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Overview on Impurity Profiling

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Abstract

The current scenario in the field of Pharmaceutical analysis have enormously focusing of the Impurity profiling of newer drug substances and their characterization.Impurities can be stated as unwanted substances which may comes along with the main pharmaceutiucal product by several sources.Each and every API,contains impurities which lessens the quality of the original product.Impurity profiling is the way of detecting,identifying and quantitatively determining all the forms of impurities both identified and unidentified one by using a group of analytical methods.The Present review focuses on the types of pharmaceutical impurities,their characterization by sophisticated instruments with special emphasization on regulatory guidelines.

1. Introduction

IMPURITY

Any molecular substance which may co exists with the original drug molecule either from the starting reactant or from the intermediates formed during the chemical reactions or it may also due to any unwanted side reactions is termed as an impurity.[1]The occurence of such impurities may detoriorate the standards of the main pharmaceutical product and its therapeutic efficacy and safety for useAll the Pharmacopoeia have established the allowable levels of impuritiers to be present and also there are some established regulatory guidelines for analysing these impuritues by validated methods.Impurities may also present due to overaging of the product,due to atmospheric contaminants and also the vessels utilized,temperature and atmospheric contaminants during the formulation.It is essential to ensure the quality of drug given to the patients should be in purest form which must be assessed in an independent manner ensuring the biological activity of pharmaceuticals.[2]

Common Analytical Terminologies in Impurities[3]

1.Intermediate/by product or penultimate product

The comppounds that are formed during the mid of nthe reaction as an intermediate during the formation of desired material.Penultimate compounds are the compounds that are formed in prior to the original compounds in a synthesis .By products are the compounds that are not planned but they may be formed in between in the desired reaction.

2.Interaction products

The degradant products which are araised as an interactive action of different types of chemical used for a particular reaction.It may be intentionally or unintentionally.

3.Related Products

The Products which are structurally and biologically similar but are not the actual product of the reaction.

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4.Degradation Product

The products which are formed as an results of decomposition of the API either with excipients or other chemicals or as a result of environmental conditions.

5.Transformation products

The compounds which are strucuturally diverse in nature but are intermediates formed in different ways.

SOURCES OF IMPURITIES IN MEDICINE[4-8]

API are formulated into pharmaceutical medicinal product.The impurities may originate from two sources,

1.The Impurities associated with API

2.The Impurities arising due to formulation parameters

1.The Impurities associated with API

Both the organic as well as inorganic medicinal products gets contaminated in the same way during their process of manufacturing.By this the contaminating impurities are classified into

Organic Impurities

Organic impurities includes both process related as well as drug related impurities.They may come from the starting materials especially the impurities arised during the multistep synthetic procedures because of the unreacted reactant occuring in the final products and improper washing followed in the synthesis.Organic impurities may also arises from the by products of the synthetic procedures due to side reactions because of the incompleteness of the original prefered reaction mainly photolysis,rearrangement,isomerization,oxidativede gradation,decarboxylation,hydrolysis,photolysis,en antiomerizationetc.The degradation products of the API may also arises as impurities mainly due to the improper storgae conditions.

Examples:Paracetamol may contains P-aminophenol as an impurity because it is the starting material,Hydrocortisone,conjugated dienes,nitroso derivatives,flavones are very suspectible to oxidative degradation.Hydrolysis is oftern seen in liquid dosage form.Ergometrine,nifedipine are liable to photo oxidation.

Inorganic Impurities

The impurities coming under this category eventually arises during the making process which may be familarly well identifiable one.The Reagents,liquids and the catalysts employed in the manufacturing process may creates a problem if not taken proper care during the process.Heavy metals are one of the main inorganic impurities which may comes from water utilized and also from the reactors due to acidification which should be minimized by use of pure water free from minerals and reactors made of glasses.Other type of formulating apparatus such as filters,charcoal beds used during the making may also contaminate the final product.Pharmacopoeial standards are well established for detection and quantification of these impurities.

Residual Solvents

The chemicals which are used foir their solvent property or those generated during the manufacturing process are called as residusl solvents,which are very tedious to remove completely.They may cause toxicity.By their possibilities of risks to humans,they are classified into three classes.

The solvents under class I category should either be avoided or to be restricted in use as they possess unacceptable toxicity.Generally they are carcinogenic in nature.

Name of the Residual Solvent	Concentration of the solvent in PPM	Effects associated with it
1,1,Dichloro ethane	8	Toxic

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1,1,1, Trichloro ethane	1500	Environment hazards
1,2 Dichloroethene	5	Toxic
Carbon tetrachloride	4	Toxic
Benzene	2	Carcinogenic

The solvents of class II type must have limited usage in pharmaceuticals due to their nature of inherent toxic.They are non-genotoxic and carcinogenic for animals and possibly neurotoxicants.

Solvent	Concentration in PPM	Permissible daily exposure mg/day
Cyclohexane	3880	38.8
Chloroform	60	0.6
Chlorobenzene	360	3.6
Acetonitrile	410	4.1

The solvents ogf class III type are lower toxic and their use does not cause any potential health hazards to humans. Acetic acid, Acetone, Anisole, 1-Butanol which are normally used as solvents coming under this category.

2. 2.Formulation Associated Impurities

In-Process Formulation related impurities

Impurities due to crystallization

During the process of crystallization,substances which are used in the process other than the material of crytsallization such as solvent may introduce its crystal product as impurities which directly affects the rate of growth of crystals and leads to agglomeration.

Stereochemistry related impurities

Stereochemistry related impurities refers that compounds which are having same strucutre but different spatial arrangement which are considered as impurities.The stereochemical aspects shows D form and L form or Racemic mixture of the same compounds.On comparing these,one form is beneficial having better pharmacological profile but other may be considered as impurities**.**

Synthetic Intermediates or by products

The Newer chemical entity may arises from the original synthesis part mainly from bulk materials and also from intermediate of the reaction which are regarded as impurities.

Impurities during Storage

Improper storage conditions during the shipping or poor transportation may leads to turning of Api and excipients inot impurities.For this purpose forced degradation studies should be performed for prediction,evaluation of drug safety.

Metallic Impurities

The metals may be considered as impurities mainly from the API and excipients used.Three classes of metals arebeing classified,

Class I metals which are having significant safety concern.Ir,Pt,Cr,Rh,Ni are class I metals.Class II metals have lower safety concern which includes Cu,Mn.The metals such as Fe,Zn are having minimal safety concern grouped under Class III.

Functional group related Degradation

Degradation of the functional group of the active moeity takes place by various reaction processes termed hydrolysis,oxidation,Photolytic cleavage etc.Aromatic amines,aldehydic

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group,epoxies,polyaromatic carbons are more prone to degradeds by losing their functional group moeity.

Exposure of the product to light causes origination of impurities and the oxidative degeneration in the organic compounds and heterocyclic ring undergoes oxidation produces impurities.

Impurities associated with Aging

Interaction between the ingredients used

Various vitamins such as B_1,B_{12},B_5,B_9 does not give degradation products individually,but the mutual interaction as if presence of nicotinamide in the above formulation may cause degradation of above vitamins to a substandard levels,so it should be stored within a 1 yr shelf life of these vitamins.

Impurities from packaging materials

The containers and closures which bare used for the packaging the manufacture formulation may cause the introduction of impurities.The drugs which mainly having water,electrophiles,peroxides,metals,extractables and leachables from glass,rubbers and plastics used are the main reactive species acts as asources of impurities under this category.

Genotoxic impurities [9]

Impurities which are having the ability to damage DNA at certain levels of exposure are called as genotoxic impurities,which may lead to the formation of the tumours.According the toxicological evaluation,genotoxic impurities are five classes which are represented under the regulatory guidelines ICH M7.

Class I Genotoxic impurities having established mutagenicity and carcinogenicity with severe risks.It should be eliminated by modification process.

Class II Genotoxic impurities are having establised mutagenecity but their ability to act as a carcinogen is unknown.So it should be controlled.

Class III genotoxic impurities are having unknown genotoxic potential,it includes impurities having different strucutres not relating to original drug structure,SAR studies are here used to find the toxicity.

Class IV genotoxic impurities are non genotoxic impurities whose structure is related to the original drug strucutures with extra functional moities which may prone to produce some effect but are non genotoxic.

Class V genotoxic impurities are non genotoxic one which are treated as normal,controllable impurities as of ICH guidelines.

IMPURITY PROFILING[10-13]

Impurity profiling of drugs refers to the descriptive information of both identifiable and unidentifiable impurities that may be existing in the new drug suubstances.In our Pharmaceutical industry,Impurity profiling is the main thrust area beacause of the following reasons,

1. Possibilities of knowing the structures of the impurities of a new drug so as to avoid its formation by changing the conditions of the reactions or else the quantity of impurity formation is minimized as of their level of acceptance limit.

2. Impurity profiling standards should be set while developing a suitable analytical method for quantification to use for routine analysis.

3. To assure safety,the impurities identified should be isolated and gone for toxicological evaluation.

4. For drug manufacturing industries and authorities,the profiling of New drug substances and products acts as benchmark finger print for effectively carrying out the manufacturing process.

Need of Impurity Profiling[14]

Impurity profiling is a very crucial phase in the drug development.

1.The Presence of impurities may cause incompatabilities with other compounds

2.It can reduce the $t_{90\%}$of the formulated product.

3.It may cause the formulation process difficulty.

4. Their presence can alter the physiochemical behaviour of the formulated substances.

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5.Reduction in therapeutic efficiacy and safety.

6.It may show toxic effect affecting the safety of use.

7.The presence of impurities above the specified limit is very injurious to human health.

ICH GUIDELINES FOR IMPURITY PROFILING [15,16]

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"

5) US FDA NDA's Impurities in New drug substances

6) US FDA ANDA's Impurities in New drug substances

Regulatory bodies focusing on the controlling impurities:

The International Council for Harmonisation (ICH)

The United States Food and Drug Administration (USFDA)

The European Medicines Agency (EMA)

Acceptance criteria for impurities

Criteria	**For drug substances**	**For drug products**
Each identified specific impurity	0.5%	-
Each unidentified impurity	0.3%	-
Total impurity	1%	-
Each identified specific degradation products	-	1%
Each unidentified degradation product	-	0.5%
Total degradation products	-	2%

ANALYTICAL METHODOLOGIES FOR IMPURITY PROFILING [17-20]

The Analytical methods used for the quantification of impurities shoulb be selective and sensitive to measure the very lowest level i.e ultra trace levels in sub mg quantification.The selection of the particular methods depends on the difference in the compounds and their selected impurities.At various stages of the development of new drug following analtical criteria to be followed,

1. Selection of sample

2. Controlling of chromatographic conditions like phase,elution technique and solvent selection etc

3. Optimization of the selected parameters for effective method validation for robustness and ruggedness.

The impurities can be identified predominantly by following methods

Reference standard method[21]

Reference standard used for developing analytical method will be used for determining the safety use of drug for patients to consume,not only for

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API,standards should be established for impurities,forced degradation products,other possible sources of impurities from starting materials,excipients etc

Spectroscopic method [22-24]

UV - Visible spectroscopy

It is used for identification and elucidation of structure of impurities without their chromatographic separation.The impurities gets absorbed in the UV region above 200 nm with the specifyinchromophoric action which is directly proportional to the concnetration.

Ex- Amphotericin B containing the tetraenes imprities is detected by UV -visible spectroscopy.

FT-IR

To detect or resolving the existence of chemically similar impurities in raw materials and detects the presence if it is in the above assured limit.Statins impurities are particularly detectable in FT-IR method.

NMR spectroscopy

For strucutral elucidation it is used by providing information regardingthe bonding strucuture and stereochemistry.Traditionally it is less used because of its insensitivity and sample requirements are on the order of nealry 10 mg when compared with MS having 1mg.

Mass Spectroscopy

Mass spectroscopy emerged as significantly trending analytical method for the development process of pharmaceuticals.The interface helping the separation method with MS plays a vital role for easier identification and quantification.Coupling of these techniques is used routinely for impurity profiling.

Raman Spectroscopy

Raman spectroscopy gives mainly details on the chemical structure,polymorphy,crystallinity,molecular interactions and phases.When a monochromatic light radiation are passed on to the sample containing impurity it gets absorbed,scattered and reflected.which having the different frequencies.

Separation methods[25,26]

CPE is used when there is very low quantity of sample and at the same time when higher resolution is needed.Varities of impurities from common drugs such as fluvoxamine,minocycline,lincomycin are separated using CPE.Orthogonal separation involving super critical fluid chromatography are now widely used for impurity profiling.The quantification of impurities from salbutamol sulphate is acheieved by axchiral SCF.TLC is used for tracer amount identification for development of stability indicating analytical method.It is used for quantitative estimation with a detection using densitometry i.e HPTLC.TLC was very much useful for the identification of the degradation products.

HPLC

High Performace liquid chromatography is a very useful separation tool as it extends to wider variety of samples with volatility.Stability problems in the separation technique is enhanced than other techniques which uses various detectors providing accurate and precise method for quantification.Reproduceability and automation along with higher resolution are the main advantages.

GC

Gas Chromatography is used when the nature of the sample is volatile and thermo stable with a very shorter runtimes and greater sample thoroughput in which the sample can be vapourized at relatively reasonable temperatures without decomposing the samples.Even the non volatile sample can be made as volatile and used.It is used for both quantitative and qualitative estimation of impurities.

Isolation methods [27]

The use of instrumental methods directly characterizes the impurities.There is need of isolation of impurities is necessary.So chromatographic techniques are used for separation of impurities.chromatographic reactors using analyticl grade column acts for both medium for separation and also flow through reservoir.Recently by this method using high performance liquid

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chromatography the impurity ofloratidine was separated from the drug loratidine.

Characterization methods [28-30]

Coupling of two different analytical methods for their detection and characterization and qyuantification ie hyphenation such LC-MS, GC-MS, CE-MS have also been reported is very sensitive,less time consuming.

LC-MS

For testing and Identification of impurities even in few hundred PPM is possible with concentration > 0.1%.Single quadropole mass spectrometers and ToF mass analyzers are mainly used for genotoxic and organic impurities quantification.

LC-UV

For Identification of impurities and degradants,HPLc coupled with UV is used.It is based onb absorption maxima,because of its higher selectivity it is used for usedfor the routine quantitative analysus on impurity profiling.

APPLICATIONS

The various separation and quantification methods used in impurity profiling has so far detected various impurities in drug substances and drug products which are listed in the given table3.

Table -3 Drugs and impurities with separation techniques

S. No	Drug Name	Impurities	Separation method	References
1	DEFERASIROX	Salicylic acid (impurity-A), Salicylamide (impurity-B)	HPLC	31
2	CARVEDILOL	1-(4-(2-Hydroxy-3-(2-(2-methoxyphenoxy) ethylamino) propoxy)-9H-carbazol-9-yl)-3-(2-(2-methoxyphenoxy) ethylamino) propan-2-ol	HPLC	32
3	EFAVIRENZ	6-chloro-2- cyclopropyl-4-(trifluoro methyl) quinolone,Imp -2:(s)-2-(2-amino-5-chlorophenyl)-4- cyclopropyl-1,1,1-trifluoro-but-3-yn-2-ol.	HPLC	33
4	MORPHINE	6 mono acetylmorphine	HPLC	34
5	MORPHINE SULPHATE	5-(hydroxymethyl)2-furfural	HPLC	35
6	10-HYDROXYMORPHINE	10-oxomorphine	HPLC	35
7	CIMITIDINE	1,8-bis(N'cyano-N''-methyl)guinidino]-3,6-dithiaoctane	HPLC	36
8	AMPHOTERICIN B	Teteaenes	UV	37
9	ETHAMBUTOL HCL	2 -amino butanol	TLC	38

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10	CELECOXIB	[5-(4-methylphenyl)-3-triflurомethyl-1H-pyrazole],4-[5-(2'-methylphenyl)-3-(triflurомethyl-1H-pyrazole-1-yl]-benzenesulphonamideand[4-(4'-methylphenyl)-3-triflurомethyl)-1-Hpyrazole-1-yl]-5-benzenesulphonamide	HPLC, LC, LC-MS-MS	39
11	ETHYNODIOLDI ACETATE	17a-ethinylestr-4-ene-3a,17-diol-3-acetate-17-(3'-acetoxy-2'- butenoate) 17a-ethinylestr-4-ene-3a,17-diol-3-acetate-17-(3-oxo-butanoate)	HPLC	40
12	REPAGLINIDE	4-carboxymethyl-2-ethoxybenzoic acid, 5-cyclohexylaminocarbamoylmethyl 2ethoxy-benzoic acid, 1-cyclohexyl-3-[3-methyl-1-2(piperidine1-ylphenyl)-butyl]-urea,1,3-dicyclohexylurea	GC,LC-MS/MS	41
13	METHAMPHETAMINE	N-formylphedrine,N-acetylephedrine, O-acetylephedrine,methamphetamine dimmer	GC	42

3. Conclusion

The present review focuses on the impurities and its profiling according to the regulatroy guidelines.Impurity profiling is a vital approach making the standards of drugs in terms of quality,safety and efficacy.It created major impact in the quality monitoring and designing of drugs.At present it is compulsory recruitment in the established pharmacopoeias about the impuritues.It is merely an quality control tool assuring the quantification limits with unique specifications.It also ensures the stability profiles of all types of pharmaceutical products either it is naturally produced or syntheticlly made or recombinantly produced.So far profiling of drugs such as alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids, miscellaneous compounds were validated by different specific methods.

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