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Review Article

Recent trends in impurity profiling of pharmaceutical products

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ABSTRACT

Impurity plays a major role in pharmaceuticals therefore profiling of impurity is very important. There are various forms of impurities incorporated in the pharmaceuticals. These impurities are classified into three main categories such as organic, inorganic and residual solvents. Organic impurities include intermediate, starting material, degradation products, reagents, ligands, catalyst and by products. Whereas inorganic impurities are heavy metals, residual solvent, inorganic salt, filter-aids, charcoal and reagents. In pharmaceuticals impurities originate from various sources like formulation related impurities, synthetic intermediates, impurities arising during storage, impurities related to stereochemistry of the compound and most important is functional group related impurities. There are several methods used for the identification of impurities in pharmaceuticals but characterization of impurities is an important method of identification. Characterization includes nuclear magnetic resonance spectrometry (NMR) and mass spectrometry (MS). There are some recent hyphenated techniques for impurity profiling coupled with mass spectrometry like LC-MS, LC-MS-MS, GC-MS, HPLC-DAD-MS, HPLC-DAD-NMR-MS, capillary electrophoresis-mass spectrometry and tandem spectrometry.

1. INTRODUCTION

Impurity may be defined as the substance which exists with original drug as an intermediate or a primary material that is formed due to any change in condition of reaction or a reactant. Basically pharmaceutical impurities can be divided into three types. First is the impurity related to final product and that which comes from the route of reactions. Second are impurities obtained due to sudden fast decomposition of the main drug during storage or the drug exposed to hazardous chemicals. The third type of impurity is obtained from the primary material and may be present as it is in the final product [1].

Impurities present in the product around a concentration of 0.1% can be identified by various techniques. There are techniques in which the structure of impurity can be elucidated. If we already known about the structure of the impurity that may be present in the active pharmaceutical ingredient, we can decreases the quantity of impurity by changing the route of reaction. There are different methods that help us to obtain the pure compound with less toxic effect that is safe in drug medication therapy, such as isolation, identification and quantification etc**.** In pharmaceutical industries impurities should be qualified. If no such data is available, then studies to obtain such data may be required to be done, that matches with the standard quality guidelines. For example, as per the ICH guidelines the maximum daily dose qualification is considered less than or equal to 2gm/day (0.1%) or 1mg/day intake greater than or equal to 2gm/day, 0.05% of total daily intake (TDI) of the degradation product in drug molecules [3]. ICH also gives some rules and guidelines for impurity analysis in new drug substance for human [4].

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2. IMPURITY PROFILE

There is no as such official definition of impurity profile. But, to understand, we can define the impurity profile as the proper description and detailed information about the identified and unidentified impurities present in the whole batch of the active pharmaceutical ingredient that is bulk drug manufactured by the special controlled and specific production method. [5] The symbols or signs and some analytical design, range of each type of impurity are also included in it. The profiling basically depends on the process or method of manufactured of the API.

Impurity profiling gives the information or help to identify the impurities which are present in the pharmaceutical preparation with the help of relative techniques of analysis. Various impurities are present in the pharmaceutical product, like intermediate product, interaction product, impurity formed due to degradation of drug product, by product, transformation product and related product. Impurity profiling gives an account for investigation of impurities which are present in the drug product [6].

3. CLASSIFICATION OF IMPURITIES IN PHARMACEUTICAL PRODUCTS

Impurities can be classified mainly in three classes are as follows:

3.1. Organic impurities

Organic impurities are those substances which are formed in the drug substance during the process of synthesis of drug product or even formed during the storage of drug product. This type of impurity includes- intermediate, starting material, degradation product, reagents, ligands, catalyst and by product [7].

3.1.1. Intermediate: Intermediates are substances which are produced during the manufacturing of the desired material or as a part of the manufacturing or synthesis of drug material [8].

3.1.2. Starting material: It is very important to take care about this type of impurities. These types of impurity are very common impurities which present in the API, if care is not taken during the synthesis. This type of impurities may play crucial role in forming the starting material of next step. But in multistep synthesis, although the last product is washed with solvents but there will be chances of traces amount of starting material present in the next step as impurity [9]. For example, in the synthesis of paracetamol, p-aminophenol is usually found as impurity which is the starting material for synthesis of paracetamol or sometimes if phenol is used as starting material, it is formed as intermediate [10].

3.1.3. Degradation product: Degradation of pharmaceutically active ingredient takes place in the presence of heat, light and moisture leading to decomposition of active ingredients to form other unusual product which acts as impurity in pharmaceuticals. Most common impurity in the API are formed due to aging [11]. For example: degradation products formed in formulations of penicillin's and cephalosporin [12].

3.1.4. Reagent, Ligands and Catalyst: There are very less chances of formation of this type of impurity. When method of synthesis is not controlled properly then there will be a chances of formation of these type of impurities. Reagent, ligands and catalyst can be used to form the final product so they carried up to last step with traces of impurities. Some reagent has degradative effect on the final product. For example- trimethylamine. Sometime reagent and catalyst react to form an intermediate byproduct which is carried to the final product [13]. Example pyridine used as catalyst in the synthesis of mazipredone, react with intermediate to form pyridinium as impurity [14].

3.1.5. By product: In the pharmaceutical organic chemistry 100% yield of the desired product is not always possible and there is a chances of getting the small amount of byproduct. This type of compound present or formed in the reaction due to excess of reagent, interaction between the reagent and catalyst, or some time due to ligand binding to the catalyst or reagent, form the byproducts. In some cases there will be a side reaction, overreaction, demonization and rearrangement due to which excess of by products are formed [15].

3.2 Inorganic Impurities

Inorganic impurities present mainly include heavy metals, residual solvents, inorganic salts, filter aids, charcoal, reagent, ligands and catalyst.

These are described as follow:

3.2.1. Heavy Metals: Water is the main source of heavy metal, which contains large amount of heavy metals such as Cd, Na, Ar, Mg, etc. Water is generally used for manufacturing processes of API. Due to the presence of heavy metals, acid hydrolysis and other reaction takes place which are hazardous to the process of API manufacturing. Due to that the new drug product may contain impurity or decrease the stability of pharmaceutical product. So the heavy metal impurities can be easily avoided with the help of or using demineralized water or glass lined reactors [16].

3.2.2. Filters aids and charcoal: Filter and filter aids are daily used in the manufacturing of bulk drug. Equipment like centrifuge bags are also used which contain charcoal. Charcoal may be a source of impurity in the manufacturing processes of bulk drugs [17]. So, the regular use of fibers and black particles in the manufacturing processes of bulk drugs is also important to avoid the contamination.

3.2.3. Reagent, ligands and catalyst: There will be a very less chances of having these types of impurities unless manufacturer takes proper care during production process.

3.2.4. Residual solvents: Residual solvents are the solvents that may be organic or inorganic liquids used during the process of manufacturing of pharmaceutically active ingredient [18]. Some solvent are very toxic and it is very difficult to remove the solvents completely by work process. Therefore, toxic solvent should be avoided in the manufacturing of bulk drug. Depending upon the toxicity of solvent on human health, they are divided into three main classes:

Class – 1 solvents: Carbon tetrachloride (4ppm), toluene (890ppm), methanol (3000ppm), pyridine (200ppm), methylene chloride (600ppm), benzene (2ppm). (The value in bracket shows

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the limit of solvent as per standards). These solvents should be avoided in the pharmaceutical products because they are known as carcinogenic solvent. They are suspected to cause human cancer and environmental hazards or pollution [18-19].

Class – 2 solvents: Example- acetonitrile (410 ppm), N, N-dimethylformamide (880 ppm). These solvents are also harmful or dangerous to pharmaceutical products. These solvents are animal carcinogenic or other causative agents of irreversible toxicities like teratogenicity and neurotoxicity [20].

Class – 3 solvents: Example-acetone, ethanol, acetic acid. As per ICH guidelines these solvents are permitted for intake in amount 50 mg or less per day [21]. These types of solvents are less toxic than class one and class two solvents. Class three solvents have low toxicological potential to man but limit for intake is needed. As per ICH guidelines they are found negative in genotoxic studies [22].

Table 1. Some classic solvents to be limited in pharmaceutical product

S. No.	Solvent	Permitted daily exposure	Concentration limit
1.	Acetonitrile	4.1 mg/day	410 ppm
2.	Chlorobenzene	3.6 mg/day	360 ppm
3.	Chloroform	0.6 mg/day	60 ppm
4.	Cyclohexane	38.8 mg/day	3880 ppm
5.	1, 2-dichloroethane	18.7 mg/day	1870ppm

4. SOURCES OF IMPURITIES

4.1 Formulation related impurities

There are various impurities that arise in the formulation of drug product and these type of impurities can deteriorate the whole product or sometimes the whole batch of particular product. So in the formulation process drug should be kept in the particular condition of temperature and atmosphere otherwise the drug can degrade or other side reactions can starts with drug such as hydrolysis, oxidation, racemization, etc. There are two types of impurities that can forms during the formulation:

4.1.1. Method related impurities: This type of impurities form due to process deviation or change in method of synthesis. For example, in the production of diclofenac sodium, 1(2-6, dichlorophenyl) indolin-2-one is formed as impurity. When the formulation is sterilized by autoclaving, the intermolecular cyclic ring of diclofenac sodium produces sodium hydroxide and indolinone. This impurity formed depends on the initial pH of the formulation [23].

4.1.2. Environment related impurities: Most of the time impurities formed in the formulation due to changes in environmental condition. Many of formulation get oxidized when it comes into the contact of direct sunlight. Some drug show adverse reaction due to effect of temperature on it. For example, vitamin product in liquid dosage forms is degraded at high temperatures. Ergometrine injection completely degrades after it is kept in direct sunlight for 42 hours. Most of the drug are affected to humidity also, such as aspirin [13, 16, 23].

4.2. Synthetic intermediate and by product

In process of synthesis of drug product most of the time impurities can be generated from solvents, raw materials and extracted products [24]. These are called as intermediate. The drug product which is formed should have high purity than the raw material used. Sometime feed container may contain impurities and after adding the raw material in feed container they react with chemical used in synthetic process to form impurities. Synthetic intermediate are carried as impurity from starting of synthesis process to the final product.

4.3. Impurities arising during storage

Many of the times impurities are generated during the storage of drug product. After the duration of shelf life of drug product, it can degrade to form different compound. Some time polymorphism occurs and there is observed reduction in the level of drug activity. When drug products are transported there may be chances of drug degradation due to improper storage during transportation. Drug degradation can also be caused due to impurities present in the drug container.

4.4 Stereochemistry related impurities:

It is the most important parameter to look for, because this type of impurity is obtained after the formation of the drug product. Sometimes isomeric forms of drug show adverse effect. These compounds have similar chemical structure but different spatial orientation, so these compounds are taken into the consideration as impurity in the APIs. Chiral molecules are called enantiomers containing four different groups to its adjacent side. These enantiomers are obtained in two forms that is R and S forms. One of the enantiomer is considered as better chemical entity and it may shows better pharmacologic effect over the other form. Example- levofloxacin R and S form of ofloxacin are comparable, suggesting the lack of advantage of single isomer in this regard. The prominent single isomer drugs, which are being marketed include levofloxacin (S-ofloxacin), levalbuterol (R- albuterol) and esomeprazole (S-omeprazole).

4.5 Functional group related impurities

4.5.1 Oxidative degradation: Hydrocortisone, methotrexate, hydroxyl group are bonded to aromatic ring example: phenol derivative like catecholamine, conjugated dienes (vitamin A and unsaturated fatty acids), heterocyclic rings and nitrile derivatives can undergo oxidative degradation [25].

4.5.2 Ester hydrolysis: Drugs like aspirin, benzocaine and cocaine undergo ester hydrolysis.

4.5.3 Hydrolysis: Ester type of drug commonly shows hydrolysis especially in liquid dosage forms such as benzyl penicillin, oxazepam and lincomycin.

4.5.4 Photolytic cleavage: During manufacturing and storage of drug, the drug is exposed to light; oxidation of drug occurs called

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photo-oxidation. Example- ergometrine, nifedipine, riboflavin are those drug which are susceptible to photolytic cleavage. Sometimes in susceptible compounds photochemical energy creates free radical intermediate, which initiate chain reaction.

4.5.5 Decarboxylation: The dissolved carboxylic acids, for example- p-amino salicylic acid lose carbon dioxide from the carboxyl group when heated. Decarboxylation also occurs in the case of photoreaction of drug rufloxacin.

5. CHARACTERIZATION OF IMPURITIES

Impurities can be identified by different methods such as reference standard method, spectroscopic method, separation method, isolation method and characterization method. Characterization method is one of the recent methods of identification of impurity in pharmaceutical product. Characterization method include sophisticated technique like NMR, mass spectrometry, HPLC etc. These types of techniques are used in the pharmaceutical industry for the purpose of identification of drug, degradation product, impurities and metabolites in various drug products. These techniques are also used to characterize the drug product based upon the impurities present in that drug. So the characterization of impurities plays major role in impurity profiling of pharmaceutical products.

5.1. NMR – Nuclear magnetic resonance

One of the important aspects of NMR is the direct proportionality between peak areas and the number of nuclei responsible for the peak. NMR is also called proton NMR because it gives structural elucidation based on the number of proton pair present in the structure. The important application of NMR spectroscopy is that it gives identification and structure elucidation of organic metal, analysis of multicomponent mixture and elemental analysis etc. NMR spectroscopy provides information related to specific bonding of molecule in the structure and their stereochemistry. Pharmaceutically this instrument is made for structural elucidation. NMR spectroscopy has ability to determine the diffusion coefficient to differentiate between monomeric and dimeric substance present in the mixture of compound using the standard mixture which containing both monomers and dimers units. For example, NMR spectroscopy determined the impurity of vanadium in copper by resonance and analyzed it in terms of a nonmagnetic virtual bound state. After research it was concluded that vanadium impurities in copper are magnetically similar to cobalt impurities [22-25]. Sample requirement for NMR is in order of 10 mg and as compared with mass spectrometry is less than 1 mg. The new technique FT-NMR it is also used in the pharmaceutical for characterization of impurity.

5.2. MS – Mass spectrometry

Mass spectrometry has wide application and impact on pharmaceutical development processes from last several years. It is an advance technique in design and efficiency of interfaces. This technique is connected to various separation techniques with mass spectrometers. It has new opportunities for identification, monitoring, characterizing and quantification of drug related substance in pharmaceutical preparation [22, 23, 25]. Sometime identification of compound separated by chromatographic technique or the interpretation of complex spectrum becomes impossible. Then the chemist take help of some techniques which are coupled with or incorporated with mass spectrometer to give the detail information about compound like molecular weight, structure elucidation etc [22-25]. These techniques are hyphenated methods so such types of techniques are important as development tool for quality control. Mass spectrometry helps to determine the molecular weight of compound as well as molecular formula of compound. Mass spectrometry works in three main steps ionization, mass filtration and detection. In mass spectrometry charge separates according to their mass to charge ratio. This is the basic principle behind the mass spectrometry. Recent techniques couple with mass spectrometry used in characterization of impurities are as follows:

5.2.1 LC-MS- liquid chromatography mass spectrometry

It is an example of an reverse phase LC-MS analysis in which gradient elution with two distinct soft ionization technique consist of atmospheric pressure ionization with electrospray source (API-ESI) and the chemical ionization of d-allethrine LC-MS is similar to GC-MS (gas chromatography-mass spectrometry) because more problem arises in the removal of liquid carrier from an HPLC eluent before sample passed into the MS source. 0.5 – 0.2ml/min is the normal eluent flow rate of liquid which cant be handled by pumping system of MS, therefore some new technique are used like moving belt, inlet system, vacuum nebulizers and jet separators for the removal of solvent and passing the analyte in the source **[22, 26].** For example- investigation of 10 alpha-methoxy-1-6 dimethylergoline-8-methanol 5-bromonicotinic acid ester (Nicergoline) was performed by using methanol and ammonium acetate mixtures as mobile phase. This substance is characterized using LC-MS technique in terms of their molecular weight [27].

5.2.2 LC-MS-MS

It is recently invented analytical technique. This system is popular for complex mixture analysis of thermally liable and biologically relevant molecules for example, mosapride attributed to soft nature of atmospheric pressure chemical ionization (APCI) and atmospheric pressure ionization (APPI) techniques. The characterization and quantitative determination of four impurities in the substance piperaquine phosphate by LC-MS-MS technique was developed as per ICH guidelines. This technique is cited and certified by ICH. Another example is the identification and determination of low content of methyl methane sulfonate and ethyl methane sulfonatepresent as impurity in emtricitabine [27-28].

5.2.3 GC-MS – gas chromatography mass spectrometry :

This technique become most suitable and powerful technique available to the chemist for complete analysis of complex mixtures. Sample is injected to the GS and the spectra are generated by separation in GC and stored in the computer for

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processing. In this case GC is connected or coupled with MS technique through an interface that enriches the concentration of sample in the carrier gas with the help of diffusivity of that gas. Very fast scanning process takes place, so that MS can be obtained within the elution of a single peak from the GC unit. One major problem found is the unavailability of efficient gas separator or interface for GC-MS. Example of separation and characterization by GC- MS include impurity profiling of synthetic pesticide d-allethrine using atmospheric pressure ionization, electrospray sources (API-ESI) and chemical ionization in GC-MS technique.

5.2.4 HPLC-DAD-MS

HPLC-DAD-MS IS high performance liquid chromatography coupled with diode array UV detector and a mass spectrometer. This type of technique is invented and is almost routinely used. NMR has now added to this combination to provide HPLC-DAD-NMR-MS in commercial instrument. This technique is used for analysis of impurities like doxycycline, metacycline and 6-epidoxycycline using oxalic acid and acetonitrile as mobile phase. HPLC-DAD-MS are coupled to work together to give the complete identification, characterization and determination of impurity present in the active pharmaceutical ingredient [27-28].

5.2.5 HPLC-DAD-NMR-MS

The LC-DAD-MS/SPE-NMR hyphenation technique have been used for the identification of isobaric iridoid glycoside regioisomers as minor constituent from plant *Harpagophytum procumbence* extract [28]. Therefore, using this technique provides the spectral data needed for structure elucidation.

5.2.6 Capillary electrophoresis – mass spectrometry (CE-MS)

CE-MS was most recently developed and adopted technique of analysis which help in impurity profiling of active pharmaceutical ingredient. Capillary electrophoresis technique is based on different principle of separation technique and has various approaches of selectivity compared to other separation technique. Capillary electrophoresis connected to a mass spectrometry through various methods of ionization like ESI, APPI and APCI. CE-MS technique can be helpful for determination of impurity and structural elucidation of compound. In this technique it is possible to transfer analytes on-line from the electrophoretic capillary to the mass spectrometer without sacrificing separation efficiency. This technique separates the polar compound which is readily ionizable in solution [22, 27-29]. Some variation of publication is observed on CE-MS so this technique is not widely accepted for routine work and it has some limitations mentioned as follows:

- Limited sample volumes.
- Can be analyzed without compromising separation efficiency.
- The flow time of solute tend to change with change in temperature of environment.
- Generally non-volatile buffers are avoided in this technique [28].

5.2.7 Tandem mass spectrometry:

It is a widely accepted recent technique of analysis. It is operated using scanning modes are product ion, precursor ion and constant neutral loss that enhances the selectivity in quantitative mass spectrometry. In this technique selected ion or product ion and inert gas in which collision is induce due to that fragmentation or dissociation of ion is happen. Precursor ion can involves in the selection of the ion of interest activation of that ion can takes place and mass analysis of product ion. This technique is suitable for structure determination and bipolymer sequencing.

6. CONCLUSION

Recently in pharmaceuticals impurity profiling has gained importance. The determination of impurities in drug product is important. The above review provides the information about various impurities present in the drug substances and other bulk drugs. Impurity profiling in pharmaceuticals increases drug safety. It has received more attention from the public and social media. The present article provides detail information about pharmaceutical impurity, classification of impurity, sources of impurity and finally gives the recent technique used in the characterization of impurity. It also provides the idea about factors which are taken to be in consideration while preparing and manufacturing of bulk drugs. Guidelines and limit for impurity present in the pharmaceutical and impurity profiling as per ICH is also discussed.

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