Impurity profiling emerging trends in quality control of pharmaceuticals

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Abstract

Impurities are nothing but the unidentified, unintended substance present along with desired substance. The newer regulations of US FDA, MHRA intends for the requirements of impurities rather than purity of pharmaceuticals. The impurity profiling of pharmaceuticals can be done by using various analytical methods like UV, HPLC, LC-MS, GC-MS, SCFC etc. Mostly RP-HPLC method commonly adopted for the qualification as well as quantification of impurities. The present review is an attempt made in the respect of highlighting the some important methods, quality guidelines and applications of impurity profiling.
Keywords: Impurity, quality control, pharmaceuticals, impurity fate mapping, analytical techniques.

1.Introduction

Impurity is defined as any substance coexisting with the original drug, such as starting material or intermediates or formed, due to any side reactions. The impurity profile is a description of Identified and unidentified impurities. The impurity may be developed either during formulation or in the final product upon ageing. The Various instrumental approaches for isolating and identifying the process related impurities and degradation products are Mass spectroscopy (MS), Nuclear magnetic spectroscopy (NMR),High performance liquid chromatography (HPLC) etc., has been established to review a summary of the problems and the various possibilities offered by modern analytical chemistry. Drugs play a vital role in the progress of human civilization by curing diseases. Today a majority of the drugs used are of synthetic origin. These are produced in bulk and are used for their therapeutic effects in pharmaceutical formulations. The biologically active chemical substances generally formulated into convenient dosage forms such as tablets, capsules, suspensions, ointments and injectables. These formulations deliver the drug substances in a stable, non-toxic and acceptable form, ensuring its bio-availability and therapeutic activity.

Safety and efficacy of pharmaceuticals are two fundamental issues of importance in drug therapy. The safety of a drug is determined by its pharmacological toxicological profile as well as the adverse effects caused by the impurities in bulk and dosage forms. The impurities in drugs often possess unwanted pharmacological or toxicological effects by which any benefit from their administration may be outweighed [1]. Therefore, it is quite obvious that the products intended for human consumption must be characterized completely. The quality and safety of a drug is generally assured by monitoring and controlling the impurities effectively. Thus, the analytical activities concerning impurities in drugs are among the most important issues in modern pharmaceutical analysis.

Impurities in drugs are originated from various sources and phases of the synthetic process and preparation of pharmaceutical dosage forms. A sharp difference between the process-related impurities and degradation products is always not possible. However, majority of the impurities are characteristic of the synthetic route of the

manufacturing process. Since there are several possibilities of synthesizing a drug, it is possible that the same product of different sources may give rise to different impurities. In these studies the impurity profiles of various lots of the bulk drugs obtained from different manufactures were compared. Generally, the origin of impurities could be from any of the following steps during synthesis. [2-4]

- last intermediate of the synthesis
- products of incomplete reaction during the synthesis
- products of over reaction
- impurities in the starting materials of the synthesis
- impurities originating from the solvents of the reaction
- impurities originating from the catalysts products of side-reactions
- degradation products as impurities
- enantiomeric impurities
- residual solvents
- inorganic impurities
- impurities in excipients
- polymorphs as impurities

2. Classification of Impurities [5]

Impurities can be classified into the following categories:

  i. Organic impurities (process- and drug-related)
  ii. Inorganic impurities
  iii. Residual solvents

i. Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include:

• Starting materials
• By-products
• Intermediates
• Degradation products
• Reagents, ligands and catalysts

ii. Inorganic impurities can result from the manufacturing process. They are normally known and identified and include:

• Reagents, ligands and catalysts
• Heavy metals or other residual metals
• Inorganic salts
• Other materials (e.g., filter aids, charcoal)

iii. Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Residual solvents can be classified as follows,

Class 1 solvents (Solvents to be avoided)**:** Known human carcinogens, strongly suspected human carcinogens, and environmental hazards. Example: Benzene, carbon tetrachloride, Dichloro methane etc

Class 2 solvents (Solvents to be limited): Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities. Examples: Acetonitrile, chlorobanzene, chloroform etc.

Class 3 solvents (Solvents with low toxic potential): Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day. Example: Acetone, acetic acid, heptanes etc.

Table no. 01. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

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 no.02: Class 2 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	Concentration limit (ppm)	PDE (mg/day)
Acetonitrile	410	4.1
Chlorobenzene	360	3.6
Chloroform	60	0.6
Cumene	70	0.7
Cyclohexane	3880	38.80
Dichloromethane	1870	18.70
1,4-Dioxane	380	3.8

3. Regulatory guidelines on impurities in an active pharmaceutical ingredient: [6-8]

Ethical, economic and competitive reasons as well as those of safety and efficacy support the need to monitor impurities in drug products. However monitoring impurities and controlling these impurities mean different things to different people or to the same people at different times, even those in the pharmaceutical sciences and industry. A unified terminology is necessary to assure that everyone uses the same vocabulary when addressing questions related to impurities. The United States Food and Drug Administration (US FDA) have endorsed the guidance prepared under the guidance of the International Conference of harmonization (ICH). The ICH guideline for impurities in pharmaceuticals was developed with joint efforts of regulators and industry representatives from the European Union (EU), Japan and United States and it has helped to ensure that different regions have consistent requirements for the data that should be submitted to various regulatory agencies. The deadlines not only aid the sponsors of New Drug Applications (NDA) or Abbreviated New Drug Application (ANDA) with the type of information that should be submitted with their applications, but also assist the FDA reviewers and field investigators in their consistent interpretation and implementation of regulations1-2. The various regulatory guidelines regarding impurities are as follows:

1. ICH guidelines "stability testing of new drug substances and products"- Q1A

2. ICH guidelines "Impurities in New Drug Substances"- Q3A

3. ICH guidelines "Impurities in New Drug Products"- Q3B

4. ICH guidelines "Impurities: Guidelines for residual solvents"- Q3C

5. US-FDA guidelines "NDAs -Impurities in New Drug Substances"

6. US-FDA guidelines "ANDAs – Impurities in New Drug Substances"

7. Australian regulatory guideline for prescription medicines, Therapeutic Governance Authority (TGA), Australia.

4. Isolation and identification of impurities in active pharmaceutical ingredients[9]

An impurity profile is a description of the identified and unidentified impurities present in a new drug substance (Source: Guidance for Industry, Q3A Impurities in New Drug Substances). Impurity profiling processes usually begin with the detection of impurities, followed by their isolation and characterization. For all three types of impurities, it is critical to develop a robust method during process development that can eventually be validated and transferred to QA/QC. Developing reliable methods for impurities regulated at very low levels, such as genotoxic impurities, adds further challenges to this process. To better detect, identify, quantify, and characterize the impurities present in drug substances and products, pharmaceutical scientists rely on fast analytical tools with high sensitivity and specificity. Major analytical tools for impurity analysis include spectroscopy, chromatography, and various combinations of both, i.e. tandem techniques. The appropriate technique is selected based on the nature of the impurity and the level of information required from the analysis. There are various complex analytical problems in pharmaceutical development that require the use of more than one analytical technique for their solution. Analytical techniques such as LC/UV, LC/MS, GC/MS, CE/MS, and LC/UV provide the orthogonal detection and complementary information that can address these challenges in a time efficient manner. As a result, they play a vital role in impurity profiling of pharmaceuticals from identification to the final structure elucidation of unknown impurities.

a. **FTIR:** FTIR is very helpful for identifying and confirming the structure of an impurity or degradant because it provides a complex fingerprint that is specific to a particular compound. An FTIR spectrum of an organic molecule is determined by the functional groups present. The technique helps to identify the structure and measure the concentration of the compound under investigation. Changes in the structure can be correlated with the help of an FTIR spectrum of a patent drug compared to that of the impurity or degradant.

b. **Preparative Liquid Chromatography (LC):** Since the impurities in the drug substance are usually present at very low quantities, detailed analysis is only possible upon isolation of the impurities. However, this is a major challenge in pharmaceutical laboratories. Preparative LC helps isolate impurities (usually from impurity-enriched analytes, such as the solution remaining from the crystallization of APIs) in sufficient quantities to carry out structural analysis, usually using techniques such as FTIR, NMR, LC/MS, or GC/MS.

c. **Liquid Chromatography and Ultraviolet Spectrometry (LC/UV):** A number of impurity analysis methods found in pharmaceutical quality control (QC) laboratories use high-performance liquid chromatography (HPLC) coupled with UV detection (HPLC/UV methods). UV spectrometry helps identify impurity or degradants in drug substances based on absorption maxima. This technique is one of the most important and versatile analytical methods available for impurity profiling today due to its high selectivity (i.e., ability to quantitatively determine a number of the individual components present in a sample using a single analytical procedure), especially for routine analysis where standards are available. Newer, stationary phase systems are available which operate in several modes, such as ion pairing, increased hydrophobic interactions, and variable pH, allowing a variety of samples to be analyzed concurrently based upon their unique properties. High resolution is particularly helpful when using LC/UV analysis for impurity detection, because all impurities can be identified with less chance of error.

d. **Liquid Chromatography and Mass Spectrometry (LC/MS):** LC/MS is a powerful analytical tool that is routinely used in pharmaceutical development to test and identify product impurities. The detection limit of a few hundred ppm is readily achievable, ensuring the identification of all the impurities present at concentrations greater than 0.1 %. MS-based methods generally provide additional robustness and ruggedness compared to techniques such as UV alone, due to their high specificity and sensitivity. While single quadrupole mass spectrometers work well as analytical tools for the confirmation of known impurities and the preliminary structural assessment of unknown impurities, highly sensitive Q-TOF mass spectrometers provide higher resolution and mass accuracy that enables the unambiguous identification of unknown trace impurities, making them very useful for genotoxic impurity analysis. MS-based methods are often selected for the impurity profiling of APIs during process development, while UV-based methods are generally used to test for genotoxic impurities in QC laboratories at manufacturing sites. Triple-quadrupole (QQQ) LC/MS/MS systems have become a standard platform for the quantitative analysis of organic impurities in pharmaceutical analytical laboratories.

e. Capillary Electrophoresis (CE): The determination of drug-related impurities is currently the most important task for CE within pharmaceutical analysis because it achieves high separation efficiencies compared to other chromatographic techniques. CE can be employed when HPLC techniques are not able to adequately measure impurities, especially in the case of very polar compounds. A detection limit of 0.1 % is widely accepted as a minimum requirement for a related impurities determination method and this can be achieved using CE. In addition, CE is very useful for the separation of closely related compounds, such as diastereomers and enantiomers.

f. Supercritical Fluid Chromatography (SFC): SFC, which uses supercritical CO_2 as mobile phase, is another orthogonal technique that can be used for impurity detection because it offers HPLC-level sensitivity with reduced organic solvent usage. SFC also offers the advantage of chiral impurity analysis enabling the determination of enantiomeric excess at very low impurity levels.

g. Nuclear Magnetic Resonance Spectroscopy (NMR): NMR is a powerful analytical tool that enables the study of compounds both in solution and in the solid state. It has wide applicability because it provides specific information about bonding and stereochemistry within a molecule, which is particularly important in the structural characterization of drug impurities and degradant often present only in extremely limited quantities. The non-destructive, non-invasive nature of   NMR spectroscopy makes it a valuable tool for the characterization of impurities and degradant present at very low levels. NMR can also provide quantitative output, an important aspect of impurity profiling.

h. Inductively-Coupled Plasma Optical Emission Spectroscopy (ICP-OES) and Inductively-Coupled Plasma Mass Spectrometry (ICP-MS): The new draft elemental impurities procedure (USP) requires that an instrument-based method is used to determine elemental impurities and that the reference methods are based on either ICP-MS or ICP-OES. With both methods, sample analysis can be accomplished in three ways: directly (unsolvated), following sample preparation by solubilization in an aqueous or organic solvent, or after acid digestion using a closed-vessel microwave system.

ICP-OES: ICP-OES provides parts per billion (ppb) detection limits for most regulated elements in pharmaceutical products, easily meeting the specified limits in cases where direct sample analysis or small dilution factors are appropriate. It also provides extended dynamic range, robust plasma, and one-step measurement of major, minor, and trace elements. Therefore, ICP-OES addresses the needs of a wide range of users, including those seeking a cost-effective solution for the direct analysis of elemental impurities in bulk raw materials and pharmaceutical products.

ICP-MSL: ICP-MS is a powerful and sensitive technique that delivers a reliable trace-level analysis of all 16 elements whose limits are defined in USP. The low detection limits of ICP-MS ensure that all regulated elements in drug substances or drug products can easily be determined using the new method, at or below regulated levels, and even when large sample dilutions are required. ICP-MS can also be used in combination with a variety of separation techniques, such as HPLC, GC, and CE, providing several options for separation (or speciation) of the different chemical forms of the elements, and depending upon the nature of sample. ICP-MS achieves low detection limits for almost all elements, including those found in the more extensive analyte list proposed in the ICH Q3D, such as Au and Tl.
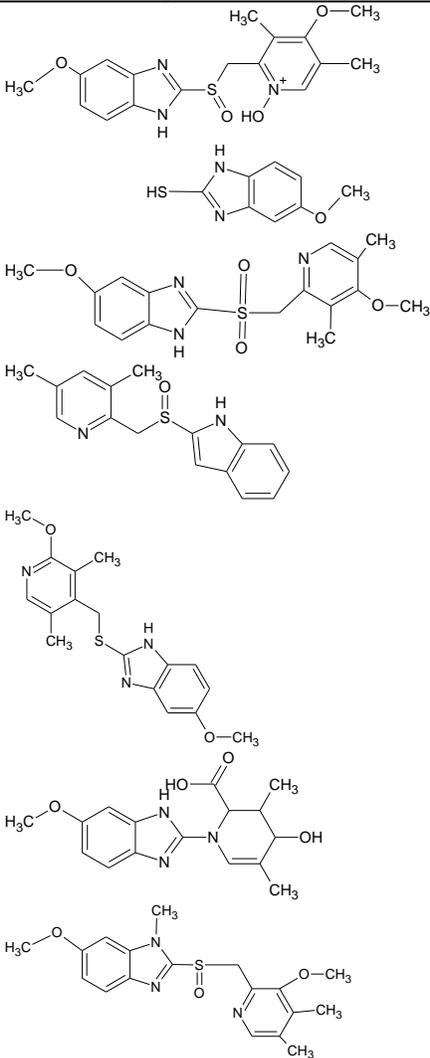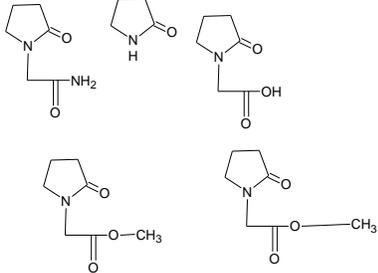
Gas Chromatography (GC): In combination with flame ionization detection (FID), GC is the standard choice for the analysis of volatile organic impurities, such as residual solvents. The gas chromatography headspace method is used worldwide for residual solvent analysis in quality control laboratories because it closely follows ICH Q3C guidelines. Sample preparation and introduction is via a static headspace which facilitates the selective introduction of volatile solvents without contamination by mostly non-volatile drug substance or drug products. Therefore, the use of an FID detector helps preferentially identify and quantify residual solvents. More recently, the combination of gas chromatography and mass spectroscopy (GC/MS) has been successfully used for confirmation and identification purposes, highlighting the flexibility of this technology.
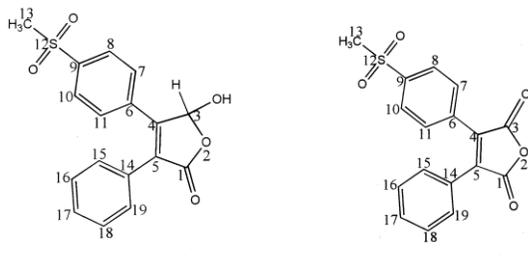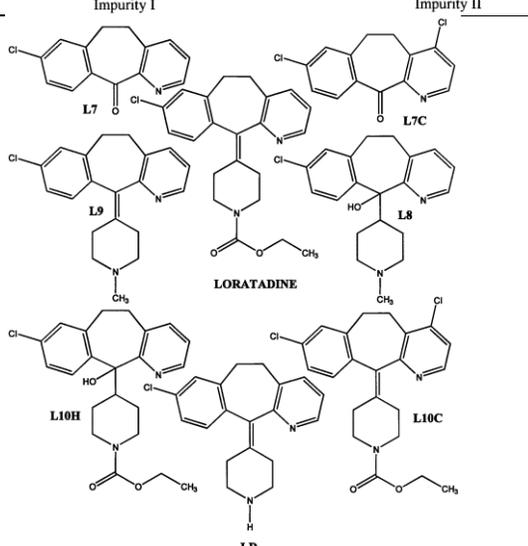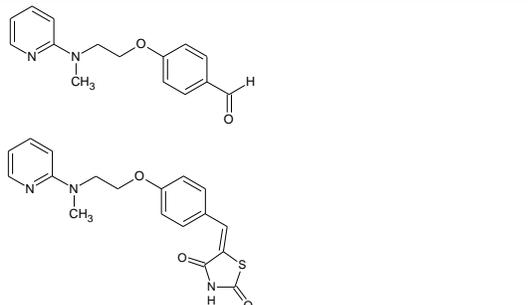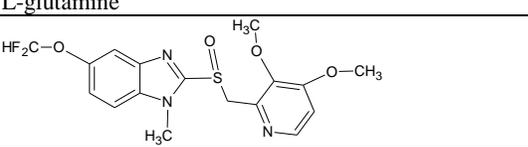
5. Applications of impurity profiling

Numerous applications have been sought in the areas of drug designing and in monitoring quality, stability, and safety of pharmaceutical compounds, whether produced synthetically, extracted from natural products or
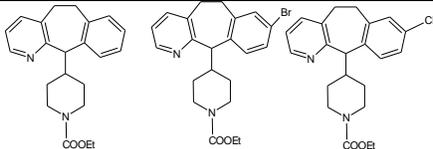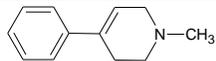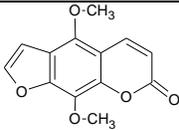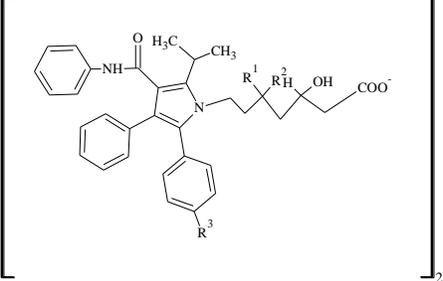
produced by recombinant methods. The applications include alkaloids, amines, amino acids, analgesics, antibacterials, anticonvulsants, antidepressant, tranquilizers, antineoplastic agents, local anesthetics, macromolecules, steroids etc. There are a few examples of impurities reported in the APIs mentioned in Table

Table no. 03: Various impurities reported in APIs

Drug	Impurity	Method	Reference
Glimepiride	glimepiride–sulphonamide; glimepiride-cis-isomer; glimepiride-meta-isomer; glimepiride-ortho-isomer ; glimepiride–urethane	**HPLC**	**10**
Omeprazole	Enantiomeric impurities	**HPLC**	**11**
Esomeprazole		**UPLC**	**11**
Niacinamide	Isonicotinic acid; Niacin Isonicotinamide; Picolinamide; 3-Cyanopyridine; Niacinamide N-oxide	**UV-HPLC**	**12**
Piracetam		**TLC**	**13**
Mangafodipir Trisodium	MnDPDP-MOA and Mn(5-methyl)- DPMP; the hydrolytic degradation product MnDPMP and the oxidative degradation product; Mn (III) DPDP.	ion-pair HPLC	**14**

Nitrendipine		HPLC	**15**
Mebendazole		HPLC	**16**
Fenbendazole		HPLC	**16**
Albendazole		HPLC	**17**

Rofecoxib	 Impurity I Impurity II	HPLC	**18**
Loratadine		HPLC	**19**
Rosiglitazone		HPLC	**20**
Thalidomide	L-glutamine	HPLC	**21**
Pantoprazole		HPLC	**22**
Repaglinide	4 – carboxymethyl – 2 – ethoxy - benzoic acid (I); 4-cyclohexyl aminocarbamoyl methyl - 2 – ethoxy - benzoic acid (II), 1-cyclohexyl-3-[3-methyl-1-(2-piperidin-1-yl-phenyl)-butyl]-urea (IV) and 1,3-dicyclohexyl urea (III)	HPLC	**23**
Pethidine	N-methyl-4-phenyl-1,2,3,6 tetrahydropyridine	HPLC	**24**
Azithromycin	Erythromycin A, Erythromycin A oxime, Erythromycin A imino ether etc.	HPLC	**25**
Methoxsalen	Isopimpinellin	HPLC	**26**
Atorvastatin	desfluoro-atorvastatin (DFAT); diastereomer-atorvastatin	HPLC	**27**
Piroxicam	2-aminopyridine	HPLC	**28**
Acetaminophen	[n-propionyl-p-aminophenol (PPAP); 3-chloro-4-hydroxyacetanilide (C-APAP); 4_- hydroxyacetophenone (4-HAP), 4-hydroxyacetophenone oxime (4-HAP Oxime); 4_-chloroacetanilide (4-CAA) and 4-acetoxyacetanilide (4-AAA)	HPLC	**29**

Loratidine		HPLC	**30**
Omeprazole and Pantoprazole	Related impurities	UV	**31**
Pethidine		HPLC	**32**
Methoxsalen		HPLC	**33**
Atorvastatin		HPLC	**34**

6. Conclusion

The plethora subscribed in this is mostly directed towards the discussion about different types of impurities that pharmaceuticals may possess along with the different analytical methods used for the detection of these impurities from bulk drugs n formulations. A list of drugs along with methods used for the separation and quantization had been given.

References

[1]. Hardman J.G, Limbird L.E, Molinoff P.B, Ruddon R.W, Gilman A.G. (Eds.), Goodman and Gillman's The Pharmacological Basis of Therapeutics, Ninth ed., McGraw Hill, New York, 1996.
[2]. Gorog S. (Ed.), Determination of Impurities in Drugs, Elsevier Sciences, Amsterdam, 1999.
[3]. Ahuja S. Impurities Evaluation of Pharmaceuticals, Marcel Dekker, New York, 1998.
[4]. Husain S, Nageswar Rao R. Monitoring of process impurities in drugs, in: Z. Deyl, I. Miksik, F. Tagliaro, E. Tesarova (Eds.), Advanced Chromatographic and Electromigration, Methods in Biosciences, Elsevier Sciences, Amsterdam, 1998, pp. 834-888.
[5]. ICH Guidelines, Q3B (R2), Impurities in New Drug Substances, October 25, 2006.
[6]. ICH Guidelines, Q3A (R2), Impurities in New Drug Substances, October 25, 2006.
[7]. ICH Guidelines, Q3 C (R5), Impurities in New Drug Substances, October 25, 2006.
[8]. ICH guidelines, Q3 D (R2), impurities in new drug substances, october 25, 2006.
[9]. Primer's, pharmaceutical impurity analysis solutions, Agilent technologies.
[10]. Mubeen Ahmad Khan, Sukumar Sinha, Santosh Vartak, Atul Bhartiya, Shankar Kumar, LC determination of glimepiride and its related impurities, *J Pharam Biomed Ana* 2005; 39: 928–943.
[11]. Leo Zanitti, Rosella Ferretti, Bruno Gallinella, Francesco La Torre, Maria Luisa Sanna, Antonina Mosca, Roberto Cirilli, Direct HPLC enantioseparation of omeprazole and its chiral impurities: Application to the determination of enantiomeric purity of esomeprazole magnesium trihydrate, *J Pharam Biomed Ana* 2010; 52: 665–671.
[12]. Santaji Uttam Nalwade , Vangala Ranga Reddy, Dantu Durga Rao, Nagendra kumar Morisetti, A validated stability indicating ultra performance liquid chromatographic method for determination of impurities in Esomeprazole magnesium gastro resistant tablets, *J Pharam Biomed Ana* 2012; 57: 109– 114.

[13]. Saji Thomas, Amber Bharti, Kalsang Tharpa, Ashutosh Agarwal, Quantification of potential impurities by a stability indicating UV-HPLC method in niacinamide active pharmaceutical ingredient, *J Pharam Biomed Ana* 2012; 60: 86– 90.

[14]. Ovalles J.F, Tettey J.N.A, McB Miller J.H, Skellern G.G. Determination of piracetam and its impurities by TLC, *J Pharam Biomed Ana,* 2000; 23:757–761.

[15]. Hallvard Gjerde , Anita Snøtun, Havard Hem, Kristin Hald Larsen, Jo Døhl, Determination of mangafodipir trisodium and related impurities in bulk substance and pharmaceutical formulation by ion-pair high-performance liquid chromatography, *J Pharam Biomed Ana* 2001; 25:109–114.

[16]. Marinkovic V., Agbaba D., Vladimirov S., Stankovic S., Simultaneous HPLC determination of nitrendipine and impurities of the process of synthesis. *J Pharam Biomed Ana* 2001; 24:993–998.

[17]. Antony Raj Gomes, V. Nagaraju, High-performance liquid chromatographic separation and determination of the process related impurities of mebendazole, fenbendazole and albendazole in bulk drugs, *J Pharam Biomed Ana* 2001; 26: 919–927.

[18]. Krishna Reddy K.V.S.R., Moses Babu J., Dubey P.K., Chandra Sekhar B., Om Reddy G., Vyas K., Isolation and characterisation of process-related impurities in rofecoxib. *J Pharam Biomed Ana* 2002; 29:355–360.

[19]. Rupe´rez F.J., Ferna´ndez H., Barbas C., LC determination of loratadine and related impurities, *J Pharam Biomed Ana* 2002; 29:35–41.

[20]. Radhakrishna T., Satyanarayana J., Satyanarayana A., LC determination of rosiglitazone in bulk and pharmaceutical formulation, *J Pharam Biomed Ana* 2002; 29: 873–880.

[21]. Jingyi Li , Markian S. Jaworsky, David I. Stirling, The determination of a potential impurity in Thalidomide drug substance and product by HPLC with indirect UV detection, *J Pharam Biomed Ana* 2003; 31:19-27.

[22]. Karljikovic-Rajic K., Novovic D., Marinkovic V., Agbaba D., First-order UV-derivative spectrophotometry in the analysis of omeprazole and pantoprazole sodium salt and corresponding Impurities, *J Pharam Biomed Ana* 2003; 32:1019-1027.

[23]. Krishna Reddy K.V.S.R., Moses Babu J., Vijayavitthal T. Mathad , Eswaraiah S., Satyanarayana Reddy M., Dubey P.K., Vyas K., Impurity profile study of repaglinide, *J Pharam Biomed Ana* 2003; 32: 461-467.

[24]. Quaglia M.G., Farina A., Donati E., Cotechini V., Bossu E., Determination of MPTP, a toxic impurity of pethidine, *J Pharam Biomed Ana* 2003; 33:1 -6.

[25]. Miguel L., Barbas C., LC determination of impurities in azithromycin tablets, *J Pharam Biomed Ana* 2003; 33: 211- 217.

[26]. Gary J. Lehr , Thomas L. Barry , John D. Franolic , Glenn Petzinger , Peter Scheiner, LC determination of impurities in methoxsalen drug substance: isolation and identification of isopimpinellin as a major impurity by atmospheric pressure chemical ionization LC/MS and NMR, *J Pharam Biomed Ana,* 2003; 33: 627-637.

[27]. Sıdıka Erturk , Esra Sevinc¸ Akta , Lale Ersoy a, Samiye Fıc¸ıcıog˘lu, An HPLC method for the determination of atorvastatin and its impurities in bulk drug and tablets, *J Pharam Biomed Ana* 2003; 33: 1017-1023.

[28]. Magda H. Barary, Mohamed H. Abdel-Hay, Suzy M. Sabry, Tarek S. Belal, Spectrofluorimetric determination of 2-aminopyridine as a potential impurity in piroxicam and tenoxicam within the pharmacopoeial limit, *J Pharam Biomed Ana,* 2004; 34: 221–226.

[29]. Marika Kamberi, Christopher M. Riley, Xiaoyan Ma (Sharon), Chen-Wen C. Huang, A validated, sensitive HPLC method for the determination of trace impurities in acetaminophen drug substance, *J Pharam Biomed Ana,* 2004; 34: 123–128.

[30]. Krishna Reddy K.V.S.R., Moses Babu J., Ravindra Kumar Y., Vishnu Vardhan Reddy S., Kishore Kumar M., Eswaraiah S., Rama Subba Reddy K., Sayanarayana Reddy M., Vijaya Bhaskar B., Dubey P.K., Vyas K., Impurity profile study of loratadine, *J Pharam Biomed Ana* 2003*;* 2: 29- 39.

[31]. Karljikovic-Rajic K., Novovic D., Marinkovic V., Agbaba D., First-order UV-derivative spectrophotometry in the analysis of omeprazole and pantoprazole sodium salt and corresponding Impurities, *J Pharam Biomed Ana*, 2003; 32:1019-1027.

[32]. M.G. Quaglia , A. Farina , E. Donati , V. Cotechini , E. Bossu, Determination of MPTP, a toxic impurity of pethidine, *J Pharam Biomed Ana* 2003; 33: 1-6.

[33]. Gary J. Lehr , Thomas L. Barry , John D. Franolic, Glenn Petzinger, Peter Scheiner, LC determination of impurities in methoxsalen drug substance: isolation and identification of isopimpinellin as a major impurity by atmospheric pressure chemical ionization LC/MS and NMR. *J Pharam Biomed Ana* 2003; 33: 627-637.

[34]. Sıdıka Erturk, Esra Sevinc¸ Aktas, Lale Ersoy , Samiye Fıccıoglu, An HPLC method for the determination of atorvastatin and its impurities in bulk drug and tablets. *J Pharam Biomed Ana* 2003; 33: 1017-1023.