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IMPURITY PROFILE: AN OVERVIEW IN PHARMACEUTICALS

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ABSTRACT

Impurity is nothing but the drug substance that containing any component, that is not the chemical matter it can define as a new drug or part of new drug. Impurity also can be any part of drug product or drug substance or excipients in the product. The process of adapting knowledge and evaluation of data that gives us safety from the particular impurity called the impurity profiling. To the pharmaceutical industries, it is a critical issue to supervise the impurities in the pharmaceutical substances and products. The regulatory authorities like US-FDA, ICH, MHRA, TGA etc, are mainly supervise and control the impurities in pharmaceutical products and API's. In the impurity profile, the multiple methods like spectroscopic and chromatographic techniques are used to evaluate and quantities the impurity in the drug substance and drug product. This review covers the study of source of impurity and also covers the necessity and comprehensiveness of impurity profiling in pharmaceuticals.

KEYWORDS: Impurity, New Drug, Impurity Profile, Pharmaceuticals, spectroscopic, Chromatographic techniques.

INTRODUCTION

Profiling of impurities is mainly concern with the representation of identified or unidentified impurities. The process of adapting knowledge and evaluation of data that gives us safety from the particular impurity called the impurity profiling.[1] An impurity as per ICH guidelines defined as "any component of drug substance that is not the chemical entity defined as new drug substance". It may affect the purity of active element or drug substance. During synthesis of chemical entity of drug product, impurities may be deliberately added or may be naturally occurred.

Impurity also can be any part of drug product or drug substance or excipients in the drug formulation. Therefore any unnecessary and unrequited material present in the drug material considered as an impurity or unwanted material, although it is totally inert or has a superior pharmacological properties.

The isolatation and gradation of impurity is done by variety of spectroscopic and chromatographic techniques. There are many different techniques for detecting and characterizing impurities with HPTLC, HPLC and TLC etc. Generally HPLC is widely used for detection and quantifying the impurities.

The estimation and quantification of impurity of many drugs can be used as method for control of quality and validation of many drug substances. The authorities like TGA, CGMP, MCA and US FDA which take controls profiling of impurities of the drug substances and products. In the new drug substances the impurities cab be inscribed by i) chemistry aspects include, impurities classification and identification, generation of reports, specification in which impurities are listed and a analytical procedures with their brief discussion. ii) Safety aspects includes, gives guidance for impurities qualification in the lower levels in manufactured batches of new drug materials used in safety and clinical studies.

CLASSIFICATION OF IMPURITIES

i) As per ICH guidelines

In the chemical synthesis, impurities produced can be classified into following categories;

- ✓ Organic Impurities (processing & drug related)
- ✓ Inorganic Impurities
- ✓ Residual Solvents

Organic impurities can be produced in the new drug material or arising during the process of manufacturing of materials.

They can be identified or unidentified, volatile or non-volatile and also include

- Raw materials
- By Products
- Intermediates
- Degradation Products

The impurities results from the process of manufacturing are nothing but the inorganic impurities. Normally they are known and identified and include;

- Reagents, Ligands and catalysts
- Heavy metals and other residual metals
- Inorganic salts
- Other materials like filter aids, charcoals

Residual solvents can be used as diluent for the manufacturing of solutions and suspensions which may be organic or inorganic liquids in the synthesis of drugs.[2,3]

ii) As per USP

The impurities described in USP can be classified in to various sections

- Impurities in official literature / publication.
- Ordinary impurities
- Organic volatile impurities[4]

LIMIT OF IMPURITIES

The ICH guidelines gives the limit for impurities in strange drug material , the estimation of impurities below 0.1%, are not as much considered necessary, unless they are potent or toxic. ***Table; 1*** gives an idea about the max daily dose threshold to be considered.

Table 1: New Drug Substance Impurities Threshold [2]

Maximum Daily Dose[1]	Reporting threshold[2,3]	Identification threshold[3]	Qualification threshold[3]
≤2g/day	0.05%	0.10% or 1.0mg/day intake (whichever is lower)	0.15% or 1.0mg/day intake (whichever is lower)
>2g/day	0.03%	0.05%	0.05%

Where,

1. The quantity of drug substance taken per day
2. Max reporting thresholds should be scientifically justified
3. Lower thresholds can be applicable if the impurity is unusually toxic

In summary, the new drug material stipulation should include, limits for;

i) Organic impurities:

- Each specified known impurity.
- Each specified unknown impurity at or above 0.1%.
- Any unspecified impurity, with absolute value of not more than 0.1%.

- Total impurities

ii) Inorganic impurities

iii) Residual solvents[2,3]

The residual solvents are classified as follows

Class I solvents: the solvents to be avoided

These solvents should be escaped in the pharmaceutical products known as human carcinogens and environmental hazards.

Table 2: solvents to be escaped in pharmaceutical products

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
CCl_4	4	Toxic and environmental hazard
1,1-Dichloroethane	8	Toxic
1,2-Dichloroethane	5	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class II: solvents used to be limited in pharmaceutical products

The class II solvents are carcinogenic or causative agents for irreversible toxicity, they are neurotoxic or teratogenic.

Class III: solvents with low toxic potential

The class III solvents are less toxic to man. These are solvents with low toxic potential, so no health based exposure limit is not needed. The amount 50mg of these solvents or less would be accepted.

Class IV: solvents for which no adequate toxicological data was found

The solvents of this class may be of interesting to manufactures of excipients, drug material and drug formulation. But there was no any acceptable toxicological data on which to base a Permitted Daily Exposure was found.[5]

Table 3; impurity type and their sources [6]

Impurity type	Impurity source
Process related drug substance	- Organic - Starting Materials - Intermediate

	- By-Product - Impurity In Starting Material
Process related drug product	- Organic or inorganic - Reagents, catalyst, etc.
Degradation drug substance or drug product	- Organic - Degradation products
Degradation drug product	- Organic - Excipients interaction

Isolation and Characterization

It is frequently necessary to isolate and characterize impurities on order to monitor them accurately, because approximate estimation of impurities are generally made against the material of interest (i.e. drug substance) and can be incorrect. These estimations are based on the assumption that impurities are structurally related to the material of interest and thus we have same detector response.[7] It is important to test this assumption because impurities frequently have different structures with significantly different detector response.[8] Most of the time it is difficult to ensure that the assumption stated above is correct.

Number of methods can be used for isolation and characterization of impurities. But the application of methods depends on the nature of impurity such that its structure, physicochemical and availability.[12]

The following methods are generally used for isolation of impurities

- Extraction
  - Liquid solid extraction
    - Soxhlet extraction
    - Steam distillation
    - Supercritical fluid extraction (SFE)
  - Liquid-liquid extraction
- Column chromatography
- Preparative separation

The impurities can be analysed by following methods

1. Ultraviolet spectroscopy
2. IR spectroscopy
3. NMR spectroscopy
4. Mass spectroscopy

5. Gas chromatography
6. HPLC[9]

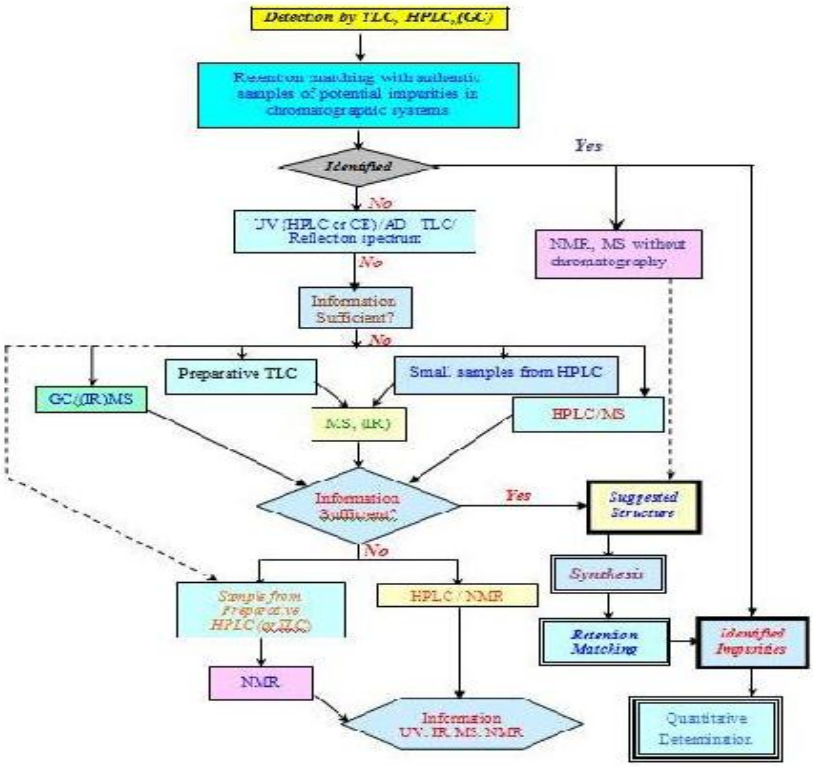

Fig 1; scheme for impurity profiling[10]

Application

Impurity profiling has many applications in drug designing, in monitoring quality, stability and safety of pharmaceutical compounds. This application includes alkaloids, analgesics, amines, antidepressant, antineoplastic agents etc.

Table 4; Goals of impurity profiling and investigation[11]

Process related impurities	Degradation related impurities
Identify significant impurities	Identify potential degradation product through stress testing and actual degradation products through stability studies.
Determine origin of impurities and method for elimination or reduction	Understand degradation pathway and methods to minimize this degradation.
Establish the control system for impurities involving; • Processing/manufacturing condition • Suitable analytical methods/ establish the specifications.	Establish the control system for impurities involving; • Processing / manufacturing condition. • Suitable analytical methods/ specification. • Long term storage condition including packaging • Formulation

CONCLUSION

The guidance for impurity profiling provides quality criteria in pharmaceuticals. This review gives knowledge on importance of impurity profiling drug substance and drug product in pharmaceuticals with various techniques of isolation and characterization of impurities.

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REFERENCES

1. Jain D, Basniwal PK. Forced degradation and impurity profiling: Recent trends in analytical perspectives. Journal of pharmaceutical and biomedical analysis. 2013 Dec 31; 86: 11-35.
2. Reynolds DW, Facchine KL, Mullaney JF, Alsante KM, Hatajik TD, Motto MG. Conducting forced degradation studies. Pharmaceutical technology. 2002 Feb; 48-56.
3. International Conference on Harmonization, Draft Revised Guidance on Impurities in New Drug Substances (2000) Federal Register Q3A(R), 65(140): 45085.
4. International Conference on Harmonization Draft Revised Guidance on Impurities in New Drug Product(2000) Federal Register Q3B(R), 65(139): 44791.
5. Guidance for Industry ANDA's: Impurities in Drug Substances, Draft Guidance, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. 1998.
6. International Conference on Harmonization Impurities Q3C – Guidelines for Residual Solvents (1997), Q3C. Federal Register, 62(247): 67377.
7. Bari SB, Kadam BR, Jaiswal YS, Shirkhedkar AA. Impurity profile: significance in active pharmaceutical ingredient. Eurasian journal of analytical chemistry. 2007; 2(1): 32-53.
8. Sharma R, Goyal A. An overview on scientific approaches for impurity profiling in new pharmaceutical substances and products: a review article. International Journal of Advanced Research in Pharmaceutical & Bio Sciences. 2014 Jul 1; 4(3): A1-.
9. Prabu SL, Suriyaprakash TN. Impurities and its importance in pharmacy. International Journal of Pharmaceutical Sciences Review and Research. 2010 Jul; 3(2): 66-71.
10. Pawale SS, Saley SP, Mundhada DR, Tilloo SK. Impurity profile in bulk drugs and pharmaceutical preparation. J Chem Pharm Res. 2012; 1(4): 1227-37.

11. S. J. Ingle, Advance Approaches for the Impurity Profiling of Pharmaceutical Drugs: A Review, IJPLS, July 2011; 2(7-suppl): 995-962.
12. Thakur A, Mishra B, Mahata PP. Pharmaceutical impurities: A review. International Journal of Pharmaceutical Chemistry. 2015 Jun 30; 5(7): 232-9.