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A REVIEW ON PHARMACEUTICAL IMPURITIES AND THEIR IMPORTANCE

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ABSTRACT

In drug discovery process, validation of safety and efficacy of drug are essential parameters and expectedly pharmaceutical companies lay stress upon these. However, every drug which is marketed is associated with several other determinate quality parameters from all of them some are identification, quantification and removal of impurities at each step of development. Recently, there has been an increased stress on impurity profiling of APIs and formulation. According to ICH guidelines, an impurity is any component of drug substance that is not a part of chemical entity and effects purity of active ingredients. from above definition, it becomes easy to realize that impurities are unavoidable and will be present in minor amounts and consequently various regulatory bodies follow workable guidelines to come up with permissible limits of impurities, to launch a drug product into the market. Impurities are not always necessarily inferior from active ingredient and sometimes may have independent pharmacological or toxicological Properties. However in majority of the cases they are a nuisance and should be curtailed. In this review article, impurities, their types, their characterization and applications have been described.

KEYWORDS: Impurity profile, Impurities, APIs, Characterization, ICH guidelines, Pharmacological, toxicological.

1. INTRODUCTION

Pharmaceutical impurities are those substances which co-exist with the API or they may develop during synthesis or ageing of both API and formulation. The presence of these impurities even in minor amounts can influence the efficacy and safety of drug. The safety of drug is dependent not only on the toxicological properties of active drug substance itself, but also on impurities that it contains. As safety and quality of pharmaceutical products can be affected by impurities present in APIs, impurity profiling of API has started gaining wider traction. Therefore identification, isolation and quantification of impurities are an important part of drug development and regulatory assessment. In synthetic organic chemistry, it is necessary to submit qualitative and quantitative report on impurities along with API's so that drug authorities and customer of bulk drug production can use these impurities as a reference standard.[1] Once chemical structure of impurities is reported the reaction conditions or process of manufacturing API can be altered so as to eliminate traceable amount of an impurity to an acceptable level. Impurity profiling gives an account of impurities present in an API/ bulk/ finished products, thus it acts as a quality control tool.

2. Regulatory guidelines on impurities in an API and/or in formulation

Monitoring and controlling of impurities implies different things. Therefore simple terminology should be used to address questions related to impurities. The United States food and drug administration (US-FDA) has endorsed the guidelines prepared by International Conference on Harmonization (ICH). The ICH guidelines for impurities were developed with joint efforts of various regulators such as European Union (EU), Japan and United States and they help in ensuring consistent requirement of data that should be submitted to various regulatory agencies. The guidelines are not only to aid the sponsors of New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) with information that should be submitted along with their applications, but also assists FDA reviewers and field investigators in consistent implementation and interpretation of regulations. The various regulatory guidelines are as follows

a. ICH guidelines "Stability Testing of New Drug Substances and Products"- Q1A.
b. ICH Guidelines "Impurities in New Drug Substances"- Q3A.
c. ICH Guidelines "Impurities in New Drug Products"- Q3B.
d. ICH Guidelines "Impurities: Guidelines for Residual Solvents"- Q3C.
e. US-FDA Guidelines "NDAs- Impurities in New Drug Substances".
f. US-FDA Guidelines "ANDAs- Impurities in New Drug Substances".

g. Australian Regulatory Guideline for Prescription of Medicines, Therapeutic Governance Authority (TGA), Australia.[3-5]

3. Common terms for addressing impurities

Various terms used for impurities by regulatory authorities are as follows

- **Intermediate**: These compounds are produced during synthesis of desired product as a part of synthetic route.
- **Penultimate intermediate**: These compounds are produced just prior to the production of final product.
- **By-products**: These are formed due to reactions other than the desired one. These can occur by incomplete reaction, rearrangement, interaction between starting material etc.
- **Transformation products**: They are similar to by-products and are related to theorized or non-theorized products formed in a reaction.
- **Interaction products**: These products are formed by interaction between various chemicals involved.
- **Related products**: These are chemically and biologically similar to the drug substance.
- **Degradation products**: By decomposition of active ingredient. Degradation products are formed by the action of heat, light and moisture.[6]

4. Classification

Impurities are classified by authorities differently.[7]

As per United States pharmacopoeia

a. Impurities in official articles.
b. Ordinary impurities.
c. Organic volatile impurities.

As per ICH

a. Organic impurity (process- and drug-related).
b. Inorganic impurity.
c. Residual solvents.

4.1 Organic impurities: These impurities arise during manufacturing process and/or storage of drug substance. These include starting material impurities, by-product impurities, degradation impurities and enantiomeric impurities.

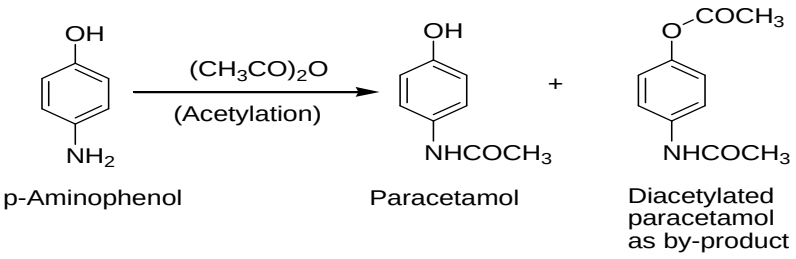
• **Starting material or intermediate impurities**

Starting materials (mostly from isomeric impurities) and intermediates (incomplete reaction or excess reagent used) are chemical building blocks used to form the final form of a drug substance. If left unreacted or when obtained with the end product due to improper removal these are considered as impurities. However despite adoption of numerous precautionary measures, there are always chances of having residuals and unreacted starting materials remaining in the final product as impurity. For example during the last step in synthesis of Baclofen- when beta-(p-chlorophenyl) glutarimide reacts with sodium hydroxide solution at room temperature, the yield of p-chlorophenylglutaric acid is synthesis related impurity.[8] Presence of isomeric 4-trifluoromethyl impurity in 3-trifluoromethyl-α-ethylbenzhydrol (Flumecinol) is a result of the presence of 4-trifluoromethyl bromobenzene impurity in 3-trifluoromethyl bromobenzene (starting material of synthesis).[9]

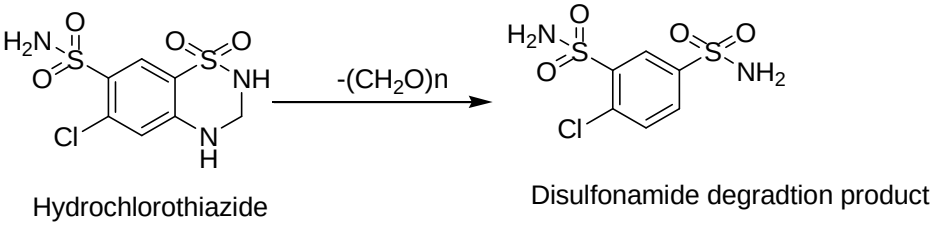
In formation of Tipranavir, aniline is the intermediate in the last step of the synthesis. Due to the similar structures of aniline and the final compound, it is difficult to totally eliminate it in the subsequent purification step. Consequently, it appears in the drug substance at around 0.1%.[10] In Paracetamol bulk, a limit test for p-aminophenol is performed because it could be a starting material for one manufacturer or an intermediate for the others.

• **By-products**

A compound with 100 % yield is rare, so there are always chances of by- products. They are formed through variety of side reactions such as rearrangement, over reaction, isomerization, dimerization and unwanted reactions between starting materials or intermediate with catalyst or reagent. In Paracetamol synthesis, diacetylated Paracetamol is formed as a by-product.[11,12]



• **Degradation products**: Degradation products are formed by decomposition of final product due to improper storage of formulation or ageing. Example: Degradation of Hydrochlorothiazide to its starting material i.e. Disulfonamide.



Hydrochlorothiazide Disulfonamide degradtion product

Other drugs susceptible to degradation are Penicillin and Cephalosporin. Presence of beta lactam ring and alpha amino group in the C6/C7 side chain plays a critical role in their degradation.[13,14] Penicillin G and penicillin V in aqueous solution are degraded by β-lactamase to their penicilloic acids and penilloic acids.[15] 7-Amino cephalosporanic acid is produced by enzymatic and chemical degradation of cephalosporin C. Ibuprofen is degraded 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 as impurities.[16]

• **Enantiomeric impurities**: In many cases, single enantiomeric form of a chiral drug is an improved chemical entity that can show improved pharmacological and therapeutic index with a more favorable adverseeffect profile.[17] For a single enantiomeric drug, the other stereoisomers of drug are considered asan organic impurity. Examples include marketed single isomeric drugs such as Levofloxacin (S-ofloxacin), Esomeprazole (S- omeprazole).[18]

4.2 Inorganic impurities: These are obtained in bulk drug formulation during manufacturing process. They are generally identified and known in nature. They include impurities like heavy metal impurities, residual solvent impurities and other material impurities such as filter aids.

• **Reagents, ligand and catalysts**

Very rarely do we come across these types of impurities. Raney Ni is used as a catalyst in most reduction reactions can sometimes lead to formation of impurities along with desired products like in case of synthesis of Linezolid.[19] Pyridinium is formed as impurity in the synthesis of Mazipredone thus pyridine is used as catalyst.[20]

• **Heavy metals**

Water is used in most manufacturing processes, but unfortunately it acts as a major source of heavy metals. Ag, Cd, Na, Mn and Mg introduced with the reaction media can lead to hydrolysis of the drug. For instance, hydrogenated oils and fats are produced by metal

catalysts which results in high concentration of metals in the final product due to leaching process. For the checking of contamination of heavy metals in pharmaceutical product demineralized water and glass lined reactors are used.[21]

- **Filter aids**

Various filtering aids are used in synthesis of drugs and they can be a source of impurities. Consequently, regular monitoring of fibers and black particles in drug needs to be conducted. Centrifuge bags and activated charcoal can also act as source of impurities.[19]

4.3 Residual Solvents: These are organic or inorganic liquids which are generally used in various manufacturing processes. They may modify properties of certain compounds or can be hazardous to human health. Some liquids exhibit toxic behavior so they need to be eliminated however it is a very tedious task to accomplish, as trace amounts are usually difficult to detect and remove.[22]. For the detection of residual solvent, gas chromatography is used because they are mostly volatile in nature. Nonvolatile solvents are converting to volatile solvents by chemical derivatization. Gas chromatographic techniques are used to determine purity of toluene, acetone, methanol, dichloromethane and also to quantify main components of each organic solvent. Residual solvents with their classification and permissible limits are listed below.[23]

Class 1: These type solvents are not employed in manufacturing of drug substances because of their toxic nature. If use of these solvents is unavoidable then their usage must be restricted to their respective limits. (Table 1).

Table. 1: Class 1 residual solvents.

S. No.	Residual solvent	Concentration limit (ppm)
1.	Benzene	2 (Carcinogenic)
2.	Carbon tetrachloride	4 (Toxic)
3.	1,1 Dichloroethane	8 (Toxic)
4.	1,2 Dichloroethane	5 (Toxic)
5.	1,1,1 Triichloroethane	1500 (Environmental hazard)

Class 2: These types of solvents should be limitedly used in pharmaceutical products because of inherent toxicity. (Table 2).

Table. 2: Class II solvents with their permissible daily exposure limits.

S. No.	Residual solvent	Permissible daily exposure (mg/day)	Concentration limit (ppm)
1.	Acetonitrile	4.1	410
2.	Chloroform	0.6	60
3.	1,2 Dioxane	3.8	380
4.	Pyridine	2	200
5.	Toluene	8.9	890

Class 3: Acetic acid, acetone, alcohol, ethanol, butanol and isopropyl alcohol, 50 mg or less/daily exposure. These solvents are less toxic to human health than class 1 or 2 solvents.

Class 4: 1, 1-Dietoxypropane, 1, 1-dimethoxypropane, isooctane, petroleum ether, isopropyl ether, trichloro acetic acid etc.[24]

4.4 Synthesis related impurities

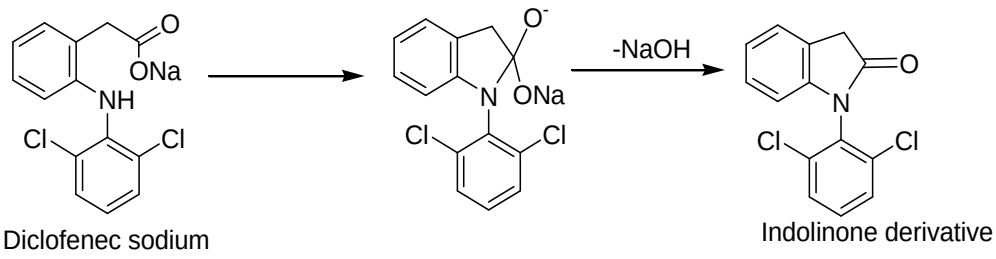
An impurity formed during synthesis of drug, even in minor amounts, could ultimately be present in final product. Therefore, synthesis related impurities require careful monitoring at every step, to minimize amount of impurity that can formed.[25] During the synthesis of Ezetimibe, an impurity, identified as (3*R*,4*S*)-3-((*S*)-3-(4-fluorophenyl)-3-hydroxypropyl)-4-(4-hydroxyphenyl)-1-phenylazetidin-2-one, is called desfluoroezetimibe (lactam-related) impurity.[26]

4.5 Formulation related impurities

After synthesis of API, the next step is to formulate it with excipients into different dosage forms like solutions, capsules, tablets, aerosols, semi-solids and other novel drug delivery systems that sometimes can lead to degradation of active compound. Numerous impurities arise due to ingredients involved in formulation apart from the drug itself. Actions such as pH modification, in order to modulate solubility of a compound, say by acidification, may accelerate its hydrolysis. Water used in formulation of solutions or suspensions, sometimes not only acts a source of impurities, but may also be involved in generation of newer impurities by accelerating hydrolysis and catalysis.[13]

Formulation related impurities are classified as

4.5.1 Method related: A known impurity is formed in Diclofenac sodium (parenteral dosage form) i.e. 1-(2, 6-dichlorophenyl) indolin-2-one during its production. Formation of this impurity depends on pH of formulation and condition of sterilization.[27]



Diclofenec sodium Indolinone derivative

4.5.2 Dosage form related: Sometimes dosage form factors influence stability of drug which forces the companies to recall their products example- Due of degradation of active ingredient, 0.05 % Fluocinonide topical solution in 60 ml bottle was recalled in USA. Liquid dosage forms are more sensitive toward degradation. In this regard, pH of solution, its water content, material used to construct primary container are crucial factors to be considered.[17] To predict such degradative eventualities, preformulation studies are carried out in pharmaceutical companies, including stability and forced degradation study, before launching of any product into market. In few cases, precipitation of key ingredient may occur due to many factors such as pH, leaching etc. Examples- In presence of 5 % dextrose in saline solution, Imipramine hydrochloride is precipitated with sodium bisulphite. In granulation of aminopyrine, papaverine, theobromine and salicylic acid tablets, sodium carboxy methyl cellulose causes tablet discoloration. Moisture absorption and tablet expansion occurs readily with lactose due to formation of monohydrate.[28]

4.5.3 Environment related: Some environmental factors can ruin nature of drug.

• **Adverse temperature**: Most APIs are sensitive to heat e.g. vitamins (folic acid, pantothenic acid, cyanocobalamine and thiamine). They tend to be unstable at higher temperature and frequently get dehydrated leading to loss of potency especially in liquid formulations. Therefore special care should be exercised to prevent drugs from thermal degradation.[29]

Light- UV light: Many pharmaceutical products become harmful by exposure of light. Ergometrine and Methyl ergometrine injection get degraded under heat and light. An investigation revealed that Ergometrine (0.2 mg/ml) gets completely degraded when kept for 42 hours in direct sun exposure. It is essential to control wavelength and intensity of light and number of photons absorbed by material. For example regular sunlight having about 8000 foot-candles can destroy nearly 34% of vitamin- B_{12} in 24 hours.[30, 31](Table 3).

Table. 3: Drugs affecting by light/ catalyst.

S. No.	API/Drug	Light/Catalyst
1.	Antipyrine	Light
2.	Ofloxacin	Light
3.	Phenothiazine	Light
4.	Epinephrine	Sodium metabisulfite
5.	Penicillin	Sodium bisulfite

• **Humidity**: It is the key destabilizing factor for hygroscopic compounds. Bulk powder and formulated dosage forms such as Aspirin and Ranitidine tablets get degraded by humidity.[32]

4.5.4 Functional group related

• **Hydrolysis**: Various drugs are derivatives of lactones, amides, imides and carbamates. Ester type drugs are prone to hydrolysis, especially in liquid formulations like Barbitol, Chloramphenicol, Lincomycin, Oxazepam and Chlordizepoxide.[33] Other drugs susceptible to ester hydrolysis include Aspirin, Ethyl paraben, Cefotaxime.

• **Photolytic cleavage**: Pharmaceutical products when exposed to light during their manufacturing, packaging or general usage can be subjected to photo oxidation. Nifidipine, Riboflavin, and Phenothiazine are labile to photo oxidation. Fluoro-quinolone antibiotics are also susceptible to photolytic cleavage. Ciprofloxacin eye drops (0.3%) whenexposed to light, results in photolysis thereby resulting in formation of ethylene diamine analogues of ciprofloxacin.[34-36]

• **Decarboxylation**: When *p*-amino salicylic acid is heated, it tends to loose carbon dioxide from carboxyl group. Example- Rufloxacin tablet when enterically coated with cellulose acetate phthalate (CAP) and sub coated with calcium carbonateis susceptible to photoreaction and hydrolysis. This can lead to conversion of CAP into acetic acid, which reacts with calcium carbonate to release carbon dioxide (a by-product) which in turn can cause capping of tablet.[37]

• **Oxidative degradation**: Drugs like Methotrexate, Hydrocortisone and Adinazolam degrade by oxidation. Auto-oxidation is a general form of oxidative decomposition by a free radical chain process. For example-cupric ion oxidize ascorbic acid to dehydro-ascorbic acid and potassium cyanide. Stability analysis on 5-amino-ethyl-1,3-benzenediol sulfate (AEB) showed that copper efficiently catalyzes AEB degradation down to 10 ppb level in presence

of oxygen, leading to discoloration of product. In AEB degradation, the effectiveness of metals follows the following order- Cu^{2+}>Fe^{3+}>Ca^{2+}.

• **Packaging Material**: Impurities formed from packaging material like closures and containers. For most drugs, water, metals, peroxides derived from the packaging material can lead to formation or introduction of impurities. various impurities such as polypropylene, zinc stearate (stabilizer in PVC), styrene, and diethylhexylpthalate (DEHP) etc. can leach in from rubber stopper and plastic material; whereas oxides like NO_2, SiO_2, CaO and MgO can be released from glassy surfaces.[37]

4.5.5 Impurities due to ageing: With passes of time, ingredient combinations (APIs or API-excipient or excipient-excipient) making up a formulation interact amongst themselves, finally forms impurities Example, in a formulation of vitamin B-complex injection, having four vitamins (Riboflavin, Nicotinamide, Pyridoxine and Thiamine), believed to have a shelf life of 1 year, thiamine gets degraded by nicotinamide to sub-standard levels rapidly.[38]

5. Studies to evaluate drug compounds and their impurities

5.1. Forced degradation study: Forced degradation studies are used to generate vast amount of data in very short time periods and used for identification of potential degraded products, pathway for degradation and intrinsic stability of drug molecule.[39] It is used in analytical validation of stability showing methods and facilitates in structural elucidation of degradation products. It should be carried out in phase 3 of regulatory submission process. Compared with stability studies, it is useful in generating degradants in much shorter span of time. It is useful in differentiating non-drug product in a formulation to generate more stable formulation and to solve stability related problems.[40]

5.2. Stability study: The Aim of stability testing is to give data on how the quality of a drug substance or drug product changes with time under the influence of a variety of environmental factors like light, temperature, and humidity allows establishing a retest period/shelf life for a drug substance and a recommended storage condition. The stress conditions utilized during stress testing include humidity (acidic/alkaline/neutral), temperature and light. The data founded from stability studies in turn allows us to constitute the recommended storage conditions. Stability of pharmaceutical compounds is a topic of more interest as it affects safety and efficacy of drugs. Analytical methods for impurities estimation should be stability showing, to regulate the stability of pharmaceutical dosage

forms during the investigational phase of drug development, and once the drug is marketed, for the continuing stability studies which must be carry out. Methods may be developed which determine the amount of drug remaining, the amount of drug lost (or the appearance of degradation products), or both. It is necessary to carry out stability studies of new drug compounds before registration of dossier. It contains long term study (12 months) and accelerated stability study (6 months) which can be carry out at conditions milder than that used in accelerated or forced degradation studies.[41]

6. Impurity detection methods

Reliable and meaningful analytical data is needed in order to evaluate drug products at every stage of synthesis. The impurities can be identified by the following methods.

- Isolation methods.
- Separation methods.
- Characterization methods.

6.1 Isolation method

Approximate estimations of probable impurities in a synthetic process are made on the basis of assumption that impurity would be somehow structurally related to compound of interest. After synthesizing hypothesized/suspected/reverse engineered impurities, next step is to isolate and monitor them during the actual synthetic process. Generally, chromatographic techniques are used for isolation of impurities. If instrumental methods can directlycharacterize impurities, then isolation step can be avoided.

6.1.1 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.

- **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.[42]

• **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.[43]

6.1.2 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.

6.2 Separation method

After isolation, the next step is to separate impurities from mixture of compounds into individual components, by various techniques.

• **Thin layer chromatography**: It is a valuable technique for separation of compounds and works upon the principle of adsorption. Silica gel plates are generally preferred for carrying out separation. Detection is usually performed by UV. To elute the desired material, the adsorbent from plates is scrapped off and then extracted with suitable solvents. TLC is used in determination of components present in plants. It is also used for analyzing dye composition of fibers in forensics, assaying the radiochemical purity of radiopharmaceuticals, monitoring organic reactions, analyzing ceramides and fatty acids, detection of pesticides or insecticides in food and water and identifying compounds present in a given substance. Example-Dehydro-apixaben impurity can be separated from mixture of other compounds using TLC.

• **Column chromatography**: It can be used for quantitative separation of impurities ranging from milligram to kilogram. UV- spectrophotometry is sued for detection of the eluent by occasionally monitoring the collected fractions from a given sample. Example- Mirabegron impurity (associated with more than one impurity) can be separated by column method.[44]

6.3 Characterization methods: Highly sophisticated instruments are available for monitoring and quantification of impurities even in minor amounts.

• **NMR**: 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.

• **MS**: 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.

• **GC-MS**: To identify different substances within a test sample, GC can be coupled with MS to provide valid information that is difficult to solve by one method. In this combination GC separates volatile and semi-volatile components whereas MS provides detailed structural information. Various residual solvents are analyzed by GC such as ethanol, hexane, benzene, carbontetrachloride etc.[45]

Drugs, corresponding impurities and method used for identification are given below in table 4.

Table. 4: Drugs, corresponding impurities and method used for identification.

S. No.	Drug name	Impurity name	Method used for detection of impurity	Reference
1.	Amphotericin B	Tetraenes	Ultra violet spectroscopy	46
2.	Atropine sulphate	Apo atropine	Ultra violet spectroscopy	46
3.	Mercaptopurine	Hypoxanthine	Ultra violet spectroscopy	23
4.	Cloxacillin	N,N dimethyl aniline	Gas chromatography	46
5.	Doxorubicin hydrochloride	Acetone and Ethanol	Gas chromatography	47
6.	Fluorescene Sodium	Dimethyl Formamide	Gas Chromatography	47
7.	Ethambutol hydrochloride	2 Amino butanol	Thin layer Chromatography	48
8.	Framycetin Sulphate	Neamine	Thin layer Chromatography	48
9.	10-Hydroxymorphine	10-Oxomorphine	HPLC	
10.	Lincomycin	Lincomycin B	Capillary electrophoresis	49
11.	Meclophenoxate	N,N-dimethyl ethanolamine	Capillary electrophoresis	50

7. Toxic manifestations for control of impurities

Impurities often possess unwanted pharmacological or toxicological effects which may outweigh Benefits obtained from administration of their parent drug/ formulation in which they are found. Impurities can have deleterious impact on efficacy, bioavailability or adverse effects. In case of chiral impurities, one isomer can show desired therapeutic activity, while the other can be inactive and show unwanted activity. For example-racemic drug of n-phthalyl-glumatic acid imide was marketed as the sedative Thalidomide. Its therapeutic activity resided exclusively in the R-(+)-enantiomer. It was discovered only after several hundred births of malformed infants that the S-(+)-enantiomer was teratogenic.[51] There are some famous single isomer drugs which are marketed like Levofloxacin (S-ofloxacin), Lavalbuterol (R-albuterol), and Esomeprazole (S-Omeprazole).[52] It is not only that one enantiomer reacts and the other does not but also in some instances different enantiomers can have different effects as shown in Table 5.

Table. 5: Pharmaceutical products and their effect of chirality.

S. No.	Drug	Isomer	Effect
1.	Barbiturates	R-isomer	Convulsant
		S-isomer	Depressant
2.	Thalidomide	R-isomer	Anti-nausea, Sleep inducing
		S-isomer	Teratogenic
3.	Labetalol	R,R-isomer	β-Blocker
		S,R-isomer	α-Blocker
4.	Penicillamine	D-isomer	Anti-arthritic
		L-isomer	Toxic
5.	Warfarin	R-isomer	Toxic
		S-isomer	Anti-coagulant
6.	Ethambutol	R,R-isomer	Blindness
		S,S-isomer	Tuberculostatic
7.	Naproxen	R-isomer	Toxic
		S-isomer	Analgesic

8. 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.[53]

9. 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 and limits of quantitation 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 plausible 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.

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