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DESIGN AND IMPORTANCE OF IMPURITIES IN PHARMACEUTICAL SCIENCE

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ABSTRACT
In the field of pharmaceutical chemistry, impurities are considered as unwanted chemicals that present in the therapeutically active pharmaceutical compounds. They are unusually potent and expected to produce toxicity; hence it may show unexpected pharmacological actions which are harmful to human health. The control of impurities is currently a critical issue to the pharmaceutical industry. The most possible source of impurities is the synthesis that involves various steps, i.e. from starting materials to finished products through the intermediate steps. Impurities in drug substances and drug products are key regulatory issues in the office of generic drugs and have significant impact on the approvability of drugs hence International Conference on Harmonization (ICH) and Food and Drug Administration (FDA) guidelines introduce the identification and qualification procedures for them, by using various analytical techniques like TLC, LC, GC, MS, NMR, IR, UV, GC-MS, LC-MS, LC-NMR etc.

KEYWORDS: Impurities, NDE, TLC, LC, GC, MS, NMR, IR, UV, GC-MS, LC-MS, LC-NMR, ICH, QSE, FDA.

INTRODUCTION
The impurity profile of a drug can be defined as "A description, characterization and quantification of the identified and unidentified impurities present in a new drug substance". In the present era, there is a tremendous upsurge for the impurity profiling of pharmaceutical products. Presence of impurities in trace quantity in drug substance or drug product is inevitable. Therefore, their level should be controlled and monitored. They can diminish or decrease the pharmacological efficacy of the active pharmaceutical ingredient (API). Sometimes, the effect produced by the impurities can be mutagenic, teratogenic or carcinogenic. Some impurities may act as genotoxic impurities, which are considered unsafe at any level because they produce genetic mutations, chromosomal breaks, chromosomal rearrangements and act as carcinogenic which interact with DNA.

Figure 1: Impurity profiling.

Hence, this can jeopardize the human health by affecting quality, safety and efficacy (QSE) of the pharmaceutical products. Therefore, it is very crucial to monitor and control the impurities in API/pharmaceutical products. Hence, API impurity profiling (Isolation, identification and characterization) is required. Their limits and threshold values should comply with the limits set given by ICH and FDA. According to the ICH guidelines on impurities in new drug products and new drug substances, identification of impurities below the level 0.1% is not necessary unless their potency and genotoxicity should be qualified. If data which is related to qualification of the given specification level of an impurity is not available then studies were required to get such data. According to the ICH guidelines the maximum daily dose qualification threshold is ≤2g/day 0.1% or 1mg/day intake and ≥2g/day 0.05%. As impurity profile received a critical attention from regulatory authorities, different Pharmacopoeias such as British Pharmacopoeia (BP), United States of Pharmacopoeia (USP), Indian Pharmacopoeia (IP), European Pharmacopoeia (EP) are incorporating limits to the allowable levels of impurities in new drug products or formulations.

Common terms for Impurities

1. Degradation product
2. Related product
3. Interaction product
4. Transformation products
5. Intermediate, Penultimate intermediate and Byproducts

1. **Degradation product:** - Degradation products are unwanted chemicals that can develop during the manufacturing, transportation, and storage of drug products and can affect the efficacy of pharmaceutical products.
2. **Related product:** - These products have similar chemical structure and potentially similar biological activity.
3. **Interaction product:** - Interaction products that could occur between various involved chemicals intentionally or unintentionally.
4. **Transformation products:** - They are very similar to by-products which relates to theorized and non-theorized products that may be produced in the reaction.
5. **Intermediate, Penultimate intermediate and By products:** - The compounds produced during synthesis of the desired material are called intermediates, especially if they have been isolated and characterized. The penultimate intermediates are the last compound in the synthesis chain prior to the production of the final desired compound. By-products are unplanned compounds produced in between the reaction. It may or may not be possible to theorize all of them.[1]

Sources of Impurities: Impurities in API may be formed from starting materials or raw materials which was then carried out by the final products through several intermediate steps. During this process that formed by-products or intermediates may be carried into the final stages of process there they may be act as a source for the formation of other impurities. Some other sources of impurities are listed below:

- Raw materials used at initial stages of synthesis.
- Reagents or solvents that are used for the reaction process. e.g, Catalysts.
- From the different side reactions during synthetic process.
- From therapeutically active ingredients.
- Impurities formed due to unfavourable conditions maintained during the process which leads some types of unwanted reactions like thermolytic, photolytic, hydrolytic degradation reaction in drugs substances.
- Impurities formed due to incompatibility of excipients, steps followed, type of equipment used and environmental conditions maintained during process.

Classification of impurities: Pharmaceutical formulations or pharmaceutical chemicals used in the production of APIs involved a major broad classification of impurities i.e.

- Organic impurities (process- and drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities (process and drug related): Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

Starting materials or intermediates:- Impurities in the form of unreacted raw materials or intermediates will be found in every drug substance if proper care not taken during the process which involved a multistep synthesis. Also products frequently exposed to solvent for washing had a chance to formation of impurities due to incomplete removal of solvent.

Reagents, Ligands and Catalysts:- The chances of having these types of impurities are rare however; these could create a problem unless the manufacturers take proper care during production.

Enantiomeric impurities:- In all cases compound in the form of racemic mixture which has equal amounts of right and left handed enantiomers are not useful. Hence, single enantiomeric form of a chiral compound is preferred as an improved chemical compound that may shows a better pharmacological profile and increased therapeutic index, with a more favorable adverse reaction profile.

Degradation products:- Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. However, degradation products resulting from storage or formulation to different dosage forms or aging are common impurities in the medicines.

Inorganic impurities:- Inorganic impurities derived from the manufacturing processes used for bulk drugs. They are normally known and identified.

Reagents, Ligands and Catalysts:- The chances of having these impurities are rare; however, in some processes, these could create a problem unless the manufacturers take proper care during production.

Heavy metals:- The main sources of heavy metals are depending on the types of reactors used (e.g. stainless steel reactors), where acid hydrolysis or acidification reaction takes place. By using of demineralized water and glass-lined reactors these impurities of heavy metals can be easily avoidable.

Organic volatile impurities:- Organic Volatile Impurities relates to residual solvents that may be found in the drug substance.

Other materials (eg. 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. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations.

Residual solvents:- Residual solvents are the volatile organic chemicals used during the manufacturing process, or generated during drug production. Several organic solvents used in the synthesis of pharmaceutical products are known to have toxic or environmentally hazardous properties, and their complete removal can be very difficult. The final purification step in most pharmaceutical drug substance processes involves a crystallization step that can lead to the entrapment of solvent, which can act as a residual impurity, or cause potential degradation of the drug. Residual solvent levels are controlled by the ICH, USP, and EP.

Residual solvents are categorized into three classes with their limits in pharmaceutical products set by ICH guidelines Q3C:
Class 1 solvents - including benzene, carbon tetrachloride, 1,1-dichloroethane, 1,2-dichloroethylene, and 1,1,1-trichloroethane, should be avoided.
Class 2 solvents - such as methanol, pyridine, toluene, N,N-dimethylformamide (DMF), and acetonitrile have permitted daily exposure limits (PDEs).
Class 3 solvents - such as acetic acid, acetone, isopropyl alcohol, butanol, ethanol, and ethyl acetate should be limited by GMP or other quality-based requirements.

Table 1: ICH limits for a selected list of common organic solvents found as volatile impurities.

Volatile Organic Impurity	Limit [ppm]	PDE [mg/day]
Acetonitrile	410	4.1
1,4-Dioxane	380	3.8
Chloroform	60	0.6
Methylene chloride	600	6.0
Pyridine	200	2.0
1,1,2-Trichloroethane	80	0.8

Others
Chiral Impurity - Compounds having similar chemical structure but different spatial orientation leading to different optical rotation are of great importance because of the resulting optical isomers. The undesired optical isomer is considered as a chiral isomer.

Synthesis related impurities - Impurities in a pharmaceutical compound or a new chemical entity [NCE] originate mainly during the synthetic process from raw materials, solvents, intermediate and byproducts. The raw materials are generally manufactured to much lesser purity requirements that a drug substance. Similarly solvents used in the synthesis are likely to contain a number of impurities that may range from trace levels to significant amounts that can react with various chemicals used in the synthesis to produce impurities.

Formulation related impurities - APIs are formulated with excipients into tablets, semi-solids, solutions, capsules, aerosols and Novel Drug Delivery Systems. During the formulation, excipients are added to API to render the product elegant. They can be sometimes heterogeneous mixtures. In such a case, compatibility problems will arises between API and excipients which may leads to formation of products with the affected therapeutic efficacy. Any undesirable reaction produced due to the impurities which is associated with excipients can provide a source for many potential reactions. The source of these potential reactions may be because of excess amount of water, which is present in API or use of hygroscopic materials.

Impurity
Impurity forms during formulation

a) **Method related impurities:** Formation of impurities depends on initial pH of the preparation and the condition of sterilization etc.
b) **Environmental related impurities:**

Temperature: The classes of compounds which are thermo liable in nature, when subjected to extreme

temperature leads to loss of potency. E.g. During formulation of vitamins and antibiotics, extreme care should be exercised to prevent them from degradation.

Light/UV light: Photolytic reaction is one of the important factor by which the formulation degrades. Exposure of light is known to be deleterious on a number of pharmaceutical substances.

For example, sunlight having about 8000 foot-candles can destruct nearly 34% of vitamin–B in 24hrs.

Humidity: Humidity is one of the important key factors in case of hygroscopic compounds. It is detrimental to both bulk powder and formulated solid dosage form.[2]

c) Formation of impurities on ageing

a. Mutual interaction amongst ingredients:- Most often, vitamins are highly prone to instability on aging in different dosage forms. i.e., degradation of vitamins such as folic acid, thiamine and cyanocobalamines does not yield toxic impurities but lose their potency.

b. Functional group- Related typical degradation

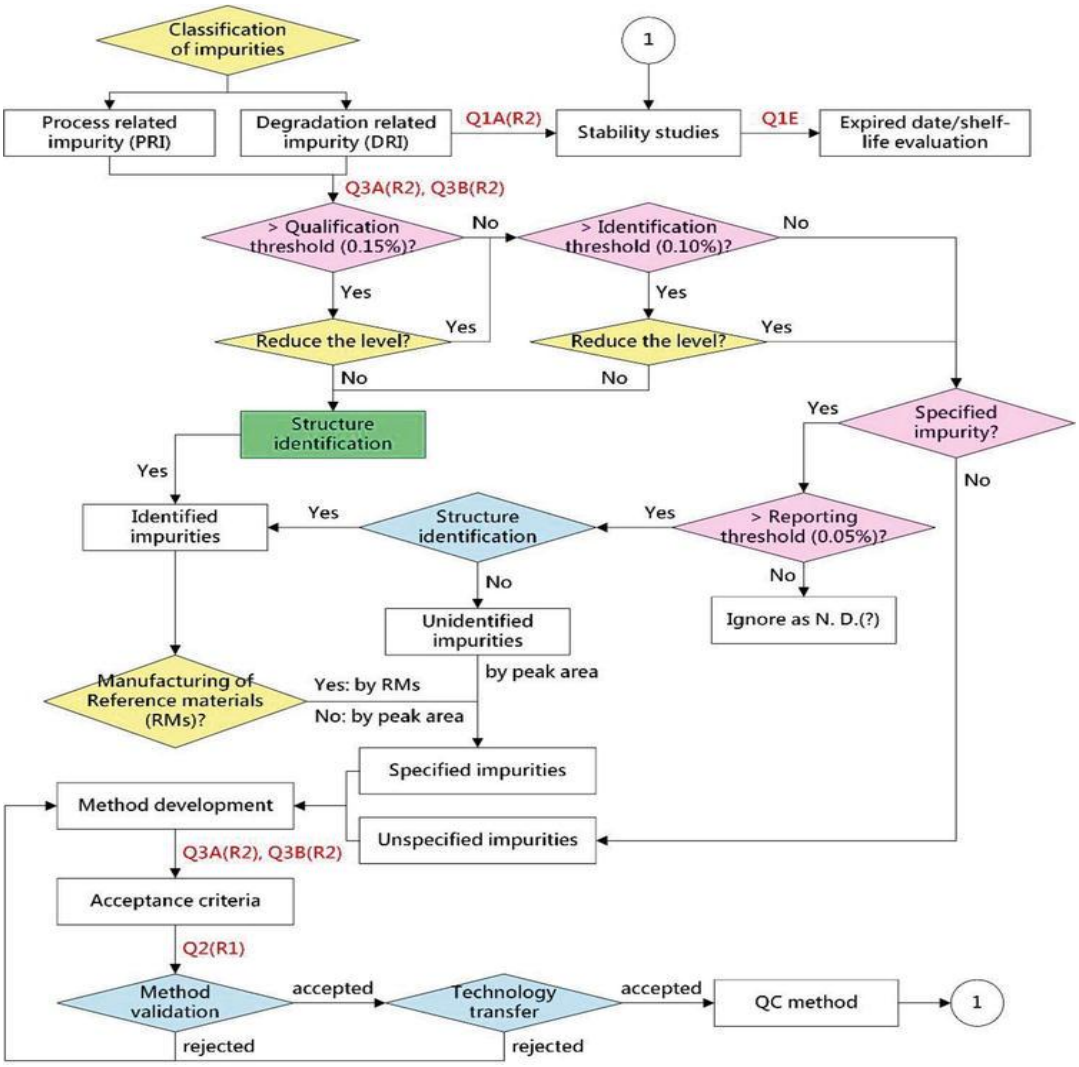


Figure 2: Protocol flowchart of impurity profiling by the ICH.

Ester hydrolysis - Ester hydrolysis or hydrolysis of an ester is the reaction of an ester with water in an acidic or basic medium to yield alcohol and carboxylic acid or carboxylate salt.

1. **Hydrolysis:-** A reaction which involved water used as a reactant causing precipitation. Examples of such reactions in pharmaceutical compounds are esters and amides. Many drugs are derivatives of carboxylic acids or contain functional groups based on the moiety which are prone to hydrolysis.
2. **Oxidative degradation:-** Hydrocortisone, methotrexate, adinazolam, catecholamine, conjugated-dienes (vit A) heterocyclic aromatic rings, nitroso and nitrite derivatives are prone to oxidation. In pharmaceuticals, the most common form of oxidative decomposition is auto oxidation through a free radical chain process.
3. **Photolytic cleavage:-** Photolytic cleavage on aging includes examples of pharmaceutical drugs or pharmaceutical products that are prone to degradation on exposure to UV-light. During

manufacturing process solid or solution, packaging or on storage, drug like nitroprusside, ergometrine, nifedipine, phenothiazine and riboflavin are liable to photo oxidation.[3]

4. **Decarboxylation:-** Some of the carboxylic acids such as p-amino salicylic acid will shows loss of carbon dioxide from carboxyl group when heat is applied. For example, photo reaction of enteric coated rufloxacin tablet with cellulose acetate phosphate (CAP) and sub-coating with calcium carbonate cause hydrolysis of CAP liberating acetic acid, which on reacting with calcium carbonate produced carbon dioxide, a by-product that blew off the cap from the bottle after cap was loosened.[4]

Isolation & Characterization: It is frequently necessary to isolate and characterize impurities in order to monitor them accurately, because approximate estimations of impurities are generally made against the material of interest (i.e. drug substance) and can be incorrect. It is important to test this assumption because impurities frequently have different structures with significantly different detector responses. Most of the time it is difficult to ensure that the assumption stated above is correct.

Number of methods can be used for isolation and characterization of impurities. But the application of any method depends on the nature of impurity (i.e.) its structure, physicochemical properties and availability.[5]

The following methods are commonly used for the isolation, they are:

1. **Extraction**
2. **Column Chromatography**
3. **Preparative Separations**

Extraction

1. Liquid-Solid extraction
2. Liquid-Liquid extraction

Liquid-Solid Extraction:- A solvent that would dissolve the impurity of interest is selected. An organic solvent blend is used for extraction where a compound contains more than one type of impurity. These solvents tend to volatilize at low temperature, facilitating concentration of impurity. Examples of common solvents used in liquid-solid extraction include toluene, methanol, water, cyclohexane etc.[6]

Table 2: List of solvents for Liquid-Solid extraction.

Solvents	Boiling Point [^{o}C]	Dielectric Constant [volts/meter]
n-Hexane	190	1.9
Cyclehexane	81	2.0
Carbon tetrachloride	77	2.2
Toluene	110	2.4
Ethyl ether	35	4.3
Chloroform	61	4.8
Methylene chloride	40	8.9
Ethanol	78	24.6
Methanol	65	32.7
Dimethyl formamide	153	36.7
Acetonitrile	82	37.5
Water	100	80
Formamide	210	111

Soxhlet extraction:- This technique is used for extracting compound of interest from crude drug products, etc, It utilizes a small volume of solvent which is repeatedly siphoned through a product to produce a concentrated extract. Natural compounds are isolated by this method, for instance isolation of Curcumin from rhizomes of Turmeric. In impurity profiling, Soxhlet extraction finds use, when the desired compound has limited solubility in a solvent, and the impurity is insoluble in that solvent. If the desired compound has a high solubility in a solvent then simple filtration can be used to separate the compound from the insoluble substance. The advantage of this system is that instead of using many portions of warm solvent being passed through the sample, just one batch of solvent is recycled.[7]

Liquid-Liquid Extraction: - It involves extraction of one liquid with another, in which one is aqueous and the other is organic with both being mutually immiscible. In this type of extraction process, a solute is distributed between two immiscible solvents. The extraction is controlled by distribution or partition co-efficient which defines the ratio of concentration of the solute in two solvents a and b; $K_d = C_a / C_b$

K_d is the distribution co-efficient or partition coefficient. The distribution co-efficient related to a single species and does not include possible products of side reactions.[8]

Column chromatography:- It can be used for quantitative separation of impurities ranging from milligram to kilogram. **UV- spectrophotometry:** It is used for detection of the eluent by occasionally

monitoring the collected fractions from a given sample. Example- Mirabegron [lowers the symptoms of over active bladder] impurity (associated with more than one impurity) can be separated by column method.[9]

Thin layer chromatography:- The separation principle of the TLC procedure is based on the given compound's relative affinity towards the mobile and the stationary phase. The process begins here by moving the mobile phase over the stationary phase's surface. During this movement, the higher affinity compounds gain less speed as compared to the lower affinity compounds. This results in their separation.

Once the procedure gets completed, different spots can be found on the stationary surface at distinct levels, reflecting various elements of the mixture. Basically, the compounds that are more attracted towards the stationary phase secure their position at lower levels while others move towards the higher levels of the surface. So their spots can be seen accordingly.[10]

Gas chromatography:- It is useful for isolation and characterization of volatile impurities or compounds that can be volatilized by derivatization. For instance, in production of Doxorubicin hydrochloride, acetone and ethanol were found as impurities by gas chromatography.[11]

Analytical methodology:- The nature and quantity of these impurities is governed by a number of factors, including the synthetic route of drug substance, reaction conditions, quality of the starting material, reagents, solvents, purification steps, and storage of the end product. As the structures of impurities are sometimes unknown, several spectroscopic and microchemical techniques have been developed which require minute quantities of material and readily enable the structural elucidation of the impurity.[12]

Strategy for method Development: Method development strategy should have the following details.

1. Physico-chemical data

- Ionization constant
- Solubility
- Water absorption
- Distribution co-efficient
- Optical rotation
- Crystal form

Impurities can be analyzed by the following instruments

1. **Ultra violet spectroscopy:** Spectroscopy is the measurement and interpretation of electromagnetic radiation absorbed or emitted when the molecules or atoms or ions of a sample move from one energy state to another energy state. UV spectroscopy is a type of absorption spectroscopy in which light of the ultra-violet region (200-400 nm) is absorbed by the molecule which results in the excitation of the electrons from the ground state to a higher energy state.[13]

Figure 3: UV-Vis spectroscopy.

2. **IR Spectroscopy:** Infrared spectroscopy (IR spectroscopy or vibrational spectroscopy) is the measurement of the interaction of infrared radiation with matter by absorption, emission, or reflection. It is used to study and identify chemical substances or functional groups in solid, liquid, or gaseous forms. It can be used to characterize new materials or identify and verify known and unknown samples.[14]

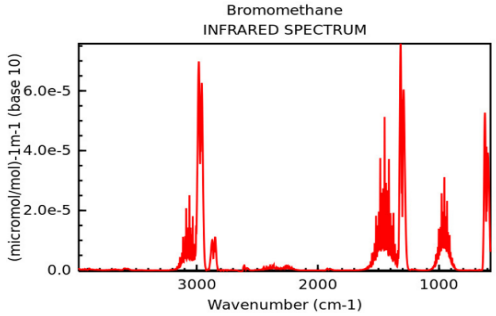


Figure-4: Sample of an IR spec. reading; this one is from bromomethane (CH_3Br), showing peaks around 3000, 1300, and 1000 cm^{-1} (on the horizontal axis).

3. **NMR Spectroscopy:** It can provide information regarding molecular structure and stereochemistry of compound. Multicomponent mixtures can be easily analyzed. For example impurities in Benzyl (4-morpholinophenyl) carbamate, Dehydro-apaxiben, Mirabegronarecan are analyzed by NMR.[15]

Figure 5: NMR Spectroscopy.

4. **Mass spectrometry:** It is the most accurate technique for determining the molecular mass and elemental composition of the desired compound. It is also used for monitoring, characterizing and quantification of drug related substances in API. If single method fails to provide necessary selectivity, coupling of this technique with GC, HPLC, and LC lead to rich information. For example- Des-fluoro impurities of Sertalin and Iinezolid have been identified and quantified by MS.[16]

Figure 6: Mass spectroscopy.

5. **Gas chromatography:** Chromatography is a technique that separates components in a mixture by the difference in partitioning behavior between mobile and stationary phases. Gas chromatography (GC) is one of the popular chromatography techniques to separate volatile compounds or substances. The mobile phase is a gas such as helium, and the stationary phase is a high-boiling liquid that is adsorbed on a solid. Because of its simplicity, high sensitivity, and the ability to effectively separate mixtures, gas chromatography has become one of the most important tools in chemistry.[17]

6. **HPLC:** HPLC is an abbreviation for High Performance Liquid Chromatography. "Chromatography" is a technique for separation, "chromatogram" is the result of chromatography, and "chromatograph" is the instrument used to conduct chromatography. Impurity profile analyses are required to demonstrate the ability to detect a wide range of impurities which may occur in pharmaceuticals. However, most impurity profile methods do not address the potential of co-elution of impurities with product peaks.[18]

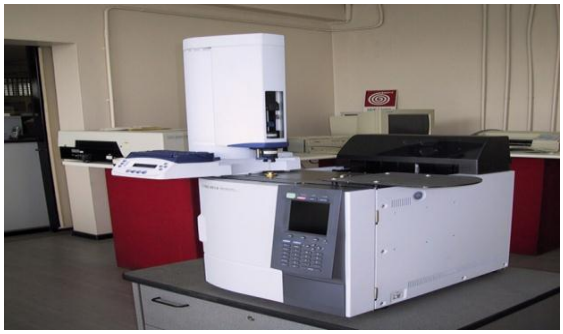


Figure 7: Gas Chromatography.

UV photodiode array detection (PDA) evaluates the UV and/or the UV/VIS spectrum of an eluting species to determine spectral homogeneity. If variations in the spectrum are observed, the possibility of a co-eluting impurity must be addressed. By establishing consistent evaluations HPLC-PDA can be used to more accurately assess impurity levels and provide analyses with much higher informational content.[19]

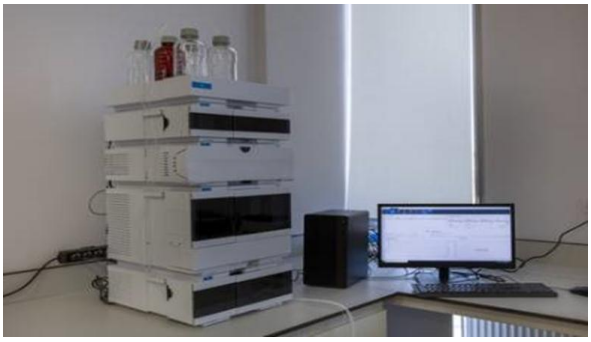
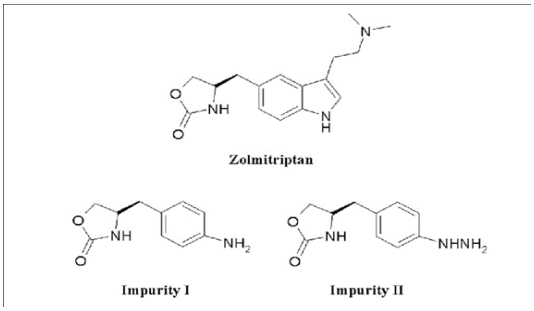
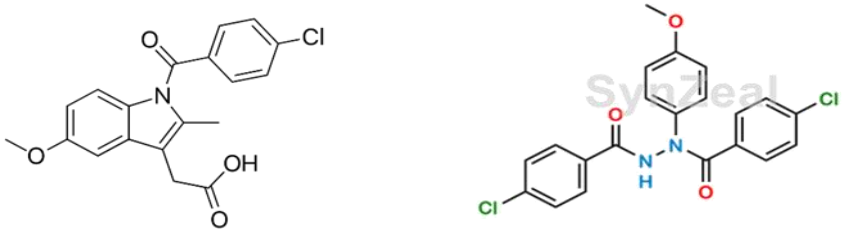


Figure 8: High performance liquid chromatography.

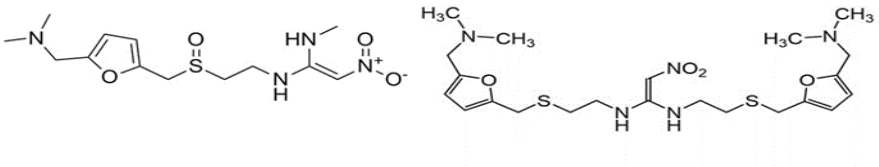
Importance of impurity profiling: Formation of drug is imperfect without identification of impurities. For market approval of drug, identification, quantification and control of impurities in drug are important. Quantitative determination of impurities is useful in validation of drug. Structural elucidation and thereafter synthesized impurity can be used as an impurity standard, which can be used for development of selective analytical methods for quantitative determination of impurities. It is essential to submit impurities to various drug authorities which will use impurities as standard for regulatory analysis. Other applications include understanding degradation pathways for amines, alkaloids, analgesics, steroids, anti-cancer drugs, tranquilizers etc. To establish a control system for impurities so that they cannot interfere with final desired compound. Impurities are essential to obtain market approval.[20]



Resperidone & Impurity



Indomethacin & Impurity



Ranitidine & Impurity

Figure-9: Drug & Impurity.

CONCLUSION

Impurity profile of pharmaceuticals have been receiving greater importance recently. It is an essential for regulatory filing of new drug candidates. Impurity profiling and reporting is also compulsory in various Pharmacopoeias. Isolation and characterization of impurities are required for acquiring and evaluating data that is used in creating biological safety datasheet of new drug products. Many instrumental methods are regularly used to isolate and quantify impurities. Thus impurity profiling may work as a Quality Control tool. It may offer fundamental data about safety, toxicity, limits of detection [LOD] and limits of quantitation [LOQ] of several organic and inorganic impurities, generally accompanying APIs and finished products. This review paper consequently focuses on basic aspects of impurities in drug substances and drug products. Thus, by implementing impurity profiling, it becomes possible to develop products where expected impurity cannot interfere in the performance of final product. Although different regulatory bodies have provided individual guidelines describing identities and permissible limits of impurities, there is an urgent need for unified specifications/standards for regulation of impurities. Management of impurities related to APIs in pharmaceutical products must be implemented in strict compliance with the regulatory requirements of pharmaceutical industry due to their quality and safety concerns. An integrated scheme in accordance with the regulatory requirements to establish analytical methods and acceptance criteria of process-related impurities (PRIs) and degradation-related impurities (DRIs) was presented, accordingly. Meanwhile, procedures for the identification and validation/verification of API-related DRIs were proposed. Validation or verification methods to evaluate the reliability of structure identification such as kinetic reactions, stress and stability studies, comparison of retention time(s) and $\Delta m/z$ between experimental and nominal values of targeting peaks, compatibility of MRM pairs with "real samples," stable isotope distribution patterns, and mass balance were demonstrated. Applying of the processes proposed in this article will help to ensure the reliability and quality of the impurity analytical results.

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