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A Comprehensive Review of Quantifications, Profiling, and Regulations of Pharmaceutical Impurities

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

In the past few decades impurity profiling has continuously gained the attention of regulatory bodies due to the rise in the number of drugs frequently entering the market. International regulatory agencies like ICH, FDA, Canadian Drug and Health Agency emphasize carrying out impurity profiling of drugs in strict compliance with the regulatory guidelines that have been laid down intending to ensure production of high quality and safe pharmaceutical drugs to serve mankind. Simple impurities can be easily evaluated by conventionally available methods whereas impurities present within complex matrix structure pose significant challenges to the analyst and require a more sophisticated approach. The work has been carried out with great efforts to make the study possible distinctively and comprehensively.

Keywords: Drugs; impurities; pharmaceutical companies; chemical reaction.

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1. INTRODUCTION

Over the last few decades, the thrust on the development of safe and effective drugs has been shifted from the purity profiling of drugs towards the impurity profiling sector. Impurity profiling is vital and should be conducted during the different stages of manufacturing of a pharmaceutical drug product. An impurity can originate from various sources or may get build up at the time of the drug synthesis, research, and production. The conversion of an API to a suitable, potent, and affordable medication, is a multistep process and involves the incorporation of various inert substances such as excipients. It includes gram scale-up preparation for pharmacological screening, scale-up procedures, and finally synthesizing drugs in bulk [1]. Despite taking all necessary precautions, there is a possibility of impurity occurrence in drug products. It is practically impossible to attain a drug product without encountering impurity presence even at minor or controlled levels, because neither a chemical substance nor a compound is pure and stable nor does a chemical reaction has 100% selectivity. Apart from that various degradation pathways induced reactions like Oxidation, Hydrolysis, and Photolysis caused by the ubiquitous presence of moisture and oxygen in the atmosphere produce enormous impact on the safety and quality of drugs. Such reactions result in the formation of degradation products in the pharmaceuticals during their period of storage [2]. Simple impurities can be easily evaluated by conventionally available methods whereas impurities present with a complex matrix structure pose significant challenges to the analyst and require a more sophisticated approach. The structure of the impurities once evaluated helps in understanding their source of origin and formation, which further aids in synthetic process improvement and optimization of formulations.

2. SIGNIFICANCE OF IMPURITY PROFILING

The quality and safety of drugs are said to be the most important fundamental aspects of drug therapy [3-4]. An API is said to be compromised in terms of safety and efficacy if the impurities present in it (even if it is in trace amounts) possess toxic and reactive actions, thereby lowering its pharmacological effectiveness. Since APIs are the basis of all formulations, it is obligatory to conduct dynamic quality tests to uphold and assure quality and purity. The impurity is describe as the complete analytical activities including detection, identification, structure elucidation and quantitative estimation of the impurities which may be present in API itself or process generated or degradation products. While controlling and monitoring the safety of the drug, it becomes highly essential to evaluate not only the beneficial effects but also the adverse effects associated with the drug itself and the impurities present in it [5]. The safety of a drug is estimated on behalf of benefit to risk ratio, which can be evaluated by the expertise of the concerned field. The toxicologist sets the limits of impurities and develops a suitable method to assess them so that the unwanted adverse effects can be eliminated or minimized to a standard level. The drug regulation authorities direct the researchers and analysts to establish the toxicological profile of a new drug to uphold the safety and quality of the drug and help the physicians seek possible side effects before introducing them into the drug therapy. Impurity profile data, therefore, contribute to the safety profile data of the drug [6].

The given review is an epigrammatic impression of the current scenario concerning analytical prospective followed in impurity profiling and degradation studies. After attaining deep insight knowledge through enormous research and an extensive survey of several research and review articles published in the last 6 years, and screening of standard books published on impurity profiling techniques, the current state of work was framed. The work has been carried out with great effort to make the study possible distinctively and comprehensively. Year wise statistics from 2015-2021 covering the analytical methods, including both hyphenated and non-hyphenated techniques are discussed in the tables.

3. PHARMACOPEIAL AND REGULATORY GUIDELINES

The regulatory agencies of different countries like Food Drugs Administration (FDA) USA, European Medicines Agency (EMA) Therapeutic Goods Australia (TGA) Medicines and Healthcare products Regulatory Agency (MHRA) UK International Council of Harmonization (ICH), emphasizing to carry out the impurity testing in active pharmaceutical ingredients as well as in pharmaceutical products with strict compliance to produce the safe and effective products. The ICH guidelines under different sections are shown below in Table 1.

Table 1. ICH-Regulatory guidelines: [7-10]

Sr No.	Section	Description
1	Q1A	"Stability testing for new drug substances and products"
2	Q3A(R2)	"Impurities in New Drug Substances"
3	Q3B(R2)	"Impurities in New Drug Products"
4	Q3C(R7)	"Impurities: Guidelines for residual solvents"
5	Q3R	Guidelines for elemental impurities
6	M7(R1)	Assessment and control of DNA reactive (Mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk
7	Q1A(R2)	Guidelines to study drug condition when subjected to the forced decomposition of hydrolysis, oxidation, dry heat, and photolysis

Table 2. ICH -New Drug substance impurity threshold

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
≤2g/day	0.05%	0.10% or 10 mg/day intake (whatever is low)	0.15% or 10 mg/day intake (whatever is low)
≥2gm/day	0.03%	0.05%	0.05%

Table 3. New drug product impurity threshold

Maximum daily dose	Reporting threshold	Identification threshold	Qualification threshold
>2g/day	0.10%	0.10%	0.15%
>100 mg-2g	0.1/0.05%	0.2% or 2gm TDI, whichever is lower	0.2% or 3gm TDI, whichever is lower
10mg-100mg	0.05%	0.2% or 2mg TDI, whichever is lower	0.5-200 µ g TDI, whichever is lower
1mg-10mg	0.05%	0.5% or 20 µ g TDI, whichever is lower	1.0% or 50 µ g TDI, whichever is lower
<1mg	0.05%	1.0% or 5µ g TDI, whichever is lower	1.0% or 50 µ g TDI, whichever is lower

4. THE THRESHOLD FOR DRUG SUBSTANCE

According to ICH Guidelines, (ICH) Q3A. impurities level below 0.1% in new drug product do not need to be analyzed and characterized, unless and until the effects associated with that are not usually toxic. The threshold dose for a particular drug is calculated by keeping the dose as 2gm/day or 1gm/day (whatever is less) i.e if the dose is less than 2gm/day then the amount of impurity it can contain is 0.1%, and if it is higher than 2g/day the limit value of allowable drops to 0.05% as shown in Table 2.

Similar guidance was provided for impurities typically found in new drug products as shown in Table 3. These impurities are usually termed degradation products.

Earlier, Pharmacopieas focus was purely compensated on monitoring the quality of API and drug formulations, as it included several assays to assess the drug purity whereas literature related to the side effects arising due to impurities or degradants were somewhat underestimated. But during the past few years, due to the ongoing rising safety concerns on commercially available products, there has been found a significant rise in the impurity profiling data of pharmaceuticals. The incorporation of limits of allowable levels of impurities in APIs and their related Formulations is now seen in Pharmacopeias as it has acquired sufficient space and separate sections within the Pharmacopieas of the latest editions [11-12].

5. CLASSIFICATION OF IMPURITIES

As per ICH, impurities are categorized as follows:

5.1 Organic Impurities

This is the most important and common type of impurity to be dealt with within a pharmaceutical product. It exists in almost every drug substance and thereby likely to be found in every Drug product. Ranging from detection in raw material, regents, the catalyst to the likelihood of being formed during the different chemical reactions as an intermediate or get formed as a by-product, or as degradant product due to improper and poor storage conditions, Organic impurities need to be evaluated [13].

For example, Acetylation of p-aminophenol results in the preparation of a product-Acetaminophen. During this reaction, the formation of Diacetylacetaminophen also takes place as a by-product due to the occurrence of side reaction, which is considered as an organic impurity in the parent drug [14].

5.2 Inorganic Impurities

Inorganic impurities are introduced during the manufacturing process. These impurities are often reagents, ligands, catalysts, heavy or residual metals, inorganic salts, filter aids, or charcoal. Inorganic contaminants can be detected and quantified using pharmacopeial standards. Out of these impurities arising due to the use of metal catalyst is most common and lethal. Metals are categorized into three groups on basis of their effect on human health [15].

5.3 Elemental Impurities

Class1 metals: Exhibit toxic effects: Chromium, Molybdenum, Nickel, Platinum, Vanadium, Rhubedium,
Class2 Metals: less harmful than class 1:Copper, Manganese
Class 3 Metals: Least harmful Iron and Zinc

5.4 Residual Solvents

These solvents are the organic volatile impurities. They play a major role during the formation of a drug or drug product. In most synthetic reactions, they also get formed as a side or by-product. Most of them are not only injurious to human health but also found to be harmful to the environment [16].

In accordance with ICH -guidelines, residual solvents are categorized into three different classes as shown in the table below:

5.4.1 Class I solvents

Class 1 solvents: These chemicals are known to cause unacceptable toxicities (carcinogenicity, environmental hazard, and pollution) and must be avoided during the manufacturing or processing of APIs, Pharmaceutical formulations. The restricted limits in accordance to only with which they are allowed to be used during the preparation of medicinal products are shown in Table 4.

5.4.2 Class II solvents

Although the chemicals/solvents of Class II are considered to be a bit less severe in toxicity as compared to class1 chemicals, they are capable to cause irreversible toxicities like Neurotoxicity and teratogenicity and being carcinogenic to animals on long term exposures. So their use must be done within specified limits to ensure the safety of human health from the hazardous side effects associated with them [14]. The Concentration limits are depicted in Table 5 against the particular chemical in use.

5.4.3 Class III solvents

These solvents are less toxic and pose a lower level of risk to human health. Their use is to be limited by the application of good manufacturing practices and shifting to echo-friendly chemicals. The concentration limits of 5000 ppm would be acceptable for the solvents listed in Table 6.

Table 4. Class 1 solvents along with their concentration(ppm) and toxic effects

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon Tetrachloride	4	Toxic and environmental hazard
1 , 2-Dichloroethane	5	Toxic
1, 1-Dichloroethene	8	Toxic
1, 1, 1-Trichloroethane	1500	Environmental hazard

Table 5. Class II solvents along with their concentration and allowable limit

Solvent	PDE Concentration	Limit ((ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cumene	0.7	70
Cyclohexane	38.8	3880
1, 2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
Dimethoxyethane	1, 2- 1.0	100
N, N-Dimethylacetamide	10.9	1090
N, N-Dimethylformamide	8.8	880
1, 4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylisobutylketone	45	4550
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulpholane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1, 1, 2-Trichloroethene	0.8	80
Xylene	21.7	2170

Table 6. List of class III solvents

Name of solvents	
Acetic Acid	Methylethylketone
Acetone	Ethyl formate
Anisole	Ethyl ether 2-Propanol
Isobutyl acetate	
Heptane acetate	Ethyl acetate 1-Propanol
1-Butanol	Dimethyl Sulphoxide (DMSO)
2-Butanol	Formic acid
Butyl acetate	Propyl acetate
3-Methyl-1-butanol	Triethylamine
tert-Butylmethyl Ether	2-Methyl-1-propanol
Pentane	Ethanol 1-Pentanol

6. SOURCES AND TYPES OF IMPURITIES

To understand the various causes of impurities, it is necessary to understand the different sources of their origin. Fig. 1 indicates the different sources and types of impurities.

Apart from the above-mentioned, certain specific impurity types include- Genotoxic impurities, Enantiomeric and Chiral impurities, which are covered in the preceding sections.

6.1 Enantiomeric Impurities

Asymmetrical synthetic reactions cause the generation of enantiomeric impurities in pharmaceutical drugs. Upon interaction with the biological systems, different enantiomers exert

their effect differently, some being beneficial while others may be deleterious. To attain better therapeutic effect and enhanced therapeutic index of a chiral drug, emphasis is given to drive stereospecific reaction to obtain the single enantiomeric form of the drug.

6.2 Genotoxic Impurities

In accordance with (ICH) S2 (R1), guideline-Genotoxic Impurities can be defined as impurities that have been demonstrated to cause deleterious changes in the genetic material regardless of the mechanism [17].

The task of determining the acceptable limits for such impurities is quite cumbersome but truly obvious. These impurities may be present in the starting material, intermediate catalyst, get processed during manufacturing, by product, degradation product, enantiomeric, or due to poor storage conditions.

The genotoxicity test, in-vivo, and in-vitro tests are conducted not only to identify hazardous compounds but also to study their mechanism by which they cause DNA damage [18]. (179) Manifestation of DNA damage is indicated by gene mutation, (change in chromosomal number that finally resulting tumor generation [19]. Several organizations from industries and regulatory authorities have developed specific guidelines to address genotoxic impurities.

ICHS2 guidance on Genotoxicity Testing and Data Interpretation directs methods to identify potent genotoxic impurities in drug substances, during conventional mutagenicity investigations. The analytical methods for the determination of genotoxic impurities have been developed by various researchers. The numbers of genotoxic impurities was earlier analysed using sophisticated analytical techniques (Table 9).

Table 7. Virtual safety data

Sr. No.	Name of Drug	Safety dose
1	Acrylnitrile	7.6µgm/day
2	2-Amino-4-nitrophenol	1007µgm/day
3	Nitrobenzene	31µgm/day

QSAR based software like MLD, DSTOPKAT, Tox boxes, Leadscope toxicity is utilized for virtual calculation of safety doses of Drugs. The data obtained through virtual screening is found to be in accordance with Carcinogenicity safety dose studies. The data of virtual safety doses for few drugs are given in Table 7.

This study suggests that in-silico estimation of structural features for mutagenicity provides a highly sensitive and conservative method for identification of potentially genotoxic impurities [20].

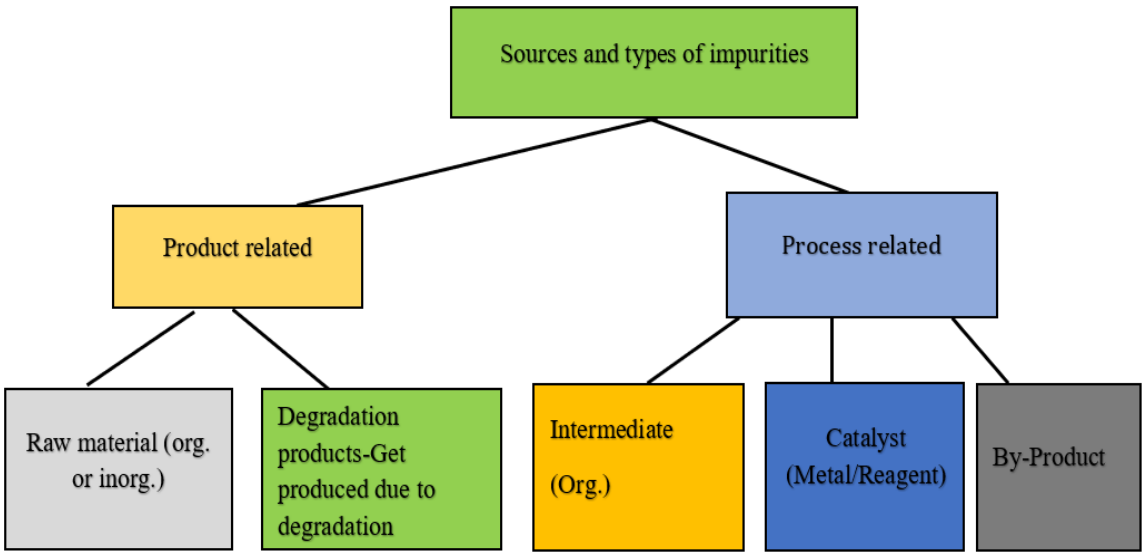

Fig. 1. Sources and types of impurities

Table 8. Abbreviations along with their directing agency

Sr No.	Abbreviation	Full form	Name of agency
1	TDI	Phase tolerable daily intake	IPCS
2	ADI	Acceptable daily intake	WHO
3	PDE	Permitted daily exposure	ICH

6.3 Threshold of Toxicological Concern

TTC was established to define the exposure level of any unexplored chemical that will not exert carcinogenic or mutagenic action. The study of nearly 343 compounds collected from the carcinogenic potency database laid the foundation of TTC [21] which further included the increasing number of carcinogens under investigation to more than the700 [22]. The value of TTC is estimated to be 1.5 µg/person/day. A TTC value of more than 1.5 is only acceptable when the interaction/exposure duration is less, life expectance is less than five years, ailment against the life-threatening condition, impurity is evaluated, and identified one.

TTC and expected daily dose of the patient are used to calculate the Genotoxic impurity concentration limit (ppm) by the following relation:

Concentration limit=TTC(µg/day)/Dose(g/day)

6.4 Safety Profiling of Impurity

Keeping the safety of patient at utmost concern, the ICH and other regulatory agencies direct guidelines to suggest acceptable levels of impurities that can be present in some residual solvents.

Given below Table 8 indicate some abbreviation along with their meaning and the directing agency [23].

To avoid confusion of differences in the values for ADI's of the same substance, current phase Permitted daily exposure is defined in the present guidance as a Pharmaceutically acceptable Intake of residual solvents.

7. ARREST THE USE OF ORGANIC VOLATILE SOLVENTS

Residual solvents are the most frequently used chemicals in the manufacturing of Pharmaceuticals. Studies have shown that their long-term exposure is harmful to the human health as well as the environment.

Intending to safeguard human health and maintain environmental integrity, several International organizations like the International Programme on Chemical Safety (IPCS), the U.S Environmental Protection Agency (EPA), and the U.S Food and Drug Administration (FDA) have come forward on a single platform and started a joint venture to arrest the utilization of hazardous chemicals to an acceptable exposure level [24]. Monographs like Environmental Health Criteria and Integrated Risk Information (IRIS) have categorized such agents as being included in the list of toxic chemicals [25-26]. Long-term studies to evaluate the maximum safe exposure limits have been conducted on such chemicals [27].

7.1 Forced Degradation Studies

Stability plays an important role in maintaining the quality standards of pharmaceutical products. A drug must be stable throughout its shelf life concerning to its quality, purity, identity, and strength.

The forced degradation study is carried out with the dual aim of finding the possible reaction that may cause degradation of the drug product, thereby altering its stability, and it also forms the part of development strategies that are integral components of the analytical method validation [28].

Specific guidelines have been issued regarding stress testing in drug products and drug substances. To address the intrinsic stability of drug substances as well as develop drug stability assay degradation products and impurities methods, degradation pathways have been issued.

7.2 Analytical Methods for Impurity Profiling: [29-30]

Controlling the quality of APIs and drug products includes the number of analytical tests such as, Assay, content uniformity, Dissolution, and Purity

control. In contrast to purity testing, impurity profiling is more challenging and critical to the analyst.

Various analytical techniques are available to detect the impurities within Pharmaceuticals as shown in Fig. 2. An analytical method must be capable enough to provide a clear impurity profile of the bulk drug, and sensitive enough to differentiate between product and process-related impurities.

7.2.1 Reference standard method

To attain clarity on the whole life cycle of impurities present in a drug, qualification, and control of impurities, Reference Standards are much needed. They are important from the viewpoint of new drug development. In the presence of reference standards, valuable information necessary to evaluate the process and product performance of drug substances, impurities, degradants, raw materials, intermediates, and excipients is provided.

7.2.2 Isolation methods

To segregate impurities from the drug and drug products, a number of methods are employed. Structure, physicochemical properties, and availability are the criteria that help the analyst to opt for the most appropriate isolation method The most generally used method of isolation includes chromatography. Apart from that certain extraction methods.

List of chromarographic [29] and Non-chromatographic isolation methods

-Solid-phase extraction
-Liquid-liquid extraction
-Accelerated solvent extraction
-Capillary Electrophoresis
-Supercritical fluid Chromatography

Separation Methods: This includes the Chromatographic techniques like TLC, HPTLC, HPLC, GC, SFC, and electrophoretic techniques like CE, Gel Permeation Chromatography.

Spectroscopic Methods: UV, IR, MS, NMR, Raman Spectroscopy are among the most widely used methods for impurity identification during the past few decades.

7.2.3 Characterization method

To simultaneously characterize the drugs and carry out their impurity profiling, conventional spectroscopic methods are modified to hyphenated ones. Coupling an MS to GC or HPLC results in the formation of inevitable tools with high sensitivity and high selectivity. Analysis of impurities in complex matrices and multicomponent mixture systems has become much easier and faster with the use of

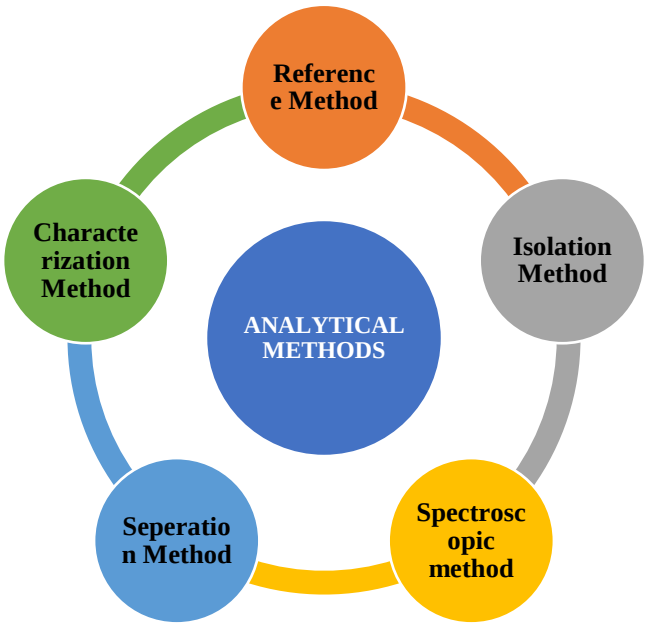

Fig. 2. Analytical methods for impurity profiling

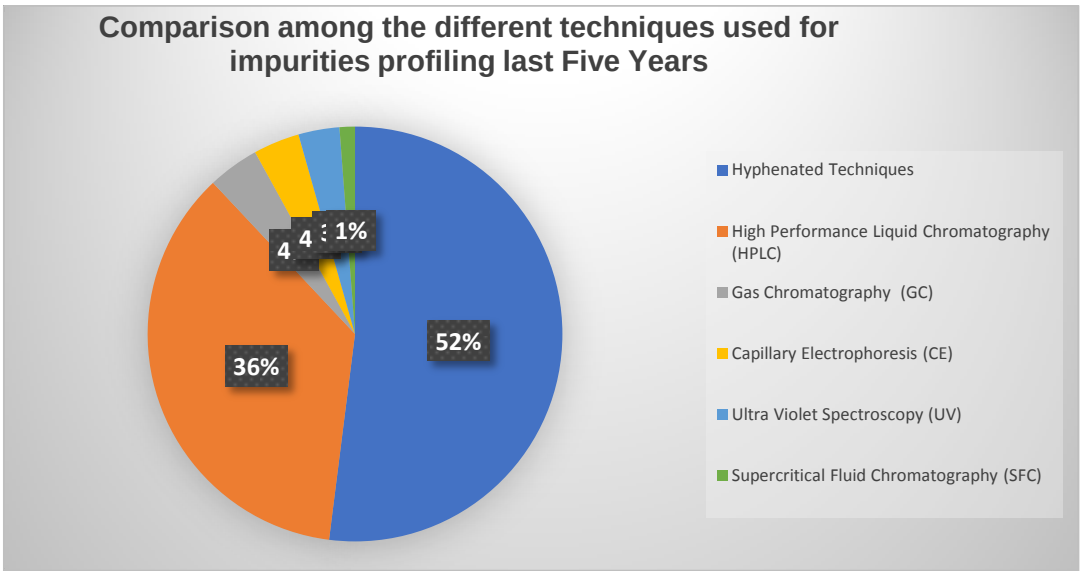

Fig. 3. Comparison of different techniques followed

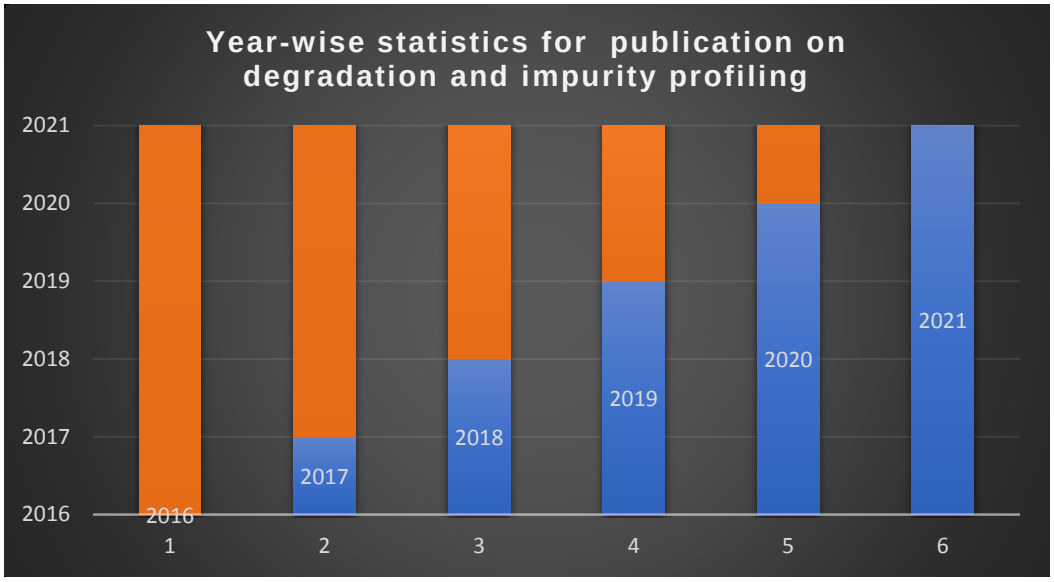

Fig. 4. Year-wise statistics for publications on degradation and impurity profiling

hyphenated techniques. Modern Pharmaceutical analysis has strongly evolved in the area of highly sophisticated and hyphenated techniques, during the past few years. For characterization of impurities, different techniques are used which are as follows:

HPLC-UV, HPLC-MS, GC-MS, LC-MS, CE-MS, MEKC-MS, CES-MS , HPLC-NMR

Nowadays hyphenated techniques have become the first-line choice of regulatory authorities to carry out impurity profiling of Pharmaceuticals. A clear comparison among the utilization of hyphenated to non-hyphenated techniques is seen during the past few decades (the ratio of hyphenated to non-hyphenated is 70%:30%)

7.2.4 The current outlook on impurity profiling

Nowadays, much more emphasis has been given to impurity profiling of drugs. The majority of the analytical journals include topics on modern analytical methods for the detection and isolation of impurities. The given below Fig. 4 clearly illustrates the progressive increase in work done in this field during the past few years.

Table 9. Summary of years of work and techniques employed for impurities profiling

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
Year 2016									
1	Azilsartan	DPs	4	LC-UV, MS^N, LC-MS-TOF	Ammonium formate(20Mm, pH3.0), MeOH and CAN(40:5:40%V/V)	IM	C18, 250mmx4.6mm, 5µm	UV 254 nm	[31]
2	Aztreonam	DPs	3	HPLC, LC, MS, NMR	A: 0.05 TFA B:ACN with 0.05%TFA	GM	C18, 150mmx4.6mm, 3.5µm	PDA 270nm	[32]
3	Agolmeltine	PRIs	6	UHPSFC, UHPLC	ACN & MeOH	GM	C18 50& 100mm	PDA 225nm	[33]
4	Bilastine	Imps	2	HPLC/HPLIC	ACN-50Mm-Ammonium acetatae in water pH 5.3 with g.a.a (90.5:9.5, v/v)	IM	Luna HILIC 100mmx4.6mm, 5µm	DAD	[34]
5	Borsetan monohydrate	Rs	4	HPLC	A:Potassium dihydrogenorthophosphate(pH 2.5) & ACN(50:50, v/v) B: Potassium dihydrogenorthophosphate(pH 2.5) & ACN(20:80, v/v)	GM	DS-3V 450mmx4.6mm, 5.0µm	PDA 225 nm	[35]
6	Civemeline	PRIs	1	HPLC -DAD,	A: MeCN (5%):0.1 % TFA in water(95%) B: MeCN (25%) :0.1 % TFA in water(75%)	GM	C18, 100mmx4.6mm, 3.5 µm	DAD 210nm	[36]
				Single-crystal XRD	Nonius Kappa CCD refractometer	-	Software CIF files: SHELXL Graphic: ORTEP-3 and Mercury		
				DSC	Mettler Toledo differential scanning calorimeter DSC1	-		Scanned from 25^0C-800^0C at 100C /min under Nitrogen purge	
				TGA	Mettler Toledo thermogravimetric analyzer TGA1/SF	-			
				GC-MS	Carrier gas Helium (99.99%)			Scanned from 25^0C-800^0C at 100C /min under	

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
								Nitrogen purge	
7	Dobutamine	PRIs GTIs	3	GCMS	Carrier gas Helium (99.99%)	-	HP-5 MS, 30mX0.25mm, 0.25µ Composition:5% phenyl and 95%dimethtylpolysiloxane	5977A Mass selective detector	[37]
8	Darunavir	PRIs	6	UPLC-MS/MS	ACN -MeOH(80:20, v/v) &5.0Mm ammonijum acetate containing 0.01% formic acid	GM	C18 50MMX2.1 MM, 1.7µm	MS/MS	[38]
9	Duloxetine 3Hydrochloride	DPs	15	LC—UV/PDA, LC-MS/TOF	ammonijum acetate buffer(32Mm, pH 5.5)&ACN	IM	C18 250 mmx4.6 mm, 3.5 µm	PDA290nm	[39]
10	Emtricitabine and tenofovir disoproxil fumurate	IMPs	6	HPLC-PDA, LC-HRMS, LC-MS^n	A: MeOH B: 10.0 mM Ammonium acetate(pH 3.75)	GM	C18 250 mmx4.6 mm, 5 µm	PDA 254nm	[40]
11	Efavirenz	PRIs GTIs	1	LC–MS/MS	5.0 mM ammonium acetate-pH 6.5 with acetic acid & methanol (35:65, v/v)	IM	Luna C18 (100 mm × 4.6 mm, 3 µm	UV	[41]
12	Enzalutamide	PRIs	6	HPLC	A: ammonium acetate buffer(10mM, pH 4.0) with G.A.A B : ACN		C18 250 mmx4.6 mm, 5 µm	UV 254 nm	[42]
				IR	Thermo Scientific Nicolet iS5 FT-IR spectroscopy				
				NMR, MS	Bruker AVANCE 400MHz NMR spectrometer instrument				
13	Furazidine	DPs	3	HS-MCR-ALS HPLC-DAD TOF-MS	A: Water B: ACN (98:2v/v)	GM	C18, 150mmx2.1 mm, 3 µm	DAD	[43]
14	Fluconazole	GTIs	1	LC-MS/MS	5 mM ammonium acetate & acetonitrile in the ratio of 65:35 (v/v)	IM	C18 , 100 mm x 4.0 mm, 3 µm		[44]
15	Fodostein	Org.Res. Imps	4	GC–MS	Carrier gas Helium g	-	30 m long with 0.32 mm i.d., 1.0 µm		[45]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
		GTIs					bonded and cross-linked polyethylene glycol		
16	Gabapentin	PRIs	1	RP-HPLC-CAD LC-MS/MS	50mM Ammonium acetate(pH 4.2 using G.A.A), ACN(80:20) B: MeoH	GM	C18, 250mmx4.6mm, 5 µm	CAD	[46]
17	Gabapentin	Imp	1	HPLC, LC-LCHESIMS/MS, NMR	0.07%Ammoinum acetate in water& CAN	1M	C8, 250mmx4.6mm, 5µm		[47]
18	Hydrocortisone	DPs	8	HPLC-UV, LC-MS, LC-HRMS, NMR	A: 85% Water and 15% ACN with 0.1 %acetic acid, B: 30% Water and 70 % ACN 0.1 %acetic acid	GM	C18, 250mmx4.6mm, 5 µm	UV DAD	[48]
19	Lamivudine &tenofovir disoproxil fumarate	Imps	12	HPLC, LC-HRMS, LC-MSn, Online H/D exchange, NMR	A: MeOH B: 10 mM Ammonium formate(pH 3.75)	GM	C18, 250mmx4.6mm, 5 µm	PDA 254 nm	[49]
20	Methionine	Imps	4	HPLC	80%(v/v) 12.5 mM aq. phosphoric acid and 20%(v/v) ACN dihydroxyphenylalanine	IM	C18, 250mmx4.6mm, 5 µm	DAD 210nm	[50]
21	Metoprolol	Imps	2	HPLC/HILIC	ACN-Ammonium formate buffer(100 Mm , pH3.2 85:15(v/v)	IM	C18, 150 mmx4.6mm, 5 µm	CAD	[51]
22	Nebivolol hydrochloride								[52]
23	Nepafenac	DPs	4	UHPLC	A: 10Mm monopotassium phosphate pH 3.0-0.05 with KOH B: CAN	GM	C8 and C18, 100mmx2.1 mm, 1.7 µm	PDA 235 nm	[53]
24	Nevirapine	DPs	3	UHPLC, LC-MS/MS	ACN & water	GM		PDA 254 nm	[54]
25	Omeprazole	PRIs	11	RP UPLC-TOF/MS	A: Ammonium acetate buffer (0.06 M) pH 8.9 with ammonia: ACN(950:50, v/v) B: ACN : MeOH(65:35, v/v)	GM	C18, 100mmx2.1 mm, 1.7 µm	PDA	[55]
26	Posaconazole	DPs	4	HPLC, LC-TOF/	A: Water-THF-Phosphoric	GM	C18, 75 mmx4.6mm, 3.5	PDA 260nm	[56]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
				MS, LC-MS/ MS, NMR	acidf(770:230:1, v/v/v) B: Water-ACN Phosphoric acid (200:800:1, v/v/v)		µm		
27.	Pralatrexate	DPs	9	LC-PDA&LC-MS	A: MeOH & Ammoniumformate(0.01M, pH 3.0) (10:90v/v) B: MeOH & Ammoniumformate(0.01M, pH 3.0) (80:20v/v)	GM	C18, 250mmx4.6 mm, 5 µm	PDA 242 nm	[57]
28	Pharmacutical API	PRIs GTIs	1	HPLC	A: 0.05% TFA in water B: 0.05% TFA in ACN	GM	C18, 150mm x 3.0 mm, 3, 5 µm	DAD 406nm	[58]
29	Permethrin	PRIs	6	HS-GC, GC-MS	Helium		15m x 0.53 mm, 3.0 µm	FID	[59]
30	Racecadotril	DPs	7	UHPLC-Q-TOF-MS/MS NMR, GC	0.1% Formic acid & CAN	- GM	C18, 100mmx2.1 mm, 1.8 µm	Q-TOF-MS	[60]
31	Rivaroxaban	DPs	3	UHPLC-Q-TOF-MS/MS	A: Water pH4.0 with NH4OH with 0.1 % formic acid B: ACN with 0.1 % formic acid	IM	C18, 50mmx2.1 mm, 1.8 µm	ESI-MS/MS	[61]
32	Sofosbuvir	DPS	7	HPLC, LC-ESI-QTOF-MS/MS	10mM Ammonium acetate (pH 5.0) buffer and ACN	GM	C18, 150mm x 4.6 mm, 5 µm	PDA	[62]
33	Sartans(irbesartan, candesartan, valsartan)	PRIs GTIs	1	UHPLC	A: 0.5 g/L Phosphoric acid B: CAN	IM	C18, 250mm x 4.6 mm, 4 µm	DAD	[63]
34	T-dCyd (NSC 764276).	PRIs	6	HPLC		GM	C18, 150mm x 4.6 mm, 3 µm	UV 282 nm	[64]
35	Ticagrelor	PRIs	5	HPLC, LC-/ESI-MS, NMR, IR	A: Sodium dihydrogen orthophosphate pH 3.5-0.05 using 2.0 M Orthophosphoric acid B: ACN-MeOH(7:3v/v)	GM	C18, 250mmx4.6 mm, 5 µm	PDA 254 nm	[65]
36	Trelagliptin succinate	PRIs	6	LC-MS/MS, NMR5, IR	A: 20mM Potaasium dihydrogen orthophosphate & 0, 25% triethylamine(pH 3.5 with phosphoric acid B: CAN	GM	C18, 250 mm x 4.6 mm, 5 µm	PDA 230nm	[66]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
37	Vortioxetine	PRI	1	HPLC, NMR	A: 0.05% TFA in water B: ACN	GM	C18, 250mmx4.6 mm, 5 µm	PDA 230 nm	[67]
38	Vidalgliptin	PRI DPs	1 6	UHPLC, FT-IR, ID NMR, 2D NMR	A: 10Mm Sodium phosphate monohydrate pH7.0 using 2.0 M NaOH B: Mixture of A & CAN(7:3v/v)	GM	C18, 150mmx4.6 mm, 3 µm	PDA 210	[68]
YEAR 201[									
1	Aprepitant	DPs	2	HPLC	0.1 % v/v Phosphoric acid aq. Sol. ACN	GM	C8, C18, 150 mmx4.6 mm, 3.5 µm	PDA 225 nm	[69]
2	Apremilast	PRIs RS DPs	1 12 2	HPLC, LC-ESI-MS, MS/MS, NMR	A: Water pH3 with formic acid B: ACN	GM	C18 250	DAD	[70]
3	Abacavir sulphate	DPs	7	HPLC, LC-ESI-Q-TOF-MS, NMR	A: MeOH B: 10 mM Ammonium formate(pH 3.75)	GM	C18, 250mmx4.6mm, 5 µm	PDA	[71]
4	Anidulafungin	Imps	8	HPLC, ESI-MS, ID&2D NMR	A: 01% formic acid in water B: ACN	GM	C18, 150mm x 4.6 mm, 3.5 µm	DAD	[72]
5	Asunaprevir	PRI	1	HPLC	THF and TFA (100:2.5v/v)	IM	C18, 150mm x 4.6 mm, 3.5 µm	UV 306 nm	[73]
6	Atazanavir	GTIS	1	LC-MS	0.01 M Ammonium formate (pH3.0 ± 0.05, with dilute formic acid), ACN and MeOH in the ratio50:40:10 (v/v/v)	GM	C-18 75 mmx 4.6 mm, 3.5 µm	MS (single QMS)	[74]
7	Ambresenten	PRIs	3	CE, NMR	100mM Borate buffer pH 9.0, 100mM SDS	GM	FSC, 50mm, 64.5 cm	UV-Vis 200 nm	[75]
8	Ceftaroline fosalmil	DPs	8	HPLC, LC-ESI-Q-TOF-MS	A: Ammonium formate buffer(50 Mm) pH 3.5 B: CAN	GM	C18, 250mmx4.6 mm, 5 µm	DAD 243	[76]
9	Clobazam	Imps	6	HPLC, LC-ESI/MSn, IR &NMR	A: Sodium dihydrogen phosphate monohydrate soln, pH 76.05-7.05 carrier gas B: Mixture of ACN Sol-a(75:25, v/v)	GM	C8, 250 mmx 4.6 mm, 5 µm	5977A Mass selective detector	[77]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
10	Cilostazol	Imp	1	LC/MS/MS, FT-IR &NMR	A: Water-CAN(70:30, v/v) B: Water-CAN(50:50, v/v)	GM	C8, 110mm x 4.6 mm, 3.5 µm	VWD	[78]
11	Cefodizime, cefmenoxime and cefonicid	Imps	11	2D-HPSECX LC-IT-TOF MSLC-UV, LC-MS, LC-HRMS, NMR	Buffer pH 7.0(0.005 mol/L dibasic sodium phosphate solution 0.005 mol/L sodium dihydrogen phosphate solution(61:39, v/v) ACN	GM	C18, 150mmx4.6mm, 5 µm	PDA	[79]
12	Doxofyylline	Imp	1	LC—IT-MS, QTOF-MS, NMR	A: 15% v/v CAN B: 85%(V/V) aq.buffer	IM	C18 250 mmx4.6 mm, 5 µm	UV 273 nm	[80]
13	Doxofylline	DPs	2	HPLC, LC/ESI-MS & IR, NMR	Water , pH :3.0 using formic acid & ACN (87:13) ACN-50Mm-Ammonium acetatae in water pH 5.3 with g.a.a (90.5:9.5, v/v)	IM	C18, 250 mm x 4.6mm, 5µm	PDA	[81]
14	Deflazacort	DPs	2	HPLC, Q-TOF, 2D-NMR&FTIR	Water :ACN (52:48, v/v)	IM	C18, 250mmx4.6mm, 5 µm	PDA 240 nm	[82]
15	Dapoxetine	PRIs	1	IR, NMR LC-MS	0.1% Formic acid & ACN (50:50, v/v)	IM	C18, 250mmx4.6mm, 3.5µm	MS(Q-TOF_MS)	[83]
16	Dalfempridine	GTImPs	5	HPLC	10 mM sol of Ammonium formate	IM	C18, 250 mm x 4.6mm, 5µm	PDA 280 nm	[84]
17	Evt-401	PRIs DPs	6 8	LC-TOF-MS, LC-MS/MS LC, MS, NMR	A: MeOH-ACN-water-formic acid(24:14:62:0.2, v/v/v/v) B: MeOH -ACN-water-formic acid(24:14:62:0.2, v/v/v/v)	GM	C18, 250 mm x 4.6mm, 5µm	DAD	[85]
18	Flomoxef Sodium	Imps	13	LC–IT-TOFMS	A: 10.0 mM aq.ammonium formtae - MeOH(84:16 v/v) B: 10.0 mM aq.ammonium formtae - MeOH(47:53 v/v) -pH 6.5 with acetic acid & methanol (35:65, v/v)	IM	C18 250 mmx4.6 mm, 5 µm	DAD	[86]
19	5-flurouracil	PRIs	7	HPLC, UV-ViS spectroscopy, LC-HRMS	A::0.1 % Formic acid in water B: 0.1 % Formic acid in ACN	IM	C18, 250 mm x 2 mm, 5 µm	DAD	[87]
20	Isoproterenol	PRIs	1	HPLC, , LC/ESI-	A: Triethylamine, pH -3	GM	C8, 250 mm x 4.6mm,	PDA	[88]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
	hydrochloride			MS& IR, NMR	B: CAN		5µm		
21	Ketoprofen	DPs	2	Online photoreactor- SPE-HPLC, HPLC-DAD/ QTOF-MS	ACN, water, and GAA (450:550:5) 7.5 mM TFA-ACN (47.5:52.5)	GM	C18, 250 mmx4.6 mm, 3.5 µm	DAD	[89]
22	Levothyroxine Sodium	PRIs	5	HPLC-HRMS/MS, Online H/D Exchange, NMR	A:0.1% formic acid in water B: .1% formic acid in AN	GM	C 18, 150mm x 4 mm, 3µm	PDA	[90]
23	Lamivudine Emtricitabine	D.Ps	6	HPLC, LC-HRMS(LC-ESI-Q-TOF-MS)	A: MeOH B: 10mM Ammonium formate (pH 3.75)	GM	C18, 250 mm x 4.6mm, 5µm	PDA	[91]
24	Liothyronine Sodium	Imps	39	LC/MS/MS, FT-IR &NMR	A: Ultrapure water containing01% (v/v) formic acid B: Formic acid in ACN	GM	C18 , 150 mm x 4.0 mm, 3 µm	PDA	[92]
25	Meglumine	IMPs	6	HPLC-HRMS, HPLC-MS, TGA, NMR,	Ammonium formate(II g/L)pH 2.8	GM	C18, 250 mm x 4.6mm, 3.5µm	DAD	[93]
26	Macrolides Josamycin, josamycin propionate &midecamycin acetate	Imp	22, 11, 20 respectively	HPLC-UV, LC/-MS	A:30 g/ml Sodium percholate monohydrate pH 2.5 B: ACN -THF(98:2, v/v)	GM	C18, 250mmx4.6mm, 3.5µm	UV 231 nm	[94]
27	N, N-ehtylenebis-I-cysteine diethyl ester(Bicisate) Co-enzyme A (coa)	DPs	2	HPLC, LC-MS/MS	A: pH 7.0, 20mM ammonium acetate aq MeOH (94:6) B: MeOH	IM	Sielc Obelisc N , HILIC, 150mmX4.6mm	CAD	[95]
28	Olanzapine	PRIs	2	HPLC, UV, FT-IR, LC-MS/TOF ID & 2D-NMR, HPLC, LC MS,	A: ACN-buffer(48:52 v/v) B: ACN-buffer(70:30 v/v)	GM	C8, 250 mmx 4.6 mm, 5 µm	VWD 230 nm	[96]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
				NMR Single-crystal XRD					
29	Pyraclostrobin	Imp	1	HPLC-ESI-MS, NMR	A: Water B:ACN	GM	C18, 250 mmx 4.6 mm, 5 µm	VWD	[97]
30	Pantoprazole	GTIMPs	3	LC-MS	A: 0.1% formic acid in 1000 ml of water used as a buffer B :acetonitrile		C18 100 mm×4.6 mm, 3.0 µm	MRM	[98]
31	Sodium chromoglycolate	DPs	9	LC-ESI-ion trap MS & LC-ESI-QTOF MS	A: 10 mM Ammonium formate(pH 3.75) B: ACN	GM	C18, 150mmx4.6mm, 3.5µm	UV-330nm	[99]
32	Tp-6076	Elemental Imps	15	ICP-MS	50mM Ammonium acetate(pH 4.2 using G.A.A), ACN(80:20) B: MeOH	-	-	-	[100]
33	Silodosin	DPs	2	HPLC, LC-ESI-MS/MS	0.1% Formic acid & CAN	GM	C18, 150 mmx4.6mm, 5 µm	PDA	[101]
34	Torasemide	PRIs	6	HRMS/LC-HRMS, MS^n, LC-ESI-Q TOF-MS	A: CAN B:10 mM ammonium formate buffer	GM	C18, 150mm x 4.6 mm, 3 µm	UV 282 nm	[102]
YEAR 2018									
1	Cannabinoid	-	-	F-LC LC-MS UHPLC-MS					[103]
2	Divalproex Sodium	GTIs	5	GC-MS	Helium Gas		DBFFAP 30mx0.32mm, 3µm		[104]
3	Febuxostate Sodium	GTIs	1	HPLC	A:0.01M Phosphate buffer pH 2.5 B: ACN	GM	C18, 250mmx4.6mm, 5µm	254 nm	[105]
4	Lingalipin	DGImp (genotoxic) PRIm	1 1	MS/MS, 1D&2D NMR	-	-	-		[106]
5		DGImps	9		A:	GM	C18, 250mmx4.6mm,	UV 254 nm	[107]

Sr no.	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
	Montelukast			LC-MS/TOF HPLC	B; Water : ACN(5:95 v/v)		5µm		
6	Rabeprazole	GTIs	2	LC-MS/MS	A: Ammonium acetate B: Ammonium formate with pH adjusted to 6.5 A:B(31/69 v/v)	IM	C8, 50mmx4.6mm, 5µm	UV/ViS 256nm	[108]
7	Tolvaptan	GTIs	1	GC-MS	Helium Gas	-	TG-5SilMS 15mx0.25mm, 0.25 µm		[109]
8	Valsartan	PRIs	1	LC-MS/MS UHPLC GC-MS, GS-MS/MS GC-TES,	A: 0.1 % formic acid B: Methanol	GM	C18, 00 mmx4.6mm, 3 µm		[110]

Sr no	Name of the drug	Type of Impurity	No. of impurities	The technique employed for detection					Ref
				Instrument used	Mobile phase	Elution mode	Column	Detector	
YEAR 2019									
1	Avanafil	DP	16	LC-MS/MS	A:10 Mm Ammonium Acetate Buffer) (Ph 4.5, Adjusted With Acetic Acid) B: ACN (60:40, V/V)	IM	C18 250 × 4.6 Mm, 5 µm -	PDA 239 Nm	[111]
2	Alalevonadifloxacin	PRIs	3	LC-MS/MS, NMR	A: 10 Mm Ammonium Formate Ph Adjusted To 2.1 With Formic Acid B: ACN		C18 250 X 4.6 Mm I.D 5 µm	UV Detector 293 Nm	[112]
3	Cefadinir	PRIs	Imps	HPLC	n-Hexane:Isopropylalcohol (70:30 v/v)		C-8 250X4.6 mm, 5µm	PDA 247 nm	[113]
4	Cannabinoid amyl-5F-Pinaca	PRIs	PRImps	FC UHPLC HRMS/MS					[114]
5	Lurasidone	GTIs	GTImps	LC-MS	10 mM Ammonium acetate ACN(70:30 v/v)	IM	C18 50X4.6 mm, 3.0 µm		[115]

				The technique employed for detection					
Sr no	**Name of the drug**	**Type of Impurity**	**No. of impurities**	**Instrument used**	**Mobile phase**	**Elution mode**	**Column**	**Detector**	**Ref**
YEAR 2020									
1	Alfuzosin & solifenacin	DPs	1 3	HPLC	ACN: phosphate buffer (pH 8) : triethylamine (60 : 40 : 0.02)	IM		DAD 210nm	[116]
2	Brivaracetam	PRIs	9	HPLC-MS, NMR HSQC, HMBC-H-COSY					[117]
3	Celecoxib	PRIs	7	UHPLC	n-Hexane Ethanol	IM	Chiral pak AD10 µM, 250X4.6 MM	UV detection	[118]
4	Chlorthalidone	PRIs	5	HPLC-MS FT-IR, NMR	A: Buffer solution (diammonium hydrogen orthophosphate (10 mM, pH 5.5) and methanol at a 65: 35 (v/v) B: buffer solution and methanol at a 50: 50 (v/v).		C_8 column 250 × 4.6 mm; 5 µm particle size	PDA 220 nm	[119]
5	Eluxadoline	PRIs	Imps	HPLC	ACN:Methanol:0.1 M Sodium acetate(40:40:20 , v/v/v)	IM	C18 250 mm x4.0 mm, 5µm	UV Detector	[120]
6	Isavuconazonium sulfate	DPs PRIs	4 1	HPLC, LC-ESI-QTOF-MS/MS	A: Acetonitrile, methanol, and ammonium formate (pH 4.5, 0.02 M) (10:10:80 v/v/v) B: Acetonitrile, methanol, and ammonium formate (pH 4.5, 0.02 M) (40:40:20 (v/v/ v)	GM	C18 (150 mm x 4.6 mm; 3 m	UV detector-285 nm	[121]
7	Imatinab Mesylate	GTIs	2	LC-MS/MS	0.02 M Ammonium formate buffer(3.4) & ACN (0.05%)	GM			[122]
8	Pantoprazole	GTIs	6	LC-MS GC-MS	A: 0.005 mol/L Ammonium acetateaq sol containing 0.1%formic acid B:Methanol (A;B 60:40 , v/v)	IM	C-18 150x4.6 mm, 5µm		[123]
9	Sildenafil	GTIs	4	H-NMR, C-13 NMR, FTIR					[124]

				The technique employed for detection					
Sr no	**Name of the drug**	**Type of Impurity**	**No. of impurities**	**Instrument used**	**Mobile phase**	**Elution mode**	**Column**	**Detector**	**Ref**
10	Sartans, Ranitidine Nizatidine Metformic	GTIs	9	LC-MS/MS, GC-MS-HS HPLC					[125]
11	Thiamine Hydrochloride	DPs	6	LC-MS/MS/QTOF	A: pH 3.1 buffer, acetonitrile and methanol in the ratio of 90:8:2 (% v/v/v) B: pH 3.1 buffer, acetonitrile and methanol in the ratio of 50:35:15 (% v/v/v)	IM	250 mm x 4.6 mm id 5 µm 250 mm x 4.6 mm id 5 µm 250 mm x 4.6 mm id 5 µm	248nm	[126]
YEAR 2021									
1	Brimonidine tartrate and Timolol			UPLC-MS	A: Heptafluorobutyric acid as a buffer and water B: Methanol, and acetonitrile			248 nm for Brimonidine tartrate and 295 nm for Timolol maleate Quadrupole Dalton analyzer	[127]
2	Codeine Phosphate	Imps	7	UHPLC		GM	2.1X100mm, 1.7µm	TUV & PDA	[128]
3	LM 49-API	PRIs	6	HRMS NMR(H-H -CSY, H-H NOESY) HMBC	A: Water adjusted to pH 2.0 with formic acid B: ACN adjusted to pH 2.0 with formic acid	GM	C-18 250 mmx4.6µm		[129]
4	Ranitidine	PRIs GTIs	7	GC-MS					[130]

**GTIs: Genotoxic Impurities , PRIs: Process related impurities , DPs: Degradation Product, IMP: Intermediate Product Rs: Related Substance*

It is worthwhile to summarize the different works done in the last 5 years in the area of impurity profiling and the study of degradation pathways in a Table 9.

8. CONCLUSION

The given review furnishes information about the different types of impurities, degradation products present in the pharmaceutical products. It provides the viewpoint of the various regulatory agencies and the principles followed by them to monitor and control the safety and efficacy of drugs. Information about recent advances made in the analytical area to isolate, characterize and quantify the impurities, genotoxic matter is sufficient enough to assure the quality of the bulk drugs and drug products and provide knowledge about their proper storage. Apart from that, a list of drugs along with their reported impurities in the Pharmacopoeias of the past few years is also included in this text.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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