial process. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantization or detection limit of the analytical methods should commensurate with the level at which the impurities need to be controlled. Appropriate qualitative analytical descriptive label included in the specification of unidentified impurities. A general acceptance criterion of not more than 0.1 % for any unspecified impurity should be included. Acceptance criteria should be set, based on data generated on actual batches of the drug substance, allowing sufficient latitude to deal with normal manufacturing and analytical variation, and the stability characteristics of the drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels could indicate that the manufacturing process of the drug substance is not adequately controlled and validated. The acceptance criteria should include limits for organic impurities; each specified identified impurity, each specified unidentified impurity at or above 0.1%, and any unspecified impurity, with a limit of not more than 0.1%, total impurities, residual solvents and inorganic impurities. If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed (when the usual qualification threshold limits given below are exceeded). According to ICH, the maximum daily dose qualification threshold is considered as follows:

≤ 2g/day 0.1 % or 1 mg per day intake (whichever is lower) ≥ 2g/day 0.05%

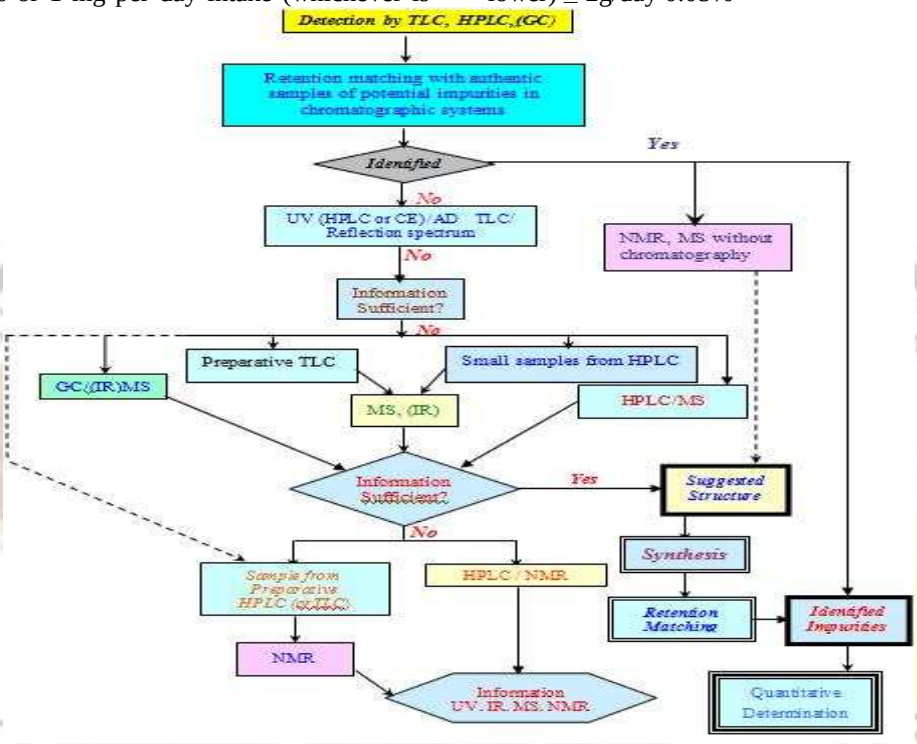

Fig. 1: schematic representation of scheme for impurity profiling of drugs

In the case of unsuccessful identification with standard samples the most reasonable way to determine the structure of impurity starts with the investigation of the UV spectra, easily obtainable with the aid of the diode-array detector in the case of HPLC and the quantification with the help of densitometer. In exceptional cases, with full knowledge of the synthesis of drug martial, the structure of the impurity can be generated on the basis of NMR spectral data.[19, 20] If the information obtained from the UV spectrum is not sufficient, the next step in the procedure of impurity profiling is to take the mass spectrum of the impurity. The major disadvantage of this method is the volatility and thermal stability problems of the impurities. The use of derivatization reactions widely used in GC/MS analysis is problematic because the side-products of the derivatization reaction can be confused with the impurities. The next step in the impurity profiling is the synthesis of the material (*impurity standard*) with the proposed structure. The retention and spectral matching of the synthesized material with the impurity in question is carried out as outlined above.[21] The possibilities of spectroscopic techniques in drug impurity profiling without chromatographic separation are also worth mentioning. Spectra obtained by using high-resolution, highly sensitive NMR spectrometers and mass spectrometers with APCI /ESI (Electromagnetic Source Imaging) facilities are suitable to provide a fingerprint picture regarding the purity of the sample.

Analytical procedures

Method Development

Method development usually requires the choice of columns, mobile phase, detectors, and method of quantization etc. The factors to be considered for the method developmentare the following, Existing method may be inaccurate, artifact, or contamination prone, or they may be unreliable (have poor accuracy or precision). Existing method may be too expensive, time consuming or energy intensive, or they may not be easily automated. Existing methods may not provide adequate sensitive or analyte selectivity in samples of interest. Newer instrumentation techniques may have evolved which can provide opportunities for improved methods, including improved analyte identification or detection limits, greater accuracy or precision and better returns on investments.

Validation of analytical methods

The validation process involves confirmation or establishing a developed method by laboratory studies, procedures, systems, which can give accurate and reproducible result for an intended analytical

application in a proven and established range. The performance characteristics of the method (accuracy, precision, sensitivity, ruggedness, etc) should meet the requirements of the intended analytical applications and the process can or provide documented evidence that the system or procedure do what it is intended for in a systematic, precise and reliable manner. According to ICH, typical analytical performance characteristics that should be considered in the validation of all the types of methods are:-

(1) *The Limit of Detection (LOD)* of an individual analytical method is the lowest concentration/amount of analyte in a sample that the method can detect but not necessarily
quantify under the stated experimental conditions. The LOD will not only depend on the procedure of analysis, also on the type of the instrument.

(2) *The Limit of Quantification (LOQ)* of an individual analytical method is the lowest concentration/ amount of an analyte in a sample, which can be quantitatively determined with suitable precision and accuracy under stated experimental conditions. The quantification limit is used particularly for the determination of impurities and degradation products.

(3) The *Linearity* of an analytical method is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample.

(4) The *Range* of an analytical method is the between the upper and lower concentration (amounts) of analyte the sample (including those concentrations) for which it has been demonstrated that analytical procedure has a suitable level of precision, accuracy and linearity.

(5) *Robustness* is the measure of the analytical method to remain unaffected by small, but deliberate variations in method parameters. It provides an indication of its reliability during normal usage.

(6) The *Ruggedness* is the degree of reproducibility of test results obtained by analyzing the same sample under variety of normal test conditions such as different analyst, instruments, days, reagents and, columns. The comparison of reproducibility of test results to the precision of assay is the direct measure of ruggedness of the method.

Applications

Numerous applications have been sought in the areas of drug designing and in 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, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, miscellaneous etc.

Conclusion

Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and the identification of impurities in Active Pharmaceutical Ingredients (API's). Qualification of the impurities is the process of acquiring and evaluating data that establishes biological safety of an individual impurity; thus, revealing the need and scope of impurity profiling of drugs in pharmaceutical research. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. There are different methods for detecting and characterizing impurities with TLC, HPLC, HPTLC, AAS *etc*. Conventional Liquid Chromatography, particularly, HPLC has been exploited widely in field of impurity profiling; the wide range of detectors, and stationary phases along with its sensitivity and cost effective separation have attributed to its varied applications. Among the various Planar Chromatographic Methods; TLC is the most commonly used separation technique, for isolation of impurities; due to its ease of operation and low cost compared to HPLC. An advancement of thin layer chromatography HPTLC, is a well-known technique for the impurity isolation. Headspace GC is one of the most preferred techniques for identification of residual solvents. The advent of hyphenated techniques has revolutionized impurity profiling, by not only separation but structural identification of impurities as well. Among all hyphenated techniques, the most exploited techniques, for impurity profiling of drugs are LC-MS-MS, LC-NMR, LC-NMR-MS, GC-MS, and LC-MS.[22,23]

An accurate method development and validation of the procedures make the impurity profiling task easy. Quality assurance is a vast, concept. This concept leads to an area of IMPURITY PROFILING. Impurity profile of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels in drug substances and products now provides the quality criteria for manufacturers. The key aspect is that the impurity profile of a new chemical entity must be shown to be qualified. With a qualification threshold pf 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology. Especially in the development phases it may be necessary to utilize methods with high selectivity, including hyphenated techniques. The importance of qualifying impurity profiles are relevant to the development scientists to

ensure consideration is given to the impurities present in the batches being used in safety studies starting from limit tests for impurities, this field of impurity identification and quantization has progressed. With newer techniques like U.V. spectroscopy with diode array detection, HPLC, GCIR (Gas Chromatography-Infrared Spectrometry), NMR, CE-MECC.[24] This project is an attempt to understand the concept of impurity profile and various aspects and techniques related to it.

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