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Review on: Ensuring API Integrity: The Role of Impurity Profiling

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Abstract

Different regulatory bodies, including the USFDA, ICH, and "Canadian Drug and Health Agency", give special attention to on identifying impurities and ensuring that active APIs meet purity standards. The process of gathering and evaluating information that outlines each impurity's biological safety is known as "qualification of the impurities." This method exposes the necessity and extent of "impurity profiling" of pharmaceuticals studies.

Chromatographic and spectroscopic methods are used to identify impurities; these methods can be used alone or in combination. Impurity detection and characterization can be done in a number of ways employing methods like "HPLC, AAS, HPTLC, TLC", etc. The disciplines of profiling impurities have made extensive use of conventional liquid chromatography, primarily HPLC; its variety of sensors, sensibility, stationary phases, and operational price effectiveness make it the industry standard. Effective separation has been attributed to the multifunctionality of its application. "Thin Layer Chromatography" is the most often utilized isolation method for impurity separation out of all the various types of planar chromatographic techniques since it is less expensive than HPLC and has a high degree of operational simplicity. An approach that is often utilized for impurity isolation is HPTLC, a variation of "Thin Layer Chromatography".

Among a most popular techniques for identifying residual solvents are headspace GC. Impurity profiling has been transformed by hyphenated techniques, which enable both solvent separation and structural identification of impurities. a combination of, "LC-NMR, LC-NMR-MS GC-MS and LC-MS" are the most popular hyphenated techniques for profiling drug impurities.

Keywords - ICH guidelines, Impurities, Standard analytical methods, Spectroscopy, Chromatographic Methods, Isolation.

INTRODUCTION

A drug product's purity is consequently assessed using an appropriate analytical method to ascertain the percentage of the indicated amount of API present in it. If certain contaminants have therapeutic efficacy comparable to or higher than the active ingredient in the medicine, their presence may not have a negative effect on its quality. Even though a drug material includes a contamination along with better toxicological or pharmacological characteristics, it can nevertheless be deemed compromised in terms of purity. Therefore, it necessary to assess the drug's properties purity separately from these unwanted extraneous components (such as inactive, harmful, or pharmacologically superior contaminants) in order to guarantee that the patient is receiving an accurate amount of the medication substance.[1]

"Profiling of Impurities" is the general term for a series to analyte evaluate procedures that include detection, identification, and quantitation of contaminants, including inorganic and organic, and residual solvents in pharmaceutical products and bulk medications. An amount or limits of impurities allowed to be found in the preparations or APIs are being increasingly included as various pharmacopoeias, including the USP (United States Pharmacopoeia), and the "British Pharmacopoeia" (BP). The following a ICH, USFDA and the "Canadian Drug and Health Agency" have been emphasizing that many impurities in API are present and their standards of purity. The ICH, USFDA, Canadian Drug and Health Agency, and other bodies are putting much emphasis upon a identification of impurities in APIs and purity requirements that need to be met.[2]

Impurity qualifications is the method for gathering and analysing information that proves given impurity's safety in a biological system, thereby demonstrating the need as well as the extent of drug impurity profiling in drug discovery research. ICH was released recommendations regarding contaminants in newly medicinal products and residual solvents. The API reference standards and the impurity-reference standards are in great demand among the pharmaceutical firms as well as among the regulatory agencies. Determination of impurity profiles in drug compounds as well as in related materials is among most significantly crucial tasks in modern examination of pharmaceuticals. For all contaminants more than 0.1%, detection should generally be made for the following reasons.[3]

Using the knowledge thus acquired, Chemicals that are synthetic organic involve frequently the ability to prevent the question in Impurities from forming as an alternative devise an extraction technique that will reduce its quantity to a manageable level.

Once an inevitable impurity's structure has been determined, it can be produced in large enough quantities to:

Conclusive proof of its structure;

Using for a "impurity standard"; and

Utilization in studies on toxicology

Aim and Objectives of Impurity Profiling

Impurity profiling: It means the detection and estimation of contaminants in pharmaceutical compounds. The main aims and objectives include,

Safety evaluation

Ensures that the impurities are not hazardous to patients' health by using their toxicological profiles.

Quality evaluation

It defines acceptable impurity levels, which ensures that the quality of the product will be uniform**.**

Regulatory compliance

Drugs can pass through different regulatory agencies, like FDA, & EMA, to meet the requirements for approval.

Process Optimization

Identification of impurities to enable an improvement of the manufacturing process by avoiding their creation.

Development of Product

Helping in development of the formulation on understanding how impurities affect stability and efficacy.

Stability Studies

Knowledge of stability of pharmaceutical products over time which can be affected by impurities.

Thus, the outcome of impurity profiling is achieved as a means to achieve the ends as it plays an important role in the development and manufacturing of safe and effective pharmaceutical products.

Advantages of Impurity Profiling

Impurity profiling has numerous benefits, especially in the fields of pharmaceuticals and material sciences, which are:

Quality Control

Evaluate the purity of the products., thus of quality with fewer chances of their presence being harmful.

Acts as a support for regulatory compliance

Helps in regulating compliance with the drug approvals and safety assessments

Stability Assessment

Determine the degradation products and help with stability studies of compounds over time.

Improved Formulations

Facilitates better efficacy and fewer side effects through determination of impurities which kind of impact they deliver.

Process Optimization

It helps in optimizing the production process as low in impurities as practicable.

Risk Management

Facilitates identification and quantification of such potential impurities that can raise the health risk.

Research and Development

This helps in further developing the chemical behaviors' understanding, thereby enabling the design of new compounds.

Consumer Trust

The culture builds transparency, so the trustworthiness is developed when dealing with customers due to high-quality standards for product quality.

Safety and Product Development Quality Impurity profiling in entirety is require soas to proceed standards in safety and product development standards.

Disadvantages of Impurity Profiling

Although it forms an important activity in any pharmaceutical and similar industries, impurity profiling carries some disadvantages with itself as well:

Complexity

It may involve sophisticated analytical techniques and requires vast technical expertise, especially in highly complex natural compounds.

Cost

It would demand high-priced apparatus and reagents, so the cost for production will be very expensive.

Time-Costly

Profiling can be highly time-consuming and, thus, a long period passes by before a new product can be formulated and launched into the market.

Regulatory Burden

Varying regulation requirements in various regions make compliance challenging.

Data Interpretation

Most of the times, data interpretation about impurities is highly challenging and, sometimes, misleadingly possible.

Resource Intensive

High quality laboratory resources with knowhow and time to develop methods are necessary.

Limiting Factors of Detection

Some impurities are missed due to low levels, or because a method is not sensitive enough.

Overemphasis on Impurities

Overemphasis on impurities may be at the cost of other critical product quality aspects.

These are contributing factors that may affect the effectiveness and efficiency of impurity profiling.

Regulatory Guidelines on Impurities in Drug

The "International Harmonization Conference" (ICH)guidance on technical specifications for pharmaceutical enrolment for the human utilization has been included by a US "Food and Drug Administration" (FDA). The FDA is tasked with making sure pharmaceutical medications are safe and effective.[4] The many regulatory guidelines pertaining to pollutants are as below:

Guidelines of ICH-(Q1. A) "stability testing of new drug substances and product".

Guidelines of ICH-(Q3. A) "Impurities in New Drug Substances".

Guidelines of ICH -(Q3. B) "Impurities in New Drug Products."

Guidelines of ICH-(Q3.C) "Impurities Guidelines for residual solvent."

Guidelines of ICH-(Q6. A) "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug products: Chemical Substances".

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

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

Therapeutic Governance Authority (TGA) of Australia's prescription medication regulations.

The International Harmonization Conference (ICH) Limits for Impurities

ICH categorizes & restricts an application of New Molecular Entities (NMEs). Variation in synthesis route, scale-up, and change in critical intermediates may alter the impurity profile of active pharmaceutical ingredients. Research must be done to make sure that the boundaries of impurities lie within the permissible limit set in Table No.1. Qualification process facilitates the collection of data along with its assessment that ensures the biological safety of a given impurity. [5]

Sr. No.	Daily dose maximum (a)	Reporting limit (b, c)	Determination limit (c)	Accreditation limit
1	> 2g/day	0.03%	0.05%	0.05 %
2	< 2g/day	0.05%	Consumption of 0.1% or 1 mg daily, whichever is less	Consumption of 0.15% or 1 mg daily, whichever is less

Table 1*: *Threshold

Where,

a is the amount daily dosage of the drug substance.

b is highest reporting thresholds must be supported by scientific justification.

cis reduced thresholds may be suitable if the impurity is particularly toxic.

Source of Impurities

A compound's characterization, quantization, and detection present a substantial analytical difficulty when it comes to drug discovery. Here, following we have summarized all classes of impurities.

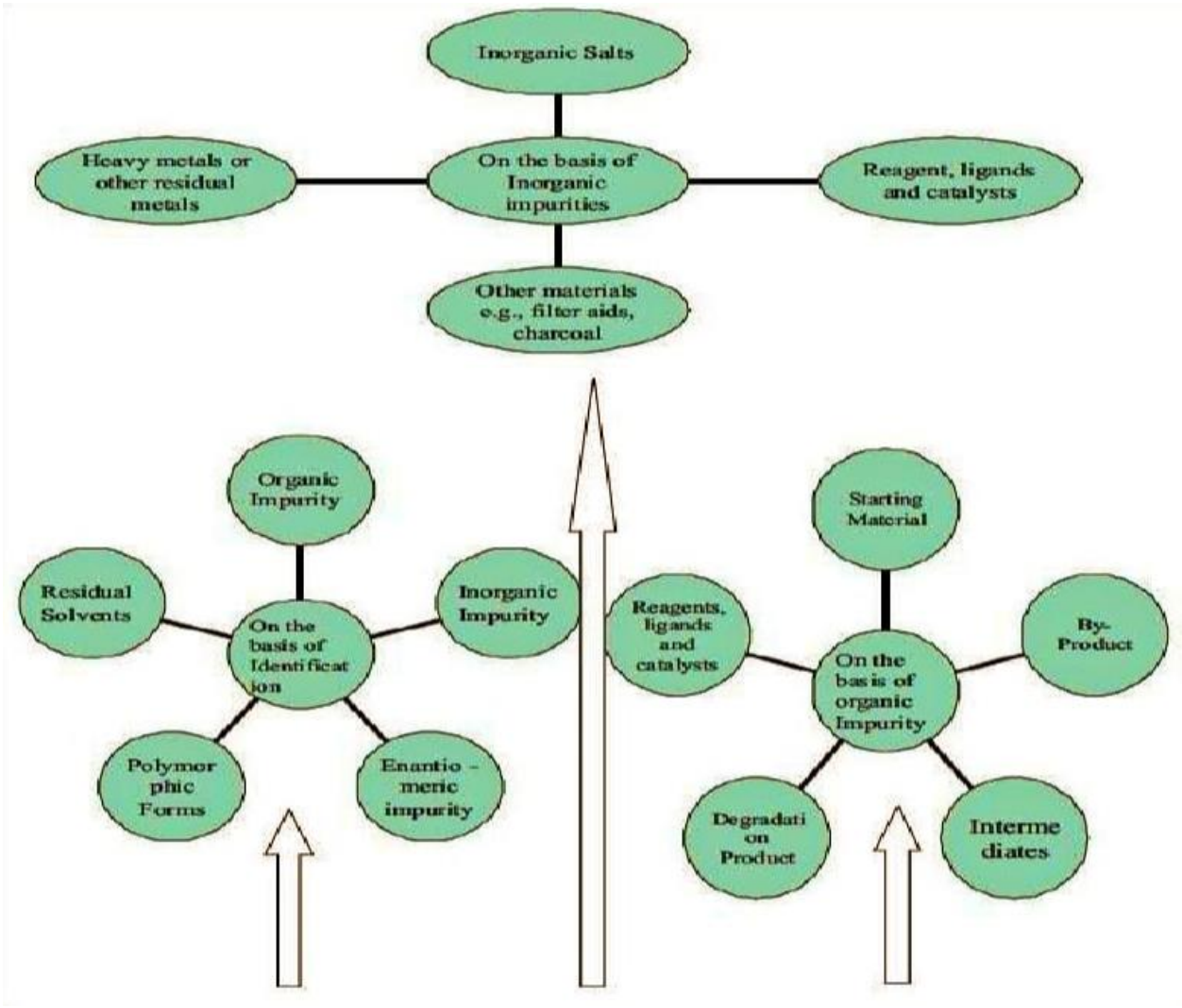

Figure 1*: *Source of Impurities

Impurities related to crystallization
Impurities linked to stereochemistry
Synthetic intermediate and by products
Residual solvent
Formulation related impurities
Impurity developed during storage
Method related Impurity
Interaction amongst ingredients
Functional group related typical degradation
Instability of the product

Impurities Related to Crystallization

The need of pharmaceutical industry for be careful about polymorphism and solventomorphism in the wake of guidelines of the regulating authorities because it was with such a requirement that the fact that the formation process of a compound's crystals could have a huge influence on the system's solid state came. That is called polymorphism when a substance may exist in many crystal packing configurations with the same elemental composition. On the other hand, solvatomorphism occurs when the same or a different substance forms different crystal packing arrangements with different elemental compositions.

Impurities Linked to Stereochemistry

In associated substances stereochemistry searching for those with a different spatial orientation but the same chemical structure is also necessary because such compounds may be considered contaminants in the APIs. Chiral compounds are commonly known as enantiomers. Now, the single chiral drug enantiomeric form is thought to be a better chemical entity than the racemic mixture with the potential of possessing a higher therapeutic index, a better pharmacological profile, and a more favorable adverse response profile. An absence of benefits of single isomer is represented by similar levofloxacin (S-isomeric form) and ofloxacin (R-isomeric form) pharmacokinetic profiles. Three of the most widely known single isomer drugs available in the market today comprise Lavalbuterol (R-albuterol), esomeprazole (S-omeprazole), and levofloxacin (S-ofloxacin).

Synthetic intermediate and by products

Raw materials, intermediates, and/or by-products are used in the synthetic process. can all become sources of impurities in medicinal compounds or novel chemical entities (NCEs). For example, using GC-MS to profile the contaminants in MDMA samples [6] and ecstasy pills resulted in intermediates containing impurities through the reductive amination route.

Residual solvent

These are impure solvents that can alter the properties of a specific compound or even be toxic to human bodies. Additionally, residual solvents change the drug's physical characteristics, including its crystallinity. Whichever impacts its ability to dissolve, thus affecting the change of color in the final product. Based Three groups of residual solvents are distinguished based on their potential health risks.

Class I Residual Solvents

Class II Residual Solvents

Class III Residual Solvents

Class I Residual Solvents

Due to their intolerable toxicity or adverse consequences, these solvents are either avoided or used sparingly in the production of excipients and medicinal compounds. In general, these are carcinogens. Examples of class l Residual Solvents show in Table No.2.

Sr. No.	Residual solvents	Limit of Concentration (ppm)
1	Carbon tetrachloride	4 (Toxic)
2	1,1 Dichloro ethane	8 (Toxic)
3	Benzene	2 (Carcinogenic)
4	1,1,1 Trichloro ethane	1500 (Environmental hazard)
5	1,2 Dichloro ethane	8 (Toxic)

Table 2*: *Residual Solvents of Class I

Class II Residual Solvents

Class II solvents are hazardous by nature; thus, they should only be used sparingly in the pharmaceutical industry. These are mostly non-genotoxic, possible neurotoxicants, and carcinogenic in animals. Examples of class II show in Table No.3.

Sr. No.	Residual solvents	Daily Allowable Exposure (mg/day)	Limit of Concentration (ppm)
1.	Pyridine	2.0	200
2.	Chlorobenzene	3.6	360
3.	Cyclohexane	38.8	3880
4.	Chloroform	0.6	60
5.	Dichloromethane	6.0	600
6.	Ethylene glycol	6.2	620
7.	Hexane	2.9	290
8.	Methanol	30.0	3000
9.	Acetonitrile	4.1	410
10	Toluene	8.9	890

Table 3: *The permissible daily exposure limits of class II residual solvents*

Class III Residual Solvents

They don't pose a significant risk to human health because they are less hazardous and less toxic than class I or class II solvents. Numerous data points indicate that long-term toxicity is typically not disclosed. Examples of class III show in Table No.4. [7,8]

Sr. No.	Residual solvents	Limit of Concentration (ppm)
1	Acetone	5000
2	Ethanol	5000
3	Ethyl acetate	5000
4	Heptane	5000
5	Isopropyl alcohol	5000

***Table 4*:** *Residual Solvents of class III*

Formulation related impurities

Excipients employed in the formulation of a medicinal ingredient can be the source of several contaminants the drug substance. Furthermore, throughout A pharmaceutical substance is subjected to certain conditions during the formulation process that may result in its deterioration or other unfavorable effects. Lot-to-lot variation could lead to a marginal product. That is unsatisfactory to be verified if the source is an excipient. The inherent vulnerability of suspensions and solutions either solvolysis or hydrolysis.[9] Topical Fluocinonide Solution USP with a strength of 0.05% was recalled in the US. stored in 60-mL containers due to sub-potency caused by deterioration and impurities.

Liquid dosage formulations are generally highly susceptible to microbial contamination and deterioration. Important considerations in this context include the primary container, anions and cations' compatibility, pH of the solution or suspension, water content and component interactions. An oral liquid product may result from microbiological growth brought on by the development of

yeast, fungus, and bacteria in a warm, humid environment. to become unfit for safe human use. Due to semi-permeable primary containers or improper application of specific preservatives in preparations, Contamination of microbes can happen throughout a multi-dose product's shelf life and subsequent usage by consumers. [10]

Impurity developed during storage

When storing or transporting pharmaceutical products, a variety of contaminants may arise. Stability studies must be performed in order to forecast, analyze, and verify pharmaceutical products' safety.

Method related Impurity

If diclofenac sodium is autoclave-sterilized, there occurs a well-known impurity during the preparation of a parenteral dosage form - 1-(2, 6-dichlorophenyl) indolin-2-one.[11] This implies with the autoclave method's conditions (i.e., 123 + 2 °C) in consideration, which requires those diclofenac sodium should undergo an intermolecular cyclic reaction, giving sodium hydroxide and an indolinone derivative, that it has been found that the contaminant is produced in a concentration depending on the formulation's starting pH.

Interaction amongst ingredients

Since the majority of 'vitamins' are highly volatile, and, with age, induce instability in any of the dosage forms presented, especially in liquid form. Although there are no harmful contaminants due to vitamin degradation, the strength of active components drops below the pharmacopoeial requirement. Within the shelf life of a year for injection of vitamin B-complex, it might be within a year that the existence with a formulation of nicotinamide that includes four vitamins, namely niacinamide, Thiamine, pyridoxine, and riboflavin, might motivate thiamine to degrade into an unsatisfactory level due to mutual interaction.[12]

The commercially available B-complex vitamins injection samples were determined to have a pH range of 2.8 to 4.0. Similar reciprocal interactions leading to deterioration were discovered when a customized formula using Simple distilled water and a traditional prepared vehicle that contained benzyl alcohol and disodium edetate were both examined.

Functional group related typical degradation

A few medications, including Cefotaxime, ethyl paraben an aspirin, benzocaine, and cefpodoximeproxetil [13] can be used to explain ester hydrolysis.

Hydrolysis is a regular occurrence for medications of the ester class, particularly for those with liquid dosage forms such as lincomycin, benzylpenicillin, and oxazepam.

Medication such as hydrocortisone, methotrexate, and the conjugated dienes (such as unsaturated free fatty acids and vitamin A), hydrocortisone, directly attached hydroxyl groups to aromatic rings (such as phenol derivatives for example morphine and catecholamines), Oxidative degradation can occur in Aldehydes, nitroso and nitrite derivatives, and heterocyclic aromatic rings (particularly flavourings).

Hydrolytic and oxidative breakdown of mazipredone pathways were examined at 80°C in sodium hydroxide and hydrochloric acid at 0.1 mol L-1. [14]

Examples of photolytic cleavage include pharmaceuticals that are exposed to the light in the form of a solid or solution during production, packing, and preservation for consumer usage in pharmacies or hospitals.

Photo-oxidation poses a serious risk to ergometrine, nifedipine, nitroprusside, riboflavin, and phenothiazines. Photochemical energy in sensitive materials produces free radical intermediates

that have the ability to restart chain processes. If exposed to UV light with high intensity radiation, the majority of compounds will break down into solutions. It has also been discovered that It has also been discovered that fluroquinolone antibiotics are sensitive to photolytic cleavage.[15]

Sunlight induces a photocleavage reaction in the preparation of ciprofloxacin eye drop (0.3%), which results in the production of a Ciprofloxacin analogue of ethylenediamine.

Certain Carboxylic acids that have been dissolved, such p-aminosalycylic acid', exhibit decarboxylation, which is the result of the carboxyl group losing carbon dioxide when heated. Rufloxacin photoreaction is an illustration of decarboxylation.[16]

As was previously seen, contaminants in pharmaceutical products might originate from the medicine itself, from excipients, or from an in-process step in which the drug comes into interact with the packaging materials.

For most drugs, the reactive species consists of;

The water has the potential to hydrolyse certain medications or affect how well dose forms work.

Aldehydes and derivatives of carboxylic acids are examples of small electrophiles.

Certain medications may be oxidized by peroxides.

The metals that have the ability to facilitate drug oxidation and degradation.

Plastic packing materials, rubber stoppers, and glass can all be extractable or leachable. Major substances that are removed or leached from glass are metal oxides that include NaO2, SiO2, CaO, and MgO. Leachable polymers and monomers, vulcanizing agents, plasticizers, accelerators, and antioxidants in general are present in the majority of synthetic substances.[17] Examples of synthetic compounds that can be extracted or leached include dioctyltin, diethylhexylphalate (DEHP, a plasticizer used in PVC), and styrene from polystyrene.[18] Captoacetate isooctylmer (a PVC stabilizer), Zinc stearate (a polypropylene and PVC stabilizer), 2-mercaptobenzothiazole (rubber stopper accelerator), and furfural from rayon.[19]

Various analytical techniques must be used to examine these impurities.

The Product Instability

Chemical Instability

Because the pharmaceutical substance is chemically unstable, impurities may form within storage. Poor storage conditions result in some pharmaceutically relevant materials to undergo chemical degradation. Amongst common catalysts to the chemical degradation are light, carbon dioxide, water vapor, residues from metallic contaminants, acidic or basic solutions and oxidation by air. Knowledge of the chemical parameters of the substance makes it simple to predict the nature of decomposition.[20] Storage conditions and practices could minimize or fully prevent any such decomposition.

Photo chemically degradable materials should be stored in darkened glass or metal containers to protect them from light. Moisture- or air-oxidation sensitive materials should be sealed in their containers. The containers may be sealed with inert gas such as nitrogen if displacing the inside air is essential. Oxidation can also be prevented by incorporating adequate antioxidants that can be oxidized despite the compounds' cost.[21]

Change in physical properties

During storage, there could be a physical property change of the drugs. Variation in the size and shape of the crystals as well as the suspended particles 'caking, agglomeration, and sedimentation' are possible. These unavoidable physical changes might widely affect the physical appearance, pharmacological properties, as well as the therapeutic benefits of the product.[22]

One major factor that dictates the bioavailability of a drug with low solubility, such as griseofulvin, is particle size and subsequently surface area. Physical alterations, for example settling and Using

clay in a suspension of many doses, pose a risk to safety because the likelihood of a drug overdose might be higher in the future.[23] Furthermore, lipid embolism can result from an Injectables emulsions' globule size increases while being stored.

Reaction with container material

It is not possible to entirely eliminate the possibility of a reaction between contents and container material that presents a safety hazard. Preparations which may react with surfaces of metal, like Ointment with salicylic acid, should not be packed in metal tubes. So, for instance alkali-sensitive substance solutions, such as injections of atropine sulphate, should be packed into glass ampoules withstanding the test of hydrolytic resistance. Thus, this type of preparation cannot be placed in soda glass containers.[24]

Because plasticizers and other unwanted additives can be released when non-aqueous solvents are present, plastic containers and closures need to be carefully considered. In addition to meeting the reduce the toxicity of animals in cats. For injectables, plastic containers should be adequately transparent to permit visual examination of the contents, as well as metal additions with particular regard to heavy metals like lead, tin, and cadmium as well as barium, as well as extractives soluble in ether. If the capacity exceeds 500 ml, these requirements must also be met. Rubber closures are more likely to absorption of antiseptics, bactericides, and medications from solutions unless they're properly prepped by being submerged in the relevant compounds' solutions. [25, 26]

Temperature

The temperature affects how quickly stored goods break down physically and chemically. To avoid undesired disintegration, the vulnerable chemicals might have certain temperature storage requirements. [27]

Standard Analytical Methodologies

In order to meet these requirements, an analytical technique must be sufficiently sensitive to detect trace amounts of contaminants. Because of this, analytical techniques that can be used to determine trace or ultratacelevels that is, nanogram scale level of different molecular species have been developed. There are numerous ways to keep an eye on contaminants. The capability to distinguish among us chemicals of concernis the main condition.

Significant & valid analytical information must be produced on different phases in the development of novel drugs.[28]

Selection of the sample set for the development of analytical methods.

The gradient elution linear solvent strength model is commonly used for analyzing chromatography conditions along with phases.

Process enhancement to improve ruggedness and ruggedness-related aspects

Listed below techniques are primarily useful for identifying the impurities:

Method of References Standard

Method of Spectroscopic

Method of Separation

Method of Isolation

Method of Characterized

Method of References Standard

Clarifying the reference standard for complete life cycle advancement and governance utilized in the creation and management for new drugs is the main goal of this. Reference standards are the standards for evaluating the safety of patient ingestion of drugs and constitute the foundation for

the evolution of process and product quality. These standards are required for contaminants, degradation products, starting materials, process intermediates, additives, and active ingredients in dosage forms. [29]

Method of Spectroscopic

Spectroscopy is the study of how matter absorbs, emits, or scatters light and other radiation**. or** The study of how matter and electromagnetic radiation interact is known as spectroscopy.

The spectroscopic techniques listed below can be applied

Ultraviolet (UV) Spectroscopic Method

Infrared (IR) Spectroscopic Method

Nuclear magnetic resonance (NMR) Spectroscopic Method

Mass Spectro-Photometry (MS)

Ultraviolet (UV) Spectroscopic Method

Analysis of UV on an identical wavelength offers very little specificity; however, the advent of diode array detectors (DAD) has made it feasible to obtain enough simultaneous information at many wavelengths to provide more selectivity. The UV region of electromagnetic spectrum range from 100-400nm.

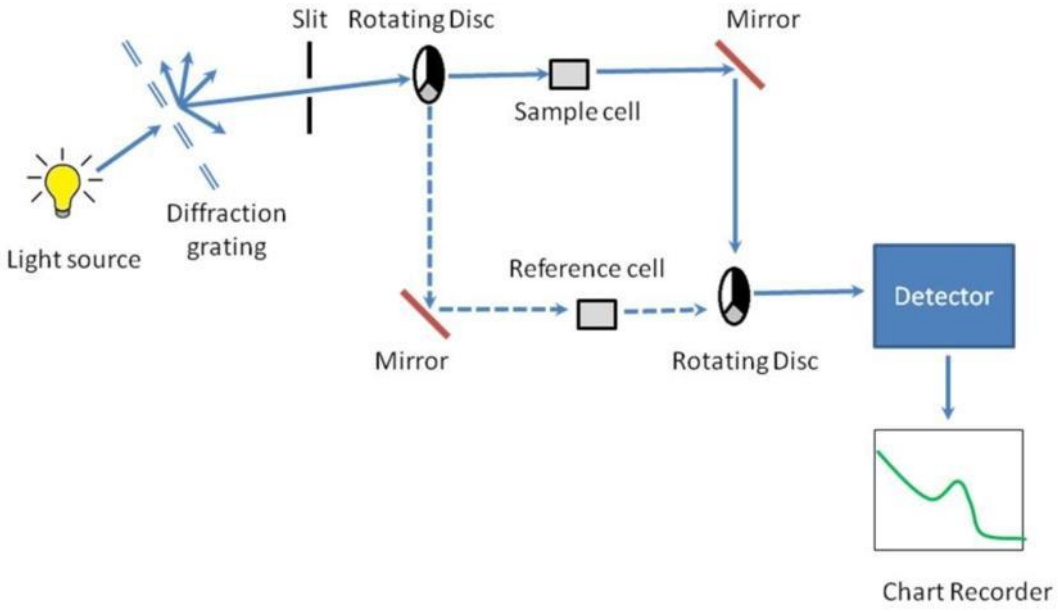

Figure 2*: *UV Spectrometer

Infrared (IR) Spectroscopic Method

IR spectrophotometry provides particular details on a few functional groups that could enable selectivity and measurement, Low level delectability, on another hand, is often an issue that may call for more complex solutions. The majority of the bands that reveal the type of functional group present are situated among 4000 and 1300 cm^{-1} as well as handprintarea between 1300 and 400 cm^{-1}.[30]

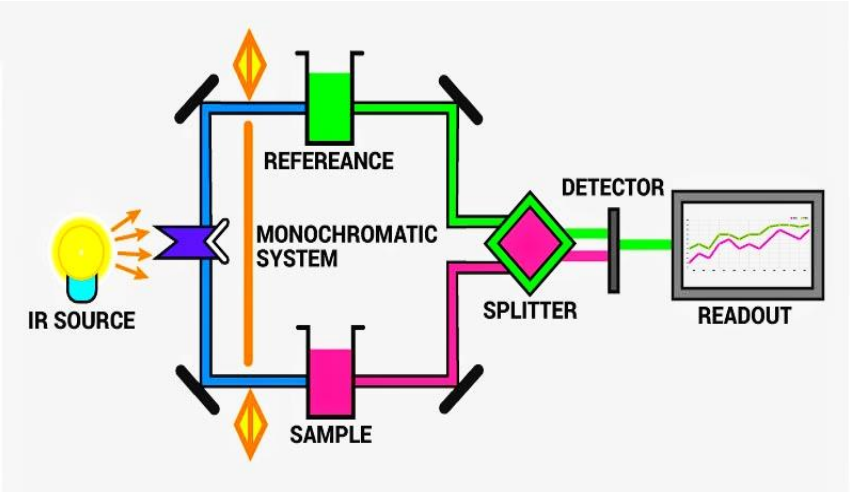

Figure 3*: *Infrared Spectroscopy

Nuclear Magnetic Resonance (NMR) Spectroscopic Method

The Magnetic Resonance of the nucleus Although spectroscopy is a highly helpful technique for characterizing impurities and offers reasonably structural information about a molecule, its application as a quantitative tool is limited due to time and expense.

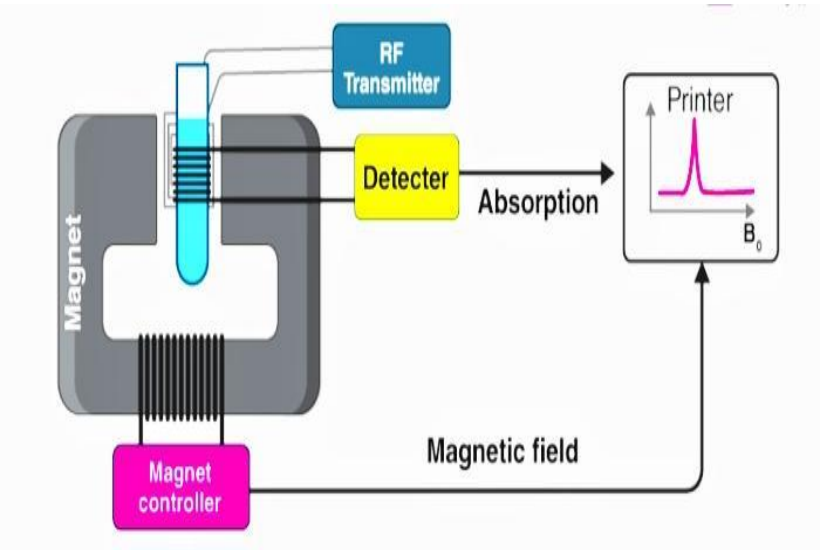

Figure 4*: *NMR Spectroscopy

Mass Spectro-Photometry (MS)

Excellent structural information is provided by mass spectrometry, and depending on the instrument's resolution, it could be a useful technique for distinguishing between molecules with slight molecular weight differences. Where due to time and expense constraint, its application as a quantitative technique is limited.

In conclusion, impurities that have been identified using any of the aforementioned approaches can be well characterized using IR, NMR, and MS. UV has been identified as being very helpful for high pressure analysis by “liquid chromatography” of the majority of materials.

Pharmaceutical analysis frequently uses this combination.

Methods of Separation

The separation techniques listed below can be applied

Thin Layer Chromatographic (TLC)Separation

Gas Chromatographic (GC) Separation

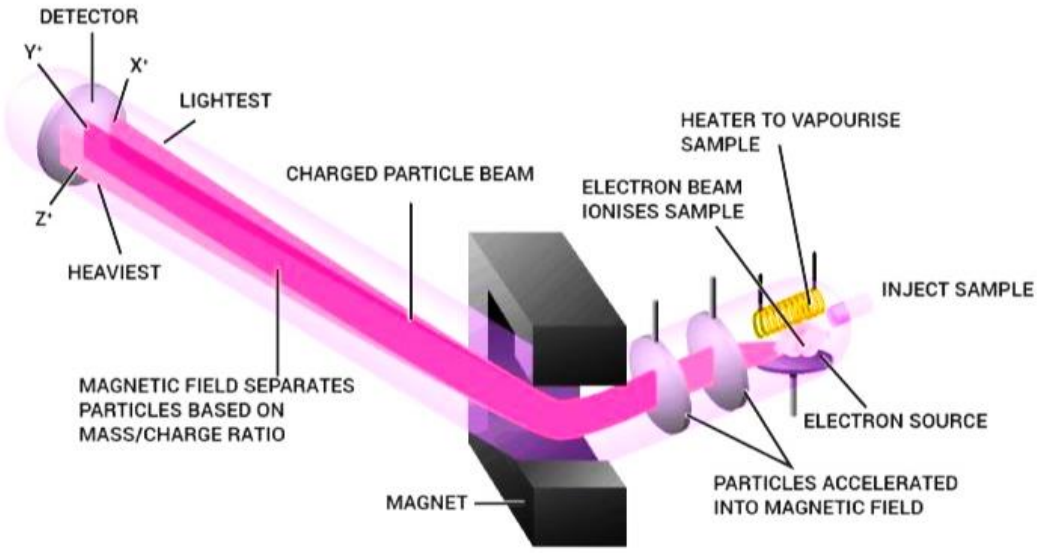

Figure 5*: *Mass Spectro-Photometry

High Performance Liquid Chromatographic (HPLC) Separation

Separation by Capillary Electrophoresis (CE)

Supercritical Fluid Chromatographic (SFC) Separation

Here is a quick overview of the techniques mentioned above and how they might be used. All of these procedures are chromatographic, with the exception of CE. Because it meets many of the same requirements as chromatography, CE, an electrophoresis method, is commonly included with chromatographic methods. It cannot be an efficient two-phase separation system, a basic need in chromatography.[31]

Thin Layer Chromatographic (TLC)Separation

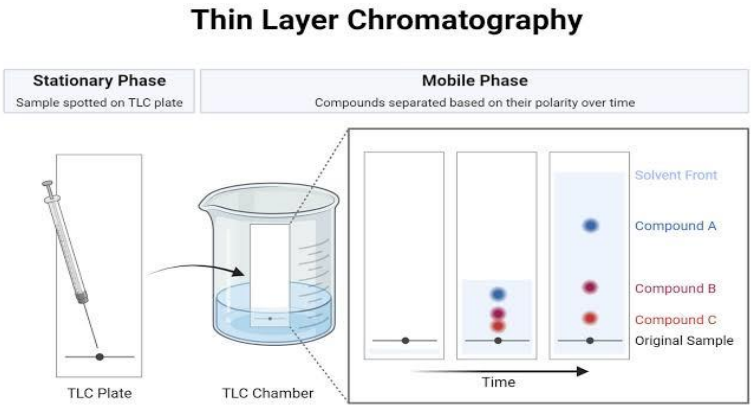

Figure 6*: *Thin Layer Chromatography

With “Thin Layer Chromatography” (TLC), a variety of compounds can be resolved by using diverse plates and mobile phases. This method's main drawbacks are its low resolution, detecting capabilities, and simplicity of quantification. The lowest cost and easiest of usage are the biggest benefits**.**

Gas Chromatographic (GC) Separation

A "Gas chromatography" (GS) is extremely effective technology to determination. May offer the required specificity, quantification and resolution simplicity. But the main drawback is that a specimen needs to be unstable or separated to make it unstable. Particularly helpful for organic volatile contaminants is this approach.

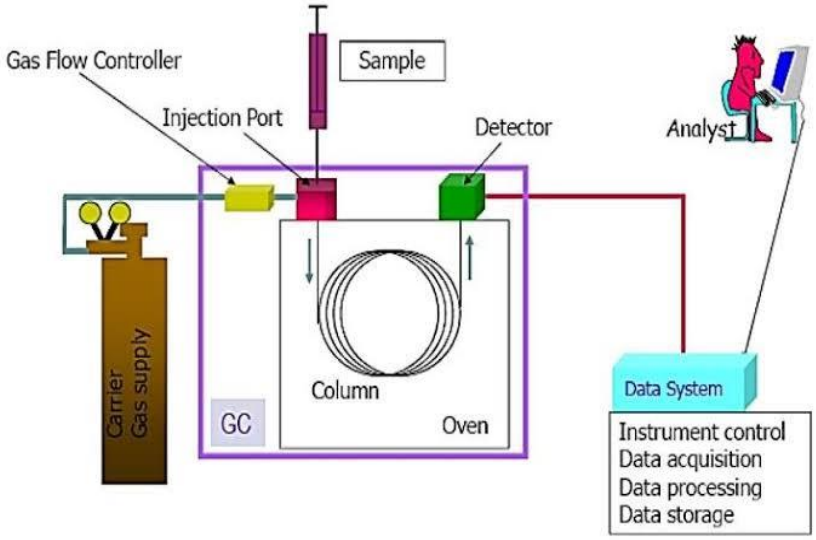

Figure 7*: *Gas Chromatography

High Performance Liquid Chromatographic (HPLC) Separation

These days, "High Performance Liquid Chromatography" is a colloquial term for high-pressure liquid chromatography. Chromatographers use all of this terminology interchangeably, and they can both be shortened to HPLC. This is a helpful method whose uses for pharmaceutical chemists have been greatly expanded by the employment of diverse detectors, including electrometric, MS, fluorescent, and so forth.

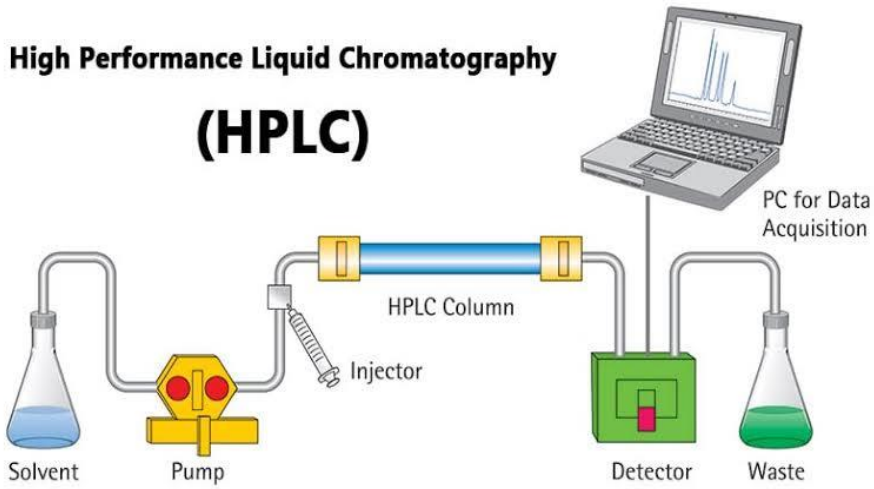

Figure 8*: *High Performance Liquid Chromatography

Separation by Capillary Electrophoresis (CE)

The method of capillary electrophoresis is helpful while extremely limited quantities of material are approachable and great resolution is necessary. Ensuring the repeatability of the injected samples is the main challenge**.**

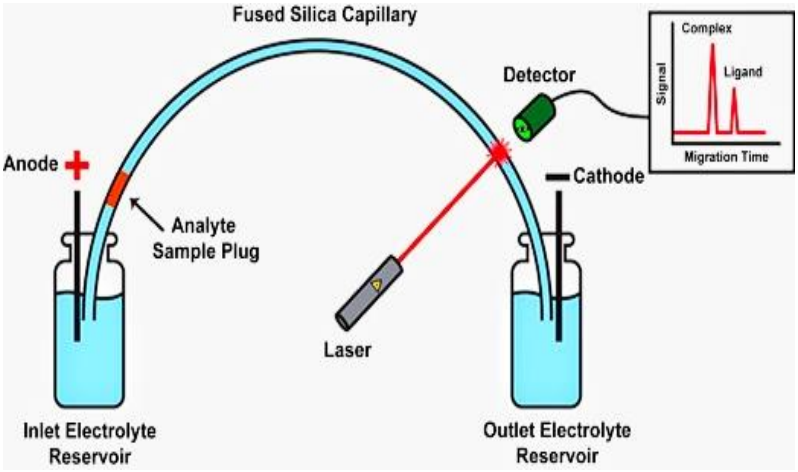

Figure 9*: *A Capillary Electrophoresis

Supercritical Fluid Chromatographic (SFC) Separation

Some of the benefits of supercritical fluid chromatography (SFC) in terms of detection and separation are due to the fact that sample mobility is not as important as it is with GC and HPLC. The largest use of this still-emerging technology has been found to be substance extraction.

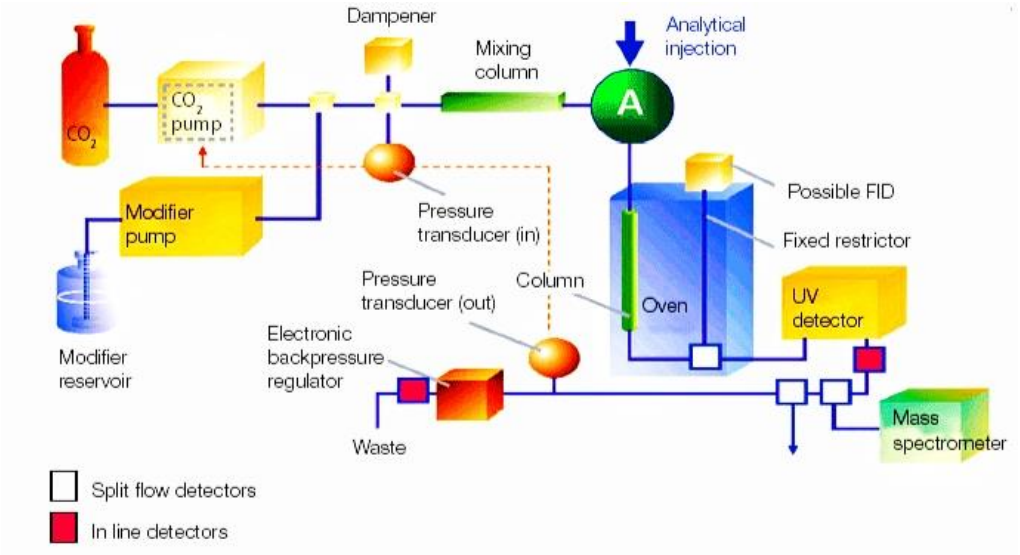

Figure 10*: *Supercritical Fluid Chromatography (SFC)

Method of Isolation

Isolating contaminants is typically required. However, when the instrumental procedures are implemented to prevent the isolation of impurities. as it describes the impurities directly. In most cases, impurities are separated before being characterized using non-chromatographic and chromatographic techniques. A utilization for every column of a quantitative analyzer as a reactor movement and a medium of distribution of the reactants output at the same time is referred to as a "chromatographic reactor." The study examined kinetics of hydrolysis in the solution phase offosaprepitantdimeglumine, an apropitant prodrug, by the use of HPLC and chromatographic reactor method. An impurity of loratadine was discovered in loratidin; more instances include 'celecoxib' and 'amikacin'.[32]

Below is a list of techniques that can be applied to impurity separation:

A Column Chromatography

Thin Layer Chromatography (TLC

Method of Solid-Phase Extraction

Gas Chromatography (GC)
Method of Liquid-Liquid Extraction
Capillary Electrophoresis (CE)
Method of Accelerated Solvent Extraction
Supercritical Fluid Extraction (SFC)
A Flash Chromatography
High Performance Liquid Thin Chromatography (HPTLC)

Method of Characterized

The characterized techniques listed below are useful for keeping checking on contaminants.
Gas Chromatography-Mass Spectroscopy (GS-MS)
Liquid Chromatography-Masa Spectroscopy LC-MS)
Liquid Chromatography-Diode Array Detector (LC-DAD)
Liquid Chromatography- Nuclear Magnetic Resonance (LC-NMR)
Liquid Chromatography – Tandem Mass Spectroscopy (LC-MS/MS)
High Performance Liquid Chromatography-Diode Array Detector-Mass Spectroscopy (HPLC-DAD-MS
High Performance Liquid Chromatography (HPLC)

Two distinct soft ionization methods- Ion Formation of d-allethrin chemically [33] and an ionization of the atmosphere's pressure using an electro spray source (API-ESI) are used as examples of reverse-phase analysis by LC-MS in gradient extraction.

The use to Liquid Chromatography– Tandem Mass Spectroscopy (LC-MS/MS) systems for evaluation of complicated mixtures of chemically unstable & physiologically significant chemicals, such Mosa pride, is mostly due to atmospheric pressure ionization's (APPI) and atmospheric pressure chemical ionization's (APCI) "soft" character. [34]

These and other methods, such as 'HPLC combined with a diode array UV detector and a mass spectrometer (HPLC-DAD-MS) are practically always employed.

Analytical Procedures

Method Development

Usually, the method development process comprises column and detector choice and mobile phase and quantization techniques. The following are the things that have Should be considered by account for approach improvements. The existing methods could be either not reliable (poor precision or accuracy) or artifact or contaminant prone or both. The present methods may not be easily automated, or they might be too costly, time- or energy-consuming. Current techniques, with such samples of interest, were incapable of offering enough sensitivity or selectivity regarding analytes. Maybe more advanced instrumentation techniques have developed, opening doors to better procedures with increased precision, quality, or limits for analyte identification or detection, as well as higher profits from financing.

Analytical Methods for Validation

In the process of validation, a created technique is confirmed or established through laboratory research, processes, and systems that may provide precise and repeatable outcomes for a planned analytical use within a range that has been tested and validated.[35] The method's performance characteristics (reactivity, precision, ruggedness, etc.) must satisfy the demands of the system and the desired analytical applications or procedure can or can offer recorded proof that it accomplishes its goals in a methodical, accurate, and dependable manner.[36] Typical analytical

performance parameters that are to be taken into account in the validation of all kinds of procedures, according to ICH. [37]

Impurities in marketed drug and the analysis methods

Sr. No.	Drugs	Impurities	Method
1.	Atropine sulphate	Atropine	UV Spectroscopy
2.	Amphotericin B	Teteaenes	UV Spectroscopy
3.	Dextrose	5-hydroxy methyl furfural	UV Spectroscopy
4.	Cloxacillinsodium	N, N-dimethyl	GC
5.	Adriamycin	Ethanol &Acetone	GC
6.	Ethambutol	Butanol-2-amine	TLC
7.	Morphine sulphate	5-(hydroxymethyl)2-furfural	HPLC
8.	Framicetin sulphate	1,3-diamino-2-propanol	TLC
9.	Morphine	6-monoacetylmorphine	HPLC
10.	10-hydroxymorphine	10- oxomorphine	HPLC

Table 5*: *Impurities in Marketed Drug and Analysis Method

CONCLUSION

Now, even in Pharmacopoeia, it is prescribed requirement that even today, the knowledge regarding such Impurities existing in the API'S is a must. The separation and description of these contaminants would be necessary to collating and analyzing information. This in turn forms the basis for biological safety; it actual reflect the requirement or the potential application of drug impurity profiling in pharmaceutical research. Isolation and quantitation of impurities require method for instrumental analysis that are in normal use.

REFERENCE

1. S. Gorog, Identification and Determination of Impurities in drugs, First Edition, Elsevier, Amsterdam, 2000, pp.38-42.
2. S. Ahuja, Impurities Evaluation of Pharmaceutical, Dekker, New York, 1998, pp. 123-129.
3. S. Ahuja, Overview Isolation and Characterization of Impurities, in: S. Ahuja, K. Alsante, Handbook of Isolation and Characterization of Impurities in Pharmaceuticals, Fifth Edition, Academic Press, San Diego, 2003, pp.1-3.
4. Savita D. Sonawane, Sanjay K. Bais, Ashlesha N. Gund, Drug Regulatory Affairs an Overview, International Journal of Pharmacy and Herbal Technology,2024:2(1):749-770.
5. Sanjay B. Bari, Bharati R. Kadam, Yogini S. Jaiswal, Atul A. Shirkhedkar, Impurity Profile Significance in Active Pharmaceutical Ingredients, Eurasian Journal of Analytical Chemistry,2007:2(1):32-53.
6. P. Jacobs, W. Dewe, A. Flament, M. Gibella, A. Ceccato, A New Validation Approach Applied to the GC Determination of Impurities in Organic Solvents, Journal of Pharmaceutical and Biomedical Analysis,2006:40(2):294-304.

7. Koji Urakami, Atsuya Higashi, Kazuichi Umemoto, Masayuki Godo, Matrix Media Selection for the Determination of Residual Solvents in Pharmaceutical by Static Head Space Gas Chromatography, Journal of Chromatography A,2004:1057(1-2):203-210.
8. Anil M. Dwivedi, Residual Solvent Analysis in Pharmaceutical, International Journal of Pharmaceutical Technology, 2003:115(5):33-41.
9. V. Buhler, Vademecum for Vitamin Formulation, Journal of Pharmaceutical Science,1998:142(13):36-47.
10. M. M. Hoq, S. B. Morsheda, D. J. Gomes, Development of Appropriate Preservative System for Liquid Antacid Bacterial Contaminants in Antacid Samples, Journal of Microbiology, 1991:8(1):5-9.
11. Jiben Roy, Mafizul Islam, Khan Anowar, Subodh C. Das, M. Akhteruzzaman, Ajay K. Deb, A. H. Mahbub Alam, Diclofenac Sodium Injection Sterilized by Autoclave and the Occurrence of Cyclic Reaction Producing a Small Amount of Impurity, Journal of Pharmaceutical Science,2001:90(5):541-544.
12. Jiben Roy, Miazddin Mahmud, A. Sobhan, M. Aktheruzzaman, M. Faooque, Erfan Ali, Marketed Vitamin B-Complex Injectables Stability and Mutual Interaction, Drug Development and Industrial Pharmacy,1994:20(13):2157-2163.
13. S. L. Hoerle, K. D. Evans, B. G. Snider, HPLC Determination of Impurities in A 3rd Generation Cephalosporine, Eastern Analytical Symposium,1992:2(1):16-20.
14. M. Gazdag, M. Babjag, J. Brlik, S. Maho, Z. Tuba, S. Gorog, Estimation of Profile of Drug and Related Materials Part 18, Impurities and Degradation Product of Mazipredone, Journal of Pharmaceutical and BiomedicalAnalysis,1998:17(6-7):1029-1036.
15. A. Smith, P. M. Pennefather S. B. Kaye, C. A. Hart, Fluroquninolones Places in Ocular Therapy, Journal of Indian Drug, 2001:61(6):747-761.
16. Jiben Roy, Diaa M. Shakleya, Patrick S. Callery, Dilip K. Sarker, Anwar H. Miah, Subodh C. Das, The Effect of Sunlight on Ciprofloxacin Eye Drop, Journal of the Mississippi Academy of Sciences 2005:50(4):224-230.
17. Diane M. Paskier, Strategy for Determining Extractable from Rubber Packaging Materials in Drug Products, Journal of Pharmaceutical Science and Technology,1997:51(6):248-251.
18. S. Malamatais, K. Tsiri, P. Goidas, Sorption of Moisture of Different Size Fraction of Some Direct Compression Excipients and Tensile Strength of Corresponding Tablets, International Journal of Pharmaceutical Science and Technology, 1992:6(5):195-204.
19. M. F. Aignasse, P. Prognon, M. Stachowicz, R. Gheyouche, D. Pradeau, A New and Rapid HPLC Method for Determination of DEHP in PVC Packaging and Releasing Studies, International Journal of Pharmaceutics,1995:113(2):241-246.
20. P. A. Michel, Influence of Processing Conditions on the Leaching Studies, International Journal of Pharmaceutics, 1998:113(6):241-256.
21. B. Ramchandra, Development of Impurity Profiling Methods Using Modern Analytical Techniques, Critical Review in Analytical Chemistry, 2017:47(1):24-36.
22. Sandor Gorog, The Importance and the Challenges of Impurity Profiling in Modern Pharmaceutical Analysis, Trend in Analytical Chemistry, 2006:25(8):755-757.
23. Rene Holm, David P. Elder, Analytical Advances in Pharmaceutical Impurity Profiling, European Journal of Pharmaceutical Science, 1997:87:118-135.
24. S. Nagpal, A Upadhyay, T. R. Bhardwaj, A Review on Need and Importance of Impurity Profiling, Current Pharmaceutical Analysis,2011:7(1):62-70

25. K. Pilaniya, H. K. Chandrawanshi, Recent Trends in the Impurity Profile of Pharmaceuticals, Journal of Advanced Pharmaceutical Technology & Research,2010:1(3):302-310.
26. P. Venkatesan, K. Valliappan, Impurity Profiling Theory and Practice, Journal of Pharmaceutical Science and Research, 2014:6(7):254-259.
27. S. Ahuja, S. Scypinsky, Handbook of Modern Pharmaceutical Analysis, Third Edition, Academic Press, United State of America, 2001, pp.1-22.
28. Deepti Jain, Pawan K. Basniwal, Forced Degradation and Impurity Profiling Recent Trends in Analytical Perspectives, Journal of Pharmaceutical and Biomedical Analysis,2013:86(1):11-35.
29. V. S. Tegeli, G. B. Gajeli, G. K. Chougule, Y. S. Thorat, U. S. Shivsharan, S. T. Kumbhar, Significance of Impurity Profiling a Review, International Journal of Drug Formulation and Research,2011:2(4):174-190.
30. Satindar Ahuja, HPLC Column for Pharmaceutical Analysis, in: S. Ahuja, M. Dong, Handbook of Pharmaceutical Analysis by HPLC, First Edition, Elsevier, United Kingdom, 2005, pp.77-115
31. P. N. Kavitha, P. Vijayanthimala, Instrumental Method of Analysis, Second Edition, Nirali Prakashan, Pune, 2013.
32. N. H. Zawilla, J. Hoogmartens, E. Adams, Improved RP-LC Method Combined with Pulsed Electrochemical Detection for the Analysis of Amikacin, Journal of Pharmaceutical and Biomedical Analysis, 2006:43(1):168-173.
33. J. Fiori, M. Bragieri, M. C Zanotti, A. Liverani, V. Borzatta, F. Mancini, V. Andrisano, LC-TMS for the Identification of Impurities in d-allethrine Samples, Journal Chromatography A, 2005:1099(1-2):149-162.
34. Y. Ravindra Kumar, J. Moses Babu, M. S. P. Sharma, B. Seshidhar, S. Srinivasa Reddy, G. Sudarsan Reddy, K. Vyas, Application of LC-MS/MS for the Identification of the Polarimpurity in Mosapride, a Gastroprokinetic Drug, Journal of Pharmaceutical and Biomedical Analysis, 2003:32(2):361-368.
35. Savita D. Sonawane, Sanjay K. Bais, Saurabh B. Navale, Introduction of Quality Control and Quality Assurance, International Journal of Advanced Research in Science Communication and Technology, 2023:3(1):386-403.
36. Savita D. Sonawane, Sanjay K. Bais, Suyash Kamble, Quality Control and Quality Assurance in Pharmaceutical, International Journal of Advanced Research in Science Communication and Technology, 2023:3(1):543-561.
37. Savita D. Sonawane, Sanjay K. Bais, Rutuja U. Dhandore, Quality control and Quality Assurance A Review, International Journal of Pharmacy and Herbal Technology, 2024:2(1):991-1012.