Recent advance study of profiling and control of impurities in API

Rutuja Mali [1,] Mayuri Patil[2], Priti Patil [3], Anuradha Savairam[4], Pritam Salokhe[5,] Nilesh Chougule[6]
Students[1-4], Ashokrao Mane Institute of Pharmacy, Ambap
Assistant Professor[5], Ashokrao Mane Institute of Pharmacy, Ambap
Principle[6], Ashokrao Mane Institute of Pharmacy, Ambap

Abstract- The review gives brief introduction about process and product related impurities and emphasizes on the development of novel analytical methods for their determination. It describes application of modern analytical techniques, particularly the UPLC, LC-MS, HRMS, GC-MS and HPTLC. In addition to that the application of nuclear magnetic resonance (NMR) spectroscopy was also discussed for characterization of impurities and degradation products. The significance of quality, efficacy and safety of drug substance/products including the source of impurities, kinds of impurities; adverse effects by the presence of impurities, quality control of impurities, necessity for development of impurity profiling methods, identification of impurities and regulatory aspects were discussed. Other important aspects that were described forced degradation studies and development of stability indicating assay methods.

Keywords: -Analytical Method, Regulatory Guidelines

I. INTRODUCTION

An impurity in a drug substance as defined by the International Conference on Harmonization (ICH) Guidelines1 is any component of the drug substance that is not the chemical entity defined as the drug substance and affects the purity of active ingredient or drug substances. Similarly, an impurity in a drug product is any component of the drug product that is not the chemical entity defined as the drug substance or an excipient in the drug product2. Therefore, any extraneous material present in the drug substance has to be considered an impurity even if it is totally inert or has superior pharmacological properties. 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 reviews5,6 address this topic and guidelines are available from US and international authorities7.

Most active pharmaceutical ingredients (API) are produced by organic chemical synthesis. Various components, including residual solvents, trace amounts of inorganic, and organic components can be generated during such a process. Those components remaining in the final API are considered as impurities. The sources and routes of formation of impurities in generics are special case8,9, they are the same as those in the reference drug product: starting materials, by-products and residual solvents from the API synthesis; degradants formed during the process and long-term storage; contaminants from packaging components and other drug products manufactured in the same facility. Impurities could be forming from the impact of heat, light, and oxidants (including air) on the drug product and might be catalyzed or accelerated by trace metal impurities, changes in the pH of the formulation, interactions with packaging components, excipients and other active ingredients, in the case of combination products.

Therefore, identification, quantification, and control of impurities in the drug substance and drug product, are an important part of drug development and regulatory assessment [1-9].

II ANALYATICAL METHOD FOR PURIFICATION OF CONPOUNDS:

Thin Layer Chromatography

It is a valuable technique for isolation and purification of compounds. All the modes of chromatography including adsorption, partition, ion exchange and gel filtration can be utilized. In addition, choosing a sorbent and an eluent for performing TLC it is necessary to select a suitable method for applying a

sample to the plate. Silica gel plates with or without fluorescent indicator are frequently used for most application. Detection is frequently performed by UV eg. 366nm or Iodine vapors can help to detect most of the organic substance. To elute the material from the plates, the simplest method is scraping the sorbent containing the material of interest and it is extracted with a suitable solvent, followed by filtration or centrifugation. The solvent is removed to collect the desired substance. If aluminum plates are used means cut the sample and eluted[10].

NMR (Nuclear Magnetic Resonance)

The ability of NMR (Nuclear Magnetic Resonance) to provide information on specific binding structures and to study the stereochemistry of drugs of interest in formulations becomes an important analytical tool to determine structural properties. The ability to measure NMR-based diffusion coefficients to distinguish between non-numeric and dimeric substances was confirmed using standard mixtures of genuine materials containing both monomers and dimers. Unfortunately, NMR has traditionally been used as a less sensitive method compared to other analytical methods. A typical sample requirement for NMR analysis of pharmaceuticals is 10 mg compared to mass spectrometry, which requires less than 1 mg.

Mass spectroscopy (MS)

Mass spectroscopy has been increasingly influential in pharmaceutical development over the past few decades. Advances in interface design and efficiency directly related to mass spectrometry (MS) separation techniques for monitoring, characterizing, optimizing and quantifying active pharmaceutical compounds present at the heart of pharmaceutical products or drugs have been reaffirmed. When one method is not suitable to provide the required selectivity, an orthogonal combination of chromatographic methods such as HPLC, high performance liquid chromatography (HPLC), and HPLC can be combined with capillary electrophoresis (HPLC) for rich spectroscopy such as HPLC-NMR. Provides analysis information. or HPLCMS, which can be a unique tool for confirming the quality of finished products [12]

High Performance Liquid Chromatography (HPLC) –

HPLC is a versatile method of analysis as it is not limited to volatile or stable sample and separation is based on the fact that certain compounds have different migration rates on a particular stationary and mobile phase. Separation of components by utilizing HPLC method with any suitable detector like refractive index detector, PDA detector, fluorescence detectors, electrochemical detectors, electrical conductivity detectors, light scattering detectors, evaporative light scattering detectors, Corona Charged Aerosol Detector (CAD), Nano Quantity Aerosol Detector (NQAD), etc. provide an accurate, precise and robust method for quantitative analysis for pharmaceutical products as well as impurities. HPLC also involves monitoring of stability of pure drug substance and in case of drug formulations. It can be applied for quantification of degradation products e.g. stability indicating method for simultaneous determination of salicylic acid.

Various advantages of HPLC are: (i) speed (minutes), (ii) high resolution, (iii) sensitivity, (iv) Reproducibility of +/- 1%, (v) accuracy, (vi) automation. While, there are some disadvantages of HPLC such as cost, complexity, low sensitivity for some compounds, irreversibly adsorbed compounds not detected, co-elution (two compounds escaping from the tubing at once) difficult to detect.

Gas Chromatography (GC) –

GC is used as a technique for qualitative and quantitative estimation of APIs, particularly with regards to detection of impurities which are volatile and thermo-stable in nature. It can be used as a limit test for solvent residue and other volatile impurities in drug substances. It is also utilized for characterization of raw materials used in synthesis of drug molecules. GC has advantages like (i) shorter run times; (ii) greater sample throughput; (iii) cheaper columns; (iv) higher signal to noise ratio. But on the other hand, it has some disadvantages like careful attention required when working on the instrument. Gas chromatography can only be used in cases where the substances can be vaporized without decomposing and where they can be vaporized at a reasonable temperature (i.e. not so hot that it destroys the column packing). The samples analysed are limited to those that are volatile or can be made volatile (reaction to form a volatile derivative). The samples must be thermally stable to prevent degradation when heated. It cannot be used to prepare samples for further analysis once separated. Problems can be encountered when injecting the sample: It is difficult to measure and inject such small samples

(approx 0.3 µl) accurately without evaporation of the sample, for example. The rubber seal through which sample is injected may leak leading to loss of the sample. Small pieces of the rubber septum may be adsorbed onto the column giving 'ghost peaks'. Sample may be injected directly into the heated part of injector so vaporization may not occur. GC is capable of same quantitative accuracy and precision as HPLC, particularly when used in conjunction with an internal standard.[11]

III. REGULATORY GUIDELINES ON IMPURITY FOR SAFTEY AND EFFICACY PURPOSE

The United States Food and Drug Administration (FDA) inscribe International Conference on Harmonization guidance of Technical Requirements for Registration of Pharmaceuticals for Human Use. The FDA has the assigned responsibility of ensuring the safety and efficacy of drugs. The various regulatory guidelines 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 of Medicines, Therapeutic Governance Authority (TGA), Australia [12-14].

IV. CHIRAL IMPURITY CONTROL

Chiral impurities-

The L-isomer of terbutaline is 3000 times more potent as a relaxant of tracheal smooth muscle than the D-isomer [19]. 1. The isomers can be resolved on AGP column with 0.003 M tetra propyl–ammonium bromide solution adjusted to pH 7.0. 2. Capillary electrophoresis can be used to resolve enantiomers with a background electrolyte that contains β-cyclodextrin or heptakis (2,6-di-O-methyl)-β-cyclodextrin

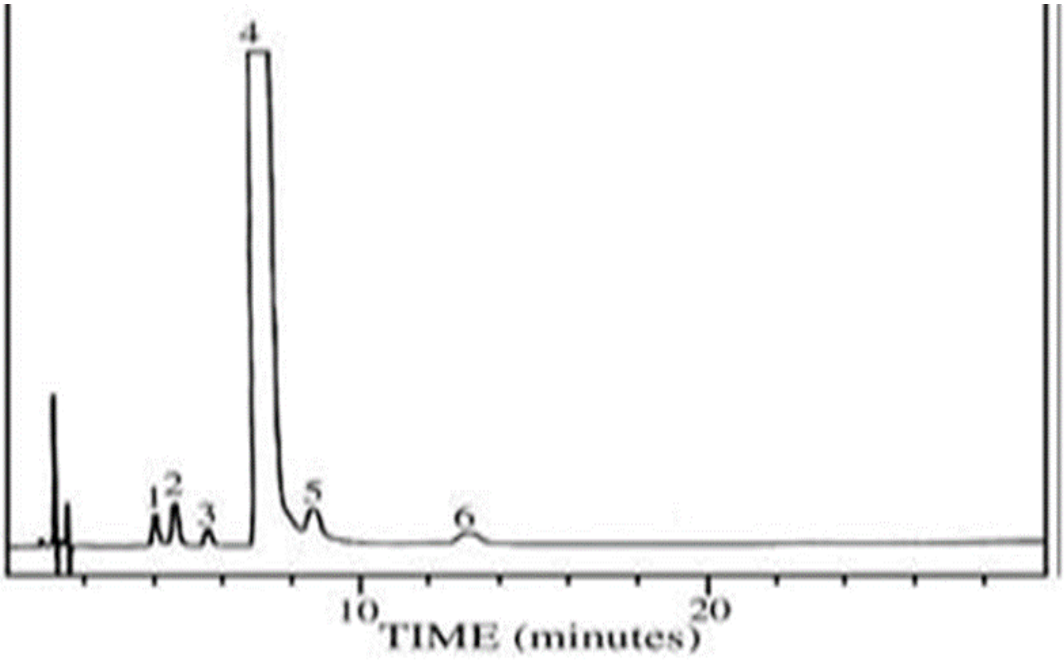
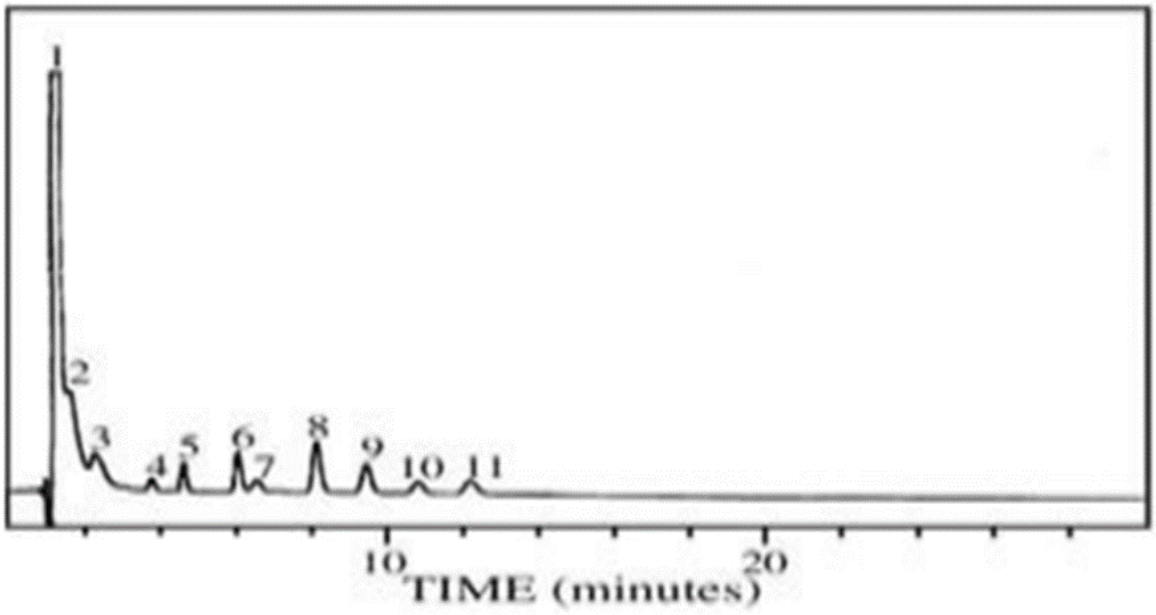


Fig. 1. Resolution of potential degradation products
1=3,5-dihydroxyacetophenone,2=3,5 dihydroxybenzaldehyde, 3=2-t-butyl-4,6,8-trihodroxy-tetrahydroisoquinoline, 4=terbutaline, 5=3,5-dihydroxy-ù-t-butylaminoacetophenone, 6=3,5-dihydroxybenzoic acid, ethyl ester

Fig. 2. Resolution of potential dibenzyloxyphenyl impurities



1=terbutaline, 2=solvent, 3=solvent, 4=α-[(t-butylamino)methyl]-3,5-dibenzyloxybenzyl alcohol, 5=α-methyl-3,5dibenzyloxybenzyl alcohol, 6=3,5-dibenzyloxyacetophenone, 7=α-[(benzyl-t-butylamino)methyl]-3,5-dibenzyloxybenzyl alcohol, 8=3,5-dibenzyloxy-2,6-dibromoacetophenone, 9=3,5-dibenzyloxy-1′-bromoacetophenone, 10=3,5-dibenzyloxy2,6,α-tribromacetophenone, 11= 1′-benzyl-t-butylamino-3,5-dibenzyloxyacetophenone[15].

V. RISK BASED APPROACH DURING MANUFACTURING OF PRODUCT AND PRODUCTION OF API

API related changes

In case where material is comparable, usable and meet all following pre-requisites, change can be implemented without need for verification or validation batches as these conditions represent minimal risk: • Change is an early manufacturing stage change in production of API • There are no changes in solubility rate, impurity profile and stability profile of API (with no changes in physical characterization of material or no changes in catalyst (if any))

• API has high solubility, is rapid dissolving and there are no other associated formulation or process changes for formulation nges are associated with this change

In case where materials are comparable and usable, minimum one verification batch in commercial setting should be produced to demonstrate that the proposed combination of process parameters (as validated) and material attributes are capable of manufacturing acceptable quality product at commercial scale. Verification strategy can use matrixing or bracketing for different strengths for same formulation. Following scenarios are example scenarios Change in late manufacturing stage of API (no impact on the physical characteristics including particle size distribution, particle shape, etc.)

• There are no changes in solubility rate of API, impurity profile and stability profile of API and • No other formulation and process changes are associated with this change

In case where materials are not comparable but usable, validation strategy (including technical batches or additional characterization, if required) should be summarized. Validation strategy should use minimum three batches and provide documented evidence that the process, operated within established parameters, using material (post change) can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

• API polymorphs are well characterized (if polymorphs exist)

• No other formulation and process change
Matrixing or bracketing or family approaches can be used based on appropriate documented rationale.
Excipient and packaging material related changes
For material considered as comparable and usable, implementation strategy should be based on regulatory and quality assessments.

For material considered as not comparable but usable, implementation strategy should be based on regulatory, quality assessments and validation requirements where applicable

VI. CONTINUOUS MANUFACTURING APPLIED TO DRUG SUBSTANCE FOR SAFE AND EFFECTIVE PRODUCT.

Recent reviews of flow chemistry (40, 41) provide many excellent examples. Continuous crystallization is often used in conjunction with flow chemistry; two recent review articles provide a current synopsis of the field. The examples of application of flow chemistry that follow have been selected to illustrate the benefits of continuous processing when applied to pharmaceutical intermediates and final drug substance. Continuous processing has been used in the manufacturing of small-molecule drug substance to achieve benefits of higher yield, safety, quality, new chemistries not feasible in batch equipment, reduced production costs, smaller reactor volumes, reduced cross-contamination potential, quality assurance of online high-performance liquid chromatography (HPLC), yield and purity advantages of multi-stage countercurrent separations, elimination of isolations, extreme temperatures, and high-pressure hydrogenations. Examples of each of these benefits are given in the following paragraphs for processes operated under cGMP conditions. A significant milestone in the adoption of new technology for the manufacture of a pharmaceutical product is the use of the technology in a cGMP process. In the past decade, perhaps the first large investment in this utilization of continuous processing in synthesis of drug substances was the commitment to the technology made by Novartis[16-20].

VII.IMPURITY PROFILING IN API

Impurity: Any Component of the new drug substance that is not the chemical entity defined as the new drug substance. 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.

Impurity Profile: A description of the identified and unidentified impurities present in a new drug substance

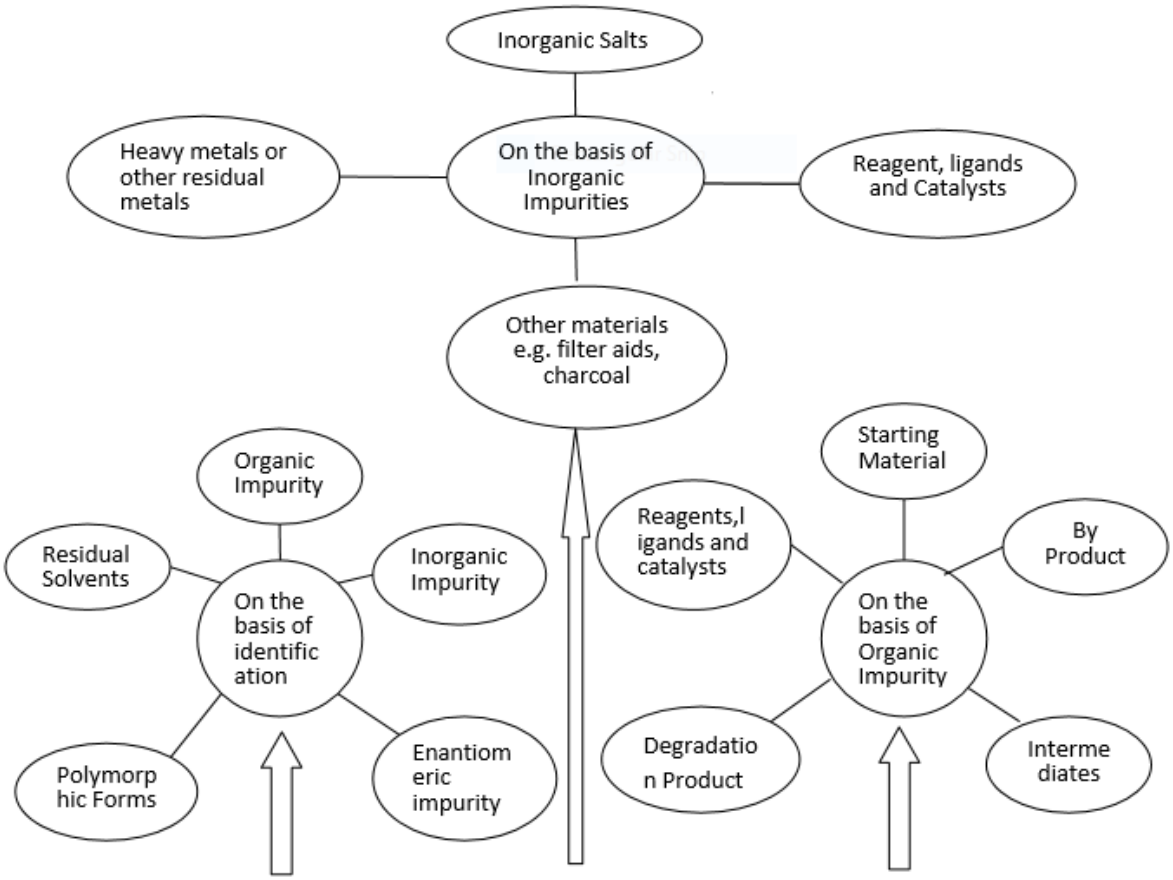
Qualification of Impurities
Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the levels specified.

New Impurities
During the course of drug development studies, the qualitative degradation profile of a new drug product may change, resulting in new degradation products that exceed the identification and/or qualification threshold. In this event, these new degradation products should be identified and/or qualified. Such changes call for consideration of the need for qualification of the level of the impurity unless it is below the threshold values as noted [21-27].

VIII. IMPURITIES IN ACTIVE PHARMACEUTICAL INGREDIENT

For each API there should be an impurity profile describing the identified and unidentified impurities present in a typical batch. The impurity profile is normally dependent upon the process or origin of the API

Classification of impurities



For each API there should be an impurity profile describing the identified and unidentified impurities present in a typical batch. The impurity profile is normally dependent upon the process or origin of the API1. According to ICH guidelines,1 impurity associated with API's are classified into the following categories:

Organic impurities (Process and Drug-related) b. Inorganic impurities c. Residual solvents.

Organic Impurities:

Organic impurities may arise during the manufacturing process and/or storage of the drug substance. They may be identified or unidentified, volatile or non-volatile, and these include the starting material, intermediates, degradation products, by-products and reagents, ligands and catalyst used at different stages of synthesis of API and drug products. These are described as follows: Starting materials or intermediates: These are the most common impurities found in every API unless a proper care is taken in every step involved throughout the multi-step synthesis. Although the end products are always washed with solvents, there are always chances of having the residual unreacted starting materials unless the manufacturers are very careful about the impurities. In paracetamol bulk, there is a limit test for p-aminophenol, which could be a starting material for someone manufacturer or be an intermediate for the other. By-products: In synthetic organic chemistry, getting a single end product with 100% yield is very rare; there is always a chance of having by-products. By-products from the side reactions are among the most common process impurities in drugs 11, 12. By-products can be formed through a variety of side reactions, such as incomplete reaction, overreaction, isomerization, dimerization, rearrangement, unwanted reactions between starting materials or intermediates with chemical reagents or catalysts 13. Degradation products: Impurities can also be formed by degradation of the end product during manufacturing of bulk drugs. However, degradation products resulting from storage or formulation to different dosage forms or aging are also common impurities in

the medicines. The degradation of penicillin's and cephalosporins is a well-known example of degradation products. The presence of a ß-lactam ring as well as that of an α-amino group in the C6/C7 side chain plays a critical role in their degradation

b. Inorganic Impurities:
Inorganic impurities can result from the manufacturing process. They are normally known and identified and include: • Reagents, ligands and catalysts • Heavy Metals or other residual metals • Inorganic salts • Other materials (filter aids, charcoal) Reagents, ligands and catalysts: The chances of having these impurities are rare however, in some processes; these could create a problem unless the manufacturers take proper care during production. Heavy metals: The main sources of heavy metals are the reactors (if stainless steel reactors are used), where acidification or acid hydrolysis takes place and water used in the processes. These impurities of heavy metals can easily be avoided using demineralized water and glass-lined reactors. Filter aids, Charcoal: The filters or filtering aids such as centrifuge bags are routinely used in the bulk drugs manufacturing plants, and in many cases, activated carbon is also used. The regular monitoring of fibers and black particles in the bulk drugs is essential to avoid these contaminations. c. Residual solvents: Residual solvents are organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products.

SOURCES OF IMPURITIES

From the earlier discussion, it is clear that impurities can originate from several sources; such as;

· Crystallization-related impurities
· Stereochemistry-related impurities
· Impurities arising during storage
· Method related impurity
· Residual solvents
· Synthetic intermediates and by-products
· Functional group-related typical degradation
· Mutual interaction amongst ingredients

Crystallization-related impurities

As per the regulations laid down by the regulatory authorities, a pharmaceutical industry has to take strong enough interest on crystallization related impurities. The nature of structure adopted by a given compound upon crystallization can exert a profound effect on the solid - state properties of that system. Polymorphism of a substance exist in more than one crystalline form whereas, when the substance different crystal packing arrangements with a different elemental composition; the phenomenon is known as Solvatomorphism.

Stereochemistry-related impurities

It is of supreme importance to look for stereochemistry related compounds, that is those compounds have similar chemical structure but different spatial orientation; these compound can be considered as impurities. Chiral molecules are frequently called as impurities. The single enantiomeric form of chiral drug may have better pharmacological action and broad therapeutic index. Single isomeric form of drug that are marketed include esomeprazole (S - omeprazole), levabuterol (R- albuterol) etc. The undesired chiral forms of drug are considered as impurity [28-35].

Future perspective:

This review provides a perspective on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is an increasing importance and drug safety receives more and more attention from the public and from the media. This article provides the valuable information about the impurities types and its classification, various techniques of isolation and characterization, analytical techniques for the determination, qualification of impurities and critical factors to be considered while preparation of the bulk drugs. Impurity profiling in pharmaceuticals increases drug safety. Identification of impurities establishes an overall profile of a drug, which includes its toxicity and safety limits, limits of quantization and detection. It has received more attention from the public and social media. The present article provides detail information about pharmaceutical impurity, classification of impurity; a source of impurity

REFERENCE

1. U.S. Food and Drug Administration. Guidance for Industry, Q3A Impurities in New Drug Substances. February 2003.

2. U.S. Food and Drug Administration. Guidance for Industry, Q3B Impurities in New Drug Products. July 2006.
3. Gorog S (Ed.), Identification and Determination of Impurities in Drugs, Elsevier Science B.V, Amsterdam, 2000.
4. Ahuja S. Impurities Evaluation of Pharmaceuticals, Marcel Dekker, New York, NY, 1998
5. Hovorka SW, Schuknecht C. Oxidative degradation of pharmaceuticals: theory, mechanisms and inhibition, J. Pharm. Sci., 2001, 90, 253-269.
6. Roy J. Pharmaceutical impurities—a mini-review, AAPS Pharm SciTech 3 (2) (2002) (article 6 (http://www.aapspharmscitech.org)).
7. ICH Harmonized Tripartite Guidelines: Impurities in New Drug Substances Q3A(R), 10 February 2003; Impurities in New Drug Products Q3B(R), November 2003; Impurities: Guideline for Residual Solvents, 24 December 1997; Stability Testing of New Drug Substances and Products Q1A(R2), November 2003 (http://www.fda.gov/cder/guidance/guidance.htm).
8. Guidance for Industry, ANDAs: Impurities in Drug Products, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, August 2005 (http://www.fda.gov/cder/guidance/6423dftrev1.htm).
9. Guidance for Industry, ANDAs: Impurities in Drug Substances, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, January 2005 (http://www.fda.gov/cder/guidance/6422dft.htm)
10. Chatwal GR. Pharmaceutical Inorganic chemistry, Vol.1. Himalaya, New Delhi, 1991
11. Nagpal S., Upadhyay A., Bhardwaj T.R. & Thakkar A. (2011). A review on need and importance of impurity profiling. Current Pharmaceutical Analysis, 7(1), 62-70
12 Shashank Rawat and Vijay Kumar, Impurity Profiling: Overview on Impurity Profiling and Reporting Methodologies Adopted by United States and Europe, World Journal of Pharmaceutical Research 2017; 6:206-207.
13.R. R. Parajuli et al. Impurity profiling: an emerging approach to pharmaceuticals, WJPPS, 2018; 7(4): 1670-1683.
14. A. Singh et al. A review on pharmaceutical impurities and their importance, WJPPS, 2017; 6(10): 13371354
15. Misra et al. Pharmaceutical Impurities: A Review, IJPC, 2015; 05(07): 232-239
16. B. S. Ahuja, Chiral Separations by Chromatography, Oxford, New York, 2000
17. Jensen KF. 2017. Flow chemistry—microreaction technology comes of age. AIChE J. 63:858–69
18.. Gutmann B, Cantillo D, Kappe CO. 2015. Continuous-flow technology—a tool for the safe manufacturing of active pharmaceutical ingredients. Angew. Chem. Int. Ed. 54:6688–728
19.. Wang T, Lu H, Wang J, Xiao Y, Zhou Y, et al. 2017. Recent progress of continuous crystallization. J. Ind. Eng. Chem. 54:14–29
20.. Zhang D, Xu S, Du S, Wang J, Gong J. 2017. Progress of pharmaceutical continuous crystallization. Engineering 3:354–64
21. O'Neal EJ, Lee CH, Brathwaite J, Jensen KF. 2015. Continuous nanofiltration and recycle of an asymmetric ketone hydrogenation catalyst. ACS Catal. 5:2615–22
22. Alsante KM, Hatajik TD, Lohr LL, and Sharp TR. Isolation and identification of process related impurities and degradation products from pharmaceutical drug Candidates. Part 1. American Pharmaceutical Review. 2001; 4(1):70-78.
23. Alsante K M, Boutres P, et al; 'Pharmaceutical Impurity Identification: A Case Study Using a Multidisciplinary Approach', Journal of Pharmaceutical Sciences (2004) 93 (9): 2296.
24. Ahuja S. impurities evaluation of pharmaceutical, Dekker, New York, 1998.
25. Humfrey C. London: R and D, SCI; 2007. Jun 07, Keeping afloat in a sea of impurities, Global Safety Assessment AstraZeneca.
26. Bari SB, Kadam BR, Jaiswal YS. Impurity profile: Significance in Active Pharmaceutical Ingredient. Eurasian J Anal Chem. 2007; 2:1
27. Kushwaha, P., Pharmainfo.net. 2008, 6(4).
28.. Sandor, G., Chemical and analytical characterization of related organic impurities in drugs. Anal Bioanal. Chem. 2003, 377, 852-862.
29. Qiu, F., Norwood, D. L., Identification of Pharmaceutical Impurities. Journal of liquid chromatography & related technologies. 2007, 30, 877-935.
30.. Krimpen, P. C., Bennekom, W. P., Bult, A., Penicillin and cephalosporins: physicochemical properties and analysis in pharmaceutical and

biological matrices. Pharm Weekbl [Sci].1987, 9, 1-23.
31.. Roy, J., Mohammad, G., Banu, A., Pharmaceutical analysis and stability of locally manufactured ampicillin trihydrate. Indian Drugs. 1993, 5(30), 211-218.
32. International Conferences on Harmonization, Draft revised Guidance on Impurities in new drug substances Q3A(R2)., 25 October 2006
33. U.S. Food and Drug Administration. Guidance for Industry, Q3A Impurities in New Drug Substances. February 2003.
34. Ahuja Satinder. Impurities Evaluation of Pharmaceuticals. Ed., New York; Marcel Dekker. 1998; 15-18.
35. Parimoo P. A Text Book of Pharmaceutical Analysis, CBS publishers and distributors, NewDelhi. 1998; 20-21.