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Impurity Profiling Of Pharmaceutical Drug Substances

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ABSTRACT:

Impurity profiling of any compound that lies under the pharmaceutical category is important to make sure that the drug is safe, efficient, and follows all regulatory compliance. This study presents comprehensive knowledge to identify and quantify impurities in any formulation that is intended for clinical use. We can use various advanced analytical techniques, like the UV spectrophotometer, to identify impurities through absorbed light at specific wavelengths. High-performance liquid chromatography coupled with mass spectrometry was employed to separate, identify, and characterize the impurities present. This study involves optimization of chromatographic conditions to improve resolution and sensitivity along with application of statistical analysis for data elucidation. Impurity levels were ensured against previously published standard pharmacopeia to make sure the drug follows safety guidelines. The results were validated by detecting the presence of several known and unknown impurities. This study helps to identify and eradicate impurity involving the pharmaceutical process of drug development.

KEYWORDS:

Impurity, ICH Guidelines, Chromatography, Pharmaceutical drug

INTRODUCTION:

Pharmaceutical impurities are the undesired chemicals that remain alongside active pharmaceutical ingredients (APIs) or within drug formulations.

Impurities in drug substances can occur during the synthesis process or originate from various sources, including starting materials, intermediates, reagents, solvents, catalysts, and byproducts of the reactions.

Certain impurities may be introduced during drug product development, starting with:

(i) Substances that were found to be inherently unstable.

(ii) The chemical interaction of the drug with the excipients, causing them to either be incompatible or to interact with the materials from which the packaging and container closure systems are made.

Level of degradation impurities in drug substances is fundamental to the final safety of pharmaceuticals, therefore acknowledging, declaring, qualifying, and controlling these impurities is essential during drug development.

The bulk drug industry is fundamental to the pharmaceutical sector, as it supplies active pharmaceutical ingredients (APIs) of specific quality. In recent decades, there has been a growing emphasis on guaranteeing quality assurance of pharmaceuticals entering the market. High-quality products have remained a challenge to the bulk drug and pharmaceutical industries alike. It will obviously mean stricter quality control measures to ensure that the quality of these materials is maintained. The purity of APIs is influenced by several factors, ranging from raw material and manufacturing quality to the crystallization and purification methods used.

Different regulatory authorities emphasize the management of impurities:

The International Council for Harmonization (ICH)

- The U.S. Food and Drug Administration (USFDA)
- The European Medicines Agency (EMA)
- The Canadian Drug and Health Agency
- The Japanese Pharmaceuticals and Medical Devices Agency (PMDA)
- The Australian Department of Health and Aged Care Therapeutic Goods Administration

Customarily, drug-related official targeted pieces enumerate the set of pharmacopoeias, namely the BP, USP, JP, EP, and ChP, to lay down the quality limits regarding the impurity levels in APIs and drug formulations. Such regulations, based on the exposure levels, compel the control of the levels of contaminans in a finished dosage form. Drug producers must, therefore, evaluate a risk assessment that takes into account contamination sources after manufacturing, such as packaging, transport, container closure system, and raw materials and manufacturing processes. The concept of purity has had a long evolution closely linked to advances in analytical chemistry. The pharmacopoeias set not only the standards for the purity but also limits on the impurities allowed. Modern analytical separation techniques are mainly for the laboratory, wherein the simultaneous separation and quantification of components enable the entire impurity analysis. Contaminants in medicine include any number of undesirable substances that can be associated with APIs, that are formed either during the manufacturing process or that may devolve in time in both APIs and final formulations. Only minute concentrations of these impurities can affect any performance or efficacy or influence toxicity in the pharmaceutical products. The limits on acceptable levels of impurity for API were fixed by different progressive pharmacopoeia like the British Pharmacopoeia and the United States Pharmacopoeia. ICH publications outlined requirements about impurities in new drug substances and products.

With their studies, Ahuja and Garag have explained many aspects of the impurities- those required by the regulations, sources, kinds, isolation, characterization, and monitoring. The impurity profile is, therefore, a detailed outline of impurities-Able to be determined and those that are not-present in any specific batch of API manufactured under controlled conditions. This area of analysis becomes slowly more crucial for pharmaceutical producers and the regulatory authorities involved for two reasons:

1.The small-scale study of the structures of impurities is very important in the development of new drugs or manufacturing technologies, as this can help chemists change reaction conditions in order to reduce or eliminate them.

2.Given an impurity's structure, researchers may be able to synthesize it and, in turn, offer decisive proof of identity, which can be otherwise inferred through spectroscopy methods.

3.The synthesized material could serve as an impurity standard during the development of a selective method to quantitatively measure the impurity, which can, in turn, be used for quality control testing of each batch.

4.The toxicity studies can be performed by synthesizing or isolating the significant impurities. These enhance the safety of drug therapies.

5.The impurity profile can be regarded as a fingerprint with respect to drug substances, indicating the manufacturing batch and its consistent levels in the bulk drug substance.

6.These techniques are critical in the quality and safety assurance of the pharmaceuticals by detecting impurities that adversely impact the potency, stability, or provoke adverse events in patients. (1)

Guidelines on impurities include:

a. ICH guidelines for stability testing of new drug substances and products (Q1A).

b. ICH guidelines addressing impurities in new drug substances (Q3A).

c. ICH guidelines regarding impurities in new drug products (Q3B).

d. ICH guidelines on impurities related to residual solvents (Q3C).

e. US FDA guidelines for New Drug Applications (NDAs) concerning impurities in new drug substances.

f. US FDA guidelines for Abbreviated New Drug Applications (ANDAs) on impurities in new drug substances.

g. Guidelines from the Therapeutic Goods Administration (TGA) in Australia. (2)

Table1: Regulatory guidelines (5)

Guideline	Depiction
Q1A	ICH guidelines "stability testing of new drug substances and products"
Q3A	ICH guidelines "Impurities in New Drug Substances"
Q3B	ICH guidelines "Impurities in New Drug Products"
Q3C	ICH guidelines "Impurities: Guidelines for residual solvents"
US-FDA	"NDAs -Impurities in New Drug Substances"
US-FDA	"ANDAs – Impurities in New Drug Substances"
Australian regulatory guideline	Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

As per the general principles provided by the ICH, the impurities in drug substances that are produced through chemical synthesis can be classified into the following three classes:

1.Organic Impurities (those associated with the process and the drug itself)

2.Inorganic Impurities (reagents, ligands, and catalysts)

3.Residual Solvents (solvents which are removed by distillation) (2)

1. Organic Impurities

Organic impurities can form before during or after a synthesis of a drug substance. These include the following:

•Starting Materials or Intermediate Impurities: In the event of multistep synthesis processes, impurities can be expected to arise as byproducts along with intermediates. There is usually a need for special precautions to ensure that the quantity of unreacted starting materials in the final product is kept as low as possible. Starting or intermediate impurities are probably found in APIs, unless glaring attention is paid to each step in the synthesis process. In general, the final products are washed with solvents such that the residual unreacted starting materials may remain unless manufacturers take due precautions in impurity control. As an example, a limit test is performed to check for the presence of p-aminophenol, an impurity that may find its way into some paracetamol preparations as a starting material for some manufacturers or as an intermediate by others.

•Byproducts: In organic chemistry, even 100% pure product is usually unattainable, as there will always be byproducts. This might arise from various side reactions-such as incomplete reactions, rearrangements, dimerization, overreactions, isomerization, or unintentional reactions between starting materials. For example, during the production of paracetamol, it is common that diacetylated paracetamol might have been formed as byproducts.

•Degradation Products: Impurities may form from the degradation of the final product in the bulk drug synthesis, and in most cases, such products appear during the storage and formulation of many dosage forms or through aging processes. For example, well-known degradation products include those from penicillins and cephalosporins. (3)

2. Inorganic Impurities

In most cases, the inorganic impurities in bulk drug formulations result as by-products of the manufacturing process. These impurities usually are well-known and can be readily identified as such.

a. Reagents, Ligands, and Catalysts

Such impurities are rare and appear only when manufacturing procedures are not strictly adhered to.

b. Heavy Metals

Water used during different operations can contaminate products with residual metals such as arsenic, cadmium, chromium, sodium, magnesium, and manganese, especially during acidification or acid hydrolysis. Using demineralized water and glass-lined reactors prevents the introduction of heavy metals.

c. Other Materials (Filter Aids, Charcoal)

Filtration aids-filters and Centro synthetic bags-are used in bulk drug manufacture together with activated charcoal, and they may introduce impurities. Regular checking for fibers and black particles in bulk drugs is requisite to ensure minimum contamination. (5)

3. Residual Solvents

Residual solvents are volatile organic compounds that are either introduced intentionally or produced in the pharmaceutical sector, during the synthesis. Eliminating these solvents altogether is practically impossible during the work-up period, but every effort must be made to minimize their levels to comply with safety standards. The use of certain toxic solvents should be limited accordingly in bulk drug production. Based on their potential impacts on human health, residual solvents are generally divided into three classes:

1.Class I Residual Solvents class substances are those solvents to be avoided or severely restricted in the production of excipients and drug substances because of their unacceptable toxicity or detrimental effects. Generally classified as carcinogens.

Table 2: Class I Residual Solvents -

Residual solvent	Concentration limit (ppm)
Benzene	2 (Carcinogenic)
Carbon tetrachloride	4 (Toxic)
1,1 Dichloro ethane	8 (Toxic)
1,2 Dichloro ethene	5 (Toxic)
1,1,1 trichloro ethane	1500 (Environmental hazard)

Other solvents include Class II. These are toxic solvents, and while their use is permitted in the pharmaceutical industry, they need to be controlled. Consequently, Class II substances are usually non-genotoxic but may be animal carcinogens or potentially neurotoxicants.

Table 3:other solvents

Solvent	Permissible daily exposure (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880

Class III solvents pose less of a toxicological risk to human health than Class I or Class II solvents, and no serious health hazard is associated with them. According to several reports, long-term toxicity is generally not observed. The acceptable levels of this class should be fifty milligrams or less. Examples that fit this class include acetic acid, acetone, anisole, and 1-butanol. (4)

Formulation Related Impurities Drug substance may vary with unfavorable conditions leading to its degradation or any other chemical reactions. Solutions and suspensions are known to undergo accelerated degradation by hydrolysis. The water used in formulation contributes its impurity and it stimulates hydrolysis and catalysis.[4]

5. Formulation-related impurity can be identified as:

i. Method Based ii. Environmental Based

The environmental factors which can be sub-classified under their influence on stability can be identified as:

a. Environmental Factors:

i. Temperature Exposure: Owing to heat or tropical temperatures, many substances become unstable. Vitamins are an example of heat-sensitive substances and easily lose potency when degraded by heat.
ii. Light Exposure: Light or UV rays can degrade photosensitive compounds that then form impurities.
iii. Humidity: Stability of bulk powders and solid dosage forms can be adversely affected by humidity.

b. Impurity Formations due to Aging

i. Mutual Interaction: Over time impurity formation may occur as ingredients in a formulation interact.

c. Functional Group Related Impurities

i. Ester Hydrolysis: Drugs such as aspirin, benzocaine, cefoxime, cocaine, and ethyl paraben may be fastened by ester hydrolysis processes.
ii. Hydrolysis: Drugs such as benzyl penicillin, barbital, and even chloramphenicol are subject to hydrolysis.
iii. Oxidative Degradation: Compounds that contain hydrocortisone, methotrexate, certain heterocyclic rings, or specific nitroso/nitrile groups may undergo oxidative degeneration.

Photolytic Cleavage: The formation of photolysis products may occur in any drugs exposed to light during manufacturing, hospital storage, or consumer use.

Decarboxylation: Some dissolved carboxylic acids such as para-aminosalicylic acid lose CO_2 when heated.[5]

Impurity Profiling of Drug Substance

Pharmaceutical drug substances can have various impurities that may affect their safety, efficacy, and stability. These impurities are often analysed using a variety of analytical techniques, as outlined by regulatory agencies like the International Conference on Harmonisation (ICH) and the U.S. Food and Drug Administration (FDA). Below is a list of some pharmaceutical drug substances and the techniques used to analyse their impurities, in accordance with these guidelines.

1. Drug: Atropine sulphate

- **Impurities:** Apo atropine
- **Techniques:**
    - UV-Visible Spectrophotometry
    - Mass Spectrometry (MS) [6]

2.Drug: Doxorubicin hydrochloride

- **Impurities: Acetone and ethanol**
- **Techniques:**
    - UV-Visible Spectrophotometry
    - Mass Spectrometry (MS) [7]

3. Drug: Framycetin sulphate

- **Impurities: Neamine**
- **Techniques:**
    - TLC [8]

4. Drug: Cimetidine

- **Impurities:**2,5-bis[(N'-cyano-N''-methyl) guinidinoethylthiomethyl]-4- methylimidazole and 1,8-bis[(N' cyano- N''- methyl)guinidino]-3,6- dithiaoctane
- **Techniques:**

    HPLC [9]

5. Drug: Norgestrel

- **Impurities:** 3,17α-diethinyl-13-ethyl-3,5- gonadiene-17-ol
- **Techniques:**
    - HPLC
    - TLC
    - UV spectroscopy [10]

6. Drug: Celecoxib

- **Impurities:** [5-(4-methylphenyl)-3- triflurомethyl-1H-pyrazole], 4- [5-(2'-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol1-yl]-benzenesulphonamide, and 4-[4-(4'-methylphenyl)-3-(triflurомethyl)-1H-pyrazole1-yl]-banzenesulfonamide
- **Techniques:**
  - HPLC
  - LC
  - LC-MS [11]

1. Drug: Methamphetamine

- **Impurities:** 1,2-dimethyl-3- phenylaziridine, ephedrine, methylephedrine, Nformylmethamphetamine, Nacetylmethamphetamine, Nformylphedrine, Nacetylephedrine,N,Odiacetylephedrine, methametamine dimmer
- **Technique:**
  - GC [12]

ICH limits / Parameter for impurities

The ICH guidelines on impurities in new drug products state that identifying impurities below the 0.1% level is generally unnecessary unless the impurities are anticipated to be exceptionally potent or toxic.[4]

As per ICH, the qualification threshold for maximum daily dose intake is as follows:

1] Identification Threshold - For doses less than 2 g/day: 0.1% or 1 mg/day intake (whichever is lower).

2] Qualification threshold: For doses greater than 2 g/day: 0.05%.

3]Recommended Threshold:

a. Table 4: Recommended Thresholds for New Animal Drug Substances

Identification	As per ICH Q3A(R2)* 0.20%
Reporting	As per ICH Q3A(R2)* 0.10%**
Qualification	0.50%

a. Higher reporting thresholds should be scientifically justified.

b. Table 5: Recommended Thresholds for New Veterinary Medicinal Products

Identification	1.0%
Reporting	0.3%
Reporting	1.0%

b. Lower thresholds may be appropriate if the impurity is unusually potent or has toxicity, immunological, pharmacological, or clinical concerns. [4]

Acceptance criteria for impurities in drug substances

Commonly accepted are a limit of 0.50% for identified impurities and 0.20% for unidentified impurities.

Acceptance in veterinary medicines

Generally, unwanted substances are not expected to be monitored or controlled in new veterinary drugs unless they are also degradation products. That is usually 1.0% for specified degradation products, whether they are identified or unidentified. (12)

Analytical Techniques Used:

a. **High-Performance Liquid Chromatography (HPLC):** High-Performance Liquid Chromatography, or HPLC, identifies and quantifies impurities in drug substances and is perhaps the most widely used technique for this purpose.High-Performance Liquid Chromatography (HPLC) is one of the key analytical techniques used in pharmaceutical laboratories for the analysis of impurities. HPLC is most famous for its ease of use, specific instrumentation, and inexpensive nature, and is indispensable for checking the safety and effectiveness of pharmaceutical products through the accurate detection and quantification of impurities.HPLC is a fundamental tool of the pharmaceutical industry, for impurity analysis. The importance lies in the reliability, versatility, and fundamental role it addresses in meeting regulatory standards. Together, these aspects assist in sontaining the pharmaceutical product's safety, efficacy, and quality.

(1) **The Ultra-High-Performance Liquid Chromatography (UHPLC)** is the next generation over conventional HPLC; its stationary phases are characterized by smaller particle sizes (normally less than 2μm). Of this immense improvement come certain advantages:

- Improved Resolution: The reduction in particle size has led to much improved separation efficiency of UHPLC columns, which accounts for higher resolution of very complex mixtures. This proves particularly beneficial in impurity analysis, where closely eluting compounds should be resolved.
- Enhancement in Rate of Analysis: Ultra-high-pressure liquid chromatography (UHPLC), being operated at higher pressure, allows faster analyses with no loss in resolution. Increased speed creates a greater laboratory throughput so that more and more samples can be processed in comparatively less time.
- Higher Sensitivity: Augmented separation efficiency and narrower bandtip in UHPLC contribute to make a method more sensitive and, therefore, able to detect lower levels of impurities. Being able to detect trace impurities is vital in identifying those that pose a direct risk to the safety and quality of pharmaceutical products.
- Less Solvent Required: The efficiency of UHPLC means less solvent required for the same analysis, which, in turn, reduces running costs and grants a consideration for the environment.

(2) - **HPLC-Coupled Mass Spectrometry (HPLC-MS)**

The coupling of HPLC with a mass spectrometer heralds a renaissance in impurity analysis, where the best of separation expertise provided by HPLC combines with the unmatched detection and identification capability of MS. Key advantages include:

- Better Detection
- Identification of structure.
- Full Profiling.
- Wide applicability.

Emerging Technologies in Impurity Analysis

New innovations developing along HPLC line:

- 2D-HPLC: This technique involves two HPLC columns with different stationary phases, providing an added layer of separation. This technique is really useful for complex samples with impurities that are closely related, since it brings in higher resolution and much better separation efficiency.

- Monolithic Columns: Monolithic columns are built from continuous porous material, allowing a high level of permeability and reduced back-pressure-and, hence-faster flow rates and reduction in analysis time without loss of resolution. Their toughness and efficiency ensure continued popularity.

- Green HPLC: Avoiding solvents and limiting hazardous waste have become the main drivers for adopting green aspects into HPLC methodologies. These include biodegradable solvents and the incorporation of SFC as a potential, sustainable alternative to conventionally HPLC.[13]

These developments, in combination with UHPLC and HPLC-MS, have greatly multiplied the possibilities for impurity analyses, thus enhancing the capability of the pharmaceutical industry to assure the general safety and quality of the produced product.

b. Gas Chromatography (GC): Commonly used for volatile impurities, residual solvents, and certain degradation products.

Introduction

A.T. James and P. Martin first time used the gas chromatography technique in 1952 for separating long chain fatty acids. The gases and vaporizable substances can also be separated by gas chromatography based on differential adsorption. In gas chromatography, gas is used as the mobile phase and solid or liquid is used as the stationary phase. When the stationary phase is solid, it is known as Gas Solid Chromatography (GSC) and when the stat ionary phase is liquid, it is known as Gas Liquid Chromatography (GLC). In gas chromatography, a moving gas phase is passed over a stationary sorbent to separate the mixture components. This technique is similar to that of liquid -liquid chromatography, with the only exception that in the former a moving gas is used as the mobile phase while in the latter it is a liquid. The stationary phase remains the same, i.e., a solid or a liquid.

Some applications of GLC are:

1) Detection of Steroidal Drugs

2) Analysis of Foods

3) Analysis of Dairy Products:

4) Drug Analysis

5) Separation of Metal Chelates. [14]

c. Nuclear Magnetic Resonance (NMR)

The Nuclear Magnetic Resonance is used to identify structural features of impurities and degradation products.

Nuclear Magnetic Resonance (NMR) spectroscopy is a highly versatile technique in the analysis of impurities, exploiting the magnetic property of certain atomic nuclei to probe the physical and chemical properties of different molecules. The importance to impurity analysis includes:

- Identification: NMR is very efficient in the identification of unknown impurities because every compound has really an individual one NMR spectrum. This uniqueness is quite unique as far as impurity identification is concerned, and one might not notice such impurities by the application of other techniques.

- Quantification: The quantification of impurities is possible using NMR spectroscopic techniques. Impurity signal intensities may be compared with a known reference for accurate measurement of impurity levels.

- Structural insight: In addition to the identification and quantification of impurities, NMR provides structural insights. This helps chemists understand how impurities interact with the main substance-a valuable asset in dealing with production problems and imparting adjustments to the processes required.

- Non-destructive testing: NMR is basically non-destructive in nature, which permits the preservation of the samples for use in other experimental techniques.

Importance in varied industries

The impurity profiling and control, therefore, are pertinent for many industries.

i. In the pharmaceuticals, it gives assurance for safety and potency to drugs.
ii. In the food industry, it guarantees public health-halt of contaminations.
iii. In aerospace and electronics sectors, it guarantees reliability and performance standards for critical parts [15].

d. UV-Visible Spectrophotometry

A method used for measuring substances that absorb light in certain wavelengths. Ultraviolet and visible spectroscopy concern themselves with recording the absorption of radiations in the UV and visible regions of the electromagnetic spectrum. The UV region extends from 10-400nm. It has two divisions: near UV (200-400nm, with parts made of quartz) and far or vacuum UV (10-200nm). The deep UV is 200-400nm. The visible region extends from 400-800nm. Absorption of electromagnetic radiation induces excitation of an electron from a lower to higher molecular orbital (energy levels). Because UV-visible spectroscopy deals with electronic transitions, it is most often called electronic spectroscopy. Organic chemists use UV and visible spectroscopy to detect the presence and elucidate the structure of conjugated multiple bonds or aromatic rings. The absorbance of a solution increases with increased sample path length. Absorbance increases with b and c, where b is the path length through which the beam passes and c is the concentration of the absorbing substance.

Main parts of a spectrophotometer are:
1) Radiation Source- D 2 lamp and Tungsten are found in a UV-visible spectrophotometer.
2) Wavelength Selector- It has three main parts;
i) Filters; mainly absorption and interference filters;
ii) Monochromator; which gives the required wavelength in the UV or visible region. iii) Two slits: entrance slit and exit slit.
3) Cells or Cuvettes: For holding the sample solution and pure solvent (reference).
4) Detector: The most common detectors are photo emissive cells, phototubes, and photomultiplier tubes.
5) Recording Device: For this purpose, a recorder pen is used.
6) Power Supply

There are two kinds of spectrophotometers:
1. Single-beam spectrophotometers,
2. Double-beam spectrophotometers.

Application

UV-Visible spectroscopy has been mainly applied for the detection of functional groups (chromophore), the extent of conjugation, detection of polynuclear compounds by comparison, etc. Some of the important applications are:

1) Detection of Functional Groups

2) Extent of Conjugation

3) Distinction in Conjugated and Non-Conjugated Compounds

4) Identification of an Unknown Compound

5) Identification of a Compound in Different Solvents

6) Distinguishes between Equatorial and Axial Conformations

7) Determination of Strength of Hydrogen Bonding

e. Thin Layer Chromatography (TLC):

A rapid, real-time method to identify the presence of impurities in comparison with known standards.

Thin layer chromatography is a sub-type of liquid chromatography with a liquid mobile phase and a stationary phase applied as a thin layer on a flat surface. TLC and paper chromatography can be combined to form planar liquid chromatography owing to the layered stationary phases or the paper being flat.

Mein, Hard, and Hall are credited for the first planned TLC technique in separating inorganic ions using starch-based binders in 1949. Kirchner proposed the classic conventional ascending skill of TLC. Izmailov and Shraiber first enunciated the principles of the TLC method. Stahl first designed the conventional apparatus for TLC, which resembles that of paper chromatography. TLC is a simple technique to achieve quick separation of the components of a mixture.

It utilizes a sheet of glass, plastic, or aluminum foil on which a thin, uniform layer of absorption (silica gel, aluminum oxide, or cellulose) is applied. This uniform absorbent layer is the stationary phase. The sample to be separated is applied over it through the stationary phase, and then a solvent or a mixture of solvents is allowed to travel upward along the plate through a capillary mechanism. Separation occurs when different analytes rise up the plate at different rates. [16]

f. LC-MS (Liquid Chromatography-Mass Spectrometry):

Combining the separation power of HPLC and the sensitivity of MS, it is mainly employed in the analysis of complex impurity profiles. LC-MS, also known as High-Pressure Liquid Chromatography-Mass Spectrometry, is an analytical technique that combines high-resolution chromatographic separation with highly sensitive and specific mass spectrometry detection. Such methods include High-Performance Liquid Chromatography (HPLC)-MS, Capillary Electrophoresis (CE)-MS, and Capillary Electrochromatography (CEC)-MS. Mixed Gas Chromatography with mass spectrometry first appeared in 1958 and became commercially available in 1967. The copulation of liquid chromatography and mass spectrometry arose during the 1980s and was considered a significant milestone for chromatography. LC-MS provides mass spectrometry with an important tool for identifying elemental composition and structural information concerning a sample.

Applications of LC-MS

LC-MS/LC-MS/MS is widely utilized in the food, pharmaceutical, and chemical industries for both quantitative and qualitative analysis. Some of the key applications of LC-MS/MS include:

-Molecular Weight Determination.

-Structural Determination/Elucidation

-Pharmaceutical Applications

-Clinical and Biochemical Applications: MALDI-TOF MS is used in applications such as SNP genotyping, DNA quantification, gene expression analysis, and DNA/RNA sequencing.

-Food and Environmental Applications

-Capillary Electrophoresis/MS Applications [17]

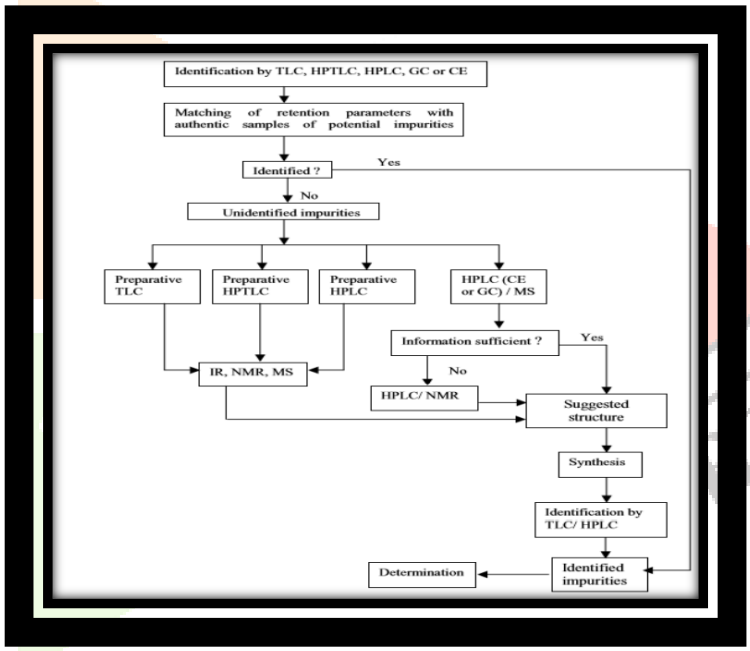

Figure no 1: Proposed chart for profiling drug impurity [18]

Discussion:

Remedies to Prevent Impurities in Pharmaceutical Products

i. Critical Manufacturing Factors: Critical factors during the manufacturing processes that affect the quality of a product should be monitored properly.
ii. Care of Operational Handling Equipment: While handling equipment, machinery, reactors, and instruments, a great deal of care should be exercised so that contamination will not result.
iii. Cleaning of Wet Cake: The cake should be washed thoroughly in order to remove any unwanted chemicals, such as residual solvents.
iv. Specification of Impurities: Product specifications must contain the maximum allowable impurity limits to ensure that quality is seriously addressed.
v. Periodic Review of Specifications: Specifications on drug substances and products should be regularly reviewed, allowing for an update of impurity profiles with acceptance criteria.

vi. Optimization of Analytical Methods: During the raw material/product analytical methods development and validation, parameters should be optimized to permit maximum detection of impurities that will help direct the synthetic chemists toward process optimization.

vii. Comprehensive Stability Studies: Such studies will ensure the detection and identification of the degradation products and, thus, establish the product's shelf life.

viii. Stress Testing: Stress investigations should be conducted to address possible transport-related issues and their influence on product quality.

ix. Packaging: Consideration should be given to environmental stress and moisture/light protection factors.

x. Regulatory Measures: Regulatory bodies should enforce more compliant standards while permitting companies to obtain licenses or approvals for products sold in regulated markets.

xi. FDA Approval and Compliance: Complete compliance with manufacturing standards must be ensured before the products are marketed, as pharmaceutical products directly impact human health. These measures, if strictly followed, could diminish the incidence of contamination issues in the sector.

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