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A Method Optimization Study for Atomic Absorption Spectrometric Determination of Nickel Content in Meclizine Hydrochloride

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Abstract: Heavy metals are naturally occurring elements. Their widespread distribution in the environment has raised questions about their possible consequences on both human health and the environment. So, the toxicological and safety assessment of these heavy metals is one of the major issues in recent days. An accurate method for the determination of nickel in bulk drugs was required due to its high toxicity risk. The aim of the current study was to develop a validated analytical technique for the determination of nickel content in bulk drugs using an atomic absorption spectrometer. The wavelength was 232 nm, and the integration duration was 5.0 seconds. It was determined that the detection and quantification limits were 0.051 mg/L and 0.15 mg/L, respectively. The recovery rates for nickel concentrations spiked by 50%, 100%, and 150% in meclizine hydrochloride were determined to be 109.33%, 96.5%, and 97.55%, respectively. The status of heavy metals and trace elements in bulk drugs were discussed in this article, along with an easy-to-use AAS approach that can be applied at the industrial level to ensure the quality and uniformity of bulk medications and other related products.

Keywords: Atomic absorption, Catalyst, Flame atomization, Heavy metal toxicity, Nickel.

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1. INTRODUCTION

Potential contaminants must be recognized at various stages of the pharmaceutical manufacturing process, particularly in the final product, to avoid potential health risks. Metals can enter active pharmaceutical ingredients through a variety of sources (raw materials generated from plants or minerals, catalysts, reactors, pipelines, and other manufacturing equipment), and their presence is regularly monitored (1). The quick measurement of numerous elements that are metallic and non-metallic in crude and animal fats and refined vegetable oils, many of which are present in parts per million, has been accomplished using atomic absorption spectrophotometry. Ca, Cu, Fe, Mg, Mn, P, and Zn were measured in various refined and crude vegetable oils (2). Nickel (Ni) as raney nickel was used as a catalyst in the process of synthesis of meclizine hydrochloride. According to Zhao et al. (3), meclizine hydrochloride was designed and synthesized by the following method. The initial constituents for the synthesis of l-[(3-methyl phenyl) methyl] piperazine dihydrochloride was 1-(chloromethyl)-3-methylbenzene and piperazine. The title chemical meclizine hydrochloride was created by acidifying with (4-chlorophenyl) phenylmethyl chloride. Humans are continually exposed to Ni due to the quantity of Ni in the earth's crust. Natural nickel shortage is uncommon because of its abundance, and a Ni-deficient diet is tough to sustain due to its prevalence in food. Human contact with Ni-polluted surroundings has been linked to a number of diseases. Chronic nickel and nickel compound exposure in the body has been linked to a number of human health consequences, which include lung fibrosis, renal failure, cardiovascular illness, and respiratory tract cancer (4). Nickel's hazardous and carcinogenic effects are linked to how it is absorbed into the body. Nickel and nickel compounds' potential toxicity was determined by their physicochemical properties, as well as the amount, duration, and route of exposure. Ni can enter the body through inhalation, food consumption, and skin absorption, though the chemical form of the element determines how it enters cells. Inhalation is the most dangerous method of nickel exposure (5).

Meclizine hydrochloride is an antihistaminic medicine used to prevent and cure nausea and vomiting caused by various illnesses, including motion sickness, ménière's disease, and hypersensitivity reactions (6). Meclizine is an antihistamine of the 1st generation (non-selective H^1 antagonist). It also possesses anticholinergic properties in the central nervous system. Meclizine's antiemetic and antivertigo activities are due to its blockade of these receptors. In the medulla, this inhibiting impact occurs in the vomiting center and the chemoreceptor trigger zone (CTZ). Signals from the solitary tract nucleus and the vestibular nuclei to the vomiting and chemoreceptor trigger zone center in the medulla are inhibited as a result of these actions via histamine neurotransmission. Vestibular incitation and labyrinth excitability are also reduced as a result of this action (7). Atomic absorption spectroscopy (AAS) is a spectroscopy analytical technique that uses free atoms in their gaseous state to absorb optical radiation (light) in order to quantitatively determine the chemical components. AAS is utilized in pharmacology, biophysics, archeology, and toxicological research. It can determine over 70 distinct elements in solution or directly in solid samples via electrothermal vaporization. The clinical study of metals in biological fluids and tissues, including whole blood, plasma, urine, saliva, brain tissue, liver, hair, and muscle tissue, is one of the many applications of atomic absorption spectrometry in chemistry. The applications of atomic absorption spectrometry include both quantitative and qualitative examination (8). Various analytical techniques for determining meclizine hydrochloride in single- and combined-dosage form were found by the literature review like UV spectrophotometer (9-13), CE (14), HPLC (15-25), LC-MS (26-27), HPTLC (28). From the literature review, it was discovered that there was no verified method for determining nickel in meclizine hydrochloride by atomic absorption spectrometry. There were many methods for the estimation of meclizine hydrochloride in bulk drugs and marketed formulations. However, there was no single method for determining nickel content in meclizine hydrochloride. Compared to all the existing methods for meclizine hydrochloride, the present method was novel because of its ability to determine nickel in meclizine hydrochloride. Compared to other methods with instruments like ICP-OES and ICP-MS, this method was preferable because it's feasible and cost-effective. Hence, the aim of the current study was to develop a validated analytical technique for the determination of nickel content in bulk drugs using an atomic absorption spectrometer according to ICH guidelines.

2. EXPERIMENTAL

2.1. Reagents and Chemicals

Meclizine hydrochloride (Figure 1) was obtained as a gift sample from Symed Labs, India. Merck supplied the nickel standard for the study. Nitric acid, perchloric acid, and hydrochloric acid of AR grade from Fisher Scientific were used. The water used was MilliQ water.

2.2. Instrumentation

A Shimadzu Corporation AA-6300 atomic absorption spectrometer with fully integrated atomizers was used for the experiment. The system was managed by a computer with an interface. The ideal operating circumstances for nickel flame atomization were shown in Table 1. An LC/GC analytical balance was used.

2.3. Preparation of Solutions

2.3.1. Nickel standard stock solution preparation

Nickel standard (1000 mg/L) solution of 10.0 mL was transferred into a 100 mL volumetric flask and diluted up to mark with the Milli Q water. This solution consisted of 100 mg/L of nickel. Transferring 5.0 mL of this solution into a 100 mL volumetric flask, it was diluted with Milli Q water to the appropriate concentration. This solution contained 5 mg/L of nickel.

2.3.2. Preparation of blank solution

Nitric acid (HNO_3) was concentrated in 10 mL, and ten milliliters of perchloric acid ($HClO_4$) were transferred to a hundred-milliliter beaker. The solution was heated until the amount was decreased to between 6 and 7.0 mL, and white vapors were released on a hot plate. Then, the solution was cooled and transferred to a ten-millilitre volumetric flask and diluted to the mark with the milli Q water.

Table 1: Optimal operating conditions for flame atomization of nickel.

Parameter	Setting
Lamp	Nickel hollow cathode lamp
Wavelength	232.0 nm
Slit Width	0.2 nm
Lamp current	7 mA
Lamp mode	BGC-D2
Prespray Time	5.0 Sec
Integration Time	5.0 Sec
Oxidant Flow (L / min)	15.0 L / min
Acetylene Flow (L / min)	1.6 L / min
Recommended Flame	Air-Acetylene
Burner height	7 mm

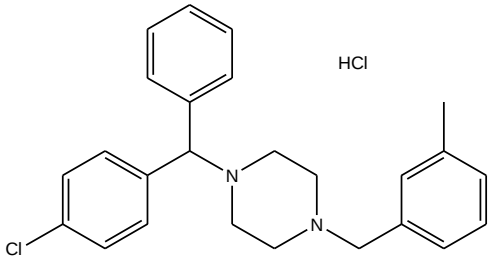

Figure 1: Structure of meclizine hydrochloride.

2.3.3. Preparation of sample solution
Precisely weighed, one gram of sample was transferred into a 100 mL beaker. 10.0 mL of concentrated HNO_3 and 10.0 mL of $HClO_4$ were added. The solution was heated until the amount was decreased to between 6 and 7.0 mL, and white vapors were released on a hot plate. Then, the solution was cooled, put into a 10.0 mL clean and dry volumetric flask, and diluted to the proper concentration with Milli Q water.

2.4. Analytical Validation Parameters
2.4.1. System suitability
With concentrations of 0.50, 1.0, 1.5, 2.0, and 2.5 mg/L, five standard nickel solutions were made and aspirated into the atomic absorption spectroscopy burner. To evaluate the applicability of the system, averages for triplicate absorbance readings at each standard nickel concentration level were established, and the correlation coefficient was verified.

2.4.2. Specificity
The specificity of the method was tested using blank, 1.0 mg/L nickel standard, and drug samples.

2.4.3. Linearity
Through the study of standard nickel concentrations ranging from 0.5, 1.0, 1.5, 2.0, and 2.5 mg/L, the suggested method's linearity was assessed. After this, a calibration curve is built, and linear regression analysis is used to calculate the r^2 value.

2.4.4. Limit of detection (LOD) and limit of quantitation (LOQ)
LOD and LOQ are used to assess an instrument's or analytical procedure's performance. The limits of detection (LOD) and quantification (LOQ) were computed using 3 and 10 SD/b, respectively, where b is the slope of the analytical curve, and SD is the standard deviation of successive observations.

2.4.5. Accuracy
The sample was spiked in three levels: 50, 100, and 150%. Three replicates were done for each concentration. The amount of nickel in each trial was computed, along with the nickel content % recovery for each method.

2.4.6. Precision at LOQ level
Six analyses of the LOQ level standard stock solution were performed in the precision. As a result, the system's consistency was shown, and the % RSD for six replicates was determined.

2.4.7. Method precision
Six separate preparations of a 100% spike sample solution of meclizine hydrochloride were made, and each was aspirated. Six preparations' nickel contents and nickel content's percent RSD were calculated.

2.5. Batch Analysis
Batch analysis was performed on any one batch of meclizine hydrochloride. 1.0033 g of sample was transferred into a 100 mL beaker. 10 mL of concentrated nitric acid and 10 mL of perchloric acid were added (Perchloric acid and perchlorates are dangerous if heated. Use extreme caution while heating). The solution was heated on a hot plate until the volume was reduced to about 6 - 7 mL and white fumes evolved. Then, the solution was cooled and transferred to a 10 mL volumetric flask and diluted up to the mark with Milli Q water.

3. RESULTS AND DISCUSSION

3.1. System Suitability
The purpose of the system suitability test was to ensure that the entire testing system, including the instrument, reagents, and analyst, was suitable for the intended application. The measure that showed the instrument was responding at its best was the correlation coefficient. Standard solutions (0.5–2.5 mg/L) were made using a nickel working standard and aspired into an atomic absorption spectrophotometer. A total of 5 concentrations were analyzed for system suitability. The correlation coefficient obtained for concentration versus absorbance in the calibration solution was found to be 0.9985. The system suitability results were tabulated in Table 2. The parameters of system suitability were assessed and determined to be within the limitations in accordance with ICH guidelines (28). Hence, the method was observed to be system suitable.

3.2. Specificity
The capacity to separate the nickel signal from the background signal and the matrix signals was the definition of parameter specificity. The 100% standard solution, sample solution, and blank solution were all used to test the method. The absorbance measured using the blank solution was discovered to be only 5% of the absorbance measured using the standard solution at 100%. The results were shown in Table 3. The specificity results meet the acceptance criteria according to ICH guidelines (29). Both matrices had no effect on the results. Thus, it was determined that the procedure was specific.

Table 2: System suitability.

S. No	Name	Absorbance	Correlation coefficient
1	Standard-1 (0.5 mg/L)	0.0405	
2	Standard-2 (1.0 mg/L)	0.0810	
3	Standard-3 (1.5 mg/L)	0.1230	0.9985
4	Standard-4 (2.0 mg/L)	0.1571	
5	Standard-5 (2.5 mg/L)	0.1295	

Table 3: Specificity.

S. No	Name	Absorbance
1	Blank	0.0025
2	100% Standard Solution	0.0748
3	Sample	-0.0201

3.3. Linearity

The range of the approach was defined using linearity studies. Examining numerous distinct concentrations of the investigated element allowed for the determination of the linearity of nickel. Aqueous standard solutions with concentrations ranging from 0.5, 1.0, 1.5, 2.0, and 2.5 mg/L were used to produce the calibration curves. The concentration of the nickel standard solution correlated with absorbance at a 0.9994 correlation coefficient. Table 4 presents the linearity results in tabular form. The calibration curve for meclizine hydrochloride is displayed in Figure 2. The linearity range of 0.5-2.5 mg/L demonstrated good linearity. The results were within the limits in accordance with ICH guidelines (29). Hence, the developed method was found to be linear.

Table 4: Linearity of nickel.

S. No	Name	Absorbance	Correlation coefficient
1	Standard-1 (0.5 mg/)	0.0368	
2	Standard-2 (1.0 mg/L)	0.0714	
3	Standard-3 (1.5 mg/L)	0.1030	0.9994
4	Standard-4 (2.0 mg/L)	0.1351	
5	Standard-5 (2.5 mg/L)	0.1697	

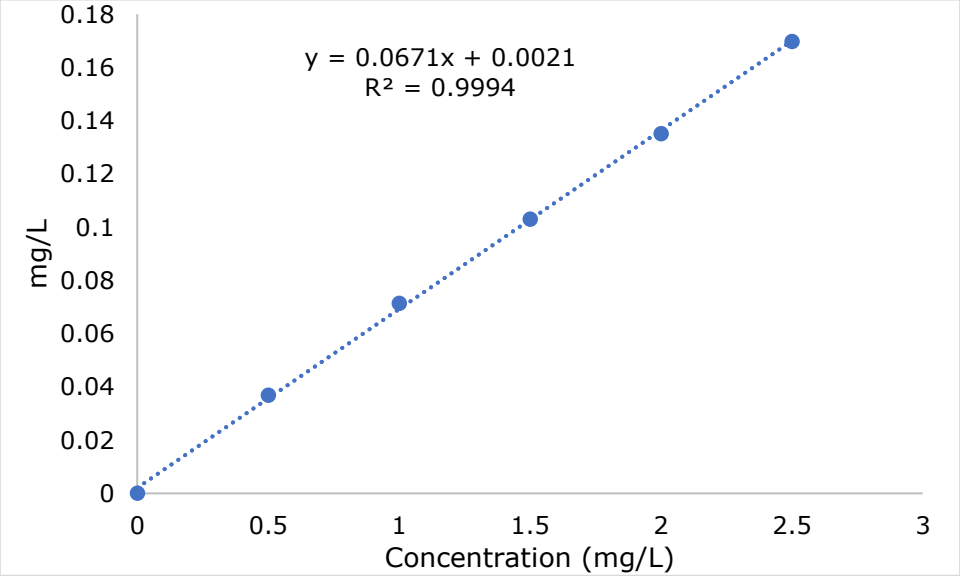

Figure 2: Linearity of nickel.

3.4. LOD and LOQ

The detection limit of a certain analytical procedure was the lowest concentration of analyte in a sample that can be detected but not always quantitated as an exact value. The quantitation limit of a certain analytical procedure was the lowest amount of

analyte in a sample that can be quantitatively quantified with sufficient precision and accuracy. The method's limit of detection and limit of quantitation parameters demonstrate its sensitivity. The calibration curve was used to calculate the LOD and LOQ of the technique. The detection and quantification limits, LOD and LOQ, were derived using the well-known 3 and 10 criteria, respectively, using the standard deviation of samples. The results of LOD and LOQ were achieved as 0.051 mg/L and 0.15 mg/L respectively. These values denote the sensitivity of the method.

3.5. Precision at LOQ Level

The precision of an analytical method was defined as the variation between a set of measurements acquired from multiple sampling of the same homogenous sample under the given conditions. The limit of the quantification level solution in six replicates was aspirated, and the relative standard deviation for a limit of the quantification solution was computed. The relative standard deviation for absorbance of nickel standard solution at the limit of quantification level from six replicates was found to be 6.24 %, less than 15.0%. Table 5 lists the results of the precision at the limit of quantification level.

Table 5: Precision at LOQ level.

S. No	LOQ solution	Absorbance
1	Aspiration-1	0.0169
2	Aspiration-2	0.0183
3	Aspiration-3	0.0165
4	Aspiration-4	0.0154
5	Aspiration-5	0.0163
6	Aspiration-6	0.0178
	Average	0.0169
	S. D	0.011
	% RSD	6.24

3.6. Method Precision

The precision of the procedure was examined to demonstrate whether the instrument response to the nickel standard solution was consistently reproducible. Method precision was measured in percentage relative standard deviation. Six replicates of the 100% spike sample solution were used for the precision test. The experimental results showed that the approach was reliable, with an RSD of 1.67 percent. The estimated findings for nickel determination in the working standard solution were shown in Table 6, together with the relative standard deviation. It was found that the results were within acceptance criteria according to ICH guidelines (29). Hence, the technique was determined to be precise.

Table 6: Method precision.

S. No	Name	Concentration (mg/L)	Sample weight (g)	Nickel content (mg/L)
1	Preparation-1	0.9463	1.0021	9.4
2	Preparation-2	0.9463	1.0018	9.4
3	Preparation-3	0.9590	1.0038	9.6
4	Preparation-4	0.9632	1.0042	9.6
5	Preparation-5	0.9802	1.0022	9.8
6	Preparation-6	0.9700	1.0025	9.7
		Average		9.6
		SD		0.1602
		% RSD		1.67

3.7. Accuracy

The closeness of the test results achieved by that method to the true value was the accuracy of the analytical procedure. Adding known amounts of standard nickel concentrations 10, 20, and 30 mg/L to three different meclizine hydrochloride standard sample solutions, the accuracy of the procedure was determined. These samples were aspirated in triplicate for each class and represented three increment levels of 50%, 100%, and 150%. The nickel content in each trail was calculated in order to determine its percentage recovery. The outcomes were summarised in Table 7. The data showed a best recovery of 93.33 % - 112.00%. Since recovery is more important in a method involving sample preparation steps like extraction or digestion, the % recovery of the sample should be of more importance while validating the method. This recovery range shows the method's accuracy. It was found to be within acceptance criteria in accordance with ICH guidelines (29). Hence, the technique was found to be accurate.

Table 7: Accuracy.

S. No	Name		Concentration (mg/L)	Sample Weight (g)	Result (mg/L)	Spiked Concentration (mg/L)	% Recovery	% RSD
1	Sample	Preparation-1	BDL	1.0004	BDL	-	-	-
		Preparation-2	BDL	0.9996				
		Preparation-3	BDL	1.0005				
2	Spiked at LOQ level	Preparation-1	0.1536	1.0005	1.5	1.5	100.00	4.03
		Preparation-2	0.1447	0.9993	1.4		93.33	
		Preparation-3	0.1388	1.0004	1.4		93.33	
3	Spiked at 50% level	Preparation-1	0.5652	1.0030	5.6	5.0	112.00	4.22
		Preparation-2	0.5652	1.0010	5.6		112.00	
		Preparation-3	0.5209	1.0001	5.2		104.00	
4	Spiked at 100% level	Preparation-1	0.9581	1.0068	9.5	10.0	95.00	1.04
		Preparation-2	0.9620	1.0072	9.6		96.00	
		Preparation-3	0.9768	1.0028	9.7		97.00	
5	Spiked at 150% level	Preparation-1	1.4691	1.0030	14.6	15.0	97.33	0.40
		Preparation-2	1.4671	1.0028	14.6		97.33	
		Preparation-3	1.4691	1.0026	14.7		98.00	

3.8. Batch Analysis

Batch analysis was performed and obtained results are reported in Table 8. The nickel content was to be less than 10 ppm. In the batch analysis, the nickel concentration was found to be below the quantification limit. The nickel concentration was found to be within the acceptance criteria. This method can be used for regular analysis.

Table 8. Batch analysis.

S. No	Batch	Nickel Content
1	Batch 1	Below quantification limit

4. CONCLUSION

Meclizine hydrochloride is a medicine that is frequently recommended to alleviate nausea, vomiting, and dizziness. Nickel, a catalyst used in the production of meclizine hydrochloride, needs to be measured because it can be dangerous to people. There were several methods reported for the estimation of meclizine hydrochloride in pharmaceutical formulations but no method was reported for estimation of nickel in meclizine hydrochloride bulk drug. The analytical atomic absorption spectrometry method for the assessment of nickel content in bulk drugs was developed and validated. This work evaluated nickel as an elemental contaminant in meclizine hydrochloride using a verified simple, exact, and accurate atomic absorption spectroscopy technique. The dissolution of samples with nitric acid and perchloric acid provided simple sample preparation without adverse effects. USP General Chapter 232 specifies a 20-ppm maximum allowed nickel concentration. The nickel content of meclizine hydrochloride can be ascertained using this quick, affordable, and accurate approach.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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