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REVIEW ON IMPURITY PEOFILING AND ITS TECHNIQUES

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Abstract

The review gives brief introduction about process and degradation related impurities and emphasizes on the development of analytical methods for their determination. It describes modern analytical techniques, particularly the HPLC, MS, TLC NMR. The significance of quality, efficacy and safety of drug substance/products including the source of impurities, kinds of impurities; adverse effects by the presence of impurities, quality control of impurities, necessity for development of impurity profiling methods, identification of impurities and regulatory aspects were discussed. Other important aspects that were described forced degradation studies and development of stability indicating assay methods.

Keywords: Impurity profiling, Classification of impurities, sources of impurities, Goals of impurities, Method of detection impurities

1.Introduction

The purity of a drug product is in turn determined on the basis of the percentage of the labelled amount of API found in it by a suitable analytical method. The presence of some impurities may not deleteriously impact on drug quality if they have therapeutic efficacy that is similar to or greater than the drug substance itself. Nevertheless, drug substances can be considered as compromised with respect to purity even if it contains an impurity with superior pharmacological or toxicological property.

Impurity profiling is the common name of a group of analytical activities, the aim of which is the detection, identification/structure elucidation and quantitative determination of organic and inorganic impurities as well as residual solvents in bulk drugs and pharmaceutical formulations. The different pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present in the API's or formulations.

Qualification of the impurities is the process of acquiring and evaluating data that establishes biological safety of an individual impurity thus, revealing the need and scope of impurity profiling of drugs in pharmaceutical research. International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents.[1]

2.Impurity profile

Impurity profiling is a collection of investigative activities,with the purpose of detection, identification/structure revelation and quantitative determination of organic and inorganic impurities, as well as residual solvents in bulk drugs substances and pharmaceutical preparations. Various regulatory establishments like USFDA, ICH, Canadian Drug and Health Agency are focusing on the clarity/purity requirements and the recognition of impurities in Active
pharmaceutical ingredient . The explanation, characterization and quantization of the celebrated and mysterious impurities present in new drug materials are acknowledged as impurity profile . It offers an account of impurities present in the bulk and final drug substances. It facilitates in identifying and quantifying the impurities present in the drug substance or in pharmaceutical formulation[2].

There is a good significant demand for the impurity-reference standards along with the API reference standards from both regulatory authorities and pharmaceutical companies. The estimation of impurity in drug and materials has most important fields of pharmaceutical analysis. In general, impurities present in excess of 0.1% should be identified, for the following reasons:

(1) On the basis of the information thus obtained synthetic organic chemists are often able to avoid the formation of the impurity in question or to develop a purification method to decrease its quantity to a tolerable level.

(2) Following the structural identification of an unavoidable impurity, it may be synthesized to provide a sufficient amount for:
a. Final proof of its structure;
b. Its use as an “impurity standard”
c. Its use in toxicological studies.

ICH Q3A covers drug substances and Q3B covers drug products. These guidelines define what investigations and documentation should be made in investigating impurities and degradation products seen in stability studies at recommended storage conditions. In general, according to ICH guidelines on impurities in new drug products, identification of impurities below the 0.1% level is not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic. In all cases, impurities should be qualified. If data are not available to qualify the proposed specification level of an impurity, studies to obtain such data may be needed (when the usual qualification threshold limits given below are exceeded). According to ICH, the maximum daily dose qualification threshold is considered as follows :
$\leq$ 2g/day 0.1 % or 1 mg per day intake (whichever is lower) $\geq$ 2g/day 0.05%[1]

3.Classification of impurities

Pharmaceuticals may be divided into two main areas active pharmaceutical ingredients (APIs) which is also called as drug substance generally known as active pharmaceutical ingredient and drug product which is also called as finished pharmaceutical product. The Impurities of pharmaceuticals are categorized on the basis of standard books and ICH guidelines.

A) General names

- Intermediates
- By-products
- Penultimate intermediates
- Degradation products
- Related products
- Interaction products
- Transformation products

B) United State Pharmacopeia

According to the United States Pharmacopoeia (USP) categorizes impurities in many sections

- Ordinary impurities
- Organic volatile impurities
- Impurities in official articles

C) ICH terminology[31]

As per the ICH guidelines, impurities in the drug substance generated by chemical synthesis can generally be classified into subsequent three categories;

- Inorganic impurities
- Organic impurities
- Residual solvents

Impurities (organic) likely to arise throughout the manufacturing process and or shelf life of the drug substance may be known or unknown, volatile or non-volatile, and may include;

- By-products
- Starting materials or intermediates
- Degradation products[2].

Reagents, ligands, and catalysts- These chemicals are less commonly found in APIs; however, in some cases they may pose a problem as impurities.

In general, an individual API may contain all of the above-mentioned types of organic impurities at levels varying from negligible to significant. A detailed investigation of impurities in semi-synthetic penicillin was performed both by the manufacturers and the different research groups. A review paper on penicillins and cephalosporins describes methods of isolation, detection, and quantification of degradation products, and antigenic polymeric by-products. Studies show the presence of traces of ampicillin polymers and hydrolyzed products in the API[42]. .It has also been found that the presence of certain chemicals such as triethylamine has a degradative effect on the product. Ampicillin trihydrate samples having triethylamine content of 2000 ppm to 4000 ppm (determined by visual colour method developed by Gist- Brocades, Delft, Holland. were found to be stable under accelerated stability testing. However, the product showed appreciable degradation

when triethylamine content became 7000 ppm. Recent pharmacopoeia[43]. included the limit tests for the traces of impurities present in ampicillin and amoxycillin bulk raw materials. The residual solvents associated with these APIs have also been determined[42].

4.Regulatory Guidelines on Impurities in Active Pharmaceutical Ingredient:

Ethical, economic and competitive reasons and those of safety, efficacy support the need to monitor impurities in drug products. However monitoring the impurities and control these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry. 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 (USFDA) have endorsed the guidance prepared under guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities was developed by regulators and industry representatives of 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[5].

On 28 March 2014, DIA and EFPIA (one of the funding member of ICH) are organizing an "Information Day on ICH" to provide an update on the status of active topics and potential new topics to be harmonized. Participants will be updated as well on recent discussions related to the ICH reforms, including increased transparency, new membership, restructured governance and
future funding models[37].

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. The various regulatory guidelines regarding impurities are as follows[30]:

1. ICH guidelines "Elemental Impurities"- Q3D[10]
2. ICH guidelines "Impurities in New Drug Substances"- Q3A[7]
3. ICH guidelines "Impurities in New Drug Products"- Q3B[9]
4. ICH guidelines "Impurities: Guidelines for residual solvents"- Q3C[8]
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[5]

5.Sources of impurity

From the preceeding discussion, it is clear that impurities can originate from several sources; such as; a)Crystallization-related impurities, b)Stereochemistry-related impurities, c) Residual solvents, d) Synthetic intermediates and by-products, e) Formulation-related impuritiy,
f) Impurities during storage, g) Method associated impurity, h) Mutual interaction between ingredients, i) Impurities formed due to functional group reaction degradation, j) Environment related impurities.

a)Crystallization-related impurities

Based on the realization that the nature of structure adopted by a given compound upon crystallization, could exert a profound effect on the solid-state properties of that system, the pharmaceutical industry is essential to take a strong awareness in polymorphism and solvatomorphism as per regulations laid by regulatory authorities. Polymorphism is the term used to indicate crystal system where substances can exist in different crystal packing arrangements, all of which have the same elemental composition.Whereas, when the substance exists in different crystal packing arrangements, with a different elemental composition; the phenomenon is known as Solvatomorphism[39].

b)Stereochemistry-related impurities

It is of paramount importance to look for stereochemistry related compounds; that is, those compounds that have similar chemical structure but different spatial orientation, these compounds can be considered as impurities in the API's. Chiral molecules are frequently called enantiomers. The single enantiomeric form of chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index with a more favourable adverse reaction profile. However, the pharmacokinetic profile of levofloxacin (S-isomeric form) and ofloxacin (R-isomeric form) are comparable, suggesting the lack of advantages of single isomer in this regard. The prominent single isomer drugs, which are being marketed, include levofloxacin (S-ofloxacin), lavalbuterol (R-albuterol), and esomeprazole (S- omeprazole)[6].

c)Residual solvents

Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Some solvents that are known to cause toxicity should be avoided in the production of bulk drugs. Depending on the possible risk to human health, residual solvents are divided into three classes . Especially, solvents in Class I, *viz* benzene (2ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided. In Class II, *viz* N, Ndimethylformamide (880 ppm), acetonitrile (410 ppm). Class III solvents, *viz* acetic acid, ethanol, acetone have permitted daily exposure of 50 mg or less per day, as per the ICH guidelines. A gas chromatography (GC) method has been developed to determine acetone purity, dichloromethane, methanol, toluene. By use of this method, the contaminants of organic solvent can be measured. Moreover, the developed method permits the simultaneous determination of ethanol, isopropanol, chloroform, benzene, acetone,dichloromethane, methanol and toluene with propionitrile as the internal standard synthetic intermediates and by-products Impurities in pharmaceutical compounds or a new chemical entity (NCE) can originate during the synthetic process from raw materials, intermediates and/or by-products. Example, impurity profile of ecstasy tablets by using GC-MS , MDMA samples, produced impurities in the intermediates via reductive amination route[38].

d) Formulation-related impurities

Many impurities in a drug product can originate from excipients used to formulate a drug substance. In addition, a drug substance is subjected to a variety of conditions in the process of formulation that can cause its degradation or have other undesirable reactions. If the source is from an excipient, variability from lot to lot may make a marginal product, unacceptable for reliability. Solutions and suspensions are inherently prone to degradation

due to hydrolysis or solvolysis . Fluocinonide Topical Solution USP, 0.05%, in 60-mL bottles, was recalled in the United States because of degradation/impurities leading to sub-potency . In general, liquid dosage forms are susceptible to both degradation and microbiological contamination. In this regard, water content, pH of the solution/suspension, compatibility of anions and cations, mutual interactions of ingredients, and the primary container are critical factors. Microbiological growth subsequent from growth of bacteria, fungi, and yeast in the humid and warm environment may causes in unsuitability of oral liquid product for safe human ingesting. Microbial contamination may occur during the shelf life and subsequent consumer-use of a multiple-dose product, either due to inappropriate use of certain preservatives in the preparations, or because of the semi-permeable nature of primary containers.

e)Impurities due to storage

A amount of impurities can create during storage or shipment of products. It is essential to carry out stability studies to predict, evaluate, and ensure drug product safety.

f)Method related impurity

A known impurity, 1-(2, 6-dichlorophenyl) indolin-2-one is formed in the production of a parenteral dosage form of diclofenac sodium, if it is terminally sterilized by autoclave[44]. The conditions of the autoclave method (i.e., 123 + 2 oC) enforce the intramolecular cyclic reaction of diclofenac sodium forming an indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on initial pH of the formulation.

g)Mutual interaction amongst ingredients

Most vitamins are very labile and on aging they create a problem of instability in different dosage forms, especially in liquid dosage forms. Degradation of vitamins does not give toxic impurities; however, potency of active ingredients drops below Pharmacopoeial specifications.

Because of mutual interaction, the presence of nicotinamide in a formulation containing four vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) can cause the degradation of thiamine to a sub-standard level within a one year shelf life of vitamin B-complex injections[6].

h)Impurities formed due to functional group reaction degradation

Degradation products of drugs are considered to be transformation products of the drug substance formed due to the effect of heat, solvents (including high and low pH), oxidising agents, other chemical reagents, humidity and light.

Hydrolysis

Hydrolysis is a common phenomenon for ester and amide type of drugs, especially in liquid dosage forms. Certain drugs which undergo hydrolysis are benzylpenicillin, barbital,chloramphenicol, chlordiazepoxide, lincomycin
and oxazepam

Oxidation

The oxidative decomposition of pharmaceutical compounds is responsible for the instability of a considerable number of pharmaceutical preparations. These reactions are mediated either by free radicals or by molecular oxygen. Drugs

which undergo oxidative degradation are hydrocortisone, methotrexate, adinazolam, hydroxyl group directly bonded to an aromatic ring (eg, phenol derivatives such as catecholamines and morphine), conjugated dienes
(eg, vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives and aldehydes (eg, flavorings)[45].

i)Environment related impurities: 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.
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- B12 in 24 hours[46.]

6.Identification of impurities
The impurities can be identified by the following methods.

- Reference standard method
- Spectroscopic method
- Separation method
- Isolation method

Reference standard method: It is the method in which reference standard prepared for use as the standard in an assay, identification, or purity test. By this method we can evaluate both the process and product performance. It is not only gives the information for the active ingredient in dosage form but also for the impurities, degradation product, starting materials, and excipients.

Spectroscopic method: The UV, IR, MS, NMR, and Raman spectroscopic methods are routinely being used for characterizing the impurities.

a) Ultraviolet spectrometry: It is a physical technique of the spectroscopy that uses light. It is determine concentration of absorber in the solution. By rapidly change in absorbance we can determine the impurity.

b) Infrared spectroscopy: Its used in research to identify samples, do quantitative analysis, or detect impurities. It can also used on solid, liquid or gaseous samples and also does not destroy the sample in process.

c) Mass spectrometers: It provides the accurate mass measurements of sample molecules, sample identification, and quantitation of the samples. It can used with GC-MS and LC-MS. It is a combine feature of gas and liquid chromatography.

d) NMR Spectroscopy: It is very sophisticated system which is based on the use of nuclear magnetic resonance technology. sed to test atomic and molecular properties of the sample. It is very sensitive in nature.

e) Raman spectroscopy: It is used to study vibrational, rotational and other low frequency modes in a system. It is fairly good sensitivity and detect the process related impurities.

Separation method: The following separation methods are as follows.
a) Thin-layer chromatography: It is a chromatography method which is normally used to separate the mixtures. It is done on sheet of the glass, plastic, and aluminum foil, where it is been covered with the adsorbents such as cellulose, silica gel and aluminium oxide. As sample has applied on plate then a solvent mixture is drawn up by the capillary action. After some time the mixture gets separate.

b) Gas chromatography: It is used for separating and analyzing the compounds. Mainly it is of two types i.e Gas-Liquid chromatography and Gas chromatography. Mostly this chromatography is beneficial for testing of purity or splitting the different components of the mixtures. It is helpful in the preparation of the pure compounds from the mixtures.

c) High-pressure liquid chromatography: It is used to isolated, identify plus quantify the compounds. HPLC have different types of stationary phases and a pump and also there is a detector to carry the characteristic material. It is co-operative to check the quality of the API and also signify the unknown impurities.

d) Capillary electrophoresis: It is used to isolated the ionic species by their charge and size with an electrolyte. It is built on the dissimilar separation principles and also used for quality control of products.

e) Supercritical fluid chromatography (SFC): It is the chromatography in which we separate one component from other component by using the super critical fluid. Carbon dioxide is used as a supercritical fluid where ethanol or methanol used as a co-solvent. In this we provide temperature of 31oc with critical pressure of 72 bars.

Isolation method: It is necessary to isolate the impurities. Generally chromatographic and non-chromatographic techniques are used for the isolation of the impurities. There are various methods by which we can isolate the impurities such as.

a) Solid-phase extraction method: It is the method which is used to trace the organic compound as well as eliminate the interfering complex to obtain a clear extract. Mainly this technique is used for the extraction and purification of the compounds. Main use of this method is to clean up the sample before use for the chromatographic technique to count the analyte in the sample.

b) Liquid-liquid extraction method: This method is used to separate mixtures built on relative solubility's in two unlike immiscible solutions. The method is perform in the separating funnel. Commonly solvents used for liquid-liquid extraction are ethyl acetate, methylene chloride and hexanes.

c) Accelerated solvent extraction method: This technique is used for the extraction of solid and semi-solid samples. To get the fast and efficient removal of analysts from the samples process is done at the elevated temperature and pressure. It perform the trial in less time with by small amount of solvent[3].

Classification of solvents on the basis of their in parts per million (PPM)[40]

Category	Name of the solvents/limit	Unit/Specification
Class 1	Benzene (2ppm), Carbon tetra chloride(4ppm), methyl chloride (600ppm), methanol(3000ppm),pyridine(200ppm)	More than this should be avoided
Class 2	N,N-dimethylformamide(800ppm),Acetonitrile(410ppm)	More than this should be avoided
Class 3	Acetic acid, ethanol,acetone(50mg)	Have permitted daily exposure of 50mg or less per day as per ICH guidelines

7.Analytical procedures:

a. Method Development: Method development normally requires the choice of columns, method of quantization mobile phase and detectors etc. Existing method may be inaccurate, contamination prone, or they may be unreliable. Existing method may be too costly, time consuming or energy intensive, existing methods may not provide acceptable sensitivity or analyte selectivity in samples of interest.

b. Validation of Analytical Methods: The validation procedure includes establishing a developed technique by laboratory studies, procedures, systems, which can give accurate and reproducible result for an intended analytical use in a proven range[1]. According to ICH, typical analytical performance characteristics that should be considered in the validation of all the types of methods are:-

(1) The Limit of Detection (LOD) of an individual analytical method is the lowest concentration/amount of analyte in a sample that the method can detect but not necessarily quantify under the stated experimental conditions. The
LOD will not only depend on the procedure of analysis, also on the type of the instrument.

(2) The Limit of Quantification (LOQ) of an individual analytical method is the lowest concentration/ amount of an analyte in a sample, which can be quantitatively determined with suitable precision and accuracy under
stated experimental conditions. The quantification limit is used particularly for the determination of impurities and degradation products.

(3) The Linearity of an analytical method is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample.

(4) The Range of an analytical method is the between the upper and lower concentration (amounts) of analyte the sample (including those concentrations) for which it has been demonstrated that analytical procedure has a suitable level of precision, accuracy and linearity.

(5) Robustness is the measure of the analytical method to remain unaffected by small, but deliberate variations in method parameters. It provides an indication of its reliability during normal usage.

(6) The Ruggedness is the degree of reproducibility of test results obtained by analyzing the same sample under variety of normal test conditions such as
different analyst, instruments, days, reagents and, columns. The comparison of reproducibility of test results to the precision of assay is the direct measure of
ruggedness of the method[41].

8.Goals of Impurity Investigation[35]:

1) **Process- related impurities:**
   - Identify important impurities
   - Regulate origin of impurities
   - technique for elimination or reduction
   - Found a control system for impurities including:
     1) Processing/manufacturing conditions
     2) Suitable analytical method/specifications

2) Degradation- related impurities:

- Classify potential degradation product through stress testing and degradation products through stability studies
- Understand degradation pathway plus methods to reduce degradation
- Establish a control system for impurities involving:
  1) Processing/manufacturing conditions
  2) Suitable analytical methods/specifications
  3) Long term storage conditions including packaging.
  4) Formulation

9.Method of detection of impurity

This is significant to validate sample for estimations. If the evaluations indicate that particular impurity content is greater than 0.1% after that it must be assessed as per the FDA guideline. Hyphenated methods for example mass spectroscopy, gas chromatography or the numbers of other chromatographic-spectroscopic relationship are suitable for preliminary characterization of the impurities.

A. Spectroscopic Techniques.
B. Chromatographic Techniques.
C. Combination of Spectroscopic and chromatographic Techniques[2].

Highly complicated instrumentation such as Mass Spectrophotometer attached to a Gas Chromatography or HPLC are expected tools in the identification of negligible components in various preparations. Different approaches are used; for characterization of impurities, which are as follows-

(1) Nuclear Magnetic Resonance (NMR) These give information pertaining the specific bonding structure and stereochemistry study of formulations interest. NMR has traditionally been practical as a less sensitive method related to other analytical methods. The ability of NMR based diffusion coefficient determination to distinguish between nonnumeric and dimeric substances were validated via standard mixture of authentic materials having both monomers and
dimers. unluckily, NMR has traditionally been applied as a less sensitive method compared to other analytical methods. Conventional sample requirements for NMR analysis of

pharmaceutical preparations are 10 mg, as compared with Mass Spectroscopy, which consumes less than 1mg[33].

(2) Mass spectroscopy (MS) has a more important impact on the pharmaceutical advancement process over several decades. Development in the design and efficiency of the interfaces, which directly correlate with the separation techniques with Mass Spectrometers have gained new identification for monitoring, characterizing, optimizing and quantification of active pharmaceutical compound present in the core of pharmaceutical product or formulation[2]. Development in the design and efficiency of the interfaces, which directly correlate with the separation techniques with Mass Spectrometers (MS) have gained new identification for monitoring, characterizing, optimizing and
quantification of active pharmaceutical compound present in the core of pharmaceutical product or formulation. If single method does not pass to provide the essential selectivity, orthogonal coupling of chromatographic techniques such as HPLC-TLC, High performance liquid chromatography (HPLC) and HPLC are coupled with Capillary Electrophoresis (HPLC-CE) provide rich spectroscopic analysis information like HPLC-NMR or HPLC-MS which may be a unique tool for authentication of quality of the finished product[34].

(3)Thin-Layer Chromatographic (TLC) Methods

Thin-layer chromatography (TLC) is a broadly used separation method because of its ease of use, cost-effectiveness, speed of separation. TLC plays an vital role in the early stage of drug development when knowledge about the impurities and degradants in drug substance and drug product is limited[4].

(4)Hyphenated Methods:

- LC-MS-MS
- HPLC-DAD-MS
- HPLC-DAD-NMR-MS
- GC-MS
- LC-MS

A common goal for investigation of both process and product degradation-related impurities is to determine which of the many potential impurities are, in fact, produced in the manufacturing process and which occur under a given set of storage conditions[29].

10.Sample to be profiled

Impurity profiling should be done for the following samples:
Active ingredient
Process check (synthesis or formulation)
Final product[36].

Table 2: Various impurities reported in APIs

Drug	Impurities	Method	Ref No.
Budensonide	Impurities or degradation products	HPLC	11
Cefdinir	Related substance	HPLC	12
Donepezil	Process related impurities	HPLC	13
Linezolid	Process related impurities	HPLC	14
Loratidine	Process related impurities	HPLC	15
Repaglinide	Process related impurities	HPLC	16
Rofecoxib	Process related impurities	HPLC	17
Zaleplon	Process related impurities	HPLC	18
AmphotericinB	Process related impurities	UV spectroscopy	19
Doxorubicin hydrochloride	Residual Solvents	GC	20
Framycetin sulphate	Process related impurities	TLC	21
Cimetidine	Process related impurities	HPLC	22
Norgestrel	Related substance	TLC,HPLC&UV spectroscopy	23
Celecoxib	Process related impurities	HPLC,LC-MS-MS	24
Ethynodiol diacetate	Process related impurities	HPLC	25
Methamphetamine	Process related impurities	GC	26
Morphine	Process related impurities	HPLC	27
Morphine sulphate	Related substance	HPLC	28

Conclusion:

From the over study , it has been concluded that the identification 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. To isolate and quantify the impurities, various instrumental analytical techniques are routinely been used.

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Conflict of interest:

There is no any conflict of interest by authors to declare regarding this investigation.

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