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Review Article

Pharmaceutical Impurities: A Review

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Abstract

A quality drug when marketed, has various factors associated with it one of the crucial factors being impurities identification at each stage of its development. Maintaining the quality, safety and efficacy of a drug indirectly protects the consumers' right to health. A well accepted fact is that some impurities are unavoidable and will be present in trace amounts hence ICH comes into picture and through its guidelines and policies establishes the specification limits, evaluation and control of impurities. The regulatory bodies and drug development authorities look up to these guidelines for launching a quality drug into the market. Validation of analytical process for impurity identification is performed to establish the impurity profile of any drug substance. Hence the major focus of this review article is on characterization of impurities, its sources, establishment of impurity profile and analytical approaches to establish its profile.

Keywords: Impurities, International Conference on Harmonization, Formulation, Profiling, Isolation.

1. Introduction

Consumer's protection depends on a products safety, characteristics, purity of the components. All these are regulated by The U.S. Food and Drug Administration (FDA). Small amount of impurity can change the efficacy, toxicity of any pharmaceutical compounds. International Conference on Harmonization said that impurities are unwanted chemicals that remain with the Active Pharmaceutical Ingredients (APIs) or develop during formulation or develop upon ageing of both APIs and formulated APIs [1-3].

The major challenge of any industry is to produce quality product and for that reason, it is necessary to conduct vigorous quality control checks in order to maintain the quality and purity of output from each industry. Raw materials, manufacturing method, crystallization and purification process play an important role to maintain the purity of any product. Analytical chemistry which is related to the developmental concepts in industry also changes with time. Stringent limits of purity and impurity is specified by the various pharmacopoeias. Modern separation methods are advanced as these methods simultaneously separate and quantify the components to make the separation and characterization of impurities easier.

As safety and quality of pharmaceutical products can be affected by the impurities present in the Active Pharmaceutical Ingredients (APIs) the impurity profile study of the API to be used in the manufacturing of drug substance. Thus, impurity profiling like identification, Isolation & characterization are done and their threshold values comply with the limits set and specified by official bodies.

"Issue related to impurities" addressing must be the same for each and every sectors and there must be a unified system to ensure it. International Conference on Harmonization (ICH) has published guidelines for validation methods for analysis of impurities in new drug products, new drug substances, residual solvents & microbiological impurities [4-6] for registration of pharmaceuticals. ICH defines impurities as "substance in the API itself." For pharmaceutical products, impurities are defined as "substances in the product that are not the API itself or 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 International

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Conference on Harmonization (ICH) guidelines identifying and characterizing all impurities that are present at a level of 0.10% or more are recommended [7].

Different pharmacopoeias such as United States of Pharmacopoeia (USP), British Pharmacopoeia (BP), Indian Pharmacopoeia (IP) and European Pharmacopoeia (EP) are slowly incorporating limits to allowable levels of impurities present in new drug substances or API and formulations to give critical regulatory attention [8].

2. Regulatory Guidelines on impurity

International Conference on Harmonization guidance of Technical Requirements for Registration of Pharmaceuticals for Human Use is inscribed by The United States Food and Drug Administration (FDA).

The FDA has the assigned responsibility of ensuring the safety and efficacy of drugs. The various regulatory guidelines [2] regarding impurities are as follows:

1. ICH guidelines “stability testing of new drug substances and products"- Q1A
2. ICH guidelines “Impurities in New Drug Substances”- Q3A
3. ICH guidelines “Impurities in New Drug Products”- Q3B
4. ICH guidelines “Impurities: Guidelines for residual solvents”- Q3C
5. US-FDA guidelines “NDAs -Impurities in New Drug Substances”
6. US-FDA guidelines “ANDAs – Impurities in New Drug Substances”
7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia

Table 1: Regulatory Guidelines on Impurity

Q1A(R) Stability Testing of New Drug Substances and Products	ICH
Q3A(R) Impurities in Drug Substances	ICH
Q3B Impurities in Drug Products	ICH
Q3C Impurities: Residual Solvents	ICH
Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	ICH
NDA: Impurities in Drug Substances	FDA
ANDA: Impurities in Drug Substances	FDA

3. Qualification of Impurities

The impurity profile of drug substance may vary for processes like scale-up changes, synthetic route change and changes made to key intermediates. New Molecular Entities (NMEs) limits are classified and restricted by the ICH. Studies are needed to be done to ensure that the impurity limits does not exceed beyond the range given in the Table no 2. Qualification process helps to acquire and evaluate data that establishes the biological safety of an individual impurity [9].

Table 2: Thresholds

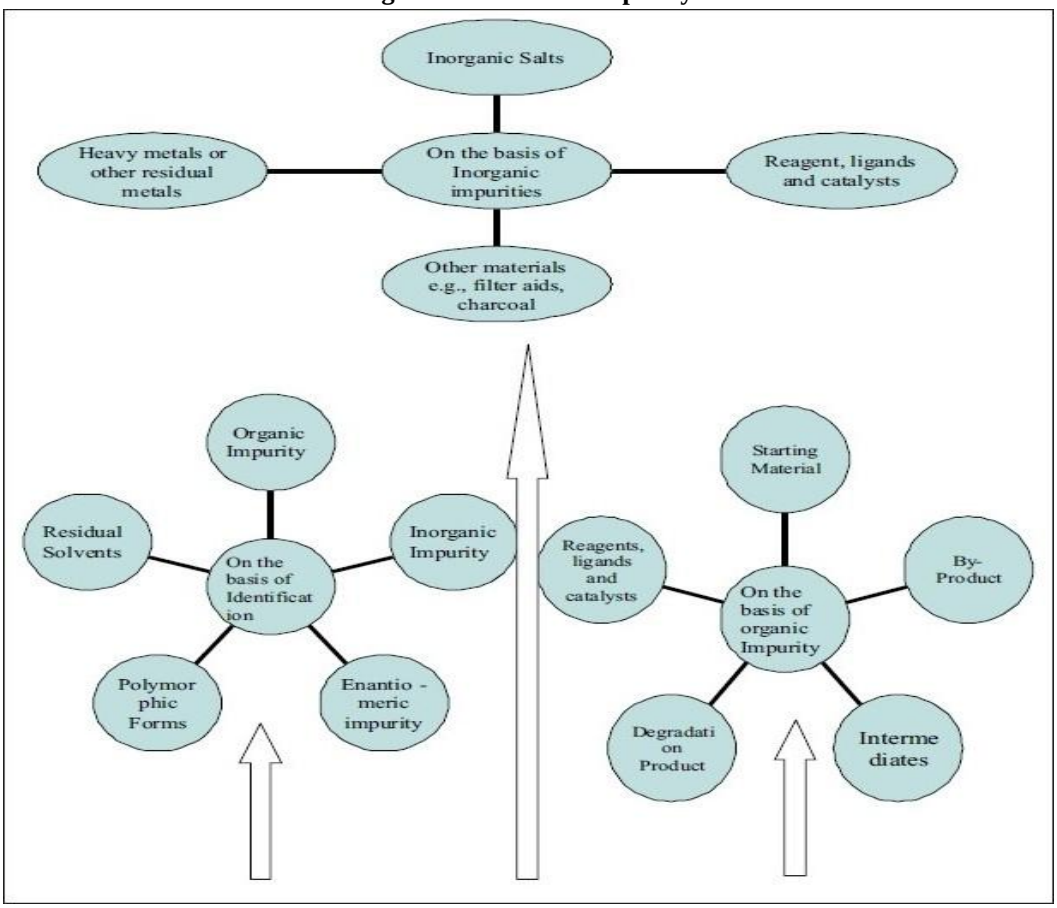
Maximum daily dose[x]	Reporting threshold [y, z]	Identification threshold [z]	Qualification threshold
< 2g/day	0.05%	0.1% or 1 mg per day intake (whichever is lower)	0.15% or 1 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

x. The amount of drug substance administered per day.
y. Higher reporting thresholds should be scientifically justified.
z. Lower thresholds can be appropriate if the impurity is unusually toxic.

4. Sources of Impurity

Compound investigated in drug discovery leads to a significant analytical challenge for the characterization, quantization, and detection of the compounds [10]. Here, in Figure 1, we have summarized all classes of impurities.

Figure 1: Sources of impurity



4.1 Synthesis Related Impurity [11]

Impurities in pharmaceutical compounds are mainly formed through the synthesis process as the product is contaminated by raw materials, solvents, intermediates and by-products. A general idea of these impurities is given below.

Table 3: Sources of impurity

Process related drug substance	Organic or Inorganic Reagent Catalysts	Process related drug Substance
Degradation drug Substance	Organic Degradation Products	Degradation drug Substance
Degradation drug product	Organic Excipient interaction Products	Degradation drug Product

4.2 Organic Impurities

These types of impurities form during the manufacturing process or during storage of the drug substance. The sub- types of these impurities are given below.

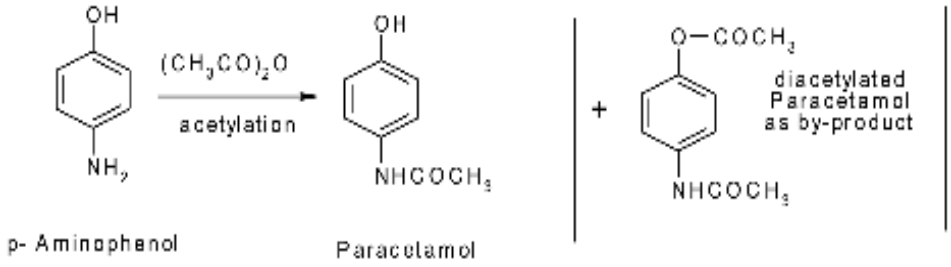
4.2.1 Starting Materials or Intermediate Impurities

During multistep synthesis process there are high chances of impurities formed as by products, intermediates are produced. So, special care is needed. It results in unreacted starting material in the final product.

Example:

In the synthesis of Baclofen, the last step carried out with β-(p-chlorophenyl) gutarimide, which on reaction with NaOH/sodium hypochlorite solution at room temperature yields a potential impurity p-chlorophenyl glutaric acid, which has to be evaluated

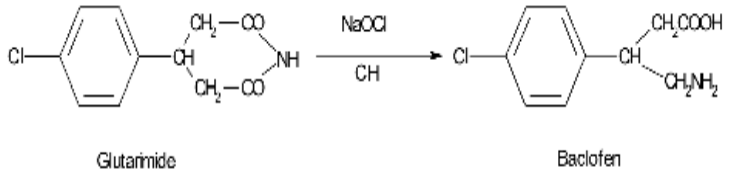
Figure 2: Synthesis of Baclofen



4.2.2. Degradation products

Product degradation happens during the synthetic process, storage, formulation of dosage form [12] and aging. Authoritative examples for impurities from degradation products are penicillin and cephalosporin. Another degradation pathway is shown in Hydrochlorothiazide through which it degrades to the disulfonamide in its synthesis [13].

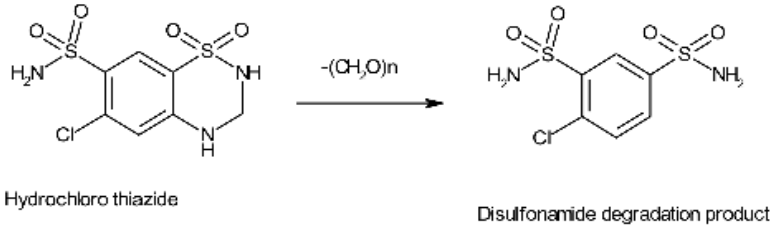
Figure 3: Disulfonamide degradation product



4.2.3. By-products

In organic chemistry 100% pure product is not generally formed as there is always a chance of having by-products. By products can be formed through variety of side reactions, such as incomplete reaction, rearrangement, dimerization, over reaction, isomerization or unwanted reactions between starting materials [14]. For example diacetylated paracetamol may forms as a by-product In the case of paracetamol production [15].

Figure 4: Production of paracetamol from intermediate *p* – Aminophenol



4.3. Inorganic Impurities

Inorganic impurities are also obtained from the manufacturing processes which are used in bulk drug formulation. They are normally known and identified.

4.3.1. Enantiomeric impurities

Single enantiomeric form of a chiral drug provides greater chemical entity. It also helps to provide better therapeutic Index. Conversely, the pharmacokinetic profile of ofloxacin (R-isomeric form) and levofloxacin (S-isomeric form) are similar, suggesting the lack of advantages of single isomer [16].

4.3.1.1. Reagent, Ligands and Catalysts

These impurities are pretty rare. Proper care during the manufacturing process avoids the chance of these kinds of impurities.

4.3.1.2. Heavy Metals

Water is essential during manufacturing process and it is the main source of heavy metals, like Ar, Cd, Cr, Na, Mg, Mn, etc. These can be avoided by the use of demineralization plant, reverse osmosis technique that produces mineral free water.

4.3.1.3. Other Materials (Filter Aids, Charcoal)

The filters or filtering aids are routinely used in the bulk drugs manufacturing plants and sometimes activated carbon is also used which acts as a source of impurity. For that reason regular monitoring of fibres and black particles are needed to avoid the contamination.

4.3. Residual solvents

They are potentially undesirable substances which either hazardous to human health or modify the properties of certain compounds. The residual solvents also affect physicochemical properties like crystalline of bulk drug, which affect the dissolution properties, colour changes in finished products. ICH classified these substances in to four types [17, 18].

4.3.1. Class I solvents

These solvents are either avoided or restricted to a limit in the manufacture of excipients and drug substances because of their unacceptable toxicity or their deleterious effects. These are generally carcinogens.

Table 4: Class I Residual Solvents

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

4.3.2. Class II solvents

As Class II solvents are inherently toxic, their usage should be limited in pharmaceutical Industry. These are generally Non-genotoxic, animal carcinogens and possible neurotoxicants.

Table 5: 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
Solvent	**Permissible daily exposure (mg/day)**	**Concentration limit (ppm)**
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

4.3.3. Class III Solvents

As they are less toxic and possess lower risk to human health than class I or class II solvents, they do not have any serious health hazard. According to several data's, long term toxicity is generally not reported.

4.4. Formulation-related impurities

Drug substance varies with conditions that lead to its degradation or other chemical reactions. Solutions and suspensions are prone to degradation due to hydrolysis. Water used in formulation contribute to not only its impurity but also provide stimulation for process like hydrolysis and catalysis.

The formulation related impurities can be classified as follows:

i. Method related
ii. Environmental related

The primary environmental factors that can reduce stability can be sub classified

i. Exposures to adverse temperatures
ii. Light-especially UV light
iii. Humidity

Dosage form related

i. Mutual interaction amongst ingredients
ii. Functional group- related typical degradation
   a) Ester hydrolysis
   b) Hydrolysis
   c) Oxidative degradation
   d) Photolytic cleavage
   e) Decarboxylation

4.5. Metabolite impurities

By products formed by drugs after instigation in body are generally known as Metabolite impurities. Metabolite impurities can be formed during metabolism as the API and drug product in the body is exposed to various enzymes [19].

Examples are asenapine *N*-oxide, asenapine desmethyl, and ciprofoxacin ethyl diamino impurity, which are formed as process impurities, but are also metabolites of the same process.

5. Analytical method development

Meaningful and reliable analytical data is needed to produce new drug various stages of the development [20-22].

a) Sample set selection for analytical method development

b) Screening of Chromatographic conditions and Phases, typically using the linear solvent- strength model of gradient elution.

c) Optimization of the method to fine-tune parameters related to ruggedness and robustness

The impurities can be identified predominantly by following methods:

i. Separation method
ii. Isolation method
iii. Characterization method
iv. Reference standard method
v. Spectroscopic method

Table 6: Achiral method development process

Impurity type	Impurity source
Process-related drug substance	- Organic - Starting material - Intermediate - By-product - Impurity in starting material
Process-related drug product	- Organic or inorganic - Reagents, catalysts, etc
Degradation drug substance or drug product	- Organic - Degradation products
Degradation drug product	- Organic - Excipient interaction

6. Remedies

Critical factors for controlling impurities in active pharmaceutical ingredients (API). During crystallization chemicals from mother liquor causes the degradation of drug if they are entrapped. So the manufacturer of API should take care to produce finer crystals to prevent entrapment. Proper washing is needed to remove unwanted chemicals including residual solvents. Light sensitive pharmaceuticals have to be packed in proper way to prevent exposure of light. Production method selection should be stability study dependent. In case of diclofenac sodium injections, the aseptic filtration process has been used instead of the autoclave method to produce quality product [29]. Over all pharmacopoeias should be more limit specific, precise and regulatory authorities like ICH and FDA should be strict regarding this matter.

Table 7: Current marketed formulation which contain impurity [23]

Drug	Impurity	Method
Amphotericin B	Tetraenes	Ultra Violet Spectroscopy
Atopine sulphate	Apo atopine	Ultra Violet Spectroscopy
Cloxacilin	N,N, dimethylaniline	Gas Chromatography
Doxirubicine hydrochloride	Acetone &Ethanol	Gas Chromatography
Dextrose	5-hydroxy methyl fulfural	Ultra violet spectroscopy
Ethambytal Hydrochloride	2 amino butanol	Thin layer Chromatography
Flurescene sodium	Dimethyl formaamide	Gas Chromatography
Farmyctin Sulphate	Neamine	Thin layer Chromatography
Marcptopurine	Hypoxinthine	Ultra violet spectroscopy

7. Applications

Numerous applications have hunted for the areas of drug designing, in monitoring quality, stability, and safety of pharmaceutical compounds. The applications include alkaloids, amines, analgesics, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, macromolecules, steroids etc [24].

Table 8: Goals of impurity investigations [25]

Process-related impurities	Degradation–related impurities
Identify significant impurities	Identify potential degradation product through stress testing and actual degradation products through stability studies.
Determine origin of impurities and method for elimination or reduction	Understand degradation pathway and methods to minimize degradation.
Establish a control system for impurities involving: 1) Processing/manufacturing conditions 2) Suitable analytical methods/ specifications	Establish a control system for impurities involving: 1) Processing/manufacturing Conditions 2) Suitable analytical methods/ Specifications 3)Long term storage conditions including packaging 4) Formulation.

8. Conclusion

A quality drug helps in consumer protection hence identifying impurities during the developmental stages should be one of the primary agendas of manufacturing companies .identification of impurities establishes an overall profile of a drug which includes its toxicity and safety limits, limits of quantization and detection. Identification and isolation of impurities should start right from using API till the finished dosage form of a drug.

There should be well established and standard specifications in the guidelines for overall control and isolation of impurities which should serve as a guiding specification to all the regulatory agencies and manufacturers. Validation of methods to identify and characterize impurities is a good approach and is currently being in practice for evaluation of impurities. It's been rightly said that change is the only constant hence we should always look for innovation to establish methods and techniques to identify and isolate impurities for safe and effective drug products.

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