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Impurity Profiling of Pharmaceuticals

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Abstract

Impurity profiling is that the method of procure and evaluating data that establishes biological safety of a non-public impurity; thus, divulge its need and scope in pharmaceutical research. There isn't any clear definition for impurity within the pharmaceutical world. Impurity profiling includes identification, structure elucidation and quantitative determination of impurities and degradation products in bulk drug materials and pharmaceutical formulations. Impurity profiling has earn importance in modern pharmaceutical analysis because of the actual fact that unidentified, potentially toxic impurities are hazardous to health and then on extend the safety of drug therapy, impurities should be identified and determined by selective methods. Terms like residual solvents, by product, transformation products, degradation products, interaction products and related products are habitually accustomed define impurities. Identification of impurities is finished by diversity of Chromatographic and Spectroscopic techniques, either alone or along with other techniques. This review immerses various aspects related to the impurity profiling of a stuffed with life pharmaceutical ingredient.

Keywords*: - Impurity profiling, Impurities, Identification and isolation of impurities, validation, application*

INTRODUCTION

The bulk drug industry forms base of all pharmaceutical industries because it is that the source of active pharmaceutical ingredients (APIs) of specific quality. Over the previous couple of decades much

consciousness is paid towards the standards of pharmaceuticals that enter the market. The intense trouble for both bulk drug industries and pharmaceutical industries is to supply quality products. Purity of active pharmaceutical ingredient depends on several elements like raw materials, their method of manufacture and also the sort of crystallization and purification process. The pharmacopoeias specify not only purity but also puts limits which might be very stringent on levels of varied impurities. Impurity profiling is that the common name of a bunch of analytical activities, the aim of which is that the detection, identification, elucidation and quantitative determination of organic and inorganic impurities also as residual solvents in bulk drugs and pharmaceutical formulations. the various pharmacopoeias, like nation Pharmacopoeia (BP) and therefore the us Pharmacopoeia (USP) are slowly incorporating limits to allowable levels of impurities present within the API's or formulations.

Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and thus the identification of impurities in Active Pharmaceutical Ingredients (API's). International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances, products and residual solvents.

The estimation of impurity profiles in drug substances and related materials has become one altogether the foremost important fields of activity in contemporary pharmaceutical analysis. In general, all impurities present in more than 0.1% should be identified, for the following reasons:

1. On the concept of the info thus obtained synthetic organic chemists are often able to avoid the formation of the impurity in question or to develop a purification method to decrease its quantity to a tolerable level.

2. Following the structural identification of an unavoidable impurity, it should be synthesized to provide a sufficient amount for:
   a. Final proof of its structure;
   b. Its use as an "impurity standard";
   c. Its use in toxicological studies.

ICH Q3A covers drug substances and Q3B covers drug products. These guidelines define what investigations and documentation should be made in investigating impurities and degradation

products seen in stability studies at recommended storage conditions. In general, to keep with ICH guidelines on impurities in new drug products, identification of impurities below the 0.1% level isn't considered to be necessary unless the potential impurities are expected to be unusually potent or toxic in all cases, impurities should be qualified. If data aren't available to qualify the proposed specification level of an impurity, studies to urge such data are additionally needed (when the quality qualification threshold limits given below are exceeded). Per ICH, the utmost daily dose qualification threshold is taken under consideration as follows:

≤ 2g/day 0.1 % or 1 mg per day intake (whichever is lower) ≥ 2g/day 0.05%

Impurities commonly found in Medicinal preparations:

- Activity depressing impurities.
- Due to colouring or flavouring substances, e.g., Sodium Salicylate.
- Humidity.
- Decrease period of your time.
- Physical and chemical properties.
- Impurities due to which substances become incompatible.

IMPURITIES IN ACTIVE PHARMACEUTICAL INGREDIENT

For each API there should be an impurity profile describing the identified and unidentified impurities present in an exceedingly typical batch. The impurity profile is typically dependent upon the tactic or origin of the API.

1 per ICH guidelines, impurities related to API's is classified into the subsequent categories:

a. Organic impurities (Process and Drug-related)
b. Inorganic impurities
c. Residual solvents

a) ***Organic impurities*** can arise during the manufacturing process and/or storage of the new drug substance. They'll be identified or unidentified, volatile or non-volatile, and include:
   - Starting materials
   - By-products
   - Intermediates
   - Degradation products
   - Reagents, ligands and catalysts

b) ***Inorganic impurities*** may end up from the manufacturing process. they're normally known and identified and include:
   - Reagents, ligands and catalysts

- Heavy metals or other residual metals
- Inorganic salts
- Other materials (e.g., filter aids, charcoal)

c) ***Residual Solvents*** are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions within the synthesis of a replacement drug substance. Since these are generally of known toxicity. Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced within the manufacture of drug substances or excipients, or within the preparation of drug products. The solvents aren't completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics like crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter within the synthetic process. This guideline doesn't address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified. Since there isn't any therapeutic enjoy residual solvents, all residual solvents should be removed to the extent possible to satisfy product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than could also be supported by safety data. Residual solvents are often classified as follows,

Class 1 solvents (Solvents to be avoided): Known human carcinogens, strongly suspected human carcinogens, and environmental hazards. Example: Benzene, resolvent, Dichloro methane etc.

Class 2 solvents (Solvents to be limited): Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity like neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities. Examples: Acetonitrile, chlorobanzene, chloroform etc.

Class 3 solvents (Solvents with low toxic potential): Solvents with low toxic potential to man; no health-based exposure limit is required. Class 3 solvents have PDEs of fifty mg or more per day. Example: Acetone, acid, heptanes etc.

Table: 01 Class 1 solvents in pharmaceutical products (solvents that should be avoided)

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

Table: 02 Class 2 solvents in pharmaceutical products (solvents that should be avoided)

Solvent	Concentration limit (ppm)	PDE (mg/day)
Acetonitrile	410	4.1
Chlorobenzene	360	3.6
Chloroform	60	0.6
Cumene	70	0.7
Cyclohexane	3880	38.80
Dichloromethane	1870	18.70
1,4-Dioxane	380	3.8

ORGANIC IMPURITIES PRESENT IN FOOD PRODUCTS

A current interest of the food chemistry dedicated to the precaution of human health concerns synthetic dyes which are commonly added to a decent number of foodstuffs and largely preferred to natural colors, essentially because of their greater stability along the assembly process. The use of artificial change food incorporates an extended history. Within the 18th and 19th centuries, both 'unnatural' color and vegetable extracts were employed in food and drink. Sweets, as an example, were colored with chromate, mercuric sulfide, lead oxide and copper arsenite. Legislation and also the newly developed chemically synthesized dyes eliminated the utilization of these metallic compounds.

The synthetic dyes were much brighter, cheaper, more uniform, more stable (in their reactions to high processing temperatures, acids, CO2, storage and light) and fewer assailable (i.e., less may possibly be accustomed gain the identical effect) than anything seen before and offered a wider range of shades, so they'd great advantages over natural dyes furthermore because the utilization of recent dyes became more popular, their toxic properties also became apparent. Since that time, there has been an increase in synthetic dye use, but we have also become even more tuned in to toxicity.

The toxicity risk generally isn't due to the dye itself, whose use is regulated by EEC directives, but it would derive from impurities present in compounds utilized in the synthesis or from side-products formed within the synthesis process itself. Recently, very alarming sources of such an undesired product are envisaged within the degradation reactions that may naturally occur within the commercial products, because of unsuitable conservation conditions this is often the case of sentimental drinks that, in summer, are often exposed to strong conditions of temperature and sun light.

The dyes that are the foremost commonly employed in mixtures and in commercial soft drinks, namely: Tartrazine, Quinoline Yellow, Sunset Yellow,Carmoisine, Amaranth, New Cocaine, Patent Blue Violet, and Brilliant Blue FCF.

Overseas agencies have recently reported the presence of benzene in some beverages within the past, testing by the u. s. Food and Drug Administration also confirmed the presence of benzene in some soft drinks. Reformulation of some soft drinks was said to possess resolved the problem in some cases, but not all manufacturers have reformulated.

Many beverages contain vitamin C (vitamin C) and benzoate of soda. When benzoate salts and water-soluble vitamin are available contact with high levels of sunshine and/or heat, there's a powerful chance that a activity will occur. Benzene is that the merchandise of this process. Benzene formation may occur at part per billion (micrograms per kilo) levels in some beverage formulations. Benzoate could also be a permitted food preservative that may be added to many food products to form sure the microbiological safety of the food. Antioxidant is additionally an approved additive (antioxidant) which may be added to drinks. It also occurs naturally

in fruit and fruit juices. Vitamin C reacts with metals (copper, iron) found in water to create hydroxyl radicals, which react with acid to create low levels of benzene.

Worldwide there is not any specific benzene limit for soft drinks and drinking water; limits vary from country to country. The WHO potable guideline is 10 ppb which is used within the united kingdom and New Zealand, other water guidelines are 5 ppb within the US and 1 ppb in Europe and Australia. The National Health and Medical Research Centre (NHMRC) Water Quality Guidelines aren't mandatory standards; however they provide a guide for determining the safety and quality of potable. Benzene levels are likely to be higher in beverages where acid and antioxidant are deliberately added to create sure microbial safety.

ISOLATION AND IDENTIFICATION OF IMPURITIES IN ACTIVE PHARMACEUTICAL INGREDIENTS: [25-27]

The process of identification of impurities and/or degradants begins early in drug development. The first step of the strategy is to work out at what level the unknown impurity is present. per the ICH guidelines on Impurities in New Drug Substances, 'the studies conducted to characterize the structure of actual impurities present within the new drug substance at grade greater than 0.1% (depending on the daily dose, calculated using the response factor of the drug substance) should be described. Note that every one specific impurity at tier greater than the identification threshold in batches manufactured by the proposed commercial process should be identified. Degradation products observed in stability studies at recommended storage conditions should be similarly identified. When the identification of an impurity isn't feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included within the applying.'

Identification of impurities below the 0.1% level is sometimes not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic. Therefore it's imperative to work out the number of the unknown impurity early within the method. If the unknown impurity is below 0.1% threshold, then a discussion will need to happen among the project team members soon see if isolation and identification is very important. However, if the unknown is at or above the 0.1% limit, then effort should be put for isolation and identification.

a. **FTIR:** FTIR is incredibly pleasant for deciding and authenticating the structure of an impurity or degradant because it provides a fancy fingerprint that's specific to a selected compound. An FTIR spectrum of an organic molecule is decided by the functional groups present. The technique helps to spot the structure and measure the concentration of the compound under exploration. Changes within the structure may be coordinated with the assistance of an FTIR spectrum of a patent drug equated to it of the impurity or degradant.

b. **Preparative Liquid Chromatography (LC):** Since the impurities within the drug substance are usually present low at very quantities, detailed analysis is merely possible upon isolation of the impurities. However, this is often a serious challenge in pharmaceutical laboratories. Preparative LC helps isolate impurities (usually from impurity-enriched analytes, like the answer remaining from the crystallization of APIs) in sufficient quantities to hold out structural analysis, usually using techniques like FTIR, NMR, LC/MS, or GC/MS.

c. **Liquid Chromatography and Ultraviolet Spectrometry (LC/UV):** variety of impurity analysis methods found in pharmaceutical internal control (QC) laboratories use high-performance liquid chromatography (HPLC) including UV detection (HPLC/UV methods). UV spectrometry helps identify impurity or degradants in drug substances supported absorption maxima. This system is one amongst the foremost important and versatile analytical methods available for impurity profiling today because of its high selectivity (i.e., ability to quantitatively determine variety of the individual components present during a sample employing a single analytical procedure), especially for routine analysis where standards are available. Newer, stationary phase systems are available which operate in several modes, like ion pairing, increased hydrophobic interactions, and variable pH, allowing a spread of samples to be analyzed concurrently based upon their unique properties. High resolution is especially helpful when using LC/UV analysis for impurity detection, because all impurities will be identified with less chance of error.

d. **Liquid Chromatography and Mass Spectrometry (LC/MS):** LC/MS may well be a strong analytical tool that's routinely utilized in pharmaceutical development to test and identify product impurities. The detection limit of some hundred ppm is instantly achievable, ensuring the identification of all the impurities present at concentrations greater than 0.1 %. MS-based methods generally provide additional robustness and ruggedness compared to techniques like UV alone, thanks to their high specificity and sensitivity. While single quadruple mass spectrometers work well as analytical tools for the confirmation of known impurities and therefore the preliminary structural assessment of unknown impurities, sensitive Q-TOF mass spectrometers provide higher resolution and mass accuracy that allows the unambiguous identification of unknown trace impurities, making them very useful for genotoxic impurity analysis. MS-based methods are often selected for the impurity profiling of APIs during process development, while UV-based methods are generally used to test for genotoxic impurities in QC laboratories at manufacturing sites.

e. **Capillary Electrophoresis (CE):** The determination of drug-related impurities is currently the foremost important task for CE within pharmaceutical analysis because it achieves high separation efficiencies compared to other chromatographic techniques.

f. **Nuclear resonance Spectroscopy (NMR):** NMR may be a powerful analytical tool that permits the study of compounds both in solution and within the solid state. It's wide applicability because it provides specific information about bonding and stereochemistry within a molecule, which is especially important within the structural characterization of drug impurities and degradant often present only in extremely limited quantities. NMR may also provide quantitative output, a very important aspect of impurity profiling.

g. **Gas Chromatography (GC):** together with flame ionization detection (FID), GC is that the standard choice for the analysis of volatile organic impurities, like residual solvents. The gas chromatography headspace method is

employed worldwide for residual solvent analysis in internal control laboratories because it closely follows ICH Q3C guidelines. Sample preparation and introduction is via a static headspace which facilitates the selective introduction of volatile solvents without contamination by mostly non-volatile drug substance or drug products. More recently, the mixture of gas chromatography and spectrographic analysis (GC/MS) has been successfully used for confirmation and identification purposes, highlighting the flexibleness of this technology.

VALIDATION OF IMPURITY METHODS

The real goal of the validation process is to challenge the strategy and determine limits of allowed variability for the conditions needed to run the tactic.

In keeping with U. S. pharmacopoeia, 'Validation is that the process of providing documented evidence that the strategy does what it's intended to do'. It's important to own a well-conceived validation plan for testing the tactic and acceptance criteria before starting the validation process. During impurity profiling, the developed method has to be validated to fulfill with the compliances. The performance characteristics of assay validation include specificity, accuracy, precision, limit of detection, limit of quantitation, linearity, range, and robustness. In addition, it's also recommended that analysts should examine sample solution stability and establish an appropriate system-suitability testto verify the correct functioning of the equipment employed in performing the analysis.

APPLICATIONS OF IMPURITY PROFILING

Numerous applications are sought within the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids etc. There are some samples of impurities reported within the APIs mentioned in Table 3.

Table 03: various impurities reported in APIs

Numerous applications are sought within the areas of drug designing and in monitoring quality, stability and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods. The applications include different classes of medication namely alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic

Drug	Impurities	Method	Ref No.
Budensonide	Impurities or degradation products	HPLC	7
Cefdinir	Related substances	HPLC	8
Donepezil	Process related impurities	HPLC	9
Linezolid	Process related impurities	HPLC	10
Loratidine	Process related impurities	HPLC	11
Repaglinide	Process related impurities	HPLC	12
Rofecoxib	Process related impurities	HPLC	13
Zaleplon	Process related impurities	HPLC	14
AmphotericinB	Process related impurities	UV spectroscopy	15
Doxorubicin hydrochloride	Residual solvents	GC	16
Framycetin sulphate	Process related impurities	TLC	17
Cimetidine	Process related impurities	HPLC	18
Norgestrel	Related substances	TLC, HPLC & UV spectroscopy	19
Celecoxib	Process related impurities	HPLC, LC-MS-MS	20
Ethynodiol diacetate	Process related impurities	HPLC	21
Methamphetamine	Process related impurities	GC	22
Morphine	Process related impurities	HPLC	23
Morphine sulphate	Related substances	HPLC	24
Drug	Impurities	Method	Ref No.
Budensonide	Impurities or degradation products	HPLC	7
Cefdinir	Related substances	HPLC	8
Donepezil	Process related impurities	HPLC	9
Linezolid	Process related impurities	HPLC	10

agents, local anesthetics, macromolecules, steroids and miscellaneous.

CONCLUSION

Impurity profiling of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels in drug substances and products provides the standard criteria for manufacturers. The key aspect is that the impurity profiling of a replacement chemical entity must be shown to be qualified. With a qualification threshold of 0.1%, or lower for top dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology. Especially within the development phases it should be necessary to utilize methods with high selectivity, including hyphenated techniques. The importance of qualifying impurity profiles are relevant to the event scientists to confirm that due consideration is given to the impurities present within the batches getting used in safety studies. Beginning with limit tests for impurities, this field of impurity identification and quantitation has progressed. Isolation and characterization of impurities is required for acquiring and evaluating data that establishes biological safety which reveals the necessity and scope of impurity profiling of medicine in pharmaceutical research.

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