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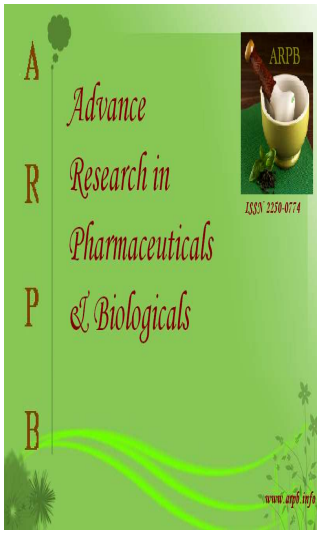

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IMPURITY PROFILING OF PHARMACEUTICALS

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ABSTRACT:

Impurity profiling is the process of acquiring and evaluating data that establishes biological safety of an individual impurity; thus, revealing its need and scope in pharmaceutical research. There is no clear definition for impurity in the pharmaceutical world. Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Impurity profiling has gained importance in modern pharmaceutical analysis due to the fact that unidentified, potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, impurities should be identified and determined by selective methods. Terms such as residual solvents, byproduct, transformation products, degradation products, interaction products and related products are frequently used to define impurities. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. The advent of hyphenated techniques has revolutionized impurity profiling, by not only separation but structural identification of impurities as well. The present review covers various aspects related to the analytical method development for impurity profiling of an active pharmaceutical ingredient.

KEYWORDS: Impurity profiling, Impurities, Identification, Analytical, Elucidation.

INTRODUCTION

The bulk drug industry forms base of all pharmaceutical industries as it is the source of active pharmaceutical ingredients (APIs) of specific quality. Over the last few decades much attention is paid towards the quality of pharmaceuticals that enter the market. The major challenge for both bulk drug industries and pharmaceutical industries is to produce quality products. It is necessary to conduct vigorous quality control checks in order to maintain the quality and purity of output from each industry. Purity of active pharmaceutical ingredient depends on several factors such as raw materials, their method of manufacture and the type of crystallization and purification process. Concept about purity changes with time and it is inseparable from the developments in analytical chemistry. The pharmacopoeias specify not only purity but also puts limits which can be very stringent on levels of various impurities. Modern separation methods clearly play a dominant role in scientific research today because these methods simultaneously separate and quantify the components hence making the separation and characterization of impurities easier.

Impurities in pharmaceuticals are unwanted chemicals that remain with the Active Pharmaceutical Ingredients (APIs) or develop during formulation or develop upon ageing of both APIs and formulated APIs to medicines[1-4]. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products. Different pharmacopoeias such as British pharmacopoeia (BP) and the United States pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations[4]. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents[5-7]. In addition, Ahuja and Gorog have published books covering different aspects of impurities including regulatory requirements, sources and types of impurities, isolation, characterization and monitoring of impurities found in drug products[5-7]. Impurity profile is description of the identified and unidentified impurities present in a typical batch of API produced by a specific controlled production process[8-10]. It is one of the most important fields of activity in contemporary industrial pharmaceutical analysis. The main reasons for the increasing interest of drug manufacturers and drug registration authorities in the impurity profiles of bulk drug substances are as follows[8]:

a. In the course of the development of a new drug or a new technology for manufacturing an existing drug it is essential to know the structures of the impurities: by possessing the information synthetic organic chemists are often able to change the reaction conditions in

such a way that the formation of the impurity can be avoided or its quantity reduced to an acceptable level.

b. Having suggested structures for the impurities, they can be synthesized and thus provide final evidence for their structures previously determined by spectroscopic methods.

c. The material synthesized can be used as an 'impurity standard' during development of a selective method for the quantitative determination of the impurity and the use of this method as part of the quality control testing of every batch.

d. In case of major impurities the synthesized or isolated material can be subjected to toxicological studies thus greatly contributing to the safety of drug therapy.

e. For drug authorities the impurity profile of a drug substance is a good fingerprint to indicate the level and constancy of the manufacturing process of the bulk drug substance.

Regulatory Guidelines on Impurities in an Active Pharmaceutical Ingredient:

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. However monitoring impurities and controlling these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry[2]. A unified terminology is necessary to assure that everyone uses the same vocabulary when addressing questions related to impurities. The United States Food and Drug Administration (US FDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The guidelines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations[1-2]. The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines "stability testing of new drug substances and products"- Q1A
2. ICH guidelines "Impurities in New Drug Substances"- Q3A
3. ICH guidelines "Impurities in New Drug Products"- Q3B
4. ICH guidelines "Impurities: Guidelines for residual solvents"- Q3C

5. US-FDA guidelines "NDAs -Impurities in New Drug Substances"

6. US-FDA guidelines "ANDAs - Impurities in New Drug Substances"

7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia

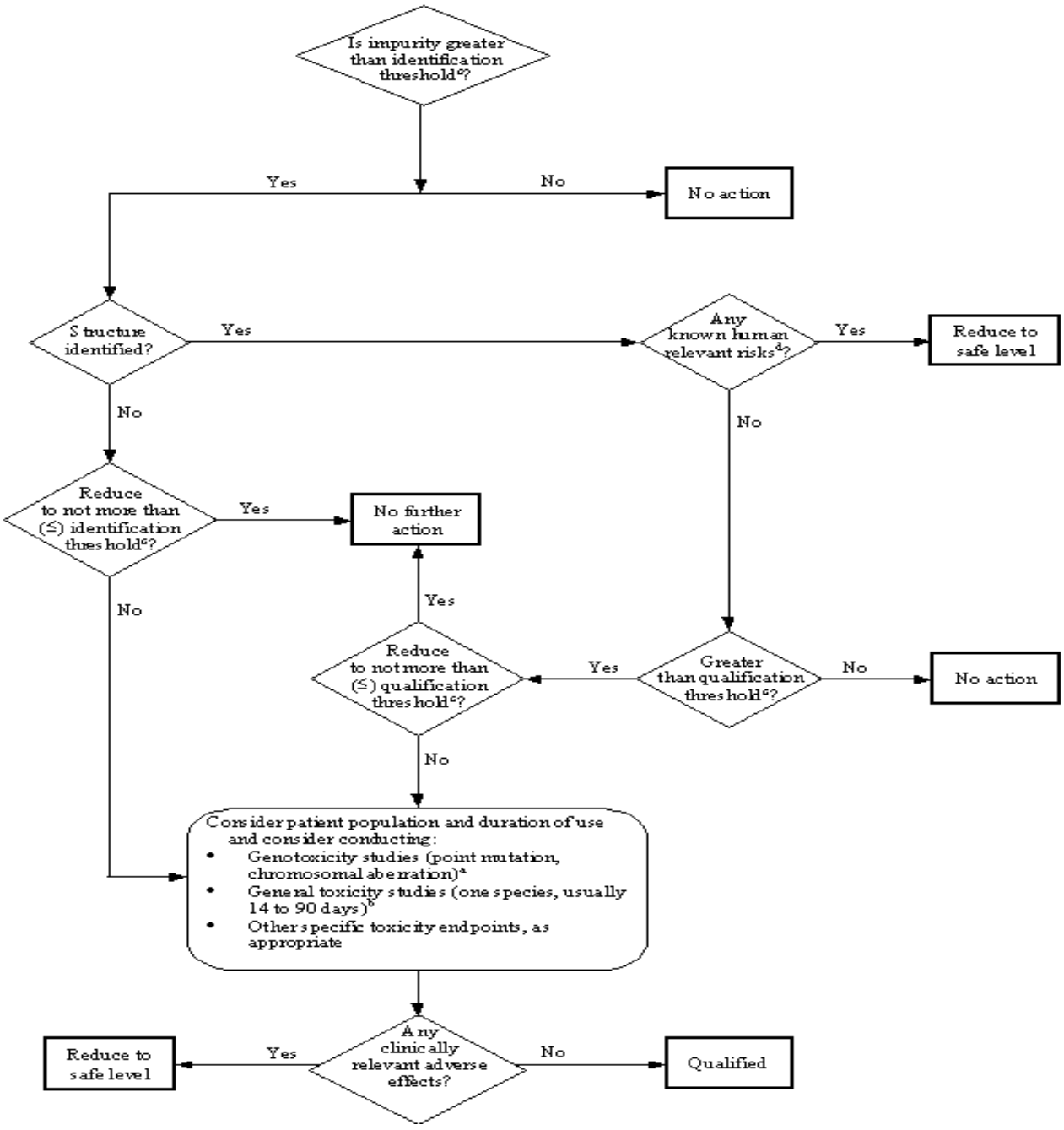

Fig. 1: ICH decision tree for Identification and Qualification of Impurities

Rationale for Reporting of Impurities in Active Pharmaceutical Ingredient:

The setting of limits for allowable impurities in bulk drugs is a complex process which depends on number of factors like toxicology of impurities related to drug, route of administration, daily dose, target population, source of drug substance and duration of therapy. The basis behind setting limits on level of impurities is that impurities in drug substance must be controlled to ensure the safety and efficacy and quality of API throughout its development and use as a product, as some of these impurities might possess certain undesirable toxicological potential.

ICH guidelines, 'Impurities in New Drug Substances' (Q3A) states "The applicant should summarize the actual and potential impurities most likely to arise during synthesis, purification and storage of the new drug substance. This should be based on sound scientific knowledge of the chemical reactions involved in the synthesis, impurities associated with raw materials and possible degradation products. Also the applicant should summarize the laboratory studies conducted to detect impurities in new drug substances. This summary should include results from batches from the development process as well as batches from commercial process. Also the studies conducted to characterize the structures of the impurities present above the identification threshold should be described. When identification of impurity is not possible, a summary of laboratory studies demonstrating the unsuccessful effort should be reported. The identification of impurities present at the level less than the identification threshold is not generally considered necessary. But analytical methodology needs to be developed for the impurities that are expected to have unusual toxic pharmacological effects."

Specifications for Impurities[5]:

The specifications for a new drug substance should include limits for impurities. Stability studies, chemical development studies and routine batch analysis can be used to predict those impurities likely to occur in the commercial product.

A rationale for the inclusion or exclusion of impurities in the specifications should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of material manufactured by the proposed commercial process.

Reporting of Impurities[1,5]:

All impurities above (>) reporting threshold should be reported

Identification of Impurities[1,5]:

All impurities above (>) identification threshold are supposed to be identified. These include development of a suitable technique for

isolation of desired impurities and their identification/characterization using various spectroscopic techniques to know the chemical structure of these impurities, and to suggest a possible synthetic route for formation of these impurities.

Qualification of Impurities[1,5]:

The profile of impurities in a new drug substance may change for a variety of reasons, such as process scale-up changes, synthetic route change and changes made to key intermediates. ICH decision tree help to classify quality and select limits for New Molecular Entities (NMEs). If an impurity exceeds the qualification threshold listed in Table 1.1, studies are needed to qualify that impurity in drug substances.

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Table 1: Thresholds[1,2,5]

Maximum daily dose[a]	Reporting threshold[b,c]	Identification threshold[c]	Qualification threshold
≤ 2g/day	0.05%	0.1% or 1 mg per day intake (whichever is lower)	0.15% or 1 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

a. The amount of drug substance administered per day.

b. Higher reporting thresholds should be scientifically justified.

c. Lower thresholds can be appropriate if the impurity is unusually toxic.

SOURCES AND TYPES OF IMPURITIES[11]:

The impurities usually encountered in pharmaceuticals are synthesis-related, formulation-related or degradation-related. There are two types of impurities in medicines**:**

1) Impurities associated with active pharmaceutical ingredients (APIs).

2) Impurities that are formed during formulation and or with ageing or that are related to the formulated forms.

According to ICH guidelines, Impurities associated with APIs are classified into the following categories:

- Organic impurities (Process and Drug-related)
- Inorganic impurities
- Residual solvents

Organic impurities[4,10]:

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile including

starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. Starting materials or intermediates are the most common impurities found in every API unless a proper care is taken in every step involved in throughout the multi-step synthesis. Although the end products are always washed with solvents, there are chances of remaining residual unreacted starting materials unless the manufacturers are very careful about the impurities. In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of formation of by-products. For example, in the case of Paracetamol bulk, diacetylated paracetamol (**Fig. 2**) may form as a bi product.

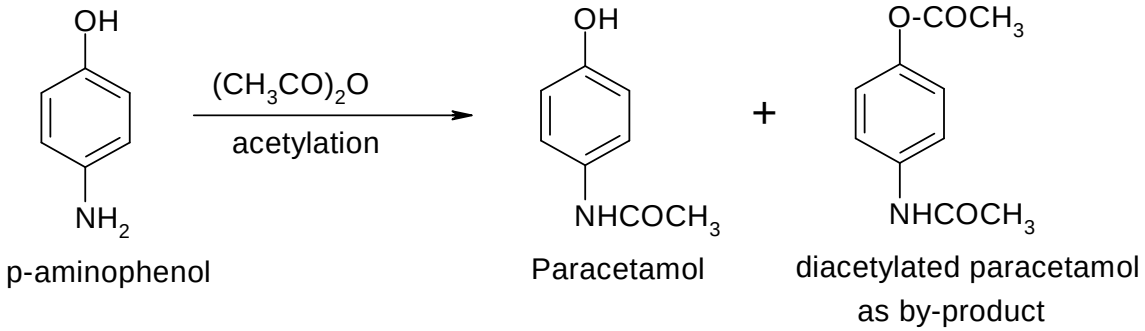

Fig. 2: Production of Paracetamol from intermediate p-aminophenol

Impurities can also be formed by degradation of the end product during manufacturing of APIs. However, degradation products resulting from storage or formulation to different dosage forms or ageing are other common organic impurities in APIs. In addition for an optically active single isomer drug there could be an enantiomeric impurity present in the API.

Inorganic impurities[4]:

Inorganic impurities may also arrive from manufacturing processes used for bulk drugs. They are normally known and identified and include the following:

- **Reagents, ligands and catalysts**- The chances of presence of these impurities are rare. However, in some processes, these could create a problem unless the manufacturer takes proper care during production.
- **Heavy metals**- The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glass-linked reactors.
- **Other materials (filter aids, charcoal)**- The filters or filtering aids such as centrifuge bags are routinely used in bulk drug 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 contaminants.

Residual solvents[1,4]:

Residual solvents are organic or inorganic liquids used during the manufacturing process. It is very difficult to remove these solvents completely by the work-up process. Some solvents that are known to cause toxicity should be avoided in the manufacturing of bulk drugs. Depending upon the possible risk to human health, residual solvents are divided in three classes.

- **Class I:** Solvents like benzene (2 ppm limit) and carbon tetrachloride (4 ppm limit) should be avoided.
- **Class II:** Methylene chloride (600 ppm limit), methanol (3000 ppm limit), pyridine (200 ppm limit), toluene (890 ppm limit) and acetonitrile (410 ppm limit) are the most commonly used solvents.
- **Class III:** Acetic acid, acetone, isopropyl alcohol, butanol, ethanol and ethyl acetate have permitted daily exposures of 50 mg or less per day.

Formulation related impurities[4,10]:

Apart from bulk drug related-impurities the formulated form of API may contain impurities that are formed in various ways.

- **Method related impurities:** Some impurities are generated during the formulation process either due to exposure to heat, light, change of pH, solvents etc. (e.g. Formation of impurity 1-(2,6-dichlorophenyl)-indolin-2-one on autoclaving of Diclofenac sodium).
- **Environment related impurities:**
  - ❖ Due to exposures to adverse temperatures (e.g. Vitamins as drug substances are very heat-sensitive and degradation frequently leads to loss of potency in vitamin products, especially in liquid formulations)
  - ❖ Due to exposure of light specially UV light (e.g. Ergometrine as well as methyl-ergometrine is unstable under tropical conditions such as light and heat)
  - ❖ Humidity (Humidity is considered detrimental for hygroscopic products e.g. Aspirin and Ranitidine)
- **Dosage form factors related impurities**

Formation of impurities on ageing [4, 10]:

1. **Those formed due to mutual interaction between ingredients** e.g. Degradation of Thiamine in the presence of Nicotinamide in formulations containing Vitamin B complex.
2. **Functional group related typical-degradation impurities**

➢ Ester hydrolysis e.g. Formation of Salicylic acid impurity from aspirin.

➢ Hydrolysis e.g. Bezylpenicillin, Chlordiazepoxide.

- Oxidative degradation e.g. Hydrocortisone, Methotrexate.
- Photolytic cleavage e.g. Photolytic cleavage of Ciprofloxacin in eye preparation.
- Decarboxylation e.g. Photoreaction of Rufloxacin.

ISOLATION AND IDENTIFICATION OF IMPURITIES IN ACTIVE PHARMACEUTICAL INGREDIENTS [12-13]

The process of identification of impurities and/or degradants begins early in drug development. The first step of the process is to determine at what level the unknown impurity is present. According to the ICH guidelines on Impurities in New Drug Substances, '*The studies conducted to characterize the structure of actual impurities present in the new drug substance at a level greater than 0.1% (depending on the daily dose, calculated using the response factor of the drug substance) should be described. Note that all specific impurities at a level greater than the identification threshold in batches manufactured by the proposed commercial process should be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. When the identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application.'*

Identification of impurities below the 0.1% level is generally not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic[14,15,16]. Therefore it is imperative to determine the level of the unknown impurity early in the process. If the unknown impurity is below 0.1% threshold, then a discussion will need to take place among the project team members in order to determine if isolation and identification is necessary. However, if the unknown is at or above the 0.1% limit, then effort should be put for isolation and identification.

Methods for Isolation and Identification of Impurities[17,18,19]

A number of methods can be used for isolating impurities. Three of the most utilized techniques are thin-layer chromatography (TLC), flash chromatography (column chromatography) and preparative high performance liquid chromatography (HPLC). The actual technique to be used depends upon the nature of the impurity and/or degradant, including the amount present in the original material from which it must be isolated. Extraction techniques are used some times for isolation of impurities, on the basis of difference in the solubility of impurity and drug substance in various solvents. It is possible to extract impurities selectively on the basis of acidity, basicity or neutrality of impurities in question. The extraction

procedure usually involves liquid-liquid extraction where one phase is aqueous while the other is non-polar organic phase. By appropriate adjustment of pH of aqueous phase one can extract acidic, basic or neutral impurities. The technique work well when a few impurities are present and their polarity or pKa of impurities is sufficiently different from that of drug substance[20]. If necessary, further separations can be achieved by chromatographic methods. Other methods which are used for isolation of impurities include Solid Phase Extraction methods (SPE), Supercritical Fluid Extraction (SFE), Capillary Electrophoresis (CE) and Supercritical Fluid Chromatography (SFC). Some of the techniques listed above like SPE and SFE are normally used for sample clean up before analysis. Capillary electrophoresis is largely used for analysis of impurities in protein pharmaceuticals[21,22,23].

Different spectroscopic techniques like UV-spectroscopy, IR-spectroscopy, Mass Spectrometry and Nuclear Magnetic resonance Spectroscopy are used in identification of isolated impurities. Structural elucidation of impurities using these spectroscopic techniques is known as characterization of impurities.

Hyphenated techniques

Hyphenated techniques are first line of defense in impurity determination. Hyphenated techniques are those techniques, where two or more analytical techniques are combined. The various hyphenated techniques used for impurity characterization are LC-MS, LC-NMR, LC-MS-NMR, LC-MS-MS, GC-IR and GC-MS. The two most commonly used hyphenated techniques for impurity profiling are LC-MS and LC-MS-NMR. In these techniques chromatographic techniques are coupled with a spectroscopic detector. Thus impurity structure determination can be performed in real time during chromatographic separation and both isolation and characterization is performed in one single step.

The use of hyphenated techniques for impurity determination is on rise due to easy availability of bench-top instrumentation and their distinct advantages like versatility, sensitivity, possibility of profiling sub structural analysis and rapid selective quantitative determination of targeted compound even in mixtures. The only limitation of hyphenated techniques is the heavy cost of instrumentation due to which their use is not common and spread worldwide like GC, HPLC, MS or NMR systems. As on today these sophisticated techniques are mainly used for the purpose of monitoring, characterization and identification of impurities but they can be used for other analytical purposes as well.

VALIDATION OF IMPURITY METHODS [14, 15]

The real goal of the validation process is to challenge the method and determine limits of allowed variability for the conditions needed to run the method. According to United States pharmacopoeia, 'Validation is the process of providing documented evidence that the method does what it is intended to do'. It is important to have a well-conceived validation plan for testing the method and acceptance criteria before starting the validation process. During impurity profiling, the developed method needs to be validated to meet with the compliances. The performance characteristics of assay validation include specificity, accuracy, precision, limit of detection, limit of quantitation, linearity, range, and robustness. In addition, it is also recommended that analysts should examine sample solution stability and establish an appropriate system-suitability test to verify the proper functioning of the equipment employed in performing the analysis[20, 24-25].

APPLICATIONS OF IMPURITY PROFILING

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids etc. There are a few examples of impurities reported in the APIs mentioned in Table 2.

Table 2: various impurities reported in APIs

Drug	Impurities	Method	Ref No.
Budensonide	Impurities or degradation products	HPLC	26
Cefdinir	Related substances	HPLC	27
Donepezil	Process related impurities	HPLC	28
Linezolid	Process related impurities	HPLC	29
Loratidine	Process related impurities	HPLC	30
Repaglinide	Process related impurities	HPLC	31
Rofecoxib	Process related impurities	HPLC	32
Zaleplon	Process related impurities	HPLC	33
AmphotericinB	Process related impurities	UV spectroscopy	34
Doxorubicin hydrochloride	Residual solvents	GC	35
Framycetin sulphate	Process related impurities	TLC	36
Cimetidine	Process related impurities	HPLC	37
Norgestrel	Related substances	TLC, HPLC & UV spectroscopy	38
Celecoxib	Process related impurities	HPLC, LC-MS-MS	39
Ethynodiol diacetate	Process related impurities	HPLC	40
Methamphetamine	Process related impurities	GC	41
Morphine	Process related impurities	HPLC	42
Morphine sulphate	Related substances	HPLC	43

CONCLUSION

Impurity profiling of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels in drug substances and products provides the quality criteria for manufacturers. The key aspect is that the impurity profiling of a new chemical entity must be shown to be qualified. With a qualification threshold of 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology. Especially in the development phases it may be necessary to utilize methods with high selectivity, including hyphenated techniques. The importance of qualifying impurity profiles are relevant to the development scientists to ensure that due consideration is given to the impurities present in the batches being used in safety studies. Beginning with limit tests for impurities, this field of impurity identification and quantitation has progressed. Isolation and characterization of impurities is required for acquiring and evaluating data that establishes biological safety which reveals the need and scope of impurity profiling of drugs in pharmaceutical research.

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