WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 11, 417-425. Review Article ISSN 2277– 7105

REVIEW ON IMPURITY PROFILING

Dhavale Om Manikrao* and Katkar Chaitanya Pradip

Anand Charitable Sanstha's Collage of Pharmaceutical Science and Research Ashti, Dist. Beed.

Article Received on
27 July 2020,

Revised on 17 August 2020,
Accepted on 07 Sept. 2020,

DOI: 10.20959/wjpr202011-18672

***Corresponding Author**
Dhavale Om Manikrao
Anand Charitable Sanstha's Collage of Pharmaceutical Science and Research Ashti, Dist. Beed.

ABSTRACT

Impurities are is the undesirable chemicals or organic substances which remains with active pharmaceutical Ingredient (API's). The impurities is not acceptable for drug administration. The existence of these undesirable chemicals or substances may influence the safety and the efficacy of the pharmaceutical finished products. Highly sophisticated instrumentation such as mass spectra meters attached to a gas chromatography or HPLC are inevitable In identification of minor components (drug, impurities, degradation products, metabolites) in various matrices.

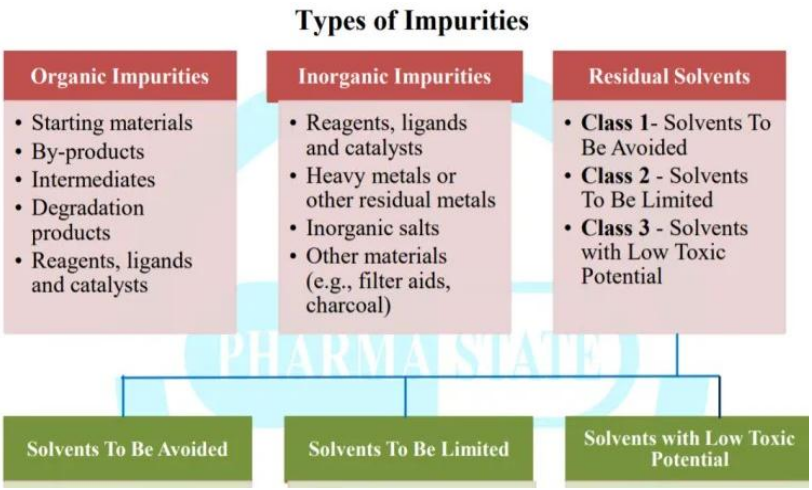
KEYWORDS: Impurity profiling, API, Gas chromatography, HPLC.

INTRODUCTION

Impurity profiling is the process of evaluating the data that establish biological safety of an individual impurity. For maintaining the stability or efficacy of the API we do the profiling of impurities. It helps in identifying and quantifying the impurities in API. It gives maximum possible types of impurities present in drug substance (API) and in pharmaceutical formulations. The impurity control in the pharmaceutical product is the main goal of the drug development and for controlling the impurity, there are various regulatory guidelines which monitored the impurities in API.

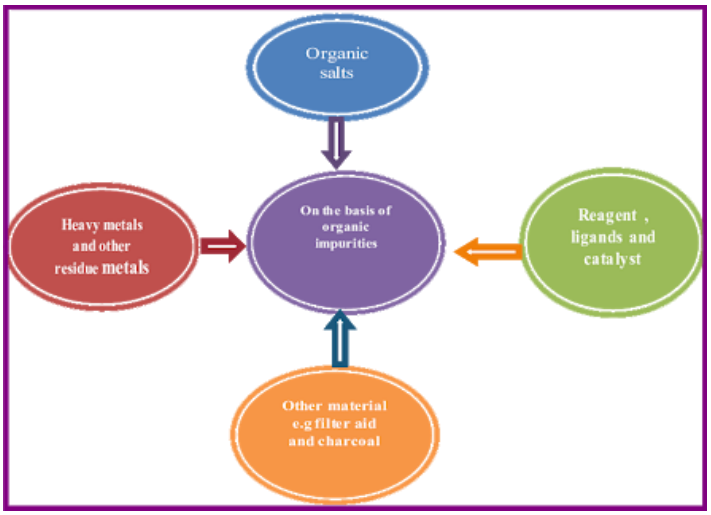
Classification of impurities in API

According to the ICH impurities are classified as organic impurities, inorganic impurities and residual solvents. Organic impurities may arise from starting materials, by products, synthetic intermediates and degradation products.



1) Organic Impurities

Organic impurities are mainly polyaromatic hydrocarbons (PAHs) (Taylor et al., 1980). They correspond to partially unconverted fuel that has been reabsorbed onto carbon black.



2) Inorganic impurities

Inorganic impurities may be derived from the manufacturing process and are normally known and identified as reagents, ligands, inorganic salts, heavy.

Organic impurities 1980). They correspond to partially unconverted fuel that has been reabsorbed onto carbon black.

Metals, catalysts, filter aids and charcoal etc. Residual solvents are the impurities introduced with solvents.

3) Residual solvent

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques.

As per ICH guidelines, the solvents are classified into three categories:

1) Class 1 Solvent

Solvents to be Avoided Known human carcinogens

Strongly suspected human carcinogens Environmental hazards. These solvents are not employed in the manufacture of drug substances, excipients and formulations because of their unacceptable toxicity effect.

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

Class 1: Solvents to be avoided in pharmaceutical products.

2) Class 2 Solvent

Solvents to be Limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 2 Solvents

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Solvents to be limited

Solvents in class 2 should be limited in pharmaceutical products because of their inherent toxicity. Examples of class 2 solvent in the below table.

Solvent	*PDE (mg/day)*	*Concentration limit (ppm)*
Acetonitrile	4.1	410
Chloroform	0.6	60
Cyclohexane	38.8	3880
Formamide	2.2	220
Methanol	30	3000
N-Methylpyrrolidone	5.3	530
Tetrahydrofuran	7.2	720
Xylene	21.7	2170
Toluene	8.9	890

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3) Class 3 solvent: Solvents with Low Toxic Potential Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents may have PDEs of up to 50 mg or more per.

Class 3 Solvents (Continue)

Examples of Class 3 solvents which should be limited by GMP or other quality based requirements.

Acetone	Methylisobutyl ketone	Ethyl ether
Acetic acid Heptane	Dimethyl sulfoxide	Ethyl formate
Anisole	Ethanol	Formic acid
Methyl acetate	Ethyl acetate	3-Methyl-1-butanol
Butyl acetate	tert-Butylmethyl ether	Isobutyl acetate
1-Butanol	Methylethyl ketone	1-Pentanol
2-Methyl-1-propanol	Heptane	Isopropyl acetate
2-Butanol	Pentane	1-Propanol

Identification of impurities

According to the ICH Q3A(R2) and Q3B(R2) guidelines, impurities in any dosage form, or API, must be identified during the product development. Additionally, any degradation product, observed in stability *studies* at recommended storage *conditions*, at a level greater than the identification threshold should also be identified.

1) Separation methods

HPLC Impurity profiling

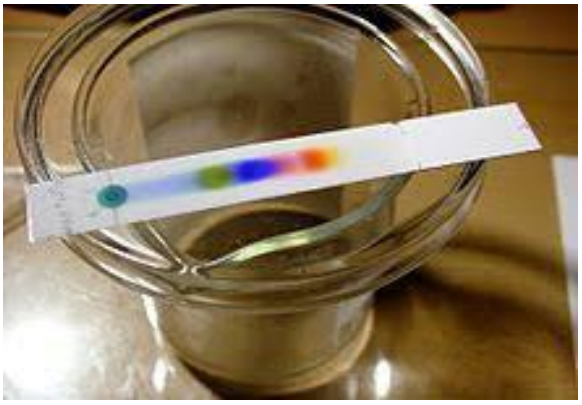
High performance liquid chromatography (HPLC) is routinely used for determination of both assay and impurities in both bulk active and formulated drug products. Impurity profile analyses are required to demonstrate the ability to detect a wide range of impurities which most impurity profile methods do not address the potential of co-elution of impurities with product peaks. UV photodiode array detection (PDA) evaluates the UV and/or the UV/VIS spectrum of an eluting species to determine spectral homogeneity. If variations in the spectrum are observed, the possibility of a co-eluting impurity must be addressed.

Gas chromatography (GC) impurity profiling

Gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS) are commonly used for the impurity profiling of illegal drugs. For the impurity profiling of methamphetamine, it is very important to obtain information about impurities related to the manufacturing route and the precursor chemicals [B. Remberg, A.H. Stead, Drug characterization/impurity profiling, with special focus on methamphetamine: recent work of the United Nations International Drug Control Programme, Bull. Narcotics LI (1999) 97–117.[1] There are many artifact impurities arising from the preparation of samples and conditions of GC. Moreover, some impurities pose a barrier to the statistical processing of methamphetamine profiling.

Thin Layer Chromatography

Thin layer chromatography (TLC) is a chromatography technique used to separate mixtures. Thin layer chromatography is performed on a sheet of glass, plastic or aluminum foil, which is coated with a thin layer of adsorbent material, usually silica gel, aluminium oxide or cellulose. This layer of adsorbent is known as the.



Thin layer chromatography finds many applications to determine the components that are contained in plants. It is also used for monitoring organic reactions and analyzing ceramides and fatty acids; for the detection of pesticides or insecticides in food and water; for analyzing the dye composition of fibers in forensics and identifying compounds present in a given substance, and for assaying the radiochemical purity of radiopharmaceuticals. A number of enhancements can be made to the original method, to automate the different steps, to increase the resolution.

4) ISOLATION METHODS

Solid phase extraction method

It is an extractive technique by which compounds that are dissolved or suspended in a liquid mixture are separated from other compounds in the mixture according to their physical and chemical properties.

SPE uses the affinity of solutes dissolved or suspended in a liquid (known as the mobile phase) for a solid through which the sample is passed (known as the stationary phase) to separate a mixture into desired and undesired components. The result is that either the desired analytes of interest or undesired impurities in the sample are retained on the stationary phase. The portion that passes through the stationary phase is collected or discarded, depending on whether it contains the desired analytes or undesired impurities.

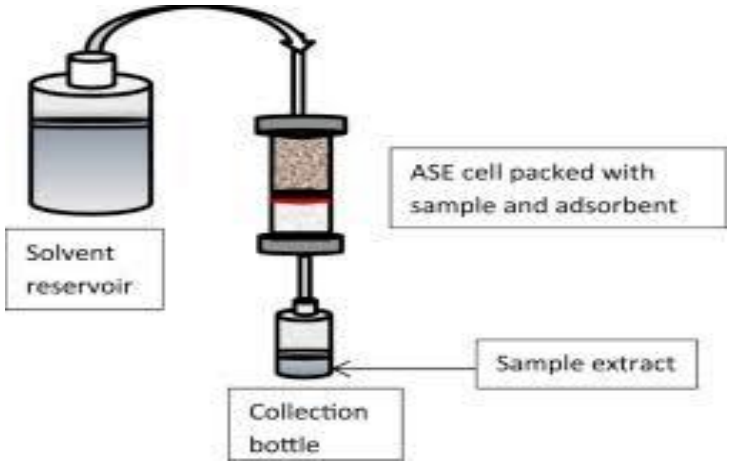
Liquid- liquid extraction method

Liquid – liquid extraction, also known as solvent extraction and partitioning, is method to separate compounds based on their relative solubilities in two different immiscible liquids, usually water and an organic solvent. It is an extraction of a substance from one liquid phase into another liquid phase. Liquid liquid extraction is a basic technique in chemical

laboratories, where it is performed using a separating funnel. This type of process is commonly performed after a chemical reaction as part of the workup.

Accelerated Solvent Extraction Method

Methods for the solvent extraction of organic analytes from a sample are provided. An organic solvent system is used to extract analytes under elevated temperatures and pressures above 100 psi but below supercritical conditions in short times and with low amounts of solvent. The extracted organic analytes are then removed by flowing a purge fluid through the extraction cell, the cell being maintained at a constant volume throughout the extraction and purging, afterwards the analytes being analyzed.



1) Spectroscopic methods

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

a) Ultraviolet spectroscopy: Impurity spectra have been measured and identified using a newly designed ultraviolet and visible (UV/visible) spectroscopic system in the tandem mirror GAMMA 10. It is constructed using two spectrometers to obtain an entire wavelength range of UV/visible impurity spectra with a high wavelength resolution in one plasma shot.

b) Infrared spectroscopy: In this work attention is focused on impurity profile analysis in combination with infrared spectroscopy and chemometric methods. A tree regression algorithm based

c) On infrared spectra is used to predict the relative content of impurities in the drug products investigated.

d) **Mass spectrometer:** Impurity isolation and subsequent off-line mass spectrometry have often been used to confirm the identity of drug impurities and degradates by comparison, if possible, to synthesised reference materials.

e) **NMR spectroscopy:** NMR spectroscopy is used in drug impurity profiling mainly after off-line or on-line separation of the impurities, this technique can be a useful tool even without full analyte separation.

CONCLUSION

Thus impurity profiling can act as a Quality Control tool. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantitation of several organic and inorganic impurities, usually accompany with APIs and finished products.

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