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DETERMINATION OF TOXIC HEAVY METALS IN CHOLIC ACID USING QUADRUPOLE INDUCTIVELY COUPLED PLASMA MASS SPECTROMETRY

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ABSTRACT

Objective: The information on the presence of toxic heavy metals in pharmaceutical starting materials and finished product is very crucial from the viewpoint of human life and its hazardous impact on the worldwide environment. The present work deals with the detailed quantification of the toxic heavy metals, namely, V, Co, Ni, Cd, Hg, Pb, and As, present in cholic acid using quadrupole inductively coupled plasma mass spectrometry (Q-ICPMS) with prior microwave-assisted digestion. Moreover, the preliminary characterization of commercially available cholic acid by FT-IR, NMR (1H and 13C), SEM-EDAX has also been carried out.

Methods: Cholic acid of synthesis grade, Nitric acid (65%) AR grade, ethylene diamine tetra acetic acid sodium salt AR grade, and certified reference metal stock standard solutions (1000 mg/L) of multiple elements prepared in 2–3% HNO₃ of analytical grade were purchased from Merck (Darmstadt, Germany). All the samples were treated with nitric acid and microwave-assisted digestion. For the accurate determination of the elemental amount, various digested solutions and post-digestion diluents were tested. The linearity, accuracy, precision, limit of detection (LOD), and limit of quantification (LOQ) of the analytical technique were evaluated in accordance with the United States Pharmacopoeia 233 standard.

Results and Discussion: The Q-ICPMS-based analytical method was validated for specificity, LOD, LOQ, linearity, accuracy, precision, and uncertainty. The estimated detection limits of the toxic heavy metals in cholic acid were in the range 2–180 µg/L. The quantification limits were in the range of 1.5–60 µg/L. Mean recoveries ± standard deviations at different spiking levels were in the range 75.3 ± 2.1–104.9 ± 8.5%. The coefficients of variation were in the range of 0.5–8.1%.

Conclusion: The precision of the analytical method, in terms of relative standard deviation, was below 1.95%. The uncertainty in the quantification of all the validated elements was found to be ≤ 1.70% for Sample 1.

Keywords: Cholic acid, Metal impurities, Heavy metals, Quadrupole inductively coupled plasma mass spectrometry, Analytical method development and validation, Microwave acid digestion.

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INTRODUCTION

Cholic acid is a primary bile acid. Bile acids are biological compounds belonging to the steroidal family generated in humans (liver) and the majority of animals [1,2]. Lipid-rich diet may be the source of the accumulation of toxic elements, such as Zn, Cu, Cd, Mn, and Ni in the liver, that produces bile acids. As a result of the accumulation of toxic heavy metals in the liver, the enzymatic activity is inhibited and the metabolic pathways are altered. Moreover, the presence of such toxic heavy metals increases the risk of tumor formation [3].

Monitoring and quantification of the presence of toxic heavy metals in the liver or the byproducts of the liver like those of bile acids is a necessity from a health perspective. Though a web of science search with the keywords, namely, cholic acid and toxic heavy metals shows four results, none of them match with either the objective or the outcome of the present study. The aim of this work is to have the complete information on the amount of toxic heavy metals present in cholic acid-containing drugs which are consumed by humans in everyday life and to ensure whether it is under the permissible limit set by the United States Pharmacopoeia (USP) 233 standard.

Harmful effects of the presence of toxic heavy metals, such as vanadium (V), nickel (Ni), cadmium (Cd), mercury (Hg), lead (Pb), and arsenic (As) in water, food, drugs, and environment are well known and mankind is no stranger to bearing the heat of such contaminants and this needs no elaborate introduction [4-12]. Pharmaceutical regulatory agencies have set the permitted levels of heavy metals in medication, which are consistently monitored using limit tests. These tests confirm that no inorganic impurities are introduced into the medications during any of the manufacturing phases. The USP, the British pharmacopoeia, the European pharmacopoeia, and the Japanese pharmacopoeia are all jointly monitoring the total metal impurity contents in pharmaceutical products. However, the procedures adopted are non-specific, insensitive, and time-consuming, needing improvement in accuracy excepting the few new legislations namely USP 232 and 233. Thus, very sensitive and selective procedures are urgently needed for determining trace toxic heavy metals in pharmaceutical compounds, not only to meet the demanding regulatory criteria but also to ensure the safety and efficacy of medication intended for human consumption [13].

In Quadrupole inductively coupled plasma mass spectrometry (Q-ICP-MS), the energy source, namely, plasma is advantageous over other energy sources, such as flame ionization, because it allows ionization to occur in a chemically inert environment, preventing oxide formation and the ionization is more complete. Q-ICP-MS analysis of toxic heavy metals is superior to other methods such as atomic absorption spectrometry, X-ray fluorescence spectrometry, and ICP optical emission spectrometry owing to exceptionally low detection limits for a large range of elements. Some components can be measured to the billionth of a trillionth of a trillion [14]. Many researchers have previously applied this sophisticated analytical technique of Q-ICP-MS for bioanalytical purposes successfully [15-17].

In addition to QCP-MS of the toxic heavy metals in cholic acid, for comparison, ICP-OES analysis was carried out. Moreover, cholic acid commercial sample was further systematically characterized using SEM-EDAX to know the purity of the sample Fig. 1.

The goal of this study is to develop a fast, effective, simple, and accurate method of cholic acid sample preparation in conjunction with QCP-MS to accurately determination of above mentioned toxic heavy metal impurities in oral medicinal products in a single test.

METHODS

Materials and solutions

Cholic acid of synthetic grade used in the study is procured from Sordisbaur Laboratories. Nitric acid (69%), ethylene diamine tetra acetic acid sodium salt AR grade, and certified reference metal stock standard solutions (1000 ng/L) of V, Co, Ni, Cd, Hg, Pb, and As prepared in 2-3% HNO₃ of analytical grade were purchased from Merck (Darmstadt, Germany). Deionized water was prepared using a Milli-Q water purification system from Millipore (Bedford, MA, USA). Various standards for ICP TraceCERT® (1000 ng/L, V in nitric acid), In-house standard for ICP TraceCERT® (1000 ng/L, Ni in nitric acid), nitric acid 69.0%, TraceSELECT™ for trace analysis from Honeywell were used for the study. All the chromatography vials, centrifuge tubes, and plastic bottles were cleaned by soaking in 20% v/v HNO₃ analytical grade reagent for 4 h, followed by rinsing with deionized Milli-Q water three times. Element impurities according to ISO Q90 Standard 1 containing 15 ppm of Arsenic (As), 5 ppm each of Lead (Pb) and Cadmium (Cd), 50 ppm of Mercury (Hg), 50 ppm of Cobalt (Co), 100 ppm of Vanadium (V), 200 ppm of Nickel (Ni) and three other elements i.e., 150 ppm each of Selenium (Se) and Silver (Ag) and 8 ppm of Thallium (Tl) multi standard were procured from Sigma-Aldrich.

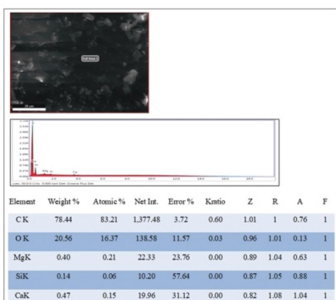


Fig. 1. SEM-EDAX analysis of cholic acid (commercial sample)

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Table 1: Dilution of standard for calibration

Solution name (%)	Volume of standard stock solution (mL)	Make up volume (mL)	Concentration (µg/L)						
			V	Co	Ni	Cd	Hg	Pb	As
LOQ (20)	0.3	50	30	15	60	1.5	9.0	1.5	4.5
50	0.5	50	50	25	100	2.5	15	2.5	7.5
80	0.8	50	80	40	160	4.0	24	4.0	12
100	1.0	50	100	50	200	5.0	30	5.0	15
120	1.2	50	120	60	240	6.0	36	6.0	18
200	2.0	50	200	100	400	10	60	10	30

LOQ: Limit of quantification

Table 2: Dilution for spiked sample preparation

Level of spiked sample preparation (%)	Amount of calibration standard stock solution to be added (mL)
LOQ (20%)	0.3
100%	1.0
150%	1.5

LOQ: Limit of quantification

RESULTS AND DISCUSSION

Internal standard for the detection of toxic heavy metals

While using QCP-MS for elemental analysis, selecting an appropriate internal standard is critical. This would have a significant impact on the accuracy and precision of the results.

Optimization of operation parameters of QCP-MS

Various optimized QCP-MS parameters were reported (Table 3).

Method validation

In analytical chemistry method validation is one of the technical aspects of the overall quality assurance scheme. Selectivity and specificity are determined by the element chosen and the corresponding possible potential interferences. It is always about "to extent to which the approach may be employed to determine the specific analytes in mixtures or matrices without interference from other components that behave similarly [18]. The selectivity of the current approach was investigated using primary isotopes of each element: ⁵¹V, ⁵⁸Co, ⁵⁸Ni, ¹¹⁴Cd, ²⁰¹Hg, ²⁰⁸Pb, and ⁷⁵As. A validation study was conducted to determine and prove the method's reliability. Some analytical characteristics were used to validate the approach.

Estimated LOD

The lowest concentration of an analyte in a sample that can be detected, but not necessarily quantified, is known as the LOD. It is a limit test that determines whether an analyte is above or below a certain threshold from the calibration function using Equation (1) [19].

$$LOD = \frac{3\sigma}{S} \quad (1)$$

where, σ is standard deviation

S is slope derived from the calibration curve

The estimated LODs were found to be 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, and 0.10 µg/L for V, Co, Ni, Cd, Hg, Pb, and As, respectively. The minimum practical concentrations of tested elements in the analyzed samples, which can be determined with acceptable accuracy were performed by analyzing 3 replicates at 30 µg/L for V, at 15 µg/L for Co, Ni, Cd, Hg, Pb, and As, respectively. The minimum LODs were found to be 0.01, 0.01, 0.01, 0.02, 0.02, 0.02, and 0.10 µg/L for V, Co, Ni, Cd, Hg, Pb, and As, respectively. The minimum practical concentrations of tested elements in the analyzed samples, which can be determined with acceptable accuracy were performed by analyzing 3 replicates at 30 µg/L for V, at 15 µg/L for Co, Ni, Cd, Hg, Pb, and As, respectively.

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80	0.8	50	80	40	160	4.0	24	4.0	12
100	1.0	50	100	50	200	5.0	30	5.0	15
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$$LOD = \frac{3\sigma}{S} \quad (1)$$

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Co, at 9.0 µg/L for Hg, at 1.5 µg/L for Pb, and at 4.5 µg/L for As. The results were reported in Table 4.

Estimated LOQ

The lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the method's stated operational circumstances is known as the LOQ. The ratio of signal ratio for LOQ should be 1:10. The estimated LOQs were found to be 30, 15, 60, 1.5, 9.0, 1.5, and 4.5 µg/L for V, Co, Ni, Cd, Hg, Pb, and As, respectively. The results are reported in Table 4 [20].

Table 3: Typical QCP-MS instrument parameters for the analytical method

Parameter	Setting
RF power (W)	1000
RF matching (V)	1.80
Sampling depth (cm)	4.6
Carrier gas (L/min)	1.02
Spray chamber temperature (°C)	2
Nebulizer pump (revolutions per second, rps)	0.1
Exhaust 1 (V)	-100
Exhaust 2 (V)	12
Cell exit (V)	-42
Plate bias (V)	-42
OP bias (V)	-4.6
ICP RF (V)	100
ICP Bias (V)	-7.0

RF: Radio frequency; V: Volt; Quadrupole; Torch: Torch

Table 4: Estimated LODs, practical LODs, and maximum permissible limits (number of replicates=6) for Sample-1

Element	Estimated values		Practical values		CV%	Maximum permissible limits (µg/L)		
	Standard deviation	LOD (µg/L)	LOQ (µg/L)	Mean concentration±SD		Egyptian	EU	WHO
V	0.004482	0.01446	30	30.9±0.20	1.00	-	-	-
Co	0.003981	0.00803	15	15.2±0.10	1.90	-	-	-
Ni	0.003559	0.1795	60	59.8±1.31	2.19	20	20	70
Cd	0.003663	0.001525	1.5	1.6±0.07	4.52	5	5	20
Hg	0.004465	0.02271	9.0	9.7±0.55	3.61	1	6	6
Pb	0.004446	0.0066	1.5	1.6±0.081	4.52	5	5	20
As	0.000723	0.09737	4.5	4.7±0.32	6.80	10	10	10

LOQ: Limit of quantification, LOD: Limit of detection

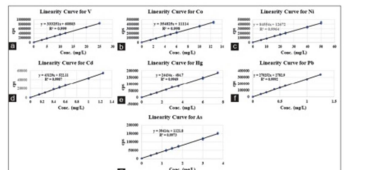


Fig. 2: Method linearity (a) V (0-250 µg/L), (b) Co (0-15 µg/L), (c) Ni (0-60 µg/L), (d) Cd (0.15-1.5 µg/L), (e) Hg (0-9.0 µg/L), (f) Pb (0.15-1.5 µg/L), and (g) As (0.45-4.5 µg/L)

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respectively. The results on the accuracy of each element in cholic acid are presented in Table 6. The study was extended to three more commercial samples of cholic acid and similar results were obtained as shown in Table 7.

Blank study (recovery test)

The spiking levels used for the recovery test were at 1.5, 5, and 7.5 µg/L for ⁶⁷Ge, ¹⁰⁹Ag, 45, 15, and 22.5 µg/L for ¹⁰⁹Ag, 9, 30, and 45 µg/L for ¹⁰⁹Ag, 15, 50, and 75 µg/L for ¹⁰⁹Ag, 60, 200, and 300 µg/L for ¹⁰⁹Ag, 30, 100, and 150 µg/L for ¹⁰⁹Ag. The mean recovery/standard deviation at different levels varied between 75.32±1.9% and 104.85±5.5% with coefficient of variation expressed as RSD ranged from 0.5% to 8.1%. Percentages attaining analytical chemistry courses are referred to the elegant review on ICP-MS technique by Willebeek and Bunt.

CONCLUSION

The measurement of heavy metals in cholic acid using a microwave-assisted acid digestion process and Q-ICP-MS analysis was satisfactorily confirmed in this study for trace metal analysis of cholic acid, it is considered to be a good, reliable, and rapid approach. The accuracy of the present method (10–150% of the target value) and precision value (CV%) successfully achieved the criteria defined by WHO, AOAC, USP, FDA, KHL, and USP (23). The proposed method was effectively applied for the routine analysis of heavy metals in cholic acid. LOD, LOQ, linearity, repeatability, reproducibility, accuracy, and precision have all been successfully assessed using the validated method. The suggested validated method is highly simple, quick, easy, cost-effective, and reliable, making it ideal for quantification of these hazardous metals in regular laboratory analysis.

AUTHORS CONTRIBUTIONS

Thakur Meen Kumar: Performed experiments and collection of data. Sheth Jyoti: Calculation of results in Excel format. Indra Neel Pulindindi: Given name suggestion. Sathar Vaishali: Made figures and wrote rough draft. Sharma Pankaj: Conceptualization, Methodology, Formal analysis, Writing an original draft, Supervision, Writing reviews, and editing.

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest.

AUTHORS FUNDING

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ELECTRONIC SUPPLEMENTARY INFORMATION (ESI)

Table S1. Conditions of microwave digestion of cholic acid samples

Digestion conditions	Temperature (T) (°C)	Pressure (P) (Bar)	Ramp (C/min)	Hold Time (min)	Percentage (%)
1	170	30	5	2	80
2	200	30	2	2	90
3	50	20	2	5	0

Table S2. Impurities classification and specification limit.

Name of Element	Class	Specification Limit (µg/L)
Co	2A	5
Cr	2A	1
Cd	1	0.5
Hg	1	3.0
Pb	1	0.5
As	1	1.5

Table 6. Accuracy of heavy metal analysis (V Co, Ni, Fe, Mg, Al) from Q-ICP-MS analysis.

Sample	Conc. (µg/L)	Recovery (%)	Mean % Recovery	Standard Deviation	CV (%)
1000 µg/L-1	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-2	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-3	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-4	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-5	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-6	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-7	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-8	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-9	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-10	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-11	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-12	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-13	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-14	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-15	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-16	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-17	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-18	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-19	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-20	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-21	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-22	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-23	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-24	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-25	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-26	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-27	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-28	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-29	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-30	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-31	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-32	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-33	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-34	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-35	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-36	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-37	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-38	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-39	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-40	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-41	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-42	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-43	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-44	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-45	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-46	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-47	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-48	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-49	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-50	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-51	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-52	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-53	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-54	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-55	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-56	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-57	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-58	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-59	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-60	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-61	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-62	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-63	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-64	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-65	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-66	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-67	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-68	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-69	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-70	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-71	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-72	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-73	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-74	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-75	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-76	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-77	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-78	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-79	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-80	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-81	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-82	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-83	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-84	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-85	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-86	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-87	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-88	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-89	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-90	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-91	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-92	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-93	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-94	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-95	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-96	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-97	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-98	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-99	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-100	1000	98.5	98.5	0.2777312	0.281

Table 7. Accuracy of heavy metal analysis (V Co, Ni, Fe, Mg, Al) from Q-ICP-MS analysis.

Sample	Conc. (µg/L)	Recovery (%)	Mean % Recovery	Standard Deviation	CV (%)
1000 µg/L-1	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-2	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-3	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-4	1000	98.5	98.5	0.2777312	0.281
1000 µg/L-5	1000	98.5	98.5	0.2777312	0.281

Table S4. Precision test of toxic heavy metals (V, Co, Ni, Cd, Hg, Pd, As) from Q-ICP-MS analysis.

Sample	Sample wt. (g)	Conc (ppb)	cps	Int. Std. cps	cps ratio	Calculation based on cps ratio				Calculation based on cps			
						Result (ppm)	Mean Result (ppm)	SD	% RSD	Result (ppm)	Mean Result (ppm)	SD	% RSD
1) Precision in the quantification of V													
As such-1	0.1019	0	84842.57686	1355290.6	0.062601022	0.07	0.07	0.003	4.56	0.27	0.27	0.002	0.61
As such-2	0.1019	0	87126.67839	1371981.5	0.063504266	0.08				0.28			
As such-3	0.1019	0	85818.70966	1361540.6	0.063030592	0.07				0.27			
100% spiked-1	0.1018	10	3262920.367	1406230	2.320331928	9.44	8.967	0.285	3.17	8.70	8.27	0.286	3.45
100% spiked-2	0.1022	10	3114073.807	1387849.2	2.243812805	8.96				8.38			
100% spiked-3	0.1016	10	3096700.06	1404991.6	2.20407016	8.97				8.28			
100% spiked-4	0.1025	10	3023864.33	1410965.1	2.144535205	8.68				7.99			
100% spiked-5	0.1031	10	3040183.287	1420922.6	2.139584019	8.67				7.92			
100% spiked-6	0.1008	10	3110912.56	1405752	2.21298818	9.08				8.38			
2) Precision in the quantification of Co													
As such-1	0.1019	0	3620.59626	1355290.6	0.002671454	-0.02	-0.02	0.001	-3.33	0.08	0.08	0.001	0.71
As such-2	0.1019	0	3930.673464	1371981.5	0.002864961	-0.02				0.08			
As such-3	0.1019	0	3440.551401	1361540.6	0.002526955	-0.02				0.08			
100% spiked-1	0.1018	5	1664934.767	1406230	1.183970451	4.58	4.498	0.097	2.15	4.23	4.15	0.106	2.56
100% spiked-2	0.1022	5	1674632.317	1387849.2	1.206638529	4.59				4.29			
100% spiked-3	0.1016	5	1661582.263	1404991.6	1.182627899	4.58				4.23			
100% spiked-4	0.1025	5	1607591.59	1410965.1	1.139356027	4.39				4.04			
100% spiked-5	0.1031	5	1647933.727	1420922.6	1.15976319	4.47				4.09			
100% spiked-6	0.1008	5	1578386.173	1405752	1.122805568	4.38				4.05			
3) Precision in the quantification of Ni													
As such-1	0.1019	0	23680.41713	1355290.6	0.017472575	0.13	0.13	0.003	2.61	0.54	0.54	0.003	0.48
As such-2	0.1019	0	24101.1056	1371981.5	0.01756664	0.13				0.54			
As such-3	0.1019	0	24251.45472	1361540.6	0.017811775	0.13				0.54			
100% spiked-1	0.1018	20	1765044.143	1406230	1.255160353	20.36	19.504	0.471	2.42	18.74	17.98	0.474	2.64
100% spiked-2	0.1022	20	1691073.777	1387849.2	1.218485248	19.42				18.13			
100% spiked-3	0.1016	20	1696093.257	1404991.6	1.20719103	19.60				18.07			
100% spiked-4	0.1025	20	1658666.853	1410965.1	1.175554841	18.99				17.45			
100% spiked-5	0.1031	20	1685167.79	1420922.6	1.185967336	19.19				17.50			
100% spiked-6	0.1008	20	1671783.257	1405752	1.1892448	19.47				17.95			
4) Precision in the quantification of Cd													
As such-1	0.1019	0	130.1355718	1355290.6	9.60204E-05	-0.01	-0.01	0.000	-5.23	0.00	0.00	0.000	24.79
As such-2	0.1019	0	140.1459446	1371981.5	0.000102149	-0.01				0.00			
As such-3	0.1019	0	100.1037279	1361540.6	7.35224E-05	-0.01				0.00			
100% spiked-1	0.1018	0.5	23627.92	1406230	0.016802315	0.53	0.516	0.011	2.20	0.48	0.47	0.013	2.74
100% spiked-2	0.1022	0.5	23531.11	1387849.2	0.016955091	0.52				0.49			
100% spiked-3	0.1016	0.5	23263.61333	1404991.6	0.016551831	0.52				0.48			
100% spiked-4	0.1025	0.5	22805.77333	1410965.1	0.016163244	0.50				0.46			
100% spiked-5	0.1031	0.5	22725.55667	1420922.6	0.015993522	0.50				0.45			
100% spiked-6	0.1008	0.5	23330.5	1405752	0.016596455	0.52				0.48			
5) Precision in the quantification of Hg													
As such-1	0.1019	0	6361.783352	10267123.5	0.000619627	0.27	0.27	0.007	2.57	0.20	0.19	0.007	3.98
As such-2	0.1019	0	6081.58011	10194305.8	0.000596566	0.26				0.19			
As such-3	0.1019	0	6051.66617	10336583	0.000585461	0.26				0.18			

(Contd....)

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Table S4. (Continued)

Sample	Sample wt. (g)	Conc (ppb)	cps	Int. Std. cps	cps ratio	Calculation based on cps ratio				Calculation based on cps			
						Result (ppm)	Mean Result (ppm)	SD	% RSD	Result (ppm)	Mean Result (ppm)	SD	% RSD
100% spiked-1	0.1018	3	74766.46	11226846.7	0.006659614	3.03	3.037	0.058	1.92	2.79	2.78	0.068	2.46
100% spiked-2	0.1022	3	75966.35333	11234982.6	0.006761591	3.06				2.83			
100% spiked-3	0.1016	3	75393.62333	11298447.3	0.006672919	3.06				2.81			
100% spiked-4	0.1025	3	76167.69667	11483387.4	0.00663286	3.06				2.76			
100% spiked-5	0.1031	3	73215.23	11446110.9	0.006396516	2.93				2.65			
100% spiked-6	0.1008	3	75624.92667	11325018.6	0.006677687	3.09				2.83			
6) Precision in the quantification of Pb													
As such-1	0.1019	0	193738.0744	10267123.5	0.018869752	0.69	0.69	0.006	0.81	0.71	0.70	0.011	1.50
As such-2	0.1019	0	193948.3042	10194305.8	0.019025161	0.69				0.71			
As such-3	0.1019	0	191196.1575	10336583	0.018497037	0.68				0.69			
100% spiked-1	0.1018	0.5	329014.9	11226846.7	0.029306083	1.19	1.195	0.022	1.81	1.11	1.11	0.022	1.95
100% spiked-2	0.1022	0.5	326491.8567	11234982.6	0.02906029	1.17				1.10			
100% spiked-3	0.1016	0.5	332611.2967	11298447.3	0.029438673	1.20				1.12			
100% spiked-4	0.1025	0.5	333765.2767	11483387.4	0.029065054	1.19				1.10			
100% spiked-5	0.1031	0.5	332678.45	11446110.9	0.029064759	1.18				1.09			
100% spiked-6	0.1008	0.5	339113.0467	11325018.6	0.029943708	1.23				1.15			
7) Precision in the quantification of As													
As such-1	0.1019	0	18112.29	1355290.6	0.013364138	0.42	0.42	0.011	2.62	0.43	0.42	0.013	3.00
As such-2	0.1019	0	17331.15	1371981.5	0.012632204	0.40				0.40			
As such-3	0.1019	0	18062.3	1361540.6	0.013266075	0.42				0.42			
100% spiked-1	0.1018	1.5	94358.08	1406230	0.067100033	2.32	2.130	0.104	4.87	1.95		0.098	5.02
100% spiked-2	0.1022	1.5	87272.44	1387849.2	0.06288323	2.14				1.98			
100% spiked-3	0.1016	1.5	82815.21	1404991.6	0.058943562	2.04				1.87			
100% spiked-4	0.1025	1.5	87187.7	1410965.1	0.061792953	2.13				1.94			
100% spiked-5	0.1031	1.5	84163.11	1420922.6	0.059231312	2.04				1.85			
100% spiked-6	0.1008	1.5	84734	1405752	0.060276635	2.10				1.93			

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List of Papers presented in Conferences/Seminar/Workshop

1. **Poster Presentation:** International Seminar on “Advanced Materials and Applications” **Meetkumar Thakar**, Pankaj Sharma^{*}; held on (18th July, 2022); Organized by Applied Physics Department and Applied Chemistry Department, Faculty of Technology and Engineering, M.S.University of Baroda and Luminescence Society of India. (Regd. No: GUJ/1156).

 सत्यं शिवं सुन्दरम्	INTERNATIONAL SEMINAR ON ADVANCED MATERIALS AND APPLICATIONS 18th JULY, 2022 Organized by Applied Physics Department and Applied Chemistry Department Faculty of Technology and Engineering, M.S University of Baroda, Baroda- 390 001. India and Luminescence Society of India (Regd. No: GUJ/1156)	
CERTIFICATE		
<p>This is to certify that Prof./Dr/Mr./Ms <u>Meet Thakar</u> is a registered participant of INTERNATIONAL SEMINAR ON ADVANCED MATERIALS AND APPLICATIONS. He/ She presented an Invited Talk/ Invited Technical Talk/ Oral / <input checked="" type="checkbox"/> Poster entitled <u>P-12</u></p>		
 Dr. Chetan Limbachiya Convener	 Dr. K. V. R. Murthy President, Luminescence Society of India	

2. **Participated:** International E- Conference on Recent Advances in Chemical, Physical and Biological Science (RACPBS-2021) on 29th-30th June 2021 organized by Department of Chemistry, Nabira Mahavidyalaya, Katol and Association of Chemistry Teachers (ACT), C/o Homi Bhabha Centre for Science Education (TIFR) Mumbai.



3. **Poster Presentation:** National Conference on “Modern Evolution in Material & Chemical Sciences (MEMCS-23)”

Meetkumar Thakar, Pankaj Sharma^{*}; held on (6th and 7th January, 2023); Organized by Parul University, Vadodara.



4. **Participated:** National Level Online Workshop on “Virtual Chemistry Learning for Higher Education”

Held on (18-01-2021 to 19-01-2021); jointly organized by Department of Chemistry, School of physical Sciences, & Pandit Madan Mohan Malaviya National Mission on Teachers and Teaching and School of Education, Central University of Kerala, Kasaragod, Kerala.



5. **Poster Presentation:** National Conclave on “ Promotion of Millets (Shree Anna) for Sustainable Agriculture and Nutritional Security Towards Global Prosperity : Key Challenges and Future Prospects”

Meetskumar Thakar, Pankaj Sharma^{*}; organized by Sardarkrushinagar Dantiwada Agricultural University in collaboration with Gujarat Society of Genetics and Plant Breeding (GSGPB) & Deendayal Research Institute (DRI) held at Sardarkrushinagar Dantiwada Agricultural University (Gujarat) during (30th October- 1st November, 2023).



Award and achievements

1. **Indian Pattern Published:** On “Method for Determination of Toxic Metals in Cholic Acid Analyte”

Pankaj Sharma, **Thakar Meetkumar**, Vaishali Suthar, Sheth Jateen, Indra Neel Pulidindi; Issue No: 32/2023, Application No: 202321038908 A, Publication Date: 11/08/2023.

पेटेंट कार्यालय शासकीय जर्नल		
OFFICIAL JOURNAL OF THE PATENT OFFICE		
निर्गमन सं. 32/2023 ISSUE NO. 32/2023	शुक्रवार FRIDAY	दिनांक: 11/08/2023 DATE: 11/08/2023
पेटेंट कार्यालय का एक प्रकाशन PUBLICATION OF THE PATENT OFFICE		
The Patent Office Journal No. 32/2023 Dated 11/08/2023		52662

INTRODUCTION

In view of the recent amendment made in the Patents Act, 1970 by the Patents (Amendment) Act, 2005 effective from 01st January 2005, the Official Journal of The Patent Office is required to be published under the Statute. This Journal is being published on weekly basis on every Friday covering the various proceedings on Patents as required according to the provision of Section 145 of the Patents Act 1970. All the enquiries on this Official Journal and other information as required by the public should be addressed to the Controller General of Patents, Designs & Trade Marks. Suggestions and comments are requested from all quarters so that the content can be enriched.

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11th AUGUST, 2023

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KOLKATA, 11/08/2023

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SPECIAL NOTICE

18 Months publication as required under Section 11A of the Patents Act, 1970 as amended by the Patents (Amendment) Act, 2005.

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(57) Abstract :
ABSTRACT METHOD FOR DETERMINATION OF TOXIC METALS IN CHOLIC ACID ANALYTE The present invention is related to a highly simple, quick, easy, cost effective, and reliable, method for detection of toxic heavy metals in cholic acid analyte samples. The method comprises microwave assisted digestion of the analytical sample followed by sample preparation in conjunction with Q-ICP-MS for accurate determination of mentioned toxic heavy metals impurities in oral medicinal products, or cholic acid containing samples in a single test.

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