



SOURCES OF IMPURITIES: A REVIEW

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Article Received on: 22/11/11 Revised on: 20/12/11 Approved for publication: 04/01/12

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ABSTRACT

Impurity is defined as an entity of drug substance or drug product that is not chemical entity defined as drug substance, an excipient, or other additives to drug products. In Webster's dictionary, impurity is "something that is impure or makes something else impure. In the pharmaceutical world, an impurity is generally considered as any other organic material besides the drug substance that arises out of the synthesis most of the time; inorganic contaminants are not considered as impurities unless they are toxic, such as heavy metals or arsenic. There are numerous sources of impurities and many different common terms are used for impurities such as Intermediates, Penultimate intermediates, Byproducts, Transformation products, Interaction products, related products and Degradation products. In this review, a description of different types of impurities in relation to ICH guidelines including specific examples, are presented

Key words: Impurities, drug stability, degradation

INTRODUCTION

There may be many sources for impurities in drug products and sources are same as in reference drug substances. Impurities may arise from starting materials, by-products, residual solvents, degradants formed and long term storage. Impurities can be formed from heat, light, changes in pH of formulation, interaction with packaging components and other components. Impurities can originate mainly from sources that are given below¹:

- Crystallization Related Impurities
- Stereochemistry Related Impurities
- Residual Solvents
- Synthetic Intermediates & by-products
- Formulation Related Impurities
- Impurities arising during storage
- Method Related Impurity
- Mutual interaction
- Functional groups related degradation
- Environment Related impurities

Crystallization Related Impurities

First goal in pharmaceutical manufacturing is to produce phase-pure drug substance and remains in that state as long as bulk material. It is another goal in formulation of drug substance so that it remains in same phase-pure state during manufacturing and during any storage. Solid properties of system may be affected by nature of structure adopted by compound on crystallization¹.

Stereochemistry Related Impurities

The compounds have similar chemical structure but different spatial orientation; these are considered as impurities in the API's. The single enantiomeric form of chiral drug may have better pharmacological profile and high therapeutic index. In manufacturing of single enantiomeric drug the undesirable stereoisomers are considered as organic impurities. Single isomeric drugs that are marketed include esomeprazole (S-omeprazole), levalbuterol (R-albuterol) and levofloxacin (S-ofloxacin)². The undesired optical isomer is considered as chiral impurity of drug. It is important to remember that number of chiral impurities increases with increase in number of asymmetric carbon atoms in molecule¹.

Residual Solvents

Mostly commonly used solvent in drug products is water. Water is not considered as impurity most of time. When dosage form is packaged, moisture content can be important because it may be sufficient to cause the hydrolysis. Drugs products can also be affected by water from the environment.

Hydrolysis due to presence of water causes chemical stability problems mainly in acetals & carboxylic acid derivatives. Even in non-aqueous liquid formulations, water can be present in sufficient amount that may cause degradation¹.

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 classes³. Especially, solvents in Class I, viz benzene (2ppm limit), carbon tetrachloride (4 ppm limit), methylene chloride (600 ppm), methanol (3000ppm, pyridine (200 ppm), toluene (890 ppm) should be avoided. In Class II, viz N, Ndimethylformamide (880 ppm), acetonitrile (410 ppm). Class III solvents, viz acetic acid, ethanol, acetone have permitted daily exposure of 50 mg or less per day, as per the ICH guidelines. The purity of acetone, dichloromethane, methanol and toluene are determined by selective gas chromatography (GC) method. The main contaminants of each organic solvent can be quantified by this method. The developed method allows the simultaneous determination of ethanol, isopropanol, methanol, chloroform, benzene and toluene with propionitrile as internal standard⁴.

Synthetic Intermediates & by-products

During the synthetic process, most of the impurities in pharmaceutical compounds are generated from raw materials, solvents, intermediates & by-products. A drug substance is manufactured to much more purity requirements than Raw material.

Solvents used in synthesis may contain number of impurities from traces level to higher quantity which can react with chemicals used in the synthesis to produce impurities. For example, in impurity profiling of ecstasy tablets by GC-MS

& MDMA samples⁵. Impurities are produced in intermediates via reductive amination⁶.

Formulation Related Impurities

Excipients are also sources for generation of most impurities in drug product. The drug substance undergoes various conditions during process of formulation which may cause its degradation & some undesirable reactions⁷. For example, when heat is used for drying, it may cause degradation¹. Due to hydrolysis or solvolysis, solution & suspensions are prone to degradation⁷. In US, Fluocinonide Topical solution USP, 0.05%, in 60 ml bottles was recalled because of degradation or impurities production; it leads to concentration below standard level⁸. In general, liquid dosage forms may undergo both degradation as well as microbial contamination. Water content, pH of formulation, compatibility of cations and anions, mutual interaction of the ingredients and the primary container are the critical factors. Microbiological contamination occurs due to growth of bacteria, yeast and fungi in humid and warm environment. Subsequent consumer-use of multiple-dose product either due to inappropriate use of certain preservatives or semipermeable nature of primary containers may cause the microbial contamination⁹.

In some cases, oxidation may take place for freely oxidized materials and photosensitive reactions may occur in light sensitive material¹.

Impurities arising during storage

During storage, number of impurities can be produced. For assurance of drug product safety, it is mandatory to carry out stability studies. To overcome the production of impurities, the stability characteristics can be used to store the drug substance & drug product in appropriate packaging & environmental condition. For development of best formulation the knowledge of degradation behavior of drug & its interaction with excipients is also useful¹.

Method Related Impurity

In production of parental dosage form of diclofenac sodium, 1-(2,6-dichlorophenyl) Indolin-2-one is formed as impurity when it is terminally sterilized by autoclave. The formation of indolinone derivative & sodium hydroxide occurs due to intramolecular cyclic reaction of diclofenac sodium by autoclave conditions (123+2°C). Initial pH of formulation affects formation of impurity. In BP, the concentration of impurity in final product in ampoule exceeds the limit of raw material¹⁰.

Mutual interaction: - Because of labile nature of vitamins, on aging they undergo instability in different dosage forms, mainly in liquid dosage forms. On degradation of vitamins, toxic impurities are not produced but potency of active ingredients somewhat decreases, sometimes below Pharmacopoeial specifications.

An example of mutual interaction is presence of nicotinamide in formulation containing four vitamins (Nicotinamide, pyridoxine, riboflavin & thiamine) can cause degradation of thiamine to below std. level¹¹.

Functional groups related degradation

- Ester Hydrolysis
- Hydrolysis
- Oxidative degradation
- Photolytic cleavage
- Decarboxylation

Ester Hydrolysis: - Impurities can be produced in esters due to presence of water in drug products as esters undergo

hydrolysis. Example includes -Aspirin, Benzocaine, Cefotaxime, ethyl paraben¹¹ & cefopodoxime proxetil¹².

Hydrolysis: - Hydrolysis means degradation of drug products or arising of impurities in presence of water. It is common in drugs having esters & liquid formulations e.g. benzyl penicillin, oxazepam & lincomycin¹³.

Oxidative degradation:- It means degradation of drugs due to their oxidation. Example of drugs that are susceptible to oxidative degradation includes hydrocortisone, methotrexate, and hydroxyl group directly bonded to an aromatic rings, aldehydes, nitroso and nitrite derivatives.

The hydrolytic & oxidative degradation pathways were studied in drug mazipredone in 0.1 mol/lit. HCl and NaOH at 80°C¹⁴.

Photolytic cleavage: - It means degradation of products in presence of light during manufacturing as solid or solution, packaging or during storage in shops or hospitals. Examples of the drugs that undergo Photolytic degradation is Ergometrine¹⁵, Nifedipine¹⁶, Nitroprusside, Riboflavin & Phenothiazines, fluoroquinolone antibiotics. In all these compounds, free radical intermediates are formed by photochemical energy. Most of compounds, when exposed to high energy UV exposures, they will degrade as solution¹⁷. Ciprofolxacin eye drop preparation (0.3%) is also an example of photolytic cleavage. Sunlight produces ethylene diamine analog of ciprofloxacin by photolytic cleavage¹⁸.

Decarboxylation: - It includes removal of carbon dioxide from carboxyl group when heated. It occurs in some dissolved carboxylic acid such as p-amino salicylic acid.

Photoreaction of Rufloxacin is an example of decarboxylation¹⁹.

Environment Related impurities

Environment related factors that reduce the stability of drug substances are given as

- Exposure to adverse temperature
- Light especially UV light
- Humidity

Exposure to adverse temperature Many of drug substances are labile to heat or tropical temperature. For example vitamins are very heat sensitive and undergo degradation especially in liquid formulation that causes decrease in potency²⁰.

Light especially UV light Under tropical conditions such as light and heat, Ergometrine and methyl ergometrine injection is unstable and a very low active ingredient is found when exposed to these conditions according to report of several studies. In only 50% of the marketed samples of ergometrine injections tested did the level of active ingredient comply with the BP/USP limit of 90% to 110% of the stated content. The custom-made injection of ergometrine (0.2 mg/mL) showed almost complete degradation when kept 42 hours in direct sunlight^{21, 15}.

Humidity In case of hygroscopic products, humidity may affect the bulk powder and formulated solid dosage forms. Examples of the drugs that are affected by humidity are Aspirin and Ranitidine²⁰.

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