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SCOPE OF IMPURITY PROFILING IN PHARMACEUTICAL INDUSTRY AND FOCUS ON IMPURITIES THAT MAY OCCUR IN ANTICANCER DRUGS (VINBLASTINE AND PACLITAXEL)

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Abstract:

Now a day's qualification of impurities has become a major task for pharmaceutical industry in order to maintain its biological safety. According to various regulatory authorities like ICH, USFDA, and Canadian drugs and health agency, along with purity profile, the impurity profile of drug has gained utmost importance in order to prove that the formulation is safe and efficient throughout its shelf life.

Impurities may be developed during any stage of formulation that is from procurement of raw material to the marketing of the finished products. They may also occur during the storage of the formulation. The presence of these impurities even in small quantities may affect the safety, efficacy, purity, quality and strength of the drug.

Impurity is defined as the substance other than API that decreases its activity and also reacts with it and forms new substance that is more potentially toxic.

Impurity profiling aims to identify and characterise the unwanted, potentially toxic impurities that may be present in drug substance or APIs during any stage of manufacturing.

So it is very important to have an idea regarding the source of impurities, different types of impurities, different methods used for their isolation and characterisation. It is also essential to know regarding the allowable limits of impurities according to ICH.

So present article helps us to understand about the different types and sources of impurities, different methods to isolate and characterise them and possible measures to be taken to decrease the impurity level in formulation. It also gives us a source to understand the impurities that may occur during formulation and storage of anticancer drugs like Vinblastine and paclitaxel.

Key words: *Impurity profiling, API, Toxic, Formulation, Storage, Sources of Impurities, Anti Cancer drugs.*

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INTRODUCTION:

Impurity is defined as the substance other than API that decreases its activity and also reacts with it and forms new substance that is more potentially toxic. Impurity profiling is the study and description of identified and unidentified impurities in new drug substances, formed during the process of manufacturing of API or any formulation. The impurities may be toxic or non toxic. Identification of impurities is of prime importance in the pharmaceutical industry as it affects the safety and efficacy of the drug. The intermediates formed during manufacturing process act as impurities which may be due to API or the degraded compounds formed during the stress conditions of the process.

Impurities may occur at any stage from procurement of raw material to end product distribution.

The identification of impurities with their structure and toxicity level is essential and mandatory in various pharmacopoeias and ICH guidelines.
Identification and structural elucidation of impurities can be done by spectroscopic and chromatographic techniques alone or their combination with other techniques.

I. Spectroscopic techniques such as UV, IR, NMR, MS are most widely used now a days.
II. Chromatographic techniques include TLC, HPTLC, and HPLC.

According to ICH guidelines on impurities in new drug products, identification of impurities less than the 0.1% level is not considered to be necessary, unless potential impurities are expected to be unusually potent or toxic. According to ICH, the maximum daily dose qualification threshold is considered as above; = 2g/day 0.1% or 1 mg per day intake (whichever is lower) = 2g/day 0.05%

Scope:

Identification and Quantification of impurities has gained utmost importance in pharmaceutical industry. It became a mandatory requirement in various pharmacopoeias such as BP, EP, USP.

ICH Guidelines for Impurity profile:

The ICH guidelines for impurities in pharmaceutical were developed by joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies.
ICH has published guidelines on

- Impurities in new drug substance (ICH Q3A)
- New drug products (ICH Q3B)
- Residual solvents (ICH Q3C)

In ICH guidelines impurities are addressed from two perspectives

1. Chemistry aspects include classification and identification of impurities, report generation, setting specifications, and a detail discussion of analytical procedures.

2. Safety aspects include specific guidelines for qualifying impurities that were not present in batches of new drug substances and products used in safety and clinical studies and /or impurity levels substantially higher than in those batches.

The various regulatory guidelines regarding impurities are as follows

- ICH guidelines "Stability testing of New Drug Substance and Products"- Q1A.
- ICH guidelines "Impurities in New Drug Substances"- Q3A (R) (Current Step 4 version, dated 25 October 2006).
- ICH guidelines "Impurities in New Drug Products"- Q3B (R2) (Current step 4 version, dated 2 June 2006).
- ICH guidelines "Impurities: Guidelines for Residual solvents"Q3C (R3) (Current Step 4 version, parent guideline, 97, revised Nov 2005).
- US-FDA guidelines "NDAs- Impurities in New Drug Substances".
- US-FDA guidelines "ANDAs- Impurities in New Drug Substances".
- Australian regulatory guidelines for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

Terms used to describe impurities:

Intermediate:

The compound produced as a part of synthesis of desired product that alters the nature of the final desired product.

Penultimate Intermediate:

There may be production of one or more intermediates during the synthesis of final desired product. The compound produced just prior to desired product is called as Penultimate Intermediate.

By products:

These are the substance produced during the synthesis of the desired product by the reaction between intermediates and solvents or intermediates

and catalysts or due to overreaction or incomplete reaction.

Transformation products:
These are similar to by products but any time during the reaction, the transformation products can transform their structure similar to desired product and cause the potential toxicity.

Interaction products:
As the term describes, these products are formed by the interaction between various chemicals, solvents or catalysts.

Related products:
Products those are similar to drug substances and posses similar biological activity.

Degradation products:
These are formed due to decomposition or detoriation of the API or any other chemicals used in the reaction. They may also occur due to external factors like light, heat, moisture.

Classification of Impurity:
According to USP impurities are classified into three sections

- Impurities in Official Articles
- Ordinary Impurities
- Organic Volatile Impurities

According to ICH guidelines, impurities in drug substance produced by chemical synthesis can be broadly classified into following three categories

1. **Organic Impurities** (Process and drug-related)
   - Starting Materials or Intermediate Impurities
   - By-products
   - Degradation Products

   Other Types of Organic Impurities
   - Synthesis Related Impurities
   - Formulation Related Impurities
   - Functional Group Related Impurities

   a. Ester hydrolysis: Drugs like aspirin, benzocaine, cefoxime, cocaine, ethyl paraben undergo ester hydrolysis.
   b. Hydrolysis: Commonly drugs like benzyl penicillin, barbital, and chloramphenicol undergo hydrolysis.
   c. Oxidative degradation: Drugs like hydrocortisone, methotrexate, heterocyclic aromatic ring, nitroso/nitrile derivative.
   d. Photolytic cleavage: Product exposed to light while manufacturing or storage in hospital pending use or by consumer pending use.
   e. Decarboxylation: Some dissolved carboxylic acid such as p-amino salicylic acid loose CO2 when heated.
2. **Inorganic Impurities** (Reagent, ligands, catalysts)

a. Reagent, Ligands and Catalysts
b. Heavy Metals
c. Other Materials (Filter Aids, Charcoal)

3. **Residual Solvents** (Volatile solvents)
   Residual solvents are organic or inorganic liquids used during the manufacturing process. It is very difficult to remove these solvents completely by the work-up process. Some solvent that are known to cause toxicity should be avoided in the production of bulk drugs.

Classification of solvents on basis of their limit in ppm	**Name of the solvent (limit)**	**Unit/Specification**
Class 1	Benzene(2ppm), Carbon tetrachloride(4ppm) Methyl chloride(600ppm) Methanol(3000ppm) Pyridine(200ppm) Ehanol	More than this should be avoided
Class 2	N,N-dimethyl formamide(800ppm) Acetonitrile(410ppm)	More than this should be avoided
Class 3	Acetic acid, ethanol, Acetone(50mg)	Have permitted daily exposure of 50mg or less

C**. Sources of Impurity**

The types and amount of impurity present in the chemicals or pharmaceutical substances depend upon following factors

1. Raw materials used in manufacturing
2. Method or process employed in manufacturing
3. Reagents/Solvents/Reaction vessels
4. Atmospheric contaminations
5. Particulate contamination
6. Cross contamination
7. Microbial contamination
8. Packing errors
9. Due to impact of heat, light, oxidants on drug products
10. Change in pH
11. Presence of trace metals which may catalyze and accelerate the reaction

- From the preceding discussion, it is clear that impurities can originate from several sources, such as

1. Crystallization-related impurities
2. Stereochemistry-related impurities
3. Residual solvents
4. Synthetic intermediate and by-products
5. Formulation- related impurities
6. Impurities arising during storage
7. Method related impurities
8. Mutual interaction amongst ingredients
9. Functional group- related typical degradation

Impurity types	Sources
Product related impurity	Raw materials, solvents, organic & inorganic, by products.
Process related impurity	Intermediates and transforamation products ,interaction products
Packaging and related impurities	Interation b/w coating material and drug, interation b/w primary ,secondary packing materials with that of drug
Storage conditions and related impurities	Extreme conditions- acidic, basic and high temperature.
Degradation related impurities	Oxidation, thermal decomposition and hydrolysis of the drug.

Steps involved in Analytical method development:

- Selection of sample for method development.
- Selection of appropriate parameters like column, mobile phase and its temperature.
- Optimisation of the method and tuning of all the parameters and validating the analytical method developed.

Identification of Impurities

- Reference standard method
- Spectroscopic methods - UV,IR,NMR,MS
- Separation methods – TLC,HPTLC,GC,SFC
- Isolation methods - solid phase extraction
  Liquid-liquid extraction
  Column chromatography
- Characterization methods - Hyphenated techniques like
  GC-MS
  LC-MS
  HPLC-DAD-MS
  HPLC-DAD-NMR-MS

Among all these methods hyphenated techniques are most widely used. Because these methods help us to separate, isolate and characterise the impurity along with its structural determination.

Limits for impurities:

According to 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.

Reporting and control of impurities

- **Thresholds**

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
>2g/day	0.03%	0.05%	0.05%

- **Reporting threshold:** A limit above (>) which an impurity should be reported.
- **Identification threshold:** A limit above (>) which an impurity should be reported.
- **Qualification threshold:** A limit above (>) which an impurity should be reported.

Cancer is a disease in which abnormal cells divide uncontrollably and destroy body tissue. Most common types of cancers are:
Breast cancer
Prostate cancer
Basal cell cancer
There are almost 100 different cancers which effect humans. So, this disease has become the most dangerous at present.

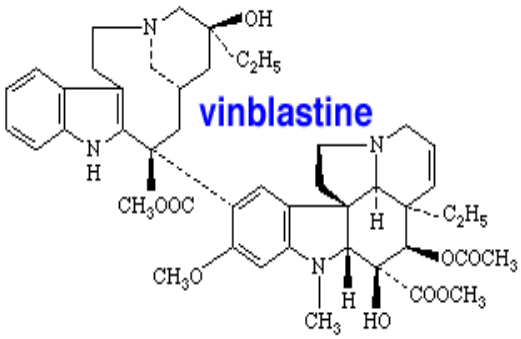
Treatment: Radiation therapy
Chemotherapy
Targeted Therapy
Surgeory.

In this article we deal with Microtubule inhibitors by which we can inhibit the cell cycle and achieve Apoptosis. In this article our main focus is on impurity profiling of Vinblastine and Paclitaxel.

Microtubule inhibitors: Docetaxel
Paclitaxel
Vinblastine
Vincristine

Microtubules are important cellular targets for anticancer therapy because of their role in mitosis. Microtubule inhibitors such as Taxanes, Vinca alkaloids, epothilones destabilize the microtubules there by suppressing microtubule dynamics required for proper mitotic function, effectively blocking cell cycle progression and resulting in apoptosis process.

VINBLASTINE:



Molecular Formula: $C_{46}H_{58}N_4O_9$

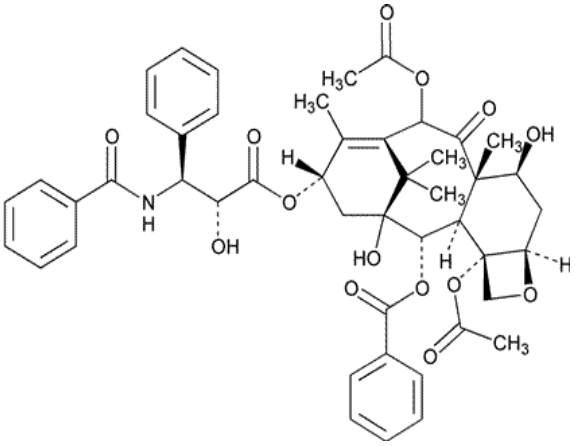
Mechanism of action: It is a vinca alkaloid antineoplastic agent. It binds to β-tubulin , there by inhibiting the assembly of microtubule. Vinblastin treatment causes M phase specific cell cycle arrest by disrupting microtubule assembly and proper formation of the mitotic spindle and the kinetochore, each of which are necessary for the separation of chromosomes during anaphase of mitosis.

Impurities that may occur during the formulation and storage of Vinblastine:

Vinblastine Impurity A $C_{47}H_{60}Cl_2N_4O_9$
Vinblastine Impurity B $C_{46}H_{58}N_4O_{10}$
Vinblastine Impurity C $C_{45}H_{56}N_4O_9$
Vinblastine Impurity D $C_{46}H_{56}N_4O_{10}$ 1
Vinblastine Impurity E $C_{44}H_{56}N_4O_8$
Vinblastine Impurity F $C_{46}H_{56}N_4O_9$
Vinblastine Impurity G $C_{44}H_{56}N_4O_7$
Vinblastine Impurity H $C_{46}H_{56}N_4O_9$
Vinblastine Impurity J $C_{47}H_{61}N_4O_9$.
Vinblastine Impurity K $C_{45}H_{54}N_4O_8$
Vinblastine Impurity M $C_{46}H_{56}N_4O_{11}$

- Impurities of Vinblastine can be identified using HPLC, NMR, Mass spectrometry, LC-MS/MS.

PACLITAXEL: $C_{47}H_{51}NO_{14}$



Mechanism of action: Paclitaxel interferes with the normal function of microtubule growth. Paclitaxel arrests their function by having the opposite effect when compared to colchicine; it hyper-stabilizes their structure. This destroys the cell's ability to use its cytoskeleton in a flexible manner. Specifically, paclitaxel binds to the β subunit of tubulin.

Impurities that may occur during formulation and storage:

IMPURITIES MOLECULAR FORMULA

1. 6-*alpha*-Hydroxy Paclitaxel
   $C_{47}H_{51}NO_{15}$
2. 10-Desacetyl Paclitaxel
   $C_{45}H_{49}NO_{13}$
3. Paclitaxel N-Butyl Analog
   $C_{45}H_{55}NO_{14}$
4. 2-Debenzoyl Paclitaxel 2-Pentenoate
   $C_{45}H_{53}NO_{14}$
5. 10-Acetoacetyl Paclitaxel
   $C_{49}H_{53}NO_{15}$
6. 3'-p-Hydroxy Paclitaxel
   $C_{47}H_{51}NO_{15}$
7. 10-Deacetyl Paclitaxel Propyl Analogue
   $C_{42}H_{51}NO_{13}$
8. 7-Acetyl Paclitaxel
   $C_{49}H_{53}NO_{15}$

- Impurities of paclitaxel can be detected by using liquid chromatography mass spectrometry(LC-MS), liquid chromatography tandem mass spectrometry(LC-MS/MS),UPLC.

CONCLUSION:

By this article we conclude that the impurity profiling plays an important role in maintaining biological safety and efficacy of the drug product. In pharmaceutical industry we can decrease the impurities by following GMP, CGMP and proper storage conditions. According to ICH guidelines impurities should always be within the limits for biological safety and efficacy.

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