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NOVEL TECHNIQUES INVOLVED IN IMPURITY PROFILING

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ABSTRACT

Different administrative specialists, for example, the International Conference on Harmonization (ICH), the United States Food and Drug organization (FDA), and the Canadian Drug and Health Agency (CDHA) are accentuating on the immaculateness prerequisites and the ID of pollutions in Active Pharmaceutical Ingredients (APIs). The different wellsprings of pollutant in drug items are — reagents, weighty metals, ligands, impetuses, different materials like channel helps, charcoal, and such, debased final results got during \ subsequent to assembling of mass medications from hydrolysis, photolytic cleavage, oxidative corruption, decarboxylation, enantiomeric contamination, etc. The various pharmacopeias, for example, the British Pharmacopeia, United State Pharmacopeia, and Indian Pharmacopeia are gradually joining cutoff points to reasonable degrees of contaminations present in APIs or plans. Different strategies are utilized to disengage and portray debasements in drugs, for example, fine electrophoresis, electron paramagnetic reverberation, gas–fluid chromatography, gravimetric examination, superior fluid chromatography, solid-phase extraction techniques, fluid extraction strategy, Ultraviolet Spectrometry, infrared spectroscopy, supercritical liquid extraction section chromatography, mass spectrometry, Nuclear attractive reverberation (NMR) spectroscopy, and RAMAN spectroscopy. Among all hyphenated procedures, the most misused methods for pollution profiling of medications are Liquid Chromatography (LC)-Mass Spectroscopy (MS), LC-NMR, LC-NMR-MS, GC-MS, and LC-MS. This uncovers the need and extent of contamination profiling of medications in drug research.

KEYWORDS: Characterization, chromatography, identification, impurities, NMR, mass spectrometry.

INTRODUCTION

The pollutions in drug items can be credited not exclusively to the medication substance or latent fixings utilized for figuring a medication product; yet they can likewise be brought into the medication item through the plan cycle or by contact with bundling of the different debasements that can be found in drug items.

"Any segment of the medication item that isn't the synthetic element characterized as the medication substance or an excipient in the medication item." (ICH Q6A: Specifications). It is imperative to give more prominent thought to these impeding pollutions. As a rule, the greater part of these pollutants are little atoms. This is particularly evident in strong measurement structures where the restricted versatility limits the reactivity of bigger atoms. For most medications, the receptive species comprise of water (which can hydrolyze a few medications or impact the measurement structure execution), little electrophiles (e.g., aldehyde and carboxylic corrosive subsidiaries), peroxides (which can oxide a few medications), and metals (which can catalyze oxidation and other medication corruption pathways). Also, some impurites can cause toxicological issues. The presence of these undesirable synthetic substances, even in limited quantities, may impact the adequacy and security of the drug items. Pollutant profiling (i.e., the way of life just as the amount of debasement in the drugs), is presently accepting basic consideration from administrative specialists. The various pharmacopeias, for example, BP (British pharmacopeias), USP (United States pharmacopeias), IP (Indian pharmacopeias, etc, are gradually joining cutoff points to the reasonable degrees of debasements present in dynamic drug fixings (APIs) or definitions. The enormous number of mixes under scrutiny in drug disclosure presents a critical investigative test for the identification, quantitation, and portrayal of the mixes alone. we have summed up all classes of pollutions.

Importance

1. Differentiate between synthesis related impurities & degradation products.
2. For pharmacological screening up to the scaling up procedure & finally the production of bulk drugs.
3. All phases of synthetic drug research & production from the gram scale preparation of new compounds.

ICH Limits

According to the ICH guidelines on impurities in new drug products, identification of impurities below 0.1% level is not considered to be necessary, unless potential impurities are expected to be unusually potent or toxic.

According to the ICH, the maximum daily dose qualification threshold to be considered is as follows; <2 g / day, % or 1 mg per day intake (whichever is lower) >2 g / day, 0.05%.

Classification of impurities

Impurities can be classified are as follows;

A. Organic Impurities
B. Inorganic Impurities
C. Residual Solvent

A. Organic impurities

In this impurities can arise during the manufacturing process or storage of the new drug substance. They can be identified, volatile or non-volatile & include;

Starting Materials

- By Products
- Intermediates
- Degradation products
- Reagents. ligand & catalyst

B. Inorganic impurities

They can result from the manufacturing process. They normally known & identified & include;

- Reagents. ligand & catalyst
- Heavy metals or other residual metals
- Inorganic salts
- Other material (e.g filter aids, charcoal)

C. Residual solvents

Residual solvents is defined as Organic volatile chemicals that are used or produced in the manufacturing of drug substance.

Sources of impurities

Impurities may also arise from physical contamination & improper storage conditions.

Organic impurities

Organic impurities are the most common impurities found in every API unless proper care is taken in every step involved, throughout the multistep synthesis. Although the end products are always washed with solvents, there is always a chance that the residual unreacted starting materials remain, unless the manufacturers are very careful about the impurities. In a paracetamol bulk, there is a limit test for paminophenol, which could be a starting material for one manufacturer or be an intermediate for others [Figure 2]. Figure 2 Production of paracetamol from intermediate, pAminophenol

Oxidative degradation

Hydrocortisone, methotrexate, adinazolam, hydroxyl group directly bonded to an aromatic ring (e.g., phenol derivatives such as catecholamines and morphine), conjugated dienes, heterocyclic aromatic rings, nitroso and nitrite derivatives, and aldehydes (e.g., flavones) are all susceptible to oxidative degradation.

Decarboxylation

Some dissolved carboxylic acids, such as paminosalicylic acid, lose carbon dioxide from the carboxyl group when heated, in the case of photoreaction of rufloxacin.

Hydrolysis

Hydrolysis is a common phenomenon for the ester type of drugs, especially in liquid dosage forms. Examples include benzyl penicillin, barbitol, chloramphenicol, chlordiazepoxide, lincomycin, ethyl paraben, and cefpodoxime proxetil.

Photolytic cleavage

Pharmaceutical products are exposed to light while being manufactured as a solid or solution, and then they are packaged. Most compounds will degrade as solutions when exposed to high energy UV exposure (Ergometrine, Nifedipine, riboflavin, and phenothiazines are very labile to photooxidation.). Fluoroquinolones antibiotics are also found to be susceptible to photolytic cleavage. In ciprofloxacin eye drops.

Enantiomeric Impurities

The single enantiomeric form of a chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index, with a more favorable adverse reaction profile. However, the pharmacokinetic profiles of levofloxacin (Sisomeric form) and ofloxacin (Risomeric form) are comparable, suggesting the lack of advantages of a single isomer in this regard. For the manufacturers of a single enantiomeric drug (eutomer), the undesirable stereoisomers in drug control are considered in the same manner as other organic impurities.

Inorganic impurities

Inorganic impurities may also be derived from the manufacturing processes used for bulk drugs. They are normally known and identified, and include the following: The chances of having these impurities are rare: however, in some processes, these could create a problem unless the manufacturers take proper care during production. The main sources of heavy metals are the water used in the processes and the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place. These impurities of heavy metals can easily be avoided using demineralized water and glasslined reactors. The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants and in many cases, activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations.

Inprocess production impurities

Impurity can be any substance other than the material being crystallized. Therefore, even the solvent from which the crystals are grown can be considered as an impurity. When impurities are added specifically to produce a desired morphological effect they are referred to as additives. The presence of impurities or additives in a crystallization system can have a radical effect on crystal growth, nucleation, and agglomeration, asn also on the uptake of foreign ions in the crystal structure. It is of paramount importance to look for stereochemistry related compounds; that is, those compounds that have a similar chemical structure, but different spatial orientation. These compounds can be considered as impurities in the APIs. The single enantiomeric form of a chiral drug is now considered as an improved chemical entity that may offer a better pharmacological profile and an increased therapeutic index, with a more favorable adverse reaction profile, for example, the pharmacokinetic profile of levofloxacin (Sisomeric form) and ofloxacin (Risomeric form) are comparable, other

examples are levofloxacin (Sofloxacin), esomeprazole (Someprazole), and lavalbuterol (R-albuterol). Residual solvents are organic volatile chemicals used during the manufacturing process or generated during the production. Some solvents that are known to cause toxicity should be avoided in the production of bulk drugs.Depending on the possible risk to human health, residual solvents are divided into three classes. Synthetic intermediates and by-products Impurities generated during storage Metal impurities Leachables / Extractable can originate during the synthetic process, from raw materials, intermediates, and / or byproducts. A number of impurities can originate during storage or shipment of drug products. It is essential to carry out stability studies to predict, evaluate, and ensure drug product safety. Metal acts as an impurity in the APIs and excepients.

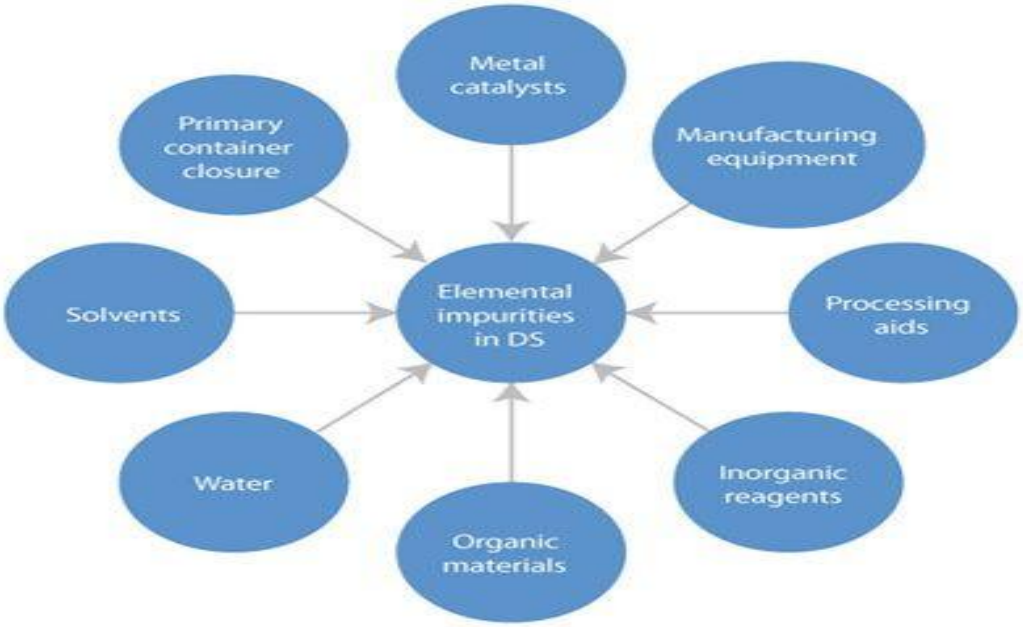

Fig. 1: Depicting sources of impurities.

ICH Guidelines for impurities

1. Q1A Stability testing of new drug substances & products.
2. Q3A Impurities in drug substance.
3. Q3B Impurities in drug products.
4. Q3C Impurities in residual substance.
5. Q6A Acceptance criteria for new drug substance

Analytical methods used for impurity profiling

Impurity profiling is the common name of a group of analytical activities, the aim of which is the detection.

A. Spectroscopic Methods

a) Ultraviolet

b) Infrared

c) Nuclear Magnetic Resonance

d) Mass Spectrometry

B. Separation methods

a) TLC

b) GC

c) HPLC

d) CF

e) SFC

C. Hyphenated methods

a) GC-MS

b) LC-MS

c) LC-NMR

A) Spectroscopic methods

a) Ultraviolet

UV is a form of electromagnetic radiations. It is study of absorption of UV radiations which ranges from 200-400nm. This Absorption is characteristic & depends on the nature of electron present.

Terms used in UV spectroscopy

Chromophore: The nucleus or any covalently bonded group responsible for the absorption of light radiation.

Auxochrome: It is also known as colour enhancing group. These are coordinately saturated or unsaturated group which themselves do not absorb radiations, but when present along which a Chromophore enhances the absorbing properties of Chromophore.

b) Infrared

Infrared radiation does not have enough energy to introduce electronic transitions as seen with UV. Infrared spectrum determine the functional group & it is important record which gives sufficient information about structure.

c) Nuclear magnetic resonance

It is a physical phenomenon in which in a strong constant magnetic field are pertubed by a weak oscillating magnetic field.

It is a technique that exploits the magnetic properties of nuclei.

d) MS

In this technique molecules are bombarded which a beam of energetic electrons.

The molecules are ionized & broken up into many fragments, some of which are the ions. It is most accurate method for determining the molecular mass of compound & its elemental composition.

B) Separation method

a) Thin layer chromatographic

TLC plays an essential role in the early stage of drug development when knowledge about the impurities & degradants in drug substance & drug product is limited. TLC is widely use method in pharmaceutical analysis both in its classical semi quantitative form. A simple TLC used for monitoring fermentation process.

b) Gas chromatography

The father of GC is Nobel Prize Winner John Porter Martin, who also developed the first liquid Gas Chromatography (1950). It is very useful for isolation & characterisation of volatile & semi-volatile organic compound in complex mixtures.

GC consist of GSC (Gas Solid Chromatography) & GLC (Gas Liquid Chromatography).

c) High performance liquid chromatography

In many cases use of traditional RP-HPLC condition & UV detection mostly employed for separation. RP-HPLC has nonpolar stationary phase & polar mobile phase.

d) Capillary electrophoresis

It is separation technique based on the differential transportation velocities of charged species in electric field through conductive medium. Primary candidates for Capillary Electrophoresis separation are ions.

e) Supercritical fluid chromatography

It is used an analytical scale. It is combination of HPLC & GC. It is important for the chiral separation & analysis of high-molecular. It can be used with universal flame ionization detector. Principle is based on super critical fluid. It is a material that can be either liquid or gas used in state above critical temperature or critical pressure where gases & liquid can coexist.

C) Hyphenated methods

a) GC-MS

It is advanced analytical instrumental technique that combine physical separation capabilities of GC with the mass analysis capabilities of mass spectrophotometer.

b) LC-MS

It is combination of liquid chromatography & mass spectrometry. It is combines physical separation capabilities of LC with the mass analysis capabilities of mass spectrometry. LC-MS is a powerful technique used for many application which has very high sensitivity & specificity. LC-MS are removing detector from the column of LC & fitting the column to interface of MS.

c) LC-NMR

It is innovative technique that connects NMR with HPLC.

For. e.g LC-NMR has been applied for the analysis of medicinal metabolites. LC-NMR is successful for impurities identification in vestipitant.

Among all hyphenated technique the most exploited technique for impurity profiling of drugs are GC-MS, LC-MS, LC-MS-MS & LC-NMR.

CONCLUSION

Taking everything into account, impurity profiling helps in adjusting rules by regulatory authorities with respect to contamination level in a medication. impurity profiling is gainful in choosing wellbeing boundaries for drugs. In these survey features the significance of pollutant profiling and utilization of novel method for a similar reason. This article gives the detailed data about the contamination type and its order different strategy of disconnection and portrayal investigative method for the assurance, capability of impurities and basic variables to be thought of while readiness of the bulk drugs. Disconnection and

Characterization of impurities is required for assessing information that sets up organic wellbeing.

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