International Journal for Pharmaceutical Research Scholars (IJPRS)

V-2, I-2, 2013 ISSN No: 2277 - 7873

REVIEW ARTICLE

Overview on Impurity Profiling

Pradeep Patil*[1], Dr. Vaidya I[1]

*[1]*Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar – 421003.*

Manuscript No: IJPRS/V2/I2/00052, Received On: 06/03/2013, Accepted On: 07/04/2013

ABSTRACT

Impurity profiling is the process of acquiring and evaluating data that establishes biological safety of an individual impurity. 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 control of impurities is currently a critical issue to the pharmaceutical industry. International Conference on Harmonization (ICH) formulated guidelines regarding the control of impurities. Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and the identification of impurities in Active Pharmaceutical Ingredient's (API's). Identification of impurities is done by TLC, HPLC, The advent of hyphenated techniques has revolutionized impurity profiling, by not only separation but structural elucidation of impurities as well. The most exploited techniques, for impurity profiling of drugs are LC-MS-MS, LC-NMR, LC-NMR-MS, GC-MS, and LC-MS.

KEYWORDS

Impurity profiling, HPLC, Hyphenated Methods, ICH guidelines.

INTRODUCTION

ICH defines impurities as for pharmaceutical products; impurities are 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 amount[1]. Presence of impurities in trace amount in drug substance is unable to avoid. They can lowered or change the pharmacological efficacy of active pharmaceutical ingredients (API). Sometimes the effect produced by impurities can be teratogenic, mutagenic or carcinogenic. This can be fetal for human health therefore; there is an ever increasing interest in controlling and monitoring impurities present in API/pharmaceutical products. Hence API impurity profiling is required.[2]

***Address for Correspondence:**
Pradeep B. Patil
Dr. L. H. Hiranandani College of Pharmacy,
Ulhasnagar – 421003. India.
E-Mail Id: ppatilpradeep@gmail.com

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 BP and USP. The United States Food and Drug Administration (FDA) have endorsed the guidance prepared under the auspices of the ICH. The impurity profile of pharmaceuticals is of increasing importance as drug safety receives more and more attention from the public and from the media. Several recent books and journal reviews address this topic and guidelines are available from US and international authorities.[3]

According to ICH guidelines on impurities in new drug products identification of impurities below the 0.1% level is not considered to be necessary unless the potential impurities are expected to be unusually potent or toxic. In all cases impurities should be qualified[4]. A number

of articles[5-7] have stated guidelines and designed approaches for isolation and identification of process-related impurities and degradation products, using Mass spectrometry (MS), Nuclear Magnetic Resonance (NMR), High Performance Liquid Chromatography (HPLC), Tandem Mass Spectrometry for pharmaceutical substances. Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an important part of drug development and regulatory assessment.

Present article reveals different impurities found in the API's, methods for identifying them and the possible measures to deal with the interferences caused by them.

Terminology for Impurity

Impurities have been named differently by various groups of scientists who deal with them. Terms that are used by official bodies such as compendia or that have been found acceptable by ICH and various regulatory bodies.

1. Common Names[8]

Various terms that have been commonly used to describe impurities are listed alphabetically below.

- By-product
- Degradation product
- Interaction product
- Intermediate
- Penultimate intermediate
- Related product
- Transformation product

2. U.S. Pharmacopeia Terminology[9]

The United States Pharmacopeia (USP) discusses impurities in various sections:

- Impurities in Official Articles
- Ordinary Impurities
- Organic Volatile Impurities

The following terms also been used to describe impurities:

- Concomitant components
- Foreign substances
- Ordinary impurities
- Organic volatile impurities
- Toxic impurities

3. ICH Terminology[4]

According to ICH guidelines impurities can be broadly classified into the following three Categories for the drug substance produced by chemical synthesis.

- **Organic impurities:** starting materials, process-related products, intermediates, and degradation products.
- **Inorganic impurities:** salts, catalysts, ligands, and heavy metals or other residual metals.
- **Residual solvents:** organic and inorganic liquids used during production.

Regulatory Guidelines on Impurity[10]

The United States Food and Drug Administration (FDA) have endorsed the guidance prepared under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

The FDA has the assigned responsibility of ensuring the safety and efficacy of drugs. This requires that an IND be filed with the FDA prior to initiation of any clinical studies. An NDA has to be filed and approved before a drug can be commercialized. Information on the chemistry, manufacturing, and control (CMC) has to be filed in the IND as per 21 CFR 312.23(a) for a drug substance and drug product.

Sources of Impurity

I. Synthesis Related Impurity[11]

Impurities in pharmaceutical compounds or new chemical entities (NCE) arise mainly during synthetic process from raw materials, solvents,

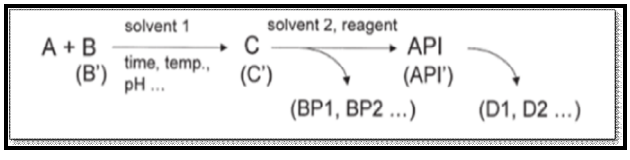
intermediates, by-products. A generalized scheme for the synthesis of a drug substance is shown in Figure below [9]

Table 1: Regulatory Guidelines on Impurity

	Title	Authorship
1	Q1A(R) Stability Testing of New Drug Substances and Products	ICH
2	Q3A(R) Impurities in Drug Substances	ICH
3	Q3B Impurities in Drug Products	ICH
4	Q3C Impurities: Residual Solvents	ICH
5	Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances	ICH
6	NDA: Impurities in Drug Substances	FDA
7	ANDA: Impurities in Drug Substances	FDA

Table 2: Sources of impurity

1.	Process-related drug substance	Organic or Inorganic Reagent catalysts	Process-related drug substance
2.	Degradation drug substance	Organic Degradation products	Degradation drug substance
3.	Degradation drug product	Organic Excipient interaction products	Degradation drug product



A, B = Starting materials

C = Intermediate

C' = Intermediate impurity with potential to form API'

API = Active pharmaceutical ingredient

API' = Modified active pharmaceutical ingredient resulting from B' and C'

B'= Starting material impurity with potential to form C' and API'

BP= reaction by-product

D= degradation product

The impurities during synthetic process categorized as;

1. *Organic Impurity -*

Organic impurities can be explained by

a) Starting Materials or Intermediates:

The impurities from the starting materials & 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. Results in unreacted starting material in the final product.

E.g. 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.

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.

c) By – Products:

By products 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. In the case of paracetamol

bulk production, diacetylated paracetamol may forms as a by-product.

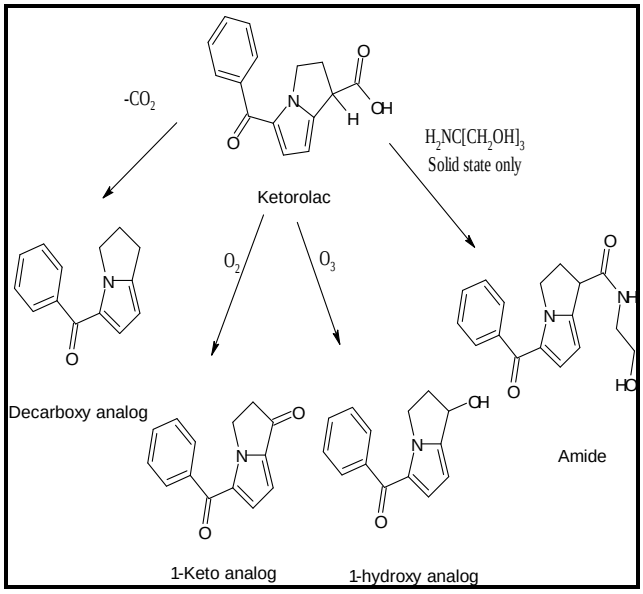


Figure 1: Degradation Pathway of Ketorolac in Solid and Solution State

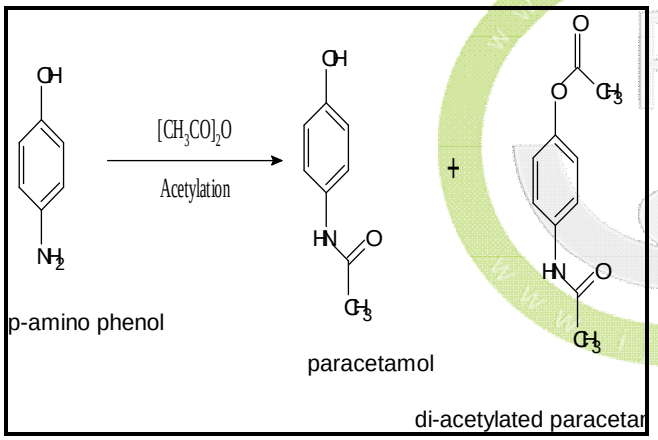


Figure 2: Production of Paracetamol from Intermediate *p* –Aminophenol

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, sodium etc. Sometimes they might present in the product during processing or they leached from packing material.

- Reagents, ligands, and catalysts
- Heavy metals
- Other materials (e.g. filter aids, charcoal)

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 classified in to four types

Class I solvents: Class I solvents and their permissible concentration limits given in the. These solvents not employed in the manufacture of drug substances, because of their unacceptable toxicity or their deleterious effects.

Table 3: 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 ethane	5 (Toxic)
1,1,1 trichloro ethane	1500 (Environmental hazard)

Class II Solvents: Class II solvents usage should be limited in pharmaceutical products because of their inherent toxicity lists class II solvents with their daily permissible exposure as follows:

Class III Solvents: These are less toxic and possess lower risk to human health than class I or class II solvents. Some of the solvents are; Acetic acid, anisole, butanol, 2-butanol, isopropyl acetate, methylacetate, butylacetate, ter-butyl methyl ether.

Table 4: Class II Solvents with their Permissible Daily Exposure Limits

Sr no	Solvents	Permissible daily conc. exposure (mg/day) (ppm)	Limit
1	cyclohexane	38.8	3380
2	Acetonitrile	4.1	410
3	Hexane	2.9	290
4	Chloroform	0.6	600
5	methanol	30.0	3000
6	Pyridine	2.0	200

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 [11]

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.

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. E.g., precipitation of imipramine HCl with sodium bisulfate 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.

b) Method Related Impurity:

Impurity, 1-(2, 6-dichlorophenyl) indolin-2-oneis formed in the diclofenac sodium ampoules when autoclave method (123±2ºC) that enforce the intramolecular cyclic reactionof diclofenac sodium forming indolinone derivative and 16 sodium hydroxide.

c) Environmental Related Impurity:

Temperature: During formulation of vitamins and antibiotics is heat liable when subjected to extreme temperature, loss of potency takes place.

Light - UV light: Light is one of the means by which the formulation degrades because of photolytic reaction. **E.g**. Sunlight having about 8000 foot-candles can destruct nearly 34% 17 of vitamin–B in 24hrs.

Table 5: The lists of compounds that affected by light or catalyst.

Sr. No.	API/DRUG	Light/Catalyst
1	Epinephrine	Sodium metabisulfite
2	Penicillin	Sodium bisulfite
3	Phenothiazine	light
4	Dihydroergotamine mesylate	Light
5	Ergometrine	Light
6	Nifedipine	Light

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

d) Impurities on Aging

Table 6: Impurities on ageing and conditions

		Thermolytic	Hydrolytic	Photolytic
1.	**Solid state**	55, 70, 85_C, Low humidity (e.g., <30% RH or no humidity control); 4–6 weeks	55, 70, 85_C, High humidity (e.g., >70% RH); 4–6 weeks	5–10_the ICH min. confirmatory exposure; (1) thin layer of powder; (2) thin film (optional)
2.	**Solution**		Aqueous solutions or slurries, pH 1–13, RT-70_C, 2–4 weeks	Aqueous solutions or slurries, 5–10 the ICH minimum confirmatory exposure; At pH's above and below relevant pK's.

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.

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. Eg. Esters, amides, lactones, lactams, imides and carbamates, which are susceptible to acid base hydrolysis,

c) Oxidation:

There are three major pathways,

(1) Autoxidation or radical-mediated oxidation,

(2) Peroxide-mediated, and

(3) Photo chemically induced.

Drugs which prone to oxidation are hydrocortisone, adinazolam, catecholamine, conjugated-dienes (Vitamin–A), heterocyclic aromatic rings, nitroso and nitrite derivatives. In pharmaceuticals, the most common for oxidative decomposition is auto-oxidation through a free radical chain process.

E.g. Auto-oxidation of ascorbic acid studies reveals that cupric ion known to oxidize ascorbic acid rapidly to dehydroascorbic acid and potassium cyanide.

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.

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 24 the bottle after cap was loosened.

f) ***Packaging Material:*** Impurities result also from packaging materials i.e., containers and closures. For most drugs the reactive species for impurities consists of; Water – hydrolysis of active ingredient. Small electrophiles Aldehydes and carboxylic acid derivatives.

Analytical Method Development

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. New drug development requires meaningful and reliable analytical data to be produced as

- Sample set selection for analytical method development.
- Screening of Chromatographic conditions and Phases, typically using the linear solvent strength model of gradient elution.
- Optimization of the method to fine-tune parameters related to ruggedness and robustness.

Stages of Analytical Method Development

- Qualification of Impurities
- Identification of Impurity
- Isolation of Impurity
- Characterization of Impurity

Qualification of Impurities[4]

Qualification

- Establishing the biological safety of an individual impurity or a given impurity profile at levels specified.
- Any impurity tested in safety or clinical studies considered qualified.
- Impurities which are metabolites present in animal or human studies are qualified.

Thresholds

Higher or lower threshold limits based on scientific rationale including drug class effects and clinical experience.

- Adverse reaction in patients (lower)
- Patient population higher
- Drug class effects higher
- Clinical experience higher

Decision Tree for Identification and Qualification[4] which is given in ICH Q3A guideline describes considerations for the qualification of impurities when thresholds are exceeded.

Table 7: Qualification Threshold for API

Max. Daily Dose	Reporting Threshold	Identificati-on Threshold	Qualification Threshold
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

Identification of Impurity

The impurities can be identified predominantly by following methods;

- Reference standard method
- Spectroscopic method
- Separation method
- Isolation method
- Characterization method

Isolation of Impurity [3]

It is frequently necessary to isolate and characterize impurities in order to monitor them accurately. These estimations are based on the assumption that impurities are structurally related to the material of interest and thus have the same detector response. It is important to

test this assumption because impurities frequently have different structures with significantly different detector responses. Most of the time it is difficult to ensure that the assumption stated above is correct.

Number of methods can be used for isolation and characterization of impurities. But the application of any method depends on the nature of impurity (i.e.) its structure, physicochemical properties and availability.

The following methods are commonly used for the isolation, they are:

- Column Chromatography
- Preparative chromatography
- Extraction

Characterization Methods

Highly sophisticated instrumentation, such as MS attached to a GC or HPLC, are inevitable tools in the identification of minor components (drugs, impurities, degradation products, metabolites) in various matrices. For characterization of impurities, different techniques are used; which are as follows;

Nuclear Magnetic Resonance (NMR):[12]

The ability of NMR to provide information regarding the specific bonding structure and stereochemistry of molecules of pharmaceutical interest has made it a powerful analytical instrument for structural elucidation. Conventional sample requirements for NMR are on the order of 10 mg, as compared with MS, which requires less than 1 mg.

Mass Spectroscopy (MS)

It has an increasingly significant impact on the pharmaceutical development process over the past several decades. Advances in the design and efficiency of the interfaces, that directly connect separation techniques with Mass Spectrometers have afforded new opportunities for monitoring, characterizing, and quantification of drug-related substances in active pharmaceutical ingredients and pharmaceutical formulations.

Validation of Analytical Procedures[13]

HPLC method validation is the process used to confirm that the HPLC procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability and consistency of HPLC results and it is an integral part of good analytical practice. Method validation has received considerable attention in literature and from industrial committees and regulatory agencies.

- ***Specificity:*** Specificity can be defined as the ability to assess unequivocally the analyte in the presence of components, which may be expected to be present. Typically, the studies may include but not limited to Impurities, degradents, matrix, etc. It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination).
- ***Accuracy:*** The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an acceptable reference value and the value found. Accuracy can be assessed on samples spiked with known amounts of Impurities and should be reported as percent recovery (percent recovery is the area obtained by spiking the Impurity in the sample.
- ***Precision:*** The precision of an analytical procedure expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.
- ***Repeatability:*** Expresses the precision under the same operating conditions over a short interval of time and is also termed as intra-assay precision.

- ***Intermediate precision:*** Expresses within-laboratories variations: different days, different analysts, different equipment, etc.
- ***Reproducibility:*** Expresses the precision between laboratories (collaborative studies, usually applied for standardization of methodology).
- ***Limit of Detection:*** The limit of detection an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value. The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.
  a. Based on Signal-to-Noise
  b. Based on the Standard Deviation of the Response and the Slope
- ***Limit of Quantitation or Quantitation Limit:*** The limit of quantitation of an individual analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy
- ***Linearity:*** The linearity of an analytical procedure is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample.
- ***Robustness:*** The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Applications

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or produced by recombinant methods.

CONCLUSION

Various regulatory authorities like ICH, USFDA, Canadian Drug and Health Agency are emphasizing on the purity requirements and the identification of impurities in Active Pharmaceutical Ingredients (API's). Qualification of the impurities is the process of

Table 8: Goals of impurity investigation

Process related impurity	Degradation related impurity
Identify significant impurities	Identify potential degradation products through stress testing and actual degradation products through stability studies.
Determine origin of impurities and method for elimination or reduction	Understand degradation pathway and method to minimize degration
Establish a control system for impurities involving: Processing/manufacturing conditions Suitable analytical methods/specifications	Establish a control system for impurities involving: Processing/manufacturing condition Suitable analytical methods/ specifications Long term storage condition including packaging Formulation

Table 9: Some examples of drugs and their Impurities

Drug	Impurity	Methods for detection	Reference
Amphotericin B	Tetraenes	Ultra violet spectroscopy	14
Atropine sulphate	Apo atropine	Ultra violet spectroscopy	14
Cloxacillin	N,N dimethyl aniline	Gas chromatography	14
Dextrose	5 hydroxy methyl fulfural	Ultra violet spectroscopy	15
Methamphetamine	1,2-dimethyl-3-phenylaziridine, ephedrine, methylephedrine, Nformylmethamphetamine, Nacetylmethamphetamine, Nformylphedrine, Nacetylephedrine, N,Odiacetylephedrine, methametamine dimmer	Gas chromatography	15
Repaglinide	4-carboxymethyl-2-ethoxy benzoic acid, 4-cyclohexylaminocarbamoylmethyl-2-ethoxy-benzoic acid, 1-cyclohexyl-3-[3-methyl-1-2-(piperidin-1-yl-phenyl)-butyl]-urea, 1,3-dicyclohexyl urea	HPLC	16
Morphine sulphate	5-(hydroxymethyl)-2-furfural, 10-hydroxymorphine, 10-oxomorphine	HPLC	17

acquiring and evaluating data that establishes biological safety of an individual impurity; thus, revealing the need and scope of impurity profiling of drugs in pharmaceutical research. Identification of impurities is done by variety of Chromatographic and Spectroscopic techniques, either alone or in combination with other techniques. There are different methods for detecting and characterizing impurities with TLC, HPLC, HPTLC, AAS etc. Conventional Liquid Chromatography, particularly, HPLC has been exploited widely in field of impurity profiling; the wide range of detectors, and stationary phases along with its sensitivity and cost effective separation have attributed to its varied applications. Headspace GC is one of the most preferred techniques for identification of residual solvents. The advent of hyphenated techniques has revolutionized impurity profiling, by not only separation but structural identification of impurities as well. Among all hyphenated techniques, the most exploited techniques, for impurity profiling of drugs are LC-MS-MS, LCNMR, LC-NMR-MS, GC-MS, and LC-MS. An accurate method development and validation of the procedures make the impurity profiling task easy. Quality assurance is a vast, concept. This concept leads to an area of IMPURITY PROFILING. Impurity profile of a substance under investigation gives maximum possible account of impurities present in it. The establishment of guidelines for impurity levels

in drug substances and products now provides the quality criteria for manufacturers. The key aspect is that the impurity profile of a new chemical entity must be shown to be qualified. With a qualification threshold 0.1%, or lower for high dose compounds, the pharmaceutical analyst must give careful thought to their analytical technology. The importance of qualifying impurity profiles are relevant to the development scientists to ensure consideration is given to the impurities present in the batches being used in safety studies starting from limit tests for impurities, this field of impurity identification and quantization has progressed. With newer techniques like U.V. spectroscopy with diode array detection, HPLC, GCIR (Gas Chromatography- Infrared Spectrometry), NMR. This article is an attempt to understand the concept of impurity profile and various aspects and techniques related to it.

REFERENCES

1. Ahuja Satinder. Impurities Evaluation of Pharmaceuticals. Ed. By New York, Marcel Dekker, 1998, 15-18
2. Indian Journal of Pharmaceutical Education and Research, 44(3), 2010.
3. S. Lakshmana Prabu, Suriyaprakash TNK, 3(2), 2010, 68- 69.
4. International Conferences on Harmonization, Draft revised Guidance on Impurities in new drug Substances. Q3A®. Federal Register. 2000.
5. Alsante KM, Hatajik TD, Lohr LL, Sharp TR, "Isolation and Identification of Process Related Impurities and Degradation Products from Pharmaceutical Drug Candidates. Part 1", American Pharmaceutical Review, 2001, 4(1), 70.
6. Lohr LL, Sharp TR, Alsante KM, Hatajik TD, "Isolation and Identification of Process Related Impurities and Degradation Products from Pharmaceutical Drug Candidates. Part II: The Roles of NMR and Mass Spectrometry", American Pharmaceutical Review, 2001.
7. Winger BE, Kemp CA, "Characterization of Pharmaceutical Compounds and Related Substances by using FTICR-MS and Tandem Mass Spectrometry", American Pharmaceutical Review, 2001.
8. Handbook of isolation and characterization of impurities in pharmaceuticals. Volume 5 of separation science and technology a reference series edited by *Satinder Ahuja*, 4-6.
9. Handbook of isolation and characterization of impurities in pharmaceuticals. Volume 5 of separation science and technology a reference series edited by *Satinder Ahuja*, 95.
10. Handbook of isolation and characterization of impurities in pharmaceuticals. Volume 5 of separation science and technology a reference series edited by *Satinder Ahuja*, 29.
11. Rao NR, Mani Kiran SS, Prasanthi NL, Indian J. Pharm. Educ. Res, 2010, 44(3), 302-306.
12. Bari SB, Kadam BR, Jaiswal YS, Shirkhedkar AA, Impurity profile: Significance in Active Pharmaceutical Ingredient. Eurasian Journal of Analytical Chemistry Volume 2, Number 1, and 2007 Copyright © 2007 by MOMENT ISSN: 1306-3057 pg no. 33, 43- 46.
13. ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: text and methodology Q2 (R1).
14. British Pharmacopoeia the Department of Health, Social Services and Public Safety, 2004.
15. Indian Pharmacopoeia Government of India, Ministry of Health and Family Welfare. Published by the Controller of Publications, Delhi, 1996.
16. Krishna Reddy KVSR, Moses Babu J, Vijayvitthal TM, Eswaraiah S, Satyanarayana Reddy M, Dubey PK, Vyas K, "Impurity profile study of repaglinide". J Pharm Biomed Anal, 2003, 32, 461.
17. Dams R, Benijts T, Lambert W, Massart D and De Leenheer a Heroin impurity profiling:

trends throughout a decade of experimenting-Review. Forensic Science International, 2001, 121, 81.

18. Horvath P, Balogh G, Brlik J, Csehi A, Dravecz F, Halmos Z, Lauko A, Renyei M, Varga K and Gorog S, "Estimation of impurity profile of drugs and related materials Part 16: identification of the side-products of the ethinylation step in the synthesis of contraceptive gestogens". J Pharm Biomed Anal, 1997, 15, 1343.