

A Review on Nickel Estimation as an Elemental Impurity by Various Analytical Techniques

Pal AK, Raja S*

*GITAM Institute of Pharmacy, Gandhi Institute of Technology and Management,
Visakhapatnam, Andhra Pradesh, India*

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ABSTRACT

Nickel is a suspected immunotoxic and immunomodulatory agent and an allergen in humans in its elemental form. Also, nickel is a carcinogen that can cause multiple types of cancer in humans. According to the International Council for Harmonization (ICH) quality guideline ICH Q3D (R1), nickel falls under category 2A. It means that nickel has a high chance of occurring in drugs, and hence the risk assessment must be done compulsorily. The goal of this review is to summarize how various analytical methods such as X-ray photoelectron spectroscopy, atomic absorption spectroscopy, and inductively coupled plasma spectroscopy have been used to quantify nickel as an elemental impurity in various sample materials such as pharmaceutical drugs, cosmetics, blood plasma, and environmental water and soil samples, among others. This evaluation serves as a guide to determining the optimal analytical approach for estimating nickel based on several aspects such as sample type, sensitivity required, skill, and method cost.

Keywords: Atomic absorption spectroscopy, Elemental Impurity, Inductively coupled plasma spectroscopy, Nickel determination, International Council for Harmonisation (ICH),

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INTRODUCTION

In recent years, the toxicity in both drug substance and drug product has been the most sort of topic. As part of this risk assessment toxicity study due to elemental impurities (EI) has also become a major part of regulatory filings. Regulatory agencies from around the world have already released guidelines for analyzing the toxicological risk assessment of these EIs. In 2018, the United States Food and Drug Administration (USFDA)¹ produced a harmonized guideline for the pharmaceutical industry in collaboration with other organizations such as the ICH² and the United States Pharmacopeial Convention (USPC) (Mahesh *et al.*, 2012).³ Elemental impurities which are also generally referred as heavy metal elemental impurities cause significant risk to patient without yielding any significant benefit to patients in return. In recent times, any modern analytical techniques have come up which can detect and quantify elemental impurities which will help in reducing the toxicity exposure to patients. The ICH has classified the elemental impurities and determined their limits in the form of permitted daily exposures (PDEs) in drug products in its quality guideline ICH Q3D (R1) titled 'Guideline for Elemental Impurities'² and the United States Pharmacopeia (USP)⁴ general chapter on elemental impurity (USP-NF 232

and USP-NF 233 elemental impurities procedures). The elemental impurities according to ICH Q3D (R1) Guideline² been classified into 3 major classes based on two factors – their toxicity level determined by permitted daily exposures (PDEs) and abundance of occurrence in nature.

These elemental impurities can be present in drug product because of many sources. Few of them include the elemental impurities from industrial manufacturing equipment, water used to wash and manufacturing, the packaging unit which is generally referred as container-closure system, excipients and drug substance used in manufacturing of drug product. Also, these impurities can be present in finished pharmaceutical product or drug products as elemental impurities which are intentionally added during synthesis procedure of drug substance such as catalysts or stabilizers. According to ICH quality guideline ICH Q3D (R1),² nickel falls under category 2A. This means that Nickel has a high chance of occurring in drugs and hence the risk assessment must be done compulsorily. This review work aims to list out various analytical techniques used for quantification of nickel as an elemental impurity in different material like pharmaceutical drugs, cosmetics blood plasma and environmental samples of water and soil etc. Based on factors like sample type, sensitively required, skill and cost

*Author for Correspondence: srja61@gmail.com

of method, this review serves as a guide to decide the best analytical technique for estimation of nickel is to be developed.

NICKEL TOXICITY

Nickel levels in environment usually is because of pollution due to nickel manufacturing or due combustion of fossil fuel. Nickel as an elemental impurity can be found in pharmaceuticals, cosmetics and food stuffs which have been manufactured in nickel equipments which leach nickel pointed out by Kusal *et al.* (2018).⁵ Nickel in the form elemental impurity is a potential immunotoxic and immunomodulatory agent and has an allergen action in humans. Also, nickel is a carcinogen which can cause multiple type of cancer in humans. It is also haematotoxic, immunotoxic, genotoxic, reproductive toxic, pulmonary toxic, nephrotoxic and hepatotoxic according to a published work according to Kusal *et al.* (2018).⁵ According to ICH quality guideline ICH Q3D (R1),² nickel falls under category 2A. This means that nickel has high chances of occurring in drugs and hence the risk assessment must be done compulsorily.

Nickel Determination Techniques

An extensive literature survey for nickel determination using various analytical techniques was reviewed and summarized in Table 1.

Andres *et al.*⁶ determined nickel along with two other trace metals copper and cobalt in industrial water and nickel covered metallic samples, by forming complexes with sodium diethyldithiocarbamate in the presence of aqueous media which is anionic micellar in nature consisting of salts of sodium and ammonium dodecylsulfates. This method has an advantage over other methods where usually solvent extraction step must be done in the micellar media by addition of sodium diethyldithiocarbamate. Nickel along with copper and cobalt forms their respective complexes of diethyldithiocarbamate which are then determined spectrophotometrically. The major advantage of this method over its other complexation method is that reduces the cost and most importantly the toxicity factor involved during the solvent extraction process.

Bermejo-Barrera *et al.*⁷ determined nickel in narcotic material like heroin and cocaine by using chemical modifiers like nitric acid and magnesium nitrate using deuterium arc to correct the background noise in atomic absorption spectroscopy technique. Nitric acid in combination with magnesium nitrate was used to achieve pyrolysis temperature of 1500 to 1600°C. The nickel recovery was good using the method. The drawback of the method pointed out by the author was that of low sensitivity compared to tradition atomic absorption spectroscopy due to introduction of a cooling step to cool down temperatures of 1500 to 1600°C temperature during analysis.

The authors^{8,9} separately determined nickel and along other trace metals using differential stripping voltammeter. Yao *et al.*⁸ used silver mercury film electrode while Zhang *et al.* (1996)⁹ used mixed binder paste electrode (MBCPE). Using these electrodes nickel was determined at a particular

pH in a buffer in human hair samples, tea and rice specimens. Garcia Rodriguez *et al.*¹⁰ developed a simultaneous multi wavelength spectrophotometry method to determine nickel along with cobalt and iron by forming complex with 1,5-bis (di-2-pyridylmethylene) thiocarbonohydrazide. The samples were scanned from 390 to 510 nm and the metal concentration was by least squares fit of pure spectra compared to mixture spectra of each metal. This method could be used to analyze biological material as well as alloys.

Padilla *et al.*¹¹ determined trace levels in water samples containing nickel by adsorptive stripping voltammetry using a disposable and low-cost carbon screen-printed electrode. In this technique nickel was determined using conventional carbon-based solid electrode. This technique had a major disadvantage of having lower reproducibility and need to be cleaned and polished properly between each determination.

A novel was developed a thin layer chromatography (TLC) technique for determination of nickel and chromium in aqueous samples by Salman *et al.*¹² Samples containing elemental impurity nickel along with Chromium were spotted on TLC plates and allowed to develop and compared with standard spots. Even though this technique was simple and easy to perform, it is more of qualitative use than quantitative technique for nickel determination.

Hol *et al.*¹³ determined nickel by chelating with 4-(2-pyridylazo) resorcinol as chelating agent for derivatizing in-column of reversed-phase high-performance liquid chromatography RP-HPLC with photodiode array detector in natural water samples. The method was specific and accurate and highly reproducible. The main downside of this approach was that chelating the elemental impurity nickel in an HPLC column was difficult and could even damage the column over time.

Büyükcınar *et al.*¹⁴ analyzed nickel in water and soil samples at trace levels using photochemical vapor generation-batch type ultrasonication assisted gas liquid separator-atomic absorption spectrometry. The method showed less standard deviation high meant that the method was highly precise, and recoveries were also satisfactory. However, photochemical vapor generation-batch type ultrasonication assistance gas liquid separator made the technique quite costly to use and required highly skilled analyst to operate.

However, Mohammadnabizadeh *et al.*¹⁵ successfully determined nickel elemental impurity along with other trace metals in tissues of *Pampus argenteus* and *Platycephalus indicus* fishes using a graphite furnace atomic absorption spectrometer. The sample preparation was simple and gave good reproducibility.

Nickel along with other elemental impurities in paracetamol tablets by graphite furnace atomic absorption spectrometry (GFAAS) was done by Nessa *et al.*¹⁶ The analytical procedure was simple and results were precise and recoveries were good.

Melnyk *et al.*¹⁷ demonstrates nickel determination along with other elements using inductively coupled plasma mass spectroscopy (ICP-MS) technique. Results of this study demonstrate that low-resolution quadrupole-based ICP-MS

Table 1: Advantages and disadvantages of Nickel determination techniques

<i>Material</i>	<i>Instrument</i>	<i>Merits</i>	<i>Demerits</i>	<i>References</i>
Industrial water	Nickel complexation with sodium diethyldithiocarbamate detected spectrophotometrically	Cost effective and low toxicity when compared with solvent extraction methods	Less sensitive method	6
Heroin and cocaine	Chemical modified and quantifying using atomic absorption spectroscopy using deuterium lamp	Good recovery	Low sensitivity due to cooling step	7
Human hair, tea and rice samples	Differential stripping voltammeter	Wide range of samples	Complex methodology	8,9
Biological material and alloys	Complexing with 1,5-bis (di-2-pyridylmethylene) thiocarbonohydrazide and detecting with spectrophotometry	Easy detection	Laborious step	10
Composite diet samples	Inductively Coupled Plasma Mass Spectroscopy with low-resolution quadrupole	Highly precise and sensitive	Costly and high skill	17
Creams	Inductively Coupled Plasma Mass Spectroscopy	Highly precise and sensitive	High skill and time for sample digestion	21
Nickel metal ores	X-ray photoelectron spectroscopy	Specific for determining nickel in mix of metals	Complex due multiplet splitting of spectra	19
Water samples	Nickel chelation with 4-(2-pyridylazo) resorcinol and derivatizing in-column RP-HPLC PDA detector.	Specific and accurate and highly reproducible	Column damage due to chelation	13
Tea leaves	atomic absorption spectroscopy	Sensitive, specific and highly reproducible	Laborious	22
Aqueous samples	thin layer chromatography	Simple and easy	Qualitative method	12
Milk	atomic absorption spectrometer	Accurate and good sensitivity	Less sensitive compared to ICP techniques	24
Fishes	graphite furnace atomic absorption spectrometer	Simple and reproducible	Less sensitive compared to ICP techniques	15
Soil extracts	Atomic Absorption Spectroscopy	Simple and easy	Soil sample digestion was complex	18
Cosmetics	inductively coupled plasma optical emission spectroscopy	Precise and accurate	Sample digestion was time taking	23
Paracetamol tablets	graphite furnace atomic absorption spectrometer	Simple and reproducible	Less sensitive compared to ICP techniques	16
Water and soil samples	photochemical vapor generation-batch type ultrasonication assisted gas liquid separator-atomic absorption spectrometry	high precision and accuracy	Costly and high skill	14
Herbal toothpaste	plasma atomic emission spectrometer using microwave assisted sample digestion technique	high precision and accuracy	Sample preparation uses high skill	25
Atorvastatin in blood samples	Nickel metal which was modified with alumina nanoparticles and detection using rapid ultrasound assisted micro-extraction technique	linear, reliable and repeatable	Low reproducibility	26
Metal ores	laser-induced breakdown spectroscopy	Highly accurate	Low sensitivity	20
Water samples	adsorptive stripping voltammetry using a disposable and low-cost carbon screen-printed electrode	Noval method	low reproducibility and need to be cleaned and polished properly between each determination	11

provides precise and accurate measurements of the elements tested in composite diet samples. However, ICP-MS is a costly method which requires a lot of skills.

Baker and Amacher¹⁸ determined the elements like nickel, copper, zinc, and cadmium in soil extracts by atomic

absorption spectroscopy. The method was simple and precise to determine multiple elements.

Biesinger *et al.*¹⁹ used X-ray photoelectron spectroscopy to determine and quantify mixed nickel metal and nickel oxide and hydroxide ores. The nickel 2p peak morphologies

of nickel metal, its oxides, and hydroxides were quantified using a technique termed the 'Kratos charge neutralizer.' The disadvantage of this method is that it is complicated due to multiplet splitting of spectra, as well as other concerns such as shake-up and plasma structure degradation. Even while the procedure is repeatable with a wide range of nickel ore specimens, it is afflicted by high sensitivity variability, as the research paper points out.

Rifai *et al.*²⁰ determined the nickel in the presence of other trace elements like copper, cobalt, iron, magnesium, and sulfur in samples of copper-nickel ores using laser-induced breakdown spectroscopy. This technique had a significant advantage in accurately measuring nickel in ores in the presence of other elements rapidly with minimum sample preparation and extraction.

A quantified nickel trace element in pharmaceutical body creams as nickel causes dermatitis in users with pre-existing skin allergy.²¹ Nickel was quantified by sector field inductively coupled plasma mass spectrometry (ICP-MS) in body creams which were digested using microwave-assisted acid digestion. The method was highly sensitive but demanded a certain degree of skill and safety precautions during microwave assisted digestion process.

Srividhya *et al.*²² determined the nickel and other trace metals like lead, manganese, copper, zinc, cadmium, and chromium in tea leaves by atomic absorption spectroscopy. The method was sensitive, specific, and highly reproducible. However, the process of extraction of metals from tea leaves was cumbersome. It involved overnight soaking of leaves followed by ashing in a muffle furnace and finally digesting on the heating plate.

A technique of inductively coupled plasma optical emission spectroscopy (ICP-OES) was used to determine nickel in the presence of other trace elements in a range of cosmetic products.²³ Different sample matrices of cosmetics were digested in various ratios of concentrated acids were used. The samples were subjected to digestion in a muffle furnace at a high temperature over a few hours.

Gürbay *et al.*²⁴ was used atomic absorption spectroscopy technique to analyze nickel trace elements in 64 samples of breast milk showing the fast sample analyzing capability of the absorption spectroscopy technique. The results were accurate, and method was highly sensitive.

Vella and Attard²⁵ determined nickel along with lead using plasma atomic emission spectrometer in various herbal toothpastes using microwave assisted sample digestion technique. The toothpaste sample matrix was digested using concentrated acids in a temperature and pressure-controlled microwave digester.

Other research work quantifies the extraction of nickel trace elements in atorvastatin. They determined nickel-metal modified with alumina nanoparticles and used it as a catalyst to synthesize atorvastatin calcium drug substance.²⁶ These modified nickel nanoparticles were determined from blood plasma samples of subjects who had consumed the drug

substance using a rapid ultrasound-assisted micro-extraction technique. The using fast ultrasound-assisted micro-extraction approach was found to be linear, reliable, and repeatable.

However, using rapid ultrasound assisted micro-extraction technique for nickel quantification has its own challenges. The ultrasound assisted micro-extraction technique is a complex procedure. For extraction process a high amount of skill is required and process is also laborious. Ultrasound assisted micro-extraction technique is mainly used for bioactive compounds or modified material. During synthesis of atorvastatin calcium drug substance, nickel is modified to nanoparticles for easy quantification. This modification of nickel is very costly and is a high skilled process.

However, using the rapid ultrasound-assisted micro-extraction technique for nickel quantification has its challenges. The ultrasound-assisted micro-extraction approach is a complex procedure. A high amount of skill is required for the extraction process, and the process is also laborious. The ultrasound-assisted micro-extraction method is mainly used for bioactive compounds or modified material. For convenient quantification, nickel is converted to nanoparticles during the manufacturing of atorvastatin calcium restorative material. This modification of nickel is very costly and is a highly skilled process.

Apart from the techniques mentioned above, nickel as an elemental impurity was determined in environmental and biological samples using multiple strategies like XRF and ICP-MS. But each method has its advantage and disadvantage. XRF is more valuable as a qualitative method, and ICP-MS is a susceptible analytical procedure that requires a lot of skill.

CONCLUSION

Nickel is a trace metal that can be utilized to complete a variety of synthetic processes in pharmaceuticals and cosmetics. Nickel can also be found as a trace element in things such as soil and water. Procedures like spectrophotometry and voltammetry were utilized to measure nickel in water and blood samples. X-ray photoelectron spectroscopy was used to identify nickel in metal ores. Nickel was detected in complex sample matrices using atomic absorption spectroscopy or inductively coupled plasma spectroscopy. The inductively coupled plasma spectroscopy method is more sensitive and precise for nickel detection.

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