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PROFILING OF IMPURITIES IN PHARMACEUTICAL FORMULATIONS

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ABSTRACT: Impurity profiling is the process of evaluating data for the biological safety of an individual impurity. Impurity profiling has gained utmost importance due to the fact that unidentified impurities present in the pharmaceutical formulations may prove hazardous to human health on consumption. Impurities in pharmaceuticals are unwanted compounds that remain or those that are present during the formulation of drugs. A number of regulatory agencies like USFDA, ICH and Canadian Drug and Health Agency are emphasizing on the purity requirements as well as identification of impurities in active pharmaceutical ingredients. Impurity profiling, helps in the detection, identification, and quantification of various types of impurities present in pharmaceutical formulations. Identification of impurities can be done by using either chromatographic or spectroscopic techniques alone or by combination of both. A number of methods have been used for detecting and characterizing impurities using HPLC, HPTLC, AAS, TLC, etc. However the most exploited techniques used today for impurity profiling of drugs include LC-MS, GC-MS, NMR-MS, LC-MS-MS and LC-NMR. Therefore, this review focuses on the importance of impurity profiling and the need for identification, quantification and qualification of impurities present in pharmaceuticals

INTRODUCTION: The major challenge for both bulk drug and pharmaceutical industries is to produce quality products. Screening of excipients for impurities and their interaction with the drug molecules has to be done to guarantee the stability of drug products¹. Therefore, the stability of active pharmaceutical ingredients depends on the excipients used and rigorous quality checks are done in order to maintain the quality and purity of pharmaceutical formulations². These checks are carried out in order to find the potential reaction between the drug and the excipients which affects their bioavailability and in turn hinders the safety and efficacy of the drug³.

Analytical techniques used to detect drug excipient compatibility include thermal methods of analysis, which are DSC- Differential Scanning Calorimetry and DTA- Differential Thermal Analysis. Other methods include FT-IR Spectroscopy, DRS-Diffuse Reflectance Spectroscopy, Chromatography; SIC-Self Interactive Chromatography, TLC-Thin Layer Chromatography, HPLC-High Pressure Liquid Chromatography can be used to detect drug excipient compatibility⁴.

Purity of pharmaceutical formulations, therefore, depends on several factors such as raw materials, method of manufacture and purification process. The pharmacopeias not only specify the purity of pharmaceutical formulations but also impose stringent rules for impurities in such formulations. Impurities present in small amounts may affect the efficacy and safety of pharmaceutical formulations. Therefore, impurity profiling in contrast to purity profiling has become essential as per regulatory requirements. Classification of such impurities is based on pharmacopeia and their guidelines. The

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aim of the present study is to discuss the importance of impurity profiling in pharmaceutical formulations and the need for identification, quantification and qualification of such impurities in pharmaceutical formulations.

1.1 As per International Conference on Harmonization (ICH):

Impurities have been classified into organic, inorganic and process based impurities. These impurities are formed by the degradation of the end product during the manufacture of pharmaceuticals. For example in the case of paracetamol, diacetylated paracetamol may be formed as a by product. Another example is the degradation of ibuprofen to 2-(4-formylphenyl) propionic acid, 2-(4-isobutylphenyl) propionic acid, 2-(4-methylphenyl) propionic acid, 2-(4-ethylphenyl) propionic acid, 4-isobutylacetophenone, 2-(4-n-propylphenyl) propionic acid and 2-(4-n-butylphenyl) propionic acid and these are reported to be impurities of ibuprofen⁵. Therefore, it can be seen that it is impossible to get a single end product with 100 percent yield, and there is always a chance of having by-products.

Organic impurities arise during the manufacturing process or during storage of the drug substance. These impurities include intermediates, by products and degradation products. Inorganic impurities are obtained during the manufacturing process of bulk drug formulations. These are visible and can easily be removed. These include heavy metal impurities and residual solvent impurities. However, it is very difficult to remove the solvent impurities by work-up process and therefore it is necessary to check whether these impurities are present within the permissible limits⁶. Process based impurities are formed due environmental defect, factor defect, method defect, mutual interaction among ingredients and functional group reaction degradation (Hydrolysis, Oxidation, Decarboxylation and Photolysis).

1.1.1 Hydrolysis:

Certain drugs that undergo hydrolysis include barbital, oxazepam, chloramphenicol, etc., and this process is a common phenomenon for ester and amide type of drugs.

1.1.2 Oxidation:

Drugs which undergo oxidation include methotrexate, hydrocortisone, etc., and oxidative decomposition of pharmaceutical compounds is responsible for the instability of a considerable number of pharmaceutical preparations.

1.1.3 Decarboxylation:

Some dissolved carboxylic acid such as p-amino salicylic acid loses carbon dioxide from the carboxyl group when heated. An example of decarboxylation is the photoreaction of rifloxacin.

1.1.4 Photolysis:

Drugs which undergo photolytic degradation are ergometrine, nifedipine, riboflavin, etc., Therefore pharmaceutical products are bared to light when held improperly in pharmacy shops or when used improperly by consumer. Most compounds degrade to solutions when exposed to UV light.

1.1 As per United States Pharmacopeia (USP):

The United States Pharmacopeia (USP) classifies impurities into ordinary impurities and organic volatile impurities. Ordinary impurities arise during the synthesis or preparation of pharmaceuticals or may arise due to degradation of chemicals. Organic volatile impurities are produced during manufacture of drug substances and these being volatile in nature, get removed at the time of storage or processing⁷.

1. Methods of identification and validation of impurities:

The impurities can be identified and validated by various methods like reference standard method, spectroscopic method, separation method, isolation method and characterization method.

Reference Standard Method:

The objective of this method is to provide clarity, qualification and governance of reference standards used in the development of new pharmaceuticals. This method serves as the benchmark for assessment of drug safety for patient consumption. This method also serves as the base for both process and product⁸.

1.1 Spectroscopic method: This is used for characterization of impurities in pharmaceuticals.

This is mainly done using UV, MS, IR, NMR and Raman Spectroscopic methods⁹.

Identification of an unknown contaminant by NMR usually begins with creating a high-resolution H¹-NMR spectrum. The chemical shifts and integration reveal the relative number of protons (aliphatic, olefinic, and aromatic) and the coupling patterns may suggest their relative proximity. Next, C¹³-NMR and DEPT (distortion less enhancement by polarization transfer) spectra are used to obtain the number of different carbons and the numbers of protons attached to each.

Often, the combination of proton and carbon data is enough to solve the structure of the unknown. Identification of an unknown contaminant by IR usually begins by mixing the pharmaceuticals (solid dosage forms) with potassium bromide and compressing to fewer than 10 tonnes pressure in a hydraulic press to form a transparent KBr pellets. The pellets formed should be scanned using IR spectrometer at the wave number range of 4000cm⁻¹ to 400cm⁻¹. From the spectrum, the impurities or degraded products of the tablets are noted. Mass spectrometers are mainly use for monitoring, characterizing, and quantification of drug related substances in pharmaceutical formulations.

1.1 Isolation method:

Isolation of impurities is necessary if instrumental methods are not used however it is avoided now-a-days by the use of instruments, thereby characterizing the impurities directly without the need of isolation. This method involves chromatographic and non-chromatographic techniques for isolation prior to their characterization. For example, by using an HPLC, chromatographic reactor approach, the solution phase hydrolysis of the Aprepitant prodrug, fosaprepitant dimeglumine, were investigated¹⁰.

Other examples include celecoxib and amikacin. The methods used for isolation of impurities include capillary electrophoresis, gas chromatography, thin layer chromatography, flash chromatography, high performance thin layer chromatography, supercritical fluid chromatography, high performance liquid chromatography.

1.1 Separation method:

This includes chiral separation, capillary electrophoresis, gas chromatography, supercritical fluid chromatography, thin layer chromatography, high performance thin layer chromatography, high performance liquid chromatography are being used for separation of impurities and degradation products.

1.2 Characterization method:

This includes highly sophisticated instrumentation, such as MS attached to GC or HPLC, for identification of minor components. NMR and MS are commonly employed for characterization, however if single method fails to provide the necessary details hyphenated methods such as LC-MS-MS, HPLC-DAD-MS, HPLC-DAD-NMR-MS, GC-MS, LC-MS can be normally used. An example of reverse phase LC-MS analysis in gradient elution with two distinct soft ionization techniques is the Atmospheric pressure ionization with electro spray source and the chemical ionization of d-allethrine¹¹.

1. Need for impurity profiling:

Impurity profiling is necessary for identification of significant impurities, potential degradation product through stress testing and actual degradation products through stability studies. It also determines the origin of impurities, the method of elimination or reduction and in understanding the degradation pathway to minimize degradation. Finally, impurity profiling establishes a control system for impurities involving processing/manufacturing conditions, suitable analytical methods/specifications, long term storage conditions including packaging and formulation.

1. Procedure for impurity profiling:

- Impurity profiling, begins with the detection of impurities using thin layer chromatography, high performance liquid chromatography or gas chromatography.
- If the identification is unsuccessful with the standard samples, then the structure determination starts with investigation using UV spectra, and the quantification with the help of densitometer.

- If the information obtained from UV spectrum is not sufficient, the next step is to take the mass spectrum of the impurity. However this method suffers from a number of disadvantages such as volatility and thermal stability of the impurities.
- The next step is the synthesis of the material (impurity standard) with the proposed structure. The spectral matching of the synthesized material with the impurity in question is then carried out.
- Validation process involves confirmation or establishing a developed method by laboratory studies, procedures, systems, which can give accurate and reproducible results for an intended analytical application.
- Finally, the performance characteristics such as accuracy, precision, sensitivity, ruggedness, *etc.*, should meet the requirements of the intended analytical applications and then the process can be used in a reliable manner¹².

2. Applications:

They have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical formulations, whether produced synthetically or extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, tranquilizers, steroids and miscellaneous.

CONCLUSION:

Impurity profiling is very important as it helps in providing the safety limit, limit of quantification, limit of detection, limit of organic and inorganic impurities along with their toxicity limit. Hence, it is mandatory to know the impurities present in pharmaceutical formulations, to make the

formulation fit for patient consumption. Therefore, it is necessary for the isolation and characterization of impurities by various methods that are mentioned above. In conclusion, with the help of impurity profiling, it is possible to design a product with a suitable method where the expected impurity cannot interfere and hence impurity profiling should be given as much importance as purity profiling.

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