Impurities in Pharmaceutical Dosage Form: A Subject Matter of Great Concern

Corresponding Author:  
Mr. Rajeev K Singla,  
Lead Faculty, Webmed Central, India, 124001 - India

Submitting Author:  
Mr. Rajeev K Singla,  
Lead Faculty, Webmed Central, India, 124001 - India

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Author(s): Kumar R., Singla R K

Introduction

According to FDA any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug.

Impurities in pharmaceuticals are the unwanted chemicals that remain with the active pharmaceutical ingredients (APIs), or develop during formulation, or upon aging of both API and formulated APIs to medicines. The presence of these unwanted chemicals even in small amounts may influence the efficacy and safety of the pharmaceutical products.

Impurity profiling (i.e., the identity as well as the quantity of impurity in the pharmaceuticals), is now receiving important critical attention from regulatory authorities. The different pharmacopoeias, such as the British Pharmacopoeia (BP) and the United States Pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations.

There is an ever increasing interest in impurities present in API’s. Recently, not only purity profile but also impurity profile has become essential as per various regulatory requirements. In the pharmaceutical world, an impurity is considered as any other organic material, besides the drug substance, or ingredients, arise out of synthesis or unwanted chemicals that remains with API’s. Impurity control in pharmaceutical products is a primary goal of drug development [1].

According to ICH, an impurity in a drug substance is defined as-“any component of the new drug substance that is not the chemical entity defined as the new drug substance”. There is an ever increasing interest in impurities present in APIs recently, not only purity profile but also impurity profile has become essential as per various regulatory requirements. The presence of the unwanted chemicals, even in small amount, may influence the efficacy and safety of the pharmaceutical products.

“In the pharmaceutical world, an impurity is considered as any other organic material, besides the drug substance, or ingredients, arise out of synthesis or unwanted chemicals that remains with API’s” The impurity may be developed either during formulation, or upon aging of both API’s and formulated API’s in medicines and can be explained using Multidisciplinary approach.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has also published guidelines for validation of methods for analyzing impurities in new drug substances, products, residual solvents and microbiological impurities.

Methods

Classifications of Impurities:
Impurities have been named differently or classified as per the ICH guidelines as follows:
A] Common names
1. By-products
2. Degradation products
3. Interaction products
4. Intermediates
5. Penultimate intermediates
6. Related products
7. Transformation products
B] United State Pharmacopeia
The United States Pharmacopoeia (USP) classifies impurities in various sections:
1. Impurities in Official Articles
2. Ordinary Impurities
3. Organic Volatile Impurities
C] ICH Terminology
According to ICH guidelines, impurities in the drug substance produced by chemical synthesis can broadly be classified into following three categories –
1. Organic Impurities (Process and Drug related)
2. Inorganic Impurities
3. Residual Solvents

Organic impurities may arise during the manufacturing process and or storage of the drug substance may be identified or unidentified, volatile or non-volatile, and may include
1. Starting materials or intermediates
2. By-products
3. Degradation products

Impurities are found in API’s unless, a proper care is taken in every step involved throughout the multi-step synthesis for example; in paracetamol bulk, there is a limit test for p-aminophenol, which could be a starting
material for one manufacturer or be an intermediate for the others. Impurities can also be formed by degradation of the end product during manufacturing of the bulk drugs. The degradation of penicillin and cephalosporin are well-known examples of degradation products. The presence of a β-lactam ring as well as that of an N, Ndimethylformamide (880 ppm), benzene (2 ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000 ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided.

**Class I:** benzene (2 ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000 ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided.

**Class II:** N, Ndimethylformamide (880 ppm), acetonitrile (410 ppm).

**Class III:** acetic acid, ethanol, acetone has permitted daily exposure of 50 mg or less per day, as per the ICH guidelines.

A selective gas chromatography (GC) method has been developed to determine the purity of acetone, dichloromethane, methanol and toluene. Using this method, the main contaminants of each organic solvent can be quantified. Moreover, the developed method allows the simultaneous determination of ethanol, isopropanol, chloroform, benzene, acetone, dichloromethane, methanol and toluene with propionitrile as the internal standard.

d. Synthetic intermediates and by-products

Impurities in pharmaceutical compounds or a new chemical entity (NCE) can originate during the synthetic process from raw materials, intermediates and/or by-product. For example, impurity profiling of ecstasy tablets by GC-MS and MDMA samples, produced impurities in intermediates via reductive amination route.

e. Formulation-related impurities

Many impurities in a drug product can originate from excipients used to formulate a drug substance. In addition, a drug substance is subjected to a variety of conditions in the process of formulation that can cause its degradation or have other undesirable reactions. If the source is from an excipient, variability from lot to lot may make a marginal product, unacceptable for reliability. Solutions and suspensions are inherently prone to degradation due to hydrolysis or Solvolysis. Fluocinonide Topical Solution USP, 0.05%, in 60-mL bottles, was recalled in the United States because of
degradation/impurities leading to sub-potency. In general, liquid dosage forms are susceptible to both degradation and microbiological contamination. In this regard, water content, pH of the solution/suspension, compatibility of anions and cations, mutual interactions of ingredients, and the primary container are critical factors.

Microbiological growth resulting from the growth of bacteria, fungi, and yeast in a humid and warm environment may result in unsuitability of an oral liquid product for safe human consumption. Microbial contamination may occur during the shelf life and subsequent consumer-use of a multiple-dose product, either due to inappropriate use of certain preservatives in the preparations, or because of the semi-permeable nature of primary containers.

f. Impurities arising during storage
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.

g. Method related impurity
A known impurity, 1-(2, 6-dichlorophenyl) indolin-2-one is formed in the production of a parenteral dosage form of diclofenac sodium, if it is terminally sterilized by autoclave. The conditions of the autoclave method enforce the intramolecular cyclic reaction of diclofenac sodium forming an indolinone derivative and sodium hydroxide. The formation of this impurity has been found to depend on initial pH of the formulation.

h. Mutual interaction amongst ingredients
Most vitamins are very labile and on aging they create a problem of instability in different dosage forms, especially in liquid dosage forms. Degradation of vitamins does not give toxic impurities; however, potency of active ingredients drops below Pharmacopoeial specifications. Because of mutual interaction, the presence of nicotinamide in a formulation containing four vitamins (nicotinamide, pyridoxine, riboflavin, and thiamine) can cause the degradation of thiamine to a sub-standard level within a one year shelf life of vitamin B-complex injections.

i. Functional group-related typical degradation
Ester hydrolysis can be explained with a few drugs aspirin, benzocaine, cefotaxime, ethyl paraben and cepodoxime proxetil. Hydrolysis is the common phenomenon for ester type of drugs, especially in liquid dosage forms benzylpenicillin, oxazepam and lincomycin. Oxidative degradation of drugs like hydrocortisone, methotrexate, hydroxyl group directly bonded to an aromatic ring (phenol derivatives such as catecholamines and morphine), conjugated dienes (vitamin A and unsaturated free fatty acids), heterocyclic aromatic rings, nitroso and nitrite derivatives and aldehydes (especially flavorings) are all susceptible to oxidative degradation.

In mazipredone, the hydrolytic and oxidative degradation pathway in 0.1 mol/L hydrochloric acid and sodium hydroxide at 80°C were studied. Ergometrine, nifedipine, nitroprusside, riboflavin and phenothiazines are very liable to photo-oxidation. In susceptible compounds, photochemical energy creates free radical intermediates, which can perpetuate chain reactions. Most compounds will degrade as solutions when exposed to high-energy UV exposures. Fluroquinolone antibiotics are also found to be susceptible to photolytic cleavage.

In ciprofloxacin eye drop preparation (0.3%), sunlight induces photo cleavage reaction producing ethylenediamine analog of ciprofloxacin. Decarboxylation of some dissolved carboxylic acids, such as p-aminosalicylic acid, shows the loss of carbon dioxide from the carboxyl group when heated. An example of decarboxylation is the photoreaction of rufloxicin.

As seen earlier, impurities in drug products can come from the drug or from excipients or can be brought into the system through an in process step by contact with the packaging material. For most drugs, the reactive species consist of:

1. Water (can hydrolyze some drugs or affect the dosage form performance)
2. Small electrophiles (like aldehydes and carboxylic acid derivatives)
3. Peroxides (can oxidize some drugs)
4. Metals (can catalyze oxidation of drugs and the degradation pathway)
5. Leachable or Extractable (can come from glass, rubber stoppers, and plastic packaging materials. Metal oxides such as NaO2, SiO2, CaO, MgO, are the major components leached/extracted from glass).

Generally most synthetic materials contain leachable oligomers/monomers, vulcanizing agents, accelerators, plasticizers and antioxidants. Some examples of leachable / extractable from synthetic materials include styrene from polystyrene, diethylhexylphalate (DEHP, plasticizer in PVC), dioctyltin isooctylmercaptoacetate (stabilizer for PVC), zinc stearate[3] (stabilizer in PVC and polypropylene), 2-mercaptobenzothiazole (accelerator in rubber stopper) and furfural from rayon.

These impurities are needed to be analyzed by using different analytical methods.

Results
Ich Limits of 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. According to ICH, the maximum daily dose qualification threshold to be considered is as figure (1). In summary, the new drug substance specifications should include, limits for

a. Organic Impurities
   Each specific identified impurity
   1. Each specific unidentified impurity at or above 0.1%
   2. Any unspecific impurity, with limit of not more than 0.1%
   3. Total impurities

b. Residual solvents

c. Inorganic impurities

References

## Illustrations

### Illustration 1

#### Figure 1

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Reporting Threshold</th>
<th>Identification Threshold</th>
<th>Qualification Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2g/day</td>
<td>0.05%</td>
<td>0.10% or 1.0 mg per day intake (whichever is lower)</td>
<td>0.15% or 1.0 mg per day intake (whichever is lower)</td>
</tr>
<tr>
<td>&gt; 2g/day</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>
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