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GENOTOXIC IMPURITIES AND IMPURITY PROFILING OF PHARMACEUTICAL DRUG SUBSTANCES

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Abstract:
The significance of drugs and their safety is based on their therapeutic use. In the context of pharmaceutical drugs and their effect caused by the presence of impurities. The drug safety and its toxicological profile have first been evaluated and further allowed for bulk formulations. The unrequired impurities of drug formations have controlled the drug effect when it is allowed for administration into the body and their continuous toxicological concern effect. Moreover, the impurities of drugs should be completely evaluated before entering the market. The formulations are significantly confident by the extreme monitoring of impurities during their process. However, the effect of impurity analysis on the drugs is based on the instruments being used. Therefore, in drug analysis analytical activities plays a crucial role in the pharmaceutical industries. The recent literature is quite global for this concern in Pharmacopoeias. It is very essential part of purity and impurity profiling for regulatory agencies. Impurities are considered like organic material and are the inner part of drug substance raised part of pharmaceutical drug synthesis. So, this article discusses impurity profiling of pharmaceutical drug substances and genotoxic impurities.

Keywords: Drug, Impurity, Genotoxic, Synthesis, etc.

INTRODUCTION

Pharmaceutical drugs are very important medications for many dangerous diseases of humans and animals. The drug is derived from “drogue” (French word), which means a dry herb. As per WHO, drugs are further termed as modifying the pathological, physiological states of the recipient. Drugs also change the physical, economical, and mental states of recipients. The ideal drug should satisfy the following conditions when administered to a host.

- Drug action must be localized, where it’s intended to act.
- It must act effectively and safely.
- Drug side effects must be minimized.

- Drug not to be having a toxic effect.
- After being administered to the host for a long duration, should not develop tolerance by the tissues.
- They do not injure the host tissues and physiological processes.

Above all the conditions are not satisfied by all the drugs, however, the medication is looking continuously for the ideal drug. Nowadays pharmaceutical drugs originate from the synthetic process. They are further distinguished by their therapeutic action, chemical identity, and pharmacodynamic and chemotherapeutic agents. Bulk drugs which are synthesized in the manufacturing units are further involved in pharmaceutical formulations and there by therapeutic activity. These drugs are further formulated as tablets, capsules, dry syrups, liquid orals, creams, ointments, lotions, dusting powders, aerosols, metered-dose inhalers (MDI), and dry powder inhalers (DPI), etc. In order to get better therapeutic activity, they are delivered for stable, non-toxic formulations. The permissible limits of impurities in active drugs and drug formulations have been incorporated by the global Pharmacopoeia markets. The impurities are sometimes either generated during the stability of active drugs or from during the formulations.

IMPURITY PROFILING OF PHARMACEUTICAL DRUG SUBSTANCES

Impurity profiling is a significant part of the interpretation of organic substances; there it is further helpful for the evaluation of quantification and detection levels in organic, and inorganic molecules. pharmaceutical industries must ensure structure interpretations of active substances and impurities. The evaluation of structures and impurities leads to the quality and stability of drug formulations. Impurities are unwanted organic or inorganic materials arising in pharmaceutical drugs.

They may generate during the synthesis or during the stability of drug substances/formulated products. Drug agencies globally standardize (ICH, USFDA, Canadian Drug, etc.,) and released the documents which are helpful for the purity of drugs. Evaluation of known or unknown impurities in pharmaceutical drugs is useful for the safety of drugs and further humans/animals, thus it becomes biological safety. Moreover, impurity profiling of active substances and products plays an essential role in drug research [34-38]. Impurities of pharmaceutical drug substances and drug formulations are shown in **Table 1.**

Table 1: group and generation of impurities in pharmaceutical active substance and drug products.

Nature of impurities	**Origin of impurities**
During the synthesis of a Drug substance	Starting material Intermediate By-products Impurities of starting material Residual solvents Reagents, catalysts
Formulation related: Drug product	Organic or inorganic Reagents Catalyst

Degradation: Drug substance or API	Organic degradation products Product-related substances
Degradation: Drug products	Excipient interaction

A drug agency defines the impurities with dissimilar definitions: USP defines rotten impurities in standard articles, ordinary impurities, and organic volatile impurities. ICH states impurities are degradation products, by-products, related products, intermediates, interaction products, and (n-1) intermediate drug products.

GENOTOXIC IMPURITIES

Chemicals used in the making of drugs sometimes form unwanted products and break-down products (degradants). Over the last ten years much effort has been concentrated on controlling extremely low levels of impurities that might be genotoxic, i.e, they can damage DNA. DNA damage can lead to mutations, and it is one of the important factors in the development of cancer, In order to control these unwanted substances into very low trace levels evaluations must be made. The pharmaceutical industry and regulatory bodies must take part in controlling of these genotoxic impurities in the early development stages of drug substances.

Drug approvals must be initiated during the process of impurities identification during the synthesis write-up evaluation before entering into the clinical trials. However, the process synthesis of every drug has been found to be a unique set of process impurities. Every industry has invested resources to notify the genotoxic impurities, and potential genotoxic impurities and thereby evaluated their limits for drug approvals. ICH addresses the impurities limits for the best part of pharmaceutical drug industries.

In consideration of the above notes, efforts must be made the controlling all drug impurities during the process development for human/animal safety. The presence of genotoxic (mutagenic) potential impurities in pharmaceutical drugs and found to be unfavourable for clinical trials and agencies' approvals. Based on the interpretation and assessment of impurities, they may be constituting genotoxicity and becomes unfavourable clinical subjects for patient concern [39].

Analytical scientist reveals the words "genotoxic" and "mutagenic" are synonymously the same. However, they are dissimilar in their Genotoxic effect. Mutagenicity specifically for mutation of gene and chromosome levels. Genotoxic is referred to interaction with helical DNA and its cellular parts.

TYPES OF GENOTOXIC IMPURITIES

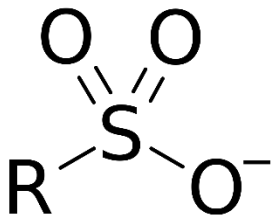
1. Drugs with sulfonate groups:

The groups with Sulfonate salts in drugs are very common for pharmaceutical drug synthesis. These groups are formed for biopharmaceutical and therapeutic activities of drugs during formulation optimization. Hence, salts of sulfonate groups play a significant role in drug formulation. After drug active substances optimization with salt groups, they become stabilized with higher melting points. The salt formation increases the drug descriptions like Solubility, and stability, and possesses some advantages of in-vivo

studies. Mesylate groups are not likely to form hydrates, in contrast to salts with strong acids, and they are further, genotoxic in the drugs during the wet granulation process. Active substances show some plastic deformation with lower melting points and this is overcome by the salt formations become higher melting points.

The advantage of higher melting point substances thereby increases the crystal lattice energies. Sulfonic acid salts are some desirable groups for the good solubility of drugs though they exhibit higher melting points. Increasing dissolution rates of haloperidol mesylate for instance <2 min in pH 2 simulated gastric media with elevated surface area, and solubility other than common ion formation. The reaction of sulfonic acids with lower alcohols to form corresponding esters and further act as alkylating agents brings in genotoxicity and carcinogenicity. Consequently, nowadays drugs with these groups must possess good safety concerns. **Figure 1** depicts the structures of common sulfonate salts.

Figure 1: Some common sulfonate salt structures.



2. Drugs with Aromatic compounds:

This section describes some aromatic groups like aromatic structure and aromatic amines. Fentanyl impurities, tremorgenic impurities, and p-nitrophenol (PNP) are discussed.

3. Drugs with Aromatic amines:

After metabolism, primary and secondary aromatic amine impurities bring to electrophilic species results Ames test positive. Few amines like 2, 4-diamino ethylbenzene, 2, 4-Diaminotoluene with nitro group act as a direct mutagen. In sense of carcinogenicity study, the substances like p-chlorinelike, and p-anisidine with positive results of Ames test rather than they noncarcinogenic on rodent bioassays.

4. Drugs with Alkyl halide and Esters groups:

Alkylating agents possess some electrophilic nature and can strongly attack nucleophilic centers of DNA. Alcohols in presence of strong inorganic acids like HCl and H_2SO_4, generate impurities (eg. Alkyl halides and mesylates) during the synthesis of drug substances. Salts formation of drugs usually plays during the formulation and formation of alkylhadie, esters are very common in many drugs.

5. Drugs with Hydrazines groups:

Drugs with Hydrazines groups are sometimes used as medicine, and also they act as key starting materials for the synthesis of new drug substances. The derivatives of Hydrazine (N-alkyl, N-aryl, and N-acyl groups) are under extensive toxicological concern and show

structural alerts for potential genotoxicity. Moreover, their effect increases with metabolism. Endogenous formaldehyde reacts with hydrazine and generates formaldehyde hydrazone. Other Consequent reactions involved and generated the diazomethane genotoxic substance (acts as alkylating agent). Derivatives of Hydrazine can react with DNA giving some adducts. During this process, methyldiazanium ions or methyl free radicals are generated.

6. Drugs with Epoxide groups:

In presence of strained epoxide rings, these groups are considered electrophilic and act as alkylating agents that reacted directly with DNA strands. The reactivity of Alkene oxides is better than arene oxides. Asymmetrically substituted epoxide compounds are better reactive than symmetrically substituted epoxides. The substances like betamethasone acetate and atenolol show herbal remedies even though they consist of epoxide impurities. Examples of active drug substances with epoxide impurities are betamethasone acetate, atenolol, and some herbal remedies. The compounds like Carbamazepine, cyproheptadine, and rotriptyline consist epoxy analogs and are more stable on their entity. Moreover, compounds like phenytoin, lamotrigine, amitryptiline, and diclofenac like form compounds of labile arene oxides. Epoxides in their metabolism are mainly involved in the absorption of enzymes glutathione S-transferase, and epoxide hydrolase. They are further involved in the synthesis of epoxides or detoxification. Above all lines states the genotoxicity of epoxy analogs.

7. p-Nitrophenol (PNP) groups:

p-Nitrophenol is used as a key starting material for some drug synthesis besides, its fungicidal activity. Aryl hydroxy amines or hydroxamic esters are generated under the PNP and other substituted nitro benzenes reductions. The generated esters possess some electrophilic nitrogen atoms and shows the genotoxic property.

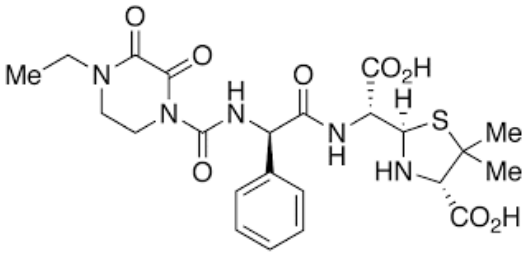
8. Impurities with β-lactam groups:

Antibiotics like piperacillin and cefotaxime, which bear interrelated β-lactam groups show genotoxicity.

(a). Piperacillin impurity-A:

Piperacillin up on degradation generated the Piperacillin impurity-A. It is formed during storage. In the S. Typhimurium strains (TA 97a, TA 98, TA 100, TA 102, and TA 1535), the presence or absence of piperacillin under metabolic studies it brings to be nonmutagenic. It is found that piperacillin impurity-A up to 5 mg/mL is considerable and nonclastogenic to CHO cell lines under the existence and nonexistence of metabolism. The structure of the impurity is shown in **Figure 2**.

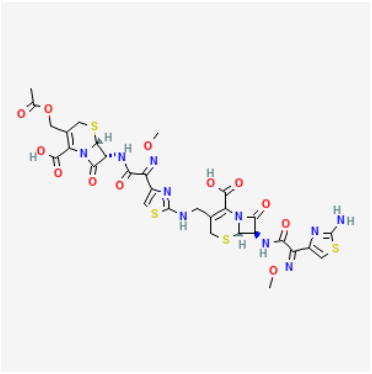
Figure 2: Chemical structure of Piperacillin impurity-A.



(b). Cefotaxime Dimeric impurity:

Dimeric impurity was generated during the storage conditions of cefotaxime and the chemical structure depicted in **Figure 3.** This impurity is the nonmutagenic under mutagenicity studies (Ames test). Chromosomal aberrations in cultured cells (45 mg per culture) were observed after the study of the in-vitro chromosomal assay. However, the results indicate no carcinogenesis in In-vitro cells.

Figure 3: Chemical structure of Dimeric impurity of cefotaxime



9. Tremogenic impurities:

These tremogenic impurities are highly toxic in pharmaceutical drug substances. The drug substances pethidine and paroxetine (3-[(1, 3-benzodioxol-5-yloxy) methyl]-4-(4-fluorophenyl) piperidine) potentially active and up on subsequent levels they are likely to be contaminated with tremorgenic impurities. 1-methyl-4- phenyl-1, 2, 3,6-tetrahydropyridine presence trace amount in Pethidine and is formed from its side chain degradation reaction. 4-(4-Fluorophenyl)-1-methyl-1,2,3,6-tetrahydropyridine potentially active in the paroxetine formation and shows toxicity. However, tremogenic impurities are extremely toxic, even though there is an uncertainty in their genotoxicity still.

10. Drugs with Fentanyl impurities:

The breakdown of the fentanyl class of medicines results in the formation of seven aromatic contaminants. Safety elegant includes the compounds propionanilide (PRP), N-phenyl-1-(2-phenylethyl)-piperidin-4-amine (PPA), 1-phenethyl-1H-pyridin-2-one (1-PPO), fentanyl N-oxide (FNO), and 1-styryl-1H-pyridin-2-one (1-SPO). PPA is one example of a chemical that has the potential to be genotoxic. Results from the Ames test were also positive for platelet-rich plasma (1-PRP), plasminogen activator (1-PPO), and oxidised

plasminogen (1-SPO).

CONCLUSION

To sum up, it can be said that impurities in pharmaceutical items are anything that doesn't add any therapeutic value but could have negative effects. In order for pharmaceutical goods to be provided to humans safely, impurity levels must be strictly monitored and managed. Impurity qualification, or the collection and analysis of data demonstrating an impurity's lack of risk to human health, highlights the importance of impurity profiling in drug development and the breadth of its application. So this paper deals short note of genotoxic impurities (GTIs), and their origin in drugs and drug formulations, the organization of GTIs, aspects of different regulatory guidelines related to estimations and their strategies on controlling. Moreover, it explains a few structural alerts that show toxicity. This paper also attempted to illustrate which need for an analytical approach to diminish the impurities in active drug substances.

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