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Pharmaceutical Impurities: An Overview

N. Rama Rao, S. S. Mani Kiran* and Prasanthi N.L.

Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur- 522034

Author for correspondence: nadendla2000@yahoo.co.in

Abstract

The impurities in pharmaceuticals are unwanted chemicals that remain with the active pharmaceutical ingredients (APIs) or develop during formulation or upon aging of both API and formulation. The presence of these unwanted chemicals even in trace amount may influence the efficacy and safety of pharmaceutical product. The control of impurities is currently a critical issue to the pharmaceutical industry. International Conference on Harmonization (ICH) formulated guidelines regarding the control of impurities. This review outlines the description of different types and origins of impurities and degradation routes with specific examples.

Keywords: *Impurities, formulation, efficacy, degradation.*

INTRODUCTION

In the present era, there is a tremendous upsurge for the impurity profiling of pharmaceutical products. Presence of impurities in trace quantity in drug substance or drug product is inevitable. Therefore, their level should be controlled and monitored. They can reinforce or diminish the pharmacological efficacy of the Active Pharmaceutical Ingredient (API). Sometimes, the effect produced by impurities can be teratogenic, mutagenic or carcinogenic. This can jeopardize the human health by affecting quality, safety and efficacy (QSE) of the product. Therefore, there is an ever-increasing interest in controlling and monitoring impurities present in API / pharmaceutical products. Hence, API impurity profiling (identification, isolation and characterization) is required. Their limits and threshold values should comply with the limits set and specified by official bodies and legislation (Pharmacopoeias and International Conference on Harmonization (ICH) guidelines). This is very important when company files Investigational New Drug Application (IND) or Abbreviated New Drug Application (ANDA). However, monitoring and controlling of impurity is different for different people. Therefore, there must be unified system to ensure that every one speaks the same language when addressing *"Issues related to impurities"*[1].

ICH has published guidelines for validation of methods for analysis of impurities in new drug substances[2a], new drug products[2b], residual solvents[2c] and microbiological impurities[2d, 2e] for registration of pharmaceuticals for human use. ICH defines impurities as *"substances in the API that are not the API itself"*. For pharmaceutical products, impurities are defined as "*substances in the product that are not the API itself or the excipients used to manufacture it"* i.e. impurities are unwanted chemicals that remain within the formulation or API in small amounts which can influence QSE, thereby causing serious health hazards. According to ICH guidelines on impurities in new drug substances and new drug products, identification of impurities below the 0.1% level is not necessary unless the potential impurities expected to be unusually potent or toxic. In all cases, impurities should be qualified. If data related to qualification of the proposed specification level of an impurity is not available then studies were required to obtain such data. According to ICH, the maximum daily dose qualification threshold is as follows[2a],

≤2g / day 0.1% or 1mg/ day intake and ≥2g/day 0.05%

As impurity profile received a critical attention from regulatory authorities, different Pharmacopoeias such as British Pharmacopoeia (BP), United States of Pharmacopoeia (USP), European Pharmacopoeia (EP) and Indian Pharmacopoeia (IP) are slowly incorporating limits to allowable levels of impurities present in new drug substances or APIs and formulations[3]. Moreover, a number of articles have stated guidelines and designed approach for isolation and identification of process related impurities and degradation products using Mass spectroscopy (MS), Nuclear Magnetic Resonance (NMR), High Performance Liquid Chromatography

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(HPLC), FT-Ion Cyclotron Resonance MS (FT-ICR-MS) and Tandem MS for pharmaceutical substances. Impurity profiling is a major concern in drug developing and processing[4,5].

CLASSIFICATION OF IMPURITIES[1]:

Impurities have been described sometimes commonly or as specified by ICH guidelines,

1. Common terminology:

Intermediates - The compounds produced during synthesis of the desired material or as part of the route of synthesis.

Penultimate intermediate – It is the last compound in the synthesis chain prior to the production of the final desired compound.

Byproduct – The compounds produced in the reaction other than the required intermediates.

Transformation product – They are theorized or non-theorized products, which produced in the reaction.

Interaction products – These products formed by the interaction of chemicals in reaction either intentionally or unintentionally.

Related products – These are chemically similar to drug substance and may even possess biological activity.

Degradation products – Compounds produced due to degradation by the effect of external factors like light, heat and moisture.

2. Official compendial terminology: According to USP impurities are discussed as;

- Impurities in official articles described as foreign substances, toxic impurities and concomitant components.
- Ordinary impurities
- Organic volatile impurities (OVI) or residual solvents

ICH terminology:

As per the ICH guidelines impurities in the new drug substances and formulations broadly classified as,

1. Organic impurities
2. Inorganic impurities
3. Residual solvents

SOURCES OF IMPURITIES[6,7]:

A detailed elaboration of various sources of impurities given here under:

Pharmaceutical formulations (medicines) or bulk pharmaceutical chemicals (BPC) used in the manufacture of APIs and formulations. Hence the two major broad sources of impurities are:

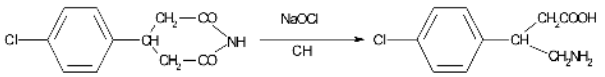
I. Synthesis related impurities.
II. Formulation related impurities.

I. SYNTHESIS RELATED IMPURITIES:

Impurities in pharmaceutical compounds or new chemical entities (NCE) arise mainly during synthetic process from raw materials, solvents, intermediates and by products. Hence, the impurities during synthetic process categorized as;

1. Organic impurities – These impurities mainly arise during synthetic process or storage of drug substance. The impurities classified as starting materials, by products, degradation products, reagents and chiral impurities.

- **a) Starting materials or Intermediates:** The impurities from the starting materials and intermediates or by products found in every drug substance if proper care not exercised to remove them in the end – product during multi step synthesis. Though products washed with solvents frequently, there is a chance for the presence of unreacted starting material in the final product. For example,
- In the synthesis of amlodipine besylate traces of 4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-2-[(2-phthalimidoethoxy)methyl]*p*-1-4-dihydroxy pyridine is the synthesis related impurity[8].
- In the synthesis of Baclofen, the last step carried out with β-(*p*-chlorophenyl) gutarimide, which on reaction with sodium hydroxide/ sodium hypochlorite solution at room temperature yields a potential impurity *p*-chloro phenyl glutaric acid, which has to be evaluated[9].

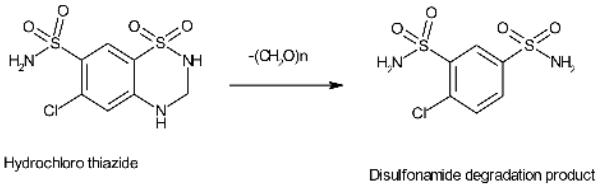


Glutarimide Baclofen

b) Degradation products:-During manufacturing of bulk drugs degradation of end products results in the formation of impurities. Degradation products arise from synthetic process, storage, formulation of dosage form and aging[10]. For example, penicillins and cephalosporins are classic examples for impurities from degradation products.

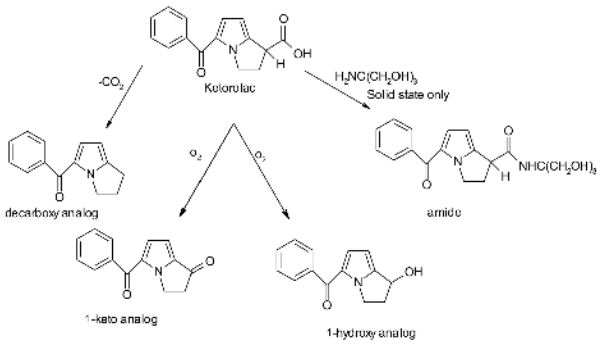
Hydrochlorothiazide has a known degradation pathway

through which it degrades to the starting material as disulfonamide in its synthesis[11].



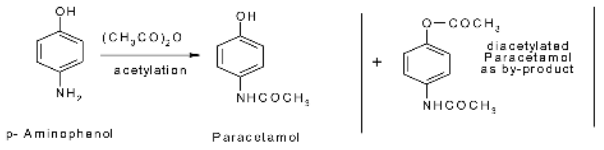
Another example, the rate of hydrolysis of mannitol containing methyl prednisolone sodium is significantly higher than lactose containing methyl prednisolone.

Degradation pathway of ketorolac in solid and solution state[11]



c) By – products: In synthetic organic chemistry, getting a single end – product with 100% yield is seldom. There is always a chance of having by-products. Because they can be formed through variety of side reactions, such as incomplete reaction, over reaction, isomerization, dimerization, rearrangement or unwanted reactions between starting materials or intermediate with chemical reagents or catalysts[12]. In the case of paracetamol bulk production, diacetylated paracetamol may forms as a by-product[3].

Production of paracetamol from intermediate *p* – Aminophenol



2. Inorganic impurities- Inorganic impurities derive from the manufacturing process and excipients. Generally, excipients contain high levels of heavy metals such as arsenic, bismuth, cadmium, chromium, copper, iron, lead, mercury, nickel and sodium. Sometimes they might present in the product during processing or they leached from packing material. For example, excipients such as hydrogenated oils and fats, which produced using metal catalysts, found to contain high concentrations of metals (platinum and palladium). This may be due to leaching from process equipment or storage container.

3. Residual solvents - Residual solvents are potentially undesirable substances. They either modify the properties of certain compounds or may be hazardous to human health. The residual solvents also affect physicochemical properties of the bulk drug substances such as crystallinity of bulk drug, which in turn may affect the dissolution properties, odor and color changes in finished products. As per the ICH guidelines, the solvents used in the manufacturing of drug substances classified in to four types[13, 14].

a) Class I solvents: Class I solvents and their permissible concentration limits given in the Table 1. These solvents not employed in the manufacture of drug substances, excipients and formulations because of their unacceptable toxicity or their deleterious effects. If use of these solvents is unavoidable, then their usage should be restricted.

b) Class II solvents: Class II solvents usage should be limited in pharmaceutical products because of their inherent toxicity. Table 2 lists class II solvents with their daily permissible exposure.

c) Class III Solvents: These are less toxic and possess lower risk to human health than class I or class II solvents[2d]. Long-term toxicity or carcinogenicity not reported, which is evident from the available data for the solvents under this category. The use of class III solvents in pharmaceuticals does not have any serious health hazard.

Some of the solvents are; *Acetic acid, anisole, butanol, 2-butanol, isopropyl acetate, methylacetate, butylacetate, ter-butyl methyl ether, pentene, cumene, Dimethyl sulfoxide, ethanol, ethylacetate, formicacid, heptane, isobutyl ketone, tetrahydrofuran, 1-pentanol, 2-propanol, methyl isobutyl ketone, propylacetate, 3-methyl-1-butanol, methyl ethylketone.*

d) Class IV Solvents: Class IV solvents, adequate toxicological data is not available. The manufacturers should justify the residual levels for these solvents in pharmaceutical products. The solvents under class IV are 1, 1-diethoxy propane, 1-1-dimethoxy propane, 2-2-

dimethoxy propane, methyl isopropyl ketone, isooctane, isopropyl ether, methyl tetrahydrofuran, petroleum ether, trichloro acetic acid.

II. FORMULATION RELATED IMPURITIES

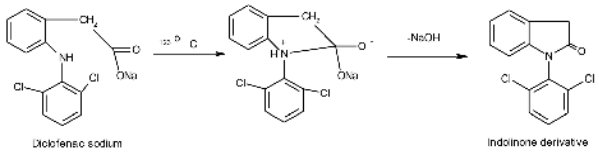
APIs formulated with excipients into solutions, tablets, capsules, semi-solids, aerosols and Novel Drug Delivery Systems. During formulation, excipients added to API to render the product elegant. They can be sometimes heterogeneous mixtures. In such a case, drug – excipient incompatibility may lead to undesirable products which can affect the therapeutic efficacy of the product. Any undesirable reaction produced due to the impurities associated with excipients can provide a ripe source for many potential reactions. The source of these potential reactions may be because of excess amount of water, which is usually present in API or excipients as residue due to use of hygroscopic materials. In addition, other solvents, which used in the synthesis of API or excipients, may also interact with excipients resulting in impurities.

a) Dosage form related impurities: - The impurities in the dosage forms like solutions can be significant. Precipitation of main ingredient can occur due to various factors like pH, environment or leaching. For example, precipitation of imipramine HCl with sodium bisulfite and pH alteration of lidocaine HCl solution in presence of 5% dextrose in saline or normal saline solution and lactated ringer solution have been reported[12]. Following are some of the examples of the excipients that affect the stability of pharmaceutical solutions as shown in Table 3. Although the pharmaceutical companies perform pre-formulation studies, including a stability study, before marketing the products, sometimes the dosage form factors that influence drug stability force the company to recall the product. Fluocinonide Topical solution USP, 0.05% in 60-mL bottles, recalled in the United States because of degradation/impurities leading to sub-potency[15].

Pharmaceutical solids: - In the presence of excipients and moisture, topochemical and nucleation reactions occur, some of these are first order reactions. For example, presence of sodium CMC during granulation of aminopyrine, papverine, theobromine and salicylic acid tablets caused reduced discoloration. Presence of lactose induces discoloration of several drugs in solid dosage forms. Moisture adsorption and tablet expansion occur more readily with α-lactose tablets due to formation of monohydrate.

b) Method related impurity: -

A known impurity, 1-(2, 6-dichlorophenyl) indolin-2-one is formed in the diclofenac sodium ampoules. Formation of this impurity depends on initial pH of the preparation and the condition of sterilization i.e., autoclave method (123±2°C) that enforce the intramolecular cyclic reaction of diclofenac sodium forming indolinone derivative and sodium hydroxide[16].



c) Environmental related impurity:-

1. Temperature: - During formulation of vitamins and antibiotics, especially extreme care should be exercised to prevent them from degradation. Because these classes of compounds are heat liable when subjected to extreme temperature, loss of potency takes place.

2. Light - UV light: - Light is one of the means by which the formulation degrades because of photolytic reaction. Exposure to light is known to be deleterious on a number of pharmaceutical compounds. For example, sunlight having about 8000 foot-candles can destruct nearly 34% of vitamin–B_{12} in 24hrs[17]. It is necessary to control the wavelength and intensity of light and number of photons actually absorbed by material. Photolytic degradation of fumagillin in ethanol was reported as a first order reaction that caused by light of wavelength below 400 nm. The lists of compounds that affected by light or catalyst are given in Table 4. Moreover, several studies have reported that ergometrine as well as ergometrine injection are unstable under tropical condition such as light and heat[18]. The custom-made injection of ergometrine (0.2mg/ml) showed almost complete degradation when kept 42hrs in direct sunlight.

3. Humidity: - Humidity is one of the important key factors incase of hygroscopic compounds. It is detrimental to both bulk powder and formulated solid dosage form. The classic examples are ranitidine and aspirin[3].

Impurities on Aging: -

a) Mutual interaction amongst ingredients: - Most often, vitamins are highly prone to instability on aging in different dosage forms. i.e., degradation of vitamins such as folic acid, thiamine and cyanocobalamines does not yield toxic impurities but lose their potency well below compendial specifications. Moreover, presence of nicotinamide in formulation containing four vitamins (nicotinamide, pyridoxine, riboflavin and thiamine) cause the degradation of thiamine to a substandard level within a one year shelf life of vitamin–B complex injection[19]. The custom-made formulation in a simple distilled water vehicle and in a typical formulated vehicle included with di-sodium edetate, benzyl alcohol also investigated and similar mutual interaction observed.

b) Hydrolysis: - A reaction in which water is the reactant causing precipitation. Well-known examples of such reactions in pharmaceutical compounds are esters and amides. Many drugs are derivatives of carboxylic acids or contain functional groups based on the moiety. For example esters, amides, lactones, lactams, imides and carbamates, which are susceptible to acid base hydrolysis, e.g., aspirin, atropine, chloramphenicol, barbiturates, chlordiazepoxide, oxazepam[12] and lincomycin.

c) Oxidation: - Drugs which prone to oxidation are hydrocortisone, methotrexate, adinazolam, catecholamine, conjugated-dienes (Vitamin–A), heterocyclic aromatic rings, nitroso and nitrite derivatives. In pharmaceuticals, the most common form of oxidative decomposition is auto oxidation through a free radical chain process. For example, auto-oxidation of ascorbic acid studies reveals that cupric ion known to oxidize ascorbic acid rapidly to dehydroascorbic acid and potassium cyanide. As a result, there is a cleavage of chain due to the formation of copper complexes. From the stability investigations on substituted 5-amino-ethyl-1, 3benzenediol sulfate (AEB) revealed that copper effectively catalyses AEB degradation down to 10 ppb level in presence of oxygen, leading to discoloration of product. The effectiveness of metals in terms of AEB degradation follows $Cu^{2+} > Fe^{3+} > Ca^{2+}$.

d) Photolysis: - Photolytic cleavage on aging includes examples of pharmaceutical drugs or products that are prone to degradation on exposure to UV-light. During manufacturing process as solid or solution, packaging or on storage, drugs like ergometrine, nifedipine, nitropruside, riboflavin and phenothiazines are liable to photo oxidation[20-22]. This oxidation involves generation of free radical intermediate, which will degrade the products. For example, the formulation of ciprofloxacin eye drop 0.3% on exposure to UV light induces photolysis thereby resulting in the formation of ethylene di-amine analogue of ciprofloxacin[23].

e) Decarboxylation: - Some of the carboxylic acids such as *p*-amino salicylic acid shown loss of carbon dioxide from carboxyl group when heated. For instance, photo reaction of rufloxacin tablet enteric coated with cellulose acetate phthalate (CAP) and sub-coating with calcium carbonate cause hydrolysis of CAP liberating acetic acid, which on reacting with calcium carbonate produced carbon dioxide, a by product that blew off the cap from the bottle after cap was loosened[24].

f) Packaging material: - Impurities result also from packaging materials i.e., containers and closures[25]. For most drugs the reactive species for impurities consists of;

Water – hydrolysis of active ingredient.

Small electrophiles – Aldehydes and carboxylic acid derivatives.

Peroxides – oxidize some drugs.

Metals – catalyze oxidation of drugs and their degradation pathway.

Extractable or leachables – Emerge from glass, rubber stoppers and plastic materials, in which oxides like NO_2, SiO_2, CaO, MgO are major components leached or extracted from glass.

Some examples of synthetic materials include styrene from polystyrene, diethylhexylpthalate (DEHP) plasticizer in PVC, dioctyltin iso octyl mercaptoacetate stabilizer for PVC, zinc stearate stabilizer in PVC and polypropylene.

Analytical methodology:

In new drug development, impurity profiling (characterization and isolation) plays a vital role. Regulatory bodies such as US FDA, EU mandates to estimate the impurity present above 0.1% level. ICH provided guidance document for evaluate and analytical validation of impurities. Thus, variety of analytical methodologies evolved to monitor impurities present in New Drug substances and new drug products. The

primary criteria of analytical methodology are to differentiate the compounds of interest and impurities. A wide variety of highly sophisticated equipments are available in characterizing the impurities such methods include spectroscopic methods, chromatographic methods and their combinations[26-29].

Remedies:

1. Critical factors for controlling impurities in API-

a) During crystallization, the manufacturer of API should take care to produce finer crystals to prevent entrapment of minute amounts of chemicals from mother liquor, which causes the degradation of drug.

b) Washing the wet cake or powder should be thorough to remove unwanted chemicals including residual solvents.

2. Packaging- Light sensitive pharmaceuticals have to pack in light protective packaging.

3. Production method selection is depending upon the stability studies. For diclofenac sodium injections, the aseptic filtration process has been recently recommended as the alternative to the autoclave method that produces impurity[16].

4. Pharmacopoeias should take measures to incorporate impurity limits for drug products made of raw materials. ICH should lay stringent regulations to incorporate limits for the impurities present in both drug substance and drug products. Diclofenac sodium is an example where an impurity limit is not mentioned in the case of injections.

CONCLUSION:

Identification of impurities is very important task during the synthesis of drug substances and manufacture of dosage forms. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantitation of several organic and inorganic impurities, usually accompany with APIs and finished products. ICH has outlined guidelines with regard to impurities but much more need to be required. There is strong requirement to have unified specifications/standards with regard to impurities.

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Table 1: Class I Residual Solvents

Residual solvent	Concentration limit (ppm)
Benzene	2 (Carcinogenic)
Carbon tetrachloride	4 (Toxic)
1,1 Dichloro ethene	8 (Toxic)
1,2 Dichloro ethene	5 (Toxic)
1,1,1 trichloro ethane	1500 (Environmental hazard)

Table 2: Class II Solvents with Their Permissible Daily Exposure Limits

Solvent	Permissible daily exposure (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,1-Dimethoxyethane	1.0	100
N,N-Dimehtyl acetamide	10.9	1090
N,N-Dimethyl formamide	8.8	880
1,2-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxy ethanol	0.5	50
Methyl butyl ketone	0.5	50
Methyl cyclo hexane	11.8	1180
N-methyl pyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloro ethane	0.8	80
Xylenes	21.7	2170

Table 3 : - Effect of Pharmaceutical Aids on Stability of Active Ingredients

Active ingredient	Pharamaceutical aid	Effect
Kanamycin	Honey, sugar syrup	Loss of activity at room temperature (RT)
Cholecalciferol	2%polyoxy ethylene ester surfactant, polysorbate	Change in pH resulted, degradation of active ingredient.
Tetracyclines	Calcium or magnesium or metal ions	Complexation
Thiomersal	Bromine, chloride, iodide	Form different soluble halides of cationic mercury compounds.
Adrenaline	Boric acid, povidone	Stabilization
Tryptophan	Sodium pyrosulfite, oxygen	Discoloration, precipitation.

Table 4: Drugs Affected By Light or Catalyst

S.No	API / Drug	Light /catalyst
1	Epinephrine	Sodium metabisulfite
2	Penicillins	Sodium bisulfite
3	Nalidixate sodium	Light
4	Antipyrine	Light
5	Phenothiazine	Light
6	Dihydroergotamine mesylate	Light
7.	Ergometrine	Light
8.	Nifedipine	Light
9.	Ofloxacin	Light
10	Nitropruside	Light
11	Riboflavin	Light
12	Fluroquinolones	Light
13	Penicillin G potassium	Monohydrogen and dihydrogen citrate ions.

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