IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Pharmaceutical Impurities And Its Importance In Pharmacy: A review

Swapnil B. Chede*, Prof. Harishkumar Rathod, Dr. Swati Deshmukh, Amit A. Khune,

Shraddha institute of pharmacy Kondala Zamre, Washim-444505.

Shraddha institute of pharmacy Kondala Zamre, Washim-444505.

Shraddha institute of pharmacy Kondala Zamre, Washim-444505.

ABSTRACT:

Impurities within pharmaceuticals can be thought of as unwelcome companions that accompany the primary active ingredients. They can originate during the manufacturing process, formulation, or even emerge as a product ages. These impurities can significantly affect the purity and overall quality of both the drug substance and the final product intended for patients' use. Regulatory bodies are actively working to provide precise definitions and guidelines to ensure the safety and efficacy of pharmaceuticals for the well-being of patients. If you have any further questions or topics you'd like to delve into, please feel free to ask. An impurity in the context of pharmaceuticals refers to any substance found in the drug substance (bulk material) or the final drug product (in its container) that is not the specified chemical entity of the drug substance, an excipient, or any other additives intentionally included in the drug product. Impurities in pharmaceuticals can manifest as unwanted chemical compounds that either persist within the Active Pharmaceutical Ingredients (APIs) or arise during the formulation process or with the passage of time, affecting both the APIs and the formulated medicines. Some key analytical methods employed to identify and quantify these impurities include Thin Layer Chromatography (TLC) and spectroscopy. These techniques are crucial for ensuring the quality and safety of pharmaceutical products.

Keywords:

Impurity, Thin Layer Chromatography (TLC), Spectroscopy, Pharmaceutical impurities

Introduction: Impurities within pharmaceuticals encompass undesirable chemical entities that either persist within the Active Pharmaceutical Ingredients (APIs), emerge during the formulation process, or develop over time in both APIs and formulated medicines. These impurities consist of chemical substances present in pharmaceutical drug products and drug substances, lacking any therapeutic benefits, and, in some cases, having the potential to jeopardize patient safety if they exceed specific limits.

Impurities can be categorized into two types: identified impurities, which are those for which structural characterization information is available, and unidentified impurities, which can only be identified through qualitative analytical parameters (such as peak retention times) as structural details are yet to be determined.

In the realm of scientific research, modern separation methods are pivotal, as they enable the simultaneous separation and quantification of components. This dual capability greatly simplifies the task of isolating and characterizing impurities in pharmaceutical products, contributing to the assurance of product quality and safety.

The safety and quality of pharmaceutical products are intricately tied to the presence of impurities within the Active Pharmaceutical Ingredients (APIs). This underscores the significance of conducting comprehensive impurity profile studies on the APIs that will be used in drug substance manufacturing. Impurity profiling encompasses crucial steps such as identification, isolation, and characterization of impurities, ensuring that their levels adhere to the limits established and specified by regulatory authorities.

Various sources contribute to the emergence of impurities in pharmaceuticals:

1) Crystallization-related impurities: Impurities that arise during the crystallization process of APIs.

2) Stereochemical-related impurities: Impurities linked to stereochemical variations within the molecular structure of the API.

3) Residual solvents: Unwanted solvents that remain in the API after synthesis or processing.

4) Synthetic intermediates and by-products: Impurities that result from the intermediate stages of the API's synthesis or as by-products.

5) Formulation-related impurities: Impurities that can be introduced during the formulation of the drug product.

6) Impurities arising during storage: Impurities that develop over time as the API or formulated drug product is stored.

Addressing these diverse sources of impurities is critical to ensuring the safety and efficacy of pharmaceutical products, and it involves a meticulous and ongoing process of analysis and control.

Types of impurities:

1) Organic Impurities: Organic impurities are biodegradable substances and can include materials such as human waste, oils, animal excrement, urea (urine), fruit and vegetable remnants, food particles, etc. In the context of pharmaceutical chemistry, organic impurities refer to residual solvents produced during the synthesis of drug substances or in the manufacturing of excipients for drug formulations. Examples include starting materials, by-products, intermediates, degradation products, reagents, ligands, and catalysts.

2) Inorganic Impurities: Inorganic impurities typically originate from the manufacturing process. These impurities are non-biodegradable and can consist of metals, phosphates, nitrates, and other inorganic compounds.

3) Residual Solvents: Residual solvents are volatile organic compounds that are either used or generated during the production of drug substances, excipients, or the preparation of drug products. They are categorized into three classes based on their toxicity:

- **Class 1:** Class 1 residual solvents are substances that should be completely avoided in the manufacturing of drug substances, excipients, dietary ingredients, or official products due to their unacceptable levels of toxicity or negative environmental impact.

- **Class 2:** Class 2 residual solvents are compounds that should be limited in drug substances, excipients, dietary ingredients, and official products because of their inherent toxic nature.

- **Class 3:** Class 3 solvents are considered less toxic and pose a lower risk to human health compared to Class 1 and Class 2 residual solvents. They are often used in the pharmaceutical industry due to their lower toxicity levels.

Thin Layer Chromatography:

The origins of thin layer chromatography (TLC) trace back to 1938 when Izmailov and Shraiber embarked on the separation of plant extracts. Their pioneering work involved employing a 2mm thick, sturdy layer of alumina affixed to a glass plate.

Fast forward to 1944, and Consden, Goden, and Martin introduced a novel twist by utilizing filter papers for the separation of amino acids, marking a significant milestone in the evolution of TLC.

By 1950, Kirchner expanded the horizons of TLC by identifying terpenes using filter paper as the substrate. Later, he experimented with glass fiber paper coated with alumina, demonstrating the versatility of this technique.

However, it wasn't until 1958 that the full potential of TLC was realized when Stahl introduced standardized equipment for the analysis of compounds via thin layer chromatography. This development marked a pivotal moment in the history of chromatography, making TLC a widely adopted and indispensable tool in various scientific disciplines. In various scientific experiments, the ability to separate a mixture into its constituent chemical compounds is crucial, either for isolating a specific compound or assessing the mixture's purity. Thin Layer Chromatography (TLC) stands out as a widely favored method for achieving this, owing to its affordability, simplicity, rapid development, high sensitivity, and reliable reproducibility.

TLC finds utility across a multitude of industries and research domains, including pharmaceutical production, clinical analysis, industrial chemistry, environmental toxicology, food chemistry, water quality assessment, inorganic and pesticide analysis, dye purity testing, cosmetics evaluation, examination of plant materials, and herbal analysis.

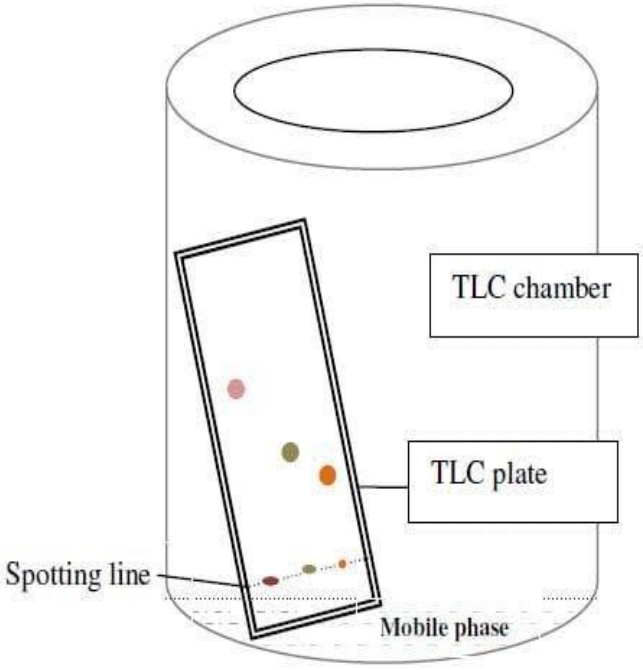
In its basic form, TLC involves applying a dissolved sample onto glass plates coated with a uniform layer of silica gel (SiO_2). These plates are then placed into a sealed container with a developing solvent and a piece of filter paper. As the solvent migrates up the plate, it carries the sample components with it. Once the solvent has nearly reached the top of the plate, the plate is removed, dried, and visualized using ultraviolet (UV) light.

Adaptations of this procedure are employed for various purposes, including pre-treating the sample, altering the sorbent material, plate composition, solvent system, development techniques, and methods of detection and visualization. Additionally, TLC can be integrated with other analytical techniques to enhance its capabilities and applications.

In Thin Layer Chromatography

There is Present 1) Stationary Phase: ex- Silica gel G.

2) Mobile Phase: ex- Chloroform.



Thin Layer Chromatography

Advantages of Thin Layer Chromatography (TLC):

1. Rapid Process: TLC is known for its simplicity and quick development time, making it a time-efficient analytical technique.

2. Visual Clarity: It provides a visual advantage by allowing easy visualization of separated compound spots on the TLC plate, aiding in qualitative assessments.

3. Isolation Capabilities: TLC is effective for isolating a wide range of compounds, making it a versatile tool for researchers and chemists.

4. High Selectivity: TLC offers high selectivity, meaning even subtle differences in chemical properties are sufficient for clear separation, enhancing its sensitivity.

5. Purity Assessment: TLC facilitates the straightforward assessment of sample purity standards, which is crucial in quality control and research.

6. Cost-Effective: It is an economical chromatographic method, making it accessible to laboratories with budget constraints.

7. Superior to Paper Chromatography: TLC offers faster and more efficient separation compared to paper chromatography, leading to the replacement of many papers' chromatographic procedures with TLC in modern analytical chemistry.

Spectroscopy:

spectrophotometry and its components:

A spectrophotometer is a scientific instrument that comprises two main types:

1. UV Spectrophotometer.

2. Visible Spectrophotometer.

Spectroscopy a branch of science is dedicated to the qualitative analysis of matter or samples using light, and the tool employed for this purpose is referred to as a spectrophotometer.

Key Components of a Spectrophotometer:

1. Source of Radiation: The ideal light source for a spectrophotometer should possess stability, intensity, and a spectral range spanning from 180 to 700 nanometers (nm). Various sources are utilized, including hydrogen discharge lamps, deuterium lamps, xenon discharge lamps, mercury arc lamps, and tungsten lamps.

- **Hydrogen Discharge Lamp:** Contains pressurized hydrogen gas and emits UV radiations when an electric discharge is passed through it. These lamps are stable and widely used.

- **Deuterium Lamp:** Similar to hydrogen lamps but filled with deuterium, offering higher intensity at a higher cost.

- **Xenon Discharge Lamp:** Operates with xenon at high pressure and provides greater intensity than hydrogen lamps.

- **Mercury Arc Lamp:** Emits sharp spectral bands but not continuous, limiting its use.

- **Tungsten Lamp:** Functions like an electric bulb but with some limitations, particularly at shorter wavelengths.

2. Wavelength Selector (Monochromator): The monochromator consists of filters, monochromators, and slits for selecting the desired wavelength.

- **Filters:** Filters offer radiation efficiency of around 50-80% and come in two types: absorption filters and interference filters.

- **Monochromators:** Used to disperse radiation based on wavelength, featuring an entrance slit, a dispersing element, and an exit slit.

Types of Monochromators:

- Prism Monochromator: A single-pass monochromator configuration is commonly used in spectrophotometers, dispersing radiation using prisms.

3. Sample Cells or Cuvettes: Transparent containers, often made of materials like quartz, fused silica, or silicate glass, hold liquid samples for analysis.

4. Detectors: Spectrophotometers employ photometric detectors to convert light signals into electrical signals. Common detectors include phototubes, photomultipliers, and photovoltaic cells.

- Phototubes: Composed of an evacuated glass tube with a photocathode and collector anode, producing a current proportional to incident light intensity.

- Photomultipliers: Employ the multiplication of photoelectrons through secondary emission, offering high sensitivity.

- Photovoltaic Cells (Barrier-layer Cells): Operate without batteries, generating a voltage difference when exposed to light, leading to current flow.

5. Recording System: The detector's signal is processed and displayed using a recording system, often involving a recorder pen.

Spectrophotometry is an invaluable analytical technique used in various fields, including pharmaceuticals, clinical analysis, environmental toxicology, and food chemistry, for its ability to qualitatively assess substances based on their interaction with light.

Conclusion: This review offers a comprehensive insight into impurities within drug substances and drug products, highlighting the growing significance of impurity profiling and the increasing emphasis on drug safety in the literature. The article presents valuable information regarding impurity types, their classification, isolation and characterization techniques, analytical methods for determination, and the essential considerations when preparing bulk drugs.

In today's regulatory landscape, it has become a mandatory requirement in various pharmacopoeias to identify and quantify impurities present in Active Pharmaceutical Ingredients (APIs) and finished drug products. As a result, impurity profiling serves as a vital Quality Control tool. It yields essential data pertaining to toxicity, safety, detection limits, and quantification limits of numerous organic and inorganic impurities commonly found alongside APIs and finished products. There is a pressing need for standardized specifications and standards concerning impurities to ensure pharmaceutical quality and safety.

Reference:

1. Impurities in New Drug Substances, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Guideline Q3A (R2), 2006. [Online] Available at: http://www.ich.org/LOB/media/ MEDIA422.pdf (Accessed on: November 12, 2014).

2. Ahuja S, Alsante K M. Handbook of Isolation and Characterization of Impurities in Pharmaceuticals, Vol. 5, Separation Science and Technology, Academic press, 2003.

3. Roy J. Pharmaceutical Impurities–a mini review, AAPS PharmSci Tech, 2002; 3(2): 1-8.

4. Federal Register (2000), ―International Conferences on Harmonization‖, Draft Revised Guidance on Impurities in New Drug Substances, Q3A(R), 45085-90.

5. International Conferences on Harmonization, Impurities—Guidelines for residual solvents. Q3C. Federal Register. 1997; 62 (247): 673-77.

6. International Conferences on Harmonization Specifications. Q6A: Test procedures and Acceptance Criteria for New drug substances and new drug products. Chemical Substances. 1999; 65 (146): 674-688.

7. International Conference on Harmonization guidelines Q3A (R) Impurities in New Drug Substances February 2002 (providing guidance for registration application on the content and qualification of impurities in new drug substances produced by chemical synthesis).

8. Alsante KM, Hatajik TD, Lohr LL, and Sharp TR. Isolation and identification of process-related impurities and degradation products from pharmaceutical drug candidates. Part 1. Amer. Pharm. Review. 2001; 4(1): 70-78.

9. ICH Harmonized Triplicate Guideline: Impurities in New Drug Substances Q3A (R2), ICH Steering Committee, Step 4 of ICH process, October 25, 2006.

10. Josephs JL, Sanders M, Shipkova P. Detection and Characterization of Pharmaceutical Metabolites, Degradants and Impurities by the Application of MS / MS Software Algorithms; Technical Program. February 25, 2007.

11. Ahuja S. Handbook of Modern Pharmaceutical Analysis. Academic Press. 2001; 298.

12. Poonam Kushwaha. The organic impurities in pharmaceuticals. Pharma info, 2008; 6(4).

13. Ahuja S. Isolation and characterization of pharmaceutical impurities evaluation. New York; Marcel Dekker. 2000.

14. Damle MC et al., Development and Validation of Stability Indicating HPTLC Method for Determination of Ofloxacin and Ketorolac Tromethamine in Combination, J. Adv. Sci. Res. 2011; 2 (3): 77-82.

15. Connor KA, Amidon GL, Stella VJ. Chemical Stability of Pharmaceuticals – A handbook for pharmacists. New York: John Wiley & Sons. 1986.

16. Parimoo P et al. 'A Text Book of Pharmaceutical Analysis', CBS publishers and distributors, New Delhi, 1998; 14.

17. Koji U. Atsuya H, kazuichi U, Masayuki G. Matrix media selection for the determination of residual solvents in pharmaceutical by static headspace chromatography, J. Chrom. A. 2004; 1057: 203 – 210.

18. Anil M. Dwivedi. Residual solvent analysis in pharmaceuticals. Int. J. Pharma. Excip, 2003: 33 – 37.

19. Tagg J. et al., Metabolic studies of tolbutamide in the rat. Beachem. Pharmacol. 16 (1) 143–153 (1967).

20. Ahuja S, (1997) Chiral Separations by Chromatography, Oxford University Press, NY, p-365.

21. Ahuja S and Scypinski S (2001) Handbook of Modern Pharmaceutical Analysis, Academic Press, NY, p. 298.

22. Ahuja S (1992) Trace and Ultra-trace Analysis by HPLC, Wiley, New York, p. 84.

23. ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: text and methodology Q2 (R1).

24. Roy J, Islam M, Khan AH, Das SC, Akhteruzzaman M, Deb AK, Alam AH M. Diclofenac sodium injection sterilized by autoclave and the occurrence of a cyclic reaction producing a small amount of impurity. J. Pharm. Sci. 2001; (90): 541-544.

25. Hogerzeil HV, Battersby A, Srdanovic V, and Stjernstrom NE. Stability of essential drugs during shipment to the tropics. BMJ. 1992; 304: 210-214.