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Impurity Profiling In Pharmaceuticals: A Review

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ABSTRACT: Impurity is not a much-liked word by pharmaCeutical and industry people, because they are concerned About quality. Here we discuss various impurities that Might be present in API formulations. To fulfill our purpose we have compiled a variety of regulatory authorities'Guidelines (i.e., ICH, WHO, and pharmacopoeias), which Serve in endlessly regulating the impurities by various Means. As the impurity present in a drug can affect its Quality and thus its efficiency, it is therefore crucial to Know about impurities. The current article reveals the Different terms, regulatory control, and basic techniques (e.g., HPLC, LC-MS, TLC) that will help novices to understand, identify, and quantitatively estimate impurities And that have the advantage of profiling. This article Primarily focuses on identification and control of various impurities (i.e., organic, inorganic, and genotoxic). For any of the substances, quality is the prime objective. Because impurities can alter quality, understanding the various impurities will help in producing quality Products.

Keywords: Impurity profiling, Impurities, Organic impurity, Inorganic impurity, International Conference on Harmonization, Identification.

I. INTRODUCTION:

Medicine is the branch of science that involves the identification, treatment, and prevention Of the disease. It is used from the ancient time to combat the various diseases. Earlier, the Drugs were extracted from the plant that may have the active compound to combat theSpecific disease. As the years past, drugs were also derived from the animals,Microorganisms, and by the chemical synthesis, thus increasing the efficacy of the drug by Removing the unwanted parts from the drugsThe drug consists of mainly the two components, one is an active ingredient that is the Chemical compound in the drug that makes the drug work on the disease, while another part Called as an inactive ingredient consists of excipients, binder, colour, and flavours. The active And inactive ingredients are purposely added to the drug. Besides these, there is another Component that gets incorporated into drug during the manufacturing of drug or on the Storage of the drug, which is called as an impurity. The origin, control, and measurement of impurities in drug substance are very important toUnderstand for the production of high-quality drug substances and this is done by the impurity Profiling. Thus, impurity profiling is an analytical activity that consists of detection, Identification and quantitative determination of impurities in the drug substances. Thus, Impurities are critically associated with the quality of the drug substances and drug product Which have potential to affect the safety and efficacy of drug substance and drug product Present even in trace amounts.The analysis of impurities is a very intensive task which involves method development, Impurity synthesis, isolation, and various analytical approaches to determine the univocalIdentification of the impurity of interest. Thus, there is always a great need for the development of new analytical methods for quality Evaluation of new emerging drugs. Impurity profiling requires a high-resolution Chromatography system capable of reliably and reproducibly separating and detecting all of The known and unknown impurities of the active compounds. Various methods need to be Developed for determination of impurities in raw material, intermediate, finished product Samples. These methods should be stability indicating and well validated with parameters Defined in the International Council for Harmonisation (ICH) guidelines and Pharmacopoeias.[1-5]

❖ Impurity profile : 6-12

Impurity profiling is a collection of investigative activities,With the purpose of detection, identification/structure Revelation and quantitative determination of organic andInorganic impurities, as well as residual solvents in bulk drugs substances and pharmaceutical preparations. VariousRegulatory establishments like USFDA, ICH, Canadian DrugAnd Health Agency are focusing on the clarity/purityRequirements and the

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recognition of impurities in ActivePharmaceutical ingredient (Vasanti and Sulabha, 2009). TheExplanation, characterization and quantization of the celebratedAnd mysterious impurities present in new drug materials areAcknowledged as impurity profile (Rishikesh and Deshmukh,2011). It offers an accounts

Of impurities present in the bulk and Final drug substances. It facilitates in identifying and quantifyingThe impurities present in the drug substance or in pharmaceuticalFormulation. It provides maximum achievable types ofImpurities present in drug substance and in pharmaceuticalPreparations(Federal, 2000).

❖ **Impurities in Pharmaceuticals:13-16**

- **Definition of impurities:** Impurities are defined by the various official pharmacopoeias, Groups, bodies, and ICH as follows. United States Pharmacopoeia (USP) general chapter <1086> Impurities in drug substance and drug product" defined impurity as follows. 'Impurity is any component of a drug substance that is not the chemical entity define as the Drug substance and in addition, for a drug product, any component that is not a formulation Ingredient.European Pharmacopoeia (EP) general chapter 5.10 „Impurities in substances for Pharmaceutical use" define the impurity as follows. Impurity is any component of a substance for a pharmaceutical use that is not the chemical Entity defined as the substances. International Council for Harmonisation (ICH) defines impurity as follows. Impurity is any component of the drug substance that is not the chemical entity defined as The drug substance'.Food and drug administration (FDA) describe the impurity in drug substances and drug Product as follows.Impurity is any component present in the drug substance or drug product that is not the Desired product, a product-related substance, or an excipient including buffer components. It May be either process-or-product related. The common definition of impurity is any Substance coexisting with drug substance, such as starting material, reagents, catalyst, raw Material or intermediates arising from synthesis or develop during storage or shipment is Called as Impurity.

❖ **Classification of impurities:17-18**

- Organic (process and drug related)
- Inorganic
- Residual solvents
- Polymorphic

Organic impurities:19-25

Organic impurities come into existence during the synthesis of the active and inactive materials. They may Occur during manufacturing or during storage of the Materials. These impurities can be deduced from degradation reactions and ongoing synthesis in active Pharmaceutical entities and drug products. Impurities Generated during the synthetic process are intermediates, by-products, and reagents, as well as ligands and Catalysts used in the chemical synthesis (Ahuja 1998, Qiu and Narwood 2007).

- **Contamination by organic impurities:26-28**

Contamination with organic impurities is not related to a Drug but might unknowingly be present in the drug. For Example, for drug substances derived from plants, her-Bicides used to protect plants may be present, such as Diquat and glyphosate, or pesticides such as carbofuran And endrin sprayed into the environment (Bauer et al. 2001).

Inorganic impurities:29-30

Inorganic impurities include filter aids, color removing Agents such as charcoal, reaction rate modifiers (cata-Lysts), ligands, and heavy metals. One example would Be a catalyst used in a substitution reaction during the Synthesis of the API or raw materials. Inorganic impurities' might have toxic effects, so they should be removed Or controlled to a minimum level. Batch-to-batch variation in impurity levels suggests that the manufacturing Or synthesis process of the drug product is not controlled (Roy 2002, Basak et al. 2007, Hulse et al. 2008, ICH Q-2009).

- **Contamination by inorganic impurities:31-33**

These are unforeseen impurities found in final product. Contaminant impurities detected in drugs have been controlled in many ways. For example, previously used glass Vessels for reaction are now replaced with acid/alkali Resisted glass (Bauer et al. 2001). So, impurities that might Be present due to leaching from glass vessel is minimized To safer levels.

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Residual solvents:34

Residual solvents in pharmaceuticals are the volatileChemicals that are produced as a result of side reactions or Used in the manufacturing of API or excipients, or in the Formulation [ICH Q-3C (R4) 2009]. Theoretically they canBe removed from the final product but practically they can Not. Therefore, it may be a vital parameter in the process For making a drug product.

Polymorphic forms:35-36

Solid material that subsists in two or more forms or in A crystalline structure is said to be polymorphic. Some Organic and inorganic compounds form different crystal-Line structures called polymorphs or polymorphic forms. The resulting change of intermolecular interactions gives Rise to different pharmacokinetic properties of medical Drugs, as well as to different properties of organic and Inorganic materials. Therefore, the unambiguous identification and characterization of polymorphs is very important, especially from the economic point of view. In 2006 a New crystal form of maleic acid had arisen when solution Of caffeine and maleic acid (2:1) in chloroform is set aside To evaporate slowly (Day et al. 2006).

❖ **ICH Guidelines for impurity profiling:37-41**

It is now getting an important critical attention from regulatory authorities. The International Conference on Harmonization has published various guidelines on impurities in drug substances and drug products as well as residual Solvents.

1) Q1A-"stability testing of new drug substances and products"
2) Q3A (R2) – "Impurities in New Drug Substances"
3) Q3B (R2) – "Impurities in New Drug Products"
4) Q3C (R5) – "Impurities: Guidelines for Residual Solvents"

❖ **Regulatory Guidelines on impurity:42**

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

❖ **Regarding impurities are as follows:42**

1) 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

❖ **Sources of impurities :43**

There may be a variety of sources of impurities in severalPharmaceutical drug and dosage form from theCommencement of product to its concluding. There are two Types of impurities in drugs: (1) impurities linked withActive pharmaceutical ingredients or drug substance and (2) impurities that may be created during formulation and Or with aging or that are related to the formulated forms (ingale, 2011) commonly, the range of impurities that are Likely to be present in pharmaceutical substances canAppear from the following sources:

1) The raw materials used in the formulation.
2) The method of manufacture of drug product adopted.
3) The instability of product.
4) The atmospheric contaminants (Ahuja et al, 2011).
5) Starting materials and intermediates
6) Impurities in the starting materials
7) Reagents, ligands, and catalysts
8) By-products of the synthesis
9) Products of over-reaction
10) Products of side reactions
11) Impurities originating from degradation of the drug substance.

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Figure no 1: Sources of impurities in drug substance and drug product

❖ **Identification of impurities:45-49**

It is one of the activities of Impurity profiling, where the goal is To identify the chemical structures of impurities present in the drug substances or observed in The stability studies above a particular threshold. Knowledge of the chemical structure of Impurity and its formation mechanism is very important to assess its toxicological Implications thus improving the synthetic chemical processes to reduce or eliminate the Impurity. Identification of pharmaceutical impurities can be done by various spectroscopic Techniques, such as Ultraviolet (UV), Infrared (IR) Mass spectrometry (MS) and Nuclear Magnetic resonance (NMR) while its quantitation can be done by chromatographic technique Such as High performance liquid chromatography (HPLC), Gas chromatography (GC), Supercritical fluid chromatography (SFC) and Thin layer chromatography (TLC/HPTLC). ICH guidelines indicate that all the impurity present in drug substance should be identifiidentification threshold.

❖ **Method of detection of impurity :50-53**

This is very significant to validate sample for estimations, When it is obtainable. If the evaluations signify that Particular impurity content is greater than 0.1% after that it Must be estimated as per the FDA guideline. Hyphenated Methods for example mass spectroscopy, gas Chromatography or liquid chromatography, or the numbers Of other chromatographic-spectroscopic relationship are Perfectly suitable for preliminary characterization of the
Impurities.

A. Spectroscopic Techniques.
B.Chromatographic Techniques.
C.Combination of Spectroscopic and chromatographic Techniques. (i.e. Hyphenated techniques) Highly complicated instrumentation, such as Mass Spectrophotometer attached to a Gas Chromatography or HPLC (High Performance Liquid Chromatography), are Expected tools in the identification of negligible Components in various preparations. For characterization of Impurities, different methods are used; which are as Follows-

1**) Nuclear Magnetic Resonance (NMR) :**

The capability Of NMR (Nuclear Magnetic Resonance) to give Information pertaining the specific bonding structure and Stereochemistry study of drug substance of formulations Interest is becoming an influential analytical instrument for Structural characterization. The ability of NMR based

Diffusion coefficient determination to distinguish between Nonnumeric and dimeric substances were validated via standard Mixture of authentic materials having both monomers and Dimers. Unluckily, NMR has traditionally been applied as a less Sensitive method compared to other analytical methods.Conventional sample requirements for NMR analysis of Pharmaceutical preparations are 10 mg, as compared with Mass

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Spectroscopy, which consumes less than 1 mg (Pavia et al., 2001; Mistry, 1999; John, 2000; Munson, 2001).

2) Mass spectroscopy MS :54 has a more and more importantImpact on the pharmaceutical advancement process over the pastSeveral decades. Development in the design and efficiency of theInterfaces, which directly correlate with the separationTechniques with Mass Spectrometers (MS) have gained newIdentification for monitoring, characterizing, optimizing andQuantification of active pharmaceutical compound present in theCore of pharmaceutical product or formulation. If single methodDoes not pass to provide the essential selectivity, orthogonalCoupling of chromatographic techniques such as HPLC-TLC,High performance liquid chromatography (HPLC) and HPLCAre coupled with Capillary Electrophoresis (HPLC-CE) provide Rich spectroscopic analysis information like HPLC-NMR orHPLC-MS which may be a unique tool for authentication ofQuality of the finished product (Pavia et al., 2001; Mistry, 1999;John, 2000; Munson, 2001;Ante, 2002).

❖ **Control of impurities:55-57**

According to theory, all impurities should be removed From the final product, but in practice, impurities cannot Be entirely abolished from the final product. So, for a Quality product, impurities should be kept within the Limits. According to a study carried out for impurity,

Very low amount of impurities in the product should be Allowed. However, in special cases, rather high quantities Of impurities are permitted, for example, biotechnologiCally derived products that have biological activity.Most of the bulk pharmaceutical chemicals (BPCs) Are obtained from various sources. Therefore, it is crucial That impurities in BPCs be monitored and controlled very Carefully.Various controlling authorities for impurity (USP 1995, ICH Q-6A 1999, ICH Q-6B 1999) are mentioned in Monographs and specifications about maximum tolerable Limits.

- **Control of organic impurity: 58**

Most often, reduction in quantity of by-products in the Reaction can be carried out by tightly controlled reaction Conditions at crucial steps of the reaction to preclude A new impurity or diverging level of impurity. Another Approach to reduce the quantity of impurity in the final Product is to use superior quality starting materials. Likewise, the use of high-grade solvents also imparts its effort To obviate the production of by-products or any unknown Entity.

- **Control of degradation impurity: 59**

This particular impurity covers degradation products of Active substance, including reaction products with excipient or container system [ICH Q-3A (R2) 2006, ICH Q-3B (R2) 2006]. Degradation products observed in stability studies Performed at recommended storage conditions should Be identified, qualified, and reported when the following

- **Control of inorganic impurities :60**

Oral/parenteral concentration limits (ppm) have been Proposed for 14 metals in active substances or excipients: Pt, Pd, Ir, Rh, Ru, Os, Mo, V, Ni, Cr, Cu, Mn, Zn, and Fe. Metals are divided into three classes as follows, and limits Have been summarized in Table 3.

❖ **SEPARATION AND ISOLATION OF IMPURITIES:61-64**

Usually, it is required to isolate the impurities as the use of only instrumental methods doesNot characterize the impurity. Generally, the chromatographic techniques are used for Isolation of impurities along with classical techniques before its characterization. If Instrumental methods are used, isolation of impurities is avoided, as it directlycharacterizes

The impurities. Often the analysis of complex materials requires, as a preliminary step that is, Separation of the analyte or analytes from a sample matrix. The following methods can be Used for the separation of impurities from drug substances and drug products.

1)Liquid-liquid extraction methods
2) Solid-phase extraction methods
3) Accelerated Solvent Extraction Methods
4) Supercritical fluid extraction
5) chromatography
6) Flash chromatography
7) Thin-layer chromatography (TLC)
8) Gas chromatography (GC)
9) High-pressure liquid chromatography (HPLC)
10) Capillary electrophoresis (CE)
11) Supercritical fluid chromatography (SFC)

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❖ **IDENTIFICATION AND STRUCTURE ELUCIDATION OF IMPURITIES:65-68**

Impurity structural elucidation or impurity profiling [14-15] (determination and Characterization of impurities associated with drugs or drug products) is increasingly viewed As a valuable and essential part of quality requirements. The characterization of impurities Generally requires the collective efforts of synthetic organic chemists, pharmaceutical Scientists responsible for formulation development, and analytical scientists. The analytical Chemists utilize the latest separation techniques (e.g., HPLC, GC, CE, etc.) and structure Elucidation methods (e.g., NMR, IR and Raman spectroscopy, X-ray crystallography, MS, Etc.) in combination with the insight provided by physical organic chemists versed in the Degradation behavior of various classes of therapeutic compounds. The online capability of Both MS and more recently NMR spectroscopy, make them renowned techniques in Providing preliminary information about the related substances profile of a drug substance orProduct obtained using HPLC separation. Subsequent changes in either synthetic route or Composition of the formulation are tracked, using the initial profile as a comparative phoresis (CE), ion chromatography (IC), thin-layer chromatography (TLC), etc. are used for classes of Compounds where they offer significant or unique advantages but HPLC remains the mostoften used separation technique in pharmaceutical research development.

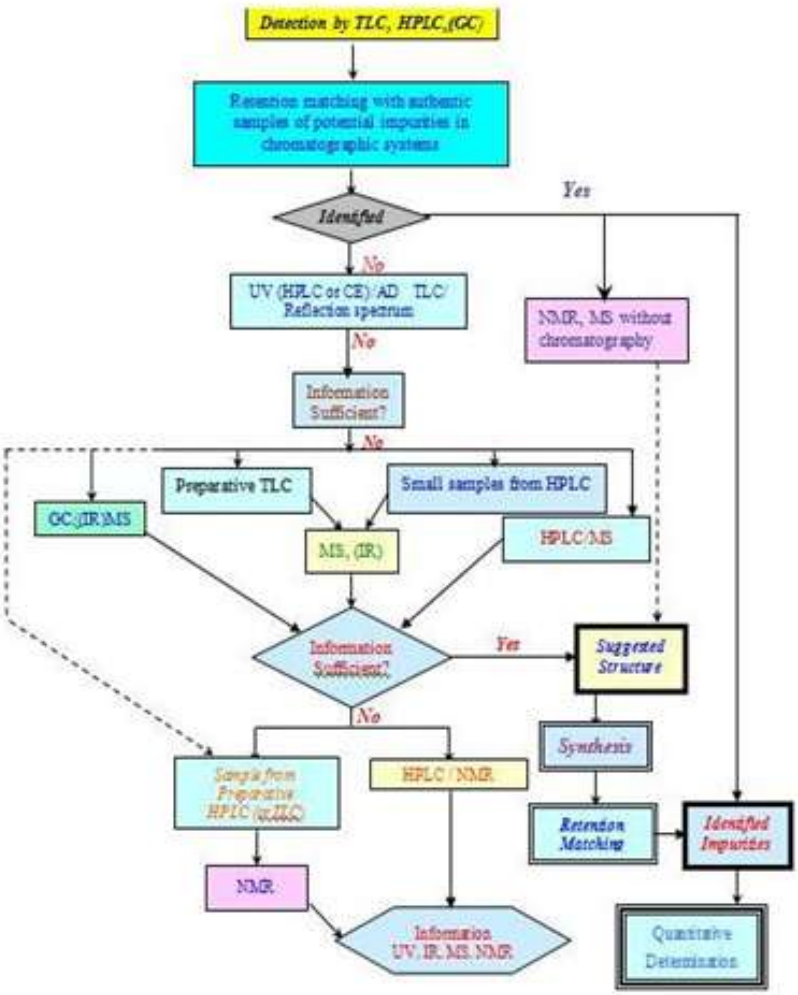

Figure no 2: Schematic flowchart for detection, identification, structure elucidation

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❖ **Applications:69-70**

Numerous applications have been sought in the areas of drug designing and in monitorinquality, Stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from Natural products or produced by recombinant methods. The applications include alkaloids, amines, Amino acids, analgesics, antibacterial, anticonvulsants, antidepressant, tranquilizers, antineoplastic Agents, local anesthetics, macromolecules, steroids, miscellaneous.

❖ **Acceptance Criteria for Impurities :71-75**

For newly synthesized drug substances, the specification should include acceptance criteria for impurities. Stability studies, Chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercialProduct. A rationale for the inclusion or exclusion of impurities in the specification should include a discussion of the impurity profiles Observed in batches under consideration, together with a consideration of the impurity profile of material manufactured by the proposed Commercial process. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the Quantitation or detection limit of the analytical methods should commensurate with the level at which the impurities need to be Controlled. Appropriate qualitative analytical descriptive label included in the specification of unidentified impurities. A general acceptance Criterion of not more than 0.1 % for any unspecified impurity should be included. Acceptance criteria should be set, based on dataGenerated on actual batches of the drug substance, allowing sufficient latitude to deal with normal manufacturing and analytical variation, And the stability characteristics of the drug substance. Although normal manufacturing variations are expected, significant variation in Batch-to-batch impurity levels could indicate that the manufacturing process of the drug substance is not adequately controlled and Validated. The acceptance criteria should include limits for organic impurities; each specified identified impurity, each specified Unidentified impurity at or above 0.1%, and any unspecified impurity, with a limit of not more than 0.1%, total impurities, residual solvents And inorganic impurities.

❖ **Nitrosamine Impurities in Drug Substances and Drug Products:76-81**

INTRODUCTION :

Food and drug administration (FDA) and European Medicines Agency (EMA) in July 2018 announced that a carcinogenic Impurities N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) are said to be present in generic Drug substances and drug product, Especially in angiotensin II receptor Blockers (ARBs) or 'Sartans'classMedicines which are used to treat patients With hypertension (high blood pressure) And heart failure (Fig.1). This Announcement leads to voluntarily recallHundreds of batches of these generic Versions by pharmaceutical distributor Worldwide. Further, the FDA and EMA investigation in year 2019 led to the Detection of these Nitrosamine impurities In Pioglitazone used for the treatment of Diabetes and Ranitindine an H2 (histamine-2) blocker used for the Treatment of acidity of the stomach.Presently, low level of NDMA impurity Found in Metformin also brought this drug Under FDA and EMA investigations.ICH M7 (R1) classifies Nitrosamine Impurities as Class 1, which is known to Be mutagenic and carcinogenic, based on both rodent carcinogenicity and mutagenicity data. These Nitrosamineimpurities impact the genetic material by means of mutations through chromosomal breaks, rearrangements, covalent binding or insertion into the DNA during replication. These changes in the genetic materials causedby the exposure to very low levels of Nitrosamine impurities can lead to cancer . Thus, it is important to identify impurities in drugs at very low levels to ensure safety to the public.

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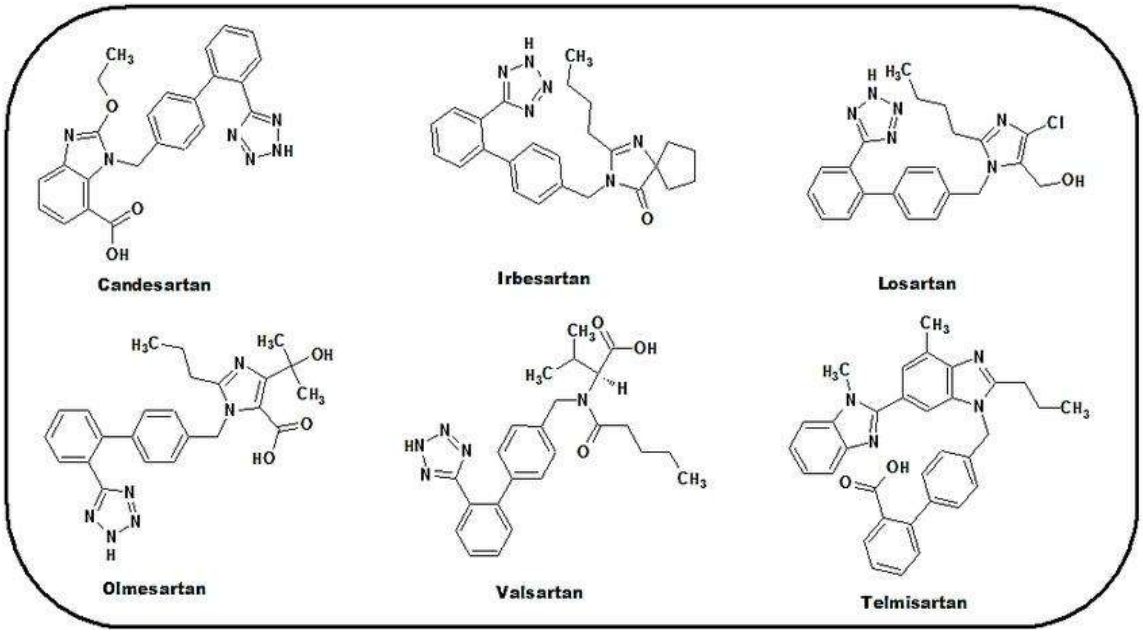

Figure 1: Structure of sartans drug.

❖ SOURCES OF NITROSAMINE IMPURITIES :82-84

Nitrosamine impurities can get Incorporated into the drug substance and Drug product basically through process Formation, direct introduction, Degradation or cross contaminationManufacturing of drug substances Involves raw material, intermediates, Solvents, chemicals and reagents [7-9]. Through these stages, if this impurity is Formed or present it may getIncorporated and carried forwarded toDrug product as shown in (Fig.2).

1. Primary, secondary, tertiary amines or Quaternary ammonium salts along with Nitrosating agents such as Sodium Nitrite are considered to be precursors For the generation of Nitrosamines Impurities. Similarly, carbamate, Amides and N-alkyl amides if Nitrosated may form NitrosamineImpurities. The extent of NitrosamineImpurity formation depends mainly on The type of reagent, their structure and The concentration of the nitrosatingAgent. Secondary amines are Considered to be more reactive (Fig.3).
2. Recovered solvents and catalysts used In the process may cause a risk for Nitrosamine formation. As these Solvents or catalysts are treated with Sodium nitrite or nitric acid in order to Destroy residual azide which may lead To the formation of Nitrosamine Impurities.
3. Contaminated starting material or raw Material supplied by the vendor may Introduce the Nitrosamine impurities in Drug substance or drug product.
4. Cross-contamination between different Manufacturing processes and productsOn the same production line may leadTo contamination of NitrosamineImpurities. A process where nitrosating Reagents are not used may still be Contaminated through the presence of Nitrite in the water used in theManufacturing process.
5. Trace amount of these impurities may Be formed due to decomposition of Solvent or other materials used in the Synthesis of drug substances.Similarly, by-products formed in the Drug synthesis process may get be Carried forward to the drug substances As Nitrosamine impurities. SolventsSuch as Dimethylformamide, Dimethylacetamide (DMF) or Diethylacetamide (DEA) may formPotential NDMA and NDEA Impurities (Fig.3).
6. Use of certain packaging materials for Finished product may for Nitrosamine Impurities. According to one Hypothesis the packing material lidding Foil containing nitrocellulose, printing Primer may react with amines in Printing ink to form Nitrosamines Impurities, which may get transferred To the drug product

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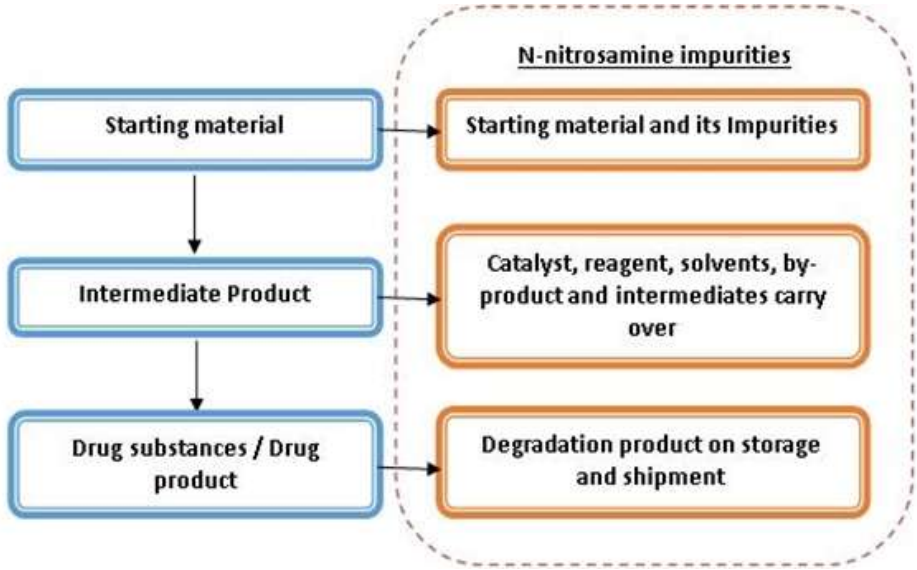

Fig 2: Sources of Nitrosamine impurities.

Experts suggest that the NDMA impurity in Valsartan could have come from sodium Nitrite, which is used to expel remaining Sodium azide reagent. Under the acidic Condition, nitrite ion forms nitrous acid, Which then could react with trace amounts of Dimethylamine, a degradation product of the Solvent Dimethylformamide (DMF). Fig. Fig

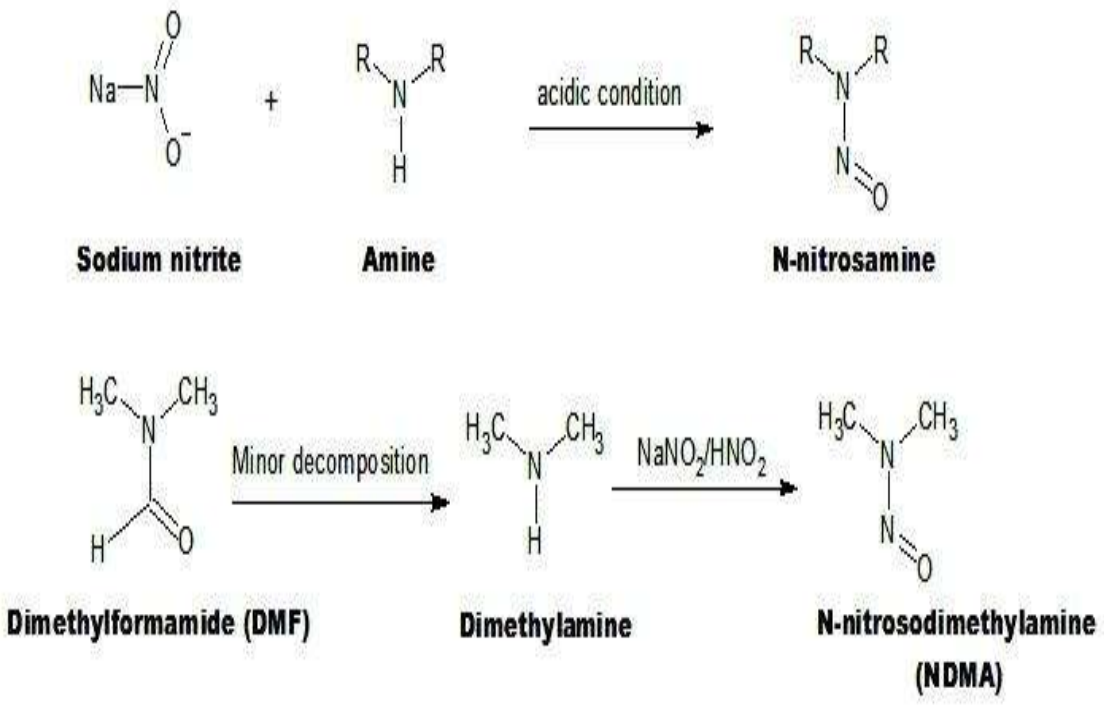

Figure 3: Formation of Nitrosamine impurities.

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Shows the formation of impurities in drug Synthesis. Some of the secondary amine and Their corresponding Nitrosamine impurities Formed are tabulated below in Table-1.

Table 1: Amines and corresponding Nitrosamine impurities.

Amines	Corresponding Nitrosamine impurities
Dimethylamine	N-nitrosodimethylamine (NDMA)
Diethylamine	N-nitrosodiethylamine (NDEA)
Dipropylamine	N-nitrosodipropylamine (NDPA)
Diisopropylamine	N-nitrosodiisopropylamine (NDIPA)
Dibutylamine	N-nitrosodibutylamine (NDBA)
Ethylmethylamine	N-nitrosomethylethylamine (NMEA)
4-(methylamino)butanoic acid	N-nitroso-N-methyl-4-aminobutyric acid (NMBA)

❖ **LIMITS AND ACCEPTABLE INTAKE :85-89**

Nitrosamine impurities are classified asClass-1 impurities as per ICH guidelines Due to its known carcinogenicity and Mutagenicity. For the calculation of its Limit, the median toxic dose TD50 (Shows Toxicity in 50% cases) is used. The TD50 Is the well-accepted by ICH M7 (R1) for The calculation of the acceptable excess Risk to calculate acceptable intake (AI) for Mutagenic and carcinogenic impurities and It is a well-recognized international Standard.The TD50 value reported for NDMA is 0.096 mg/kg/day for the most sensitive Species rat [5].The extrapolation to the excess risk level For cancer is calculated by linear back Extrapolation to the dose theoretically Causing a 1:100,000 risk by dividing the TD50 by 50,000 (50% or 0.5 x 100,000). For NDMA this translates into a dose of 1.92 ng/kg/day. For a person with a Bodyweight of 50 kg, this would result in An AI level of 96 ng/day (50 x 1.92 ng). Similarly, for NDEA, it comes out to be 26.5 ng/day. Following ICH M7 (R1) Guideline, FDA has calculated limit for NDMA and NDEA impurities in various Sartans drug as tabulated below in Table 2. Through this procedure, the limit for Nitrosamine impurities in any drug Substance or drug product can be Calculated. FDA and EMA have made Clear that these are interim limits [14-15].

Active substance (max daily dose)	NDMA		NDEA	
	AI ng/day	Limit (ppm)	AI ng/day	Limit (ppm)
Candesartan (32 mg)	96.0	3.000	26.5	0.820
Irbesartan (300 mg)		0.320		0.088
Losartan (150 mg)		0.640		0.177
Olmesartan (40 mg)		2.400		0.663
Valsartan (320 mg)		0.300		0.082

Table 2: Limit for NDMA & NDEA in sartans drugs

II. CONCLUSION :

Impurity profiling is very important during the synthesis of drug substances and manufacture of dosage forms, as 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 bulk drugs and finished products. An accurate method development and validation of the procedures Make the impurity profiling task easy.

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